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PREGNANCY AND TUBERCULOSIS

For decades, therapeutic abortion, unless some serious contraindication existed, was a routine for tuberculous patients. Main reasons for this procedure were that an active lesion worsens and a dormant lesion reactivates under this stress and strain. Far reaching changes of the physiology, and additional nutritional and other demands during pregnancy, excessive physical activity during labour, and breast 'feeding and care needed for rearing the baby were regarded as hazardous factors.

With the introduction of collapse therapy, specially after widespread use of A.P. treatment, this routine was relaxed to some extent when the disease could be well controlled before labour. Even in such cases some specialists advocated institution of P.P. for a period soon after the parturition to prevent sudden expansion of the lungs.

After the advent of anti-bacterial drugs, it became increasingly evident that pregnancy does not bring in its trail any additional danger. The fate of a tuberculous mother, therefore, is not different from her non-pregnant tuberculous sisters. Yet, the writer thinks that it is an important episode in the course of tuberculosis and certain questions must be considered before the final course of action is decided upon. For example: it is necessary to assess beforehand what chances has she to be non-infectious before delivery, specially when the baby cannot be segregated from the mother; what help can she get for rearing the child; what is her chance of normal delivery; has she to undergo any major surgical intervention, etc., etc.

In many cases therapeutic abortion and sterilisation are advised for tuberculosis, though the real cause is family planning. It may be convenient but the writer thinks that this is not a right policy. It causes misplacement of the reason, perpetuates the old and erroneous ideas on tuberculosis and harms tuberculosis and family planning programmes alike.

There had, also, been a justifiable fear that long term use of toxic anti-TB drugs may have adverse effect on the foetus. This fear can now be completely allayed as follow-up studies of babies born under this

condition did show neither favourable nor injurious effect at birth and subsequent growth.

The problem of tuberculosis of the bones and joints of the pelvis and of lower spine or, in fact, any condition where plaster fixation covering the abdomen is necessary, is different. Therapeutic abortion in such cases is often justifiable

With these changed concepts and practices, increasing number of tuberculous women will seek admission into the maternity beds, as they have greater need of this help to prevent prolonged labour and other complications. Admission into such general beds for tuberculous patients is difficult and, possibly, not desirable even though their stay may be very short. The writer takes the opportunity to suggest that a small separate room with a couple of beds may be reserved for this category of mothers in all large maternity hospitals.

In conclusion, it may be briefly stated that the course and cure of tuberculosis is not affected in any way by pregnancy. Termination of pregnancy is, therefore, unwarranted. Yet, there may be factors both medical and social, which may justify therapeutic abortion. This step can and should only be taken after careful consideration of all factors, including consultations with the obstetrician, the surgeons, and the doctor in-charge of pre-natal care. Light-hearted advice to end pregnancy should, by all means, be avoided.

TUBERCULOSIS AND PREGNANCY

B. K. SIKAND, S. P. PAMRA AND G. P. MATHUR
(New Delhi TB Centre, New Delhi.)

The relationship between tuberculosis and pregnancy has been the subject of comment from times immemorial. Hippocrates and Galen considered pregnancy beneficial, and are even said to have advocated it as a cure for the tubercular mother. This view was held more or less till the 19th century when the pendulum swung to the other extreme, and the dictum came to be, "if unmarried, no marriage; if married, no pregnancy; if pregnant, then therapeutic abortion". Therapeutic abortion thus was the order of the day for pregnant tuberculous women in the earlier stages of pregnancy.

Conflicting views were expressed in the first half of the present century about the effect of pregnancy on the outcome of tuberculosis. Whereas majority of the workers (e.g. Friedman and Garber 1940, Turner 1950, Edge 1952, Hedval 1953,) were of the opinion that pregnancy had no deleterious effect, Rist 1927, Pollak & Potter 1940, Cutler 1944, Cromie 1954, and a few others believed that pregnancy had a harmful effect on the prognosis for a tuberculous mother. Ornstein and Epstein (1939 and Hill (1928) adduced statistical evidence to prove that pregnancy does not effect tuberculous lesions adversely and that much of the high mortality amongst tuberculous pregnant mothers reported by some of the authors then was but a reflection of the high mortality among women of child-bearing age in general. They also claimed that the prognosis of pregnant women was in no way different from the non-pregnant of same age and economic status.

Experimental work of Burke (1940) and Wade (1942) on rabbits also tends to disprove any influence of pregnancy on the progress of artificially induced tuberculosis infection amongst pregnant and non-pregnant rabbits.

Cohen et al (1952) in an excellent study comprising 5 to 20 year's follow-up of 149 mothers with 401 pregnancies in the pre-

antimicrobial era, could "incriminate neither child-bearing incident nor other specific factors relating to pregnancy as potentially dangerous for TB. Anatomic extent of disease, the pathological pattern and native resistance or susceptibility of the individual patient to tuberculosis appear from the study to be the essential factors which determine the course and prognosis of tuberculous mothers". Thus even in the pre-antimicrobial era, the pendulum seemed to swing back to a neutral position with opinion veering towards harmlessness of pregnancy in tuberculous mothers.

Antimicrobials have so revolutionised the management of tuberculosis and improved the survival rates all round including pregnant and non-pregnant women that pregnancy has ceased to attract much attention, and very few studies concerning the influence of pregnancy on tuberculosis have been reported in recent years (Stewart et al 1954, Pridie et al 1961, Mehta 1961).

The present report is based on a retrospective analysis of this problem from three different angles:-

1. Is tuberculosis more common in pregnant women?
2. Is the result of antimicrobial therapy in pregnant women suffering from active pulmonary tuberculosis any different from that of the non-pregnant?
3. If 'Target Point' has been successfully achieved as a result of antimicrobial treatment, do subsequent pregnancies in any way influence the relapse rate?

Material & Results

I Prevalence of TB in pregnant women

All pregnant women attending the antenatal clinics of some Maternity and Child Welfare Centres in Old and New Delhi were referred to the New Delhi Tuberculosis Centre for miniature radiography from 1952

*'Target Point' is defined as a stage when at least two consecutive sputum/laryngeal swab cultures at intervals of three months have been negative. skiagram of the chest shows no cavity and residual lesions remain unchanged radiologically for at least 6 months.

to 1956. A total of 9,215 pregnant women were x-rayed and those found with suspicious shadows in the chest were investigated with

large x-ray and bacteriological examination. The prevalence of disease in this group is shown, age-wise, in Table 1.

TABLE 1
*Prevalence of TB among different groups of women by age
(Per thousand)*

	15-19	20-24	25-29	30-34	35-39	40-44
Delhi City (National Sample Survey)	Total Active 12.7		21.7		17.6	
	Bacillary 4.0		4.6		2.0	
Pregnancy Group	Total Active 5.4	6.7	9.9	13.0	7.0*	
	Bacillary 1.8	2.2	3.0	2.3	*	
Sterility Group	Total Active 20.3*	11.3	18.1	11.0*		
	Bacillary 5.8*	0.7	3.5			

*Percentage based on small numbers.

Similarly, 3,773 women attending 'Sterility Clinic' in the Lady Hardinge Hospital about the same time were also x-rayed at this Centre and investigated further. Table 1 also shows the prevalence rates of the disease in this group, as well as, for comparison, the prevalence rates amongst women of equivalent age in the general population in Delhi as determined during the National Sample Survey (I.C.M.R. 1959).

It would be seen that there is hardly any difference in the prevalence rate of total active disease and 'bacillary' disease in the 'pregnancy' group and general population. 'Sterility' group on the other hand, does tend to show a somewhat higher prevalence but the numbers being small, the difference is not of statistical significance.

II Fate of pregnant women suffering from pulmonary tuberculosis

For purposes of this study, all women in child-bearing age, viz. 15 to 45 years, who were not widows or spinsters, were living in our area of domiciliary service, were diagnosed to be suffering from active pulmonary tuberculosis in 1960 and completed at least 3 months' treatment were

analysed retrospectively. Out of a total of 249 such women, 32 were pregnant already when TB was diagnosed and 70 more became pregnant during the course of treatment. These 102 women constitute the 'pregnancy' group and the remaining 147 who had no pregnancy at the start or during the course of treatment constitute 'non-pregnancy' group.

Of the 102 women in the 'pregnancy' group, 10 had two pregnancies each and 92 one each. The different stages of treatment at which they became pregnant are shown in Table 2. An interesting observation has been that majority of the 17 women who became pregnant more than 13 months after the start of treatment are those who were hospitalized and their pregnancy coincided with discharge from the hospital. There being no difference in the results of women who were pregnant at the start of treatment and those becoming pregnant during the course of treatment, all 'pregnancy' cases are grouped together.

Table 3 shows the age distribution, the extent of disease, presence of cavitation and bacillary status of the patients in the two groups. There is no significant difference

TABLE 2
Patients having pregnancy at the start of
and/or during the course of treatment

Time of Pregnancy	Total number of cases	Percentage
Start of Treatment	32	31.4
1—3 months	16	15.7
4—6 months	16	15.7
7—9 months	14	13.7
10—12 months	7	6.8
13 months & above	17	16.7
Total	102	100.0

TABLE 3
Background data of pregnancy and non pregnancy
cases included in the study

	Pregnancy Group		Non Pregnancy Group	
	No.	%	No.	%
Total Cases	102	100.0	147	100.0
Age under 25 years	43	42.2	58	39.5
25-35 years	54	52.9	67	45.5
more than 35 years	5	4.9	22	15.0
Extent of Disease	13	12.7	2	1.0
Minimal Mod.	28	27.5	38	25.8
Advanced Far	61	59.8	87	59.2
Advanced				
Unilateral	47	46.1	53	36.1
Bilateral	55	53.9	94	63.9
Cavitations	49	48.0	60	40.8
Nil Present	53	52.0	87	59.2
Bacillary Status				
Positive	69	67.6	88	59.9
Negative	33	32.4	59	40.1

with regard to any of these factors in the two groups.

The patients in the two groups received the same treatment which was usually with two drugs and mostly in the home. The results therefore have been analysed, irrespective of drug schedules and place of treatment.

Table 4 shows the pattern of regularity*

TABLE 4
Regular of Treatment in both group

Regularity Scale*	Pregnancy Group		Non Pregnancy Group	
	No.	%	No.	%
Fairly Regular (80% and above)	60	58.8	96	65.3
Irregular (50—79%)	19	18.6	21	14.3
Inadequate or very irregular (Below 50%)	23	22.5	30	20.4
Total	102	100.0	147	100.0

* For definition, see text.

of treatment in the two groups. It would be seen that 58.8% in the 'pregnancy' group took treatment with 80% or more regularity. Pregnancy thus does not seem to be conducive to any appreciably higher or lower degree of regularity in drug consumption. The 42 women in the 'pregnancy' group took treatment in drug group whose regularity in treatment was less than 80% have been excluded from the following analysis, as the results of antimicrobial treatment have been shown to have a definite relationship to the regularity of treatment (Sikand et al, 1960). Number of patients achieving sputum

*Regularity is, defined as

$$100 \times \frac{\text{Time in which certain quantity of drugs should have been consumed}}{\text{Time actually taken to consume requisite quantity of drugs.}}$$

For example, if a patient has consumed 300 tablets of INH in 125 days instead of 100 days, the regularity is calculated as $100 \times 100/125$ or 80%.

conversion and cavity closure and the speed thereof have been made the basis of comparison of results, in the two groups. Tables 5, 6 and 7 compiled on modified life table pattern show the cumulative results at various stages of treatment. 'Target Point' of treatment in some abacillary cases without definite cavitation, being equivocal and liable to subjective variation, such cases

have not been compared.

The cumulative probability of reaching the 'target point', of 31 and 56 regular cavitary cases in the two groups, calculated by the modified life-table method, is shown in Table 5. The probability of reaching 'target point' after 18 months regular treatment was 0.71 and 0.63 in the 'pregnancy' and 'non-pregnancy' groups respectively and the

TABLE 5

Cavitary Cases reaching target point at successive stages of treatment in both groups

(Fairly Regular Cases)

Stages of Treatment (Months)	No. of Cases at start of period	No. reaching T.P. at end of period	Prob. of reaching T.P. during period	Prob. of not reaching T.P. during period	Prob. of not reaching T.P. up to the end of period	Prob. of reaching T.P. up to end of period
Pregnancy Group						
3-9	31	4	0.13	0.87	0.87	0.13
10-12	23	6	0.26	0.74	.65	0.35
13-18	16	9	0.56	0.44	0.29	0.71
19-24	4		0.00	1.00	—	—
25 & above	1	1	1.00	0.00	—	—
Non Pregnancy Group						
3-9	56	3	0.05	0.95	0.95	0.05
10-12	35	10	0.29	0.71	0.67	0.33
13-18	22	10	0.45	0.55	0.37	0.63
19-24	7	2	0.29	0.71	0.26	0.74
25 & above	1	1	1.00	0.00	—	—

T.P.=Target Point. Ind. J.

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TABLE 6

Sputum Positive Cases reaching target point at successive stages of treatment in both groups

(Fairly Regular Cases)

Pregnancy Group							Non Pregnancy Group					
Period of follow up (in months)	Cases at start of period	Cases reaching TP at end of period	Prob. of reaching TP during period	Prob. of not reaching TP during the period	Prob. of not reaching TP up to the end of period 0.881	Prob. of reaching TP upto end of period	Cases at start of the period	Cases reaching TP at the end of period	Prob. of reaching TP during period	Prob. of not reaching TP during the period	Prob. of reaching TP upto end of Period	Prob. of reaching TP upto end of the period
3-9	42	5	0.119	0.881		0.119	59	4	0.068	0.932	0.932	0.068
10-12	32	8	0.250	0.750	0.661	0.339	35	10	0.286	0.714	0.665	0.335
13-18	22	15	0.682	0.318	0.210	0.790	21	U	0.524	0.476	0.316	0.684

TP=Target Point,

TABLE 7

Sputum Positive Acavitary Cases reaching target point at successive stages of treatment in both groups

(Fairly Regular Cases)

Stages of Treatment in months	No. of Cases at start of period ^v	No. reached T.P. at end of period	Prob. of reaching T.P. during period	Prob. of not reaching T.P. during period	Prob. of not reaching T.P. up to end of period ¹	Prob. of reaching T.P. up to end of period
Pregnancy Group						
3-9	13	1	0.08	0.92	0.92	0.08
10-12	11	4	0.36	0.64	0.59	0.41
13-18	7	6	0.86	0.14	0.08	0.92
Non Pregnancy Group						
3-9	14	3	0.21	0.79	0.79	0.21
10-12	5	2	0.41	0.60	0.47	0.53
13-18	2	1	0.50	0.50	0.24	0.76

T.P.=Target Point.

difference is not appreciable. The number of patients who failed to reach 'target point' in 18 months, and continued treatment thereafter is too small for comparison.

Results of sputum conversion in 42 and 59 initially positive (cavitary and Acavitary) regular cases in the 'pregnancy' and 'non-pregnancy' groups respectively are shown in Table 6. Conversion rates and the time taken for conversion are more or less similar in both groups. At the end of 18 months treatment, cumulative probability of conversion was 79.0% in 'pregnancy' and 68.4% in the 'non-pregnancy' groups. Table 7 shows the results of sputum conversion in 13 acavitary sputum positive cases in 'pregnancy' group and 14 in the 'non-pregnancy' group separately.

No doubt some patients have dropped off at various stages of treatment against advice, but this cannot be helped in mass work. Table 8 shows however, that the percentage of cases leaving treatment at various stages as also the percentage of those whose sputum had already been converted when they gave up treatment is very nearly similar in the two groups and is therefore not likely to have influenced the results in Tables 5 & 7.

There was one death in the 'pregnancy' group and two in the 'non-pregnancy' group during the course of treatment. These have been counted among 'failures'.

This analysis thus tends to prove that with regular and adequate antimicrobial therapy, results are almost identical in both groups and pregnancy does not seem to influence the prognosis, of TB in any way.

TABLE 8

Sputum conversion at successive stages of treatment in the ease of both groups who left off treatment before reaching target point

(Fairly Regular cases)

	Pregnancy			Non Pregnancy		
	Sputum converted	Sputum not converted	Total	Sputum converted	Sputum not converted	Total
3—9 mths.	2	3	5	9	11	20
9—12 mths.	-	2	2	2	2	4
13 mths and above	3	4	7	3	7	10
Total	5	9	14	14	20	34

III Relationship of relapse to pregnancy

To provide for a sufficiently long period of observation, active pulmonary tuberculosis patients between the ages of 15 and 45 years who attended the Centre for the first time in 1956 and 1957 (in preference to those dealt with in Section II above) from the domiciliary area of this Centre and reached 'target point' of treatment have been reviewed retrospectively in respect of relapse and pregnancy from the date of termination of treatment up to 31.10.1962. Pregnancies during the course of treatment have been ignored. Though the health visitors make a note of pregnancy as a matter of routine, they again visited every patient specifically for verifying information regarding pregnancy.

Of these 229 women, 92 had one or more pregnancies and the remaining 137 had none. The pre-treatment data of the 93 and 137 women in the 'pregnancy' and 'non-pregnancy' groups respectively are given in Table 9. Here again, the two groups are more or less similar in respect of age distribution, extent of initial disease and bacillary status and were drawn from the same socio-economic strata. The usual treatment of these patients was

by two drugs, (one of these being INH) followed by INH alone as 'maintenance' therapy for 6 months after reaching the 'target point'. The regularity and duration of treatment (including maintenance) are shown in Table 10. Again, there is no significant difference in the two groups.

All arrested cases are required to attend periodically for check up which includes x-ray examination and laryngeal swab culture. Any radiological and/or bacteriological deterioration has been defined as relapse.

The extent of follow up in both groups is shown in Table 11. The women in 'pregnancy' group have had a better follow up record (an average follow up of 42 months as against 33 months in 'non-pregnancy' group) which may be due to the fear of relapse following pregnancy compelling them to continue attending for check up longer and more regularly.

Table 12 shows that whereas there were 6 relapses in all amongst 92 women who became pregnant at some stage or other during the follow up period, there were 15 relapses among 137 women who had no pregnancy. The relapse rate in the 'non-pregnancy' group appears to be somewhat

TABLE 9
Age distribution and initial status of pregnancy and non pregnancy cases reaching T.P.

