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TB INFECTION AND DISEASE IN THE COMMUNITY

Tuberculosis continues to be as treacherous a disease as ever before. For years epidemiologists and tuberculosis workers have been making estimates of the prevalence of infection and disease in the populatoin. Tuberculin allergy has been used to provide not only estimates of the prevalence of infection but also, although roughly of the prevalence of disease in the community.

The discovery that many reactions to tuberculin, specially, in the tropical and sub-tropical countries, are not due to infection with mycobacterium tuberculosis has posed problems not only in differentiation of specific reactions from non-specific in dignosis of cases and applications of preventive measures like BCG Vaccination but also casts considerable doubts on previous estimates of prevalance and incidence of infection. From early times, 5 mm or bigger induration to a standard dose of tuberculin has been regarded as evidence of infection. Later, the induration level, for the purpose of definite diagnosis of tuberculosis infection was raised to 8 mm. This was also expected to give benefit of BCG vaccination to a larger population who were considered doubtfully infected. Still later, 10 mm and even bigger reactions only have been regarded as evidence of definite tuberculosis infection but the choice remains somewhat arbitrary and may not always clearly demarcate the infected from the non-infected.

The longitudinal studies by the National Tuberculosis Institute, Bangalore and the Field Research Unit, Madanapalle continue to throw light on the behaviour of infection and disease in man. Now it can be said that it is only the large tuberculin reactions (15 mm and more) that represent definite evidence of tuberculosis infection and that the interpretation of a repeat tuberculin test has to be different from that of the firs! test. Because of the boosting effect of the allergy due to repeat test further measuring of the incidence of infection is not altogether a simple matter. Perhaps, only an increase in induration of 20 mm or more from one test to another, represents satisfactory evidence of new infection. If so, previous estimates of the incidence of infection also need revision. Interpretation of the tuberculin test has assumed further importance because of the application of preventive chemoprophylaxis to the infected group, specially infants and children.

Studies on co-relating the prevalence of disease with that of infection have not yielded good results possibly because neither the infected are clearly defined, nor is the definition of a case sharp enough. Bacteriological basis for diagnosis has its own limitations. It even appears not to regard the finding of only one or two bacilli under microscope as definite evidence of active pulmonary tuberculosis. On follow-up such cases do not often show evidence of progressive disease. Similarly, cases for whom sputum examination show only a few colonies on culture, have greater frequency of healing in the absence of treatment than cases in whose sputum a large number of colonies are grown. These limitations of bacteriological examination suggest that previous estimates of the prevalence of even bacteriologically confirmed disease may also need revision. Thus some concepts regarding the epidemiology of the diseases are still not very clear and need further studies and research. There is, therefore, still a great demand for developing more acurate techniques and better standards. The need is being increasingly felt and we hope that these will be made available soon for mapping out infection and disease more correctly.

These impressions are the results of field research in only one area of the country namely, within a hundred miles of Bangalore. What is happening in the rest of the country is still a guess. There is obviously need for similar studies in other parts of the country.

DISTRIBUTION OF INFECTION AND DISEASE AMONG HOUSEHOLDS IN A RURAL COMMUNITY*

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Introduction

1. Studies on distribution of infection and disease in housholds have mostly been restricted to the examination of contacts of known cases. Such examinations, primarily undertaken to extend the sphere of control of disease from the individual patient to his family, are limited to only a small selected population in the community. Further, a larger proportion of the patients diagnosed in a traditional clinic service are likely to be more advanced as compared to the total cases in the community (Sikand and Raj Narain, 1957) and their family contacts may show only an end point of prolonged exposure to infection. A representative picture of the distribution of infection and disease in households can be obtained only from a tuberculosis prevalence survey and is likely to throw more light on possibilities or limitations of some methods of casefinding such as, contact examination and preliminary screening of persons to be examined by using the results of a tuberculin test. Further, it may be possible to define certain characteristics of a case which may be associated with greater frequency of infection among their contacts. Comparison of the distribution of tuberculin reactions of infected contacts with infected persons in homes without a case could help in understanding the influence of more frequent infections in case tuberculin allergy. The present paper is a report of such an attempt from a prevalence survey in a rural community in South India.

2. Methods and Material

Data from a prevalence survey, carried out by the National Tuberculosis Institute (NTI) during 1960-61 in 62 randomly selected villages and 4 town blocks in Tumkur District, Mysore State, South India (Raj Narain et al, 1963) forms the basis of this report. The sample for the towns, being too small, has been omitted from the present study.

Survey techniques and study population have been described in the earlier report. Briefly, the de-facto population (i.e., excluding those permanent residents who were temporarily absent, but including visitors temporarily present at the time of the survey) was tuberculin tested with 1 TU RT 23 with Tween 80 and those aged 10 years or more examined by 70 mm photoflurography. All pictures were read by two independent readers. Those considered to have any abnormal shadows (including non-tubercular pathology) by either of the readers, and those with technically inadequate pictures or pictures or physical inability to attend the X-ray examination, were eligible for examination of a single spot specimen of sputum by direct smear and by culture.

The X-ray pictures, for which the two readings agreed and the disagreed films confirmed by an umpire, have been taken to represent radiologically active disease (X-ray cases). Persons, in whose sputum sample tubercle bacili were demonstrated by any method, even if no disease or no active disease was reported on the X-ray, have been called patients with bacteriologically confirmed disease (bacillary cases).

During the course of the survey information regarding the prevalence of symptoms, especially cough and its duration, was collected in 28 villages by the census takers from all persons of age 15 years or more during routine census taking, and in 34 villages by trained sociological workers from persons of age 20 years or more, who showed X-ray shadows considered by at least one reader to be of tuberculous origin (active or inactive) and matched controls (Banerji and Andersen, 1963).

The defacto population was 29,813 and tuberculin results are available for 27,115. From these, 2,638 persons who were not cases and had B.C.G. scars (definite or doubtful) and 14 non-cases without information on scar have been excluded. The remaining persons together with 11 cases without tuberculin results constituted the study population of 24,474 and was distributed over 5,266 households. Three categories of households have been considered†:

(i) Bacillary case households i.e., those with one or more bacillary cases.

*The paper has also been published in WHO Bulletin.

†1. Sixty persons X-rayed in bacillary and X-ray case households but with tuberculin test results not available have also been included for study of disease among contacts.

2. All sorting was done by hand as relevant information had not been punched earlier on the cards. There was a shortage of 4S7 cards between the total number in the three categories of households and the study population of 24,474 expected from the punched cards. The figures for bacillary and X-ray case households have been thoroughly checked. The shortage has occurred in non-case households and constitutes 2.2% of the total 21,728 persons expected. This error has not been corrected.

(ii) X-ray case households, i.e., households with at least one radiologically active case, but no bacillary case.

House-holds with only one bacillary or one X-ray case are referred to as single bacillary or single X-ray case households.

(iii) Non-case households, i.e., households without either a bacillary or an X-ray case.

There were 75 households with 77 baciliary cases: one with 3 bacillary cases and 74 with a single case each. One household with a bacillary case had a BCG scar and has been described separately. Among the remaining 73 single bacillary one case did not have the tuberculin test result available, and 2 were not X-rayed due to physical inability to reach the X-ray unit. In another, the X-ray picture was technically inadequate. Only 58 of the 73 cases in single bacillary case households and all the three cases in one household showed evidence of radiologically active disease. Information on symptoms is available for 54 of the 73 cases.

Total number of X-ray cases, including the 61 bacillary cases considered active on X-ray examination, was 357. Eleven X-ray cases were found concomitantly in bacillary case households. The balance of 285 X-ray cases included 9 with BCG scar: eight, occurring singly, have been considered separately. The remaining 277 cases, including one with BCG scar, which occurred along with another X-ray case, were distributed over 267 households; 257 being single X-ray case households. Information on symptoms is available for 215 of these 257 cases.

The non-case households number 4916.

Detailed analysis and comparisons between households for the prevalence of infection have been confined only to single case households.

The prevalence of infection was studid for each category of households separately for males and females. Sex differences were not much in most cases, particularly among children, as also reported by Hertzberg (1957). Infection rates have not been presented separately for the two sexes.

Infection among children in age groups (0-4), (5-9), and (10-14) years, has been studied. Increasing age, to a certain extent, may represent longer exposure in the home and also outside. On account of the small number of children in different age groups in bacillary case households, the combined age group of (0-14) has been used for part of the analysis. Infection in higher age groups has not been studied in detail, because such infection may not represent recent events and the influence of household infection may not be the predominant factor.

Persons with BCG scars :

The omission of persons with BCG or doubtful scar and those for whom tuberculin test results are not available may have influenced the infection rates in the different categories of households. Those excluded because of BCG scar constituted about 9 per cent only and may not have made much change in infection rates unless they are considered likely to provide an entirely different picture of infection, as compared to others, had they not been vaccinated five to eight years earlier. Comparisons made separately for different age groups may further reduce the possible influence of such exclusion.

3. Findings:

3.1 *Prevalence of disease among contacts in bacillary and X-ray case households:*

Some of the households had more than one case. If one of these is considered as an index case, the other(s) could be considered as disease among contacts. Among the 74 bacillary case households, excluding one with a case having BCG scar, only one had more than one bacillary case. Two of the 3 cases in this household could be considered as bacillary disease among the 325 contacts examined by X-ray. Similarly there were 13 X-ray cases (including the two bacillary cases) among the 325 contacts of bacillary cases giving an X-ray case prevalence rate of 4%.

Among the 267 X-ray case households, the 10 additional X-ray cases (including the one with BCG scar) gave a prevalence rate of 1% for the 985 contact examined. The contacts of both X-ray and bacillary case households, taken together, showed an X-ray case rate of 1.8% and bacillary case rate of 0.2%. For the entire village population X-rayed, the prevalence of X-ray and bacillary cases was 1.8% and 0.4% respectively (Raj Narain et al, 1963). Thus disease among contacts in bacillary case households is significantly more than in X-ray case households, and is contrary to the lack of such a difference in some studies (Sen 1959, Sikand et al, 1962).

3.2 *Prevalence of infection in different categories of households:*

The proportions infected in bacillary, X-ray and non-case households were 63%, 46% and 37% respectively for all ages combined. The corresponding infection rates for children of age (0-14) were 41%, 20% and 12% and for persons of age 15 years or more 77%. 62% and 54% respectively. The prevalence of infection is substantially different in the 3 types of households the differences being statistically significant* for all 3 age groups. The exclusion of cases, in order to get infection rates among contacts only, did not produce any material change.

Inspite of lower prevalence in non-case households, 81% of the infected children in age group (0-4), 84% in age group (0 14) and *87%* in age group 15 years or more were found in these. The influence of previous cases, no longer present at the time of the survey, is not known but for a majority of infected persons in the non-case households the source of infection must have been outside the household.

Following Hertzberg (1957) "infection intensity" (i.e. the ratio of percentage infected among contacts of age (0-14) years of a particular type of case to the percentage infected among members of non-case households in the same age-group, with assumed infection intensity of 1.0) was 3.4 and 1.6 for bacillary and X-ray case households respectively. This gives a rough measure of the degree of concentration of infection in the three types of households.

3.3 *Infection among child contacts:*

The intra-household effect of a case may be better reflected by infection in young children. Table 1 gives the proportion infected among children of 3 age groups for each category of households, and for the total population.

Among children of age (0-4) years, only 12% were infected in bacillary case households and 4% in X-ray case households. It does look surprising indeed that most of the very young children escape infection in spite of living with an open case of tuberculosis in poor congested houses and not protected by any preventive measures.

The age infection curves rise with age in all the 3 categories of households (Fig. 1). But the curves maintain different levels throughout, the bacillary case households being at the top and non-case households at the bottom. The higher proportion infected in age-group (0-4) in bacillary case households and the steep rise in infection for (5-9) years can be taken to depict the effect of household infection. For other categories of households the steeper rise in percentage infected was observed between age group (5-9) and (10-14). This delayed rise in percentage infected may be attributed to lesser infectivity of the non-bacillary X-ray cases (some of these may be occasional excretors of tubercle bacilli) or to the influence of infection acquired outside the household, both of which factors may need a longer period to cause infection. The possible influence of cases present prior to the survey in these households is not known.

Table 2 shows that many households with cases did not have any child in the age groups considered and several households with children had no infected child among them especially in age-group (0-4).

Of the 73 bacillary case households, 28 had no child and a further 37 had no infected child in age group (0-4). The prevalence of infection in this age-group may not, therefore, be as

TABLE 1

Percentage of children infected in three age-groups among various categories of households

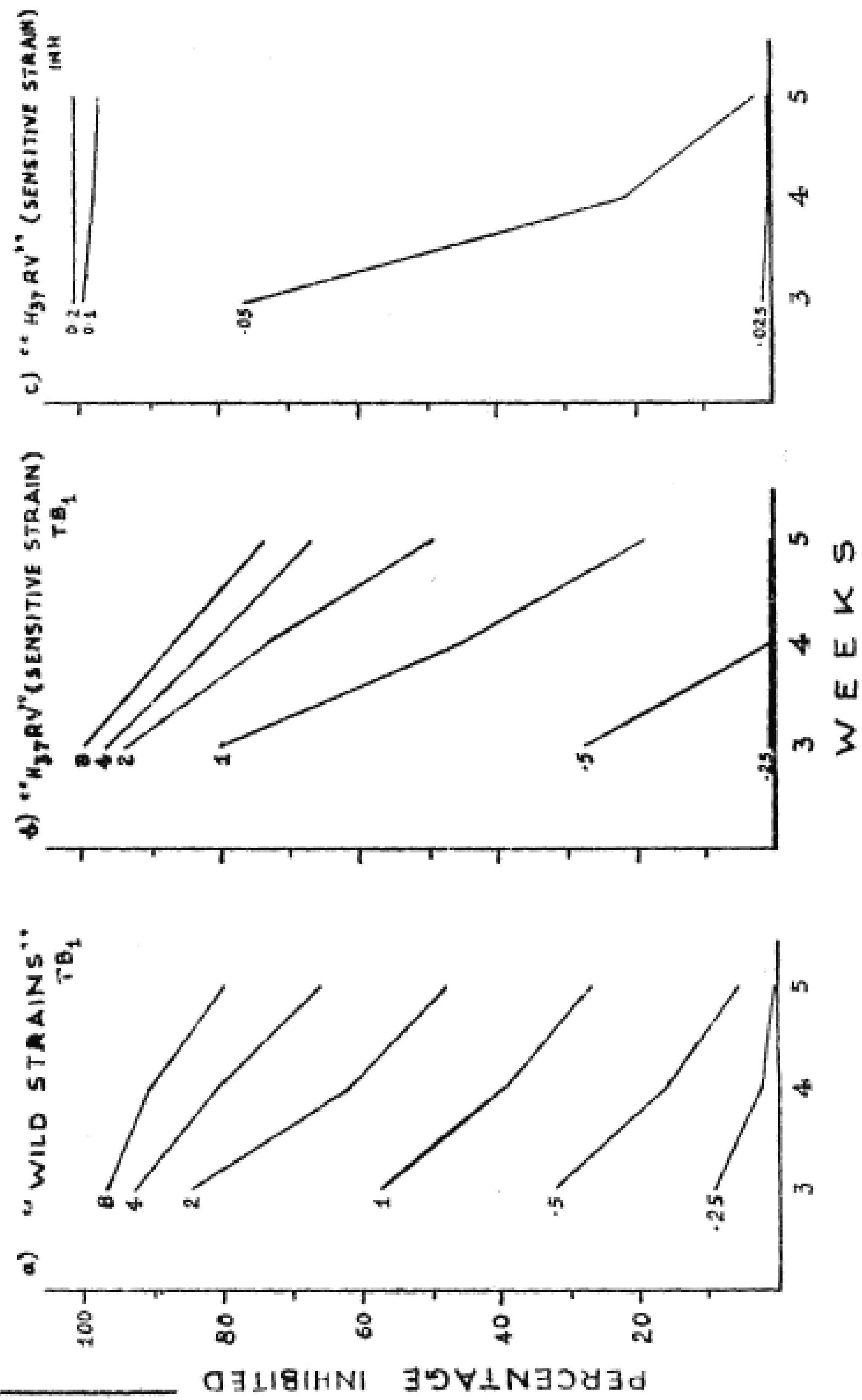
	Bacillary case households		X-ray case households		Non-case households		Total population
Age Group	No. of children	Percent infected	No. of children	Percent infected	No. of children	Percent infected	Percent infected
0—4	69	12	239	4	3634	2	3
5—9	53	53	206	20	3135	13	13
10—14	64	62	159*	42	2417	27	28
0—14	186	41	604*	19	9186	12	13

* Excludes the non-bacillary X-ray cases in this age group

* Only results with a minimum level of 95% confidence have been regarded as significant.

FIG. 1

PERCENTAGE INHIBITED AT DIFFERENT CONCENTRATRATIONS (μGM) OF TB_1 AND INH AT 3, 4 AND 5 WEEKS



good an index of disease in the community, as is generally assumed. It may not also be effective in identifying households with cases.

As children of higher ages are considered, the number of houses with no child infected falls more rapidly in bacillary case households than in X-ray case households.

3.4. Distribution of infection within households of each category:

3.4.1. Does the proportion infected vary with the size of the household?

Table 3 gives the distribution of households according to the number of persons in each for bacillary and X-ray case households as well as for a 10% random sample of non-case households; number test-read and the percentage infected are also presented. Cases have been included for counting the size of the household but, obviously, not prevalence of infection

TABLE 2

Distribution of bacillary and X-ray case households according to absence of children and absence of infected children

Age Group	Bacillary case households			X-ray case households		
	With no child	With at least one child infected	With no child infected	With no child	With at least one child infected	With no child infected
0—4	28	45	37	109	148	139
5—9	36	37	16	122	135	100
10—14	30	43	13	145	112	60
0—14	12	61	16	45	212	133

TABLE 3

Distribution of households by size and percentage infected among contacts/members of case and non-case households

* Number of persons in a household	Bacillary case households			X-ray case households			Non-case households (10% sample)		
	No.	No. of contacts test read	% infected	No.	No. of contacts test read	% infected	No.	No. of contacts test read	% infecied
1—2	5	4	50.0	20	11	54.5	74	95	65.3
3—4	11	21	71.4	46	110	49.1	144	415	44.3
5—6	17	64	62.5	65	254	36.6	142	610	34.6
7—8	15	80	65.0	50	269	39.0	72	426	28.9
9—10	12	86	55.8	33	223	45.7	39	288	42.7
11 +	13	167	56.3	43	494	41.1	29	313	43.8
Total	73	422	59.5	257	1361	41.4	500	2147	39.1

* Includes cases.

among the contacts. If the size of the household has no influence on the proportion infected, one would expect this proportion to be fairly uniform for households of different sizes in each category. On this assumption, the expected numbers infected in households of different size were computed using the percentage infected in all households of a category as an estimate of this uniform proportion. The differences between observed and expected distributions were not statistically significant for bacillary and X-ray case households (for bacillary case households; Chi-square= 1.54; d.f.=4; 0.80∠ P∠ 0.90; for X-ray case household: Chi-square = 4.80; d.f. = 4; 0.60∠P.∠0.70). Infection, therefore, does not seem to vary in case households with size of household. But observed distribution was significantly different from that expected for non-case households (Chi-square = 36.8; d.f.=4; P∠0.001). In Table 3, the percentage infected in non-case households for size 1-2 persons is highest and is significantly different from the average of all households (P∠0.001). But these smaller households are likely to consist of adults only. Even when these households of size (1-2) are excluded, the differences for non-case households continue to be statistically significant (Chi-square=20.1; d.f. = 3; P∠0.001). Infection was least in medium sized households. The different results obtained for case and non-case households may be due to either the smaller numbers available in the former or the presence of a casein the household over-riding the influence of the size of the household.

The average size of the household was nearly equal for bacillary and X-ray case households (7 -9 and 7.4 respectively). But the average number infected per household was more in bacillary case households (4.1 against 2.9 in X-ray case households). For non-case households the average size was 5.4 and the the average number infected 1.7.

3.4.2. Prevalence of infection among child contacts within households:

To study the distribution of infection within households, those with an equal number of children of age group (0 — 14) have been grouped in Table 4, and households under each group have been further distributed according to the number of infected children among them. All the four households, with an X-ray case each in the age group (10—14) years, have been excluded from the table. If prevalence of infection given in the last column for a particular 'size' of households, could be assumed to be the probability of finding an infected child, the expected number of households of that size which have 0, 1, 2 etc. infected children can be worked out on the basis of the binomial distribution. Such expected numbers are given in brackets in Table 4. Observed and expected distributions were significantly different (as judged by the combined Chi-square test) for X-ray but not bacillary case households. The different results for the two types of case households could most probably be attributed to the number in bacillary case households being too small to give significant results. If so, it can be concluded that there is concentration of infection in some case households and that all cases are not equally infectious, a finding which is supported by Table 5. The fact, that the prevalence of infection in children of (0 — 14) years involved periods of exposure varying from a few days to nearly fifteen years, makes it difficult to draw definite conclusions regarding the differences in infectiousness which can better be judged from incidence of infections.

3.5 Characteristics of a case and their influence on infection in the household:

The households were further subdivided according to various characteristics of the case, such as sex, age, tuberculin sensitivity, X-ray status, history of cough, presence of additional cases etc. For non-case households, the influence of "doubtful" X-ray cases has also been studied. The results are summarised in Table 5, in which the statistically significant differences have been underlined.

Children living in households with a bacillary case, considered active radiologically, showed significantly higher prevalence of infection as compared to those living with X-ray-non-active bacillary cases, except for children of (0—4) years. Further, the percentage of infected children of age (0—14) in households with X-ray non-active bacillary cases (24%) is not much different from that of X-ray case households (19%—Table 1).

X-ray cases if classified by both readers as "probably tuberculous and active" (coded as D in the table) were more infectious than those classified by one or both readers as "probably tuberculous, possibly active" (coded as C). Bacillary cases, though not X-ray cases, seem to be more infectious if there was a history of cough for more than one month. Surprisingly, children in contact with female cases were consistently less frequently infected than children in contact with male cases. Households with cases aged 50 years and more tended to have fewer infected children than those with cases of of younger age; significantly high infection prevalence was found in households with bacillary cases of age (49— 49) years. X-ray cases, who gave tuberculin reactions of less than 10 mm, had significantly less infection among

TABLE 4

Correlation of number infected with total number of children (0—14) years in Bacillary and X-ray case households

Number of children in the household	Frequency of households with children infected numbering						Total	Children infected (percent)
	0	1	2	3	4	5		
A. Bacillary case households:								
1	4	4	—	—	—	—	8	50
2	7 (6.0)	8 (9.9)	5 (4.1)	—	—	—	20	45
3	2 (1.8)	6 (5.5)	4 (5.7)	3 (2.0)	—	—	15	51
4	2 (1.3)	2 (3.5)	4 (3.5)	2 (1.5)	— (0.2)	—	10	40
5+	1	3	2	1	—	1	8	28
Total	16	23	15	6	—	1	61	41
B. X-ray case households:								
1	35	12	—	—	—	—	47	26
2	46 (42-6)	15 (21.4)	6 (2.7)	—	–	—	67	20
3	24 (20.0)	(15.0)	7 (3.7)	1 (0.3)	—	—	39	20
4	11 (8-2)	5 (8.2)	2 (3.1)	(0.5)	1 (0.03)	—	20	18
5	9 (7.4)	(8.1)	5 (3.6)	1 (0.8)	— (0.1)	— (0.0)	20	18
6	4	1	1	1		1	8	23
7	1	1	—	—	—	—	2	7
8	—	—	1	—	—	—	1	25
9	2	1	1	—	—	—	4	8
10	—	—	—	—	—	—	—	—
11	–	1	—	—	—	—	1	9
Total	132	48	23	4	1	1	209*	19

Figures in brackets are frequencies expected on the basis of binomial distribution using the proportion infected in the total households of each size given in the last column.

* Excludes 4 households, each with an X-ray case of age 10—14 years

TABLE 5

Infection among children according to the characteristic of the case in the household

Characteristic of the case in the household	Number of children in age-group (0-4)	(5-9)	(10-14)	(0-14)	Percentage infected in age-group (0-4)	(5-9)	(10-14)	(0-10)
A. Becillary case								
Households:								
1 . (a) X-ray active (C or D by two readers)*	55	41	45	141	13	*63*	*76*	*48*
(b) Not active by X-ray	8	8	17	33	12	*25*	*29*	*24*
2. (a) With cough	30	24	31	85	17	62	*77*	*52*
(b) Without cough	21	11	14	46	10	36	*43*	*26*
3. (a) Male	50	41	41	132	14	*61*	66	45
(b) Female	19	12	23	54	5	*25*	57	31
4. (a) 10-49 years	47	34	39	120	15	63	59	43
(b) 50 years and above	22	12	25	66	5	53	52	36
5. (a) Tuberculin +	59	43	49	151	12	53	65	41
(b) Tuberculin -	9	8	14	31	11	38	57	39
6. (a) With additional X-ray case	3	8	14	30	25	50	71	53
(b) Without additional X-ray case	61	45	50	156	10	53	60	38
B. X-ray case households:								
1. (a) D* by two readers	26	25	21	72	*15*	28	52	*31*
(b) Other X-ray cases	213	181	138	532	*5*	19	40	18
2. (a) With cough	81	81	59	221	6	21	44	22
(b) Without cough	124	96	72	292	3	19	43	18
3. (a) Male	158	143	115	416	5	20	43	21
(b) Female	81	63	44	188	2	19	36	16
4. (a) 10-49 years	118	103	83	304	4	24	46	22
(b) 50 years & above	121	133	76	300	4	16	37	16
5. (a) Tuberculin +	168	103	99	400	4	*26*	43	*21*
(b) Tuberculin —	61	69	52	182	3	*9*	33	*14*
C. Non-case Households:								
(a) With "doubtful" X-ray cases*	62	65	62	189	3	9	29	14
(b) Others	3572	3070	2353	8997	2	13	27	12

* See text for definition

their child contacts than tuberculin positive X-ray cases, (it should be noted in this connection that two-thirds of the tuberculin negative X-ray cases were above 50 years of age).

