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News & Notes * Abstracts

The Indian Journal of Tuberculosis

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No. 2

SIMULTANEOUS SMALLPOX AND BCG VACCINATION —A LEAP FORWARD

Interest in the subject of BCG vaccination has been waxing and waning from time to time. Early prejudice against BCG has been overcome. Mass campaign has given way to door-to-door vaccination. Only in 1965, elimination of the pre-vaccination tuberculin test was advocated and it has paid dividends by better coverage.

Incidentally further preliminary reports on evaluation of protective value of BCG vaccination in India are now available from the community surveys undertaken by the Madanapalle Research Unit. It has been shown that BCG definitely delays the development of tuberculous disease. It was also shown in their previous experiments that protection given by BCG was not detectable within the very first few years but it took time to show its effect. Maximum benefit is observed after five years and lasts for 10-15 further years. After that period, the benefit accrued by BCG vaccination seems to level off as has been observed in animal experiments.

Recent studies have indicated that BCG vaccination can be given with smallpox vaccination simultaneously but at different sites. Many thousands of children have now undergone such immunization procedure in different parts of the world. It has also shown that simultaneous vaccinations are acceptable to the people and these are operationally feasible. Post vaccination tuberculin allergy produced is almost identical in comparison to those vaccinated with BCG alone. There has been very convincing evidence that BCG does not interfere with smallpox vaccination and the retake rate of smallpox re-vaccination sometime after the combined vaccination is very small proving that the immunity to smallpox provided by simultaneous vaccination is highly satisfactory. Now that both vaccines are available in freeze dry form the problems of preserving the vaccine have also been minimised.

Simultaneous smallpox and BCG vaccination has opened a new chapter in the methods of conducting prophylactic immunization campaigns. There is a possibility of pooling personnel of immunization programmes and utilising them as multi-purpose vaccinators for all vaccinations. Methods of achieving that goal now deserve further study, as this will be economically gainful and will provide better coverage with the same staff.

It logically leads to an enquiry in the minds of workers whether the two vaccines can be combined and given in one shot. The combined vaccination by

intradermal method (Mantoux technique) should be considered first. But it is scientifically unsound as smallpox vaccination cannot be given intradermally by injection. Then vaccination by the recently invented jet gun technique appears very attractive. But to be operationally feasible and economic, a large number of people must be available and therefore, the method can be applicable only in schools, large congregations like fairs, factories and for army recruits. The jet gun technique is entirely unsuitable for door to door vaccination as in the present practice in smallpox and BCG Campaign. The scarification and multiple puncture methods maybe more favourably considered. These methods of vaccination have their best place in newborn children in maternity homes, in child welfare centres, in "door to door" vaccination and in the schools. It is therefore possible that scarification/multiple puncture method may only be worth trying in this combined vaccination. In other words, there are numerous hurdles on the way to successful combined vaccination.

Yet another difficulty that must be kept in mind is the possible interaction of live vaccines containing the organisms, bovine attenuated bacillus of Calmette and Guerin and the *live virus fixe of vaccinia* in one medium. It is possible that there can be two undesirable effects: (1) One may be activated by the other. This is not known at present. (2) The protective value of one vaccine may be deteriorated by the other. This can be suspected from the results of combined smallpox and yellow fever vaccination. The protective value of yellow fever vaccine is reduced by the smallpox vaccine. Whether similar effect will be observed in the combined vaccination with BCG is a problem for investigation. There may be a few more problems to be solved before combined vaccine can be given at one site.

A new field of research has been opened out needing first animal experiments before combined vaccines can be put to test on human beings. In the meantime simultaneous smallpox and BCG vaccination at different sites in the younger age groups should be intensified through maternity homes, child welfare centres, schools and by door-to-door vaccination in general population through field teams. In addition, comparative studies on the development of allergy and protective value of simultaneous vaccination should continue to be pursued.

AWARD OF T.A.I. GOLD MEDAL

The Third Award of the Tuberculosis Association of India's Gold Medal for outstanding work in the Tuberculosis field was conferred on Dr. P. K. Sen of Calcutta at the time of the 23rd National Conference on Tuberculosis and Chest Diseases held in Bombay in January 1968.



DR. P.K. Sen

Born on 31st December 1904, Dr. Prafulla Kumar Sen graduated from the Calcutta Medical College in 1929. He won "SEHR GUT", the highest distinction in M.D. degree in 1933 in the University of Berlin. He stood first in the TDD Examination in the University of Wales in 1934 and was later awarded the Ph. D by that University. He won the Deutsche Akademik and Humboldt Scholarships in Germany and Scholarships of the Indian High Commissioner and British Medical Research Council in England. He was awarded a Fellowship by the Technical Co-operative Administration of the U.S.A. He is Fellow of the American College of Chest Physicians, Indian Academy of Medical Sciences, the Medical Faculty of West Bengal and the National Institute of Science of India. The University of Calcutta awarded to him in 1952 "Coats Gold Medal" for distinguished contribution in medical science.

Dr. Sen was Chairman of the Technical Committee on Domiciliary Treatment of the International Union Against Tuberculosis,

Paris, Chairman of the International Committee on Tuberculosis of the American College of Chest Physicians and member of the Executive Committee of the International Carlo Forlanini Association, Rome. He was President of the All India Tuberculosis Workers' Conference in 1960 and Vice-President of the Indian Association for Chest Diseases. He served as Chairman of the Tuberculosis Subcommittee and Expert Group on Tuberculosis of the Indian Council of Medical Research. He was a member of the Academic Council of Patna University, Board of Studies in the University of Indore, and National Formulary Committee of the Government of India.

Dr. Sen is the Chairman of Bengal Tuberculosis Association and Chairman of the Committee on "Medical Education" of the Indian Medical Association, West Bengal. He is Honorary Professor of Medicine for Tuberculosis and Chest Diseases and the head of Department of Chest Diseases in the University College of Medicine, Calcutta. He is a consultant to the All India Institute of Hygiene and Public Health, visiting Professor of the Institute of Post-Graduate Medical Education and Research, and the Honorary Director of the B.C. Roy Research Institute of Tuberculosis. Dr. Sen's earlier original studies on 'Nutrition', 'Pneumoconiosis', 'Industry and Tuberculosis', survey in Jute Industry and other population groups of Bengal and later his studies on "domiciliary treatment" on various aspects are well-known.

In recognition of his high academic eminence, original contributions to medical science and distinguished services to the anti-tuberculosis work, the Tuberculosis Association of India honours Dr. Sen with the award of its 1968 "GOLD MEDAL".

OBSERVATIONS ON THE PROTECTIVE EFFECT OF BCG VACCINATION IN A SOUTH INDIAN RURAL POPULATION: THIRD REPORT*

J. FRIMODT-MOLLER, G.S. ACHARYULU AND R. PARTHASARATHY
(From Tuberculosis Research Unit, Madanapalle)

The Madanapalle BCG Trial was set up in the year 1950 while carrying out a complete survey for tuberculosis of the village population living within 10 miles of Madanapalle. From November 1950 to September 1955 21,000 persons were tested with 5 T.U. of Danish PPD Tuberculin and admitted to the Trial. Reactors with indurations of 5 mm and more were considered as positives and those reacting with 4 mm and less as negatives. These were divided at random into two groups of which one received BCG vaccination and the other no vaccination. Both groups were given a test with 100 T.U. at the time of reading the 5 T.U. test. The study population has been covered by a series of X-ray surveys of which the first five took place in the years 1950-55, the sixth in 1957-58 and the seventh and last in 1964-65.

The first report of the findings up to 1954 was published in 1960 as part of a report describing the observations made on the epidemiology of tuberculosis in the Madanapalle Study Population. A second report bringing the results up to June 1963 was published in 1964. Full details about the Trial as set up and conducted are given in those two reports. The present report covers the period up to September 30th, 1967. It includes cases found up to the last survey in 1964-65 either by symptoms or detected at survey. In addition, symptomatic cases observed after the last survey have been included.

In preparation for the present report very careful scanning was made of available records. All cases encountered after Round VI (1957-58) were reviewed and reclassified. As before, the review of the cases was done in such a manner that the senior author assessing the cases had no information about to which group the cases belonged. The census records of the study population from 1957-58 and 1964-65, were checked with regard to persons who had died, left or were untraceable. Close attention was given to ensure that the cases were properly identified according to their previous records as well as their previous X-ray survey films. Further details of the present analysis will be presented in a full report to be published elsewhere. The present paper gives only a brief outline of the main findings.

*) Paper presented at the 23rd National Conference on Tuberculosis and Chest Diseases, Bombay, January 1968.

Results

The number of vaccinated persons, unvaccinated controls and positive reactors admitted to the Trial are 5,069, 5,803 and 9,979 respectively. In the 1964 report the number of cases in the three groups found up to June 1963 were 11, 29 and 149 respectively and among them cases with tubercle bacilli were 3, 12 and 69 respectively. The incidence among the vaccinated was 2.2 cases per 1,000 against 5.0 among the controls. This corresponds to a reduction of 56% of cases in the vaccinated group as compared with those among the controls.

The number of cases in the three groups has risen considerably since the last analysis. *Table 1* shows that in the groups of vaccinated, controls and positives we have now observed 35, 53 and 228 cases respectively. The cases have been divided into two sub-groups of which one includes *definite cases* of tuberculosis as confirmed by demonstration of tubercle bacilli by culture or microscopy and a group of *possible tuberculosis* in whom no bacilli were found. The number of bacillary cases in the three groups areas follows: 18, 31 and 108. The incidence of cases (all types) per 1,000 was 6.9 for the vaccinated, 9.1 for the controls and 22.8 for the positives. As shown in *Table 2* the difference in the rates of the vaccinated and the control corresponds to a reduction of 24%. The rate for the bacillary cases was for the vaccinated 3.6 and for the controls 5.3. This corresponds to a reduction of 33%. The difference in rates between the two groups of cases with possible tuberculosis is insignificant. These are the overall findings. However, they do not reflect the full effect of the BCG vaccination. The figures must be broken down by further analysis.

In *Table 3* the cases are distributed according to the period when their first lesions appeared. There are four groups corresponding to the intervals between the 1st and 4th Round, the 4th and the 6th Round, the 6th and the 7th Round and finally, the period after the Round VII till September 1967. It will be seen that during the first three intervals the control cases were in excess of the vaccinated cases. The interval between Round IV and Round VI i.e. the period from 1954 to 1957-58 which corresponds to the first three to seven years after admission to the Trial,

TABLE 1

Incidence of tuberculosis observed in the Madanapalle BCG Trial upto September 30th, 1967.

	Number*	Cases of Tuberculosis		Total	Cases per 1000		All
		Definite	Possible		Definite	Possible	
Vaccinated	5069	18	17	35	3.6	3.3	6.9
Controls	5808	31	22	53	5.3	3.8	9.1
Positives	9979	108	120	228	10.8	12.0	22.8

*) 700 persons 'due, not vaccinated' are omitted.