(Follow up series)

	Pregnancy Group		Non Pregnancy Group	
	No.	%	No.	%
Total Cases	92	100.0	137	100.0
Age				
under 25 years	45	48.9	56	40.9
25-35 years	45	48.9	65	47.4
more than 35 years	2	2.2	16	11.7
Extent of Disease				
Minimal	12	13.0	15	10.9
Mod.	28	27.2	42	30.7
Advanced	55	59.8	80	58.4
Far Advanced				
Unilateral	46	50.0	58	42.3
Bilateral	46	50.0	79	57.7
Cavitation				
Nil	41	44.6	66	48.2
Present	51	55.4	71	51.8
Bacillary Status				
Positive	49	53.3	74	54.0
Negative	43	46.7	63	46.0

T.P.=Target Point.

higher than in 'pregnancy' group.

Table 13 shows the exact relationship of relapse to pregnancy. There were 47 women who became pregnant within 12 months of reaching 'target point' and one of them relapsed in the 1st year, 2 in the 2nd year, none in the 3rd year and one in the 4th year of follow up. As against this, of the 167 women who did not become pregnant within 12 months of reaching target point (some of them became pregnant subsequently) 5 relapsed in the 1st year, 3 in the 2nd year, 3 in the 3rd year and none in the 4th year. This clearly shows that pregnancy within 12 months of reaching the 'target point' does

not increase the hazard of a subsequent relapse provided the treatment has been adequate and effective. It also tends to exonerate child-rearing from influencing relapse rate. Whatever be the cause of relapse, it seems to operate equally in pregnant and non-pregnant women.

Similarly relationship between relapse and pregnancy during subsequent years of follow up was analysed (not tabulated separately), but failed to show any significant difference in the two groups. The already small number of relapses gets further fragmented by various permutations making valid conclusions not possible. Moreover, if pregnancy during the first year of follow up is not associated with increased risk of relapse, subsequent pregnancies are likely to have even less influence on relapse.

Discussion

Influence of pregnancy on tuberculosis is a subject on which a pre-planned controlled study is not possible. The best that can be done therefore, is a retrospective analysis based on matching group.

All women attending a few ante-natal clinics were x-rayed over a certain period. They represent a fair cross section of the female population in those age groups as far as socio-economic and environmental factors are concerned. They did not show any difference in the prevalence of bacillary and abacillary 'probably active' disease, as found in Delhi during the National Sample Survey. Browne and Browne (1960) came to the conclusion after x-raying 5,386 women in Hammersmith ante-natal clinic. Study of Dorfman et al (1956) involving 4,739 ante-natal examinations in USA also corroborates this finding. It is therefore reasonable to assume that the prevalence of TB in pregnant women is not higher than in women in general of the same age group and social status.

Even in the pre-antimicrobial era the influence of pregnancy on prognosis of tuberculosis had come to be questioned. The Joint Tuberculosis Council (1958) after careful appraisal of all available evidence reported "no deleterious effect of pregnancy on Tuberculosis, provided treatment was effective". Our results as also the studies of Pridie et al (1961) and Mehta (1961) are in conformity with this conclusion.

TABLE 10

Length of treatment and regularity in both groups

(.Follow up series)

	Pregnancy Group		Non Pregnancy Group	
	No.	%	No.	%
Total Cases	92	100.0	137	100.0
<i>Length of Treatment</i>				
under 12 months	28	30.4	46	33.6
12-17 months	41	44.6	56	40.9
18-24 months	15	16.3	21	15.3
25 months and above	8	8.7	14	10.2
<i>Regularity* •</i>				
(80% & above) Fairly regular (50-79%) Irregular (Below 50%)	36	39.1	50	36.5
Inadequate and very irregular	28	30.4	49	35.8
	28	30.4	38	27.7

*For definition, see text.

TABLE 11

Extent of follow up in the both groups

Period of follow up	Pregnancy Group		Non Pregnancy Group	
	No.	%	No.	%
under 12 months	2	2.2	21	15.3
12-23 months	10	10.9	33	24.1
24-35 months	12	13.0	19	18.2
36-47 months	33	35.9	25	13.9
48-59 months	27	29.3	33	24.1
60 months and above	8	8.7	6	4.4
Total	92	100.0	137	100.0

The results of antimicrobial treatment in matching groups of pregnant and non-pregnant women have been compared. The two groups were identical in respect of extent and severity of disease, bacillary status and social and environmental factors. Treatment policy and supervision was the same. The number of women reaching the 'target point' of treatment and the time taken was not influenced in any way by pregnancy. Therefore what is important is the provision of adequate treatment and not pregnancy,

Not long ago arrested cases of tuberculosis were advised to avoid getting pregnant for fear of relapse. In order to determine the relationship of pregnancy to relapse, if any, female patients who were treated successfully in 1956 and 1957 were analysed in respect of pregnancy and relapse. Women who became pregnant during follow up and those who did not, were similar in respect of age, socio-economic background, pre-treatment disease and length of treatment.

The only discernible difference between the two groups was occurrence of pregnancy. Over-all relapse figures were 6.5%

TABLE 12
*Relapses in 'Pregnancy' and 'Non Pregnancy'
 Groups (Follow up Series)*

Period of Follow up	Total Cases	Pregnancy Group		Non Pregnancy Group		
		Relapsed	Not Relapsed	Total Cases	Relapsed	Not Relapsed
under 12 months	2	-	2	21	—	21
12-23 months	10	—	10	33	1	32
24-35 months	12	1	11	19	1	18
36-47 months	33	4	29	25	5	20
48-59 months	27	1	26	33	4	29
60 months and above	8	-	8	6	4	2
Total	92	6(6.5%)	86	137	15(11.0%)	122

TABLE 13
*Relationship of Pregnancy after attainment of T.P. with relapse rate
 (Follow up Series)*

	Pregnancy within one year of T.P.		No Pregnancy within one year of T.P.	
	Total No. Followed	Relapsed	Total No. Followed	Relapsed
Relapse during 1st year of follow up	47	1	167	5
Relapse during 2nd year of follow up	36 *	2	115	3
Relapse during 3rd year of follow up	14		76	3
Relapse during 4th year of follow up	3	1	38	—

TP=Target Point.

(6 out of 92) in 'pregnancy' group as against 11.0 per cent (15 out of 137) in 'non pregnancy' group. Mehta (1961) reported relapse rates of 7.5% and 11% respectively. This would tend to prove that once the 'target point of treatment is reached, pregnancy *per se*, does not in any way increase the risk of relapse. For the same reasons prophylactic INH treatment for arrested cases of TB during pregnancy as advocated by some, appears to be redundant.

A word with regard to the policy of termination of pregnancy will not be out of place. In the pre-antimicrobial era it was common to advise termination of pregnancy in women with active disease. It is however doubtful whether this termination benefitted the patient in any way (Schaefer et al, 1954; Rosenbach et al. 1956). With the advent of antimicrobials and the tremendously improved prognosis of tuberculosis, equally in pregnant women and others, termination of pregnancy has no place in the present day management of tuberculosis and if pregnancy has no influence on the course of active disease, it should be less likely to have any effect on the fate of a stabilized lesion. The above analysis tends to support it. Thus there is no justification for advising an arrested case of TB to avoid getting pregnant on grounds of tuberculosis history only; or to advise therapeutic abortion to a pregnant woman with active or arrested lesion.

Pregnancy is a normal physiological function of the female species and should not tilt the balance one way or the other in the fight against tuberculosis. The crux of the Whole problem appears to be whether or not adequate facilities for treatment and supervision are available. If they are, pregnancy; would not mater; if they are not, avoiding pregnancy would not improve the outcome.

SUMMARY

Influence of pregnancy on prevalence, immediate result of treatment and relapse of tuberculosis among women of child-bearing age has been analysed.

Prevalence of tuberculosis among 9,215 pregnant women was found to be similar to the rate in women in general of corresponding age groups and socio-economic status.

For purposes of results of treatment and relapse, matching groups of pregnant and non pregnant women from the same socio economic environments have been compared. Cumulative probability of reaching 'target point' after 18 months regular treatment was 0.71 and 0.63 in the 'pregnancy' and 'non pregnancy' groups respectively. Similarly, women who "became pregnant after reaching the 'target point' suffered fewer relapses than those who did not become pregnant (6. 5% against 11.3%).

Value of regular and adequate antimicrobial therapy is stressed. If adequate treatment is available, pregnancy does not seem to influence the immediate fate of a tuberculous woman nor does it increase the hazard of relapse after successful treatment.

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THE RELATIVE MERITS OF VARIOUS VIRULENCE TESTS FOR MYCOBACTERIA

B. MAHAPATRA

(Department of Pathology, S.C.B. Medical College, Cuttack)

Introduction

Out of several species of mycobacteria, only the tubercle bacilli, lepra bacilli and the so called 'atypical' mycobacteria can produce infection in man and other animals, and as lepra bacilli have not been obtained in culture, the virulence study for mycobacteria is limited at present to the other two groups. The frequently observed properties in this respect are; animal pathogenicity, cording effect and cyto-chemical reactions.

In the present study the above three properties of 125 strains of mycobacteria have been observed. The purpose of the study is to find out the correlation between these virulence tests and to see if any one of them has any relative superiority over the others.

Materials And Method*

One hundred and twenty five strains of mycobacteria isolated from sputa of clinically diagnosed cases of pulmonary tuberculosis were studied along with ten known strains. Cultures were done in modified Lowenstein Jensen medium which was prepared according to the method given in the Bulletin of International Union against Tuberculosis (1955).

(a) *Animal Pathogenicity Study:* For animal inoculation, a bacillary suspension from young culture was made in saline to contain about 1 mgm semidried bacilli per ml. as recommended in the above mentioned bulletin, it was used in doses of 1 ml. intraperitoneal to guinea pigs and 0.5 ml. intravenous to the mice. The animals, if not dead, were killed and opened up after 12 weeks and examined for presence of tubercle bacilli or lesion produced by them.

(b) *Study on the cording effect:* For noting the cording effect, Aldrige's synthetic fluid medium as 'described' by Aldrige et al (1959) was used. After staining a smear with Ziehl Nelson stain, presence of cord like growth could be seen with low power of microscope, the exact nature of the cord (Serpentine, Tight or Loose) was verified with oil immersion objective.

(c) *Study on Cyto-chemical reaction (Neutral red test);*

This study was performed on the line of Wayne's (1959) modification of Dubos and Middlebrook's method and observations were noted as per the suggestion of Richmond and Cummings (1950). To carry out the test, well grown cultures (4 to 6 weeks old) were covered with 0.1 ml. of saturated solution of Neutral red in 95 per cent ethanol and incubated for one hour at 37°C in a slanting position. After incubation, the excess of dye was bleached by adding 0.1 ml. of N/10 Sodium Carbonate solution. The colour of the colonies was noted after half an hour, one hour, four hours and twenty-four hours.

Observations

(a) On animal pathogenicity: A strain was considered to be pathogenic if it could kill the animals within 12 weeks and if macroscopic or microscopic lesions and/or acid fast bacilli found in the tissue. In those animals who lived beyond 12 weeks, the strain was considered to be less pathogenic. A strain was taken to be non-pathogenic if the infected animal lived beyond 12 weeks and if there was no evidence of macroscopic and microscopic lesions.

The week-wise death rate of animals is shown in Table I and the relative pathogenicity of the strains to guinea-pigs and mice is shown in Tables II and III. The observations on animal pathogenicity is compared with other virulence tests in Table VI.

(b) On cording effect: The nature of the cord formed by different strains is shown in Table IV and it is compared with other virulence tests in Table VI. Strains showing serpentine cording or good amount of tight cording were considered virulent, loose cording were considered to be of attenuated virulence, others with clumps and no cording were taken as avirulent.

TABLE I
Showing weekwise death rate in animals after infection with Mycobacteria

Week	Guineapig	Mice
1st. week		
2nd. week	2	5
3rd. week	13	18
4th. week	17	27
5th. week	9	13
6 th . week	5	9
7th. week	7	7
8th. week	6	6
9th. week	3	4
10th. week & 11th week	3	5
12th. week.	7	5
After 12th week	37	11
Sacrificed	16	9
Total	125	125

TABLE II
Showing pathogenicity of different strains to guineapigs and mice

Nature of	No. of	Human	Bovine	Atypical	Saprophyte
Pathogenicity	strains				
Pathogenic to both	98	94	2	2	—
Pathogenic to Guineapig alone	3	3	—	—	—
Pathogenic to mice alone	21	16	—	5	—
Non-Pathogenic to both	3	—	—	1	2
Total	125	113	2	8	2

TABLE III
Showing relative pathogenicity of the strains to Guineapigs and mice

Guineapig	Mice	No. of Strains	Human	Bovine	Atypical	Saprophyte
Pathogenic	Pathogenic	51	49	2		
Pathogenic	Less Pathogenic	9	9	-		
Pathogenic	Non-Pathogenic	1	1	-		
Less	Non-			-		
Pathogenic	Pathogenic	2	2	-		
Less	Less			-		
Pathogenic	Pathogenic	11	9	-	2	
Less						
Pathogenic	Pathogenic	21				
Non-Pathogenic	Pathogenic	15	10	-	5	
Non-	less					
Pathogenic	Pathogenic	6	6	-		
Non-	Non-					
Pathogenic	Pathogenic	3	—	-	1	2

TABLE IV

Cording effect shown by Mycobacteria

Nature of cord	No. of Strains	Human	Bovine	Atypical	Sapro-phyte	Remarks
Serpentine	71	70	1	-	-	Virulent
Good, tight cords	13	13	-	-	-	"
Poor, tight cords	28	26	-	2	-	Attenuated Virulence
Loose cords	2	-	1	1	-	"
Clumps or diffused	11	4	-	5	-	Avirulent

TABLE V

Neutral-red reaction shown by mycobacteria

Colour of Colonies	No. of Strain	Human	Bovine	Atypical	Sapro-phyte	Remarks
Red. 4 hr.	113	105	2	6	—	Virulent.
or more	10	8	—	2	—	Attenuated
Pink in „						Virulence.
Colour less or Yellow	2	—	—	—	2	Avirulent.

While correlating the virulence of mycobacteria as determined by different tests, the following combinations were observed as shown in Table VI below

TABLE VI

Correlation between various Virulence Tests

Group M.	C.	N.	Nature of correlation	No. of Strains	Remarks
1			+ + + +	95	
2			— + + +	15	14 were INH resistant human type. other was atypical mycobacteria
3			+ + + +	3	3 human. 2 atypical all resistant to INH
4			+ + - +	4	2 human. 2 atypical all resistant to INH
5			+ + + —	0	
6			— + — +	5	2 human. 3 atypical all resistant to INH ;
7			- - - +	1	Atypical mycobacteria
8			- - - +	2	Both saprophytes

Key: G—Guineapig Pathogenicity,
M—Mice Pathogenicity.
C—Cording effect,
N—Neutral-red test.

+

Positive

-

Negative

(c) On Neutral-red binding power: The strains which retained red colour for four hours or more were taken as virulent. Those which were pink to light pink in four hours were considered as of attenuated virulence. Those which became yellow or colourless within that time were regarded as avirulent. The result of the observations is shown in Table V and compared with other virulence tests in Table VI.

Discussion

Although the animal pathogenicity test has been taken for granted as the index for virulence for a pretty long time, it is subject to considerable variation because it reflects the interaction between the host and the parasite. The animal pathogenicity test is affected by genetic, environmental factors and cultural condition of the microbe (Bloch 1955); the relative susceptibility of the animal species (Francis 1958). The relative low virulence of Indian strains of human tubercle bacilli to guinea-pig has been suggested by Mitchison et al. (1960) to be due to climatic effect.

Neutral-red binding power of different mycobacteria at alkaline PH (9.5) was observed by Dubos and Middlebrook (1948) and later confirmed by Hughes et al. (1954), Term (1954) and Buchanan (1955). The virulent mycobacteria bind the dye for more than four hours due to the abundant peripheral lipoprotein with negative polarity (Desbordes et al. 1959). On the other hand Goldman (1956) reported that certain saprophytes can give strong neutral red reaction and dye binding power was found to vary with the age of the culture (Fenner and Leach 1953) and Haduroy (1945) found fifty per cent discrepancy between dye binding power and virulence of the mycobacteria. In our present study complete correlation was found between all the three tests in 77.6 per cent strains. Of the 15 INH resistant strains, all were non-pathogenic to guinea-pig but their virulence was established from mice pathogenicity, cording effect and neutral red reaction. 14 of them were 1 human tubercle bacilli and one was a typical mycobacterium (rapid grower). Similar observations have been reported on the virulence of INH resistant human tubercle bacilli (Middlebrook and Cohn 1953, 1955)

and atypical mycobacteria (Runyon 1959). In three INH resistant human strains all other tests were positive except mice pathogenicity. Though INH resistant strains are more pathogenic to mice (Bloch et al 1955) they produce less extensive lesions than the sensitive ones (Vink et al 1956) and it is not improbable for some of them, not to produce any lesion at all as the above three strains of the present series.

Neutral red reaction was uniformly positive in all the virulent strains and negative in two saprophytic strains. Taking all the four tests into consideration, relative virulence could be established in 93.6 per cent strains. 6.4 per cent strains showing unusual results were human type of tubercle bacilli and all of them were INH resistant. It was found that a combination of the study on the cytochemical reaction and cording effect of mycobacteria is as much effective means of evaluating their virulence as the animal pathogenicity test which is more cumbersome, expensive, time consuming and subject to more variation. This is inspite of the fact that both the cording and cytochemical reaction may also be positive in some non-pathogenic strains. Our observations show that none of these tests is absolute in determining the virulence of mycobacteria and a combination of two or more of them give better evaluation than any single test.

Summary and Conclusions

One hundred and twenty-five strains of mycobacteria freshly isolated from clinical cases of pulmonary tuberculosis were subjected to animal pathogenicity, cording and neutral-red tests in order to establish their relative virulence.

In 77.6 percent strains there was complete agreement with all the three tests. In another 16 percent strains the observed variability in animal pathogenicity and cord forming capacity was similar to that found by other workers with the INH resistant strains.

In another 6.4 per cent strains our findings were rather unusual. These strains were INH resistant, all forming poor quality of cords and three showing negative mice pathogenicity. The probability for such unusual result is explained.

Since all the tests show variation, a better evaluation of virulence can be made by

studying more than one property rather than any single one.

The combined study of cytochemical

reaction and cord formation gives as much information as animal pathogenicity with definite advantage and can be adopted in practice.