Persons whose sputa were negative and who were classified as showing radiologically active disease by one reader only, and not by the other reader or the umpire, may be described as "doubtful" X-ray cases. There is very little difference in the percentage infected among children of 3 age groups between households with such cases and other non-case households, Further the infection in households with such "doubtful" X-ray cases is significantly less than in X-ray case households for the age groups (5—9) years. This supports the rejection of such cases by the umpire, and of their being regarded as 'false' positives of each reader.

A comparison (not shown in Table 5) of direct smear positive cases with cases positive by culture only did not show any significant difference infectivity, although disease was generally more advanced and more often cavitary in the former.

The above results may be summed up in terms of infection intensity (See Section 3,2).

Assuming the proportion of children under 15 years infected in non-case households as (1.0), the highest intensity of infection was found in bacillary case households. The intensity was (4.4) when an additional X-ray case was present in the household; the indices being (4.3) and (4.0) respectively when the case and cough or was confirmed by X-ray. When the bacillary case was not considered active on X--ray, the intensity was only (2.2) as compared to (2.6) for households with non-bacillay X-ray cases classified as active by two readers. X-ray cases showing tuberculin induration of 9 mm or less had the lowest intensity (1.2), and the infection in these households may not be very different from the non-case households.

3.6 *Effect of recent and/or repeat infections on size of tuberculin reactions:*

It is possible that recent or repeat infections may give rise to large tuberculin reactions. Both are likely to be more frequent in baciliary case homes. Fig. 2 compares histograms of the tuberculin indurations of the infected (5= 10 mm) only, in 4 age groups, for contacts in case households and the members of non-case households.

The difference between mean indurations for the bacillary (19.7 mm) and for non-case (18.5 mm) households is highly significant for "all ages" ($P<0.0001$) and for the age group 25 years and more ($P<0.001$). Similar difference for the bacillary and X-ray case households is significant for "all ages" only ($P<0.05$).

In addition to mean indurations, frequency of large reactions among the positive reactors in the three categories of households may be compared (Table 6).

Indurations of 15 mm or more and 20 mm or more have arbitrarily been chosen to represent large reactions. The percentage of large reactions of either size are significantly more in bacillary case households as compared with the X-ray or non-case households (Cochran Test for over-all differences). Such an overall difference between X-ray and non-case households is not significant. The list of significant differences for individual age groups of the bacillary and the other two categories of households is shown below the table.

Percentage of reactions of 20 mm or more among children of (0 - 14) years was higher in bacillary case households as against the other two categories of households. Louden et al (1958) also found a greater frequency of strong reactors among the tuberculin positive contacts of direct smear positive cases, as compared to contacts of cases 'positive only on culture' or 'bacteriologically negative'. Further within each of the three categories of households the proportion of such large reactions was considerably higher (highly significant) in age group (0—14) as compared to older persons. Similar differences for reactions of size 15 mm or more were significant for bacillary and non-case households. The larger proportion of the positive reactions in age group (0 —14) especially in bacillary case households would suggest that new or recent infections produce large reactions. This is in conformity with the finding (Raj Narain et al, 1965) that new infections result in an increase in allergy of at least 16 — 20 mm.

The higher percentage of large reactions in bacillary case households as compared to other type of households, among those of age group 25 years or more is probably due to greater chances of repeat infections in the former. Thus repeat or super-infections may play a role in sustaining bigger reactions in older age groups, in which the waning of allergy is probably more. Another exaplanation could be that even among those of 25 years or more, in bacillary case homes a larger proportion are recently infected.

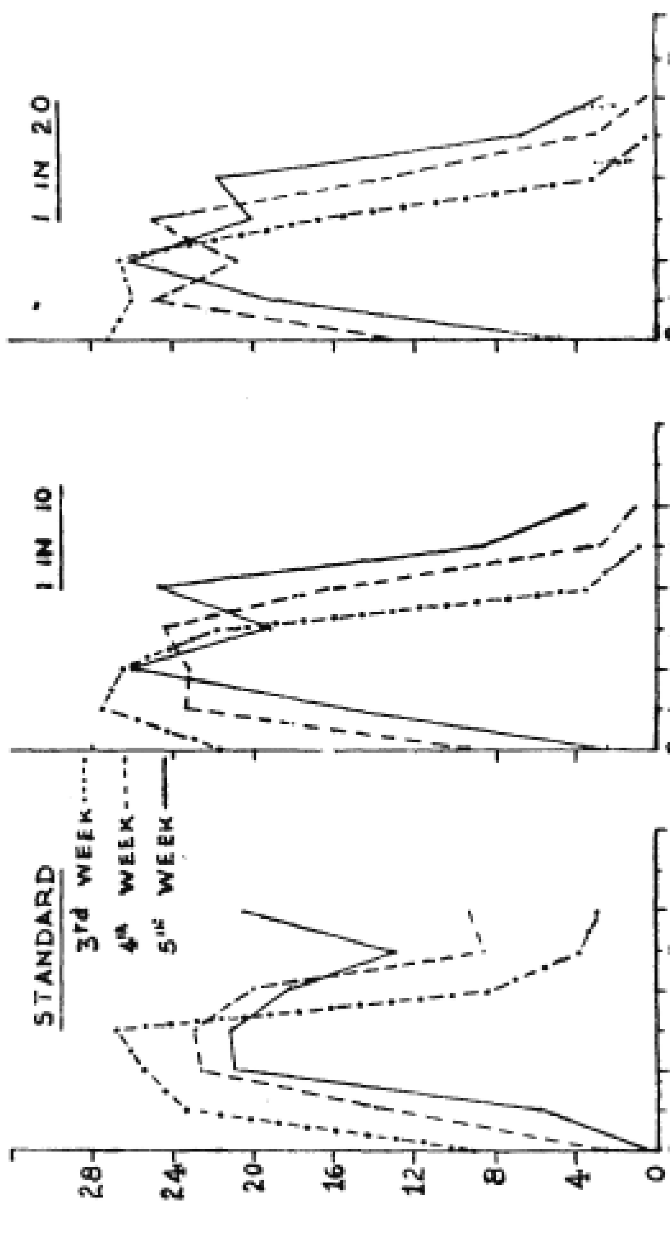
Some of the 10—14 mm reactions may not be due to infection with Myco. tuberculosis. Excluding these, among persons with 15 mm and larger reactions, percentage of 20 mm and larger reactions showed similar differences. Also the mean indurations for all ages was still significantly higher in bacillary case households than in non-case households. Therefore this exclusion did not affect the results materially.

The percentage of large reactions of 20 mm or more decreased significantly with age in non-case households. This and the consistently higher proportion of large reactions in the youngest age group are likely to be due to waning of tuberculin allergy in older age groups.

In both types of case households the

FIG. 2

FREQUENCY CURVE OF MIC LEVEL OF TB, FOR DIFFERENT STRENGTHS OF INOCULUM AND PERIODS OF INCUBATION



WEEKS	STANDARD LOG UNITS N	$\bar{x}$	SD	1 IN 10 LOG UNITS N	$\bar{x}$	SD	1 IN 20 LOG UNITS N	$\bar{x}$	SD
3	725	2·26	1·40	645	1·59	1·18	589	1·44	1·16
4	725	3·08	1·55	670	2·27	1·35	629	2·11	1·36
5	726	3·73	1·57	674	2·89	1·42	632	2·64	1·41

TABLE 6

Frequency of large indurations among reactors ≥10 mm) for contacts/members among the 3 categories of households, by age

Age Group	No. of positive reactors (≥10 mm)			Percentage of positive reactions with induration of					
				15 mm or more			20 mm or more		
	BCH*	XCH*	NCH*	BCH	XCH	NCH	BCH	XCH	NCH
0—14	76	117	1237	88.2	82.1	83.0	73.7	57.3	59.8
15—24	59	124	1527	69.5	77.4	73.5	37.3	35.5	43.0
25 years or more	116	321	6229	85.3	76.9	73.6	49.1	42.7	38.7
All ages	251	562	8993	82.5	78.1	74.9	53.8	44.1	42.3

* BCH: Contacts in bacillary case households
XCH: Contacts in X--ray case households
NCH: Members of non-case honseholds

Significant differences within each age for categories of households which differ according to Cochran test:

(a) Among percentages with induration of 15 mm or more
(BCH-NCH) for age 25 years or more (P∠0.01)
(BCH-NCH) for all ages (P∠0.0l)

(b) Among percentages with indurations of 20 mm or more
(BCH-XCH) for age (0—14) years (P∠0.05)
(BCH-NCH) for age (0—14) years (P∠0.05)
(BCH-XCH) for all ages (P∠0.05)
(BCH-NCH) for all ages (P∠0.001)
(BCH-NCH) for age 25 years or more (P∠0.05).

percentage of large reactions was lowest for the age-group (15—24) years, the differences being statistically significant for comparisons with (0—14) age group for the 20 mm and larger reactions, and for both the younger and the older age groups for 15 mm or bigger reactions in bacillary case households. The reason for this smaller proportion of large reactions in this age group is not clear.

Oedematous, bullous or ulcerative reactions were not more frequent among the bacillary cases as compared with the X-ray cases or among the infected contacts of either.

3.7 Distribution of infection and disease in households excluded from the main analysis:

One household had 3 radiologically active cases confirmed by culture. In this household 15 of the 17 persons were test-read. Only 1 of the 3 children of age (0—4), 2 of 3 in age group (5—14), and all the remaining 9 adults were tuberculin positive, on direct smear, one case was negative and the other two showed less than 3 bacilli each. Two cases were males aged 30 and 34 years and the third, a female, aged 18 years, wife of a male case.

In the household with the bacillary case having BCG scar there were 8 persons (6 test-read). The case, a girl of 12 years, showed less than three bacilli on direct smear only. There was no child below 10 years and of the two in age group (10-14), both were infected. Three out of four persons of age 15 years or more were infected.

In the ten X-ray case households with one additional X-ray case each (including one case with BCG scar), one out of nine in age-group (0-4), seven out of twenty seven in age-group (0-14) and thirty four out of forty six in the age-group 15 years or more were infected.

There were 8 households, each with one non-bacillary X-ray case having BCG scar (3 females and 5 males). Seven cases were tuberculin positive, but the eighth, a girl of 12 years, had 0 mm induration only. Only 2 out of 24 children in age group (0-14) and 19 out of

32 persons of age 15 years or more were infected.

4. Discussion

4.1 Limitations of diagnostic procedures:

Some limitations of the diagnostic procedures used in surveys have been discussed earlier (Raj Narain et al, 1962). Certain limitations relevant to the present analysis have to be kept in mind.

4.1.1 Choice of level of induration as evidence of infection:

Persons with induration of 10 mm or more to 1 TU have been considered infected with Mycobacterium tuberculosis. Figure 3 shows that the choice of any level other than 10 mm, in the range 8-16 mm, may not have materially changed the findings of the study, as these are mainly based on comparison of infection among children upto 15 years of age, in the 3 categories of households. This only confirms the earlier observation that it is difficult to choose between different levels in the range of 9-14 mm as evidence of infection (Raj Narain et al 1963) and the observation by the British Medical Research Council (1963) that the incidence of new disease during a follow-up lasting ten years was not different among those with initial indurations of (5-9) mm and (10-14) mm to 3 TU old Tuberculin.

4.1.2 Bacteriological examination of a single specimen:

As only one sample of sputum was collected some of the bacillary cases would have been missed. A second sample in survey material may add some 20 to 30% to bacillary cases found by a single sample (Raj Narain et al, 1962). Most of the bacillary cases missed are likely to have been classified as X-ray cases. If so, X-ray case households probably would have shown a still smaller concentration of infection as compared with bacillary case households and the difference between the X-ray and non-case households might have become less distinct.

Examination of more samples from each person could have resulted in a clearer demarcation in the infectiousness of the cases positive on direct smear and on culture only, as was found by Hertzberg (1957) with 3 to 6 sputum examinations of each case. A clearer picture may be available from the Longitudinal Survey, conducted by NTI, in which a larger number of sputum samples from each eligible person have been examined (data under analysis).

4.1.3 Significance of the X-ray status of a bacillary case:

Bacteriologically positive cases not showing any radiologically active tuberculous lesion are usually reported in surveys Of the 170 bacillary cases in the Delhi Zone of the National Sample Survey, 28 (18.5%) showed no radiological evidence of active pulmonary tuberculosis (Sikand and Raj Narain, 1958). In tropical Africa, of the 73 cases found positive by microscopy of direct smears, 11 had no pathology (Roelsgaard et al, 1964). In the present study, there were 13 such cases including one with BCG scar. Contacts of these cases have shown no more infection than those of non-bacillary X-ray cases. Further, none of the 9 cases for whom information was available had symptoms as against 79% of the 42 X-ray active bacillary cases. Six out of the twelve, whose results are available, were tuberculin positive and also culture positive. The remaining six tuberculin negatives comprised of 3 positive on culture; the other 3 showed less than three bacilli on direct smear only; in one of these culture was contaminated.

Five of these 13 bacillary cases were males and 8 females, as compared to 54 males and 23 females in the material.

Investigate these rather anomalous findings, these cases were re-examined in 1963. During the interval of two years, two males (aged 56 and 60 years) had died. For 10 of the remaining 11 cases the X-ray pictures on both occasions were read as either normal, non-tubercular or inactive by several readers in NTI. The last case (with BCG scar) was considered by all the readers as possibly active on her 1961 picture but inactive according to 1963 picture. Only 3 of these patients had been treated during the interval, but without any further X-ray or sputum examination.

The above findings pose the question, "Are all the X-ray non-active bacillary cases, generally found in surveys, false positives bacteriologically?" Some of these possibly do represent errors in sputum collection or labelling in the field or registration in the laboratory. But it is unlikely that all represent errors only. If so, existence of cases in a community who are sputum positive but X-ray negative and who do not show any progression of disease in course of time may have to be assumed. Such cases, if they exist, would add a new dimension in diagnosis and pose the problem of their possible significance to the community.

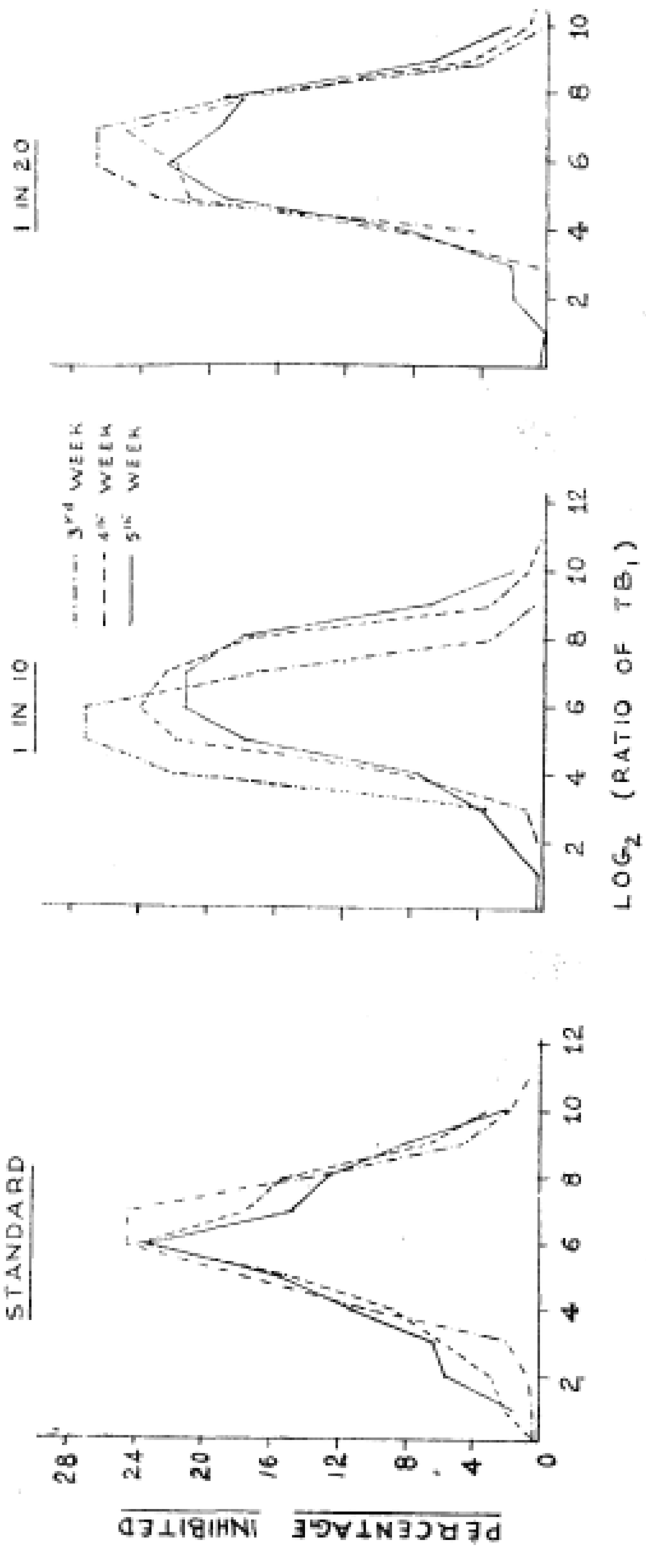
4.2 Some applications to case finding:

4.2.1 Value of contact examination:

Over 80 per cent of the total number of

FIG. 3

FREQUENCY CURVE OF RATIO $\left(\frac{\text{MIC OF WILD STRAIN}}{\text{MIC OF } H_{37} RV}\right)$ OF TB_1 FOR DIFFERENT STRENGTHS OF INOCULUM AND PERIODS OF INCUBATION



	Standard			1 in 10			1 in 20		
		LOG UNITS			LOG UNITS			LOG UNITS	
WEEKS	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD
3	711	6·26	1·64	632	5·46	1·24	563	6·49	1·20
4	686	6·07	2·01	656	6·28	1·45	602	6·38	1·41
5	687	5·85	2·02	660	6·29	1·74	609	6·33	1·71

infected persons, in any age group, occurred in non-case households. Also, persons suffering from the disease occurred mostly singly in households. Thus infection and disease were scattered in the community and the value of contact examination, under the circumstances, may be very doubtful, The disease among contacts was not more than the prevalence of disease in the total population (Section 3.1). This is in striking contrast to the general belief and impression from the examination of contacts of patients diagnosed in clinics, and may be due to the comparatively early diagnosis in a survey. In this material the radiological disease rate among contacts of symptomatic bacillary cases was definitely higher (6%). The more rewarding results of examination of contacts of cases diagnosed in traditional clinics in cities may be due to their being exposed to infection for a longer duration from a more advanced case or, perhaps, to the greater prevalence of disease in such cities. But by contact examination, at the most only two out of the 77 bacillary cases and 23 (6%) out of 357 X-ray cases would have been diagnosed, leaving the bulk of the cases in the community undetected. The position does not change when contacts of only the symptomatic cases are considered. Only 2% of the remaining asymptomatic bacillary cases and 7% of the remaining asymptomatic X-ray cases in the community would have been detected. In under-developed countries, where direct smear examination of sputum may be the only diagnostic method available, contact examination further loses its value and cannot be recommended.

Andersen and Geser (1960) also had "a certain scepticism" about the usefulness of contact examination in African communities. Boyd (1964) also considered it unlikely that the disease will occur concomitantly among many members of the same family.

4.2.2. Preliminary screening by a tuberculin test:

Preliminary screening of persons by a tuberculin test is likely to reduce the number of X-ray examinations for case finding. Among those 10 years or more of age, 51% are tuberculin reactors (at 10 mm. level), and include 84% of the bacillary and 77% of the X-ray cases (Fig. 4). Further, a fair proportion of the tuberculin negative cases "missed" by the method may not be true cases of pulmonary tuberculosis. Instead of excluding individual households with- low infection could be excluded from X-ray examination. If households with one or only one infected amongst them are excluded, only half the households need be examined and would include 88% of the bacillary and 75% of the X-ray cases. However, the advantage of these two methods may be more apparent than real in rural areas, as all the villages have to be visited by the X-ray unit. Exclusion of a substantial proprortion of the villages with very few cases, if possible, can be a real advantage. Table 7 shows that about 40-50% of the villages, covering about a third of the population can be excluded from examination, while the either bacillary or X-ray cases is only by any of the following three criteria:

1. none infected in age group (0—4),
2. less than 5% infected in age group (5-9),
3. less than 10% infected in age group (0-14).

A further advantage of this method is that a larger proportion of the villages are comparatively more difficult of approach by a mobile X-ray unit is excluded (not tabulated). By the above criteria the same proportion of direct smear positive cases is missed as of all bacillary cases.

4.3. Infection among children:

In bacillary cases households, 41% of children in the age group (0—14) were infected; Andersen and Geser (1960) reported 24% to 50% infected in households with direct smear positive bacillary eases in African communities. In our study only 12% for the children (0—4) years in bacillary case households were infected. Even in the household with 3 bacillary cases, only 1 out of 3 children (0—4) years was infected (section 3.7), and in spite of the fact that treatment or prevention are conspicuous by their absence. In the first application of Von Purquet Test in India (Gupta and Datt, 1927), in very congested, unhygienic households with an open case of pulmonary tuberculosis, 2 babies, 11 and 3 months of age, and a child of over 2 years failed to react. In another similar house, of the 3 children below 12 years, only one reacted and 2, of ages 3 and 5 years, failed to react.

It is difficult to imagine that under extremely adverse circumstances and in the absence of any preventive or therapeutic measures whatsoever, such a large proportion of children really escape infection. Hertzberg (1957) thought that this was due to better hygienic conditions. Some have considered tuberculosis as a 'minimal infection' only. It is difficut to accept such postulates when one thinks of some 'epidemics' where a single case of tuberculosis is known to have infected a large number of persons in a comparatively short time, for example, (Hyge, 1947).

FIG. 4

COORELATION BETWEEN SPOT & OVERNIGHT SPECIMENS FOR (A) RAIOS & (B) MIC FOR STANDARD INOCULUM IN 3 AND 4 WEEKS INCUBATION

"WILD STRAINS"

(3 WEEKS) **(4 WEEKS)**

RATIOS **RATIOS**

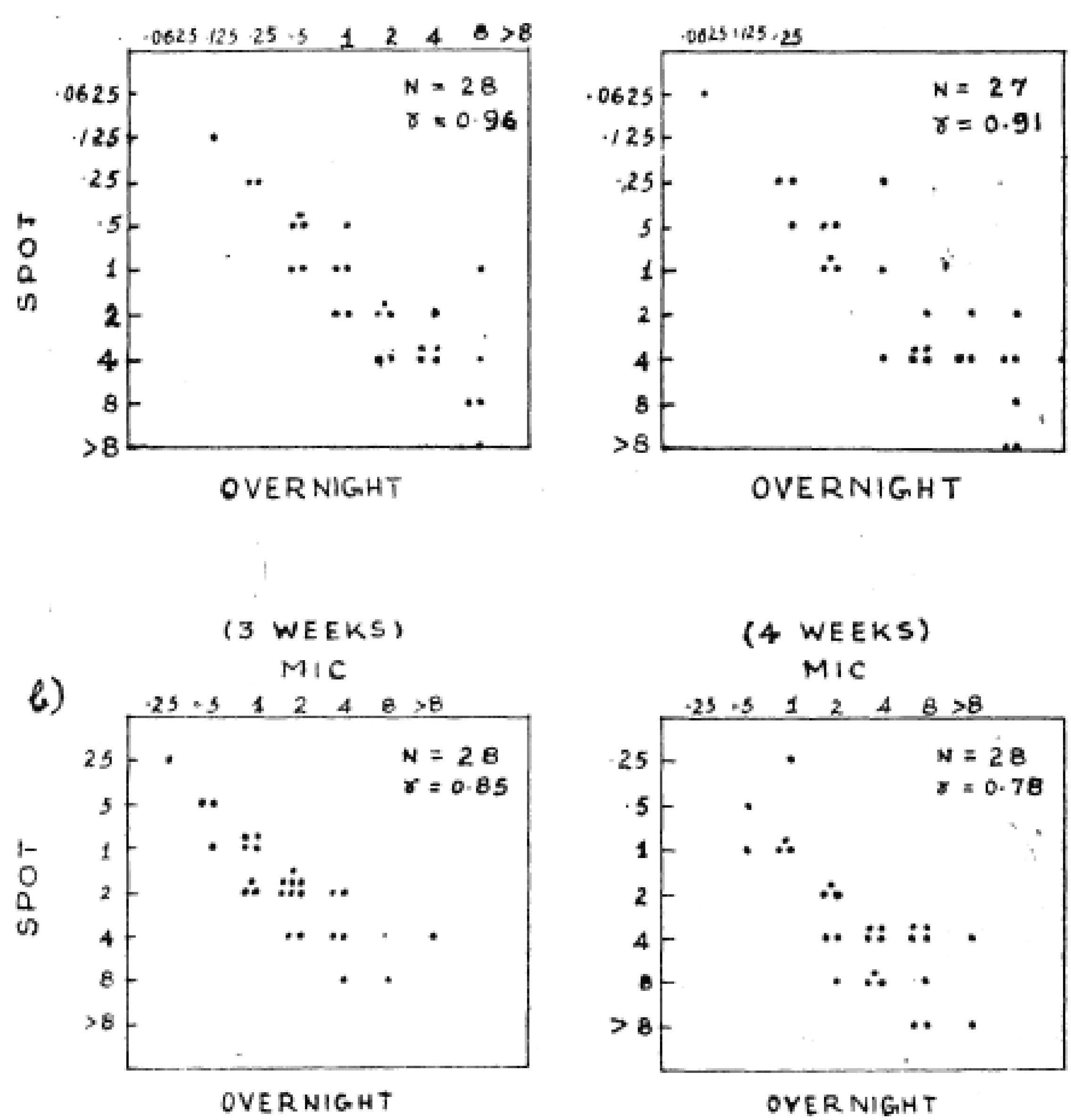


TABLE 7

Number of villages excluded and the bacillary and X-ray cases missed by their different criteria based on infection rates

	Criteria for exclusion of villages		
	None infected io age-group 0—4 years	∠5% infected in age-group 0—9 years	∠ 10% infected in age-group 0-14 years
Villages excluded:			
a. Number	30	25	30
b. Percentage	48	40	48
Percentage of population excluded	31	34	35
Bacillary cases missed:			
a. Number	16	14	14
b. Percentage	21	18	18
X-ray cases missed:			
a. Number	86	76	79
b. Percentage	24	21	22

A possible exaplanation of so little household infection from an infectious case could be that there is resistance to infection. The argument of better hygienic conditions used by Hertzberg, even if true in Norway, does not hold good in the homes in rural India. It is well known that some children even after repeated BCG Vaccination do not become tuberculin positive, although in them, the fact of "infection" is undoubted. 14% of sputum positive cases in this study were tuberculin negative (Raj Narain et al, 1963). It is felt that a large number of children under such adverse conditions, as described, do inhale tubercle bacilli, but a Primary Complex does not develop, or even if it develops, the children remain tuberculin negative. Heaf (1957) stated that some of the children do get infected but do not develop evidence of infection.