TABLE 2

Comparison of case rates:

Cases	Vaccinated	Controls	Per cent Reduction
Definite Tub.	3.6	5.3	33%
Possible "	3.3	3.8	12%
All	6.9	9.1	24%

TABLE 3

*Distribution of cases according to intervals between 'Rounds' *)*

	I-IV	IV-VI	VI-VII	VII+**)	Total
<i>Definite cases</i>					
Vaccinated	2	0	10	6	18
Controls	3	6	16	6	31
Positives	19	40	44	5	108
<i>Possible cases</i>					
Vaccinated	4	3	9	1	17
Controls	6	10	5	1	22
Positives	32	51	35	2	120
<i>All cases</i>					
Vaccinated	6	3	19	7	35
Controls	9	16	21	7	53
Positives	51	91	79	7	228

*) Round I: 1950-51
 " IV: 1954
 " VI: 1957-53
 " VII: 1964-65.

**) 1964/65-1967.

TABLE 4

Annual incidence of tuberculosis per 10,000 according to period of observation.

	Person year of Observation	CASES				All Cases No. Per 10,000	
		Definite Tub. No. Per 10,000		Possible Tub. No. Per 10,000			
(i) <i>Period up to Round VI (1957-58)</i>							
Vaccinated	23,205	2	0.9	7	3.0	9	3.9
Controls	25,749	9	3.5	16	6.2	25	9.7
Positives	45,773	59	12.9	83	18.1	142	31.0
(ii) <i>Period up to Round VII (1964-65)</i>							
Vaccinated	45,568	12	2.6	16	3.5	28	6.1
Controls	51,415	25	4.9	21	4.1	46	9.0
Positives	86,880	103	11.9	118	13.6	221	25.4
(iii) <i>Period up to September 30th, 1967</i>							
Vaccinated	53,513	18	3.4	17	3.2	35	6.5
Controls	60,866	31	5.1	22	3.6	53	8.7
Positives	101,104	108	10.7	120	11.9	228	22.6

TABLE 5

Comparison of annual incidence of cases with definite tuberculosis

Period	Vaccinated	Controls	Reduction
	per 10,000	per 10,000	
(i) Up to Round VI (1957-58)	0.9	3.5	75%
(ii) Up to Round VII (1964-65)	2.6	4.9	45%
(iii) Up to September 30th, 1967	3.4	5.1	34%

there were 3 vaccinated and 16 control cases and among the bacillary cases none among the vaccinated and 6 among the controls. During the next interval corresponding to the period from 1957-58 to 1964-65 there were found 19 cases among the vaccinated and 21 among the controls, and of these, 10 and 16 respectively were bacillary cases. The incidence among the vaccinated and the unvaccinated controls is very much the same in the earliest period (Rd. I to Rd. IV) and again in the last interval following the

last survey in 1964-65. The former points to the possibility that the earliest cases could be prevalence cases carried over in spite of the initial negative Mantoux test, and the latter points to a possible waning of the effect of the vaccination.

Table 4 presents the annual incidence of bacillary cases per 10,000 and gives the cumulative incidence of tuberculosis up to 1957-58, 1964-65 and 1967 respectively. A comparison of the rates obtained is given in Table 5. The pro-

TABLE 6

Annual incidence of bacillary tuberculosis according to age groups, up to Round VII (1964-65)

Age	Vaccinated			Controls			Production in Per cent
	Number	Cases		Number	Cases		
		No.	Per 10,000		No.	Per 10,000	
0—24 years	4288	6	1.6	4729	7	1.7	6%
25-44 "	636	5	7.9	755	15	19.8	60%
45+ "	145	1	7.3	323	3	11.3	35%
All	5069	12	2.6	5807	25	4.9	46%

tective effect of the vaccination expressed in terms of reduction of expected numbers was in 1957-58 75%, in 1964-65 46% and at end of the observation period 34%. Evidently, the vaccine was most effective in the beginning of the period.

The persons admitted to the Trial have been divided into broad age groups: those below 25 years, those between 25 and 44 years and those 45 years or more at the time of entry into the Trial (*Table 6*). Rather surprisingly, it is found that the greatest effect is seen in the age group of 25 to 44 years where the reduction was 60%. Persons aged 45 years and more showed a reduction of 35%. The children and young people below 25 years showed no significant difference in incidence. This seems rather paradoxical. We have, therefore, analysed our material further.

In *Table 7* the bacillary cases have been distributed according to age and the period when their first lesions were seen on X-ray. It will be noted, particularly from the Central group which contains the largest number of cases, that there is an association between age and the time when the cases appeared. Cases among the elderly persons developed first and the cases among the younger people, and particularly the children, developed last. The distribution of the cases leaves no doubt that this is an important observation. This leads us into a discussion of the findings.

It may be recalled that the admission of persons to the BCG Trial took place while a community-wide survey for tuberculosis was going on of the village population around Madanapalle. Everybody, irrespective of sex and age, were eligible for examination by tuberculin tests and X-ray. Therefore, all age groups were

represented. No age limit had been given for the BCG vaccination so everybody whose reactions were less than 5 mm were eligible for admission to the Trial. From the study of the epidemiology of tuberculosis in our area, we have been led to believe that the greatest risk of acquiring a primary infection takes place in ages from 10 to 20. The children would only acquire their primary infection when they in their turn reach the age when they are most exposed to infection. Although the number of cases in the youngest age group is still small, they suggest that the children might have acquired this infection at a time when the effect of BCG had started to wane. Further observations of this group must be awaited with great interest.

Can infection with non-pathogenic atypical mycobacteria produce an immunising effect against infection with M. tuberculosis ?

As described in our report from 1960 a high proportion of the population in the Madanapalle area has a low grade sensitivity shown by small reactions to the initial dose of tuberculin but producing strong reactions to tests with higher doses of tuberculin. It is assumed that this low grade skin sensitivity is caused by infection with atypical mycobacteria, commonly found in our area. Recent investigations with PPD antigens derived from various types of unclassified mycobacteria have confirmed the presence of such skin sensitivity in a high proportion of the adult population, and also in a considerable proportion among children. Palmer and associates have suggested that such infections may produce a certain degree of immunity in addition to producing an allergy. They have shown by elaborate animal experiments that vaccination with

TABLE 7

Distribution of bacillary cases according to the age at admission to the Trial and the periods of observation.

Age	Rounds				All
	IV	VI	VII	VII+	
<i>Vaccinated</i>					
0—	—	—	1	1	2
5—	—	—	4	3	7
15—	1	—	—	2	3
25—	—	—	2	—	2
35—	—	—	3	—	3
45—	—	—	—	—	—
55+	1	—	—	—	1
	2	0	10	6	18
<i>Controls</i>					
0—	—	—	—	1	1
5—	—	—	4	3	7
15—	—	1	2	1	4
25—	—	2	6	—	8
35—	2	1	4	—	7
45—	—	1	—	—	1
55+	1	1	—	1	3
	3	6	16	6	31

atypical mycobacteria can produce protection against infection with virulent bacilli which may be nearly as high as that produced by the BCG vaccination itself. If this can happen in animals, it may also happen in man.

We have analysed our material with respect to the relationship between the size of reactions to 100 T.U. at the initial tuberculin test and the subsequent incidence of tuberculosis. Formerly, the number of cases observed were far too small to warrant such an analysis. Fig. 1 shows the frequency distribution of reactors to the 100 T.U. test. They are divided into the two broad age groups: those aged less than 25 years and those 25 years or more.

The group with children and young persons shown a large proportion having no reactions, or small reactions, while a small proportion had reactions from

4 to 16 mm with a mode around 10 to 12 mm. The group of older persons shows a similar distribution around a mode about 12 mm but there are much fewer persons with small reactions than in the former group. Both curves show an upward trend at the extreme right of the distributions where the curves normally should have come down to the base line. This suggests that persons with large reactions to 100 T.U. were "false negatives" to the 5 T.U. test who ought to have shown a positive reaction to their first test.

Table 8 shows the distribution of tuberculosis cases among vaccinated and the controls with respect to their reactions to 100 T.U. In Fig. 2 the uppermost curve shows the incidence of cases among the 'controls' in the age group of 25 years or more while the lower curve shows the incidence in the age group of 0 to

TABLE 8

Incidence related to size of induration to 100 T.U. at the initial Mantoux test.

Age Groups	Size of Induration in mm	Vaccinated			Controls		
		Number tested	Cases		Number tested	Cases	
			No.	o/oo		No.	o/oo
0—24 years	0—	1167	5	4.3	1247	3	2.4
	4—	723	3	4.1	835	2	2.4
	8—	381	—	—	530	1	1.9
	12—	345	1	2.9	390	—	—
	16+	168	1	6.0	206	1	4.9
			2784	10		3208	7
25 years and over	0—	93	1	10.8	86	2	23.3
	4—	56	—	—	104	2	19.2
	8—	115	1	8.7	140	2	14.3
	12—	133	2	15.0	177	2	11.3
	16+	125	—	—	152	5	32.9
			522	4		659	13

24 in the vaccinated and controls combined.

The incidence curves are of great interest. The steep rise to the right corresponds to a high incidence among the persons who displayed very strong reactions to 100 T.U. and represents most probably persons who were infected with tubercle bacilli before admission to the Trial. The other part of the two curves corresponds to persons who are not likely to have been infected with tubercle bacilli but could have been infected with atypical mycobacteria. Although the number of cases is still too small to allow the difference in incidence rates between those with small indurations and those with large indurations to attain statistical significance, the similar pattern of the two curves strongly suggests that the persons with strong reactions to 100 T.U. have a lower incidence of tuberculosis than those who do not possess such reactions. The difference in incidence between those with strong reactions and those with small or no reactions corresponds to a reduction of 50 to 70%. Further observation of the BCG Trial population should yield more cases which could allow us

to study more precisely the interaction between the BCG vaccination and persons with 'non-specific' skin sensitivity.

The demonstration of difference in incidence between those who had non-specific sensitivity and those who did not have it with regard to subsequent development of tuberculosis is of great interest. It is to our knowledge the first time that a protective effect of infections in India with atypical mycobacteria against infections with *M. tuberculosis* has been demonstrated in man. Further analysis of the total study population at Madanapalle which covers a population which is not included in the BCG Trial, and which is greater than the BCG Trial material, should yield more information about this point.