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CORTICOSTEROIDS IN THE TREATMENT OF TUBERCULOUS PLEURAL EFFUSION

K.S. GREWAL, R.P. DIXIT AND B. DUTTA,

(*Department of Chest Diseases, Ispat General Hospital, Rourkela.*)

Steroids have been employed in the treatment of tuberculosis in man with the object of modifying the tissue reaction of the body in such a way as to render the bacilli more accessible to the drugs.

As far as is known the steroids have no direct action upon the bacillus. Their action is primarily anti-allergic, anti-inflammatory and anti-toxic. They depress the macrophage activity and the lymphocytic response and inhibit the formation of granulation tissue and fibrous tissue (1). Thus the steroids by themselves should exert a deleterious effect upon the disease. This is confirmed by clinical observations and work in experimental tuberculosis (2), (3), (4).

On the clinical side, the adverse effect of steroids was observed by several workers and the development of active, progressive tuberculosis in patients receiving treatment with steroid hormones for other conditions, was serious. In 1951 the Committee on Medical Research of the American Trudeau Society issued a warning against the use of these hormones without careful preliminary investigations to exclude tubercular disease.

However, Spain and Molomut (2) in 1960 and Hart (5) in 1951 suggested that as the effect of steroids on a tuberculous lesion consisted in damping down the inflammatory response and offering the bacillus a clear field to multiply, the results might be altogether different if the steroids were used in conjunction with effective anti-microbial agents. Since then, about a decade has passed and the steroid hormones have found their place in the treatment of certain types of tubercular disease.

It is well known that hypersensitivity reactions play a predominant role in the pathogenesis of tuberculous pleural effusion. There is evidence (1), (6), that when steroids are given in the acute phase of this condition together with the antimicrobial drugs, the clinical improvement as judged by abolition of fever, increased appetite and gain in weight and fall in erythrocyte sedimentation rate is more rapid. Radiological clearance also occurs more rapidly and

chances of residual pleural thickening with diminution of respiratory function is significantly reduced.

This study was undertaken to compare the results of treatment in cases of tuberculous pleural effusion treated with and without steroids.

Materials and Methods

Cases of tuberculous pleural effusion attending the chest department of this Hospital were divided into three groups according to the following treatment regimens:

Group I: Antimicrobial drugs + Prednisolone

Group II: Antimicrobial drugs

Group III: Antimicrobial drugs + Repeated aspiration.

In all cases antimicrobial drugs were given in dosage of streptomycin 1 gm. daily and I.N.H. 300 mg daily for a period of 4 months followed by P.A.S. 10 gms daily and I.N.H. 300 mgm daily.

Prednisolone in Group I cases was given for a total period of two months. In first 2 weeks, 20 mgms in 4 divided doses was given and subsequently 15, 10 and 5 mgms was given for the following 2-week periods.

Aspiration of fluid from the pleural cavity in Group III cases was done on alternate days and as much fluid was withdrawn at each sitting as could be done without discomfort to the patient.

All cases were admitted to the hospital initially and had hospitalisation for 1½ to 4 months.

At the time of entry every case was given a complete clinical check-up. An X² Ray of the chest was taken and a record of temperature, weight and E.S.R. made.

A diagnostic puncture was done and the fluid subjected to cytological, biochemical and bacteriological examinations.

Chest X² Rays were repeated at 15 days and 1, 3 and 6 month periods. Records of weight, E.S.R. and temperature were also taken at these intervals. As the quantity of fluid present at initial examination has an important bearing on the final result of

treatment, it was decided to study the radiological clearance in the three treatment groups at different time periods in relation to the amount of fluid seen in the first X-Ray.

According to the amount of fluid the cases were divided into five following categories (1) filling of costophrenic angle (2) below the hilum (3) upto the hilum (4.) above the hilum (5) full hemithorax.

Number of cases of different treatment groups belonging to each category were separated out and the radiological clearance rate studied at different time periods, thus giving the picture of radiological clearance not only as a whole group but also in relation to the amount of fluid present. These observations are recorded in table VI.

A close watch was kept for any complications of steroid therapy such as.

- (1) appearance of oedema,
- (2) a state resembling Cushing's syndrome oedema, hypertension, striae, pigmentation, acne,
- (3) Euphoria or depression on withdrawal of drugs,
- (4) Any disturbances of electrolyte balance, and
- (5) Rebound phenomenon, a temporary relapse shortly after withdrawal.

Also, no case with any of the contraindications to the administration of steroids such as diabetes mellitus, elderly patients with arteriosclerotic disease, patients with coronary artery disease or peptic ulceration was included. Only those cases who completed a follow-up of 6 months have been included in this study.

69 cases of tuberculous pleural effusion were treated during the period November 1961 to November 1963. Of these 33 cases were given Group I, 21 cases Group II and 15 cases Group III treatment.

During the period of treatment and observation 8 cases dropped out; 3 of these were from Group I, 2 from Group II and 3 from Group III.

Results of the remaining 61 cases are presented. The numbers in Group I, II, III were 30, 19 and 12 cases respectively.

Results

Age and Sex distribution (Table I): 42 cases were males and 19 females. The

TABLE I
Age and Sex Distribution

Age in Years	Males	Females	Total
0-10	—	—	—
11-20	9	5	14
21-30	24	12	36
31-40	6	2	8
41-50	3	—	3
51-60	—	—	—
61 and above	—	—	—
	42	19	61

maximum incidence in both sexes is in the age group 21-30 years.

Gain in weight (Table II): At 15 days

TABLE II

Gain in weight

Group	15 days	1 month	3 months	6 months
Group I	3-7 lbs (3.5 lbs)	4-11 lbs (5.5 lbs)	7-20 lbs (13 lbs)	7-19 lbs (13 lbs)
Group II	H 2-7 lbs (2.8 lbs)	3-12 lbs (4 lbs)	7-16 lbs (9 lbs)	6-16 lbs (8.5 lbs)
Group III	3-8 lbs (3 lbs)	3-11 lbs (4.2 lbs)	6-18 lbs (9.4 lbs)	7-19 lbs (9 lbs)

Group I cases recorded gain in weight ranging from 3-7 lbs. (average 3.5 lbs). Group II cases recorded 2-7 lbs (average 2.8 lbs) and Group III 3-8 lbs (average 3 lbs).

At 1 month the gain in weight in Group I, II and III was 4-11 lbs (average 5.5 lbs) 3-12 lbs (average 4 lbs) and 3-11 lbs (average 4.2 lbs).

At 3 months the gain in weight in the 3 groups respectively was 7-20 lbs (average 13 lbs), 7-16 lbs (average 9 lbs) and 6-18 lbs (average 9.4 lbs). At 6 months the weight records were practically the same as at 3 months.

(Table III): In Group I, 22 (96%)

TABLE III

Pyrexia

Number of cases apyrexial at 15 days, 1 and months

Group	15 days	1 month	3 months
Group I	29 (96%)	33 (100%)	—
Group II	14 (74%)	19 (100%)	—
Group III	8 (66%)	12 (100%)	—

cases were afebrile at 15 days. In Group II, 14 (74%) cases and in Group III 8 (66%) cases were afebrile at 15 days.

At 1 month all cases in the three groups were afebrile.

Erythrocyte Sedimentation rate: (Table IV)

TABLE IV

Number of cases with normal E.S.R. at 15 days and 1 and 3 months

	15 days	1 month	3 months
Group I	28(93%)	30 (100%)	—
Group II	10 (53%)	16 (84%)	19 (107%)
Group III	6 (50%)	10 (83%)	12 (100%)

At 15 days, 28 (93%) cases of Group I and 10 (53%) and 6 (50%) cases of Group II and III had normal E.S.R.

At 1 month all cases of Group I attained normal E.S.R., while 16 (84%) cases of Group II and 10 (83%) cases of Group III had normal E.S.R.

At 3 months all cases in all groups had normal E.S.R.

Radiological Clearance: (Table V): In Group I, 16 (53%) cases had completely cleared at 15 days. 26 (87%) cases at 1 month and 28 (93%) and 29 (96%) cases at 3rd and 6th month. Only in 1 (3.3%) case a residual shadow of thickened pleura and obliteration of costophrenic angle was seen in this Group at 6 months.

In Group II and III no case showed a completely clear X'Ray picture at 15 days.

In Group II, 5 (26%), 13 (70%) and 14

(74%) cases had completely clear X'Raies at 1, 3 and 6 months. In 5 (26%) cases residual shadows of thickened pleura were present at 6 months.

In Group III, 2 (16%) and 6 (50%) cases had clear X'Raies at 1 and 3 months and 6 (50%) cases had residual shadows at 6 months.

Table VI: Shows the radiological clearance in the three groups at different time

TABLE VI

Number of cases attaining complete radiological clearance at 15 days and 1, 3 and 6 months in different treatment groups in relation to the amount of fluid present in the X'Ray at first examination

Amount of fluid present at first X'Ray	Treatment Group No. of cases	15 days	1 month	3 months	6 months	No. of cases with residual shadows of costophrenic angle & thickened Pleura at 6 months
1. Costophrenic angle filling	I 14	4	—	—	—	—
	II 7	-	3	3	—	1
	III 2	—	2	—	-	—
2. Below the hilum	I 9	3	5	1	—	—
	II 7	—	1	5	1	—
	III 2	—	—	1	—	1
3. Upto the hilum	I 12	6	4	1	1	—
	II 3	—	1	—	—	2
	III 2	-	-	1	-	1
4. Above the hilum	I 12	1	—	—	—	1
	II 1	1	—	—	—	1
	III 4	—	-	1	1	2
5. Full hemithorax	I 13	2	1	-	—	—
	II 1	—	—	—	—	1
	III 2	-	-	—	—	2

TABLE V.

Number of cases with complete radiological clearance at 15 days and 1, 3 and 6 months

15 days	Group I	16	1 month	3 months	28	6 months	Number of cases with residual shadows of thickened pleura at 6 months
Group II			5 (26%)	13 (70%)	14 (74%)		1 (3.3%)
Group III			2 (16%)	6 (50%)	6 (50%)		5 (26%)
							6 (50%)

periods in relation to the amount of fluid seen in the X'Ray at initial entry.

Complications: 1 case developed a small quantity of effusion 2 weeks after the steroids were stopped. Steroids were given for 1 month more and the effusion cleared. Three cases showed a tendency for 'moon facing' which returned to normal 1-2 months after the stoppage of drugs.

Comments

The gain in weight has been more in Group I cases, specially at 3 and 6 months when the average gain has been 13 Ibs in this group, compared to average gains of 9 Ibs and 8.5 Ibs in Group II and 9.4 Ibs and 9 Ibs in Group III. There has been no appreciable difference in Group II and III cases at any stage.

At 15 days all but one case (96%) in Group I were apyrexial; compared to this only 74% and 66% cases in Group II and III were apyrexial. However, at 1 month all cases in the three groups were apyrexial.

Similarly, in return of E.S.R. to normal, there is a marked superiority of results in Group I cases at 15 days. This is maintained at 1 month also, though at 3 months all cases had a normal E.S.R. Thus, as far as the return of E.S.R. and pyrexia to normal are concerned Group I cases show a significant superiority particularly at 15 days and to a lesser extent at 1 month. There are no appreciable differences in Groups II and III.

The superiority of Group I results is particularly more marked where radiological clearance is concerned. At 15 days 53% of cases in Group I had completely clear X'Rays, while none had cleared in the other two groups. At 1 month also while 87% cases in Group I had completely cleared only 26% in Group II and 16% in Group III had cleared. The same trend is seen at 3 and 6 months.

At 6 months the residual shadows of thickened pleura and obliteration of the costophrenic angle were present in 6 (50%) cases of Group III and 5 (26%) cases of Group II while in Group I only 1 case (3.3%) had residual shadows.

When radiological clearance was studied in different treatment groups in relation to the amount of fluid, it was seen (Table VI) that irrespective of the initial quantity of

fluid the results were uniformly good in Group I cases. There were 3 cases of 'full hemithorax' category in Group I and of these 2 cases at 15 days and the third case at 1 month had completely clear X'Rays. There was 1 case of this category in Group II and 2 cases in Group III, none of these attained radiological clearance and all three had thickened pleura at 6 months. The same trend is seen in cases with fluid upto the hilum and above the hilum. In this category of cases the result in Group I are significantly superior to Group II and III.

It is only in cases with fluid filling the costophrenic angle, or reaching below the hilum that group II and III give satisfactory results though even in these the momentum of change is in favour of Group I.

With the newer compounds and the dosage employed in this study, undue fear of steroid treatment complications is unwarranted. Only 4 cases (6.5%) had minor and easily manageable complications. Care, however, should be taken if these cases meet with accidents or require major surgical intervention due to any cause, as there is risk of dangerous fall of blood pressure and sudden collapse. These can be avoided by giving a steroid cover preoperatively and these persons should carry cards indicating that they are receiving steroid therapy.

Summary

61 Cases of tuberculous pleural effusion, on three different treatment regimens, have been studied.

Group I: Antimicrobial drugs + corticosteroid (30 cases). Group II. Antimicrobial drugs (19 cases).

Group III: Antimicrobial drugs-)- Repeated aspiration (12 cases). The comparative results of treatment at 15 days, and 1, 3, 6 months indicate that

- (1) Clinical improvement as judged by abolition of fever, gain in weight and fall in E.S.R. is more rapid in the steroid group.
- (2) Radiological clearance at all stages and particularly at 15 days and 1 month shows a statistically significant difference in favour of the steroid group. This is particularly marked

when the effusions are upto and above the hilum level.

The incidence of shadows of thickened pleura and obliteration of costophrenic angle is significantly lower in the steroid group. The complications due to steroids are few and minor.

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**A CONCURRENT COMPARISON OF INTERMITTENT (TWICE WEEKLY)
ISONIAZID PLUS STREPTOMYCIN AND DAILY ISONIAZID PLUS
PAS IN THE DOMICILIARY TREATMENT OF PULMONARY
TUBERCULOSIS**

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS*

1 Introduction

The domiciliary chemotherapy of tuberculosis conducted from out-patient clinics is widely practised in developing countries. Under such conditions reliance is placed on the cooperativeness of the patients in self-administering their drugs orally, a practice which is known to have serious drawbacks (see review by Fox, 1962). Although fully supervised daily chemotherapy has been conducted by some (Stradling, 1957; Stradling and Poole, 1958; Velu et al., 1961b; Angel et al., 1963), Flynn M.P. this is clearly impracticable as a general policy for developing countries. If, instead, fully supervised chemotherapy could be given *intermittently*, for example, twice a week or even less frequently, it would become more generally applicable. Previous studies at this Centre suggested a rational basis for intermittent chemotherapy. In a comparison of 3 regimens of isoniazid alone with a standard regimen of isoniazid plus PAS (Tuberculosis Chemotherapy Centre, 1960), it was found that a

moderate daily dosage of isoniazid (approximately 9 mg/kg body-weight) was more effective when given in 1 dose than when given in 2 doses. There was evidence that this was because a high peak concentration of isoniazid in the serum played a more important role in the response to treatment than the maintenance of a continuous inhibitory level of the drug (Gangadharam et al., 1961). It was therefore decided to study regimens in which the interval between high doses of isoniazid was extended. It seemed unlikely that the efficacy would be seriously diminished by a limited degree of intermittency, in view of the observation that patients who showed irregularity (on the evidence of urine tests for drug) in taking isoniazid in a large daily dose (approximately 14 mg/kg responded to treatment as well as those who were completely regular (Tuberculosis Chemotherapy Centre, 1963a, 1963b). There is experimental evidence that isoniazid given once weekly in the guinea-pig (Palmer et al., 1956) or the mouse (Bloch, 1961) and streptomycin given every 5 days

*Under the joint auspices of the Indian Council of Medical Research (ICMR), the Madras State Government, the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC). The members of the scientific staff of the Centre with major responsibility for the work reported here are: Dr. Hugh Stott (WHO) Senior Medical Officer; Drs. J.J.Y. Dawson (WHO), S.R. Kamat (ICMR), C.V. Ramakrishnan (ICMR) and S. Velu (Madras Government), Medical Officers; Or. S. Devadatta (ICMR), Assistant Medical Officer; Dr. J.B. Selkon (WHO) succeeded by Dr. E.M. Mackav-Scolay (WHO) in January 1962, and Dr. S.P. Tripathy (ICMR), Bacteriologists; Mr. C. Narayanan Nair (ICMR), Assistant Bacteriologist; Mr. D.V. Krishnamurthy (FCMR), Bio-chemist; Mr. C.V. Jacob (ICMR) and Miss S. Joseph (ICMR), Laboratory Research Assistants; Mr. K.L. Thomas (WHO) succeeded by Mr. P.M. Hinchliffe, (WHO), Laboratory Technician; Mr. K. Ramachandran (ICMR) and Mr. P.R. Somasundaram (ICMR), Statisticians and Mr. B. Janardhanam (ICMR) and Mr. N. Nataraja (ICMR), Senior Assistant Statisticians.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Dr. P.V. Benjamin, Convenor, succeeded in July 1962 by Dr. N.L. Bordia, Dr. J. Frimodt-Moller and Dr. K.S. Sanjivi), the Director of ICMR (Dr. C.G. Pandit), the Director of Medical Services, Madras State (Dr. V.R. Thayyurnmaswamy succeeded in November 1961 by Dr. (Miss) A.B. Marikar, a WHO representative (appointed for each meeting), an MRC representative (appointed for each meeting) and the Senior Medical Officer of the Centre (Dr. Hugh Stott). The joint secretaries are Mr. D. Chakravarti, and Mr. B.S. Verma succeeded by Mr. V.S. Talwar in April 1962. The British Medical Research Council is responsible for advising the WHO on the research in accordance with plans prepared by the Project Committee. Close contact is maintained between this Centre, Dr. P.D. Arcy Hart (MRC Tuberculosis Research Unit), Dr. Wallace Fox (MRC Tuberculosis Research Unit), Dr. Ian Sutherland (MRC Statistical Research Unit) and Dr. D.A. Mitchison (MRC Group for Research on Drug Sensitivity in Tuberculosis).

The great majority of the patients in the present study were referred to the Centre from the Government Tuberculosis Institute, Madras (Director: Dr. M.A. Hamid) and the Corporation Tuberculosis Clinic, Pulianthope (Medical Officer in charge: Dr. V.S. Selvapathy).

in the guinea-pig (Corper and Cohn, 1947) are effective in suppressing the development of tuberculosis. Further, Grumbach et al. (1952) have shown that an intermittent regimen of a combination of streptomycin in a dosage of 7.5 mg/kg body-weight plus isoniazid in a dosage of 150 mg/kg given to mice every 3 days, is as effective in controlling tuberculous infection as a continuous daily regimen of the combination in one-third of the dosage.