Resistance to disease governed by factors such as age, sex, race, heredity, socio-economic conditions etc. is well known. Different degrees of resistance and susceptibility to infection may explain as to why under conditions of heavy exposure, only some develop evidence of infection. More children in bacillary case homes especially in countries like India, where infection has been unhindered for centuries, may have such resistance to infection. It may be possible to test this hypothesis If such a hypothesis is true, in the Longitudinal Survey, incidence of new infection in case households need not be higher than in non-case households in spite of the higher risk involved in the former.

Summary

Data from a Tuberculosis Prevalence Survey in *62* villages of Tumkur District, South India, have been analysed to study infection and disease in households divided into 3 types viz.,

(i) Bacillary case households i.e., those with one or more bacillary cases.

(ii) X-ray case households, i.e., households with at least one radiologically active case, but no bacillary case.

(iii) Non-case households, i.e., households without either a bacillary or an X-ray case.

The main findings are:

1. Among the three categories of house holds the highest concentration of infection and disease was in households with bacillary cases, and the lowest in households without a case.

2. However over 80% of infected children of (0—4) years and nearly 90% of infected chil-

dren of (0—14) years were found scattered in non-case households which constituted about 93% of all households

3. In Bacillary Case Households:

(a) 2 out of 325 contacts of the "index" cases showed bacteriologically confirm ed and 4% radiologically active disease.

(b) Only 12 per cent and 41 per cent of children in age groups (0 — 4) years and (0—14) years respectively were found to be infected.

(c) X-ray status of the bacillary case, presence of cough, age and sex were found to be associated with higher infection in some households of this category.

(d) Direct smear positive cases, found by examination of a single sample of sputum in such a survey, were not more infectious than those positive on culture only, as judged by the number of infected home contacts of each.

4. In households with an X-ray case not confirmed bacteriologically:

(a) About 1% of the contacts had radiologically active disease.

(b) 4% and 19% of children in age groups (0 —4) years and (0 —14) years respectively were found infected; these percentages are higher than those observed in non-case households.

(c) Radiologically more advanced disease, tuberculin sensitivity, sex and age may be factors which contribute towards higher infection in some households of this category.

(d) Presence of cough did not make the X-ray cases more infectious.

5. Percentage infected in non-case households was only 2 for (0—4) age group and 12 for (0 — 14) age group.

6. A study of the average size of reactions among the infected contacts in bacillary and X-ray case households and members of non-case households showed that the reactions among those of age 25 years or more were significantly larger in bacillary case households as compared to non-case households. This is taken to indicate that repeat or super infectious cause larger reactions among those with wanted allergy.

7. Similarly the percentage of large reactions of 15 mm. and more and 20 mm. and more among the infected was higher in bacillary case homes and in age group (0—14) in all categories of households. This suggests that new or recent infection results in large reactions there by indicating that wanting of tuberculin allergy takes place in older age groups.

8. Comparison of some criteria for preliminary screening of persons for X-ray examination, using tuberculin test, showed that the omission of entire villages with less infection among young children could be an economical method for case-finding programmes in developing countries.

9. A hypothesis of resistance to infection — apparent or real—has been put forward to explain the unexpectedly low prevalence of infection in very young children, living with untreated cases excreting tubercle bacilli in poor and congested houses with no preventive measures.

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REFERENCES

1. Anders n, S. and Geser, A. (1960) *Bull. Wld Hlth. Org.,* 22, 39-60.

2. Banerji, D. and Andersen S. (1963) *Bull. Wld Org., 29,* 665-683.

3. Boyd, J. F. (1964) *Brit. J. Dis. Chest.,* 58, 17-30.

4. British Medical Research Council, Tuberculosis Clinical Trials Committee (1963) *Bril. Med. J.,* 1,973-78.

5. Gupta, B. N. and Hiren, K. Dutt (1927) *Indian Med. Gazette.,* 62, 202-204.

6. Heaf, F.R.G. (1957) *Symposium on Tuberculosis,* London Cassel and Company Ltd., p. 12.

7. Hertzberg, G. (1957) *Acta. tuberc. scandinav. duppl.,* 38.

8. Hyge, T. V. (1957) *Acta. tuberc. scandinav. Suppl.* 38.

9. Loudon, R G., Williamson, J., and Johnson, J. M. (1958) *Am. Rev. Tuberc.,* 77, 623.

10. Raj Narain, and Subramanian, M. (1962) Tuberculosis Association of India, *Proceedings of the Eighteenth Tuberculosis and Chest Diseases Workers' Conference held in Bangalore,* New Delhi, pp. 64-85.

11. Raj Narain, Geser, A., Jambunathan, M. V. and Subramanian, M. (1963) (a) *Ind. J. Tuberc.,*10, 85-116, (b) *Bull. Wld Hlth Org., 29,* 641-664.

12. Raj Narain, Nair, S. S., Chandrasekhar, P., and Ramanatha Rao, G. (1965) (a) *Ind. J. Tuberc.,* (b) *Bull. Wld Hlth Org.,*

13. Roelsgaard, E., Iversen, E., and Blocher, C. (1964) *Bull. Wld Hlth Org.,* 30, 459-518.

14. Sen, P. K. (1959) *Indian J. Tuberc.,* 6, 111-115.

15. Sikand, B. K. and Raj Narain (1957) *Indian J. Tuberc.,* 5, 1-10.

16. Sikand, B. K. and Raj Narain (1958) Tuber culosis Association of India, *Proceedings of the Fourteenth Tuberculosis Workers' Conference, held in Madras,* New Delhi, pp. 75-84.

17. Sikand, B. K., Pamra, S.P., and Malhur, G.P. (1962) Tuberculosis Association of India, *Proceedings of the Eighteenth Tuberculosis Workers' Conference held in Bangalore,* New Delhi, pp. 89-106.

AN INVITRO STUDY ON SENSITIVITY OF TUBERCLE BACILLI TO THIACETAZONE

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Introduction

1.0 Thiacetazone has been found to be clinically effective as a companion drug with isoniazid in the treatment of pulmonary tuberculosis. In all comparative clinical trials of drug regimen with thiacetazone, in vitro drug sensitivity tests for thiacetazone have been conducted for evaluation of treatment. In many respects these tests are unsatisfactory and less informative, as often times, it is difficult to interpret these and correlate with the results obtained in vivo. The results of pretreatment sensitivity tests for thiacetazone have been shown to vary from patient to patient, laboratory to laboratory and between specimens from the same patient collected at short intervals (East Africa/BMRC, 1960). Even the standard strain $H_{37}RV$, when tested in different regional laboratories in East Africa, showed considerable differences between laboratories in the minimum inhibitory concentration of thiacetazone. The reason for such variations and differences is still not known and consequently the bacteriological criteria of resistance to thiacetazone has yet not been well defined. Many factors are likely to affect anti-tuberculosis activity in vitro and among these factors, size of inoculum, stability of the drug and length of incubation may influence significantly the results of sensitivity test in general. The same factors have been studied in respect of drug sensitivity test for thiacetazone and are discussed in the present paper. Since the bacteriological criteria of resistance to isoniazid has been well defined and generally accepted, the influence of the same factors on isoniazid drug sensitivity test has been studied in parallel to compare the results of thiacetazone sensitivity test.

In addition it was also studied whether there is any difference in the growth rate between cultures sensitive and resistant to the three major antituberculosis drugs viz. Streptomycin, Isoniazid and P-amino salicylic acid, on primary isolation and in subcultures in order to find out:

(a) existence of any association between growth rate and amount of growth in each case,

(b) optimum period of incubation necessary for reading of the results of sensitivity tests.

2.0 Materials and methods

Cultures of tubercle bacilli isolated and identified as human type from single spot specimens collected from new patients attending State TB Demonstration and Training Centre, Bangalore were tested for drug sensitivity. The material also includes the cultures isolated from specimens collected in a mass casefinding in Tumkur town and nearby villages. Two specimens, a spot and an overnight, were collected from each individual for evidence of pulmonary tuberculosis before initiation of treatment with isoniazid 300 mgm. and thiacetazone 150 mgm.

The total number of positive cultures examined were 735. Of these 707 were obtained from spot specimens collected at State TB Demonstration and Training Centre, Bangalore and 28 in Tumkur casefinding programme. Prior to treatment with TB1, culture positives isolated from overnight specimens and examined were 25. All specimens were cultured by swab method (Nassau, 1954) and the primary diagnostic cultures were read every week for recording the first appearance of growth and their degree. Cultures showing growth earlier than 4 weeks were taken out of the incubator for sensitivity tests only at 4 weeks with other cultures showing growth at the same time. Cultures growing later than 4 weeks were taken out after 8 weeks incubation and such cultures were 35 out of 735 isolates. Sensitivity tests were invariably done within a week from the date of removal of cultures from the incubator.

2.1 Procedures for sensitivity tests

The sensitivity tests were carried out in 1 oz. screwcapped universal containers having slopes of Lowenstein Jensen medium without potato starch (Jensen 1955). The following serial concentrations of each drug were incorporated into the medium before inspissation.

Isoniazid (INH)	Test strain	0.2, 1, 5 and 50	
	$H_{37}RV$	0.025, 0.05, 0.1, 0.2 and 1	µgm/ml.
Thiacetazone* (TB1)	Test strain	0.25, 0.5, 1, 2,4 and 8	
	$H_{37}RV$	0.25, 0.5, 1, 2, 4 and 8	
Para-amino salicylic acid (PAS)	Test strain	4 and 8	
	$H_{37}RV$	0.0625, 0.125, 0 25, 0.5 and 1	µgm/ml.
Streptomycin (SM)	Test strain	16 and 32	
	$H_{37}RV$	1,2,4 and 8	µgm/ml.

* Thiacetazone was dissolved in triethylene glycol before incorporation into the medium as it is insoluble in water.

A standard bacterial suspension was prepared by addition of a loopful of bacilli, taken as a representative sample from all parts of the culture growth with a 1 mm. loop (SWG 22), to a 1/4 oz. bijou bottle containing 0.5 ml of sterile distilled water and 3 glass beads and shaking in a Griffin's electrical shaker for two or three minutes. The standard suspension was also diluted 1/10 (2 drops to 18 drops sterile distilled water) and 1/20 (1 drop to 19 drops sterile distilled water) using a 50-dropper Pasteur pipette. The drug slopes were inoculated with standard suspension, using a 3 mm. loop (SWG 22). The diluted suspensions were inoculated on additional sets of drug slopes comprising the same range of concentrations of INH and TB1 as used for the standard suspensions. SM and PAS were not used in these sets inoculated with diluted suspensions. Standard suspension of sensitive strain $H_{37}RV$ was inoculated on drug slopes of INH, SM, PAS and TB1 on each day of test and 1 in 10 and 1 in 20 dilutions thereof on drug slopes of INH and TBl only. The sensitivity tests were read at 3, 4 and 5 weeks from the date of setting up of cultures and minimal drug inhibitory concentration (MIC) was taken as the lowest concentration in which less than 20 colonies grew. The drugfree control slopes of the test strain and the standard strain $H_{37}RV$ were read daily for a week to observe any growth of contaminants and weekly thereafter to record first appearance of visible growth of tubercle bacilli and their degree.

2.2 Grading of cultures

Growth on primary diagnostic cultures and subcultures of sensitivity tests were recorded indicating the number, if colonies were less than 20; + if colonies grown were between 20 and 100; ++ if innumerable discrete colonies were grown and + + + when growth was confluent.

2.3 Definition of sensitive and resistant cultures

INH : No growth or less than 20 colonies on 0.2 µgm of INH was considered sensitive, growth of 20 colonies or more on 0.2 µgm, but not on 1 µgm as doubtful resistant and growth of colonies or more on 1 µgm or higher concentrations as resistant.

SM : A resistant ratio i.e., $\frac{\text{MIC of test strain}}{\text{MIC of } H_{37}RV}$ of 2 or less as sensitive, 4 as doubtful resistant and 8 or more as definite resistant.

PAS : As for streptomycin

Based on the sensitivity results at 4 weeks of 735 positive cultures of spot specimens, those sensitive to INH, SM and PAS has been referred to as 'sensitive cultures' and resistant to one or more of these as 'resistant cultures'. Wherever findings show no difference between the groups they have been combined. Of the 735 positive cultures examined 511 were sensitive to all the three drugs and 224 (30.5 ./.) resistant to one or more of these drugs. Among the resistant cultures 124 (55.4 ./.) were resistant to INH only, 3 (1.3 ./.) to SM only, 4 (1.9./.) to PAS only, 67 (30./.) to INH and SM, 12 (5.3 ./.) to INH and PAS, 1 (O.4./.) to SM and PAS, and 13 (5.8 ./.) to all the three drugs. 216 were resistant to INH (96.5 ./.).

Tests became void due to (a) contamination of entire set of inoculated media slopes or (b) contamination of the drug-free control slope or (c) contamination of a drug slope at the end point in which case the MIC could not be determined. These numbers so excluded sometimes varied between different weeks and different suspensions, that the figures in different tables do not tally always.

3.0 Results

3.1 First appearance of growth in primary and subcultures

The distribution of the sensitive and resistant cultures* according to interval between setting up and first appearance of growth on primary isolation and subcultures is shown in table 1. The average number of days for growth to appear in primary diagnostic cultures were 21.3 and 20.0 for sensitive and resistant cultures respectively. Nearly 85 ./. of the sensitive cultures and 87./. of the resislant cultures had shown growth by three weeks. Over 90 ./. of subcultures on drug-free control slopes inoculated with a standard suspension had shown growth by 2 weeks (92 and 94 ./. respectively for sensitive and resistant cultures). The average number of days for the growth to appear were 14.4 and 14.3 respectively. No difference was observed between sensitive and resistant cultures in their first appearance of growth on primary diagnostic cultures or drug-free subculture slopes inoculated with standard suspension. But growth was slower in primary cultures than in subcultures made out of them.

When bacillary population was reduced by dilution of the standard suspension to 1 in 10 and 1 in 20, there was gradual increase in the average number of days for growth to appear on subcultures of both sensitive and resistant

* Resistant cultures considered in the study are likely to consist of mixed bacillary population and as such the conclusions may not be applicable to pure resistant strains.

cultures. The percentage of cultures showing growth after 14 days gradually increased for both sensitive and resistant cultures. These results show that there is no significant difference between sensitive and resitant cultures in the rate of growth when subcultured with a standard bacillary suspension or its dilutions, but larger the bacillary population inoculated on subcultures quicker is the appearance of growth.

3.2 **Growth rate of standard strain $H_{37}RV$**

Standard sensitive strain $H_{37}RV$ shows nearly the same results as subcultures of "wild" strains (see tables 1 and 2). Nearly 96 ./. of subcultures showed growth not later than 14 days and the average number of days for subcultures inoculated with standard suspension was 14.1.

Decreasing the bacillary population of $H_{37}RV$ showed similar delayed growth as for "wild" strains, but the increase in the average number of days for growth to appear was not so marked.

3.3 **Incubation period and degree of growth**

In table 3, the first appearance of growth of sensitive and resistant cultures on primary isolation has been correlated with their degree

TABLE 1

First appearance of growth of sensitive and resistant cultures of Myco. tuberculosis on primary isolation and subcultures

	Sensitivity result	Total cultures	Percentage culture according to growth first appeared (days) 7	14	21	28	35	56	Average No. of days
Primary Cultures	Sen	511	0 0	32.1	53.2	9.4	—	5.3	21.3
	Res	224		41.1	46.0	9.4	—	3.6	20.0
Subcultures (a) Standard suspension	Sen	511	1.8	90.6	7.6	0 0.4	0	0 0	14.4
	Res	222	1.4	92.8	5.4		0		14.3
(b) 1 in 10 suspension	Sen	507	0	57.8	39.1	3.0	0.2	0 0	17.2
	Res	221	0	63.3	35.7	0.9	0		16.6
(c) 1 in 20 suspension	Sen	504	0 0	46.4	46.4	6.5	0.6	0 0	18.3
	Res	220		46.4	49.5	3.6	0		18.0

X^2 test calculated between sensitive and Resistant cultures shows no significant difference.

TABLE 2

First appearance of growth of standard sensitive strain $H_{37}RV$ on subculture

	No. of sub cultures	Percentage cultures according the growth first appeared (days) 7	14	21	28	35	56	Average No. of days
$H_{37}RV$								
(a) Standard suspension	111	1.8	94.6	3.6	0	0	0	14.1
(b) 1 in 10 suspension	111	0	82.2	18.0	0	0	0	15.3
(c) 1 in 20 suspension	111	0	73.0	25.2	0.9	0	0	15.9

of growth at 4 weeks. Higher the degree of growth, more rapid is the appearance of growth in both sensitive and resistant cultures. Among those cultures showing first appearance in 2 or 3 weeks (numbers could be calculated from the table), the distribution according to degree of growth was similar for both sensitive and resistant cultures. Further for any degree of growth the average interval between setting up of culture and first appearance of growth was the same for sensitive and resistant cultures.

Bacillary population estimated on the strength of suspension in subculturing (table 1) or degree of growth observed in primary culture (table 3) show similar findings that larger bacillary population appear more rapidly whether they are sensitive or resistant cultures.

3.4 TBI Sensitivity test

Positive cultures examined for TBI sensitivity tests were isolated from patients who were presumably not treated with TBI previously. Sensitivity test results on cultures sensitive and resistant to other drugs were separately analysed with a view to exclude the possibility of cross-resistance and since the findings were similar they have been combined.

Figure 1 (a) shows the percentage of cultures of wild strains inhibited at different concentrations of TBI in 3, 4 and 5 weeks incubation. Figure 1 (b) and 1 (c) show respectively the percentages of subcultures of $H_{37}RV$ inhibited at different concentrations of TBI and INH in 3, 4 and 5 weeks incubation. The cultures inhibited at lower concentrations can be assumed to be inhibited at higher concentrations also. Therefore, the cumulative figures have been taken to work out the above percentages.

Fig. 1 (a) and (b) show that the proportion of wild strain and $H_{37}RV$ inhibited at each concentration of TBI decreases at 4 and 5 weeks incubation. A similar trend is also seen in figure 1 (c) at 0.05 µgm concentration of INH, although it is not appreciable at the higher concentration of 0.1 µgm which appears to be a threshold concentration to inhibit nearly 100 ./. of the subcultures of standard strain. The lower concentration of 0.025 µgm appears to be well below a concentration to inhibit at all, as only 0.9 ./. of subcultures are inhibited at 3 weeks and none at 4 and 5 weeks incubation. Such a trend uniformally observed in figure 1 (a) and (b) at all levels and in Figure 1 (c) at a concentration of 0.05 µgm may be due to deterioration of the drug during incubation and if this is true then TBI deteriorates much more rapidly than INH in the concentration range used in the study.

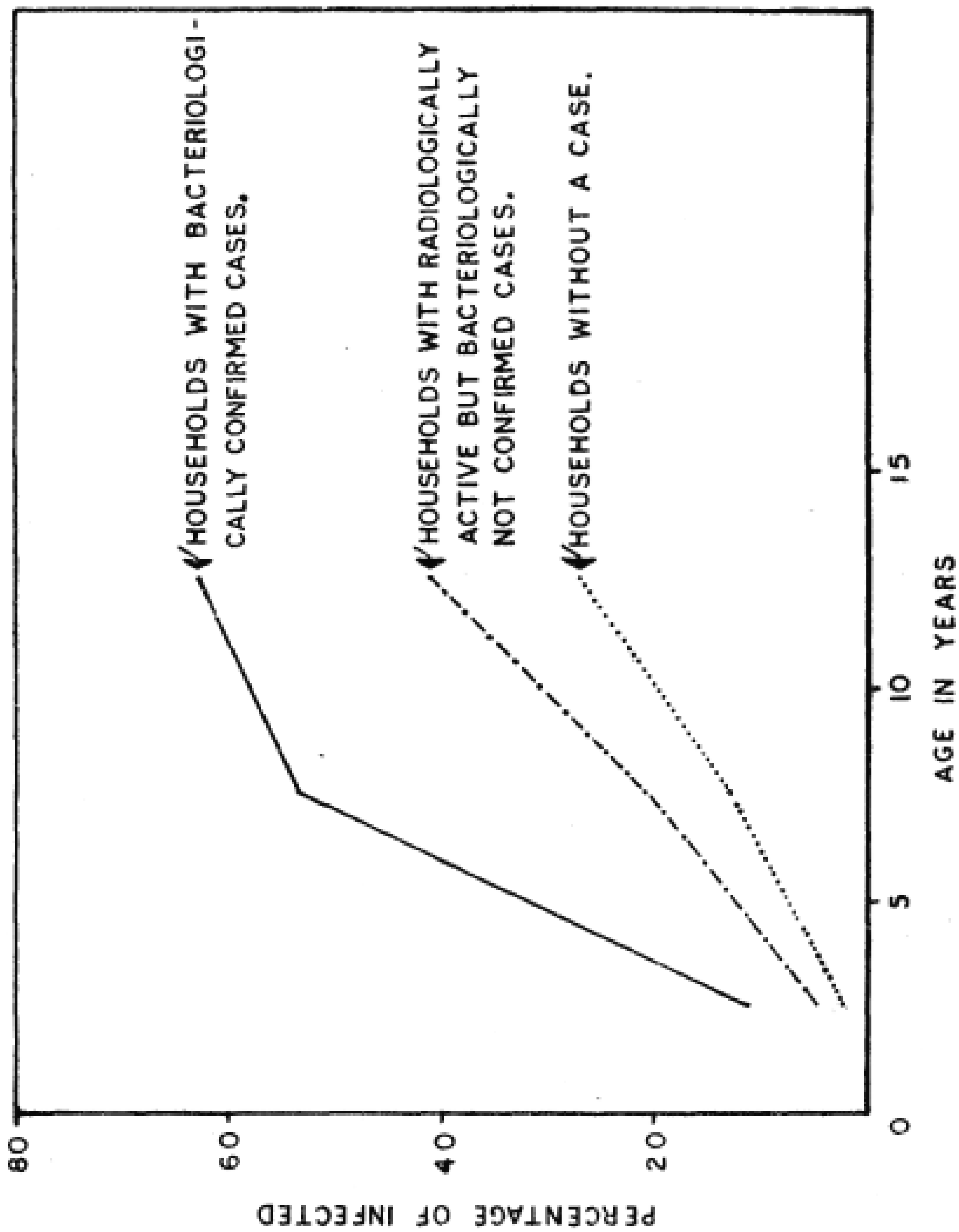
TABLE 3

First appearance of growth of sensitive and resistant culture of Myco. tuberculosis on primary isolation by degree of growth at 4 weeks

	Degree Of growth	No. of cultures	Percentage cultures according to growth first appeared (days)						Average No. of
			7	14	21	28	35	56	days
Primary cultures									
Sensitive	<20 colonies	70	0	4.3	51.4	31.4	—	12.9	27.4
	+	296	0	27.7	57.8	8.8	—	5.7	21.7
	+ +	140	0	53.6	45.7	0	—	0.7	17.5
	+ + +	5	0	80.0	20.0	0	—	0	15.4
Resistant	< 20 colonies	20	0	15.0	40.0	30.0	—	15.0	27.3
	+	142	0	33.8	52.8	10.6	—	2.8	20.4
	+ +	62	0	66.1	32.3	0	—	1.6	16.9
	+ + +	0	0	0	0	0		0	

X^2 test calculated between sensitive and resistant cultures according to degree of growth at 2 and 3 weeks shows no difference.

FIG. I. PERCENTAGE OF INFECTED CHILDREN IN THREE AGE GROUPS FOR DIFFERENT CATEGORIES OF HOUSEHOLDS



The above figures also illustrate the behaviour of wild strains and $H_{37}RV$ to TB1 and INH. Starting with an initial concentration of TB1 at which none of the wild cultures of $H_{37}RV$ is inhibited, several two fold serial concentrations of the drug are required to attain nearly 100 ./. inhibition at 3 weeks. Further, even the highest concentration of 8 µgm will only inhibit 90 ./. of wild strains and 86 ./. and 74 *J.* of subcultures of $H_{73}RV$ in 4 and 5 weeks incubation respectively. In contrast, such a multiple stepwise increase in drug concentration to attain 100 ./. inhibition is not evident for INH in any period of incubation [see Fig. l(c)]. The response of wild strains and $H_{37}RV$ to TB1 is very much more graded. Such a graded response of the wild strains to TB1 distributed over a wide range of concentrations is likely to cause difficulty in classifying sensitive and resistant strains.