Concluding, we would stress that the investigation confirms that BCG vaccination does reduce the incidence of tuberculosis, at least for a time. The vaccinations took place in the years 1950-55 when the potency of the vaccine was suspect. It might not have been so potent as it may be today. Even so, it was able to reduce the incidence quite substantially, at least

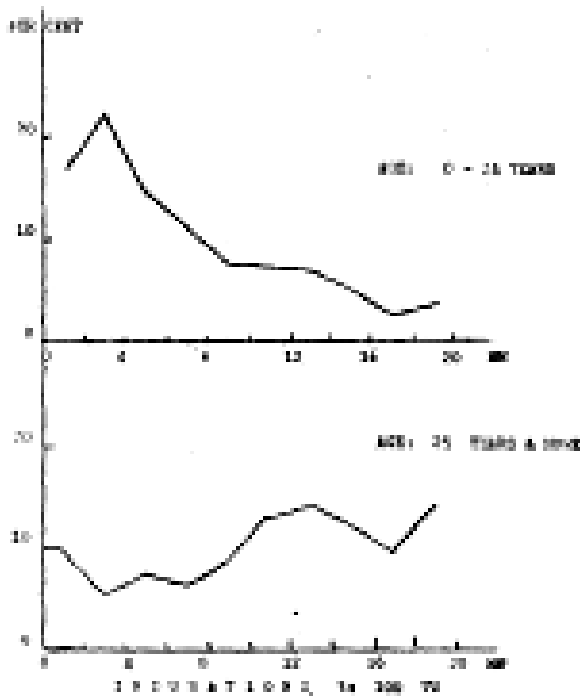


Fig. 1. FREQUENCY DISTRIBUTIONS OF REACTIONS TO MANTOUX TESTS WITH 100 TU-

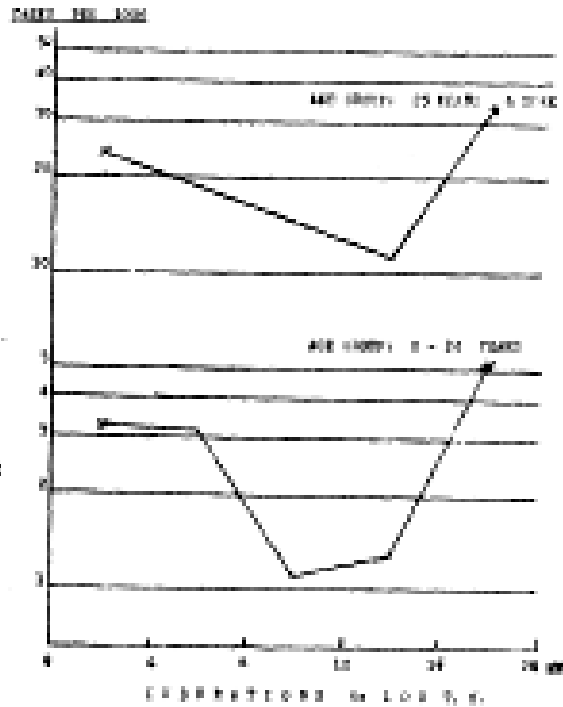


Fig. 2. INCIDENCE OF CASES OF BACILLARY TUBERCULOSIS RELATED TO SIZE OF REACTIONS TO 100 TU AT THE INITIAL MANTOUX TEST.

to begin with. It is rather paradoxical that the children should not show any effect of the vaccination but this is presumably due only to their being infected very late when the effect of the vaccination had begun to wane or the children had acquired protection from infection with atypical mycobacteria.

If BCG should have only a limited period of immunising effect, it should be used mainly shortly before the population to be protected is exposed to infection with tubercle bacilli. In epidemiological situations similar to that pertaining to the Madanapalle area, it would seem a waste of effort to vaccinate newborn children. Instead, the vaccination should take place in school age, and probably better at the end of the primary school than at the beginning. Further, revaccination at school leaving age should be contemplated.

Acknowledgements

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Research, the World Health Organisation and with support of the PL 480 Funds in connection with a cooperative study into the classification of Indian Mycobacteria. We are indebted to many doctors who have assisted us from the beginning of the BCG Trial at Madanapalle while employed at the Union Mission Tuberculosis Sanatorium. We are grateful for assistance given by the staff of the Madanapalle Tuberculosis Research Unit and the U.M.T. Sanatorium.

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SIMULTANEOUS BCG AND SMALL-POX VACCINATION*

S.P. PAMRA AND G.P. MATHUR
(from New Delhi Tuberculosis Centre, New Delhi)

Although the protection offered by BCG vaccination to the uninfected has been rated as 14—80% under varying conditions (Hart 1967), there seems to be general agreement that BCG vaccination is useful wherever the prevalence of tuberculosis is high. The impact of BCG vaccination on the incidence of disease will however depend on how quickly and to what extent the vulnerable population is afforded this protection. During the first 15 years of the mass BCG campaign in India, nearly 90 million individuals were vaccinated against a vulnerable population of over 150 millions, and what is more, during these years the population of the country increased by about 75 millions (Barua 1967). Consequently vaccination of new borns and direct vaccination (i.e. without prior tuberculin testing) up to the age of 15 or 20 years are now being advocated to bring about a quicker and a higher coverage. These procedures have been proved to be safe and efficient (Sikand et al 1964 a, b; Gothi et al 1964).

If BCG could be combined with some other vaccine as in the case of the triple antigen or it could be given simultaneously (but separately) with some other essential immunization in infancy, its coverage could be further improved. With this end in view the possibility of simultaneous BCG and small-pox (S.P.) vaccination has been engaging attention since 1957. Kawasaki (1959) and Huang (1962) found simultaneous BCG and S.P. vaccination quite satisfactory in guinea pigs. Shimokawa (1960) after a study on a small number of Japanese infants came to the conclusion that whether these two vaccines were given in combination or separately but simultaneously, the results were comparable to those of separate and sequential vaccination. A large number of Chinese children have been given these two vaccinations simultaneously in Hong Kong (Moodie and Cheng, 1962) and Taiwan (Lin and Hyg, 1965) with encouraging results.

A trial to study the effects of simultaneous BCG and S.P. vaccination in Indian infants was carried out in 1966 by the New Delhi TB Centre in co-operation with 11 Maternity & Child Welfare Centres (M&CWC) in the city.

Material & Methods

The intake was started on 6th June, 1966

*Paper presented at the 23rd National Conference on Tuberculosis and Chest Diseases Bombay Jan. 1968.

and lasted for 12 weeks. During this period 545 infants (3 days to 4 months old) were given BCG and S.P. vaccinations in accordance with the following procedures:—

During the 1st, 3rd, 5th, 7th, 9th and 11th weeks all infants received BCG and S.P. vaccination simultaneously (Group I). During other weeks only the S.P. vaccination was given to start with and BCG vaccination was given 3 weeks later (Group II). It was intended to have a third group too wherein infants would have been given BCG to start with followed by S.P. vaccination three weeks later. This, however, was not acceptable to the health authorities due to the requirements of the small-pox eradication programme.

BCG vaccination was carried out intradermally in the left deltoid region with the liquid vaccine supplied by the BCG Laboratory, Guindy, Madras. For tuberculin testing, 1 TU RT XXIII with tween 80 was intradermally and for reading, the transverse diameter was measured 72 hours later. S.P. vaccination was carried out with Russian freeze dried vaccine in the right arm, but in some cases the latter instruction was not rigidly adhered to. BCG vaccination, tuberculin testing and reading were carried out by a single trained and experienced BCG technician. Small-pox vaccination was done by the vaccinators attached to the respective M&CW centres. All readings and recordings were however made by the BCG technician.

The following examinations were carried out at different periods:—

1. Local reactions both to S.P. and BCG vaccinations were observed at the end of 1 week; in addition, the S.P. vaccination was also inspected at the end of 3 weeks. The reaction was also measured in millimetres. Complications such as glands etc. were also noted.

2. A tuberculin test was carried out 6 months after the BCG vaccination.

In all, 545 infants were included in the study of these, 138 had attended the MCW centres voluntarily on the day of intake and the remaining 407 had to be visited and vaccinated in their homes. For subsequent follow up, almost all infants were visited in their homes.

Table 1 shows the number of infants included in the study and available at various stages of the follow up.

TABLE 1

Extent of coverage during follow-up

	Total infants at start	Infants available at the end of		
		1 week	3 weeks	6 months
Group I	258	248 96.1%	244 94.6%	181 70.2%
Group II	287	280 97.6%	266 92.7%	186 64.8%
Total	545	528 96.9%	510 93.6%	367 67.3%

TABLE 2.

Results of small-pox vaccination at 1 week

	infiltration at			Total
	2 sites	1 site	None	
Group I	185 74.6%	39 15.7%	24 9.7%	248 100%
Group II	209 74.6%	46 16.4%	25 8.9%	280 100%

Of the 17 infants not available for examination at the end of one week, 4 had left the area and 13 could not be traced.

Of the infants in whom S.P. vaccination had "taken" at 1 week, 32 could not be observed at 3 weeks (1 infant had meanwhile died, 13 had left the area and the remaining were not available at the time of visit).

Post-vaccination allergy to tuberculin could be measured in 367 infants only. The test, though given, could not be read in 49 and the remaining 129 infants were not available for testing (62 because the family had left the area, 48 were temporarily out of town, 3 could not be traced, 6 because the parents did not permit the test, 2 because they were unwell and the remaining 8 had died). Deaths were due to pneumonia (3), diarrhoea (2), septic cord (1), marasmus (1) and fever (1). Two deaths occurred in group I and six in group II. One infant in group II died of fever of uncertain origin between the 1st and the 3rd week and the remaining 7 deaths occurred between 3 weeks and 6 months. The number and causes of death had been verified by the MCW staff.

Results

S.P. Vaccination

The reaction to S.P. vaccination has been compared in respect of "take" rate, pattern of reaction where the vaccination had taken and healing of the vaccination lesions in the two groups. It would be seen that the percentage of infants where vaccination did not "take" at all or only one or both lesions had taken is almost identical in both groups. The vaccination did not take at all in 9.7% in group I and 8.9% in group II, the difference being insignificant.

Table 3 shows the distribution by size of the S.P. lesions at 1 week. Here again, there is hardly any difference in the two groups. The size of the mean reaction was 9.8 mm in group I and 10.1 mm in group II, the difference being insignificant. Only two infants showed excessive reaction and both were in group I. The excessive reaction was however considered to be due to secondary infection and responded satisfactorily to treatment with penicillin.

SIMULTANEOUS BCG AND SMALL-POX VACCINATION

TABLE 3

Distribution of size of small-pox lesions at 1 week

	0	1-3 mm	4—7 mm	8-11 mm	12 mm & over	Total	Mean (mm)
Group I	24	0	9	119	96	243	9.8
Group II	25	0	10	121	124	280	10.1
Total	49	0	19	240	220	528	10.0

TABLE 4

Status of small-pox lesions at 3 weeks

	Pustule	Scab	Scar	Total*
Group I	117 29.1%	41 10.2%	244 60.7%	402 100.0%
Group II	132 30.1%	23 5.2%	284 64.7%	439 100.0%
	249	64	528	841

*This refers to the total number of vaccinations which had 'taken' at 1 week and which were available for observation at 3 weeks.

TABLE 5

Distribution of size of tuberculin reaction 6 months after BCG vaccination.
(mm)

	4	5	6	7	8	9	10	11 & above	Total	Mean
Group I	20	20	14	25	20	5	23	54	181	8.5
Group II	17	17	15	14	16	14	35	58	186	9.0
Total	37	37	29	39	36	19	58	112	367	8.8

$X^2 = 10.90$ for 7 df. $10 < p < .20$, not significant.

The status of S.P. vaccination lesions at 3 weeks, to indicate the speed of healing is shown in Table 4, Nearly 70% of the lesions had healed by the 3rd week in both the groups.

BCG Vaccination

The results of BCG vaccination have been compared in the two groups in respect of post-vaccination allergy and the size of BCG scar 6

months after vaccination. Local reaction to BCG one and 3 weeks after vaccination could not be compared as it was measured only in one of the groups owing to an error in interpretation of the word instructions.

Table 5 shows distribution by size of the tuberculin reaction 6 months after vaccination. Since allergy conferred by BCG is low and develops slowly in infants, an induration of 5

mm to 1 TU PPD RT XXIII with tween 80, six months after vaccination has been taken as criterion of conversion. The conversion rate was 89% in group I and 90.9% in group II and the mean reaction 8.5 mm and 9 mm in two groups, respectively. The differences are not significant.