In view of the findings in this Centre and the above experimental evidence it was decided to test the effectiveness of a combination of the 2 most potent standard anti-tuberculosis drugs, namely isoniazid and streptomycin, given under supervision, twice weekly, the minimum interval considered to offer substantial practical advantages over & daily regimen. Isoniazid was to be given in a high dosage of approximately 14 mg/kg body-weight and streptomycin in a uniform dose of 1g, which, in view of the light weight of the patients in Madras, is a higher dosage than usual.

The detailed results of a controlled comparison for a year of this supervised intermittent regimen with the standard, unsupervised, daily regimen of isoniazid plus PAS is presented in this report. The bacteriological results at 6 and 9 months have already been reported in a preliminary communication (Tuberculosis Chemotherapy Centre, 1963c).

II. Plan And Conduct of the Study

The patients were drawn from the same area in Madras City as in previous investigations (Tuberculosis Chemotherapy Centre; 1960, 1963a, 1963b). As before nearly all came from the poorest sections of the population and the great majority were referred to the Centre from tuberculosis clinics where they had attended with symptoms. They were admitted on the same criteria as in the earlier investigations. In particular they had bacteriologically confirmed pulmonary tuberculosis, were aged 12 years or more, were judged to be co-operative (that is, were prepared to have 1 year of domiciliary chemotherapy and to attend for subsequent follow-up) and had either received no anti-tuberculosis chemotherapy or had received it for not more than 2 weeks;

Pre-treatment Investigations

The important pre-treatment investigations were :

- (1) A full clinical examination, including the assessment of the general clinical condition, weight (lb), and examination of the urine for albumin and sugar.
- (2) A full-plate postero-anterior chest radiograph and a standard series of tomographic cuts.
- (3) The examination by direct smear and culture of a minimum of 4 sputum specimens; 2 were produced overnight in the home (collection specimens) and 2 were expectorated under supervision at the Centre (supervised spot specimens).
- (4) Tests of sensitivity to isoniazid, streptomycin and PAS on 2 cultures.
- (5) The determination of the rate of inactivation of isoniazid.

Chemo herapeutic Regimens

The two chemotherapeutic regimens studied were an intermittent supervised regimen of isoniazid plus streptomycin given together twice weekly (SHTW), and a standard unsupervised daily regimen of isoniazid plus PAS (PH).

It was decided to use a high dosage of isoniazid in the intermittent regimen in order to achieve high peak serum levels. The dosage selected was known to have little risk of acute toxicity even when given daily (Tuberculosis Chemotherapy Centre, 1963a, 1963b).

The dosage of isoniazid and PAS was graded according to the patient's weight (Table I). The streptomycin was given in a uniform dosage of 1 g to all patients irrespective of weight. For example, the details of the dosage for a patient weighing 100 lb. (45.5 kg) were as follows :

SHTW:

Streptomycin sulphate by intramuscular injection in a dose equivalent to 1 g of streptomycin base plus isoniazid in a single oral dose of 650 mg (as 3 tablets containing 200 mg each and 1 tablet containing 50 mg of isoniazid); both drugs were given together twice weekly, at intervals of 3 and 4 days alternately.

PH:

Isoniazid 200 mg daily plus PAS (sodium salt) 10 g daily; the 2 drugs were given together in 8 cachets (4 in the morning and 4 in the evening), each cachet containing 25 mg of isoniazid and 1.25 g of PAS (sodium salt).

For patients in the SHTW series, the mean daily dosage of streptomycin at the start of treatment was 27.0 mg/kg body-weight (range 18.2-53.7 mg/kg) and the mean initial dosage of isoniazid was 13.9 mg/kg (range 12.5 - 16.1 mg/kg). For patients in the PH series, the mean daily dosage of isoniazid at the start of chemotherapy was 44 mg/kg body-weight (range 3.7 - 6.3 mg/kg) and that of PAS, .22 g/kg (range .18 - .32 g/kg).

Both chemotherapeutic regimens were prescribed for a period of 12 months in the first instance.

Allocation of Chemotherapy

On the basis of the postero-anterior radiograph and the tomographic series, each patient was classified into 1 of the following 3 categories by the Centre's medical staff:

- (1) patients with no definite cavitation;
- (2) patients with cavitation, the diameter of the largest cavity not exceeding 3 cm; and
- (3) patients with cavitation, the diameter of the largest cavity exceeding 3 cm.

The allocation of treatment was done by the statistics department from 3 separate series of sealed envelopes (one for each of the above 3 groups), based on random sampling numbers. Nobody had prior knowledge of the chemotherapy which any individual patient would receive.

The first allocation was made on 21st June, 1961 and the last on the 10th January, 1962 by which date 165 patients had been allocated to treatment, 83 to the SHTW series and 82 to the PH series. General Management

All patients were treated on a domiciliary basis. The SHTW patients attended the Centre twice weekly and received a dose of isoniazid under the direct supervision of the clinic staff followed by an injection of streptomycin. The PH patients attended the Centre once a week for a supply of cachets which were to be taken at home. If any patient failed to attend on the appointed

day, a home visit was paid by the health visitor the next day as a reminder; the management of patients who failed to attend despite the reminder was decided by the Centre's medical staff.

In other respects the management of the patients followed the same lines as in previous investigations at this Centre (Tuberculosis Chemotherapy Centre, 1960, 1963a, 1963b). In brief, 2 visits were usually paid by the health visitors to all patients every month at approximately fortnightly intervals; at 1 visit (which was an unannounced one in the middle of the month) the stock of cachets was counted and a specimen of urine was collected from the PH patients but no routine procedure was undertaken in the case of the SHWT patients. The other visit (at the end of each month) was to deliver a sputum specimen bottle.

Patients who were initially too ill to attend the Centre had their chemotherapy administered at home (SHTW series) or had a stock of cachets delivered to them at home once a week (PH series). As soon as they had improved sufficiently, which was usually at the end of 1 month, they were changed to the ordinary routine of clinic and home visits. The majority of patients were ambulant much of the time.

Assessments Of Progress

Assessments made at monthly intervals after the start of chemotherapy included (a) the weight, (b) a postero-anterior chest radiograph, (c) the examination of 2 collection and 1 supervised spot specimen of sputum by smear and culture and (d) tests of sensitivity to the allocated drugs on 1 positive culture.

Urine Testing For Isoniazid Of PAS

In order to check the self-administration of medicine in the PH patients, a urine specimen was obtained at each weekly visit to the Centre and at the unannounced visit to the home each month and tested for PAS by the ferric chloride test (Simpson, 1956). In the early stages of the study a single urine specimen was collected in about a third of the SHTW patients approximately 24 hours after the supervised administration of their drugs. This was tested by the combined naphthoquinone-mercuric chloride test (Gangadharam et al, 1958).

III. Bacteriological And Assay Procedures

Examination of Sputum Specimens, and Sensitivity Tests

The methods used for examining sputum specimens and for performing sensitivity tests to isoniazid, streptomycin and PAS are similar to those described elsewhere (Tuberculosis Chemotherapy Centre, 1959). In brief, sputum smears were examined by fluorescence microscopy and were graded as 3-plus, 2-plus, 1-plus or negative. Sputum specimens were cultured, after treatment with 4% Na OH for 20 minutes, on Lowenstein-Jensen medium which did not contain potato starch (Jensen, 1955). The cultures were examined weekly for between 8 and 9 weeks and were reported as negative if no growth was present by that time. Sensitivity tests were set up on Lowenstein-Jensen medium slopes containing the concentrations of drug set out below as well as on a drug-free slope as a control. The standard sensitive strain, H37Rv, was also set up with each batch of tests. Sensitivity tests for PAS were set up as recommended by Selkon et al. (1960), using a 1.10 dilution of the standard suspension and employing the 20-colony end-point. The tests were read after 4 weeks' incubation at 37°C. The drug concentrations used were as follows :

Drug	Drug concentration in ug/ml	
	Test strain	H37 Rv
Isoniazid	0.2, 1, 5, 50	0.025, 0.05, 0.1, 0.2, 1
Streptomycin	4, 8, 16, 32, 64	1, 2, 4, 8
Sodium PAS dihydrate	0.5, 1, 2, 4, 8, 16	0.125, 0.25, 0.5, 1, 2

Definitions Of Bacterial Drug Resistance

In the following definitions of resistance "growth" has been defined as 20 colonies or more :

Isoniazid:

- (1) *Pretreatment tests:* Resistance was defined as
 - (a) growth on 1 ug/ml on one culture irrespective of the results on the other culture.
 - (b) growth on 0.2 ug/ml but not on 1 ug/ml followed by growth on 0.2 ug/ml in a repeat test on the same culture, irrespective of the results on the other culture,

or (c) growth on 0.2 ug/ml but not on 1 ug/ml on both cultures, irrespective of the results of repeat tests. (2) *Tests during treatment :* Resistance was defined as growth on 0.2 ug/ml irrespective of the result of the repeat test.

Streptomycin:

- (1) *Pretreatment tests;* Resistance was defined as
 - (a) a resistance ratio (RR) of 8 or more on one culture irrespective of the results on the other culture,
 - (b) an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture, irrespective of the results on the other culture,
 or (c) an RR of 4 on both cultures, irrespective of the results of repeat tests.
- (2) *Tests during treatment;* Resistance was defined as an RR of 8 or more, or an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture.

PAS:

- (1) *Pretreatment tests;* Resistance was defined as;
 - (a) an RR of 8 or more on both cultures,
 - (b) an RR of 8 or more on one culture, and an RR of 4 in the second culture followed by an RR of 4 or more in a repeat test on the same culture,
 or (c) an RR of 4 followed by an RR of 4 more in a repeat test, on both cultures.
- (2) *Tests during treatment:* Resistance was defined as an RR of 8 or more, or an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture.

Serum Isoniazid Assays

The rate of inactivation of isoniazid was determined for each patient before treatment following the method described by Gangad haram et al. (1961). The result will be -reported elsewhere.

IV. The Patients Admitted To Treatment

In all, 165 patients were admitted to treatment, 83 to the SHTW and 82 to the PH series. Of these 15 (4 SHTW, 11 PH) were subsequently found to have been excreting organisms resistant to isoniazid or streptomycin on admission; they have been excluded from the main analysis. There remain 150 patients (79 SHTW, 71 PH) in the main analysis who, on admission to the study, (a) had organisms sensitive to isoniazid and streptomycin, (b) had so far as is known, no previous chemotherapy, or in 8 patients (3 SHTW, 5 PH) up to 2 weeks' chemotherapy and (c) had followed the prescribed regimen for 12 months apart from minor variations, unless chemotherapy was terminated owing to death, tuberculous deterioration, major toxicity or un-cooperativeness.

Only 2 of the 150 patients yielded organisms resistant to PAS on admission. Since both patients were in the SHTW series, they have not been excluded from the main analysis.

Pre-treatment Comparison Between The 2 Series

Of the 79 SHTW patients 58% were males compared with 69% of the 71 PH patients. About half the patients were between the ages of 15 and 34, namely 49% of the SHTW and 51% of the PH series. The distributions of the general condition of the patients on admission were very similar; thus 13% of the SHTW patients and 17% of the PH patients were in good condition, 70% and 65%, respectively, in fair condition and 16% and 18%, respectively, in poor or very poor condition. The 2 series had broadly similar weight distributions (Table 1).

TABLE 1

Dosage of Drugs in Relation to Body-weight

Regimen	Body-weight (lb)	Actual amount of drug given			Dosage in relation to body-weight			Number of patients (on admission)
		Isoniazid (mg)	Streptomycin (g)	PAS (sodium salt) (g)	Isoniazid (mg/kg)	Streptomycin (mg/kg)	PAS (sodium salt) (g/kg)	
SHTW (Twice weekly)	40-49	300	1.0	—	16.7-12.4	55.6-44.6	—	2
	50-59	350	1.0	—	15.6-13.0	44.4-37.2	—	1
	60-69	400	1.0	—	14.8-12.7	37.0-31.7	—	11
	70-79	450	1.0	—	14.2-12.5	31.6-27.8	—	13
	80-89	550	1.0	—	15.2-13.5	27.7-24.6	—	26
	90-99	600	1.0	—	14.7-13.3	24.6-22.6	—	13
	100-109	650	1.0	—	14.4-13.1	22.1-20.1	—	9
	110-119	700	1.0	—	14.1-12.9	20.1-18.5	—	3
	120-129	800	1.0	—	14.7-13.6	18.4-17.0	—	1
PH (Twice daily)	50-59	150	—	7.50	6.7-5.6	—	0.33-0.28	3
	60-69	150	—	7.50	5.6-4.8	—	0.28-0.24	6
	70-79	150	—	7.50	4.7-4.2	—	0.24-0.21	19
	80-89	175	—	8.75	4.8-4.3	—	0.24-0.22	14
	90-99	175	—	8.75	4.3-3.9	—	0.21-0.19	16
	100-109	200	—	10.00	4.4-4.0	—	0.22-0.20	10
	110-119	200	—	10.00	4.0-3.7	—	0.20-0.18	2
	120-129	200	—	10.00	3.7-3.4	—	0.18-0.17	1

The extent of cavitation, the total extent of the radiographic lesion and the number of lung zones involved in disease were assessed as described previously (Tuberculosis Chemotherapy Centre, 1960), from a single full-plate radiograph by an independent assessor (Dr. J. Frimodt-Moller) who was unaware of the treatment series of any patient. Cavitation was present in 95% of the SHTW and 94% of the PH patients, it being extensive or moderate in 62% and 58%, respectively (Table 2). Extensive or gross disease was

TABLE 2

Radiographic and Bacteriological Condition on Admission to Treatment

Condition on admission to treatment	SHTW patients		PH patients	
	No.	%	No.	%
<i>Extent of cavitation:</i>				
Nil	4	5	4	6
Slight	26	33	26	37
Moderate	30	38	30	42
Extensive	19	24	11	15
<i>Total extent of disease:</i>				
Trivial or slight	6	8	1	1
Limited	16	20	22	31
Moderate	35	44	26	37
Extensive or gross	22	28	22	31
<i>Number of lung zones involved in disease:</i>				
1, 2 or 3	41	52	34	48
4, 5 or 6	38	48	37	52
<i>Bacterial content of sputum:</i> (First or only collection specimen)				
Direct smear negative	8	10	7	10
Direct smear positive:				
1-plus (scanty)	18	23	13	18
2-plus (moderate)	41	52	4	62
3-plus (heavy)	12	15	7	10
Total patients	79	100	71	100

present in 28% of the SHTW patients compared with 31% of the PH patients, and more than 3 lung zones were involved in 48% and 52%, respectively.

Considering the bacterial content of the first or only collection specimen of sputum, 67% of SHTW patients had a 2-plus or 3-plus smear compared with 72% of the PH patients; only 10% of patients in each series had a negative smear.

To summarize, the two series of patients had, on the average, similar pretreatment condition.

V. Comparison Of The Response To Treatment In The 2 Treatment Series (Clinical)

Deaths

Three patients died of pulmonary tuberculosis, 1- (SHTW) within 24 hours of admission, 1 (PH) in the first week, and 1 (SHTW) in the sixth month. This last patient yielded negative cultures at 3 and 4 months but she had a serious radiographic deterioration in the fifth month and died in a seriously malnourished state with very extensive disease: unfortunately no culture results were available at 5 months. One other patient (PH), all of whose cultures were negative from the first month, died suddenly from a non-tuberculosis cause (believed to be pulmonary embolism) in the eighth month. Permission for autopsy was refused for all 4 patients.

Premature termination of the originally prescribed chemotherapy due to radiographic deterioration.

If a patient was considered by the Centre's medical staff to have a definite radiographic extension of the disease which had not been present at 1 month, a course of penicillin was given for a minimum of 10 days. If the lesion persisted or showed a further spread the complete radiographic series was shown to an independent assessor. Dr. K.S. Sanjivi, who was unaware of the treatment the patient was receiving. He decided whether or not the extension was sufficiently serious to warrant termination of the prescribed chemotherapy. Two patients (1 SHTW, 1 PH) had their prescribed chemotherapy terminated in the twelfth month for this reason. No patient had treatment terminated for serious clinical deterioration.

Premature termination of the originally prescribed chemotherapy due to toxicity

As in a previous study (Tuberculosis Chemotherapy Centre, 1960) patients whose prescribed chemotherapy was stopped for more than 6 weeks on account of toxicity were classified as having had the chemotherapy terminated for toxicity; this applied to 3 patients (all PH), treatment being terminated in the first, fifth and ninth month, respectively. However a decrease in the dosage of streptomycin because of toxicity (page 175), or the addition of pyridoxine for the treatment of isoniazid toxicity (page 176) to the chemotherapeutic regimen was not regarded as a termination of chemotherapy due to toxicity.

Premature termination of chemotherapy owing to unco-operativeness

Eight patients (7 SHTW, 1 PH) became unco-operative and stopped treatment, 2 in the third, 1 in the seventh, 3 (including the PH patient) in the eighth, 1 in the ninth and 1 in the tenth month.

Presentation of the results for the patients who died, whose chemotherapy was prematurely terminated or who became unco-operative

Patients who died of tuberculosis or whose prescribed chemotherapy was terminated due to deterioration of their disease remain in the totals for the whole year. The patient who died of a non-tuberculous cause has been included up to the time of death and those whose originally prescribed chemotherapy was terminated (for reasons of toxicity or unco-operativeness) have been included up to the time of termination of treatment.

Weight changes

During the 12-month period 84% of 68 SHTW patients and 91% of 66 PH patients assessed gained weight, the average change in weight being a gain of 8.9 lb. (4.0 kg), and 8.1 lb. (3.7 kg), respectively.

Radiographic changes

The radiographic changes were evaluated by an independent assessor, Dr. J. Frimodt-Moller, who was unaware of the treatment which any patient had received. The changes were assessed for the first 6 months and then for the year; the findings are presented in Table 3.