Whereas none of the subcultures of $H_{37}RV$ were inhibited at 0.25 µ*gm* of TB1 after 3 weeks incubation, nearly 10 ./. of the wild strains were inhibited at this level. This shows that some of the wild strains are comparatively more susceptible to TB1 than the standard strain.

Fig. 2 shows frequency curve of minimum inhibitory concentration of TB1 for wild strains for different periods of incubation and strengths of bacillary suspension. There is a constant shift in the distribution with passage of time and also with change in the bacillary population. The influence of the former seems to be more predominent than the latter. If this is true among pretrealment strains, the differentiation of sensitive and resistant strains by expression of MIC is not likely to be dependable.

There was a very high degree of correlation between sensitivity test results in duplicate specimens collected from patients at short intervals. This high degree of correlation between duplicate tests rules out to a large extent the possibility of experimental errors being responsible for the variations observed.

In order to overcome the effect of these variations, the ratio of MIC of test strain to MIC of $H_{37}RV$, for the readings of 3, 4 and 5 weeks incubation of standard and diluted bacillary suspensions, were calculated. The frequency distribution of these values are shown in Figure 3. The curves are symmetrical in different weeks and for different suspensions and resemble closely the normal curve ($\beta_1 0.002.$ $\beta_2=3.5$). Further the shift from week to week and fluctuations observed in the distribution of MIC are no longer in Figure 3.

As shown in the lower portions of the Figures 2 and 3 the mean plus twice standard deviation of the MIC distribution is 8.3 and of the ratio distribution 11.3. Taking the nearest drug concentration of 8 MIC and nearest ratio of 8, the percentage of sensitive cultures which would be wrongly classified as resistant on the basis of more than 8 µgm and a ratio of more than 8, are given in Table 4 (Cols 8 and 11).

TABLE 4

Comparison of MIC of INH with MIC or ratio of TB1 for different strengths of inoculum and periods of incubation

Weeks	Suspensions	INH (MIC) Total No.	≤ .2 %	>.2 %	TBl (Ratio) Total No.	≤8 %	>8 %	TBl (MIC) Total No.	≤8 %	>8 %
	Standard	733	71.5	28 5	711	97.2	2.8	725	97.0	3.0
3rd	1 in 10	678	73.3	26 7	632	100.0	—	645	100.0	—
	1 in 20	624	74.7	25 .3	563	99.6	0.4	589	100.0	—
	Standard	734	70.7	29 3	686	96.7	3.3	*115*	90.6	9.4
4th	1 in 10	711	71.7	28 3	656	98.9	1.1	670	99.1	0.9
	1 in 20	674	72.3	27 7	602	98.7	1.3	629	99.5	0.5
	Standard	735	70.3	29 7	687	98.1	1.9	726	79.5	20.5
5th	1 in 10	720	71.5	28 5	660	98.3	1.7	674	96.3	3.7
	1 in 20	682	72.3	27 7	609	97.9	21	632	97.6	2.4

FIG 2 DISTRIBUTION OF POSITIVE REACTIONS (≥ 10 mm) AMONG CONTACTS / MEMBERS IN THE THREE CATEGORIES OF HOUSEHOLDS BY AGE

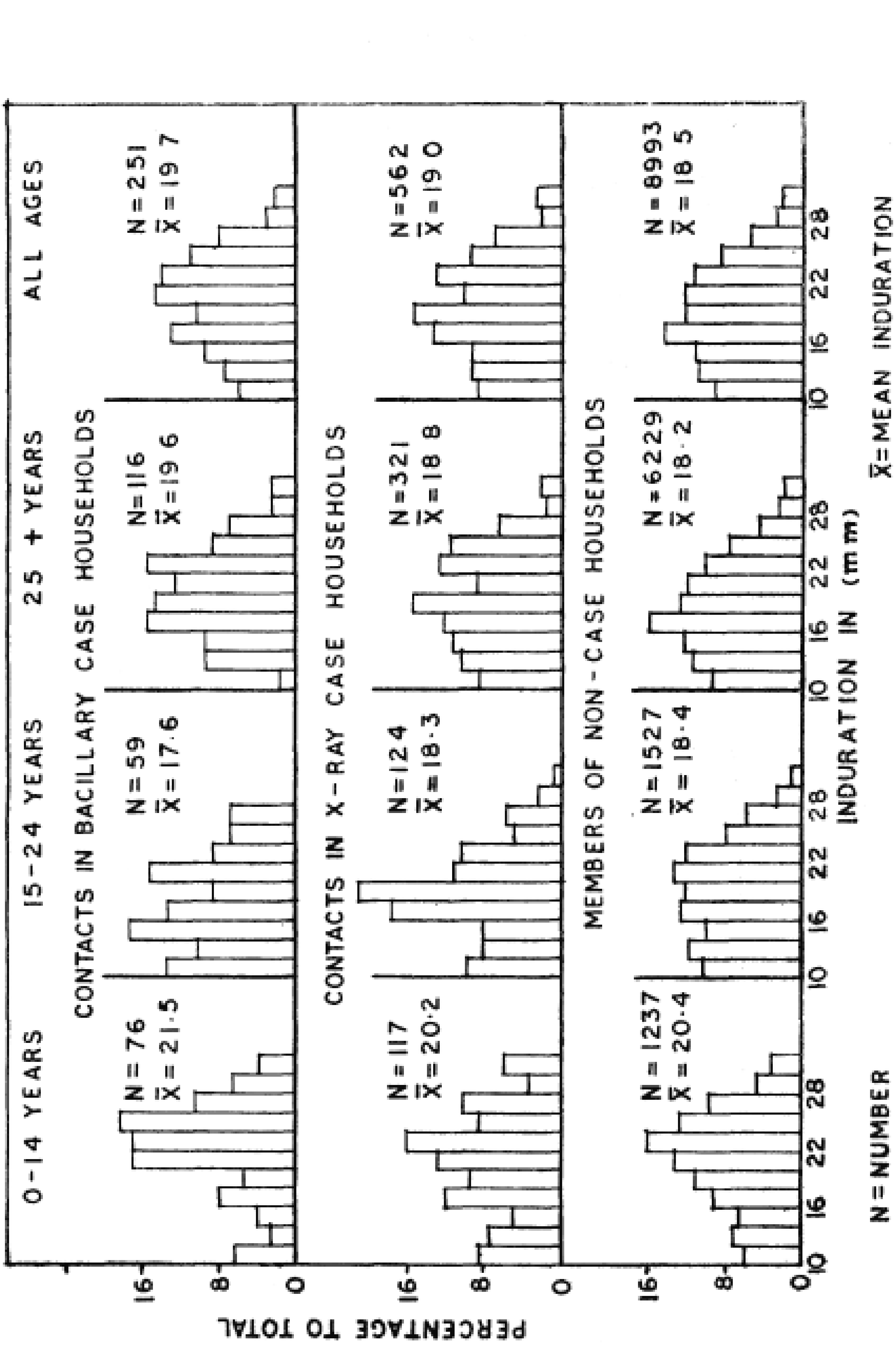
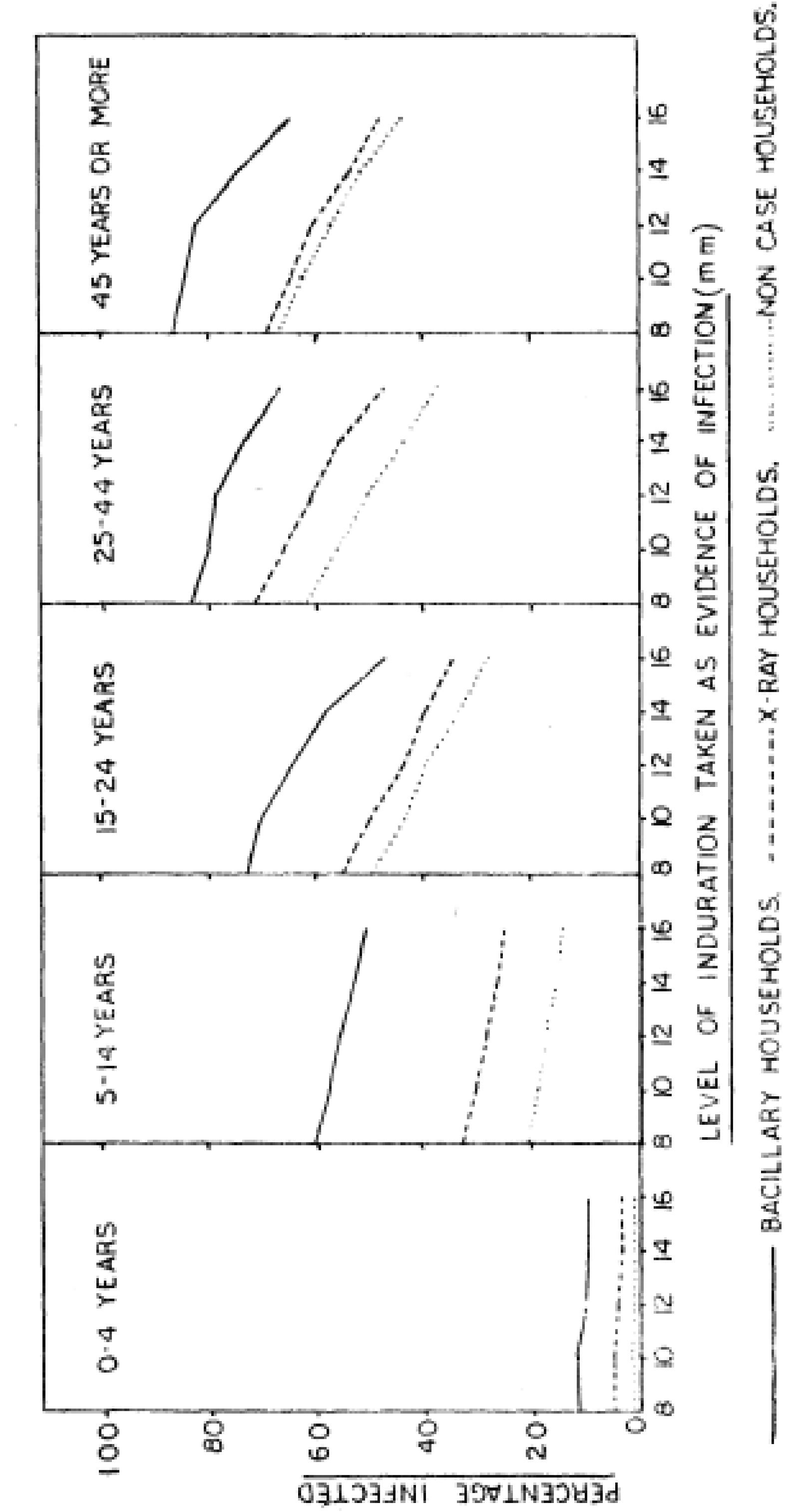


FIG. 3. PREVALENCE OF INFECTION IN THE BACILLARY, X-RAY AND NON CASE HOUSEHOLDS.



It can be seen that percentage of sensitive cultures of TBl is more uniform between weeks and between suspensions when defined by ratio than by MIC and also that the degree of error is more in the latter than in the former method of classification. The variations between weeks or between suspensions in the same week of the proportion of sensitive cultures to TBl, defined by the criterion of ratio are very similar to those of INH. However, the study did not include specimens excreted by patients not responding to treatment with TBl; therefore the extent of error of classifying resistant cultures as sensitive on the basis of this criterion cannot be assessed.

The standard deviations of the distribution of MIC or ratio at 3, 4 and 5 weeks show a steady increase for both standard suspension and its dilutions. These differences being statistically significant, it seems preferable to read sensitivity tests at 3 weeks when the distribution for the sensitive cultures is least spread out and the chances of overlapping by distribution for resistant cultures are minimum.

3.5 **Variation between specimens**

There were 28 duplicate culture positives from spot and overnight specimens, tested for sensitivity to TBl, 25 from pretreatment and 3 from post-treatment specimens. All duplicate tests were available for readings in 3 weeks and only 27 for readings in 4 weeks. The reproducibility of the results of sensitivity tests between two cultures are shown in Figures 4 (a) and (b). The correlation is shown for both ratios calculated and MIC for readings taken in the 3rd and 4ih week.

These results show a high degree of association between MIC values or ratios obtained from spot and overnight cultures in both 3 and 4 weeks incubation. Nearly 60 percent of the results in 3 weeks incubation either for ratios or MIC values were identical, 36 percent had shown higher or lower MIC value or correlated ratios and only 4 percent showed differences beyond these adjacent values.

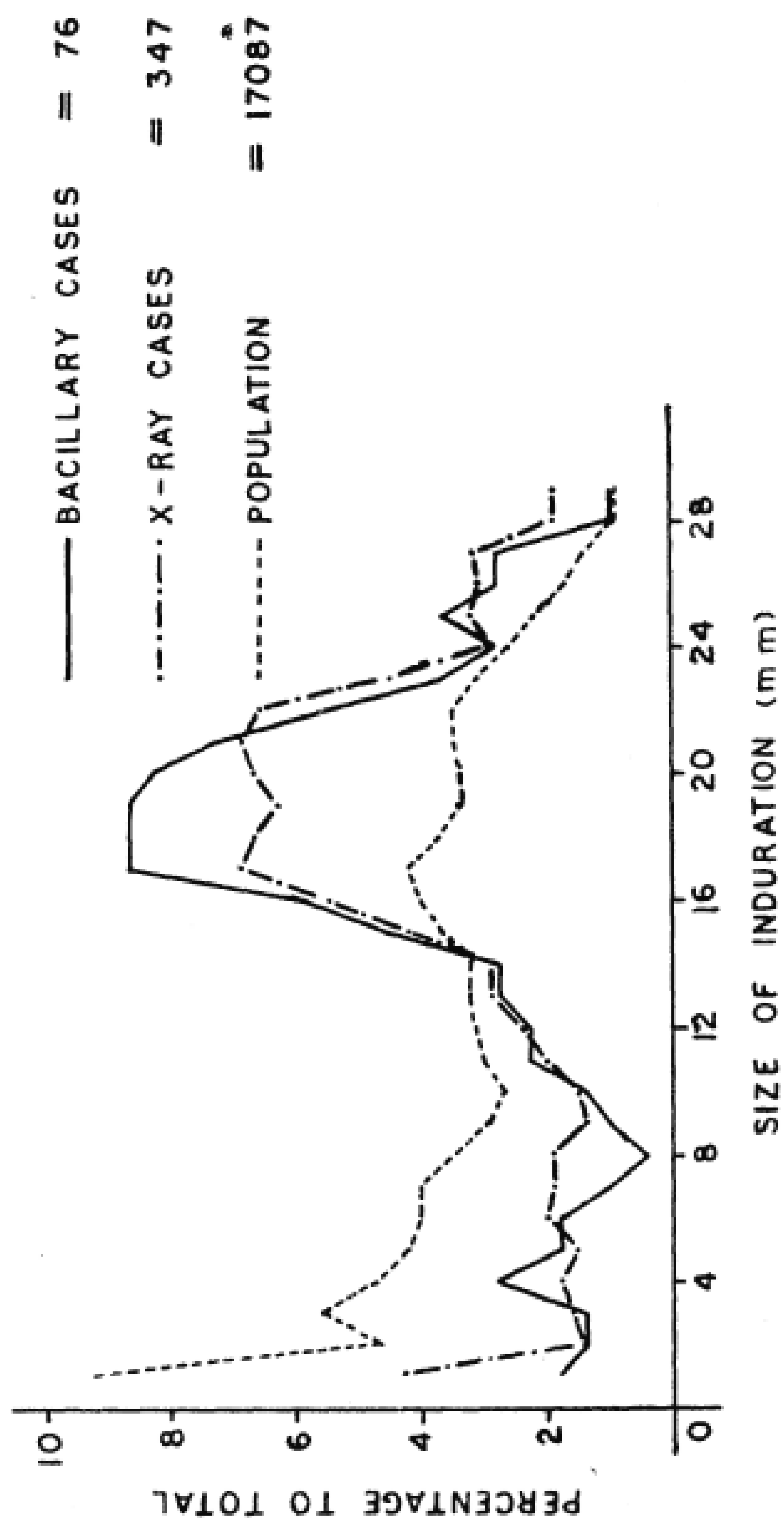
4.0 **Discussion**

In order to determine the criteria of resistance to TBl, strains isolated from patients before treatment and those who are excreting tubercle bacilli not responding to the drug should be studied. But this report is solely based on the drug susceptibility tests carried out in the laboratory on strains isolated from patients prior to administration of treatment with TBl.

The main consideration in the present analysis was to investigate the influence of bacillary concentration in inoculum and the length of incubation on the results of TBl drug sensitivity tests and reproducibility in tests carried out on two specimens collected from a patient at shorter intervals. It is shown that bacillary population, estimated on the basis of strength of suspension or amount of growth seen on drug free control slopes, influenced the drug inhibitory concentration level of TBl even for "sensitive" cultures. Larger sensitive bacillary populations required higher concentration of TBl to inhibit the growth. It was also observed that when the bacillary population was reduced there was a gradual increase in the average number of days for growth to appear on culture slopes. These findings confirm the importance of standardising the inoculum size for sensitivity tests.

Prolonged incubation of drug slopes similarly showed a profound influence on the level of drug inhibitory concentration of TBl. There was an appreciable fall in the percentage of sensitive cultures inhibited at any concentration of the drug used in the test with increase in period of incubation. This fall was noticed in both wild strains and control strain $H_{37}RV$. In seeking an explanation for this fall in the percentage of cultures inhibited, it is rather tempting to accept that tuberculostatic drug TBl undergoes destruction gradually and when it reaches below the bacteriostatic concentration, the bacilli start multiplying and manifest visible growth. It could also be ascribed partly adaptation of bacilli to drugs temporarily while in contact (Dean and Hinshelwood 1953). Whichever is true, it manifests much more clearly in TBl as compared to INH. Which of these two factors operate and to what extent during prolonged incubation of drug slopes of TBl, is difficult to assess. Nevertheless, the implications are discernible that sensitive cultures may be classified resistant depending on the amount of destruction of the drug of rapidity with which the bacilli adapt themselves when exposed to the drug or both. To obviate the adverse effects of prolonged incubation, it is appropriate to consider reading of the sensitivity tests at the earliest suitable period when sufficient growth has appeared in the drug-free control slope. The fact that over 90 percent of the standard subcultures of both sensitive and resistant cultures showed growth by 14 days and nearly 100 percent by 21 days questions the current practice of reading the sensitivity tests at 4 weeks. Considering the advantages of earlier availability of results, less chances of drug deterioration and/or adaptation of bacilli and minimum spread for distribution of MIC or ratios, reading of sensitivity tests at 3 weeks is likely to be a

FIG. 4. DISTRIBUTION OF BACILLARY AND X-RAY CASES, AND OF POPULATION 10 YEARS OR MORE BY SIZE OF TUBERCULIN REACTION.
(3 mm MOVING AVERAGES)



better method. This leads to an assumption that in cultures having mixed population of sensitive and resistant bacilli, the latter do not have a slower growth rate than the former. This assumption has not been proved in the present study by investigating the growth rate of homogenous sensitive and resistant strains, although no differential growth rate between sensitive and resistant cultures was observed. Whatever be the comparative rate of growth of sensitive and resistant strains in drug free medium, it is possible that the resistant bacilli could grow more freely in the presence of drug than the sensitive strain. Both these aspects merit thorough investigation.

It is customary to express the results of sensitivity tests either minimal inhibitory concentration (MIC) or ratio of MIC of test strain to MIC of standard strain $H_{37}RV$. The readings of 3, 4 and 5 weeks incubation were expressed both ways and it was found that the ratio gives more consistent results than the MIC. There was no significant difference between ratio calculated for 3rd week reading and the 4th week reading. It is therefore reasonable that indirect drug sen-itivity test for TB1 performed with a standard suspension may be read at 3 weeks incubation in order to avoid pseudoresistant strains. This statistical definition viz., to consider a ratio of more than 8, to classify strains as resistant to TB1, needs further study since it was derived from the distribution of ratios for pretreatment cultures only and did not take into account the magnitude of the error of wrongly classifying resistant strains showing a ratio of 8 or less as sensitive. This will depend on the extent of overlapping between the distribution of ratios of sensitive and resistant strains.

Summary

The effect of bacillary concentration and length of incubation on TB1 drug sensitivity test was investigated on 735 cultures of Mycobacterium tuberculosis human, isolated from patients presumably had no previous treatment with TB1. Both the factors were found to influence the minimal drug inhibitory concentration. The standard sensitive strain $H_{37}RV$ and wild strains were shown to be inhibited over a wide range of concentrations of the drug. Such a graded response of the strains is likely to offer difficulty in classifying sensitive cultures from the resistant.

Variation of minimal drug inhibitory concentration from 3 to 5 weeks incubation was overcome to some extent by calculating the ratio (ratio of MIC of wild strain to MIC of $H_{37}RV$) and therefore the latter method is to be preferred for expressing the results. Also the advantages of reading the results of sensitivity test to TB1 at the end of 3 weeks incubation has been discussed within limitations of the study.

Cultures classified sensitive to the three drugs streptomycin, isoniazid and P-aminosalicylic acid or resistant to one or more of these drugs showed no difference in the pattern of sensitivity to TB1.

There was a high degree of correlation between two pretreatment specimens in the results of sensitivity test to TBI, collected at short intervals from a patient, whether by criterion of MIC or ratio in 3 and 4 weeks incubation.

Acknowledgements

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REFERENCES

1. Dean, A.C.R., and Hinshelwood, C.N. (1953) Sym. Sec. Gen. Microbiol. 3—21.
2. Jensen K.A. (1955) Bull. TNT. UN. Tuberc. 25, 89.
3. Nassau, E, (1954) Tubercle Lend., Colonial Supplement No. 3.
4. East African/BMRC. Thiacetazone/Diphenyl Thiourea Investigation (1960) Tuberc. Lond **41,** 399.

THE OPTIMUM DOSAGE, RHYTHM AND DURATION OF ISONIAZID THERAPY IN PULMONARY TUBERCULOSIS

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Introduction :

Isoniazid is the most effective, cheapest and most widely used drug in the chemotherapy of pulmonary tuberculosis. The optimum dosage, rhythm and duration of therapy with this drug are those which are maximally effective with minimal risk of toxicity. This paper is based mainly on studies carried out at the Tuberculosis Chemotherapy Centre, Madras, India and also, to a lesser extent, on those in Great Britain and East Africa. It discusses the implication of these studies on isoniazid therapy for the developing as well as for the economically favoured countries and indicates possible lines for future investigations.

Condition of patients on Admission to Treatment in Five Madras Studies :

It is necessary to consider the extent of the disease in patients before dealing with the therapeutic efficacy of the various regimens. Table 1 shows the results of pretreatment radiographic and bacteriological assessments undertaken on 775 patients in the main analyses of the 5 studies carried out at Madras, (Tuberculosis Chemotherapy Centre, Madras 1959, 1960, 1963a, 1963b, 1964). It will be seen that most of th; patients had advanced disease on admission to study. Thus, 89.8% of the patients had cavitated disease including 63.1% with moderate or extensive cavitaties. In all, 64.6% of the patients had 4 or more lung zones involved. Isoniazid-sensitive tubercle bacilli were obtained from all the patients and 87.5% had a positive smear from a single overnight collection sputum specimen.

Dosage and Rhythm of Isoniazid alone Regimens in Relation to Response to Treatment

Table 2 relates dosage and rhythm of isoniazid administration to bacteriological quiescence-[1] at the end of a year of treatment in patients admitted to 3 Madras Studies (Tuberculosis Chemotherapy Centre, 1960, 1963a, 1963b). In all 44% of patients on 2.2 mg/kg body weight twice daily, 58% on 4.4 mg/kg body weight twice daily, 73%, on 8.7 mg/kg body weight once daily and 68% on 13.9 mg/kg body weight once daily, attained bacteriologically quiescent disease.

a These include patients classified as having disease of bacteriologically "doubtful" status for reasons given by Vein et al (1960, 1961).

The patients had multiple specimens of sputum (usually 2 overnight collection and 2 'spot') examined by smear and culture before commencement of treatment. In the 3 most effective isoniazid alone regimens there were altogether 26 patients in whom the direct smear examination of the first collection specimen was negative although the culture was positive for tubercle bacilli. All these patients attained bacteriologically quiescent disease (not tabulated).

Table 3 relates the rate of inactivation and peak serum isoniazid concentrations to the proportion of patients who responded favourably. The method of determination of inactivation rates and serum levels have been described

TABLE 1

Condition of patients on admission to treatment to 5 Madras studies

Assessment on admission to treatment	All patients No.	All patients %
Extent of cavitalion		
Nil	79	*10.2*
Slight	206	*26.8*
Moderate	348	*44.8*
Extensive	142	*18.3*
Number of lung zones involved		
1, 2 or 3	274	*35.4*
4, 5 or 6	501	*64.6*
Bacterial content of sputum		
Direct smear negative	97	*12.5*
Direct smear positive		
1-plus (scanty)	139	17.9
2-plus (moderate)	310	*40.0*
3-plus (heavy)	229	*29.5*
Total patients	775	*10 00*

elsewhere (Gangadharam et al 1961a, 1961b). There is a consistent but slight (and statistically no-significant) association between the rate of inactivation and response to treatment in *each* of the 4 regimens (Table 3, second and fifth columns see also Selkon et al 1961). There was a definite association between the peak serum isoniazid concentrations, up to that attained by patients receiving isoniazid 8.7 mg/kg body weight once daily, and response to treatment (Table 3, third and fifth columns).