Table 6 shows the distribution by size of the BCG scar at 6 months. Again the distribution is more or less identical in the two groups.

TABLE 6

Distribution by size of BCG vaccination scar at 6 monthy.

	>5 mm	<6 mm	Total
Group I	170	11	181
Group II	179	7	186
Total	349	18	367

$X^2-1.05$ for 1 df .30<p<.50

No complaints or complications were met with, even though the MCW staff was in close touch with the families. Only one infant in group II showed enlargement of the left axillary gland a little more than the size of a pea. Otherwise there was no significant enlargement of axillary glands on any side or in any group.

Discussion

The desirability of simultaneous vaccination would depend upon the likely advantages of operational cost and convenience and the likely drawbacks of one vaccine interfering immunologically with the other and excessive reaction or complications of either of the two vaccinations.

In a study of this sort, degree of protection conferred by the two vaccines respectively cannot be measured directly. "Take" rate of S.P. vaccination and post-vaccination tuberculin allergy constitute the best available criteria to compare the success of S.P. and BCG vaccinations respectively.

The data presented above show that simultaneous BCG and S.P. vaccination in infants up to the age of 4 months does not influence the immunological response to BCG as measured by post-vaccination allergy and response to S.P. Vaccination as measured in terms of "take" rates. The "take" rate in both groups

has been over 90% which furthermore, is in keeping with the general "take" rate in Delhi (Sharma 1967). The size of S.P. reaction and its healing was also similar in two groups, even though the success of S.P. vaccination is measured only in terms of "take" rate and not the size of reaction. Unduly severe reaction of S.P. vaccination was seen only in 2 children. It may thus be concluded that simultaneous BCG vaccination did not interfere in any way with the S.P. vaccination.

Similarly the pattern of post-vaccination tuberculin allergy was also comparable in two groups. Although the control group where BCG preceded S.P. vaccination was not available in the study, there were 49 infants in the total material where S.P. vaccination did not 'take' at all and the mean tuberculin reaction in these was 8.3 mm; i.e. almost similar to the mean of infants given BCG simultaneously or 3 weeks after S.P. vaccination. Further the mean reaction compares favourably with the results of an earlier study on BCG vaccination in new borns (Sikand & Pamra 1964 b).

Complications to any of the vaccinations have been conspicuous by their absence. In our experience, axillary lymph gland enlargement after BCG vaccination is negligible if vaccination is given carefully and properly (Sikand and Pamra 1964 a, b).

As for the other advantages, it is obvious that if two or more vaccinations could be given simultaneously without any risk or excessive reaction, it would be more convenient for the parents. The procedure was readily accepted and there were no refusals. The study as it was conducted, however, did not lead to any saving in the operational cost. If two technicians have to visit the home for giving one vaccination each, whether they go together or follow each other, does not make much difference. Saving could only be effected if the same technician could give both vaccinations at the same time. In other words, S.P. vaccinators should be trained in BCG vaccination or vice versa. S.P. vaccination technique is simpler and easier to learn. Intradermal BCG vaccination, especially in new borns is more difficult. Moodie and Cheng (1962) carried out BCG vaccination by multiple punctures with an ordinary needle, a technique simple and somewhat akin to the one used for S.P. vaccination; but whether that technique gives as efficient results as intradermal vaccination still remains to be confirmed.

In conclusion it may be mentioned that the two vaccinations given simultaneously are as

safe and as effective as when given between them. Simultaneous vaccination, however, can serve its real purpose only if the same technician is capable of giving both vaccinations efficiently. Possibility of administering both vaccines in combination and an appropriate technique thereof is worth exploring.

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SIMULTANEOUS SMALL POX AND BCG VACCINATION*

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The Mass BCG Campaign was started in our country in 1951, with a view to protect the largest number of susceptible individuals in the shortest possible time. While campaign was in progress two main drawbacks were observed. The coverage of the eligible population with BCG was inadequate and further the new additions, to the population, that is, the new-borns, were diluting the already poor coverages. Such a poor performance of the vaccination programme could not be expected to achieve the desired results.

In order to obviate the first drawback, operational changes such as House-to-House registration and vaccination and Direct vaccination of the younger age groups were introduced. Now a stage has been reached when this kind of mass programme has to give place to an integrated programme by which the new additions to the population have to be taken care of on a continuous and permanent basis. Some of the possibilities of such an integrated BCG programme could be as follows:

- i. BCG and MCH (Vaccination of Service Newborns)
- ii. BCG and School Health Services (Vaccination of the School entrants)
- iii. BCG and other immunisation programme (Simultaneous Small Pox and BCG Vaccination)

At the present stage of the development of our country, integration of BCG with the first two services namely the MCH and the school health services may not achieve success especially in the rural areas as these services are not fully developed. Moreover, only a small proportion of the new-borns in the rural areas is covered by the MCH service and a sizeable proportion of school age children is not registered in the schools.

The only other alternative seems to be integration of BCG with other immunisation programmes. As all of us are aware, there is only one kind of popular immunisation programme in the country and that is small pox vaccination programme. This programme has been in practice in our country since many decades and therefore, not only the urban and

the rural populations are aware of it, but it is also acceptable to them. It is estimated that high proportion of eligible children are systematically covered by small pox vaccination both in the urban and rural areas. The programme that was carried on by small pox vaccinators is slowly being taken over by other multipurpose health workers like basic health workers and auxiliary nurse midwives. It would be a great operational advantage if these workers could administer BCG vaccination at the same time as small pox vaccination.

Before recommending such a procedure, one must be absolutely certain that the simultaneous small pox and BCG vaccination is technically sound and that one does not interfere with the other. Therefore, a study of simultaneous BCG vaccination with small pox vaccination under normal small pox vaccination programme was undertaken.

The methods and material and the findings will now be presented.

The study was designed to have 3 groups of children all under the age of 1 year, as children are usually vaccinated against small pox during this period, mostly at about 4 months. Therefore, very young children under the age of 15 days have been excluded. From statistical point of view it was considered adequate to have about 250 children in each group.

The study area was one of the divisions of the Corporation of Bangalore City. BCG technicians along with the small pox vaccinators visited the houses in a systematic manner and registered all the eligible children and vaccinated them according to the random allocation previously determined. One group was given simultaneous vaccinations, BCG on the right arm and small pox on the left; another group small pox alone; the third group BCG alone.

The liquid BCG vaccine, normally used in the campaign was given in the usual dosage and technique. Liquid or freeze dried small pox lymph was used by scarification method with a rotary lancet commonly used by the small pox vaccinators all over the country. The tuberculin test to elicit post vaccination allergy was done with 5 TU RT 22.

The follow-up examination of each child

*Summary of paper presented at the 23rd National Conference on Tuberculosis and Chest Diseases, Bombay, January 1968.

TABLE 1

Intake of children in the study

Age in Months	Allotment of Vaccines							
	Small Pox + BCG		Small Pox alone		BCG alone		Total	
	No.	%	No.	%	No.	%	No.	%
0—2	29	9.2	36	14.1	26	11.9	91	11.5
3-5	93	29.5	81	31.8	66	30.1	240	30.4
6—8	95	30.2	60	23.5	60	27.4	215	27.2
9+	98	31.1	78	30.6	67	30.6	243	30.8
Total	315	100	255	100	219	100	789	100

included in the study was carried out on 4 occasions namely the 5th, 21st, 90th and 93rd days after the vaccination. The 5th and 21st day follow-up was mainly to study the development and healing of small pox vaccination lesion whereas the 21st and 90th day follow-up was for the development and healing of BCG vaccination lesion. The 90th and 93rd day follow-up was also for tuberculin testing and tuberculin test reading. On each occasion of follow-up, axillary glands were palpated to note their enlargement and other changes.

A total of 980 children were eligible for the study of whom 211 or 21.5% were excluded for various reasons including refusals leaving a total number of 789 children who were taken into the study and were finally analysed.

Table 1 shows the distribution of the children into the 3 groups allocated to the 3 kinds of vaccine regime.

Follow-up coverage for the 3 groups on all the 4 occasions was quite high as seen in *table 2*.

The take rate of small pox vaccine as evidenced by appearance of vesicles on the 5th day is to be seen in *table 3*. It is similar

in both the groups |96.7% BCG + Sp.|
|92.2% Sp. alone|

Table 4 demonstrates the healing rate of small pox lesion as evidenced by the appearance of either scar or scab on the 21st day. No difference is seen in the two groups.

BCG vaccination has, therefore, not inter-

TABLE 2

Percentages of vaccinated children followed-up on different days

Day of follow-up	Percentage followed-up		
	SP+BCG	SP alone	BCG alone
5th day	97.5	96.1	96.3
21st day	90.4	91.4	92.7
90th day	87.9	87.5	88.6
93rd day	87.0	85.1	86.8

fered with the normal development and healing of the small pox vaccination lesions.

BCG Vaccination: Post Vaccination Allergy

Figure 1: (Slide No. 5) shows the distribution of the post-vaccination allergy after 90 days. The distribution is almost similar for both BCG + Sp. and BCG alone groups. It is quite different for Sp. alone group showing that small pox has not interfered with the development of post-vaccination allergy.

BCG Lesions

Table 6 shows the development of the BCG lesion as nodule, pustule and ulcer on the 5th, 21st and 90th days.

It is seen that the development of lesion is similar in both the groups. Pustules were not observed on the days of examination.

TABLE 3

The take rates of small pox vaccination as evidenced by the presence of vesiculation at the site of vaccination

	BCG + SP			SP alone		
	No. read	Vesiculation Present		No. read	Vesiculation Present	
		No.	%		No.	%
Both insertions	307	277	90.2	245	203	82.9
At least one insertion	307	297	96.7	245	226	92.2

TABLE 4

Healing of small pox vaccination lesion as evidenced by scab or scar formation on the 21st day of vaccination

	No. read	Scar Present		Scab Present	
		No.	%	No.	%
		BCG + SP	295	40	13.6
SP	233	41	17.6	192	78.1

FIG 4

DISTRIBUTION OF THE SIZE OF TUBERCULIN INDURATION! 90 DAYS AFTER VACCINATION BY TYPE OF VACCINATION.

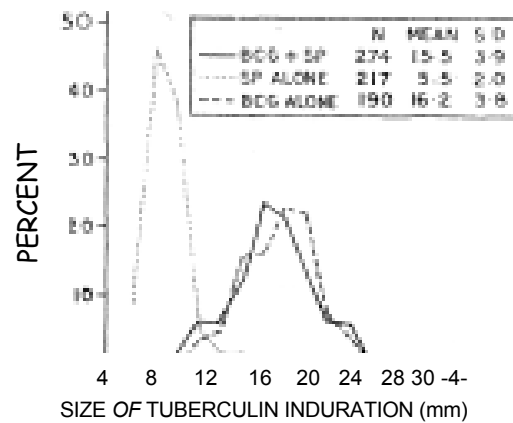


TABLE 5

Proportion of children showing nodule pustule or ulcer at the site of BCG vaccination on different days of lesion reading

	% showing lesion to BCG among those vaccinated with BCG + SP			% showing lesion to BCG among those vaccinated with BCG alone		
	Nodule	Pustule	Ulcer	Nodule	Pustule	Ulcer
5th day	29.3	—	—	14.2	—	—
21st day	98.6	—	0.3	97.5	—	1.5
90th day	—	—	74.0	—	—	77.8

Axillary Glands

Though difficult, attempts are made to palpate and measure the axillary glands and when they are found to be more than 10 mm. in size, they are taken into consideration.