TABLE 3

*Changes in Radiographic Appearances in the 12-month Period**

Period	Treatment series	Total patients †		Improvement				No. change	Termination of prescribed chemotherapy during the period due to deterioration		Tuberculous death No. %							
				Exceptional		Considerable							Moderate		Slight.			
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%					
0-6 months	SHTW	77	100	0	0	0	35	45	32	42	8	10	0	0	0	0	2	3
	PH	69	99		9	29	42	34	49	4	6	1	1	0	0		1	1
0-12 months	SHTW	72	100	3	4	41	57	22	31	2	3	1	1	1	1		2	3
	PH	66	102	2	3	37	56	23	35	1	2	1	2	1	2		1	2

* Two separate assessments on standard radiographs

† Excluding patients who died of a non-tuberculous condition or where chemotherapy was terminated on account of toxicity or non-cooperation.

During the first 6 months, 87% of 77 SHTW patients compared with 91% of 69 PH patients showed moderate or greater improvement. The proportions of patients who showed radiographic deterioration or who died of tuberculosis, were 3% and 1%, respectively. Over the full 12 months 92% of 72 SHTW patients and 94% of 66 PH patients showed moderate or greater im-

provement, and 4% and 3%, respectively, died of tuberculosis or had their chemotherapy terminated for deterioration. Thus, the radiographic progress of the two treatment series was similar.

Changes in cavitation

Table 4 presents the changes in Cavitation

TABLE 4
Changes in Cavitation in the 12-Month Period in Patients with Cavitation on Admission to Treatment @

Extent of cavitation on admission to treatment	Treatment series	Total patients*		Disappearance of cavitation		Cavities smaller or fewer	No change	Cavities larger or more numerous	Termination of prescribed chemotherapy during the period due to deterioration		Tuberculous death
		No.	%	No.	%				No.	%	
Extensive	SHTW	18	101	1	(6)**	16 (89)	0 (0)	0 (0)	0	(0)	1 (6)
	PH	9	101	1	11	7 (78)	0 (0)	1 (11)	0	(0)	0 (0)
Moderate	SHTW	26	100	4	75	19 73	0 0	1 4	1	4	1 4
	PH	29	99	4	14	21 72	2 7	0 0	1	3	1 3
Slight	SHTW	26	100	12	46	13 50	1 4	0 0	0	0	0 0
	PH	25	100	8	32	15 60	2 8	0 0	0	0	0 0
Total patients with Cavitation	SHTW	70	99	17	24	48 69	1 1	1 3	1	3	2 3
	PH	63	101	13	21	43 68	4 6	1 2	1	3	1 2

*Excluding patients whose chemotherapy was terminated on account of toxicity or non-cooperation
**The parentheses indicate percentages based on fewer than 25 observations

or the 12- month period as assessed by the
dependent assessor. Cavitation disappeared
in 24% of 70 SHTW patients compared with
21% of 63 PH patients with initial cavitation
and became less on 69% and 68%, respective-
ly. The progress of the 2 series was also
similar when patients with extensive, mode –
rate or slight cavitation initially were consi-
dered separately.

Five patients (2 SHTW, 3 PH) had no
cavitation; in 1(PH) of them it appeared
at 12 months.

Bacteriological Results

Smear and culture result

The smear and culture result of the first

(or only) collection specimen of sputum at months, 82 percent of 76 SHTW and 72 per each month are shown in Table 5. At 3 cent of 69 PH patients were negative on GUI-

TABLE 5
Presence of Tubercle Bacilli in Single Collection Specimens of Sputum taken from Patients at Monthly Intervals

Months after start of chemotherapy	Treatment series	Total patients@	Termination of prescribed chemotherapy* or tuberculous death	Culture positive		Culture negative**	
				Smear positive	Smear negative	No.	%
0	SHTW	79	0	71	7	1	1
	PH	71	0	63	6	2	3
1	SHTW	78	1	35	23	9	24
	PH	70	1	24	30	15	21
2	SHTW	75	1	15	21	38	51
	PH	69	1	13	16	39	57
3	SHTW	76	1	5	8	62	82
	PH	69	1	4	14	50	72
4	SHTW	72	1	3	9	59	82
	PH	68	1	5	5	57	84
5	SHTW	74	1	2	4	67	91
	PH	64	1	6	2		55
6	SHTW	75	2	3	3	67	89
	PH	67	1	3	4	59	88
9	SHTW	72	2	2	1	67	93
	PH	65	1	2	4	58	89
12	SHTSV	72	3	1	0	68	94
	PH	66	2	3	2	59	89

@The patient who died of a non-tuberculous condition is excluded after his death and patients who had their prescribed chemotherapy terminated on account of toxicity or non-cooperation are excluded thereafter

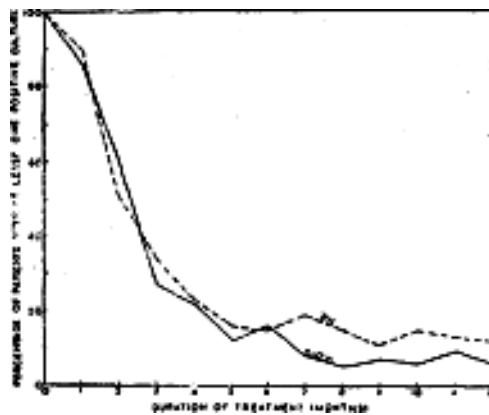
*On account of radiographic deterioration

**Even if the smear was positive

ture, at 6 months the proportions were 89% and 88% at 9 months 93% and 89% and at 12 months 94% and 89% respectively.

Multiple specimens were examined for each patient monthly, the average number of test results per month ranging from 2.6 to 2.9 for patients in both series. The percentage of patients with at least 1 positive culture result is shown for the two series each month, in Figure 1. In both series, there was a rapid decline in the proportion of patients with at least one positive culture, and, in the second six months, this proportion was usually slightly smaller in the SHTW series.

PERCENTAGE OF PATIENTS EACH MONTH WITH AT LEAST ONE POSITIVE CULTURE FROM MULTIPLE BACTERIOLOGICAL SPECIMENS



Sensitivity tests

Isoniazid. The results of isoniazid sensitivity tests are set out in Table 6. (These were not available for 10 (2.6%) of 383 cultures). At three months, a resistant culture was obtained from three (4%) of 76 SHTW patients and from two (3%) of 69 PH patients. The corresponding proportions at six and 12 months were 5% and 10% and 1% and 6% respectively. Considering the proportions of positive cultures that were resistant, three of 20 cultures at three months were resistant in the SHTW series as compared with two of 20 in PH series; at six months the proportions were four of nine and seven of eight cultures, respectively. In

the second six months of treatment, 12 (80%) of 15 cultures in the SHTW series and 41 (84%) of 49 cultures in the PH series were resistant.

Streptomycin. At one month, two (3%) of 78 SHTW patients yielded a streptomycin-resistant culture: this proportion remained practically the same for the rest of the year. In the second six months of treatment 11 of 15 positive cultures tested were resistant, all with resistance ratios of more than eight.

Emergence of resistance in the SHTW patients. Resistance to isoniazid or streptomycin (or both) emerged during treatment in 10 of the 78 SHTW patients. Sputum conversion (that is, three consecutive months of culture negativity) occurred after the emergence of resistance in five patients; in four of these, only a single culture was resistant (two to isoniazid, one to streptomycin and one to both) and the fifth patient had two cultures resistant to isoniazid. A further three patients each yielded an isolated positive culture which was resistant (two to isoniazid and one to both isoniazid and streptomycin) after sputum conversion. All these eight patients were regarded as having had a favourable response to treatment at 12 months (see page 174). Of the remaining two patients, both of whom were classified as having had an unfavourable response to treatment, one had isoniazid resistant cultures at each month from two to 12 months, the cultures at three, five, seven and subsequent months being streptomycin-resistant also. The other patient had isoniazid-resistant cultures at each month from two to 11 months when treatment was terminated owing to radiographic deterioration. The cultures in this patient were streptomycin-resistant at one, three, and five to 11 months. In both patients the majority of cultures were fairly highly resistant to isoniazid (growth, on 5 g/ml) and to streptomycin (RR of more than 8).

Of the remaining 68 patients, who never yielded a resistant culture during treatment, none remained consistently bacteriologically positive with isoniazid-sensitive and/or streptomycin-sensitive organisms throughout the 12 months.

Emergence of resistance in the PH patients. Resistance to isoniazid emerged during treatment in 14 of 69 PH patients. In three, sputum conversion occurred after the emergence of a single isoniazid-resistant culture. A further four patients produced one or more resistant cultures after sputum conversion. One of these produced an isoniazid-resistant culture at 11 months but an isoniazid-sensitive culture at 12 months, and has been classified as having had an unfavourable response to treatment. Of the other three, one produced resistant cultures at five and eight months, another at seven, eight, nine and 10 months and the third at 10, 11 and 12 months; according to definition, only the last patient has been regarded as having had an unfavourable response to treatment. A further seven patients had bacteriologically active disease throughout with resistant cultures first emerging at one, three, four, four, four, four and five months respectively. (All the cultures isolated during treatment from four of these patients were sensitive to PAS).

Of the remaining 55 patients, who never yielded an isoniazid-resistant culture during treatment, only one was persistently bacteriologically positive with isoniazid-sensitive organisms throughout the year; this patient was irregular in taking his drugs, had treatment changed to twice-weekly streptomycin plus isoniazid in the ninth month on account of toxicity to PAS, continued to excrete isoniazid-sensitive organisms for the rest of the year, and has been regarded in this section as having had an unfavourable response to treatment.

Resistance to PAS emerged during treatment in 13 patients. Eight of these yielded a PAS resistant culture on one occasion only and sputum conversion occurred thereafter in five; the other three (including the one who persistently produced isoniazid sensitive cultures) produced the resistant culture at seven, 10 and 12 months, respectively, and had an unfavourable response. A further four patients yielded two resistant cultures each; in three, this was followed by five or more months of culture negativity and the fourth, who produced resistant cultures at six and nine months had bacteriologically active disease at 12 months. Finally, one patient produced resistant cultures at seven, nine and 10 months and had active disease

throughout. (Of the five patients with PAS-resistant strains who had an unfavourable response to treatment, isoniazid resistance preceded PAS resistance in four; the fifth was isoniazid sensitive throughout).

In summary, isoniazid resistance emerged in nine of the 78 SHTW patients and in 14 of the 69 PH patients. However, in only three SHTW and 10 PH patients were two or more resistant cultures produced; two of the former and eight of the latter had an unfavourable response to treatment. Resistance to streptomycin was observed in five SHTW patients; two of these yielded resistant cultures on more than one occasion and both had an unfavourable response. PAS resistance emerged in 13 PH patients and was associated with an unfavourable response in five.

Both patients in the SHTW series who remained consistently bacteriologically positive yielded organisms with fairly high degrees of resistance to isoniazid and streptomycin. Isoniazid resistance emerged in seven of eight patients who remained consistently bacteriologically positive in the PH series, and PAS resistance in four.

RESPONSE TO TREATMENT DURING THE 12 MONTHS

Table 7 presents a classification of all the patients at 12 months, based primarily on the bacteriological response to treatment. In all, 92% of 72 SHTW patients as compared with 80% of 66 PH patients had bacteriologically quiescent disease and 3% and 5%, respectively, had disease of bacteriologically doubtful status which is also regarded as a favourable response to treatment (Velu et al., 1960, 1961a). The proportions of patients with an unfavourable response to treatment, defined as death from tuberculosis, bacteriologically relapsed or active disease at 12 months including termination of prescribed chemotherapy owing to deterioration, were 6% for the SHTW and 15% for the PH series this difference is not statistically significant ($P > 0.1$).

Twelve patients (7 SHTW, 5 PH) are not included in the above totals, eight (7 SHTW, 1 PH) because they had their prescribed

TABLE 6

Results of Isoniazid-Sensitivity tests in the 12-Month Period@

Months after start of chemotherapy	Treatment series	Patients culture positive with sensitivity test results						Total resistant
		Total (on prescribed chemotherapy)	Sensitive	Resistant				
				No growth on 0.2 ug/ml	Growth on 0.2 but not on 1 ug/ml	Growth on 1 but not on 5 ug/ml	Growth no 5 but not on 50 ug/ml	
1	SHTW PH	67 60	67 56	0 4	0 0	0 0	0 0	0 4
2	SHTW PH	45 35	41 34	1 0	2 1	1 0	0 0	4 1
3	SHTW PH	20 20	17 18	1 1	0 1	1 0	1 0	3 2
4	ISHTW PH	14 14	12 8	0 1	0 0	1 2	1 0	2 6
5	SHTW PH	8 9	4 1	1 0	1 5	1 1*	1 2	4 8
6	SHTW PH	9 8	5 1	0 0	0 4	1 2*	3 1	4 7
7	SHTW PH	3 12	1 4	0 0	0 4	1 3	1 1	2 8
8	SHTW PH	2 9	0 1	0 0	0 4	1 2	1 2	2 8
9	SHTW PH	3 6	1 0	0 0	0 1	1 3	1 2	2 6
10	SHTW PH	2 9	0 1	0 0	0 3	1 2	1 3	2 8
11	SHTW PH	4 7	1 0	1 0	0 1	0 2	2 4	3 7
12	SHTW PH	1 6	0 2	0 0	0 0	0 3	1 1	1 4

@A11 patients had strains sensitive to isoniazid before treatment

* No test result on 50 ug/ml

TABLE 7

Classification of all Patients at the end of 12 Months According to their Response to Treatment

Classification at the end of 12 months		Treatment series			
		SHTW		PH	
		No.	%	No.	%
<p><i>Patients with bacteriologically quiescent disease:</i></p> <p>That is, patients whose cultures were all negative for at least the last 3 monthly examinations – i.e., at 10, 11 and 12 months</p>	First month of persisting culture negativity				
	1	9		6	
	2	16		19	
	3	17		7	
	4	7		9	
	5	6		6	
	6	1		1	
	7	7		1	
	8	2		3	
	9	0		1	
10	1		0		
Total		66	92	53	80
<p><i>Patients with disease of bacteriologically doubtful status :</i></p> <p>that is, patients whose culture? were all negative at 3 or more consecutive monthly examinations but who produced a single positive culture at 1 the last 3 monthly examinations— i.e., at 10, 11 or 12 months</p>		2	3	3	5
Total patients with favourable response		68	94	56	85
<p><i>Patients with bacteriologically relapsed disease :</i></p> <p>that is, patients whose cultures were all negative at 3 or more consecutive monthly examinations, but who produced 2 or more positive cultures in the last 3 monthly examinations— i.e., at 10, 11 and 12 months</p>		0	0	3	5
<p><i>Patients with bacteriologically active disease :</i></p> <p>that is, (a) patients whose cultures were never all negative at 3 consecutive monthly examinations or (b) patients who deteriorated and had their prescribed chemotherapy terminated</p>		1	1	5	8
Tuberculous deaths		1	1	1	2
Total patients with unfavourable response		2	3	10	15
Total		72	100	66	100
Patients who became uncooperative and stopped treatment		7	-	1	-
Patients who had their prescribed chemotherapy terminated on account of toxicity		0		3	-
Non-tuberculous death		0		1	-
All patients		79.	—	71	—

chemotherapy terminated on account of toxicity, 1 (PH) because he died from a non-tuberculous cause.

Four of the 7 unco-operative SHTW patients stopped treatment in the third, eighth, ninth and tenth months, after 1, 6, 4 and 4 months, respectively, of consecutive culture negativity. One had cultures examined at 10, 11 and 12 months, a second at 11 and 12 months, and the other 2 at 12 months. All were culture-negative and consequently the four patients were regarded as having had a favourable response to treatment. Two others had an unfavourable response to treatment, one stopped treatment in the seventh month after 6 months of smear and culture negativity and produced two positive cultures (isoniazid-resistant, streptomycin-sensitive) at 12 months. The other, who had stopped treatment in the third month after one month of culture negativity, was examined at seven months when he produced one positive culture (sensitive to both isoniazid and streptomycin); he subsequently died of pulmonary tuberculosis in the eleventh month. The seventh patient stopped treatment in the eighth month after five consecutive months of culture negativity; she refused to attend the Centre subsequently for examination and it was therefore not possible to assess the status of her disease at 12 months. The unco-operative PH patient, who had been persistently sputum positive with isoniazid resistant organisms, stopped treatment in the eighth month; at 10 and 11 months, he produced isoniazid-resistant strains and has been regarded as having had an unfavourable response. If the seven unco-operative patients (six SHTW, one PH) whose response could be assessed are taken into consideration in assessing the therapeutic efficacy of the two regimens, the proportions with favourable response became 92% of 78 SHTW patients and 84% of 67 PH patients (PIS 0.2).

Three patients (all PH) had their originally prescribed chemotherapy terminated on account of toxicity, one in the first month, one (culture negative at four months) in the fifth month and one, who had been persistently sputum positive on smear and culture with isoniazid-sensitive strains, in the ninth. One patient (PH), who had consistently negative cultures from the first to the seventh

month, died from a non-tuberculous cause in the eighth month.

VI. Response To Treatment Related To Various Factors On Admission To Treatment

Table 8 relates factors in the pretreatment condition to the frequency of unfavourable response to treatment (defined on page 196). Of 44 SHTW patients with extensive or moderate cavitation 9% had an unfavourable response compared with none of 28 with slight or no cavitation; the corresponding proportions for PH patients were 24% of 38 and 4% of 28. Of 21 SHTW patients who had gross or extensive disease 10% showed an unfavourable response compared with 4% of 51 with less extensive disease; the corresponding proportions for PH patients were 40% of 20 and 4% of 46. Of 36 SHTW patients with four or more lung zones involved in disease 6% had an unfavourable response compared with 6% of 36 with fewer zones involved, the corresponding figures for PH patients were 29% of 34 compared with none of 32. Regarding the bacterial content of the sputum 6% of 48 SHTW patients with 3-plus or 2-plus smears showed an unfavourable response compared with 4% of 24 with 1-plus or negative smears, and among PH patients 15% of 47 compared with 16% of 19, respectively.

In Summary, there was some evidence from both series that an unfavourable response to treatment occurred more frequently in patients with larger radiographic lesions than in patients with larger radiographic lesions than in patients with relatively small lesions. However, the differences were significant only in PH series in respect of total extent of disease and the number of lung zones involved in disease (PIS 0.001).

VII Toxicity And Other Complications Drug Toxicity

Of the 150 patients in the main analysis 2 (1 SHTW, 1 PH) who died within a week of starting treatment, have been excluded from the analysis of drug toxicity as they were observed for so short a period. There remains 78 SHTW and 70 PH patients.