Incidence of Isoniazid Toxicity

Nearly all patients who developed isoniazid toxicity in these studies manifested symptoms and signs of a peripheral neuropathy but a few

TABLE 2

Dosage and rhythm of isoniazid alone regimens in relation to response to treatment fur 1 year

Regimen	No. of patients	Single dose of isoniazid (mg/kg)	No. of doses a day	Percentage of Patients with bacteriologically quiescent disease (%) at 1 year
H_{650}*x_1	143	13.9	1	*68*
H_{400}*x_1	64	8.7	1	*73*
H_{200}*x_2	66	4.4	2	*58*
H_{100}*x_a	86	2.2	2	*44*

* These figures represent the single dose of isoniazid in mg for a 45.4 kg (100 Ib) patient.

TABLE 3

Dosage rate of isoniazid inactivation and peak Serum concentration in relation to response to treatment

Regimen	Rate of isoniazid inactivation	Peak serum concentration (ug/ml)	Number of patients	Percentage with quies-cent disease at 1 year %
H_{650}	Slow	(10.9)*	81	*69*
	Rapid	(7.0)*	62	*66*
H_{400}	Slow	6.6	36	*69*
	Rapid	4.2	32	*66*
$H_{200}x_2$	Slow	2.6	39	*59*
	Rapid	1.9	27	*56*
$H_{100}x_2$	Slow	1.2	46	*48*
	Rapid	0.7	36	*44*

* The peak serum level in these patients are not available, but have been extrapolated on the basis of the values obtained in patients on the other 3 regimens. It was assumed that the peak concentration increased proportionally with the individual dose of isoniazid.

psychosis and/or convulsions (see Devadatta et al 1960, Tuberculosis Chemotherapy Centre 1963a, 1963b). Table 4 relates isoniazid dosage, rate of inactivation, and peak serum concentrations to the proportion of patients with toxicity. Development of toxicity was associated with isoniazid dosage and rate of inactivation Table 4, first and fifth columns). The proportion ranged from 0% in patients receiving 2.2 mg/kg body weight twice daily to 27% in those receiving 13.9 mg/kg body weight once daily. The proportion among the slow and rapid inactivators in the 3 regimens where toxicity occurred was 46% and 10%, 28% and 6%, 14% and 0% respectively. All these differences attain statistical significance. There is, however, a poor association between peak serum isoniazid concentrations (Table 4, column 3) and the proportion of patients who developed toxicity (column 5).

Mitchison (1962) has related an empirical function P/Kt, with the proportion of patients with isoniazid toxicity, where P was the peak serum concentration (ug/ml), K was the descending slope of the line joining the 2 hour and 6 hour serum isoniazid concentrations on a logarithmic scale (Kslow ≡ 0.100 or 0 10 and Krapid ≡ 0.198 or 0.20 to two significant figures) and t was the period in hours between the doses of isoniazid (24 for the once and 12 for the twice a day regimen). Table 5 relates the proportion of patients developing isoniazid toxicity with P/Kt. There is a good correlation (r=+0.986), and the regression equation was $N = \frac{118P}{kt} - 7.4$. Where N is the percentage of patients expected to develop toxicity and K has been multiplied by 10 for simplification and is, therefore, 1.0 for slow and 2.0 for rapid inactivators.

There was also a good correlation between the peak serum concentrations of isoniazid in the three regimens where these were directly determined and the individual dose of isoniazid (r for the slow inactivators was+0.996 and for rapid inactivators was+1.000).

The regression equations are

$$P_s = 0.84D - 0.81$$

$$P_r = 0.54D - 0.48$$

where P_s and P_r are the peak serum isoniazid concentration (ug/ml) in the slow and rapid inactivators respectively and D the individual dose of isoniazid (mg/kg body weight). From these three equations it is possible to derive, by elimination of P, ones correlating the incidence of isoniazid toxicity with the dose and rhythm of administration of isoniazid.

These are

$$N_s = \frac{99D - 96}{t} - 7.4 \text{ and } N_r = \frac{64D - 57}{2t} - 7.4$$

where N_s and N_r are the percentage of patients expected to develop toxicity among the slow and rapid inactivators respectively.

The rate of isoniazid inactivation was determined in 480 patients in 3 Madras Studies and of these 282 (58.8%) were slow and the remainder rapid inactivators (Gangadharam et al 196la, Tuberculosis Chemotherapy Centre, 1963a, 1963b). It is therefore possible to derive an equation for a South Indian population namely

$$N = \frac{143D - 136}{2t} - 7.4$$

Clinical Features of Isoniazid Toxicity

Of the 40 patients with toxicity (Table 4), encountered in three isoniazid studies all but one developed peripheral neuropathy (Devadatta et al 1 960, Tuberculosis Chemotherapy Centre, 1963a, 1963b). The remaining patient had convulsions. Of the patients with peripheral neuropathy 3 also developed convulsions, 2 psychosis and 1 convulsions and psychosis. All *5* with convulsions and 2 of the 3 with psychosis were encountered in patients receiving the high dosage of isoniazid (13.9 mg/kg body weight once daily).

The neuropathy was mainly sensory in nature. The usual course was a slow progression of the symptoms and gradual spread of the physical signs proximally. Usually, the first signs elicited were loss of vibration sense in the toes and ankles and loss of ankle jerks, followed by anaesthesia, loss of position sense in the toes and loss of knee jerks.

The Time of Onset of Isoniazid Toxicity

There was a tendency for an earlier development of toxicity with increasing individual daily dose of isoniazid. Thus of the 21 patients who developed toxicity on 13.9 mg/kg body weight once daily (Table 4), 12 first complained of toxic symptoms in the first 3 months, 9 in the next 3 months and none in the remaining part of the therapeutic year. The corresponding figures for 13 such patients receiving 8.7 mg/kg body weight once daily was 4, 5 and 4 respectively and for the 6 patients receiving 4 4 mg/kg body weight twice daily they were 2, 0, and 4 respectively.

Prevention and Treatment of Isoniazid Toxicity

Pyridoxine in a dosage of only 6 mg. once

TABLE 4

Dosage, rate of inactivation and peak serum concentration in relation to isoniazid toxicity

Regi-men	Rate of inactiva-uon	Peak serum concen-tration (ug/ml.)	Number of patients	Patients with toxicitv*		
				No.	%	
$^{H}650$	Slow	10.9	37	17	*46*	*27*
	Rapid	7.0	42	4	*10*	
$^{H}400$	Slow	6.6	39	11	*28*	*18*
	Rapid	4.2	32	2	*6*	
$^{H}200x2$	Slow	2.6	44	6	*14*	*8*
	Rapid	1.9	28	0	*0*	
$^{H}100x2$	Slow	1.2	51	0	*0*	0
	Rapid	0.7	36	0		
				40*	0	

* All but one developed peripheral neuropathy. Five of them developed convulsions also and 3 psychosis.

TABLE 5

An empirical serum concentration-time function related to isoniazid toxicity

Regimen	Rale of inactivation	Proportion of patients with toxicity (%)	$^{P}/kt$*
$^{H}650$	Slow	*46*	4.54
$^{H}400$	Slow	*28*	2.75
$^{H}200x2$	Slow	*14*	2.17
$^{H}650$	Rapid	*10*	1.46
$^{H}400$	Rapid	*6*	0.88
$^{H}200x2$	Rapid	*0*	0.79
$^{H}100x2$	Slow	*0*	1.00
$^{H}100x2$	Rapid	*0*	0.29

* P=Peak serum isoniazid concentration (ug/ml.)
K=A constant 0.10 for slow inactivators and 0.2 for rapid inactivators (see text, page 2).
t=Time interval in hours between each dose of isoniazid.

a day was effective both in the prevention and treatment of toxicity in patients receiving a high dosage of isoniazid, namely 13.9 mg/kg body weight once a day (Tuberculosis Chemotherapy Centre, 1963a, 1963b). On an isoniazid dosage of 13.9 mg/kg body weight once daily, of 24 patients who received a Vit B complex preparation without pyridoxine 7 (29%) developed peripheral neuropathy compared with none among 26 who received pyridoxine 6 mgm with each dose of isoniazid (Tuberculosis Chemotherapy Centre, 1963b). In 3 toxicity studies 17 patients who developed the neuropathy were treated with 6 mgm of pyridoxine either alone or in combination with other constituents of Vit. B complex *while isoniazid was continued* (Devadatta et al, 1960, Tuberculosis Chemotherapy Centre, 1963a, 1963b). In 15 patients, there was improvement, in 2 no change and in 1 deterioration of the maniflstations of the neuropathy. It was possible to continue isoniazid for a full year in all but the last patient. One patient who developed a psychosis and another convulsions were treated successfully with pyridoxine 6 mg daily in combination with other constituents of Vit. B complex, while isoniazid in a dosage of 13.9 mg/kg body weight once a day was continued. Since Vit. B complex without pyridoxine was unsuccessful both in the prevention and treatment of isoniazid toxicity it is obvious that the 6 mgm of pyridoxine was the effective agent in patients developing both the peripheral nerve and cerebral toxicity. In another study one patient developed peripheral neuropathy and another convulsions on a twice weekly high dosage (13.9 mg/kg body weight) of isoniazid in combination with streptomycin. Both patients were successfully treated with pyridoxine 6 mgm given with each dose of isoniazid without modification of the chemotherapy (Tuberculosis Chemotherapy Centre, 1964).

Dosages of Isoniazid when used with other anti-tuberculosis drugs

Table 6 shows the therapeutic efficacy of various dosages of isoniazid used in combination with other drugs in Madras, East Africa and Great Britain on patients excreting drug sensitive tubercle bacilli. Isoniazid in a dosage of 100 mgm. (2.2 mg/kg body weight) twice daily in combination with paraminosalycylic acid (PAS) twice a day for a year produced bacteriological quiescnece of the disease in 87% of patients in Madras (Tuberculosis Chemotherapy Centre 1959, 1960, 1964), 84% in East Africa (East African/British Medical Research Council, 1960a, 1960b, 1963) and 82% in Great Britain (British Medical Research Council, 1962). At Madras the proportion for the 27 patients without cavitation was 96% (not tabulated). Isoniazid in a dosage of 300 mgm. in combination with thiacetazone 150 mgm. once a day for a year produced bacteriological quiescence of the disease in 88% of patient in East Africa. However, on the regimen of isoniazid 200 mgm. with thiacetazone 150 mgm. once a day only 64%, of patients attained bacteriological quiescence of the disease (East African/British Medical Research Council 1963). In a Madras Study isoniazid in high dosage (650 mgm. for a 100 Ib. patient or 13.9 mg/kg body weight) in combination with streptomycin both given *twice weekly* for a year produced bacteriological quiescence of the disease in 94%, of patients (Tuberculosis Chemotherapy Centre 1964). In Great Britain bacteriologically quiescent disease is achieved in 100% of patients receiving isoniazid 100 mgm. twice or

TABLE 6

Isoniazid in combination with other drugs

Place of study	Number of patients	Dose of soniazid (mg)	Companion drug and I dose	Rhythm	Percentage of patients with quiesent disease %	Percentage of patients with isoniazid toxicity %
Madras	315	100	PASSg	Twice a day	*87*	*0.3*
East Africa	238	100	PAS5g	Twice a day	*84*	*0.0*
Great Britain	74	100	PAS 5 g	Twice a day	82	*0.0*
East Africa	60	300	Thiacetazone 150 mg	Once a day	*88*	*1.6*
East Africa	70	200	Thiacetazone 150 mg	Once a day	*64*	*1.4*
Madras	72	650	Streptomycin 1 g	Twice a week	94	*2.8*

thrice a day in combination with streptomycin once a day (not tabulated, see Crofton 1959).

Duration of Chemotherapy

Table 7 shows the effect of isoniazid alone in a dosage of 200 mgm. (4.4 mg/kg body weight) once daily in the second year in patients with bacteriologically quiescent disease after a year of chemotherapy in a Madras Study (see Velu et al 1961). In patients without residual cavitation at 1 year bacteriological relapse occurred in the second year in none of the 103 patients on isoniazid and 10 (9%) of 107 on a placebo. This difference is statistically significant. On the other hand, among patients with residual cavitation there was little difference between the proportion of relapsing on isoniazid and the proposing relapsing on a placebo in the second year. The proportion of these patients (with the open negative syndrome) at the end of a year who relapsed in the second year was 8 out of 97 patients.

Table 8 shows the effect of 100 mgm. of isoniazid in combination with PAS 5 g. twice daily in the second and third years in patients, with bacteriologically quiescent disease with residual cavitation at the end of a year of chemotherapy, in a study in Great Britain (British Medical Research Council 1962). The proportion relapsing bacteriologically in the second and third years among patients who had their chemotherapy stopped at the end of 1 year was 12 (24%) of 50, among patients who continued chemotherapy in the second year (but not in the third) was 2 (6%) of 34 and among those who continued chemotherapy in the second and third years was 1 (4%) of 24 patients.

DISCUSSION

Isoniazid is always used in the treatment of patients with newly-diagnosed pulmonary tuberculosis. Most authorities believe that the best results are achieved when isoniazid is combined with at least one other anti-tuberculosis drug. However as pointed out by Fox (1964), in many clinics, in developing countries, where patients present with advanced disease, it is economically possible to administer only isoniazid. It is therefore important to deterimine the optimum dosage, rhythm and duration of therapy with isoniazid either alone or in combination with other drugs.

The Madras Studies have shown that the therapeutic efficacy of isoniazid alone in a dosage of 8.7 mg/kg body weight (400 mg. for a 100 Ib. patient) once a day was superior to the same dosage divided into 2 daily doses. However, no further increase in therapeutic efficacy was noted when the dosage of isoniazid was increased to 13.9 mg/kg body weight (650 mgm. for a 100 Ib. patient) once daily. The maximum effect of isoniazid alone in the Madras patients, the great majority of whom had advanced disease (Table 1), was the attainment of bacteriologically quiescent disease at the end of a year of chemotherapy in about 70%. However, all 26 patients receiving the three most successful isoniazid alone regimens, in whom the first or only overnight 'collection' sputum specimen was negative on direct smear examination, attained bacteriologically quiescent disease. Phillips (1959) found that isoniazid alone was as effective as isoniazid plus PAS in

TABLE 7

The effect of isoniazid alone in the second year on patients with bacteriologically quiescent disease at the end of 1 year of chemotherapy (Madras)

Treatment during second year	All patients	Bacteriological relapse in second year
Non-cavitated		
Placebo	107	10 (9%)
Isoniazid*	103	0 (0%)
Cavitated		
Placebo	42	4 (10%)
Isoniazid*	55	4 (7%)

* 4.4 mg/kg body weight once daily (200 mg for a 100lb patient).

TABLE 8

*The effect of isoniazid plus pas in the second and third year on patients with the "open-negatire" syndrome at the end of a year of chemotherapy**

Duration of chemotherapy*	All patients	Bacteriological relapses in the 2nd and 3rd years
One-year	50	12 (24%)
Two-years	34	2 (6%)
Three-years	24	1 (4%)

* From British Medical Research Council (1962).
** Isoniazid 100 mg in combination with PAS 5 g twice a day.

minimal or moderately advanced non-cavitated disease in American patients. Furthermore, isoniazid alone may be more acceptable to patients than a combined regimen, and thus may yield better therapeutic dividends in smear-negative non-cavitated patients, even in the economically favoured countries.

Since the maximum effect of the isoniazid alone regimens in *all* the Madras patients was sputum conversion in about 70% of patients, it is interesting to speculate whether any better results could be obtained with more intensive regimens of isoniazid alone in developing countries. The minimum single daily dosage required to obtain the maximum therapeutx effect in the Madras patients is not known. This dosage is greater than 4.4 mg/kg body weight and may possibly be 6.6 mg/kg or 8.7 mg/kg body weight (300 or 400 mg. for a 100 Ib. patient). It is therefore possible that regimens of 6.6 mg/kg or 8.7 mg/kg *twice* daily might produce bacteriologically quiescent disease in more than 70% of the patients. However, in East Africa isoniazid alone in a dosage of 10 mg/kg body weight twice daily produced bacteriological quiescence in only 40% of patients: (East African/British Medical Research Council 1960a). This proportion was 51% in another study where isoniazid 300 mgm. was given in combination with thiacetazone 100 mg. once a day (East African/ British Medical Researeh Council 1963).

Several possible explanations could be suggested for the poorer response to isoniazid of the East African patients than could be expected from the Madras studies. First, large doses of pyridoxine were given with isoniazid 10 mg/kg body weight twice daily and there is experimental evidence (Me Cune et al 1957) that pyridoxine may interefere with the anti-tuberculosis activity of isoniazid. It is uncertain precisely what effective dosage of isoniazid these patients received. The patients in the second East African study mentioned, however, did not receive any pyridoxine. Secondly, it is possible that the East African patients had, on average, more extensive disease on admission to treatment than the Madras patients. Thirdly, it is possible that pretreatment cultures of tubercle bacilli from East African patients, on average, were more virulent than those from Indian patients (see Mitchison 1964).

Since the reason for the difference in response to isoniazid between the East African and Madras patients is not known with certainty there is a case to assess the therapeutic efficacy of a moderate dose of isoniazid (300 mg. or 400 mg.) twice a day, in some other developing area. It is possible that the efficacy of this regimen might approach, equal or even exceed that of the usual low dose of isoniazid (100 mg.) in combination with PAS twice daily.

The most frequent manifestation of isoniazid toxicity encountered in the Madras Studies was peripheral neuropathy. Convulsion and psychosis occurred much less frequently. It was found that the proportion of patients who developed toxicity was associated with the individual dose of isoniazid (D) and the rate of inactivation. It was also associated with a ratio of the peak serum isoniazid concentration (P) to a constant (K which varied with rate of inactivation) and the time interval between the individual doses of the drugs (t). Since P is related to D, it was possible to derive an equation expressing the proportion of patients expected to develop isoniazid toxicity in terms of D and t for the slow and rapid inactivators. A similar equation was also derived for a population in which the proportion of slow inactivators is assumed to be 58.8% as in the Madras patients.

It is obvious that these equations are of limited value and probably only applicable to South Indian patients, since there may be factors like the pyridoxine content of the diet affecting the occurence of isoniazid toxicity. Other possible factors are the criteria used in the diagnosis of isoniazid neuropathy and duration of therapy. For example, in West Africa, peripheral neuropathy was encountered in 16 of 84 patients on isoniazid 2 mg/kg. to 3 mg/kg. body weight in combination with PAS twice a day (Money, 1959) compared with only 1 of the 324 patients from 3 Madras Studies receiving similar chemotherapy. On the other hand in an East African Study only 1 of 145 patients on isoniazid 300 mgm. (6.6 mg/kg body weight) once daily in combination with thiacetazone developed the neuropathy but from the equation derived from the Madras Studies the expected proportion on this regimen of isoniazid is 9%.

A Madras Study has shown that pyridoxine in as low a dose as 6 mgm. can prevent toxicity due to isoniazid 13.9 mg/kg. body weight once a day. This finding is of obvious importance to developing countries. Other workers have used much higher doses ranging from 25 mg. (Oestreicher et al 1954) to 300 mg. (East African/British Medical Research Council 1960a). Pyridoxine 6 mgm once a day was also successful in the therapy of patients developing toxicity even when isoniazid was continued. Although such patients can be managed by substituting isoniazid by another drug, there are definite advantages in retaining the most powerful and cheapest anti-tuberculosis drug.

Thus pyridoxine 6 mgm can be given prophylactically with each dose, if the suggested isoniazid regimen of 300 mg. or 400 mg. twice daily is investigated. Alternatively, as a less expensive measure, pyridoxine can be given in the same way only to patients who develop toxicity. This is feasible as isoniazid neuropathy is of the slowly progressive sensory type. This is true even when a high dosage of 650 mg. (13.9 mg/kg body weight) once a day is used, although the symptoms occur rather earlie than when a lower dosage is used.

Low doses of isoniazid given twice a day have been used in combination with other antimicrobial drugs and thus isoniazid toxicity is not a problem in such regimens. Isoniazid in a dosage of 100 mg. (2.2 mg/kg body weight) in combination with PAS 5 g., twice a day for 1 year was found in 3 Madras Studies to produce bacteriological quiescence in 87% of the patients. This result is much better than any of the isoniazid alone regimens used there. Since in the lower ranges the response to treatment is associated with peak serum isoniazid concentrations even better therapeutic results might be obtained with 300 to 400 mg. in combination with PAS once daily.

Of the 27 patients in 3 Madras Studies, without cavitation before commencement of treatment with isoniazid 100 mg in combination with PAS 5 g. twice a day, 26 (96%) had bacteriologically quiescent disease at the end of a year of chemotherapy. This observation suggests that isoniazid when combined with PAS is probably as effective as when combined with streptomycin in patients without cavitation. In the United States of America, Livings (1959) found no bacteriological or radiographic advantage of isoniazid plus streptomycin over isoniazid plus PAS at the end of eight months.

In an East African Study a cheap combination of isoniazid 300 mgm with thiacetazone 150 mgm once a day for a year produced bacteriologically quiescent disease in 88% of patients. An increase in the isoniazid dosage to 400 mgm might further increase the efficacy of the regimen. In the study a marked fall in the therapeutic efficacy was observed when isoniazid in this combination was reduced to 200 mgm once a day.

In Great Britain isoniazid in dose of 100 mgm twice a day in combination with streptomycin or 1 g. a day has produced bacteriological quiescence of the disease in 100% of patients (Crofton 1959). However, if the patient is receiving this treatment as an outpatient, it is easier to administer 200 or 300 mgm isoniazid in 1 dose under supervision with the streptomycin injection.

A Madras Study has shown that isoniazid in a dosage of 13.9 mg/kg body weight (650 mgm for a 100 Ib. patient) with streptomycin *both* given twice *weekly* produced bacteriological quiescence of the disease in 68 (94%) of 72 patients. If a patient who died on the day treatment was begun is excluded this proportion increases to 96%. It is not known whether a lower dose of isoniazid (say 6.6 mg/kg or 8.7 mg/kg body weight) or the substitution of streptomycin by PAS or an increase in the intermittency of the regimen would equally favourable results. The last principle is being investigated at Madras.

The high efficacy of this twice weekly regimen is of great importance in developing countries as it is much cheaper than the usual daily combination of isoniazid plus PAS. It is also possible that this intermittent regimen, which approaches 100% success in patients with advanced disease at Madras may be completely successful in certain economically favoured countries where the disease, on average, is less advanced. It may produce less streptomycin toxicity and may be more acceptable to patients and therefore prove more successful than the usual daily regimens of isoniazid plus streptomycin.

"We know when to begin chemotherapy for tuberculosis, but we do not know when to stop" (Annotation, Lancet, 1962). Studies at Madras and Great Britain have shed light on this problem. In the Madras Studies isoniazid 200 mgm (4.4 mg/kg body weight) once daily for the whole of the second year prevented bacteriological relapses in the second and third years in patients with bacteriologically quiescent disease *without* residual cavitation at the end of a year of chemotherapy. This observation may be applied to the treatment of patients even in the economically favoured countries It is not known whether a shorter period of isoniazid therapy in the second year (say 6 months) would also have prevented relapses. Isoniazid in a dosage of 200 mgm once daily for the whole of second year did not, however, prevent relapse in patients with bacteriologically quiescent disease *with* residual cavitation (open negative syndrome) at the end of a year of chemotherapy. Bacteriological relapses occurred in 8% of such patients. In Great Britain isoniazid 100 mgm in combination with PAS 5 g, twice a day in a second year considerably reduced bacteriological relapse in the second and third years in patients with the 'open-negative syndrome' at the end of one year. Continuation of this combined chemotherapy for another (third) year did not confer additional benefit.

Thus these studies have shown that the optimum duration of chemotherapy in all patients, irrespective of the extent of the disease pretreatment, is 2 years. They, therefore, do not support the views that chemotherapy should be given for indefinitely prolonged periods (Worbec et al 1960) or in selected cases for life (American Thoracic Society 1961). The patients whose disease has attained bacteriological quiescence without residual cavitation at the end of one year can be given isoniazid alone for another year and those with residual cavitation isoniazid plus PAS. It is, however, unrealistic to consider combined chemotherapy for a second year in patients in developing countries but it is possible that a higher dosage of isoniazid (e.g. 300 or 400 mgm once a day) could prevent relapses in patients with residual cavitation.

Summary

(1) This paper is based mainly on the Madras Studies and also, to a lesser extent on those carried out in Great Britain and East Africa. From the results of these studies suggestions are made regarding the optimum dosage, rhythm and duration of isoniazid therapy in pulmonary tuberculosis.

(2) Of the isoniazid *alone* regimens studies in patients at Madras, the great majority of whom had advanced disease, 8.7 mg.kg body weight once a day (400 mgm for a 100 Ib patient) has yielded the best results. This dosage produced bacteriologically quiescent disease in 73% of 64 patients.

(3) The therapeutic response was associated with the peak serum concentration of isoniazid up to that achieved by a dosage of 8.7 mg/kg body weight *once daily.* A higher single daily dosage, producing a higher peak concentration, did not produce better therapeutic results.

(4) Nearly all patients who developed isoniazid toxicity manifested symptoms and signs of peripheral neuropathy but a few of convulsions and/or psychosis. Toxicity occur red significantly more frequently in the slow than in the rapid inactivators of isoniazid.

(5) An equation was derived relating the proportion of patients expected to develop isoniazid toxicity with the individual dose of isoniazid and the interval between the doses for the slow and rapid inactivators. Since the proportion of slow and rapid inactivators among the Madras patients is known an equation was also derived for a South Indian population.

(6) Pyridoxine in a low dosage of 6 mgm was successful in the prevention of toxicity due to isoniazid administered in a dosage of 13.9 mg/kg body-weight (650 mg. for a 100 Ib. patient) once daily. 6 mg. of pyridoxine was also successful in the treatment of toxicity even when the isoniazid was continued.