Table 7 shows that higher proportion of children have enlarged glands in the right

TABLE 6

Proportion of children showing enlarged (—10 mm) axillary lymph glands on different follow-up days

	BCG vaccinated side (Right axillary)		SP vaccinated side (Left axillary)	
	BCG+SP alone	BCG	BCG + SP alone	SP
5th day	1.3	0.9	13.4	9.0
2 1st day	1.0	1.0	13.9	11.6
90th day	22.4	24.7	2.2	

axilla (BCG vaccinated side) in both the BCG + Sp. and BCG alone groups on the 90th day. Whereas higher proportion have their left axillary (Small Pox vaccinated) glands

TABLE 7

Eligible for vaccination, excluded, refused by parents and those vaccinated among those eligible

	BCG + SP		SP alone		BCG alone	
	No.	%	No.	%	No.	%
Total eligible	392	100	296	100	290	100
Excluded	67	17	38	12.7	47	16.2
Refused	10	2.6	5	1.6	24	8.3
Vaccinated	315	80.4	255	85.7	219	75.5

enlarged in both the groups on 5th and 21st days.

Only on the BCG vaccinated side in both the groups about 5% of children showed softening of glands. In only 3 or 4 children, the softened glands had burst, but healed in a few days.

It shows that small pox vaccination has not interfered with the enlargement or other changes in the axillary glands.

Acceptability of Simultaneous Vaccination

Table 8 Refusal rate is more for BCG alone than for BCG + Sp. or small pox alone.

Operational Aspects of Simultaneous Vaccination

Although technically simultaneous vaccination appears to be feasible, there are many operational factors which have to be studied. Some of them are:

- Training and equipment for the B. H. W.
- Supply and maintenance of the vaccine in the field.
- Methodology of assessment.
- Necessity of re-vaccination.

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SIMULTANEOUS PRIMARY SMALL-POX AND BCG VACCINATION IN CHILDREN 0-2 YEARS*

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Introduction

In a developing country where resources are poor and newer vaccines are being added every year, it becomes essential to plan economical, administratively convenient but good vaccination schedules particularly against smallpox, diphtheria, tuberculosis tetanus, pertussis, poliomyelitis, typhoid and cholera.

Killed vaccines have been used in a variety of mixtures, and serological responses have been as good as with single antigens.¹

The use of simultaneous smallpox and BCG vaccination in infants involves the problems of use of two live vaccines, one of which is viral and the other bacterial vaccine.

BCG and smallpox vaccines at separate sites have been administered to 3-day old and older infants without complications and without impairment of efficacy of either.

The problem that needs to be investigated is the persistence of induced immunity against both the diseases.

The simultaneous administration of live poliomyelitis vaccine and BCG vaccine by the oral route has been reported to give good conversion rates for both vaccines.

W.H.O. Expert Committee on Tuberculosis² (1964) has recommended simultaneous use of smallpox and BCG vaccines specially from the point of view of appreciable economic and operational gains.

The maternal antibody may impair the Serological responses, therefore, the age at which, the smallpox and BCG vaccination could be given simultaneously without reducing the efficacy needs to be looked into. Hence we have planned this study in infants.

Material and methods

The work of simultaneous smallpox and BCG vaccination was started at the TB Demonstration and Training Centre, Agra in April 1966 and upto July 1967 a total of 1291 simultaneous vaccinations were given; out of

these 53 were infants in whom follow-up has been done for a period of twelve months. Nine infants, who were close contacts of sputum positive pulmonary tuberculosis cases have also been given simultaneous smallpox and BCG vaccination.

Fresh smallpox lymph from tubes supplied by the State Vaccine Institute, Patwa Dangar (U.P.), was used by rotary lancet at two separate sites in the right arm.

Fresh liquid BCG vaccine prepared at BCG Vaccine Institute, Guindy was used in a dose of 1 ml in left arm near the shoulder after a pre-vaccination screening test with One T.U. P.P.D. R.T. XXIII tuberculin. Both the vaccinations were given simultaneously but at different sites.

The results of smallpox vaccination were observed at 7th day, 2 months and 4 months and 12 months.

The results of BCG vaccination and tuberculin allergy were observed at 3rd day, 2 months, 4 months, and 12 months.

Results

Results of simultaneous smallpox and BCG vaccination in infants show that there is absolutely no risk and there are negligible febrile reactions. The parents of these infants are under treatment for their chest conditions and attend the institution regularly, they bring the infants for check-up, and so far any untoward side effect and complaint has not been reported.

Response to smallpox vaccination

The incidence of successful primary smallpox vaccination in infants receiving simultaneous BCG vaccination as judged by no take-up after secondary smallpox vaccination is 89 percent in 0-6 months age group and 100 percent in infants from 6 months to 2 years.

The great majority of infants developed lesions of 1 cm. or less in diameter which is characteristic of primary smallpox vaccination (Table I).

Secondary smallpox vaccination did take up in 5 infants out of 53 (11 percent), that

* Paper presented at 23rd National Conference on Tuberculosis and Chest Diseases, Bombay Jan. 1968.

TABLE 1
Results of simultaneous smallpox and BCG vaccination in infants

Mean sizes

Age in months	No.	Initial mantoux	Mantoux after BCG 4 months	BCG scar.	Primary smallpox vacc. take up		Primary smallpox scar.	Secondary smallpox vaccination
					No.	%		
0-3	28	8.3 mm	15.1 mm	5.7 mm	28	100%	8.4 mm	25— No take up — Successful 3— Take up— Unsuccessful
3-6	17	9.2 mm	77.7 mm	5.7 mm	17	100%	8.5 mm	15— No take up — Successful 2— Take up --Unsuccessful
7—24	8	8.9 mm	16.3 mm	4.7 mm	8	100%	10.3 mm	8— No take up — Successful

Contacts of sputum positive cases

0-3	5	9 mm	15.8 mm	4.6 mm	5	100%	8.6 mm	4— No take up— Successful 1 — Take up — Unsuccessful
3—6	2	10 mm	22.5 mm	5.5 mm	2	100%	5 mm	2— No take up — Successful
7-24	2	9 mm	15 mm	4 mm	2	100%	10mm	2— No take up

TABLE 2

Results of BCG vaccination in infants already vaccinated for smallpox

Age in months	No.	Mean sizes		
		Initial mantoux	BCG scar 4 M.	Mantoux Convn. 4 M.
0-3	18	9.0 mm	5.6 mm	17.7 mm
3-6	8	9.1 mm	5.7 mm	17.5 mm
6-24	29	9.5 mm	4.6 mm	18.5 mm
Total	55			

may indicate that either the immunity after primary vaccination had not developed, or it had waned out due to interaction with the maternal antibody (Table I).

Response to BCG vaccination

Of 53 infants, 51 converted (96 percent) and became tuberculin positive when BCG and smallpox vaccinations were given simultaneously. But, younger infants upto 3 months of age give a larger BCG vaccination scar 5.7 mm small mean size of post vaccination allergy 15 mm. In infants older than 6 months post vaccination scars were smaller but mean size of tuberculin allergy was larger.

In tuberculin negative infants who are contacts of sputum positive cases the mean size of post vaccination allergy is large possibly due to booster infections from index patients (Table I).

Response to BCG vaccination in already smallpox vaccinated infants

There is no statistically significant difference but there is an indication that in younger in-

fants of 0-3 months post vaccination tuberculin allergy is higher 17.7 mm. (Table II).

Conclusions

Simultaneous smallpox and BCG vaccination given to infants of 0-2 years of age have not produced any untoward side effects of reactions.

Heterologous antigens of the two vaccines do not appear to compete with each other. Immune response to smallpox vaccination is good and post vaccination tuberculin allergy is fairly high.

Simultaneous smallpox and BCG vaccination can be carried out safely and on a mass scale in infants above 3 months of age. In case of infants between 0-3 months it would be desirable to do the secondary smallpox vaccination at the earliest opportunity preferably at the end of one year.

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CORTICOSTEROIDS IN ENDOBRONCHIAL TUBERCULOSIS

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The main aim of the treatment of Tuberculous Endobronchitis is to re-establish the airway so as to maintain a perfect bronchial drainage. Before the advent of Chemotherapy the treatment was mainly based on stimulation of local tubercular lesion so that healing was facilitated. Treatment in pre-chemotherapeutic era consisted of

- (i) Diet rich in vitamin C (Hawkins 1939; Jenks 1940)
- (ii) Cauterisation of ulcers and granulations by 30% silver Nitrate solutions (Davies 1943; Macrae et al 1950). In stenotic lesions due to large granulations and Tuberculomate the granulations were punched out by bite forceps and the base was then cauterised. Cauterisation is, however, still used by some but only in cases with streptomycin resistant strains.
- (iii) Application of ultraviolet light by means of an electrode which could be introduced through the bronchoscope and applied for 2-3 minutes. It was considered a better method than cauterisation as the healing was with softer and more easily dilatable scar.

The treatment resulted in scar tissue structure which have to be treated by the use of glove-stretch dilators and by the passage of bougies. Paulson (1951) advocated surgical repair by making a longitudinal incision in the posterior wall of the mucous membrane and filling the defect with a skin graft enforced by wire.

The results of the above procedures were not always satisfactory and the procedures had their own hazards. Chemotherapy has brought

new hopes in the treatment of Tubercular endobronchitis; (Brewer and Bogen 1947; O'Keefe 1949; Olsen and Hinsaw 1949; Cohen and Yue 1949; Macrae et al 1950; Duggeli & Trendelenburg 1953; Noti 1953). All the reports in Literature are on a small number of cases. It was, therefore, decided to conduct the present scientifically controlled trial.

Plan of Work: After a thorough clinical, radiological and a direct smear examination for A.F.B., a bronchoscopic examination was carried out in all the previously untreated cases of Pulmonary Tuberculosis admitted in the Kasturba T.B. Clinic and Hospital, Lucknow from May 1961 to October 1965. Thus a total of 300 cases were bronchoscoped. The examination revealed presence of Endobronchial disease in 131 (43.7%) cases. In sputum negative cases the diagnosis of Endobronchial disease was based on histopathological examination. The various types of Endobronchial lesions found (Classified according to the recommendations of Research Committee of B.T.A. 1953) were as follows:

- (a) Minor Mucosal changes—35 (26.7%)
- (b) Gross Mucosal changes—89 (67.9%)
 - Oedema —16
 - Tubercles and granulations —49
 - Ulecerations —24
- (c) Stenosis (5.3%)

By random allocation these were put on, three different therapeutic regimens consisting of;

Group No.	Regimen
1. Streptomycin-Isoniazid	SM— 1 Gm OD., I.M.I.) for 40 INK— 5 mg/Kgm B.W.) days followed by SM— 1 gm Biweekly I.M.I. INH— 10 mg/Kgm B.W.
2. Isoniazid-PAS	INH— 10 mgm/Kg B.W. PAS— 12gm per day
3. Streptomycin-Isoniazid as in Group 1 and Prednisolone	Prednisolone 5 mgm Q.ID. for 5 weeks 5 mgm T.D.S. for 4 weeks 5 mgm B.D. for 3 weeks 5 mgm O.D. for 4 „ and then withdrawn

Out of these only 100 cases have been presented in final analysis because—

- 3 cases—expired before the follow-up was due
- 6 cases—left against medical advice
- 22 cases—refused a second bronchoscopic examination.