Streptomycin

Complaints of giddiness were used to assess the incidence of streptomycin ototoxicity. Only spontaneous complaints were recorded; in order to prevent the patients and nursing staff from becoming unduly conscious about the occurrence of symptoms

and signs of toxicity, it being the policy not to interrogate the patients to elicit symptoms. In the present study, giddiness occurred $\frac{1}{2}$ an hour to 2 hours after the injection and was normally short lasting, rarely persisting overnight. Spontaneous complaints of giddiness were

TABLE 8

*Response to Treatment Related to Various Factors on Admission to Treatment**

Condition on admission to treatment	SHTW series		PH series	
	Total patients	Unfavourable response †	Total patients	Unfavourable response †
<i>Extent of cavitation:</i>				
Extensive	18	1	9	3
Moderate	26	3	29	6
Slight	26	0	25	1
Nil	2	0	3	0
<i>Total extent of disease:</i>				
Gross or extensive	21	2	0	8
Moderate or limited	46	2	45	2
Slight or trivial	5	0	1	0
<i>Number of lung zones:</i>				
6, SOT 4	36	2	34	10
3, 2 or 1	36	2	32	0
<i>Bacterial content of sputum:</i>				
(Direct smear grade on first or only collection specimen)				
3-plus	10	1	5	0
2-plus	38	2	42	7
1-plus	17	1	13	3
Negative	7	0	6	0
Total patients	72	4	66	10

*Excluding the patient who died of a non-tuberculous condition and the patients who had their prescribed chemotherapy terminated on account of toxicity or non-co-operation.

† For definition, see text (page 13)

recorded at some time during the year in 27 (35%) of 78 SHTW patients—in 17 on 1 occasion, and for 10 on more than 1 occasion (namely, twice in 5, 3 times in 3, 4 times in

(1 and 5 times in 1). Of the 10 patients who complained more than once, five had their dosage of streptomycin reduced to approximately 15 mg/kg body-weight, three of them

for the rest of the year and two for only two and four weeks, respectively; giddiness was complained of subsequently by three on only one occasion and by one on two occasions. Of the 17 patients who complained on a Single occasion five did so in the first three months, one in the second three months and 11 in the last six months. Of the 10 patients who complained on more than one occasion, the numbers who complained for the first time in the corresponding periods were four, four and two, respectively.

It is uncertain how often the complaints of giddiness were due to streptomycin toxicity as giddiness was also noted in eight (11%) of the 70 PH patients even though it was less likely to have been recorded in them because it is not a recognized toxic manifestation of therapy with PAS plus isoniazid.

Hypersensitivity reactions to streptomycin were not encountered.

Isoniazid

Two (3%) of the 78 SHTW patients and none of 70 PH patients developed toxic reactions attributed to isoniazid, 1 had convulsions a few hours after the administration of chemotherapy on 2 occasions- namely, in the first and six weeks, and these did not recur after pyridoxine in a dosage of 6 mg twice weekly was added to the patient's chemotherapy. The other patient developed peripheral neuropathy in the second month; pyridoxine in a dosage of 6 mg twice weekly was added to the patient's chemotherapy with subsequent improvement. In both, the SHTW regimen was continued.

PAS

Three of the 70 PH patients developed cutaneous hypersensitivity reactions to PAS, 1 in the first and 2 in the second month of treatment. Treatment had to be terminated in these patients in the first, fifth and ninth month, respectively, as the reactions could not be controlled in spite of attempts at desensitization under cover of corticosteroids.

As in earlier studies (Tuberculosis Chemotherapy Centre, 1959, 1960) gastro-intestinal side-effects were unimportant and it was not necessary to reduce the dosage of the drug in any patient.

In summary, giddiness was a common complaint and occurred in 35% of the

patients in the SHTW series and 1-1% of the patients in the PH series; however, a reduction of streptomycin dosage became necessary only in five SHTW patients, isoniazid toxicity occurred in two SHTW patients and was treated successfully with a small dosage of pyridoxine PAS hypersensitivity led to termination of chemotherapy in three PH patients.

Unco-operative Patients

Seven SHTW patients became unco-operative and stopped treatment, 2 in the third, 1 in the seventh, 2 in the eighth, 1 in the ninth and 1 in the tenth month. One, who had severe asthma, stopped because he was disappointed that his treatment was not controlling his asthmatic attacks; a second who was an alcoholic, spent a term in prison and refused to attend the Centre after his release. Four others (including 1 alcoholic) complained of giddiness (on 4, 2, 1 and 1 occasions), the dosage of streptomycin being reduced in 1, and streptomycin toxicity may have been a contributing factor in these 4. The seventh patient stopped treatment for no apparent reason whatsoever. One PH patient, who was an alcoholic, became unco-operative and stopped treatment in the eighth month.

Hospital And Sanatorium Admissions

Two patients were admitted to sanatorium on account of pulmonary tuberculosis. One (SHTW) died of tuberculosis (in the sixth month) the day after admission and the other (PH) stayed there for 43 weeks for a pyo-pneumothorax with a broncho-pleural fistula. In-patient treatment for non tuberculous conditions was given to 4 SHTW patients for 3, 5, 5 and 27 weeks, respectively, and 5 PH patients for 1, 2, 2, 5 and 8 weeks.

VIII. Regularity Of Administration Of Chemotherapy

Missed or late attendances in the SHTW series

As stated earlier it was a rule that patients should attend the Centre for their treatment. However, chemotherapy was given in the home on 148 occasions to 13 patients who were too ill to attend the Centre. To discourage the rest of the patients

from defaulting deliberately in order to obtain treatment at home, chemotherapy was very seldom given to them in the home—namely, to 3 patients on a total of 4 occasions.

During the year each patient was scheduled to attend on 104 occasions for the supervised administration of chemotherapy. Early attendances did not cause any extra work to the Centre's staff, but each late or missed attendance entailed 1, 2 or 3 additional home visits.

An analysis was undertaken to study the regularity with which the patients attended the Centre for treatment. In brief, 6335 (87.0%) of the 7279 scheduled attendances were made on the appointed day, 8.3% were missed altogether and on 4.7% of occasions, the patients attended 1 to 3 days late. The detailed findings are presented in Table 9.

TABLE 9

Regularity of Administration of Chemotherapy to the SHTW Patients as Assessed by Missed or Late Attendances for Treatment

Percentage of attendances missed*	Patients**		Of these, number of patients who attended late	Total number of late attendances
	No.	%		
0	7	9	2	5
1-4	25	32	18	67
5-9	20	26	18	81
10-14	6	8	6	53
15-24	12	75	12	79
25 or more	8	10	7	90
Total	78	100	63	379

* Excluding periods in hospital or sana onum. For patients who died of, tuberculosis or whose chemotherapy was terminated on account of deterioration or nonco-operation, the percentage is based on attendance, up to the time of death or termination.

** Excluding 1 patient who died within 24 hours of admission.

It will be seen that 7 (10%) patients received all the prescribed chemotherapy during the year, 44 (62%) patients failed to receive chemotherapy on 1-9% of occasions, 15 (21%) on 10-24% of occasions and 7 (25) on 25%

or more occasions.

Patients who were frequently non-attenders also attended late more frequently; thus of 7 patients who never missed an attendance only 2 attended late on 1 or more occasions during the year compared with 18 of 25 who missed 1-4% of attendances, 17 of 19 who missed 5-9% and 20 who missed 10% or more.

An analysis (not tabulated here) was undertaken to study whether there were any differences in the regularity of attendance during the course of the year. In the first 3 months of treatment, 46% of 71 patients attended on the appointed day on all occasions compared with 23% of 69 in the second 3 months, 28% of 69 in the third, and 22% of 68 in the last 3 months of the year of treatment. The proportions who failed to attend on 25% or more occasions during each 3-monthly period were 4%, 13%, 19% and 31%, respectively. Thus there is evidence of an association between irregularity and length of treatment.

Seven patients who discharged themselves from treatment during the year have been excluded from the above analyses. Six missed 15% or more of their scheduled attendances compared with 14 of 71 co-operative patients, a difference which attains statistical significance ($P < 0.01$). Thus the unco-operative patients were more irregular even before they stopped treatment.

Supervision of the administration of isoniazid in the SHTW series

Since it is known that pills may be expectorated even when given under supervision (Gilroy, 1952), it was desirable to obtain confirmation that isoniazid had been swallowed. For this purpose urine specimens obtained at home visits were tested for isoniazid (Gangadharam et al., 1958), using a test for which a negative result indicates, in a large proportion of patients, that no drug has been taken for at least 24 hours previously (Tuberculosis Chemotherapy Centre, 1963). Specimens of urine collected from 28 SHTW patients all gave positive results 24 hours after a dose; 15 of 16 further specimens collected at 24 hours from 9 of these patients were also positive.

Urine test results in the PH series

The regularity of self-administration of chemotherapy in the PH series was assessed by testing, for the presence of PAS, urine specimens obtained at the weekly routine visits to the Centre. A negative urine test result means that no PAS has been taken for 14 hours, so that the equivalent of at least a day's supply of medicine has, in all probability, been missed (Tuberculosis Chemotherapy Centre, 1960). It is likely that the degree of irregularity has been underestimated by using the results of clinic urine specimens, as the fact that a visit was due may have acted as a reminder to take the drug; also many patients knew that the specimens were tested for drug. (The results of tests on urine specimens at surprise visits to the home, though useful for supervision, have not been presented because ill patients are more likely to be at home and more frequent visits are often requested by the doctors for patients whose test results are negative.)

The average number of clinic urine tests per month per patients was 3.8. From Table 10 it will be seen that 28% of the 68 patients

had no negative urine test results during the year, 31% had 1-9% negative results, 22% had 10-24%, and 19% had 25% or more negative results. The proportions of patients who had no negative test results during the 4-3 monthly periods were 54% of 68, 66% of 67, 60% of 65 and 47% of 64, respectively, and of those who had negative test results on 25% or more occasions were 16%, 19%, 18% and 23..., respectively. Thus, there was no evidence of an association between duration of treatment and irregularity. The PH patient who became unco-operative and discontinued treatment had 15% of his test results negative.

Response To Treatment In Relation To The Regularity Of Administration Of Chemotherapy SHTW series

Of the 3 SHTW patients who survived more than 1 month and had an unfavourable response, 1 who had his chemotherapy terminated for deterioration in the eleventh month attended on all of 96 occasions, the second who had active disease at 1 year missed 8 of 104 attendances, and the third who died in the fifth month missed 1 of 36 attendances. Of the 68 patients who had a favourable response, 7 (10%) missed 20% or more of their scheduled attendances.

TABLE 10

*Regularity of Self Administration of Chemotherapy in PH Patients as Assessed by Tests on Clinic Urine specimens**

Percentage of urine test results which were negative**	No.	%
0	19	28
1-4	15	22
5-9	6	9
10-14	7	10
15-24	9	13
25-34	5	7
35 or more	8	12
Total	69	101

* Excluding 1 patient who had his prescribed chemotherapy terminated on account of toxicity and 1 patient who died of tuberculosis, both in the first month.

** For patients who, after the first month, died or had a termination of chemotherapy for deterioration, toxicity or non-cooperation, the percentage is based on the test results up to the time of death or termination.

PH series

Analyses not presented here showed that there was no association between irregularity in self-administration of chemotherapy, either in the first 3 months or over the whole year, and response to treatment; thus three 16% of 19 patients who had no negative urine test results had an favourable response compared with two 10% of 21 with 1-9% negative urine test results, and four 16% of 25 patients with 10% or more negative urine test results.

IX. Patients With Resistant Organisms On Admission To Study

Fifteen patients (4 SHTW, 11 PH), all of whom received the allocated regimen, were excluded from the main analysis because they had resistant organisms at the start of treatment, 7 to isoniazid, 5 to streptomycin and 3 to both drugs. These patients were interrogated again during the course of treatment, as their relations with the Centre's staff

became more firmly established, to discover whether they had concealed having received previous chemotherapy; 4 (3 isoniazid-resistant, 1 resistant to both drugs) admitted to previous chemotherapy. It is presumed that the remaining 11 patients (4 isoniazid-resistant, 5 streptomycin-resistant and 2 isoniazid- and streptomycin-resistant) had been infected with resistant organisms.

All 4 patients (1 SHTW, 3 PH) with acquired isoniazid resistance had an unfavourable response to treatment. The detailed results of sensitivity tests to isoniazid and streptomycin on 2 pretreatment cultures are set out in Table 11. Of the 6 patients (2 SHTW, 4 PH) with primary isoniazid resistance, 2 (1 SHTW, 1 PH) had a favourable response to treatment and the remaining 4 had an unfavourable response.

There was one SHTW patient with primary streptomycin-resistant but isoniazid-sensitive strains, and he had an unfavourable response to treatment. The detailed results of pretreatment sensitivity tests are set out for those seven patients in the lower part of Table 11.

According to the definitions given only two patients (both SHTW) yielded organisms resistant to PAS on admission to treatment. These patients were included in the main analysis. A less stringent definition of resistance, similar to that adopted in other studies (East African/British Medical Research Council, 1959, 1960a, 1960b, 1963), is as follows: an RR of 8 or more on one pretreatment culture, or an RR of 4 followed by an RR of 4 or more in a repeat test on the same culture, or an RR of 4 on both cultures irrespective of the results of repeat tests. Using this definition, the organisms from 17 patients (13 SHTW, four PH) would be considered resistant (Of these, only one patient (SHTW), whose organisms were also resistant to isoniazid on admission, has been excluded from the main analysis). For reasons to be reported elsewhere, this definition probably overestimates the prevalence of PAS resistance. Of the four PH patients with pretreatment PAS resistance (as defined above) three had a favourable response and the fourth had bacteriologically active disease at 12 months.

X. Discussion

In the chemotherapy of pulmonary tuberculosis it is standard practice to give 2 or more drugs in 1 or more doses daily; the drugs are normally self-administered and irregularity of drug taking, sometimes of a serious degree, is common. Supervised administration of the drugs could overcome this disadvantage but would only be practical in developing countries if treatment could be given intermittently—say, twice a week or less frequently. Such intermittent chemotherapy might have additional advantages over daily treatment in being more economical and probably less toxic (and therefore more acceptable) to the patients.

Several forms of intermittent chemotherapy in the treatment of pulmonary tuberculosis have been reported in the literature. Regimens consisting of 1 drug (isoniazid or PAS) given daily plus another (usually streptomycin) given intermittently on 2 or 3 days in a week have been investigated and are no longer regarded as adequate by most authorities (Medical Research Council, 1955; Crofton, 1960; McDermott, 1960; Canetti, 1962). Regimens in which both drugs are given intermittently has been used as a continuation treatment after a period of daily drug therapy; thus, intermittent streptomycin plus isoniazid, both drugs being given together every other day, has been used with good results after an initial period of 1 to 3 months of daily combined chemotherapy by Mackay-Dick (1954, 1959), Hutton et al. (1956), Todd et al. (1956) and Bade et al. (1959). There have been a few reports of intermittent chemotherapy, from the start of treatment. Fridodt-Moller et al. (1953) in a controlled trial compared isoniazid alone every fourth day with daily isoniazid given as a quarter of the intermittent dosage, and found similar radiographic responses in the 2 series at 12 weeks. Holmes et al. (1962) treated 29 patients having far advanced disease with a large dose of isoniazid alone, given once a week for periods of up to 3 months, but found that only 2 patients became, culture negative. Schaefer (1955) reported on 15 American-Indian patients treated with an in-

TABLE 11

Response to Treatment Related to Sensitivity Test Results on Admission in Patients with Acquired or Primary Resistance to Isoniazid or/and Streptomycin

	Serial number	Treatment	Sensitivity on admission				Response to treatment
			MTC of isoniazid (ug/ml) on 2 cultures		Resistance ratio to streptomycin on 2 cultures		
Acquired resistance	97	SHTW	50	>50	0.5	0.5	Unfavourable*
	32	PH	>50	>50	2	1	Unfavourable
	41	PH	50	50	0.5	1	Unfavourable
	163	PH	5	5	8	4, 1	Unfavourable
Primary resistance	94	SHTW	>50	>50	0.5	1	Unfavourable
	33	SHTW	5	50	1	0.5	Favourable**
	113	SHTW	1.02	0.05	4, 2	4, 2	Unfavourable
	124	PH	1, 1	1, 1	1	0:5	Unfavourable
	141	PH	>50	0.05	0.6	2 8	Unfavourable
	63	PH	1, 1	1, 1	8		Unfavourable
	87	PH	50	50	>8	>8	Favourable
	7	PH	0.1	0.2	>16	1	Favourable
	27	PH	0.1	0.2	4, 1	4, 1	Favourable
	151	PH	0.1	0.2	>8	>8	Favourable
	157	PH	0.1	0.2	8	8	Favourable

* Tuberculous death or bacteriologically active disease at 12 months including change of chemotherapy for persistent sputum positivity. ** Bacteriologically quiescent disease or disease of doubtful status at 12 months.

tramuscular injection of streptomycin plus isonicotinylic acid hydrazide-sulphate every 3 days. Of 9 patients who were culture positive on admission, 3 were culture negative at 4 months; while at 8 months, all of 5 patients examined were culture negative. Katz et al. (1954) and Chambers et al. (1955) reported on a small group of patients treated with streptomycin 2 g plus isoniazid 500 mg twice weekly; They concluded that the response in these patients was inferior to earlier in daily isoniazid

plus twice-weekly streptomycin. Tyrrell (1956) gave newly diagnosed patients streptomycin 1 g plus isoniazid 400 mg on the same day twice weekly, half being treated in hospital and half as ambulatory out-patients. At 6 months sputum conversion had occurred in 78% of 45 in-patients and in 80% of 46 out-patients.

Efficacy

The present report confirms the conclusions based on interim findings which were

published in a preliminary communication (Tuberculosis Chemotherapy Centre, 1963c). Thus, streptomycin plus high-dosage isoniazid, both drugs being given together twice a week under supervision (SHTW regimen), has proved to be successful in the treatment of newly-diagnosed, far advanced, bacteriologically positive pulmonary tuberculosis, and at least as effective as a standard oral two-drug regimen of PAS plus isoniazid prescribed for self-administration daily (PH regimen). Thus, at one year, 94% of 72 SHTW patients compared with 85% of 66 PH patients had bacteriologically quiescent disease (including disease of bacteriologically doubtful status) and 92% and 94%, respectively, showed moderate or greater radiographic improvement.