(7) Isoniazid in a low dosage of 2.2 mg/kg body weight (100 mg. for a 100 Ib. patient) in combination with PAS 5 g. twice a day for a year produced bacteriological quiescence of the disease in 87% of patients in Madras, 84% in East Africa and 82% in Great Britain. In the 27 Madras patients with cavitation this proportion was 96%.

(8) Isoniazid 300 mg in combination with thiacetazone 150 mg once daily for a year produced bacteriologically quiescent disease in 88% of patients in East Africa,

(9) Isoniazid 100 mg twice or thrice a day in combination with streptomycin 1 gm once a day has produced bacteriologically quiescent disease in 100% of patients in Great Britain.

(10) Isoniazid in a high dosage of 13 9 mg/kg body weight in combination with streptomycin 1 gm both given twice weekly for a year has produced bacteriologically quiescent disease in 94% of patients in Madras.

(11) Studies in Madras and Great Britain have revealed that the optimum duration of chemotherapy is 2 years. Isoniazid alone 200 mgm once a day can be given in the second year to patients with bacteriologically quiescent disease without cavitation at the end of a year of chemotherapy. Patients with the "open-negative syndrome" at the end of one year should *if possible* receive combined chemotherapy in the second year.

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REFERENCES

American Thoracic Society (1961) *Amer. Rev. Resp. Dis.* **84,** 609.

Annotation (1962), *Lancet, 2.* 1364.

British Medical Research Council, (1962), *Tubercle 43. 201.*

Crofton J, (1959;, *Brit. Med. Jour. 1,* 1610.

Davadatta S., Gangadharam P.R.J., Andrews R.H., Fox W., Rarrukristinan C.V., Selkon J.B., and Velu S. (1960), *Bull. Wld. tilth. Org.* 23, 587.

East African/British Medical Research Council, Isoniazid Investigation (1950a), *Tubercle,* **41,** 83.

East African/British Medical Council, Second Thiacetazone Investigation, (1963), ibid, 44, 301.

East African/British Medical Council Thiacetazone/ Diphenyl thiourea Investigation, (1960b) ibid, 41, 399.

Fox W., (1964), *Brit. Med. Jour.* 1, 135.

Gangadharam P.R.J., Bhatia A.L , Radhakrishna S., Selkon J.B., (196la), *Bull. Wld. Hlth. Org.* 25, 765.

Gangadharam P.R.J., Devadatta S., Fox W., Nair C.N., and Selkon J.B., (1961b) ibid, 25, 793

Livings (1959), Transactions of the 18th Conference of the Chemotherapy of Tuberculosis held on February 2nd to 5th, 1959, at St. Louis, Missouri, Washington, D.C., U.S. Government Printing Office, p. 18.

McCune, R., Deuschle K., and McDermott W., (1957), *Amer. Rev. Tubercle,* 76, 1100,

Mitchison D.A., (1962) *in Drugs, Parasites and Hosts.* edited by L.C. Goodwin and R.H. Nimmo-Smith, Churchill, London, p. 267.

Mitchison D.A., (1964), *Bull. Int. Un. Tuberc.* 35, 287.

Money G.L., (19:9), /. *Trap. Med. Hyg.* 62, 198.

Oestreicher R., Dressier S.H., and Middlebrook G.. (1954), *Amer. Rev. Tuberc.* 70, 504.

Philiips S., (1959), ibid., **80**, 641.

Selkon J.H. Fox W., Gangadharam P.R.J., RamachandranK., Ramakrishnan C.V., Velu S., (1951), *Bull. Wld. Hlth. Org.* 25, 779.

Tuberculosis Chemotherapy Centre, (1959) ibid., 21, 51.

Tuberculosis Chemotherapy Centre, (1960), 23, 535.

Tuberculosis Chemotherapy centre, (1963a), ibid, 28, 455.

Tuberculosis Chemotherapy Centre, (1963b), ibid 29, 457.

Tuberculosis Chemotherapy Centre, (1964), ibid, 31, 247.

Velu S., Andrews R. H., Angel J. H. Devadatta S., Fox W., Gangadharam P. R. J. Narayana A. S. L., Ramakrishnan C. V., Selkon J. B., and Somasundaram P. R. (1961), 25, 409.

Velu S., Andrews R. H. Devadatta S., Fox W., Radhakrishnan S., Ramakrishnan C. V. Selkon J. B., Somasundaram P. R., Subbaiah T. V. (I960), ibid, 23,511.

Worbec T., Krasher L., and Fox R. T. (1960) in Transactions of the 19th Conference on the Chemotherapy of Tuberculosis p. 119, Washington D. C.

A 5-YEAR STUDY OF PATIENTS WITH PULMONARY TUBERCULOSIS IN A CONCURRENT COMPARISON OF HOME AND SANATORIUM TREATMENT FOR ONE YEAR WITH ISONIAZID PLUS PAS*

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An earlier publication from the Tuberculosis Chemotherapy Centre, Madras (1959), reported on the findings of a controlled comparison of home and sanatorium treatment of pulmonary tuberculosis, in which all patients received isoniazid plus *p*-aminosalicylic acid (PAS) for one year. The results in the two series were similar in the first year. Subsequently, all patients were followed up at home and the second, third, fourth and fifth years of all the patients originally admitted to the comparison and also gives the status of their disease at five years. The relapse rates in the second and third years have already been reported to be similar for the home and sanatorium patients with bacteriologically quiescent disease at one year (Velu et al., 1960a; Devadatta et al., 1961).

I. Plan and Conduct of the Study

Chemotherapy During the 5-Year Period

In the first year, the patients were prescribed isoniazid plus PAS (approximately 4-6 mg/kg body-weight of isoniazid and 0.2-0.3 g/kg of sodium PAS)[1] to be taken in the form of cachets twice a day (Tuberculosis Chemotherapy Centre, Madras, 1959). The treatment policy for the second and third years has been fully described elsewhere (Devadatta et al , 1961). In brief, patients with bacteriologically quiescent disease at one year (see definition - overleaf) were allocated at random to treatment for the second year with isoniazid (approximately 4-6 mg/kg body-weight daily, in a single tablet) or to a placebo, calcium gluconate (500 mg daily, in a single tablet). During the third year half (selected at random) of those who were treated with isoniazid in the second sear, and whose disease remained quiescent, continued to receive that drug and all the remaining patients with quiescent disease received the placebo. All patients with quiescent disease at three years received the placebo daily in the fourth year. Those with quiescent disease at four years did not receive any medicament subsequently.

Patients with bacteriologically active disease atone year (see definition—overleaf) or those who had a bacteriological relapse were usually treated with streptomycin plus pyrazinamide in the first instance. Patients who failed to respond to this regimen received cycloserine with either ethionamide or thioacetazone.[2]

In a small proportion (5%) of the patients, the disease was classified at one year as of bacreriologically doubtful status (see definition overleaf). The treatment received by these patients in the second and subsequent years is described on page 52.

Investigation in the second, third, fourth and fifth years

Patients with bacteriologically quiescent disease at one year were examined clinically and radiographically at monthly intervals in the second year, and at 3-monthly intervals in the third, fourth and fifth years. The planned intensity of bacteriological examinations is set out in Table 1. The standard procedure was to obtain 14 bacteriological specimens in the second year, 9 in the third, 9 in the fourth and 11 in the fifth year. Occasionally, extra specimens were examined, especially if a positive result had been obtained after a sequence of negative results. Tests of sensitivity to isoniazid and PAS were set up at each of these examinations if a positive culture was obtained. The techniques employed for smear and culture examination and sensitivity tests have been described in detail earlier, as also the details of the grading of smear and culture results and the definition of isoniazid resistance (Tuberculosis Chemotherapy. Centre, Madras, 1959).

Patients with active or relapsed disease were examined monthly throughout the period they were receiving chemotherapy. The monthly examinations included a chest radiograph, examination by smear and culture of two collection specimens of sputum, and examination by culture of a pair of laryngeal swabs. Tests of sensitivity to the drugs the patient was

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[1] For instance, a patient weighing 100 Ib (45kg) received 200 mg of isoniazid and 10 g of sodium PAS.

[2] Thioacetazone is the recommended international non-proprietary name (see World Health Organization, 1962) for 4'—formylacetanilide thiosemicarbazone (thiacetazone. Tb 1-698).

TABLE 1

Planned intensity of bacteriological examinations for patients with bacterioiogically quiescent disease at one year

Year	Month	Type and number of specimens	Total number of specimens
Second	12 to 23	One collection specimen[a] *or* a pair of laryngeal swabs[a]	14
	24	Two collection specimens and a pair of laryngeal swabs	
Third	27, 30 & 33	One collection specimen and a pair of laryngeal swabs	9
	36	Two collection specimens and a pair of laryngeal swabs	
Fourth	39, 42 & 45	one collection specimen and a pair of laryngeal swabs	9
	48	Two collection specimens and a pair of laryngeal swabs	
Fifth	51,54& 57	One collection specimen and a pair of laryngeal swabs	11
	59 ½	One collection specimen and one supervised spot specimen	
	60	Two collection specimens and a pair of laryngeal swabs	
Total specimens during the 4-year period of follow-up			43

receiving were set up on one positive culture at each of these examinations, using techniques described previously (Tuberculosis Chemotherapy Centre, Madras, 1959; Angel et al,, 1963).

Collapse therapy and resection

The policy was not to use collapse therapy or resection. In the event, two patients had surgical treatment—one a pneumonectomy (see page 545) on the other a decortication for a pyopneumothorax with a bronchopleural fistula (see page 543).

a For the method of obtaining the specimen, see Velu, Narayana & Subbatah (1961).

Definitions used in this report

At one year

Bacterioiogically quiescent disease : that is, all cultures (usually 7-9) negative at 10, 11 and 12 months.

Disease of bacterioiogically doubtful status : that is, a single positive culture at 10, 11 or 12 months, following culture negativity at three or more consecutive monthly examinations.

Bacterioiogically active disease : that is, either

(a) serious radiographic deterioration with one or more positive cultures necessitating a change of chemotherapy during the first year; or

(b) cultures never all negative at three con secutive monthly examinations; or

(c) a total of two or more positive cultures at 10, 11 and 12 months following culture negativity at three or more consecutive monthly examinations.

During the second, third, fourth and fifth years

Bacteriological relapse : that is, two or more positive cultures in any 6-month period. In the second year, this meant a total of two or more poeitive cultures in seven consecutive monthly examinations. In the subsequent years, when examinations were performed every three months, this meant a total of two or more positive cultures in three consecutive 3-montly examinations—for example, at 30, 33 and 36 months.

At five years

Bacterioiogically quiescent disease :[1] that is, all cultures (usually 9) negative from 54 to 60 months, inclusive.

Bacterioiogically active disease: that is, a total of two or more positive cultures from 54 to 60 months, inclusive.

II. Classification of Patients

Of 193 patients who were admitted to the study (Table 2), 96 were allocated to treatment at home (home series) and 97 to treatment in sanatorium (sanatorium series). The main analysis of the findings in the first year (Tuberculosis Chemotherapy Centre, Madras, 1959) concerned 163 patients (82 home, 81 sanatorium) who (a) had organisms sensitive to isoniazid and PAS on admission, *(b)* had had no previous chemotherapy (two had received up to

[1] Seven patients, who each produced one positive culture between 54 and 60 months, are also included in this category. In all seven, the culture was an isolated positive (see definition on page 540).

two weeks' chemotherapy) and (c) had followed the allocated treatment regimen for 12 months, apart from minor variations, unless they died or had a change of chemotherapy because of deterioration: of these, 130 had bacteriologically quiescent disese at one year, 10 had disease of bacteriologically doubtful status, 19 had active disease and four had died (three of tuberculosis and the fourth from electrocution). The remaining 30 patients (14 home, 16 sanatorium) were excluded from the main analysis for reasons given in Table 2.

Plan of the present report

The progress in the second, third, fourth and fifth years is described for patients with bacteriologically quiescent disease at one year in section III. for those with disease of bacteriologically doubtful status at one year in section IV, for patients with active disease at one year in section V and for patients not included in the main analysis in section VI. Section VII summarizes the disease status at five years of all the 193 patients admitted to the study. (See also Table 2.)

III. The Progress of Patients with Bacteriologicavvy Quiescent Disease at one Year During A 4-Year Periad of Follow-Up

Of the 130 patients with bacteriologically quiescent disease, four were not allocated at

TABLE 2

Classification of patients in the present report

		Home	Sana-torium	Both series	Section of report in which progress is considered
Patients included in the main analysis[a] in the first year, according to the classification of their disease status at one year[b]	*(a)* Bacteriologieally quiescent disease	60	70	130	III
	(b) Disease of bacteriologically doubtful status	1	3	10	IV
	(c) Bacteriologicallv active disease;	13	6	19	V
	(d) Death	2	2	4	—
	Total	82	81	163	
Patients excluded from the main analysis in the first jear	(a) Isoniazid-organisms on admission	6	3	9	VI
	(b) PAS-resistant organisms on admission	4	2	6	
	(c) Previous chemotherapy of more than two weeks' duration, but with organisms sensitive to isoniazid and PAS	2	2	4	
	(rf) Prolonged desensitization to PAS	0	1	1	
	(e) Premature discharge from treatment	0	7	7	
	(/) Sanatorium stay of more than six weeks (home patients)	1	—	I	
	(g) Non-tuberculous death from diseases which influenced the course of the tuberculosis	1	1	2	
	Total . .	14	16	30	
All patie		96	97	193	VII

a For definition, see preceding page.
b For details of classification, see preceding page.

random to treatment in the second year for reasons given by Velu et al. (1960a). Their progress is reported on page 542.

Of the remainining 126, 57 had been treated at home in the first year (home series) and 69 in sanatorium (sanatorium series); 65 were allocated to isoniazid alone (isoniazid series) and 61 to calcium gluconate (calcium series). On the basis of a postero-anterior radiograph and tomograms, 42 of these were classified by an independent assessor (Dr. J. H. Angel) as having residual cavitation at one year (cavitated series) and 84 as having no residual cavitation (non-cavitated series). Their progress is now considered.

Deaths

Three patients died during the 4-year period of follow-up, all from non-tuberculous causes. One (home, cavitated, isoniazid) died suddenly in the 17th month, possibly due to a spontaneous pneumothorax, another (home, non-cavitated, calcium) died in the 41st month from carcinoma of the bronchus, and the third (sanatorium, cavitated, calcium) died in the 51st month from cirrhosis of the liver. These patients had only negative cultures for 14, 39 and 49 months, respectively, before death (apart from the first, who had one positive culture two months before death).

Bacteriological Relapse in the 4-year Period of Follow-up

During the 4-year period of follow-up, 11 (8.7%) patients had a bacteriological relapse, eight (6.3%) in the second year (thus is, in the first year of follow-up), one (0.8%) in the third, none in the fourth and two (1 6%) in the fifth year. Thus, most of the relapses occured in the second year.

Table 3 presents the relapse rates for the 126 patients referred to above, according to:

(a) the place of treatment in the first year (home or sanatorium);

(b) the cavitation status at the end of the first year (cavitated or non-cavitated);

(c) the treatment received in the second year (calcium or isoniazid).

The two series in each of the above three contacts were compared for the condition of disease at the end of the first year, that is, at the starting-point of the study of relapse. The detailed findings have been reported earlier by Velu et al, (1960a), who concluded that patients in the home series had rather more extensive residual radiographic lesions than those in the sanatorium series as did the cavitated -compared with the non-cavitated series, while the calcium and the isoniazid series were fairly similar, both clinically and radiographically, at the end of the first year.

The proportion of patients who had a bacteriological relapse during the 4-year period of follow-up was 7% of 57 home patients, as compared with 10% of 69 sanatorium patients; 10% of 42 patients with cavitation at one year, as compared with 8% of 84 with non-cavitated

TABLE 3

Relapse rates during the 4-year period of follow-up for the three contrast

Contrast		Total patients	Patients who had a bacteriological relapse during the 4-year period of follow-up	
			No.	—
Place of treatment in the first year	Home Sanatorium	57 69	4 7	7 10
Cavitation status at one year	Cavitated Non-	42 84	4 7	10 8
Treatment during the second year	Calcium Isoniazid	61 65	8 3	13 5
	Total	126	11	8.7

disease at one year; and 13% of 61 who received calcium gluconate, as compared with 5% of 65 who received isoniazid alone. (The intensity with which patients were examined bacteriologically during the 4-year period of follow-up was similar for the two series in each of three contrasts above.) None of the differences are statistically significant.

In Table 4, the 126 patients with quiescent disease at one year are classified into 8 subgroups according to the place of treatment in the first year, thecavitation status at the end of the first year and the treatment during the second year; further, the numbers of relapses are set out year by year. It will be observed that, in patients with no residual cavitation at one year, seven of 42 who received calcium gluconate in the second year had a relapse, as compared with none of 42 who received isoniazid, statistically a highly significant difference (P<0.02). The findings were, however, different in patients with residual cavitation at one year. Thus, one of 19 patients who received calcium gluconate had a relapse, as compared with three of 23 who received isoniazid. In conclusion, whereas isoniazid given alone in the second year prevented relapse among the patients with non-cavitated disease at one year, it apparently conferred no benefit on the patients with cavitated disease at one year.

Isoniazid Alone in the Third Year in the Prevention of Bacteriological Relapse

Sixty patients, who had received isoniazid alone in the second year and had bacteriologically quiescent disease at two years, were allocated at random to treatment in the third year, 30 to isoniazid alone and 30 to calcium gluconate.

An analysis of the clinical and radiographic condition of the two groups at the cime of original admission to treatment, at the end of one year and at the end of two years showed no important differences between them (Devadatta et al., 1961). Also, the intensity of bacteriological investigation during the third, fourth and fifth years was similar. During this period, there were no relapses in either the isoniazid or the calcium group, which suggests that the administration of isoniazid alone in the third year did not apparently confer any benefit.

Details of the patients who had a Bacteriological Relapse

Table 5 gives the details of the 11 patients

TABLE 4

Patients in the eight subgroups who had a bacteriological relapse during the 4-year period of follow-up

Place of treatment during the first year	Cavitation status at one year	Treatment during the second year	Total patients	Patients who had a bacteriological relapse					
				No.	%	Year of relapse			
						Second	Third	Fourth	Fifth
Home Sanatorium	Cavitated	Calcium	11	1	*(9) a*	1	0	0	0
		Isoniazid	10	0	*(0)*	0	0	0	0
	Non-cavitated	Calcium	18	3	*(17)*	1	1	0	1
		Isoniazid	18	0	*(0)*	0	0	0	0
	Cavitated	Calcium	8	0	*(0)*	0	0	0	0
		Isoniazid	13	3	*(23)*	3	0	0	0
	Non-cavitated	Calcium	24	4	*(17)*	3	0	0	1
		Isoniazid	24	0	*(0)*	0	0	0	0
All	patients		126	11	*8.7*	8	1	0	2

a The parentheses indicate percentage based on fewer than 25 observations.

TABLE 5

Details of the patients who had a bacteriological relapse, their chemotherapy and disease status at five years

Serial number	Place of treatment during the first year	Cavitation status at one year	Treatment during the second year	Months at which one or more positive cultures were isolated[a]	Results of isoniazid sensitivity tests[b]	Month retreat-ment started	Chemotherapy[c]	Disease status at five years[d]
P163	Hom :	Cavitated	Calcium	22, 23, 24 (2)	S, S, U	24	SZ (18)[e]	Quiescent
P181	Sanatorium	Caviatted	Isoniazid	13, 15, 17, 18, 20, 21, 23, 24 (2), 25	All R	26	SZ(6)	Quiescent
P159	Sanatorium	Cavitated	Isoniazid	15 (3)	R	17	SZ (25)	Quiescent
P90	Sanatorium	Cavitated	Isoniazid	18 (3), 22 (2), 23 (3)	S, R, S	24	SZ(2); PH (4); CEP(3)	Tuberculous death
P132	Sanatorium	Non-Cavitated	calcium	14, 15, 16, 25, 28 (6)	C, R ,R, S, R	29	SZ (18)	Quiescent
P191	Sanatorium	Non-Cavitated	Calcium	14, 15 (3), 16 (2)	All S	17	SZ (8); PH (24)	Quiescent
P182	Home	Non-Cavitated	Calcium	16, 21, 24, 28, 30, 53, 54 (5)	S, S, U, S, S, S, S,	54	SZ (6)	Active
P60	Sanatorium	Non-Cavitated	Calcium	17, 18, 19, 20, 21, 22	S, S, U, S, S, U	22	SZ (9); PH (17)	Quiescent
P34	Home	Non-Cavitated	Calcium	2(72), 42, 45, 51, 54 (4)	All R	54	SZ (6)	Active
P19	Sanatorium	Non-Cavitated	Calcium	43, 54 (3), 55 (4), 56 (2)	All S	56	PH (4)	Active
P154	Home	Non-Cavitated	Calcium	57, 6	Both S	—	Nill	Active

[a]When more than one positive culture was obtained in a month, the number is indicated in parentheses.
[b]S=sensitive; R=resistant; C—contaminated; U—untested.
[c]H=isoniazid; P=PAS; S=streptomycin; Z—pyrazinamide; C=cycloserine;; E=ethionamide.
[d]For details of classification, see page
[e]The figures in parentheses give the duration in months.

who had a bacteriological relapse. Clear-cut radiographic deterioration, confirmed by an independent assessor (Dr. K.S. Sanjivi), followed the bacteriological relapse in 10 of these patients (including PI54 in whom it occurred at 62 months). The 11th patient (PI81) produced positive cultures repeatedly.

At the time of relapse, six of the patients who received calcium excreted isoniazid-sensitive organisms, as compared with one of the three who were receiving isoniazid, and even in the case of this patient, who was very irregular in taking isoniazid, the next positive culture was isoniazid-resistant. (All patients had oniy isoniazid-sensitive cultures during the first year of treatment.)

Nine of the 11 patients were treated with streptomycin plus pyrazinamide. Four patients responded favourably and had quiescent disease at five years. Three patients (including one who refused streptomycin injections) failed to respond to this regimen and, because they had had a relapse with organisms sensitive to isoniazid, were re-treated with isoniazid plus PAS; two achieved quiescent disease at five years and the third died of tuberculosis at 39 months despite a further change of regimen to ethionamide, cycloserine and PAS. At five years, the remaining two patients had not completed 12 months of treatment with streptomycin plus pyrazinamide; one had had positive cultures throughout the six months of treatment and the other, although having active disease by definition, had had only negative cultures at the last three monthly examinations. The 10th patient, who had a relapse at 54 months with isoniazid-sensitive organisms, had, at five years, been treated with isoniazid plus PAS for four months and had had negative cultures at the last three monthly examinations. The 11th patient, who had a positive culture at 57 months, did not have treatment restarted before the end of five years because the second positive culture was only obtained at 60 months. In summary, of the 11 patients who had a bacteriological relapse, six had bacteriologically quiescent disease at five years, four had active disease and one died of tuberculosis.

Prognostic Importance of Various Factors in the Occurrence of Relapse

The prognostic importance of various factors in the occurrence of relapse in the 4-year period have been investigated. The erythrocyte sedimentation rate (ESR), extent of cavitation and grade of smear positivity of the sputum on admission were not of prognostic importance, nor were the month of sputum conversion in the first year and the ESR at one year. However, of 29 patients who had unilateral disease on admission to treatment and bacteriologically quiescent disease at one year, none had a relapse during the 4-year period of follow-up, as compared with 11 of 97 patients who had bilateral disease on admission; this difference does not, however, attain statistical significance (P=0.1). Similarly, none of 32 patients who had unilateral disease at one year had arelapse subsequently, as compared with 11 of 90 patients who had bilateral disease (P-006).

Patients with Isolated Positive Cultures

In this report, an isoloted positive culture is defined as one positive culture in any 6-month period during the second or subsequent years. A total of 18 (14%) patients had an isolated positive culture (Table 6), five of them in the second, one in the third, seven in the fourth and five in the fifth year. Eleven of the isolated positive cultures were obtained from sputum specimens and all were negative on direct smear examination; the remaining seven specimens were from laryngeal swabs. A single colony grew in seven of the cultures and only four cultures grew more than 100 colonies (2+ or 3+ growth). The organisms were sensitive to isoniazid in 10 of the 15 cultures with test results available (including three from patients who were receiving isoniazid when the culture was produced).

An isolated positive culture was produced by seven (11%) of 61 patients who received the placebo in the second year, as compared with 11 (17%) of 65 patients who received isoniazid in the second year (P=0.5). Of 84 patients with non-cavitated disease, 12 (14%) had an isolated positive culture, as compared with six (14%) of 42 patients with cavitated disease. Thus, the occurrence of the isolated positive result (sometimes even in the fifth year) was apparently not influenced either by the cavitation status at one year, or by whether or not the patient had received isoniazid subsequently.

The occurrence of isolated positive culture result did not carry a bad prognosis. Thus, only one (6%) of 18 patients with an isolated positive culture had a relapse and one died of a non-tuberculous cause; the remaining 16 patients had bacteriologically quiescent disease at five years and have been regarded as having had bacteriologically quiescent disease throughout the period of follow-up.