The effect of therapy was noted on parenchymal lesion and the specific changes were classified as IMPROVED/STATIONARY/DETERIORATED. The improvements were sub-divided into considerable, moderate or slight as follows:

Considerable:

More or less complete clearing of infiltration, and/or cavity closure, and/or clearing of atelectasis.

Moderate:

Diminution in size of cavity, and/or radiological clearing of infiltration of one zone at least.

Slight:

Radiological clearing of infiltration less than one zone.

All the hundred cases were subjected to bronchoscopic examination again after two months and four months of treatment and the effect of therapy on Endobronchial lesion was classified as follows:

Improved/stationary/worse

The cases showing improvement were sub-classified into those with complete resolution of lesion (Grade I) and those with moderate to slight resolution of lesion (Grade II). The presence of complete resolution was confirmed by biopsy of bronchial mucosa.

Analysis

(A) Pretreatment status

The distribution of cases in each therapeutic group was as follows:

Group I —35 cases

Group II —31 cases

Group III —34 cases

These cases have been analysed as regards sputum bacteriology (Table No. 1), Type of parenchymal disease (Table No. 2), Extent of parenchymal disease (Table No. 3), Type of Endobronchial disease (Table No. 4).

TABLE 1

Sputum Bacteriology

Sputum Bacteriology	Therapeutic Regimens		
	Group I	Group II	Group III
Positive for A.F.B. — 61 cases	22	19	20
Negative, for A.F.B. — 39 cases	13	12	14

TABLE 2

Type of Parenchymal disease

Type of Parenchymal disease	Therapeutic Regimens		
	Group I	Group II	Group III
Exudative — 75 cases	24	21	30
Productive — 10 cases	4	4	2
Fibrotic — 15 cases	7	6	2

TABLE 3

Extent of Parenchymal Disease

Extent of Parenchymal Disease	Therapeutic Regimens		
	Group I	Group II	Group III
Stage I —5 cases	2	2	1
Stage II —15 cases	6	4	5
Stage III —80 cases	27	25	28

TABLE 4

Type of Endobronchial Disease

Type of Endobronchial Diseases	Therapeutic Regimens		
	Group I	Group II	Group III
Minor Mucosal changes	8	10	7
Gross Mucosal changes	26	21	24
— Oedema	5	4	3
— Tubercles and granulations	15	12	14
— Ulcers	6	5	7
Stenosis	1	—	3

(B) Result of treatment

(I) The effect of treatment on endobronchial disease was observed after 2 months and after 4 months. The results are depicted in table Nos. 5 and 6 respectively.

TABLE 5

Effect of therapy on endobronchial disease	Evaluation after 2 months		
	Group I	Group II	Group III
(i) Improved — 84 cases	29(82.8%)	23(74.2%)	32(94.1%)
Grade I 44 cases	15(42.8%)	7(22.5%)	22(64.7%)
Grade II 40 cases	14(40.0%)	16(51.6%)	10(29.4%)
(ii) Stationary 15 cases	6(17.1%)	7(22.5%)	2(5.9%)
(iii) Worse 1 case	—	1(3.2%)	—

TABLE 6

Effect of therapy on Endobronchial disease	Evaluation after 4 months		
	Group I	Group II	Group III
(i) Improved — 89 cases	31(88.5%)	25(80.6%)	33(97.0%)
Grade I — 69 cases	23(65.7%)	21(67.7%)	25(73.5%)
Grade II — 20 cases	8(22.8%)	4(12.9%)	8(23.5%)
(ii) Stationary 10 cases	4(11.4%)	5(16.1%)	1(2.9%)
(iii) Worse 1 case	—	1(3.2%)	—

(2) Correlation of complete resolution after 4 months therapy with different types of bronchial disease gave following results:

TABLE 7

Endobronchial Disease	Group I		Group II		Group III	
	No. of cases	Complete resolution	No. of cases	Complete resolution	No. of cases	Complete resolution
Minor Mucosal changes	8	8(100%)	10	10(100%)	7	7(100%)
Gross Mucosal changes						
— Oedema	5	5(100%)	4	4(100%)	3	3(100%)
— Tubercle and granulation	15	7(46.6%)	12	5(41.6%)	14	11(78.5%)
— Ulcer	6	3(50.0%)	5	2(40.0%)	7	4(57.1%)
Stenosis	1	—	—	—	3	—

(3) Effect of 4 months chemotherapy on parenchymal disease gave following results :

All cases showed improvement.

TABLE 8

Improvement in parenchymal Disease	Group I	Group II	Group III
Considerable — 18 cases	5	4	9
Moderate — 61 cases	22	20	19
Slight — 21 cases	8	7	6

(4) Correlation of complete resolution with the improvement in parenchymal disease gave the following results:

TABLE 9

Improvement in parenchymal disease	Group I		Group II		Group III	
	No. of cases	Complete resolution	No. of cases	Complete resolution	No. of cases	Complete resolution
Considerable	5	5(100.0%)	4	4(100.0%)	9	9(100.0%)
Moderate	22	15(68.2%)	20	12(60.0%)	19	14(73.7%)
Slight	8	3(37.5%)	7	5(71.4%)	6	2(33.3%)

(5) Effect of 4 months chemotherapy on sputum bacteriology:

TABLE 10

Sputum Positive for A.F.B.	Group I	Group II	Group III
On admission	22	19	20
After therapy	4	5	1

(6) Correlation of complete resolution with the sputum bacteriology:

TABLE 11

Sputum Bacteriology	Group I		Group II		Group III	
	No. of cases	Complete resolution	No. of cases	Complete resolution	No. of cases	Complete resolution
Sputum positive	22	13(59.0%)	19	11(57.9%)	20	13(65.0%)
Sputum negative	13	10(76.9%)	12	10(83.3%)	14	12(85.7%)

(7) Correlation of complete resolution with sputum conversion gave following results;

TABLE 12

Sputum conversion	Group I		Group II		Group III	
	No. of cases	Complete resolution	No. of cases	Complete resolution	No. of cases	Complete resolution
Sputum Conversion	18	12(66.6%)	14	10(71.4%)	19	13(68.4%)
Persistently positive sputum	4	1(25.0%)	5	1(20.0%)	1	0(0%)

Discussion

One hundred cases of Pulmonary Tuberculosis with Endobronchial disease were followed up to note the effect of chemotherapy on tubercular endobronchitis.

(7) Therapeutic efficacy of various regimens:

After 2 months of chemotherapy the complete resolution of endobronchial disease was achieved in 42.8%, 22.5% and 64.7% cases under the therapeutic regimens Group I, Group II and Group III respectively. Complete resolution of lesion is thus achieved early with Group III and Group I regimens, the former being more superior regimen. Since in both SM and INH are common drugs it clearly indicates that addition of prednisolone favours early achievement of complete resolution.

The superiority of these regimens may partly be attributed to Streptomycin. A high concentration of Streptomycin has been reported in the bronchial secretions comparable to that in the blood, (Steenken et al 1947). The lesions, therefore, besides being subjected to Streptomycin via blood stream are constantly bathed in a topical application of mucous containing similar concentrations of drug, (Richards 1952). The efficacy of Streptomycin in the treatment of Endobronchial Tuberculosis has been reported by Bewer and Bogen (1947); O'Keefe (1948), Olsen and Hinshaw (1949), Cohen and Yue (1949), Macrae et al (1950). In the report of British Medical Research Council (1951) excellent results were achieved with Streptomycin.

Marked Improvement or complete healing	—68% cases
Slight improvement	—20% cases
No change	— 9% cates
Deterioration	— 3% cases

It is interesting to note that by prolonging the treatment for another 2 months.

- (i) the figures for complete healing rise to 65.7%, 67.7% and 73.4% (refer tables 5 and 6) and
- (ii) similar results are achieved under Streptomycin Isoniazid (Group I) and Isoniazid—PAS (Group II) groups;

the superiority of streptomycin-Isoniazid-Prednisolone (Group III) group becomes further manifest in that a higher percentage (statistically

significant) of cases show complete resolution of endobronchial lesion (refer table .6)

(2) Response of different types of lesions to therapy :

All the cases with minor mucosal lesions and oedema of bronchial mucosa showed complete resolution of lesion under all the three therapeutic regimens. On the other hand, out of the cases with tubercles and granulations only 46.6%, 41.6% and 78.5% cases showed complete resolution of disease under group I, II and III regimens respectively. The difference between Group I and Group II regimens is not statistically significant but Group III is definitely superior to the other two groups for the treatment of granulomatous lesions. Complete resolution of ulcerative lesion was noticed in 50.0%, 40.0% and 57.1% under Group I, II and III respectively.

Thus as far as the response of minor mucosal changes and oedema are concerned all the three regimens are fully effective but for the ulcerative and granulomatous lesions Group III regimen is superior to other two.

(3) Correlation of the course of bronchial lesion with improvement in parenchyma] disease:

Complete resolution was obtained in all the cases who had considerable parenchymal improvement, but in those cases who had moderate parenchymal improvement only 68.2%, 60.0% and 73.7%, cases under Group I, II and III respectively showed complete resolution of bronchial disease. Thus it is clearly demonstrated that those cases which after 4 months of chemotherapy show considerable improvement in parenchymal lesion, are expected to achieve complete resolution of bronchial disease also.

(4) Correlation of the course of endobronchial lesion with sputum conversion:

Those cases in which the sputum became negative after therapy showed an incidence of complete resolution in 66.6%, 71.4% and 68.4% cases under Group I, II and III respectively, but cases in whom the sputum was persistently negative from the onset of therapy, the clearance was 76.9%, 83.3% and 85.7%. This shows a direct relation of sputum negative cases with the incidence of complete resolution and the effect of therapy is better in persistently negative cases than those who had a positive sputum initially (Refer tables 11 and 12).

It needs special mention that a complete resolution of lesion was also achieved in 2 cases out of 10 with persistently positive sputum under the various therapeutic regimens.

(5) *Period for which treatment of endobronchial disease is to be continued:*

Total number of cases showing improvement of endobronchial lesion (inclusive of Grade I and II) after 4 months therapy exceeded only by few as compared to those observed after two months therapy (Refer tables 5 and 6). This finding was significant in that after 2 months of therapy a reasonably accurate estimate of cases that would improve with therapy can be made. However to achieve complete resolution of lesion in a majority of cases the therapy should be continued at least for 4 months.

Summary

The present work clearly demonstrates that

- (1) Streptomycin-Isoniazid-with Cortico Steroids is the best combination for the treatment of Tubercular Endobronchitis. Streptomycin Isoniazid is the next best.
- (2) The addition of corticosteroids favours early achievement of complete resolution and is of added value in ulcerative and granulomatous lesions.
- (3) Earlier is the stage of mucosal disease better are the results of chemotherapy.
- (4) Improvement in parenchymal disease has a direct relation with bronchial change in most cases. Change in sputum bacteriology is also directly related to improvement in bronchial disease.