It is of interest to compare the findings in this study with those obtained by the Medical Research Council (1955). In the latter, streptomycin was given intermittently in a dose of 1 g twice a week (about 18 mg/kg body-weight) and isoniazid daily in a dosage of 200 mg. Thus, the total weekly dosage of isoniazid and streptomycin was approximately the same in the both studies although the individual doses in the present study was much higher in the case of isoniazid (650 mg) and, because of the light weight of the Indian patients, relatively higher for streptomycin (27 mg/kg body-weight). Considering the results at three months, 98 (74%) of 132 patients in the Medical Research Council study yielded a negative culture compared with 62 (82%) of 76 SHTW patients in the present study. Further, 12 (9%) patients in the former compared with only three (4%) in the latter developed resistance to isoniazid by this time. The better results in the present study may be due to the high dose of isoniazid, and perhaps the relatively high dosage of streptomycin, rather than to the effect of giving *both* drugs together intermittently. The findings of Gangadharam et al. (1961b) this high peak serum concentrations of isoniazid play a more important role in the response to treatment than the maintenance of a continuous inhibitory level of isoniazid lend support to such an inference. *Toxicity*

Isoniazid toxicity occurred in two of 78

SHTW patients (convulsions in one and peripheral neuropathy in the other) as compared with none of 70 PH patients. Both patients were treated successfully with 6 mg of pyridoxine twice weekly without reducing the dosage of isoniazid.

With regard to toxic reactions to the drug used with isoniazid, spontaneous complaints of giddiness were made by 27 (35%) of 78 SHTW patients; the giddiness, which usually occurred half an hour to two hours after the injection, was mild and of short duration. Further, it is unlikely that the complaints were always due to streptomycin as similar complaints were made by eight (11%) of the 70 PH patients, in whom they were less likely to have been recorded. None of the SHTW patients had chemotherapy terminated on account of toxicity, but for five who complained of giddiness, the dosage of streptomycin was reduced to approximately 15 mg/kg body-weight, for three of them for the rest of the year and for two for a short period only. In contrast, three (4%) of the 70 PH patients had chemotherapy terminated on account of hypersensitivity reactions to PAS; other manifestations of PAS toxicity among patients in this series, were unimportant.

It is of interest to compare to incidence of isoniazid toxicity in this study with that in patients in our earlier studies who did not receive any effective prophylactic supplement. Of 60 patients in the earlier studies who received approximately 14 mg/kg body-weight of isoniazid *daily*, 18 (30%) developed isoniazid toxicity (Tuberculosis Chemotherapy Centre, 1936b) as compared with only two (3%) of those who received the same dosage *twice weekly* in the present study; on the other hand, only one of 440 patients who received isoniazid (either alone or in combination with sodium PAS) in a large total weekly dosage than in the present study—namely, 4 to 6 mg/kg *a day* (Tuberculosis Chemotherapy Centre, 1959, 1960 and the present report)—developed toxicity. There is a similar finding in respect of streptomycin toxicity; thus, of 69 patients who received a uniform dosage of 1 g of streptomycin *daily* in an earlier study (Velu et al., 1964), 24 (35%) had to have the dosage reduced to approximately 15 mg/kg body-weight as compared with five (6%) of 78

patients who received the same dosage *twice weekly* in the present study, and four (6%) had to have their treatment terminated on account of toxicity in the earlier study as compared with none in the present study. Thus, there has apparently been a considerable reduction in the incidence of toxic reactions, both to isoniazid to streptomycin, by reducing the frequency of drug-administration from daily to twice weekly (keeping the dose the same).

It is likely that even the small amount of isoniazid toxicity occurring with the intermittent regimen can be prevented by giving 6 mg of pyridoxine twice weekly, since it has been shown that, when given daily in this dosage with 14 mg/kg of isoniazid daily, pyridoxine prevents peripheral neuropathy (Tuberculosis Chemotherapy Centre, 1963b); furthermore, both patients who showed isoniazid toxicity in the present study responded to 6 mg of pyridoxine given twice weekly. The interpretation of the findings on streptomycin toxicity is less clear and special attention is therefore being paid in a current study to the assessment and prevention of such toxicity.

Co-operation

With regard to the co-operation obtained in the two series, seven SHTW patients became so uncooperative as to stop treatment against medical advice. (In four of these, streptomycin toxicity might have been a contributory factor.) As might be expected, these patients were more irregular, even before they stopped treatment, than the 71 who remained on their prescribed chemotherapy. The latter patients attended on the appointed day or earlier on 87% of the occasions, were late by one day or more on 5% of the occasions and missed an attendance altogether on 8% of the occasions. The late and missed attendances, which caused extra work for the Centre's staff, became more frequent towards the end of treatment; thus the proportion of patients who, on 25% or more of the occasions, attended after the appointed day or did not attend at all in each of the four quarters of the year were 4%, 13%, 19% and 31%, respectively. Of the PH patients, only one became so uncooperative as to stop treatment; however, 72% of the remainder were

found to be irregular in taking their drugs on one or more occasions, as assessed by urine test results.

It should be remembered that the SHTW patients had to attend the Centre *twice* a week *and* receive an injection of streptomycin; thus they came under the special attention of the Centre's staff every time they missed a scheduled injection; on the other hand, the PH patients had to attend only *once* a week for a supply of the drug, and it would thus have been easy for them to omit doses without the Centre's staff necessarily becoming aware of it. It is therefore difficult to compare the acceptability of the supervised intermittent regimen and the unsupervised daily regimen; however, despite the irregularities observed, both regimens proved sufficiently robust to achieve high rates of therapeutic success.

Conclusion

Summarizing the findings, the SHTW regimen was therapeutically effective; the incidence of temporary giddiness was rather high but this appeared to have no long-term importance or lasting effects, nor did it appear unduly to affect the co-operation of the patients. However, because of the uncertain significance of the complaints of giddiness in the present study, special attention is being paid in a current trial to investigating the side-effects and the acceptability of intermittent regimens which include streptomycin injections.

The success of intermittent chemotherapy in this trial has suggested a new method of treatment and possibly of the control of tuberculosis in developing countries—namely, changing the regimen from the present daily self-administration to intermittent and fully supervised administration. Although the twice-weekly regimen in this study has been found to be successful, a regimen with a smaller dosage of streptomycin and with longer intervals between the doses would offer still further advantages; it might be not only less toxic and more acceptable to the patients, thus leading to their greater co-operation, but also more economical and easier to apply in mass treatment. Further studies along these lines are at present in progress at the Centre.

XI. SUMMARY

1. One hundred and sixty-five South Indian patients with pulmonary tuberculosis were allocated by a random procedure to ambulatory out-patient treatment with streptomycin plus isoniazid given together *under supervision twice weekly* (SHTW series, 83 patients) or to a standard unsupervised regimen of PAS plus isoniazid for daily self-administration (PH series, 82 patients).

2. The dosages of the drugs for patients weighing 100 lb. (45.5 kg) were 1 g. Streptomycin plus 650 mg. of isoniazid in a single dose for the SHTW regimen and 10 g. of PAS (sodium) plus 200 mg of isoniazid in two divided doses for the PH regimen.

The mean initial dosages were:

SHTW series :

Streptomycin	27.0 mg/kg body-weight
	(range 18.2-53.7 mg/kg)
Isoniazid	13.9 mg/kg body-weight
	(range 12.5-16.1 mg/kg)

PH series:

PAS	0.22 g/kg body-weight
	(range 0.18-0.32 g/kg)
Isoniazid	4.4 mg/kg body-weight
	(range 3.7-6.3 mg/kg)

3. Fifteen patients (4 SHTW, 11 PH) were excluded from the main analysis because they had organisms resistant on admission to the study. There remained 79 SHTW and 71 PH patients in the main analysis who (a) had, on admission, organisms sensitive to isoniazid and streptomycin, (b) had had no previous chemotherapy apart from eight who had had up to two weeks' chemotherapy and (c) followed the allocated regimen for 12 months, apart from minor variations, unless it was terminated due to death, deterioration, toxicity or non-co-operation.

4. The clinical, radiographic and bacteri-

ological condition of the patients in the 2 series was similar at the time of admission to treatment.

5. During the year there were 4 deaths, 3 (2 SHTW, 1 PH) from pulmonary tuberculosis and 1 (PH) from a non-tuberculous condition; serious radiographic deterioration necessitating termination of chemotherapy occurred in 1 patient in each series.

6. At 1 year, 94% of 72 SHTW and 85% of 66 PH patients had bacteriologically quiescent disease or disease of doubtful status. On including the 7 uncooperative patients (6 SHTW, 1 PH) whose response could be assessed, the proportions with favourable response became 92% of 78 SHTW patients and 84% of 67 PH patients.

7. At 12 months, single collection specimens of sputum were negative on culture for 94% of 72 SHTW and 89% of 66 PH patients.

8. The majority of patients showed at least moderate radiographic improvement over the year—namely, 92% of 72 SHTW and 94% of 66 PH patients. Cavitation disappeared in 24% of 70 SHTW patients and 21% of 63 PH patients.

9. Three (4%) of 70 PH patients had their originally prescribed chemotherapy terminated because of cutaneous hypersensitivity reactions to PAS for which they could not be desensitized. None of 78 SHTW patients had chemotherapy terminated on account of toxicity although 17 (22%) spontaneously complained of giddiness on 1 occasion and 10 (13%) on 2 or more occasions during the year; five of the latter had their dosage of streptomycin reduced to 15 mg/kg body-weight. Two (3%) patients (both SHTW) developed toxicity to isoniazid, 1 having convulsions and the other peripheral neuropathy; both responded to 6 mg of pyridoxine given with each dose of isoniazid.

10. 7(9%) SHTW patients and 1(1%) PH patients became very uncooperative and stopped treatment during the year; this may have been due partly to toxic effects of streptomycin in 4 SHTW patients and to reasons uncon-

nected with the regimens in 3 other patients (2 SHTW, 1 PH); the remaining (SHTW) patient stopped treatment for no apparent reason.

11. Lesser degrees of non-cooperation manifested by irregularities in taking the prescribed chemotherapy occurred frequently in both series. Thus, only 10% of the SHTW patients received all of their prescribed chemotherapy during the year, and as many as 28% failed to receive their treatment on 10% or more of the occasions. In the PH series, 72% of the patients were irregular in taking their drug at some time or other including 19% who were irregular on at least a quarter of the occasion. However, there was no evidence that these irregularities were associated with unfavourable response to treatment.
12. The encouraging results of this trial suggest a possible change in the orientation of drug administration for tuberculosis in developing countries. Further investigations are under progress in this Centre.

ACKNOWLEDGEMENTS

It would not have been possible to complete this study without the devoted work of the entire staff- clinical, radiological, laboratory, statistical, secretarial and administrative. The efforts of the public health nurses, health visitors, clinic nurses and social workers made a particularly important contribution to keeping the co-operation of the patients.

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DIARRHOEA AND VOMITING DUE TO ISONIAZID

A case report

FRANCIS JOSEPH

(*Ramalingam Tuberculosis Sanatorium, Perundurai*)

The side reactions to I.N.A.H. most often reported in association with the alimentary System are dryness of the mouth, nausea, occasional vomiting and constipation. Constipation has been attributed to inhibition of the gut by Isoniazid—(David et al).¹ Experiments have shown that Hydrazides can antagonize the action of methacholine and this can account for constipation—(Drill)². It is unusual to have vomiting and diarrhoea as a result of Isoniazid therapy, not responding to usual therapies except the withdrawal of Isoniazid. Therefore a single case is reported below.

Case Report

N.R., aged 45 years, Muslim male was admitted in the above Sanatorium on 10-2-60 for the treatment of extensive bilateral pulmonary tuberculosis. History revealed that treatment had been started one year ago with dihydrostreptomycin injections and isoniazid tablets, but since he developed diarrhoea and vomiting after isoniazid, it was replaced by Sodium Para-Amino-Salicylate granules. Investigations—Sputum—Positive for Acid Fast Bacillus. E.S.R.—124 mm. in 1st Hour (Wintrobe's). Hb. —13.5 Gms. R.B.C.—4.5 millions/c.mm. W.B.C. Total Count — 11,000/c.mm, Differential Count Stab 8%, Seg 55%, Eosinophil 1%, Lymphocytes 35%, Monocyte 1%. Urine and Stool - normal.

On 11-2-1960 Ambystrin (Squibb-dihydrostreptomycin sulphate 0.5gm+ streptomycin sulphate 0.5 gm)—1 gm i.m. biweekly and Nydrizid (Squibb-Isonicotinic Acid Hydrazide 100 mg. Tablet) 1 Tablet t.i.d. were started. On the same day the patient had six loose motions and vomited three times. Routine treatment with Mist. Bismuth et Kaolin and Stemetil tablets did not control either the diarrhoea or vomiting. Repeated examinations of the stool were normal except for excess of mucus. The vomitus contained undigested food with gastric juice and some mucus. In view of the past history Nydrizid was stopped on 13-2-1960. This resulted in the prompt

cessation of diarrhoea and vomiting.

Since diarrhoea and vomiting as side effects of Isoniazid were not observed by us so far, we tried to administer this drug from various Pharmaceuticals and in different forms to this patient, during his stay of one and a half years. Every attempt to start Isoniazid resulted in diarrhoea and vomiting which subsided after withdrawal of this drug.

DISCUSSION

In the present case during one year and seven months of his stay in the sanatorium, whenever he was given I.N.A.H. in any form either as tablets or syrup or in combination with P.A.S. he developed diarrhoea and vomiting. The frequency of vomiting varied from 3 to 6 times a day and that of loose motions 4 to 8 times a day. The only positive finding in the stool was the excess of mucus. Diarrhoea did not respond to the usual therapies of Mist. Bismuth et Kaolin and starch and opium enema. Stemetil, Largactil and Anthisan did not do much good to the vomiting.

Psychosensitivity of the patient to this drug could be excluded as aversion to a particular drug can produce nausea and/or vomiting, but surely not such intense vomiting and diarrhoea. Syrup Opizide was put in another bottle containing the label 'Maltovit' and was given to the patient saying that it was a general tonic. But still he developed diarrhoea and vomiting.

Surprisingly no gastro intestinal symptoms were observed when he was on P.A.S. alone or in combination with dihydrostreptomycin; but when he had P.A.S. in combination with I.N.A.H. or when I.N.A.H. was given alone, he developed vomiting and diarrhoea.

Vomiting and diarrhoea developing immediately even after the first dose of Isoniazid showed that the alimentary system got disturbed at once.

SUMMARY

A case of pulmonary tuberculosis with

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bilateral extensive disease with cavitations, positive sputum and high E.S.R. is being reported, who developed diarrhoea and vomiting as untoward manifestations to isoniazid given in any form either as tablet, syrup, or in combination with P.A.S. from different companies. Diarrhoea and vomiting did not respond to the usual therapy of Mist Bismuth et Kaolin, starch and opium-enema, Stemetil, Largactil and Anthisan,

but stopped on withdrawal of isoniazid.

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NEWS & NOTES

Formation of State TB Association in Goa

A TB Association for Goa, Daman and Diu was inaugurated on 2nd October before a large gathering.

Technical Adviser

The Tuberculosis Association of India has appointed Dr. N. L. Bordia, TB Adviser to the Government of India, as the Honorary Technical Adviser vice Dr. P. V Benjamin.

Chest & Heart Association Scholarship

The Tuberculosis Association of India selected Dr. H. B. Dingley, Medical Superintendent, Tuberculosis Hospital, Mehrauli, Delhi for the 1964 Chest & Heart Association Scholarship. He has returned after visiting the U.K., France, Switzerland and Italy.

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, 1965. 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 month's 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 of practical training in the field.

The minimum qualification for admission to this course is Intermediate with Science/ or Hygiene and Physiology in the Matriculation.

Fifteenth Seal Sale Campaign

The fifteenth TB Seal Sale Campaign commenced on 2nd October, 1964—Gandhiji's birthday, and will terminate on 26th Jan., 1965—the Republic Day.

A TB Seal costs Ten Paise only. It is

available at all public places throughout the country.

TB Workers to Meet in Ahmedabad

The xxth Conference of TB and Chest Diseases workers in India organised by the Tuberculosis Association of India will be held in Ahmedabad (Gujarat) from 3rd to 5th February, 1965.

The main subjects to be discussed at the conference are: Symposia on "The place of Surgery in Pulmonary Tuberculosis" and "Drug Therapy of Tuberculosis", Panel discussions on "The role of General Practitioners and Public Health Services in TB control", "Case finding Programme in Tuberculosis" and papers on "Drug Resistance", "Sociology and Economics" etc.

Workers in the tuberculosis field who wish to attend the conference in Ahmedabad may contact the Tuberculosis Association of India, New Delhi, or their concerned State TB Associations.

Post Graduate Refresher Courses

The New Delhi TB Centre will organise two weeks' refresher course in Tuberculosis for general practitioners in Delhi sometime in November/December this year.

The Maharashtra State Anti-TB Association organised a short term course in the last week of September in Bombay.

The Bengal Tuberculosis Association also organised a short term course from 16th November to 28th November.

TB Health Visitors' Course: Patiala

The Tuberculosis Association of Punjab has started a TB Health Visitors' Course at the TB Centre, Patiala in cooperation with the State Government.

Similar courses are being conducted in Maharashtra, Kerala, West Bengal and Madhya Pradesh.

TB Association of Bihar

The Bihar TB Association is taking steps to reorganise itself. An ad hoc Committee of 15 members has been appointed to amend its rules and regulations.

Food & Drug Administration: U.S.A.

Food & Drugs Administration, Washington has informed the Drugs Controller, India, Directorate General of Health Services, New Delhi that they have been receiving large number of reports of serious renal and/or liver damage related to systemic therapy with the Tetracycline type drugs. The Administration further requests that the following precautionary statement be appropriately inserted in the labelling of all drugs intended for systemic administration and containing, either alone or in combination, any of the following; Chlortetracycline, Oxytetracycline, Tetracycline, Dimethylchlortetracycline and N-Pyrrolidinomethyl-tetracycline;

“Under certain conditionsused either orally or parenterally may cause serious kidney and/or liver damage. Deaths attributed to intensive parenteral treatment have been reported and most of these cases were treated for infections during pregnancy. These adverse effects appear to be related to the condition of the kidneys and/or liver prior to treatment and to the dosage and duration of treatment with When considering long term and or intensive systemic administration of these drugs (particularly parenteral use during pregnancy or in individuals with known or suspected renal impairment) it is advisable to run serial blood urea nitrogen determinations (BUN) and do appropriate liver function tests prior to and during therapy. The mild to moderately severe adverse reactions of this type have usually been reversible upon discontinuation of the drug and institution of appropriate measures.”