Other Assessments of Progress

This subsection presents the findings of the radiographic assessments and ESR determinations for the 112 patients who had bacteriologi-

TABLE 6

Patients who produced an isolated positive culture during the 4-year period of follow-up

Serial number	Place of treatment in the first year	Cavitation status at one year	Treatment during the second year	Treatment during the third year	Month of positive culture	Bacteriological results		Result of isoniazid sensitivity test[2]
						Smear[1]	Culture	
66	Home	Cavitated	Calcium	Calcium	42	—	1+	R
185	Sanatorium	Cavitated	Calcium	Calcium	42	—	1 colony	R
152	Home	Cavitated	Calcium	Calcium	45	—	1 colony	S
30[3]	Home	Cavitated	Isoniazid	—	15	0	1+	No growth
59	Home	Cavitated	Isoniazid	Calcium	48	—	1+	S
77	Home	Cavitated	Isoniazid	Calcium	54	—	1 colony	S
11	Home	Non-cavitated	Calcium	Calcium	16	0	3+	S
15	Sanatorium	Non-cavitated	Calcium	Calcium	24	—	1+	R
19	Sanatorium	Non-cavitated	Calcium	Calcium	43	0	2+	S
158	Sanatorium	Non-cavitated	Calcium	Calcium	60	0	1 colony	S
26	Home	Non-cavitated	Isoniazid	Calcium	13	0	4 colonies	S
6	Sanatorium	Non-cavitated	Isoniazid	Calcium	14	0	1+	S
139	Sanatorium	Non-cavitated	Isoniazid	Calcium	39	0	1 colony	No growth
81	Sanatorium	Non-cavitated	Isoniazid	Calcium	54	0	2+	Contaminated
130	Home	Non-cavitated	Isoniazid	Calcium	60	0	1 colony	R
114	Sanatorium	Non-cavitated	Isoniazid	Calcium	36	—	16 colonies	S
121	Home	Non-cavitated	Isoniazid	Calcium	45	0	1 colony	S
148	Sanatorium	Non-cavitated	Isoniazid	Calcium	59	0	2+	R

[1] A dash (—) indicates that the specimen was a laryngeal swab and therefore had no smear result.
[2] S=sensitive; R=resistant.
[3] This patient died in the 17th month (see page 536).

cally quiescent disease throughout the period of follow-up; of the remaining 14 patients, 11 had a bacteriological relapse and three died of non-tuberculous causes; eight of the relapses and one of the deaths occurred in the second year. All the radiographic assessments were undertaken by an independent assessor (Dr Raj Narain).

Changes in radiographic appearances

In 58 (52%) of the 112 patients, changes in radiographic appearances had occurred between one and five years. There was improvement in 33 (29%), which was classified as moderate in 2 and slight in 31, and deterioration in 25 (22%), which was classified as moderate in 3 and slight in 22.

Radiographic changes, interpreted as deterioration (usually slight), occurred at some time or other during the period of follow-up (four assessments were undertaken) in as many as 35 (31 %) of the patients.

Cavitation changes were assessed by using standard radiographs and tomograms. Of 36 patients with cavitation at one year, cavitation had disappeared by five years in 33%, had decreased in 36%, had remained unchanged in 11% and had increased in 19%. Of 76 patients with no cavitation at one year, cavitation was present at five years in five (7%). Thus, increase in or appearance of cavitation occurred in 12 (11%) of the 112 patients with persisting bacteriologically quiescent disease.

Erythrocyte sedimentation rate

The proportion of patients who had an elevated ESR (more than 10 mm) was 75% at one year, 70% at two years, 72% at three years, 65% at four years and 60% at five years. The corresponding proportions were 51%, 35%, 43%, 43%, and 54%, respectively, for an ESR of 21 mm or more, and 12%, 7%, 11%, 13% and 11%, respectively, for an ESR of 51 onm or more.

In summary, minor radiographic changes (interpreted as deterioration), minor changes in cavitation and elevated ESRs occurred not infrequently in patients with persisting bacteriologically quiescent disease.

Patients not allocated at random

Of the four patients not included in the random allocation to treatment one (home, cavitated) died of carcinoma of the oesophagus in the 15th month, having had negative cultures for the preceding 13 months; two others (I home, 1 sanatorium; both non-cavitated) received no further chemotherapy and had negative cultures throughout the 4-year period, and the fourth (home, cavitated), who continued on isoninzid plus PAS, had a bacteriological relapse in the 15th month with isoniazid-resistant organisms, was treated with streptomycin plus pyrazinamide for 18 months and had quiescent disease at five years.

IV. Patients with disease of bacteriologically doubtful status at one year

Ten patients were classified as having disease of bacteriologically doubtful status at one year the single positive culture occurring in the 10th month in three, in the 11th in two and in the 12th in five patients. In the second year, seven patients received calcium gluconate, two isoniazid, and one continued on isoniazid plus PAS. Five patients had negative cultures throughout the 4-year period of follow-up. Two produced an isolated positive culture at 33 and 54 months, respectively, which was sensitive to isoniazid. In the remaining three patients, the positive culture obtained at 12 months proved to be the beginning of a bacteriological relapse. One of these patients, who received isoniazid in the second and third years, had four positive cultures in the second year followed by a series of negative cultures and then three more positive results in the third year; she had one more positive result at 39 months, but 22 subsequent cultures were negative and the disease was quiescent at five years. The remaining two patients were treated with streptomycin plus pyrazinamide for 15 and 18 months, and had quiescent disease at five years.

In summary, the three patients who had a bacteriological relapse had positive cultures at 12 and 13 months—that is, the positive culture at 12 months proved to be the commencement of a relapse. Finally, all 10 patients who had disease of bacteriologically doubtful status at one year had bacteriologically quiescent disease at five years.

V. Patients with bacteriologically actiue disease at one year

There were 19 patients with bacteriologically active disease at one year their chemotherapy during the 4-year period of follow-up and their disease status at five years are set out in Table 7. One of the 11 who continued with isoniazid plus PAS in the second year attained and maintained bacteriologically quiescent disease as did two of the three who received isoniazid alone. In all, 1ft patients received streptomycin plus pyrazinamide. Of these, seven had bacteriologically quiescent disease at five years, one died from a non-tuberculous cause (bronchial carcinoma), two died of tuberculosis, and six others failed to respond to treatment. Of the six patients who failed to respond to treatment, four were treated with cycloserine plus eithionamide; at five years, three of these had bacteriologically quiescent disease and the fourth, who was still under treatment, had had only negative cultures at the last two monthly examinations. The remaining two patients were treated with cycloserine plus thioacetazone followed by other regimens (see Table 7): one died of tuberculosis and the other had active disease at five years.

In summary, of the 19 patients with bacteriologically active disease at one year, 13 had bacteriologically quiescent disease and two had bacteriologically active disease at 5 years, four had died, three from tuberculosis and one from a non-tuberculous cause.

VI. Patients not included in the main analysis

Of the 30 patients excluded from the main

TABLE 7

Chemotherapy during the 4-year period of follow-up and disease status ai five years for patients with bacteriologically active disease al one year

Serial number	Place of treatment during the first year	Regimens of chemotherpcy during the 4-year period of follow-up[1]	Disease status at five years[2]
P67	Home	PH (12)[3]	Quiescent
P43	Home	H(24)	Quiescent
Pill	Sanatorium	H (24)	Quiescent
P23	Home	SZ (24[	Quiescent
P69	Home	SZ (23)	Quiescent
P100	Home	SZ (21)	Quiescent
P42	Sanatorium	SZ (12)	Non-tuberculous death
P115	Home	SZ (9)	Tuberculous death
P88	Home	PH (12); SZ (24)	
P127	Home	PH (18); SZ (24)	Quiescent
P149	Sanatorium	PH (12); SZ (28)	Quiescent
P179	Home	H (5); SZ (24)	Quiescent
P75	Home	PH (7);5Z (2)	Tuberculous death
P177	Sanatorium	PH (8); SZ]6); CE (18)	Quiescent
P13	Home	PH (12); SZ (9); CE (18)	Quiescent
P38	Home	PH (13); SZ (7).CE (18)	Quiescent
P31	Sanatorium	PH (14); SZ (1), CE (4)	Active
P135	Home	PH(4); SZ(7); CT(3); CE(5); CH (10);H(3); EH(5)	Active
P116	Sanatorium	PH (5); SZ (8); CT (12); H (3); CE (8)	Tuberculous death

[1] H = isoniazid; P = PAS; S = streptomycir; Z = pyrazinamide; C =- cycloserine; E = eithionamide; T = thioacetazone.

[2] For details of classification, see page 535.

[3] The figures in parentheses give the duration in months.

analysis, three died during the first year, one from tuberculosis in the first month and two from non-tuberculous causes in the eighth and ninth months, respectively (Tuberculosis Chemotherapy Centre, Madras, 1950). For the remaining 27 patients, the chemotherapy during the 4-year period of follow-up and the disease status at one and at five years are set out in Table 8.

Of the eight patients with isoniazid-resistant organisms on admission, two responded unfavourably to treatment: one died of tuberculosis in the 18th month while receiving streptomycin plus pyrazinamide and the other had bacteriologically active disease at five years in spite of having received five different regimens of chemotherapy; both had had active disease at one year. The remaining six patients, two of whom had had active disease and four quiescent disease at one year, had quiescent disease at five years (including one (PI07) who had had a decortication for a pyopneumothorax with a bronchopleural fistula). Four of these (including one of the cases with active disease at one year) did so without receiving reserve regimens; the fifth, who had had active disease at one year, attained quiescent disease on streptomycin and pyrazinamide; and the sixth, who had a relapse, attained quiescent disease on cycloserine plus ethtonamide after failing to respond to streptomycin plus pyrazinamide,

Of the seven patients who discharged themselves from treatment during the first year, three responded unfavourably: two died of tuberculosis (in the 18th and 50th months, respectively,), the first having had no further chemotherapy after the first year and the second while receiving his third reserve regimen; the third patient, who was very uncooperative and had only had seven months of treatment with isoniazid plus PAS after the first year, had active disease at five years. The remaining four patients, three of whom had received further chemotherapy (two at other tuberculosis clinics) and one, who had apparently received no further treatment, had quiescent disease at five years.

The remaining 12 patients attained quiescent disease at five years (including one (P22) who had had a pneumonectomy), the only two with active disease at one year having subsequently received treatment with a reserve regimen—namely, streptomycin plus pyrazinamide.

In summary, at five years, 22 patients had bacteriologically quiescent disease, two had active disease and six had died, four from tuberculosis and two from non-tuberculous causes. The six patients who were classified at five years as having had an unfavourable response had either had isoniazid-resistant organisms on admissijn or had discharged themselves from treatment in the first year.

Vir. Disease status at five years of all patients

There were 96 patients who were treated at home and 97 patients who were treated in sanatorium in the first year. During the subsequent four years, 12 of the home patients and 6 of the sanatorium patients had to be hospitalized for tuberculous conditions, a non-significant difference. The period of hospitalization was less than one month in two *(I* home, 1 sanatorium), 1-3 months in four (3 home, 1 sanatorium), 3-6 months in four (3 home, 1 sanatorium), 6-12 months in four (3 home, 1 sanatorium) and one year or more in four (2 home, 2 sanatorium).

During the 5-year period, eight patients (5 home, 3 sanatorium) died from non-tuberculous causes: seven had consistently had negative cultures for 2, 4, 13, 14, 18, 39 and 49 months, respectively, before death and the eighth (sanatorium) had positive cultures at the time of death, which was due to carcinoma of the tongue. Of the remaining 91 patients in the home series. !<2 (90%) had bacteriologically quiescent disease at five years, as compared with 84 (89%) of the 94 sanatorium patients; five (5%) and six (6%) respectively, had died of tuberculosis and four (4%) ia each series had bacteriologically active disease (Table 9). Thus, the condition of the home and sanatorium series was very similar at five years. Considering both series together, 90% of the patiens had bacteriologically quiescent disease at five years, 4% had active disease and 6% had died of tuberculosis.

VII. Discussion

The present report is concerned with the progress during a 5 year period of 193 patients with pulmonary tuberculosis who ware admitted to a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. The patients had newly diagnosed, untreated and usually far-advanced disease on admission to treatment, and came mostly-from the poorest sections of the community in Madras City. Unless their condition necessitated a period of treatment *in hospital* (which was uncommon), during the 4-year follow-up period all the patients lived in their normal home environment—that is they were housed in poor and overcrowded accommodation, had a low dietary intake and engaged in strenuous physical activity, often working for long hours (Ramakrishnan et al 1961 Ib 1966).

TABLE 8

Chemotherapy during the 4-year period of follow-up and disease status at one and five years for patients excluded from the main analysis

Reason for exclusion from main analysis	Serial number	Place of treatment in the first year	Disease status at orie year[1]	Regimens of chemotherapy during the 4-year period of follow-up[2]	Disease status at five yearsi
Isoniazid-resistant organisms on admission	P40	Home	Active	SZ (5)[3]	Tuberculous death
	P64	Sanatorioum	Active	PH (12); SZ (10):CT (11); CE (7); H (8)	Active
	P33	Home	Active	PH (5); SZ (24)	Quiescent
	P98	Home	Active	—	Quiescent
	P119	Sanatorium	Quiescent	SZ (8); CE (24)	Quiescent
	P107	Home	Quiescent	SPH (2); PH (9)	Quiescent
	P133	Home	Quiescent	H(27)	Quiescent
	P29	Sanatorium	Quiescent	H(12)	Quiescent
Premature discharge from treatment	P108	Sanatorium	Active	—	Tuberculous death
	P126	Sanatorium	Active	CT (8); CE (2); ZE (2)	Tuberculous death
	P76	Sanatorium	Favourable[1]	PH(7)	Active
	P73	Sanatorium	Active	PH (13); H (6)	Quiescent
	P63	Sanatorium		Received chemotherapy elsewhere but details not complete	Quiescent
	P93	Sanatorium	Favourable[5]		Quiescent
	P138	Sanatorium		—	Quiescent
PAS-resistant organisms on admission	P25	Sanatorium	Active	PH (18);'JSZ (12)	Quiescent
	P27	Home	Quiescent	H(24)	Quiescent
	P193	Home	Quiescent	H (13)	Quiescent
	P24	Sanatorium	Quiescent		Quiescent
	P55	Home	Quiescent	—	Quiescent
i	P151	Home	Quiescent	—	Quiescent
Previous chemotherapy of more than two weeks' duration, but with organisms senstive to isoniazid and PAS	P123	Home	Active	PH (6);SZ(13)	Quiescent
	P22	Sanatorium	Quiescent	PH (24) H(24)	Quiescent
	P187	Sanatorium	Quiescent	—	Quiescent
	P188	Home	Quiescent	—	Quiescent
Prolonged desensitiza. Tion to PAS	P17	Sanatorium	Quiescent	H(12)	Quiescent
Sanatorium stay of more than six weeks (home patients)	P113	Home	Quiescent	H(27)	Quiescent

[1] For details of classification, see page 535.
[2] H = ispniazid: P = PAS; S= streptomycin; Z — pyrazinamide; C = cycloserine; E= ethionamide; = Tthioacetazone.
[3] The figures in parentheses give the duration in months.
[4] This patient had four negative cultures at 12 months.
[5] These patients had four, one and three negative cultures, respectively, at 12 months.

TABLE 9

Disease status at five years for all home patients and all sanatorium patients admitted to study

	Bacteriological classification of disease status at five years [a]									
	Home series					Sanatorium series				
	Total	Quiescent		Active	Tuberculous death	Total	Quiescent		Active	Tuberculous death
		No.	%				No.	%		
Patients included in the main analysis in the first year										
(a) Bacteriologically quiescent disease at one year	57	54	*95*	3	0	69	67	*97*	1	1
(b) Disease of bacteriologically doubtful status at one year	7	7	*(100)*[a]	0	0	3	3	*(100)*	0	0
(c) Bacteriologically active disease at one year[a]	13	10	*(77)*	1	2	5	3	*(60)*	1	1
(d) Tuberculous death in the first year	1	—	—	—	1	2	—	—	—	2
Patients excluded from the main analysis in the first year										
(a) Isoniazid-resistant organisms on admission	6	4	*(67)*	0	2[b]	3	2	*(67)*	1	0
(b) PAS-resistant organisms on admission	4	4	*(100)*	0	0	2	2	*(100)*	0	0
(c) Previous chemotherapy of more than two weeks' duration but with organisms sensitive to isoniazid and PAS	2	2	*(100)*	0	0	2	2	*(100)*	0	0
(d) Prolonged desensitization to PAS	0	—	—	—	—	1	1	*(100)*	0	0
(e) Premature discharge from treatment	0	—	—	—	—	7	4	*(57)*	1	2
(f) Sanatorium stay of more than six weeks (home patients)	1	1	*(100)*	0	0	—	—	—	—	—
Total patients..	91	82	*90*	4	5	94	84	*89*	4	6
Non-tuberculous death during the 5-year period..................	5	—	—	—	—	3	—	—	—	—
All patients admitted to study..............................	96	—	—	—	—	97	—	—	—	—

[a] The parentheses indicate percentages based on fewer than 25 observations.
[b] Including one in the first year.

Relapse in patients with bacteriologically quiescent disease at one year

About 90% of the patients with bacteriologically quiescent disease at one year maintained this state throughout the 4-year period of follow-up. There were 11 (8.7%) bacteriological relapses; eight of these occurred in the first year of follow-up, so that the risk of relapse was maximal during this period. The relapse rate was no higher in the home series than in the sanatorium series; thus, four (7%) of 57 home patients had a relapse, as compared with seven (10%,) of 69 sanatorium patients.

Isoniazid alone, given in the second year, prevented relapse among the patients with bacteriologically quiescent disease and no residual cavitation at one year; none of 42 such patients had a relapse, as compared with seven (17%) of 42 who received a placebo (calcium gluconate), statistically a highly significant difference (P<0.02). On the other hand, isoniazid alone in the second year apparently had no effect in preventing relapses among the patients with residual cavitation at one year, since three (13%) of 23 cavitated patients who received it had a relapse, as eompared with one (5%) of 19 who received the placebo.

A subsidiary study, based on random allocation, showed that, in patients with bacteriologically quiescent disease at two years following a year of isoniazid plus PAS and a year of isoniazid alone, the administration of isoniazid in the third year conferred no apparent benefit, there being no relapses in either the treated or the control group. Although based on small numbers this finding underlines the importance of control groups in interpreting the results of long-term chemotherapy studies and, in particular, the need for caution in assessing recommendations made by some workers for very prolonged chemotherapy (Doonief, Hite & Bloch, 1955; Hyde, 1960; Pfuetze, Watson & Pyle, 1960; Worobec, Krasner & Fox, 1960).

Thomas (1965) reported 1.7% of relapses in a 5-year follow-up of 483 sputum-positive patients (72 more could not be followed up), notified in Birmingham, England, who had been treated daily for about two years, first with the three main anti-tuberculosis drugs and subsequently, when pretreatment sensitivity test results became available, by an appropriate 2-drug regimen; all the patients were in hospital for an "adequate" period of time and completed a period of therapy "to the satisfaction of the physician". Home (1964; personal communication, 1965) from Edinburgh reported a relapse rate of 2.8%, over an average follow-up of about six years (range 3-9 years), in 761 sputum positive patients who had been successfully treated with triple drug chemotherapy followed by a 2-drug regimen. (Over 10% of these patients had surgical treatment.) He found that the relapse rates were influenced by the duration of treatment; thus seven of 10 patients who had received less than six months' chemotherapy had a relapse, as compared with 13 of 171 who had received treatment for 6-18 months and one of 580 who had more than 18 months of treatment. Although the relapse rate of 8.7% for the 4-year follow-up in the present study is higher than those reported above, it cannot be regarded as unduly high in view of the regimen used and the duration of chemotherapy. Furthermore, if the patients with no residual cavitation at one year had all received isoniazid in the second year, and those with residual cavitation had continued with isoniazid plus PAS (see Great Britain, Medical Research Council, 1962), then the relapse rate would, in all probability, have been substantially lower than that reported here. However, if for economic or administrative reasons (Fox, 1964) it is not feasible to administer chemotherapy for more than one year, it is likely that a routine re-examination at two years would detect the majority of relapses, if indeed the patients had not already presented themselves for re-examination because of a recurrence of symptoms.

There has been considerable uncertainty concerning the prognosis of patients with the "open-negative" syndrome, but there is increasing evidence that this is not in itself a particularly dangerous state (Ryder, 1958; Worobec, 1959; Hyde, 1961). Our findings lend support to this view for, considering only those patients who received the placebo in the second year and thus had only one year of chemotherapy (isoniazid plus PAS), one (5%) of 19 with residual cavitation at one year had a relapse, as compared with seven (17%) of 42 without cavitation.

Occurrence of isolated positive cultures

A positive culture occurring as an isolated event in any 6-month period, sometimes as late as the fifth year, was found in 18 (14%) of the patients with quiescent disease at one year, thus showing that, even in patients who did not have a bacteriological relapse, chemotherapy failed in some to be sterilizing. These isolated positive cultures usually showed only a very few colonies, were often isoniazid-sensitive and were infrequently followed by a relapse ((6%) of 18 patients). This supports the observations of Raleigh (1957), Velu et al, (1960a. 1961a) and Devadatta et al, (1961) that an *isolated* positive result in patients with quiescent disease, who are under intensive bacteriological investigation, does not carry a bad prognosis

Other assessments of progress

This study has shown that measurements of ESR and assessments of changes in radiographic appearances and cavitation can often be misleading in following the progress of patients with bacteriologically quiescent disease. Thus, in patients with *persisting* quiescent disease over a 4-year period, radiographic changes, interpreted as deterioration, occurred at some time or other in 31% increase in or appearance of cavitation occurred at five years in about 10%, and an elevated ESR was obtained for at least 60% of the patients at each of the yearly examinations.

The re-treatment of patients with active or relapsed disease

Streptomycin plus pyrazinamide has been found to be an effective 2-drug regimen in the re-treatment of patients excreting isoniazid-resistant organisms, who had either failed to attain bacteriologically quiescent disease with the initial regimen of isoniazid plus PAS or who had a bacteriological relapse subsequently (Velu et al., 1960b, 1961b). Of the 34 patients in the present study who were treated with streptomycin plus pyrazinamide, one became uncooperative in the second month and refused further injections, one died of a non-tuberculous cause and two were still under treatment at five years. Of the remaining 30 patients, 17 (5%) achieved bacteriological quiescence of the disease.

Cycloserine plus ethionamide has also been found to be an effective 2-drug reserve regimen (Angel et al., 1963: Ramakrishnan et. al., in preparation). In the present study, of five patients who received cycloserine plus ethionamide as a "third-line" regimen after failing to respond to streptomycin plus pyrazinamide, four had a favourable response while the fifth was still under treatment at five years. In contrast, cycloserine plus thioacetazone was disappointing, for all four patients who received it had an unfavourable response (see also Angel et al., 1963).

Disease status at five years of all patients originally admitted to the study

It is of interest to consider the disease status at five years of all the patients admitted to treatment in the first year at home (96 patients) or in sanatorium (97 patients). Death due to a non-tuberculous cause occurred in five home and three sanatorium patients. Considering the remainder, 90% of the home patients and 89% of the sanatorium patients had bacteriologically quiescent disease at five years, 4% in each series had bacteriologically active disease and 5% and 6%, respectively, had died of pulmonary tuberculosis. It is noteworthy that only two patients, one in each series, had surgical treatment.

Considering all 193 patients admitted to the study, eight died of non-tuberculous causes and, of the remaining 185, 90% had bacteriologically quiescent disease at five years, 4% had active disease and 6% had died of tuberculosis. There was some evidence, albeit based on small numbers, that the outcome at five years was, relatively frequently, unfavourable in patients who had isoniazid-resistant organisms on admission to treatment, who discharged themselves prematurely from treatment or who had bacteriologically active disease at one year.

The results in the present series of patients do not compare unfavourably with other follow-up series reported from technically advanced countries (and covering approximately the same period of time, namely, 1956-62), especially in view of the very severe disease under treatment in the Madras series. Thomas (1965) reported a failure rate of 4.8% among 672 sputum-positive patients notified in Birmingham during the years 1957-58 and followed up for five years (77 more were untraceable and their failure rate is not known). Home (1964; personal communication, 1965) had a failure rate of 1.8% in a hospital series of 771 sputum positive patients followed up during 1955-60 in Edinburgh.

Conclusion

The 5-year findings abundantly confirm that the results of domicilliary chemotherapy, as carried out in this study, are sufficiently close to the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home (Tuberculosis Chemotherapy Centre. Madras, 1959; Velu et al., 1960a; Devadatta et al., 1956), despite the adverse environmental factors of poor diet, overcrowded living conditions and long hours of work often involving strenuous physical activity (Ramakrishnan et al., 1951b; 1966). It has also been shown that the family contacts of the patients who were treated at home were exposed to no special risk, either in the first year (Andrews et al., 1960) or over a 2-year period (Ramakrishnan et al., 1961a) or over a 5-year period (Kamat etal., 1966), in comparison with those of the patients treated in sanatorium in the first year. Considered together, these studies have firmly established the value of well-organized domicilliary chemotherapy, even in the most adverse environmental, economic and dietary circumstances.

IX. Summary

1. A total of 193 patients was admitted to a controlled comparison of home and sanato rium treatment of pulmonary tuberculosis, all patients receiving a standard regimen of isoniazid plus PAS for one year. The present report deals with the progress of all these patients (96 home, 97 sanatorium) during the second, third, fourth and fifth years.

2. Of the 193 patients, 163 (82 home, 81 sanatorium), who had drug-sensitive organisms initially, were included in the main analysis and 30 were excluded because they did not con form to this or other important criteria.

3. Of the 163 patients in the main analysis, 130 bad bacteriologically quiescent disease at one year, 10 had disease of bacteriologically doubtful status and 19 had active disease; four had died, three from tuberculosis and one from a non-tuberculous cause.

4. Of the 130 patients with bacteriologi cally quiescent disease at one year, 126 (57 home, 69 sanatorium) were randomly allocated to treatment during the second year, either with isoniazid alone or with a placebo, calcium gluconate; 65 (23 cavitated, 42 non-cavitated) received isoniazid and 61 (19 cavitated, 42 non-cavitated) the placebo.