- (5) Effect of therapy is better in cases with persistently negative sputum than those who have a positive sputum initially.

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TWICE WEEKLY STREPTOMYCIN AND ISONIAZID REGIMEN WITHOUT SUPERVISION

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Introduction

The Tuberculosis Chemotherapy Research Centre, Madras, have reported the excellent results of an entirely supervised chemotherapeutic regimen consisting of twice weekly administration of streptomycin and isoniazid (SHTW) in cases of pulmonary tuberculosis (Tuberculosis Chemotherapy Centre, Madras 1964). Following the publication of this paper the Directorate General of Health Services, Government of India supplied streptomycin and isoniazid to the TB clinics in the country for free administration to patients of pulmonary tuberculosis strictly according to the above regimen and only on a domiciliary basis. The supplies of streptomycin and isoniazid thus received can not be used in any other manner except on an intermittent basis giving one gramme of streptomycin by injection on two days a week alongwith oral administration of 650 mg. of isoniazid on the basis of 14 mgm./Kg. of the body weight on the same two days a week (vide circular No. 6-8/64-tub., dated 7/10th March, 1964). The Amritsar TB Centre also received sufficient supplies of these two drugs to be used in the prescribed manner in the month of June, 1964 and it was decided to treat the patients with this regimen.

But the vast majority of patients presenting at the TB Centre, Amritsar, come from far off villages and even other districts in the Punjab where suitable clinic arrangements do not exist. Clearly therefore, it is not practicable to ask these patients to report at the TB Centre, Amritsar on two days every week for one year. Since these patients needed treatment and drug supplies were available it seemed reasonable to issue the drugs to these patients for one month at a time to be administered to them without insisting upon the supervision at the TB Centre, Amritsar. Facilities for the administration of injections of streptomycin were, however, available at the TB Centre, the R. B. Rattan Chand TB Clinic and the R. B. Sir Gujjar Mai Kesra Devi TB Sanatorium, Amritsar for those willing to do so. As it is, however, all patients did self-administration of isoniazid in their homes and majority of them got themselves injected at places convenient to them. It will be obvious therefore that the regimen lacks the advantages of both viz. the daily intake of the self-administered regimens as well as the super-

vision of the intermittent regimen. This paper presents the results of such a regimen given for one year at the TB Centre, Amritsar.

Material and Methods

Patients for this study were selected from those presenting voluntarily with symptoms of pulmonary tuberculosis at the TB Centre, Amritsar.

The following criteria were employed in the selection of patients.

- (1) Patients were above 12 years of age.
- (2) They had either not taken any previous chemotherapy or treatment with anti-TB drugs for not more than 15 days.
- (3) Patients were suffering from active pulmonary tuberculosis as judged by X-ray chest and clinical symptoms. Sputum may or may not have been found positive on smear examination.
- (4) Patients were prepared to accept the twice weekly regimen of injections and tablets for one year and were judged to be reasonably co-operative in completing the one year treatment.
- (5) They were not suffering from any complications like caries spine, Diabetes Mellitus etc. which would make the treatment more difficult.

All fresh previously untreated patients of pulmonary tuberculosis belonging to Amritsar district or as near to Amritsar district as possible were included in the study beginning from 17th September, 1964, if they were judged to be reasonably co-operative in completing one year's treatment. Patients were explained the treatment regimen at great length. All patients were- advised to get streptomycin injected on Tuesdays and Fridays to ensure uniformity. The dosage of streptomycin was 1G by injection irrespective of the weight of the patient while that of isoniazid was on the basis of 14 mgm./Kg. of the body weight being 650 mg. for a patient weighing 100 lbs or more. When during treatment the weight of the patient increased, the dose of isoniazid was enhanced at the next visit of the patient. Patients were supplied 8G of streptomycin and the calculated number of tablets of isoniazid for one month at a time. They were advised to get streptomycin

injected either at one of the three TB Institutions of Amritsar or at any place more convenient to them if they came from outside the city of Amritsar. Injections at one of the three TB Institutions of Amritsar was not made obligatory. The regimen was explained first by a doctor and then by Medical Social Workers and at the time of collection of the drug supply by the dispenser. A complete history with thorough interrogation regarding the history of previous chemotherapy was elicited, thorough clinical examination was done and weight was recorded. A 70 mm. X-ray of the chest, tuberculin test with I.T.U. and sputum examination for A.F.B. by smear method was done in every case. Cultures for tubercle bacilli and their sensitivity tests were not done due to lack of facilities for the same. Patients were re-examined every 3 months when a new 70 mm. X-ray and sputum examination by smear method was repeated. But every month when the patients came for collection of drugs they were asked about any untoward symptom or difficulty and weight was recorded. Patients were again motivated regarding the continuation of drug treatment and the twice weekly regimen explained again. The Health Visitors visited the patients belonging to the city of Amritsar specially if they had defaulted.

The patients admitted to treatment

In all 458 patients were admitted for the treatment beginning from 17th September, 1964 and ending on 6th March, 1965. All these patients have been followed for one year till March, 1966, when the last patient completed 12 months of chemotherapy. Out of these 251 patients did not complete full one year of treatment as advised but defaulted. Therefore these have been excluded from the study though they will be discussed separately. The remaining 207 patients are discussed below: —

Deaths: 15 patients (7.2%) died of pulmonary tuberculosis, 3 in the 1st week, 5 in the fourth week, 6 in the eighth week and 1 in the 12th week of beginning of treatment on the above regimen. All these patients had extensive disease with positive sputum at the beginning of treatment and in addition suffered from severe mal-nutrition.

Changes in the regimen due to drug toxicity

In 9 patients (4.3%) the regimen had to be changed due to severe drug toxicity due to streptomycin. 7 patients developed severe giddiness after 3 weeks of therapy. 6 of these patients were above 55 years of age. 2 patients developed drug allergy to streptomycin and in them the regimen was changed.

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Results of treatment at 1 year

Deducting the 15 patients who died and 9 patients in whom the regimen had to be changed, out of the above 207 patients 183 completed full 12 months of chemotherapy. The results are given below:—

Age and Sex:—The age and sex distribution is shown in Table I.

TABLE I

Age and sex distribution.

Age in years.	Male	Female	Total
12-14	2	3	5
15-24	39	46	85
25-34	19	30	49
35-44	12	7	19
45-54	5	7	12
55 and above.	6	7	13
All ages.	83	100	183

There were 83 males and 116 females. Their ages ranged from 12 years to 70 years. The maximum number of cases (85) belonged to the age group of 15 to 24 years.

Sputum conversion

93 of the 183 patients had positive sputum on direct smear examination and 90 had negative sputum at the start of treatment. The sputum conversion on treatment is shown in table-II.

At the end of 3 months treatment 31.1% were positive on smear and at the end of 1 year of treatment 16.1% were positive on smear. Of those positive at the end of 1 year there were 4 patients whose sputum was initially negative, but it became positive after the 9th month of treatment. There were a total of 15 cases with positive sputum at the end of one year of treatment with SHTW regimen and all these cases were considered to have failed on this regimen and were admitted in the T.B. Sanatorium, Amritsar for alternative treatment regimens.

TABLE II.

Showing sputum conversion (on smear examination) with SHTW

Bacterial content of sputum	Before start of treatment	After 3 months of chemotherapy		After 6 months of chemotherapy		After 9 months of chemotherapy		After 12 months of chemotherapy	
		No.	%	No.	%	No.	%	No.	%
Direct smear negative.	90	154	68.8	159	74.2	163	78.5	168	83.9
Direct smear positive.	93	29	31.2	24	25.8	20	21.5	15	16.1

Radiological Assessment

Table III shows extent of disease in these 183 patients at the beginning of treatment. This assessment was made on 70 mm x-ray films but in minimal cases a full plate x-ray was sometimes taken.

Majority of the cases had moderately advanced disease but 46.4% had far advanced disease. 42% had single or multiple cavitation.

Table IV shows radiological improvement on treatment.

The changes in the radiographic appearances

TABLE III

Showing extent, type, zone and cavity status of patients as assessed on 70 mm. radiograph before treatment.

Status	No. of cases	Percentage
No. of patients	183	100
Extent of disease		
Minimal	31	16.3
Moderately advanced	101	55.2
Far advanced	51	28.5
Bilateral disease	98	53.6
Unilateral disease	85	46.4
Zones:		
Less than 1	22	12.0
1	36	19.6
2	37	20.2
3	35	19.0
4	41	22.3
5	11	6.0
6	1	0.6
Cavitation		
No cavity	106	58.0
Single cavity	59	32.3
Multiple cavities	18	9.7

TABLE IV.
Showing radiological changes after chemotherapy.

Period months	Total patients assessed	IMPROVEMENT						No change.		Deterioration	
		Marked		Moderate		Slight		No.	%	No.	%
		No.	%	No.	%	No.	%	No.	%	No.	%
0-3	183	18	9.7	129	69.4	16	8.6	18	9.7	2	1.0
0-6	183	33	17.5	115	62.2	15	8.0	18	9.7	2	1.0
0-9	183	49	26.8	104	56.8	8	4.3	16	8.6	6	3.7
0-12	183	100	54.6	50	27.2	10	5.4	15	8.2	8	4.3

TABLE V.
Showing weight changes in patients during 12 months (in pounds)

Period (months)	WEIGHT GAIN								Weight loss less than 5		Average gain in weight per lbs patients
	20 lbs or more		15 to 19 lbs.		5 to 14 lbs.		less than 5 lbs.		No.	%	
	No.	%	No.	%	No.	%	No.	%	No.	%	
0-3	6	3.2	4	2.1	42	22.9	123	67.2	8	4.3	4.0
3-6	1	0.6	1	0.6	26	14.2	142	77.6	13	7.1	8.8
6-9	1	0.6	1	0.6	16	8.6	152	83.0	13	7.1	8.5
9-12	4	2.1	0	0	27	14.6	143	78.0	9	4.8	9.9

were read duly by both the authors on 70 mm films. At 3 months 79.1% patients showed moderate to marked improvement. At 6 months 79.7% patients showed moderate to marked improvement. At 9 months the figures for moderate to marked improvement were 83.6% and at 12 months 81.8% showed moderate to marked improvement. In 15 cases there was no improvement radiologically though they were better bacteriologically and clinically. In 40 patients (51.9%) cavities disappeared completely.

Changes in weight

Table V shows changes in weight during treatment.

The average weight of patients at the

beginning of treatment was 91.8 lbs. The average gain in weight at the end of 12 months of treatment was 9.9 lbs. Weight loss was noticed in patients who deteriorated and those who were pregnant and later delivered children (9 patients) No untoward symptoms in the mother or the child were reported by these patients,

Minor toxic effects

A few patients specially women complained of giddiness on the day of streptomycin injection. This was however not complained of after reassurance. One patient developed peripheral neuropathy which improved with pyridoxin 12 mgm daily while isoniazid was also continued.