The labelling for a parenteral dosage form should also point out that the product is indicated only where oral therapy is not adequate or tolerated, and that oral therapy should be instituted as soon as possible.

Bombay Obstetric and Gynaecological Society

The Bombay Obstetric and Gynaecological Society has invited a thesis or essay on “Any original work on human sterility” and “Evaluation of the treatment of Genital Prolapse” for Dr. S. N. Bhansali and Dr. De Silva prizes for 1963.

For details, contact Secretary of the Society, Purandare Griha, Chowpatty Sea Face, Bombay.

Our Library

The Library of the Tuberculosis Association of India at 3, Red Cross Road, New Delhi will be available for use by the Tuberculosis workers on following conditions:-

1. The reading room will be open for consultation of Reference books and Journals between 3 to 5.30 P. M. on all working days. No new or unbound Journals or Reference books will be given on loan.
2. One book or a bound volume of Journals can be borrowed from the library for a period of 14 days at a time.
3. Persons borrowing books or journals have to deposit Rs. 50/- with the office of the Secretary, Tuberculosis Association of India, in advance. This may be waived off for T.A.I. employees.
4. If any book is lost, the T. A. I. will purchase the lost book and recover the cost from the concerned person or deduct the loss from the deposit. The person will have to replenish the deposit to make up the total deposit of Rs. 50/-.

Removing books from the shelves is prohibited. Readers are requested to consult the Librarian.

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ABSTRACTS

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A Comparison of the Heaf and the 'Tine' Disposable Multiple Puncture Tuberculin Tests

(Peter A-E Mecson and Eileen M. Shand: *Tuber; Land*, (1964), 45, 36.)

The two tests were carried out at the same time on the opposite arms in 711 apparently healthy subjects.

The Heaf test reactions were of higher grade than the 'Tine' test reactions in 420 subjects, of the same grade in 243 and in 48 subjects the 'Tine' test grade was higher than the Heaf test grade.

'Tine' test false positive reactions occur in about 1.3% of negative tuberculin reactors, but negative reactions occur in more than 15% of tuberculin positive reactors.

The 'Tine' disposable unit is convenient to use and is approximately equivalent to 5 T.U. Mantoux Test.

Prolonged Streptomycin and Isoniazid for Pulmonary Tuberculosis

(R. N. Johnston; D. H. Smith, R. T. Ritchie and W. Lockhart: *Brit. Med. Jour. Satur.* June 27th '64.)

A total of 138 patients with active pulmonary tuberculosis were allocated at random to three regimens to examine:

1. Advantages of high dose isoniazid.
2. Addition of pantothenic acid to mitigate streptomycin induced vestibular damage.
3. Reduction of daily dose of streptomycin from 1 to 0.75 grams. Patients were treated for 18 months and results analyzed two years after stopping treatment.

Lowering of daily dose of streptomycin to 0.75 grams reduced complicating vertigo

from 30% to 7% without loss of therapeutic efficacy.

There was no long term advantage with high dose of isoniazid, but it proved more toxic.

There was no additional advantage of giving pantothenic acid.

The Significance of Large Reactions to the Multiple Puncture Tuberculin Test

(D. Van -Zwanenberg: *Tub. Land*; (1964), 45, 21.)

In 139 children with large reactions to human tuberculin using multiple puncture test revealed that 30% had definite evidence of contact with tuberculous disease and 22% had definite evidence of tuberculous disease.

In 95 children with smaller reactions to human tuberculin who were believed to be recently infected only 7% had evidence of contact with tuberculous disease and none with evidence of tuberculous disease.

Large tuberculin reactors and their contacts should be carefully investigated.

A Continuing Study of Primary Drug Resistance in Tuberculosis in a Veteran Population within the United States

(Gladys L. Hobby-et-al. *Amer. Rev. Resp. Dis. March* (64) Vol. 89, No. 3.)

Observations made by direct test on 477 strains of mycobacteria isolated, suggested that incidence varied depending on the criteria of resistance used, but did not exceed 4.7 percent to streptomycin, 6.1 percent to para-amino salicylic acid and 6.0 percent to isoniazid.

Observations made by indirect test on 1204 strains of M. Tuberculous isolated from untreated tuberculous patients showed

that incidence of primary drug resistance was low i.e. it did not exceed 3.1 percent to streptomycin, 2.1 percent to para-amino-salicylic alone and 2.4 to isoniazid alone.

Multiple drug resistance was observed infrequently i.e. 0.3 percent of strains were resistant to both isoniazid and para-amino salicylic acid, 0.7 percent to both Isoniazid and streptomycin, 0.08 percent to both streptomycin and para-amino salicylic acid and 0.4 percent to all three drugs.

B.C.G. Study at a State School for Mentally Retarded

(*On. L. Bettag, Alexander A. Kaluzny DAN Morse and David B. Radner. Dis. Chest, May 64, Vol. 45, No. 5.*)

In 1947 five hundred thirty-one mental retardates of a State School were given B.C.G. Vaccination, whose chest X-ray findings and tuberculin tests were negative.

Four hundred ninety-four were designated controls.

In 1948, 522 of the vaccinated were retested with old Tuberculin 1: 1000 of 262 who were doubtful or negative 258, were revaccinated.

In November, 1960 evaluation was made. 12 of the B.C.G. vaccinated individuals had developed tuberculosis with four deaths from disease.

Eight of the control had developed tuberculosis with two deaths from disease.

Recoverability of Acid fast Bacilli from Resected Pulmonary Tuberculous Lesions as Related to the Duration of Pre-Operative Anti Tuberculous Drug Therapy.

(*Duncan A. Killen, John H. Fostur, W. G. Rhea, R. C. McCrachen, Walter L. Dively and W. W. Hulebard: Journ. Thor. Surgery Vol. 47 No. 5, May 64.*)

In a series of 405 patients, resected tuberculous pulmonary specimens were examined for Acid Fast bacilli by smear or culture.

Smear examination showed a higher incidence as compared to the culture examination.

The incidence was higher in cavitary

lesions than in non-cavitary lesion.

The incidence of recoverability of acid fast bacilli by smear of the resected specimens did not vary greatly with the duration of pre-operative drug therapy except when the duration of therapy was greater than one year; when there was greater incidence of positive smears.

The incidence of recoverability of acid fast bacilli by culture of the resected specimen decreased with increase of the duration of pre operative drug therapy up to 6'10 months.

Changes in the Pattern of Respiratory Tuberculosis in an Urban Community following a Mass Radiography Campaign.

(*James Af. Wallace, Tubercle 1964, 45, 7.*)

In a mass miniature radiography campaign in 1957 in Aberdeen, 106,430 persons (75.6 percent of the available population) were x-rayed. During the subsequent 5 years, 336 fresh cases were notified, 218 amongst those who had been x-rayed in the campaign and 118 amongst those who were eligible but were not x-rayed. Even though the rate of notification was falling before the campaign, the rate of decrease during 5 years following the survey has been accelerated. In 1958-59 the total notifications were about 2/3rd of the expected figure, which proportionately continued to decrease gradually till in 1962 it was less than half of the expected figure. A striking feature is the acceleration of the decrease in notification rate, also amongst those who were not X-rayed in 1957, as an indirect ultimate benefit.

A 5-year follow up has also provided a clue to the optimum interval between x-rays of the average individual. The maximum effect of a single x-ray is exerted and expanded within the first year, after which it diminishes gradually; but if the first x-ray was normal, the person remains, for 3 years at least, less liable to develop respiratory tuberculosis or if he does contract the disease within this period, it will probably be in a milder form. Thus, in groups not at special risk, a 3-year period between examinations would be reasonable. The total effect of a campaign however depends on the propor-

tion of the population x-rayed and the prevalence of disease in the community.

An attempt to Determine the Background to Pulmonary Tuberculosis in Adolescent Males

(*J. P. Boyd. Brit. J Dis. Chest* 1964, 58, 17.)

A comparative study of the tuberculous contact histories of 3 groups of soldiers—139 healthy group, 70 with primary tuberculosis and 355 with post-primary tuberculosis was made in 1950. Most of the soldiers were in the age group, 18 to 23 years.

The contact history data from patients with primary tuberculosis did not differ significantly from the data obtained from healthy soldiers. Soldiers with post-primary tuberculosis, however, yielded a significantly heavier contact history than the soldiers with primary tuberculosis. This difference persisted even after making allowance for the differences between average ages of the groups.

The explanation for this difference appears to be the entry of patients with post-primary tuberculosis in a tuberculous environment roughly 4 years earlier than patients with primary tuberculosis. The average period between tuberculin conversion and the appearance of post-primary tuberculosis in male adolescents appears to be 3 years in this survey carried out in 1950.

What Price Apathy—A School Epidemic of Tuberculosis

(*Charles K. Fetter. Dis. of Chest.* 1963, 44, 5, 87).

A TB epidemic in a school in a well-to-do industrial, urban community of about 11,000 population in Lake County, Illinois with a death rate of 2.6 per 100,000 is described. A 12-year boy with intermittent cough and fever lasting 4 months was found suffering from Pulmonary Tuberculosis with positive sputum. The tuberculin positive rate shot up from 3.5 percent before this event to 20 percent in the entire school and 76 percent in the class to which that boy

belonged. Fifty new patients are under treatment now as a result, 12 for Pulmonary Tuberculosis and the remaining for covert or overt primary disease.

The study emphasises the fallacy of letting up on control efforts and complacency even in economically well-to-do and enlightened communities.

Pulmonary Edema by Ascending to High Altitudes

(*E. Marticorena et al, Dis. of Chest.* 1964, 45, 273).

Clinical, radiological and electro-cardiographic observations in 36 persons, most of them under 20 years of age who developed acute pulmonary edema upon their return to altitudes over 13,000 feet, after being at lower altitude or at sea levels for 4 to 75 days are described. None of them had any prior evidence of pulmonary or cardiac disease.

Onset of edema was 3 to 48 hours after return to high altitude, accompanied most frequently by headache, restlessness, increasing dyspnoea, dry cough, palpitation, precordial discomfort and nausea. Severe respiratory distress followed within a few hours. Two patients died within 53 hours.

Predominant roentgenologic appearance was a coarse mottling exudate, more confluent in both para-hilar regions. Heart size remained normal. The electrocardiogram showed acute ventricular overloading and primary disturbances of repolarization, probably related to right ventricular myocardial ischemia. Cardiac catheterization performed in one patient during the recovery period revealed normal pressures in the pulmonary artery and the capillary bed. Treatment was by administration of humid oxygen inhalations.

Pulmonary edema of high altitude appears to be the result of hemodynamic changes due to rapid exposure to environments of hypoxia and low temperature. These changes are an increase in cardiac output and pulmonary blood volume, pulmonary vaso-constriction at pre-capillary level with secondary pulmonary hypertension and increased pulmonary capillary permeability.

Tuberculosis as a cause of the Increasing Mortality from Emphysema.

(Julius Katz and Solomon Kunofsky. *Amer. Review. Resp. Dis.* 1964, 89, 673).

The mortality rate from Emphysema has risen in upstate New York from 0.2 per 100,000 to 5.8 between 1940 and 1961; whereas the corresponding rate from tuberculosis has decreased from 32.7 to 4.0 over the same period. The antimicrobial drugs reduce the number of deaths from tuberculosis and the patients live long enough to develop Emphysema secondary to the extensive destruction of lung tissue by the tuberculous disease. Although other pulmonary diseases benefitting from chemotherapy may also give rise to Emphysema, the number of such cases is likely to be very small.

Data obtained from death certificates for 1961 show a frequent association of tuberculosis and Emphysema, regardless of whether these diseases were primary or secondary causes of death. From this association, the authors conclude that tuberculosis is an important and possibly the major cause of the increased mortality from Emphysema.

Prevalence of Drug Resistance in Previously Untreated Patients.

(United States Public Health Service Cooperative Investigation. *Amer. Rev. Resp. Dis.* 1964, 89, 327).

The United States Public Health Service is conducting a survey of drug resistance among the newly diagnosed untreated adults with active pulmonary tuberculosis in co-operation with 22 State and City hospitals in U.S.A. Of the 2,400 strains isolated from September, 1961 to July, 1962, 1.6% were resistant to INH, 2.8% were resistant to Streptomycin and 0.8% were resistant to PAS. Only 0.6% of the strains were resistant to both INH and Streptomycin. The frequency of resistant strains was not associated with age, race, sex, extent of disease or the presence of cavitation.

A striking feature of the series extending over a decade is that in the same laboratory, using same methods to determine resistance

in strains from similar patients from the same hospitals, there has been no significant increase in primary drug resistance during the past decade. The absence of change would indicate that the primary drug resistance detected today in U.S.A. is due, not to infection by persons whose bacilli became resistant during treatment but to the presence of naturally resistant organisms.

Activity in Radiographically unchanged Tuberculous Lesions.

(Z.M. Hall, P.A. Zorab & K.E. Jafferson. *Tubercle* 1964, 45, 51).

Fifty five patients with low density tuberculous shadows which had been radiologically stable for at least 3 years and had never before received chemotherapy have been followed for 5-6 years. Half of them—27 were given PAS & INH for the first year of study and the remaining 28 were untreated controls.

Amongst the treated, 3 improved during the year of treatment and 5 subsequently and one deteriorated after the treatment was stopped. Amongst the untreated, one deteriorated during the first year and 4 deteriorated during subsequent years while one showed spontaneous improvement. In 3 of the patients who deteriorated, tubercle bacilli were grown from their sputum.

Thus lesions in 15 out of the 55 were really active though apparently stable-looking for at least 3 years. No radiographic features were found which could give a clue to future behaviour.

Medical Supervision in a Non-hospitalized Tuberculous Population.

(D. Hochstrasser & S. Lerner. *Amer. Review. Resp. Dis.* 1964, 89, 416).

The study was designed to determine the relation of human factors to patterns of medical supervision in 119 non-hospitalized patients on the active-file case registers in a area of central Kentucky. The patients belonged by and large to economically and educationally handicapped group. None of the standard background variables—age, sex, race, years of schooling, income, marital

status—seem to make any significant difference in their behaviour and amenability to domiciliary supervision. Even the so called “Un co-operative” tuberculous patients cannot be stereotyped as drifters or marginal people, always on the bottom rung of the socio-economic ladder.

Hodgkin's Disease of the Lung with Cavitation.

(*S.J. Steel. Amer. Rev. Resp. Dis. 1964, 89, 736*).

Among 36 patients with intra-thoracic Hodgkin's disease admitted to the Brompton Hospital and the London Chest Hospital from 1952 to 1962, 14 had pulmonary lesions, 4 of which showed cavitation. Generalized pruritus was reported by one patient during the preceding 2 years. Alcohol-induced pain was noticed in the latter stages by 2 patients. Erythema nodosum was seen in one patient. All were Mantoux positive and none had periodic pyrexia of Pel-Ebstein type.

Bronchoscopy findings were inconclusive in all and there were no distinguishing radiographic features. All patients showed neutrophilia, eosinophilia, a raised sedimentation rate and an increase in the serum gamma globulin. Sputum was repeatedly negative for AFB. Only one patient had an

enlarged supraclavicular lymph gland, biopsy of which clinched the diagnosis. In the remaining 3, the diagnosis was confirmed by thoracotomy. Scalene node biopsy done in one patient was negative.

Treatment of choice is resection of the damaged lung followed by radiotherapy and cytotoxic drugs.

Estimation of Ventilatory Function by Blowing Out a Match.

(*AD. Carilli & J.R. Henderson. Amer. Rev. Resp. Dis. 1964, 89, 680*).

Ventilatory measurements were performed on 146 subjects and were correlated with the maximal distance at which the subject could blow out a match. Positive significant correlation co-efficients were obtained comparing distance with one-second forced expiratory volume (FEV), maximal breathing capacity (MBC), per cent of predicted MBC, and maximal mid-expiratory flow rate (MMF). Scatter diagrams and regression equations for these data are presented. The physical principles involved in this manoeuvre are discussed along with its value as a screening procedure in estimating ventilatory function. If an individual can extinguish a match at 75 cms while blowing through a mouth-piece attached to a 3 inches long tube, his per cent of predicted MBC will be 50% or greater.

BOOK REVIEW

TUBERCULOSIS IN CHILDREN: Evolution, Control & Treatment by E.J.W. Miller, R.M.E. Seal and Mary D. Taylor (Pp. 619 plus 119 illustrations -and 6 coloured plates £6) J. & A. Churchill Ltd., London, W. 1.

The book is an account of the Clinical manifestations of tuberculosis in children and has been written from the practical and clinical experience gained by the authors in the wards and the laboratory, after the introduction of chemotherapy and vaccination.

The pathology, treatment, control and prevention of Tuberculosis have been described in detail.

For prevention of disease and for the reduction of morbidity in those who are infected, the emphasis on natural history and epidemiology of the disease has been very well illustrated and described.

Separate chapters have been devoted to describing the biological characteristics of the tubercle bacilli, anatomy of the lymph nodes and lymphatics of the lung and mediastinum, pathology of primary tuberculosis with special reference to the respiratory tract along with, the development and technique of tuberculin test and the use of B.C.G. vaccination.

The clinical manifestations have been considered topographically and the clinical manifestation and its treatment has been discussed particularly taking into considera-

tion the natural history of infection.

Emphasis has also been placed on the special characteristics of tuberculosis in infancy and adolescence.

The book is of special importance to countries where the disease is still widely prevalent in both adults and children.

H.B. DINGLEY.

PRACTICE OF DERMATOLOGY: by Pran Nath Behl. Forward by B.L. Taneja (Pp. 504 and 142 illustrations of skin disease, 12 of dermatological instruments and 53 explanatory line drawings. Rs. 35.00) Allied Pacific Private Ltd., Bombay (India).

The book fulfils an urgent need for students, professors and practitioners of dermatology.

The subject matter has been dealt with in a comprehensive and rational manner with emphasis on diagnosis, etiology, prognosis and treatment with illustrations which leaves a very clear impression on the mind of the reader.

This has been the result of several years of study, practice and teaching of the author. The first part of the book gives information about the anatomy, physiology and embryology of the skin. The second part gives details of skin diseases with special emphasis on etiology, diagnosis, prognosis and treatment.

H.B. DINGLEY.