5. During the 4-year period of follow-up, 11 (8.7%) of these 126 patients had a bacterio logical relapse, eight of them in the first year of follow-up. Of the 57 home patients, four (7%) had a relapse, as compared with seven (10%) of 69 sanatorium patients. Of 84 patients with no residual cavitation at one year, seven (17%) of 32 who received calcium gluconate had a relapse, as compared with none of the 42 who received isoniazid ($P<0.02$). Of the 42 patients with residual cavitation at one year, one (5%) of 19 who received calcium gluco nate had a relapse, as compared with three (13%) of the 23 who received isoniazid. Six of eight patients in the calcium series and one of three in the isoniazid series had a relapse with isoniazid-sensitive organisms.

6. Sixty patients, who received isoniazid alone in the second year and had bacteriologi cally quiescent disease at two years, were allocated at random to treatment in the third year, 30 to isoniazid alone and 30 to the placebo. There were no relapses in either group during the third, fourth or fifth years.

7. Of 18 (14%) patients who produced an isolated positive culture, only one had a bacteriological relapse subsequently.

8. Of the 10 patients with disease of bacte riologically doubtful status at one year, three had a bacteriological relapse; in all three, the positive culture at 12 months proved to be the commencement of a relapse. All 10 patients had bacteriologically quiescent disease at five years.

9. All of the 19 patients in the main ana lysis who had bacteriologically active disease at one year received further chemotherapy. At five years, 13 had bacteriologically quiescent disease, two had active disease and four had died, three from tuberculosis and one from a non-tuberculous cause.

10. Of the 30 patients excluded from the main analysis, those who had isoniazid-resistant organisms on admission and those who dis charged themselves prematurely from treatment had, relatively frequently, an unfavourable out come at five years.

11. Of the total of 193 patients admitted to the study, eight died from non-tuberculous causes during the 5-year period. Of the remain ing 185, 90% had bacteriologically quiescent disease at five yeas, 4% had active disease and 6% had died of pulmonary tuberculosis. The proportion of patients who had quiescent dis ease at five years was very similar for the home and the sanatorium series, being 90% and 89%, respectively.

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REFERENCES

Andrews, R.H., Devadatta, S.. Fox, W., Radhakrishna, S., Ramakrishnan, C. V. & Velu, S. (1960) *Bull. WldHlth Urog.*,**23**,*463*

Angel, J. H., Bhatia, A. L., Devadatta, S., Fox, W., Janardhanam, B., Radhakrishna, S , Ramakrishnan, C. V., Selkon, J. B., Stott. H. & Velu, S. (1963) *Tubercle (Land.),* **44**,215

Devadatta, S., Andrews, R. H., Angel, J. H., Bhatia, A. L., Fox, W., Janardhanam, B., Radhakrishna, S., Ramakrishnan, C. V., Subbaiah, T. V. & Velu, S. (1961) *Bull Wld Hlth Org.,* **24**, 149

Dooneief, A. S., Kite, K. E. & Bloch, R.G. (1955) *Arch, intern. Med.,* **69**, 470

Fox, W. (1964) *Brit, med. J.,* **1**, 135

Great Britain, Medical Research Council (1962) *Tubercle (Land.),* **43**,201

Home, N. W. (1964) *Tubercle (Land.),* **45**, 174

Hyde, L. (1960) In: *Transactions of the 19th Conference on the Chemotherapy of Tuberculosis held February 8th to llth., I960, at Cincinnati, Ohio,* Washington, D.D., US Government Printing Office, p. 122

Hyde, L. (1961) In: *Transactions of the 20th Research Conference in Pulmonary Diseases held February 61/1 to 9th, 1961, at Memphis, Tennessee,* Washington, D.C., US Government Printing Office, p. 89

Kamat, S.R., Dawson, J. J. Y., Devadatta, S., Fox, W., Janardhanam, B., Radhakrishna, S., Ramakrishnan, C.V. Somasundaram, P.R., Stott, H. & Velu, S. (1966) *Bull. Wld tilth Org.,* **34**. 517

Pfuetze, K.H., Watson, M. & Pylh, M.M. (1960) In: *Transactions of the 19th Conference on the Chemotherapy of Tuberculosis held February 8th to 11th, 1960, at Cincinnati, Ohio,* Washington, D.C., US Government Printing Office, p. 112

Raleigh. W.J. (1957) *Amer. Rev. Tuberc.,* **76**, 540

Ratnakrishnan, C.V., Andrews, R.H., Devadatta, S., Fox, W., Radhakrishna, S., Somasundaram, P.R. & Velu, S. (I961a) *Bull. WldHlth Org.,* **24**, 129

Ramakrishnan, C.V., Kanthi Rajendran, Jacob, P.O., Fox, W. & Radhakrisbna, S. (I961b) *Bull. Wld Hlth Org.,* 25, 339

Ramakrishnan, C.V., Kanthi Rajendran, Mohan, K.. Fox, W. & Radhakrisbna, S. (1966) *Suit. Wld Hlth Org.,* **34**, 553

Ryder, J.B. (1958) *Tubercle (Land.),* **39**, 113

Thomas, H.E. (1965) *Tubercle (Lond.),* **46**, 352.

Tuberculosis Chemotherapy Centre, Madras (1959) *Bull. Wld Hlth Org.,* 21, 51

Velu, S,, Andrews, R.H., Angel, J H., Devadatta, S., Fox, W., Gangadharam, P.R.J., Narayana, A.S.L., Ramakrishnan, C.V., Selkon, J.B. & Somasundaram, P.R. (1961a) *Bull. Wld Hlth Org.,* 25, 409

Velu, S., Andrews, R.H., Angel, J.H., Devadatta, S., Fox, W., Jacob, P.G , Narayanan Nair, C. & Ramakrishnan, C.V. (I961b) *Tubercle (Lond.),* 42, 136

Velu, S., Andrews, R.H., Devadatta, S., Fox, W., Radhakrishna, S . Ramakrishnan, C.V., Selkon, J.B., Somasundaram, P.R. & Subbaiah, T.V. (I960a) *Bull. Wld Hlth Org.,* 23, 511

Velu, S., Andrews, R. H., Devadatta, S., Fox, W., Ramakrishnan, C.V. & Subbaiah, T.V. (1960b) *Indian J. Tuberc., 7,* 85

Velu, S., Narayana, A. S. L. & Subbaiah, T. Y. (1961) *Indian J. Tuberc.,* 8, 129

World Health Organization (1962) *Cumulative list of proposed International nonproprietary names for pharmaceutical preparations,* Geneva, p. 46

Worobec, T. (1959) In: *Transactions of the l$th Conference on the Chemotherapy of Tuberculosis held February 2nd to 5th, 1959, at St. Lauis, Missouri,* Washington, D.C. US Government Printing Office, p. 173

Worobec, T., Krasner, L. &Fox, R.T. (1960) In : *Transactions of the 19th Conference on the Chemotherapy of Tuberculosis held February 8th to llth, 1960, at Cincinnati, Ohio,* Washington, D.C., US Government Printing Office, p. 119

BILATERAL SPONTANEOUS PNEUMOTHORAX COMPLICATING PULMONARY TUBERCULOSIS

A Case Report

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Pneumothorax occurring on both sides simultaneously have been reported with broncho-Pneumonia, whooping cough, asthma and mediastinal emphysema (Heichman, Hyde & Hyde and Rurief). Similarly Pneumothorax on one side and later on opposite side (after complete expansion of former) have been mentioned by Hyde and Hyde, Reostsma and two cases have have occurred in our Hospital also. But when Pneumothorax is present on both sides simultaneously in bilateral Pulmonary Tuberculosis it is usually the terminal event and such reports are very few in literature. Gray in 1910 presented a case of bilateral Spontaneous Pneumothorax in a course of bilateral Pulmonary Tuberculosis after which the patient soon died. Committee (1953) reported a case of bilateral Spontaneous Pneumothorax complicating milliary Tuberculosis.

Case-Report

A 24 year aged teacher was admitted to TB Hospital, Nowgaon on 2-4-60. He was given B.C.G. Vaccination in 1954 and his brother and latter's wife were also getting treatment for Pulmonary Tuberculosis. Patient came after taking 1200 Grams P.A.S and 630 tablets of Isoniazide. Screening chest showed a small cavity on right side with infiltration. Sputum was negative for AFB and EST was 80 m.m. 1st hour.

Inspite of Streptomycin and Isoniazid treatment, X-ray on 4-6-60 revealed multiple cavities on right side and patient developed continuous fever. Deltacortil was given. Though fever sub-sided, X-ray revealed hydropneumothorax on 9-9-60 on right side. Repeated aspirations were done. Disease progressed and sputum became positive for AFB on 22-9-60. PAS was added. Disease still progressed clinically as well as radiologically. Patient had haemoptysis on 9-9-60 and was discharged on 1-3-61 with advice to continue all the three drugs (Till that time he had received Streptomycin 96 grams, PAS 1840 grams, Isoniazid 4320 tablets and Deltacortil 360 tablets).

Patient came to TB Clinic, Indore on 21-9-61 with broncho-pleuro-cutaneous fistula on right side. Anaemia and oedema on feet. He was admitted to Rao Sanatorium. He had hydropneumothorax on right side with infilbration on left base. Sputum was positive for AFB. He was given all three drugs. (In H, PAS and Sm).

On 21-9-61 at midnight he suddenly got dyspnoea and cyanosis and was found to have developed pneumothoraxonleft side. Screening chest confirmed it. Injection morphia gr. 1/4 was given and aspiration was done on left side, but patient again became dyspnoeic next day and was transferred to M. R. T.B. Hospital, Indore. X-ray revealed bilateral pneumothorax. Intrapleural pressure on left side was l.P. + 12-4 when repeated aspirations on left side failed to relieve dyspnoea, a needle was put in the intercostal space through a catheter and was connected to an underwater seal. Patient improved a bit but developed sub-cutaneous emphysema. Needle on left side was replaced by a catheter and lung on left side expanded completely on 7-10-61. But Pneumothorax on right side increased and became of tension type (I.P. + 12 + 6). Intercostal catheter was put on right side after removing from left. 15 oz. of frank pus came out (AFB ++). Patient again developed sub-cutaneous emphysema and Pneumothorax on left side recurred. Repeated aspirations done but ultimately patient died on 19-10-1961.

Discussion

Though the incidence of Spontaneous Pneumothorax complicating Pulmonary Tuberculosis with the advent of anti-tubercular drugs is much less but it is not very rare. Bilateral Spontaneous Pneumothorax occurring during Pulmonary Tuberculosis present special problem and specially if they are of tension type, on either side and are complicated with serous fluid or pus due to presence of broncho-pleural fistula. The Intra-pleural pressures being positive on both sides, lung on both sides does not expand properly. The mediastinum being mobile shifts to one or the other side when active intervention is done for the treatment of pneumothorax by producing negative intra-pleural pressure to expand the lung. Repeated aspirations or continuous inter-costal drainage through catheter under-water-seal are the only possible measures that can be taken to expand the lung on one side and then on the other.

The present patient vaccinated with BCG in the past had moderate disease on right side in the beginning. But he deteriorated continuously inspite of all the three anti-tubercular drugs and developed hydro-pneumothorax on right side (under Cortisone therapy) and later on left side. Sputum also became positive: —

He was probably resistant to all the three tubercular drugs. The tension pheumothorax on left side disappeared after continuous drainage under water-seal but due to mediastinal shift to left (due to negative pressure produced therein) Pneumothorax on right side increased and became of tension type. When Pneumothorax on right side was drained, mediastinum shifted to right and Pneumothorax recurred on left side and ultimately patient died. Management of Pneumothorax simaltaneously on both sides is a very difficult practical problem. Simultaneous intercostal drainage is not feasible.

Summary

A case of Bilateral Spontaneous Pneumothorax complicating Pulmonary Tuberculosis has been reported. Though the outcome was fatal the management has been discussed.

REFERENCES

(1) Deichman, J: Diseases of Chest, 33:433, 1958.

(2) Hyde & Hyde: Amm. Rev. of Tuberculosis, 61:883; 1950.

(3) Gray, E. A,: Quoted by Fishberg M: Pulmonary Tuberculosis Philidelphia and New York 1922, P. 526.

(4) Cunnittee, J. P.: J, Irish. M, 35:384; 1954.

(5) Saxena, N. M.: Gupta, C. K. and Akbarali, "Observations on Spontaneous Pneumothorax with special reference to management". Thesis for M. D. (Medicine), Vikram University, 1962 unpublished.

(6) Turiaf Jetal: Abstt: Amm. Rev. of Tuberculosis, 74:69; 1956.

Role of General Practitioners in TB Control

Extract from the minutes of the meeting of the Standing Technical Committee of the Tuberculosis Association of India held on 15th and 16th July, 1965.

(1) The outlook of the general practitioners should be reoriented with a view to enable them to cooperate with the National Tuberculosis Programme, specially in regard to; (a) Notification of TB patients to the TB Control services, and (b) utilisation of existing TB Services for diagnosis and advice on treatment of their cases.

The Committee felt that it was highly desirable that all patients receive adequate drug treatment continuously for a year at least or longer if advised. TB patients under the treatment of general practitioners should be followed up till the disease was fully healed. The general practitioner may follow up his cases himself or seek the help of the clinic service.

(2) During the period of treatment the cases of general practitioners may be referred to the TB Service for continuation of treatment. If the patient did not report to the general practitioner at the expected time such cases should be reported to the TB services for retriving defaulters, and continuation of treatment.

(3) The homes of notified cases should normally be visited by the TB service staff who should examine the contacts unless desired in writing to the contrary by the concerned general practitioner.

(4) The TB service should provide diagnostic services free of charge or at a minimum cost and cooperate with the general practitioner in extending all available facilities that the TB service can provide.

(5) Efforts should be made to educate the general practitioner by frequent publications on current aspects of tuberculosis control work in the Journals of the Indian Medical Association and other Medical Journals by providing atleast one page news items. This should be undertaken by Government agencies and voluntary bodies.

NEWS & NOTES

Tuberculosis Health Visitors Course

The Tuberculosis Health Visitors' Course conducted by the Association will commence in New Delhi TB Centre in the first week of January, 1967. The duration of the course is one year of which one month will be in the College of Nursing, seven months in the New Delhi TB Centre and one month in the Lady Linlithgow Sanatorium, Kasauli. The candidates will be examined at the end of nine months training and those who are successful will be required to do practical work in home visiting for three months at the New Delhi TB Centre. Certificates will be awarded at the end of one year after successful completion or practical training in the field.

The minimum qualification for admission to this course is Intermediate with Science or Hygiene and Physiology in the Matriculation. Applications on the prescribed form should reach the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi, on or before 21st November, 1966.

Seventeenth Seal Sale Campaign

On the eve of inauguration of the 17th TB Seal Sale Campaign Dr. S. Radhakrishnan, President of India and Patron of the Association, has given the following message:

"I am glad to know that the Seventeenth TB Seal Sale Campaign will be launched in October, 1966. Continued and intensive efforts are needed to combat tuberculosis in our country where its incidence is still high. The cooperation of the public in this task is no less important and essential than the discovery of effective drugs to combat the disease and I hope this co-operation will be forthcoming in generous manner. I send my best wishes for the success of the campaign".

This campaign will commence as usual on October 2.

Conference of TB and Chest Diseases Workers: Hyderabad

The twenty second conference of Tuberculosis and Chest Diseases Workers in India will be held in Hyderabad from 3rd to 6th February, 1967 instead of in January.

Dr. Khushdeva Singh, Chairman of the Standing Technical Bommittee of the Association, is President of the Conference.

The programme will include Symposia on "TB in industry" and "Drug defaults—its psychological, social, economic and administrative factors". There will be also Panel discussions on "Prevelance of drug resistance" and "Clinical significance of Drug resistance" and "Emergencies of Chest Practice". The conference will also include sessions on "BCG Vaccination" aud "Type of tuberculosis developing among BCG vaccinated persons and the course of disease among them" and on "Economics of Health".

Arrangements for the conference are being made by the TB Association of Andhra Pradesh.

Maharashtra State TB & Chest Diseases Workers Conference

The fifth Maharashtra State TB & Chest Diseases Workers Conference will be held at K.E.M. Hospital, Parel, Bombay, on 26th, 27th and 28th November, 1966. The Conference will be inaugurated by the Mayor of Bombay.

There will be a Seminar on TB control in Maharashtra State and the participants include Drs. K.N. Rao, N.L. Bordia, M.D. Deshmukh, H. B. Dingley, S. P. Pamra and Shri B. M. Cariappa.

Mysore State TB & Chest Diseases Workers' Conference

The Second Mysore State TB & Chest Diseases Workers' Conference will be held in Mangalore on 14th & 15th January, 1967. Programmes for the conference are being finalised now.

Refresher Course in Tuberculosis: Calcutta

Bengal Tuberculosis Association will be conducting a week-long refresher course in Tuberculosis in Calcutta from 21st November, 1966 for the benefit of registered medical practitioners. Applications for this course are being invited by the Honorary General Secretary, Bengal TB Association, 21, Dr. Sundari Mohan Avenue, Calcutta-14.

Meeting of the Eastern Regional Committee: Tokyo

The first meeting of the Eastern Regional Committee of the International Union Against Tuberculosis will be held in Tokyo from 3rd to 7th October, 1966. The Japan Anti-TB Association will play host to the conference.

Princess Chichubi of Japan will inaugurate the conference.

Indian delegation to the conference will consist of Dr. N.L. Bordia, Adviser in TB, Government of India; Shri B.M. Cariappa, Secretary General, Tuberculosis Association of India, Dr. H.B. Dingley, Medical Superintendent, TB Hospital, Mehrauli (New Delhi), and Dr. M.D. Deshmukh, TB Specialist, J.J. Group of Hospitals, Bombay.

Drs. N.L. Bordia and H.B. Dingley will present papers on "TB in Children" res-pectively. Shri B.M. Cariappa will present a paper on "Voluntyary movement against TB Problems in organizing Associations".

Internation TB Conference

The 19th International Tuberculosis Conference under the auspices of the International Union Against Tuberculosis will be held in Ammsterdam (Netherlands) from the 3 rd to 7th October, 1967. The Programme Committee of the International Union will be fanalising the programme of this Conference. Further details can be had form the Office of the Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

Meeting of the Eastern Regional Committee

The Tokyo meeting of the Eastern Regional Committee of the International Union Against Tubverculosis ahs decided that the Sixth meeting of this Committee be held in Kuala Lumpur (Malalysia) in October, 1968. The Tuberculosis Association of Malaysia will pay host to this meeting. Further details can be had from the Office of the Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

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ABSTRACTS

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An International Co-operative Investigation into Thiacetazone Side Effects :

A.B. Miller, Wallace Fox and Rulh Tall. Tub., London; (1966), 47, 33.

Determination of the Incidence of side effects to Thiacetazone in combined chemotherapy was conducted as a double blind controlled comparison of two regimens; Streptomycin 1 gm. daily with a daily tablet containing Isoniazid 300 mgm. plus Thiacetazone 150 mgm. (STH regimen) and Streptomycin 1 gm. daily with a daily tablet of identical appearance containing Isoniazid 300 mgms. only (SH regimen).

Patients were treated for eight weeks (8-week series) in 13 countries. In eight countries patients were treated for 16 weeks (16 week series).

Of the total 2,077 patients, 1,002 S.T.H. and 987 S.H. patients were analyzed in the eight week series.

During the 8-week period 21 (13 STH, 8 SH) patients died, 16(10 STH and 6 SH) of tuberculosis, one (STH) patient died of hepatitis in the sixth week and the rest two (1 STH, 1 SH) died after 8 weeks with Jaundice.

Side effects occurred in 214 (21.4%) of the S.T.H. patients compared with 77 (7.8%) of the S.H. patients, a statistically highly significant difference. Treatment was not interrupted in 11.5% ST.H. and 5.3% S H. patients. It was interrupted in 6.5% and 1.6% and stopped in 3.4% and 3.9% respectively.

Nausea or abdominal discomfort occurred in 4.0% S.T.H. and 1.0% S.H. patients, vomiting in 4.3% and 0.5%, Jaundice or Hepatitis in 0.2% and 0.3% respectively. Flushing or Itching occurred in 1.3% S.T.H. and 0.5% S.H. patients and rashes in 3.9% and 1.0% respectively.

Dizziness or giddiness occurred in 9.6% S.T.H. and 2.9% S.H.

Vertigo and ataxia in *2.3%* and 0.7% Tinitues and Deafness in 1.1% and 0.0% respectively.

Agranulocytosis occurred in 2 (STH) patients.

Of the episodes of side effects 50% in the STH and 61% in the SH patients commenced in the first 4 weeks; 45% and 60% respectively lasted 6 days or less and 50% and 63% respectively were mild.

Of the 18 STH and 2 SH patients with cutaneous hypersensitivity leading to a major departure from treatment, 9 (8 STH, 1 SH) had hypersensitivity to Streptomycin and 4 (3 STH, 1 SH) had hypersensitivity to the oral medicament.

There were 299 S.T.H. and 310 S.H. patients in the 16-week series (all were in the 8-week series also).

During the 16 week period 8 (4 STH, 4 SH) patients died, 7 (3 STH, 4 SH) of tuberculosis and 1 (STH) with Jaundice.

Side effects developed in the first 8 weeks in 25.1% S.T.H. and 11.0% S.H. patients compared with 7% and 5.5% respectively in the second 8 week.

H.B.D.

Isoniazid With Thiacetazone in the Treatment of Pulmonary Tuberculosis in East Africa — Third Investigation—

The effect of an initial Streptomycin Supplement:—

Tub., London; (1966), 47, 1

The aim of the study was to investigate:—

(a) The effect of adding Streptomycin 1 Gm. daily for an initial period of two months to the Standard daily regimen of Thiacetazone 150 mgm plus Isoniazid 300 mgm in one dose.

(b) The value of a planned routine of 2 surprise home visits per month after discharge from Hospital at the end of 2 months.

425 patients were allocated at random to the 4 Treatment Series.

I. STH/HV

Daily thiacetazone 150 mgm plus Isoniazid 300 mgms plus Streptomycin with Home Visiting.

II. STH/No. H.V.

Daily thiacetazone 158 mgms plus Isoniazid

300 mgms plus Streptomycin without Home Visiting.

III. TB/HV.—

Daily Thiacetazonc 150 mgm plus Isoniazid 300 mgms with Home Visiting.

IV. TH/No. HV: -

Daily Thiacetazone 150 mgm plus Isoniazid 300 mgms without Home Visiting.

All the patients were in the Hospital for the first two months of treatment.

Results have been presented at 12 months for 343 patients who had sensitive strains to both Isoniazid and Streptomycin.

Eleven patients died, 6 (1 STH, 5 TH) from active tuberculosis, 2 (STH) from non-tuberculous causes but active tuberculosis, 1 (STH) from gas gangrene but with Quiscent disease and in 2 (1 STH, 1 TH) death was due to drug toxicityl

Sputum cultures were negative at six months in 93% of the STH and 81",, of the TH patients and at twelve months in 90% and 82% respectively.

At six months, 84% of the 25 TH patients with positive cultures had Isoniazid resistant strains and at twelve months 100% of 21 Isoniazid resistance emerged slowly in STH series and proportion of resistant strains was low and fluctuated.

90% of 162 STH patients had a favourable status compared with 79% of 181 TH patients a statistically significant difference (P/.0.01).

There were 6 patients in the STH series and 1 in TH series with an unfavourable Bacteriological response at 12 months who excreted only Isoniazid sensitive strains throughout the year.

A favourable status at twelve months was achieved by 91% of 85 STH/HV patients, 92% of 77 STH/No HV, 75% of 89 TH/HV and 83% of 92 TH/No HV patients.

Default from treatment occurred in 3 STH/HV, 14 STH/No HV, 13 TH/HV and 7 TH/No HV patients representing 8% of the combined Home Visits series and 11% of the combined No Home Visits series.

Drug Toxicity to thiacetazone was reported in 6(1.4%) Isoniazid in 2 (0.50%) of 420 patients receiving the drugs and Streptomycin toxicity in 12 (5.7%) of 211 patients receiving Streptomycin as supplement.

A co-operative study in the East African Hospitals and Laboratories with the collaboration of East African and British Medical Research Councils.

H.B.D.

An Appraisal of the Chemoprophylaxisof Tuberculosis in the Students Population of Lublin, Poland Following Thirty Months Observations: -

Amer. Rev. Rcsp Dis , Helene, Mysa, Rowska ct al. April, 66; Vol 93, No. 4 Page 628.

The results of 30 months observation of the chemoprophylaxis of tuberculosis in 389 students, whose Mantoux R Skin reactions were 12 m.m. or more, have been reviewed.

No case was reported in the group that received Isoniazid and P.A.S. whereas there were 2.2% new cases among the control during the first nine months of observation. Students showing strong positive Tuberculin test should have chemoprophylaxis.

H.B.D.

Pulmonary Drug Resistance in Pulmonary Tuberculosis in Great Britain—Second National Survey 1963: —

A.B. Miller, Ruth Tall and Wallace Fox, K.J. Leffoid and D.A. Mitcliison: Tubir., London (1966), 47, 92.

Sputum specimens of 1,292 newly diagnosed patients from 125 Chest Clinics were cultured for tubercle bacilli at a Central Laboratory. Of the 911 positive cultures, 894 were myco. tuberculosis, 2 Myco. Bo vis and 15 anonymous Bacteria.

Incidence of Primary drug resistance to Isoniazid, Streptomycin and P.A.S. alone or in combination was 4.1%. Resistance to one drug occurred in 3%,, to two drugs in 0.9% and to all three drugs in 0.2",,. The total resistance to Isoniazid was 1 7% to Streptomycin 3.0% and to P.A.S. 0.8%.

Most single drug resistance was to Streptomycin. Most double drug resistance was to Isoniazid and Streptomycin.

The prevalence of Primary drug resistance was statistically significantly higher among immigrants than among British and Irish patients.

The prevalence was higher among the recently arrived immigrants than among immigrants who had been in Great Britain for 5 or more years.

A comparison of the findings between the 2 National Surveys shows that there has been no change in prevalence over the 7 year period,

H.B.D.