TABLE VI

Showing reasons for default

Serial No.	Reasons for default	No. of patients defaulted
1.	Indo-Pak conflict of August-September, 1965.	62
2.	Experienced difficulty in getting streptomycin injected.	48
3.	Felt better and did not consider necessary to continue treatment.	38
4.	Wanted daily streptomycin injections and started supplementing their own injections.	29
5.	Had no money to travel to Amritsar to collect drugs.	20
6.	Address incomplete and untraceable.	14
7.	Did not feel improvement with treatment.	11
8.	Reasons unknown.	11
9.	Preferred oral treatment.	7
10.	Left the area.	5
11.	Delivered children and stopped treatment.	3
12.	Family problems.	3
Total :		251

Defaulters

Out of the total of 458 patients initiated the SHTW treatment 251 patients did not complete the 12 months chemotherapy. More than half of the defaulters 129 (51%) defaulted within the first 3 months, (23%) between 3 and 6 months and the remaining later during the year. An analysis into the possible causes of default brought out the following reasons given in table VII.

The single most important cause of default in this group was the Indo-Pakistan conflict in August-September, 1965. Amritsar district is situated on the border between India and Pakistan and normal life in many villages near the border was completely disrupted during this period. This however is an exceptional cause and cannot be considered in discussing the common causes of default, though it has unfortunately vitiated the results of this study considerably. All the other causes of default are very well known to TB workers. Whereas 48 patients experienced difficulty in getting streptomycin injected, there were 29 patients who were not satisfied with the twice weekly

regimen so much that they started supplementing daily streptomycin from their own pocket. 38 patients felt better after some treatment and therefore did not feel it necessary to continue the treatment further. This is a very common cause and though enough motivation and education was done it was not possible to prevent it in this, group of patients.

Discussion

In the developing countries oral drug regimens on a domiciliary basis have been tried and found efficacious (Tuberculosis Chemotherapy Centre, Madras 1959). These regimens require self-administration of drugs by the patients for prolonged period of a year. Under such conditions reliance has to be placed on the co-operation of the patients in taking drugs with all its attendant pitfalls (Fox-1962). To get over these drawbacks Tuberculosis Chemotherapy Centre, Madras (1964) reported highly successful results of an entirely supervised chemotherapy entailing the injections of streptomycin 1 G on two days a week alongwith a high dose of isoniazid (14 mgm/Kg body weight), on the same two days

a week at their TB centre. On the basis of this report the Directorate General of Health Services, Government of India, supplied streptomycin and isoniazid to TB clinics requiring them to use the above drugs in the same regimen under supervision. But what may be a highly successful regimen under ideal conditions on a small but selected group of patients may not necessarily be equally practicable in the actual prevailing conditions in most TB clinics in India. This paper reports the results of treatment on a large number of 458 patients at the TB centre, Amritsar, with the above regimen but without supervision. Patients presenting at most TB clinics in India comprise a large number from the neighbouring villages also and it is obviously not possible to compel them all for twice weekly attendance at the city TB clinic for supervised chemotherapy. Though it is the ultimate aim that these rural patients will be supervised through the existing peripheral health agencies like the Tehsil Hospitals and primary Health Centres, the evidence available from the work already reported does not generate great hopes that such a supervision will be acceptable or successful. Gothi (1965) thinks that the administration of twice weekly streptomycin injections to 5,000 patients in a district and the defaulter action required is an enormous task. He calculates that on an average each primary health unit will have to organise 30 injections per day and 5-10 defaulter actions besides, the other routine work of a primary health centre. He therefore doubts the applicability of such injection treatments. Govindaswamy and Savic (1965) in studying a once weekly supervised streptomycin regimen at the peripheral health facilities, though did not experience difficulty in getting the injections administered at the peripheral health agencies, yet found the regimen unacceptable to majority of the patients. 58% of patients were irregular even in the first 6 months though the facility was provided at as near their homes as possible. Even when one month's drug supply was provided at the primary health centre near to the patients' homes, Basu Chowdhary and Chakravarty (1965) found 32% were irregular in collecting their drug supply of thrice weekly streptomycin plus daily isoniazid regimen, and the patients discontinued within 6 months.

Therefore the results presented here of an unsupervised intermittent chemotherapy in which there has been a very high default rate of 54.7%, probably could not have been improved much more even if the supervision had been obtained through the peripheral health agencies. Actually if the 62 defaulters due to the Indo-Pakistan conflict were to be

excluded, as it is not a normal cause of default, then the default rate for one year comes down to 41% which compares favourably when peripheral health agencies are utilized. Further in this study any patient who did not collect full 12 months of chemotherapy has been considered a defaulter and an attempt has not been made to see what was the default rate at various periods during the year, as in most such reports. At the Amritsar TB centre relatively few fresh previously untreated patients present themselves from the city of Amritsar. Majority of them usually have already been treated for more than two weeks by the private practitioners and general hospitals. These could not therefore be included in the above study which was restricted to the previously untreated patients. However, a small number of 24 city patients who did fulfil this criterion are also included in this study. Though facilities for free injections were made available only a few of these patients took the advantage of this facility. It will thus be seen that in the actually prevailing conditions both at the TB centre as well as in the peripheral health agencies an entirely supervised intermittent chemotherapy is neither practicable nor acceptable if all the large numbers of patients presenting at the TB clinics are to be offered the benefits of this regimen. Therefore, if this regimen has to be given in the existing conditions it will have to be unsupervised as has been done at Amritsar.

On the other hand, the results of unsupervised twice weekly intermittent chemotherapy in patients who did complete one year of such regimen have been quite encouraging. In the 183 patients who completed the collection of 12 months of chemotherapy, sputum became negative on smear in 83.9%. If the 15 tuberculous deaths are included in it then there were 30 failures out of a total of 108 sputum positive patients with success rate of 68%. Radiologically 81.8% patients out of the total of 183 who collected 12 months supply of drugs showed from moderate to marked improvement. If the 15 tuberculous deaths are included then the success rate falls to 75.6%. Thus the regimen of unsupervised twice weekly streptomycin with high dose of isoniazid has proved highly efficacious in the patients. There were 15 deaths (7.2%) mostly in the severely ill and malnourished patients. It is therefore felt that such patients should be admitted in a sanatorium and given a more vigorous daily drug regimen alongwith supportive therapy. The incidence of toxic effects to streptomycin was seen specially in the older age group and in 7 patients streptomycin had to be withdrawn due to severe giddiness.

Transient giddiness on the day of injection was complained of more frequently specially by women patients but it did not necessitate stoppage of treatment. Remarkably little toxic effects were noted due to isoniazid. In only one case peripheral neuropathy was found which got well with pyridoxin. No toxic effects were complained of in the 9 pregnant women who delivered children while carrying out the treatment.

Co-operation

There was a considerable difficulty in explaining the regimen to poor and illiterate patients. For many it was difficult to remember the Tuesdays and Fridays and the exact numbers of tablets to be taken. The regimen being a newly introduced one, still greater difficulty was felt in explaining to the practitioners to give the twice weekly regimen. Even then a fair number of patients did make mistakes like taking the dose of 650 mgm daily or dividing it into a smaller dose of 200 mgm daily usually on the advice of a practitioner. Daily streptomycin was frequently advised by the practitioner in preference to twice weekly streptomycin. Though the regimen is effective in a large number of moderately ill patients who completed 12 months of collection of drugs it has not been practicable to make it an entirely supervised regimen. Further it was our impression that seriously ill patients should be given rather more intensive daily chemotherapy with streptomycin in a sanatorium. It was also our impression that the radiological healing was less dramatic and was accompanied with more fibrosis than is seen with vigorous daily streptomycin and isoniazid.

Summary

1. Interrupted twice weekly streptomycin with high dose of isoniazid has been given to domiciliary patients without supervision in 458 patients.

2. 251 patients (54.7%) did not collect the full 12 months drug supply.

3. 15 patients (7.2%) died due to tuberculosis and in 9 patients (4.3%) drug regimen had to be changed due to toxicity.

4. Of the 93 sputum positive patients who collected full 12 months drug supply 83.96% became sputum negative on smear. 81.8% showed moderate to marked radiological improvement.

5. It is concluded that though the regimen is highly successful in those who will complete 12 months treatment, in the existing conditions at the TB centre, Amritsar, it is not practicable to supervise the regimen.

ACKNOWLEDGEMENT

The free supply of streptomycin and isoniazid by the Directorate General of Health Services, Government of India which was provided to the above patients is gratefully acknowledged.

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Reproduced below are the main recommendations of the Standing Technical Committee of the Association which met in Bombay at the time of the National Conference on TB & Chest Diseases held in January, 1968.

1. Utilisation of Vacant Beds

It is a matter of deep concern that in spite of the fact that a very limited number of hospital beds are available in the country for the treatment of tuberculosis, a large bulk of this which are maintained by the voluntary bodies are lying vacant while at the same time public sector organisations like the Railways, Employees' State Insurance Corporation, etc. have constructed or contemplate constructing new hospitals for the treatment of tuberculosis. In the considered view of the Committee, funds spent for the establishment of new institutions can be utilised for other nation-building purposes if the concerned authorities utilise the existing beds for treating tuberculous patients. In order to bring this position to the notice of the authorities and to suggest a policy, it was resolved that members of the Standing Technical Committee should meet the Union Health Minister and the President of the Association and submit a Memorandum to the Government of India giving relevant details in this regard and requesting the Union Ministry of Health to draw the attention of the State Governments and other organisations again to utilise the existing beds instead of establishing new institutions.

2. Supply of Drugs

(a) The Committee recommended its considered view that while supplying anti-tuberculosis drugs the demands of all tuberculosis institutions including those at the peripheral level should be adequately met. The Committee emphasised that the policy suggested by the international bodies to limit the administration of their drugs to patients declared tuberculous on sputum examination only was likely to leave untreated many infectious cases and therefore recommended that all cases of tuberculosis should be entitled to receive anti-tuberculosis drugs whatever the source of supply be.

(b) The Committee felt that allocation of funds for drugs to TB institutions in the country was inadequate and recommended that the Government of India should substantially increase the provision so that their centrally sponsored scheme of drug supply will be able to make a dent on the TB problem. It was resolved that this recommendation be conveyed

to the Government of India and the international bodies such as the World Health Organisation and the U.N.I.C.E.F.

(c) The Committee emphasised that State TB Associations and their District branches should train and utilise the services of local voluntary workers for the supervision of intake of drugs in their areas so that regular administration and intake of drugs by the patients is ensured and the default in drug taking prevented.

3. Tuberculosis and Family Planning

The Committee emphasised that integration of tuberculosis control programme with family planning programme was of paramount importance. It recommended that health educators of Family Planning units should propagate the philosophy of family limitation among tuberculosis families also. Since Family Planning programme had ample resources in funds, men and material including transportation facilities reaching upto the periphery, the Committee recommended that the district tuberculosis control programme should be strengthened by collaboration with the Family Planning units. The Committee suggested that close liaison should be maintained between these programmes in regard to educative propaganda also.

4. Statistics

The Committee felt that the existing epidemiological data based on 1957-58 National Tuberculosis Survey about TB may not be adequate as it was possible that with the passage of years the situation may have changed. It was therefore recommended that early steps be taken to repeat morbidity surveys on a national scale or by scientific studies acceptable to statisticians so that reliable information became available for future planning. The Committee suggested that the Association should obtain the advice of Dr. C. Chandrasekhar, Director of Institute of Demography, Bombay, who was associated with the 1957-58 national sample survey.

5. Research

The Committee endorsed the view that research should be carried out on operational aspects of tuberculosis control work such as

immunization, chemotherapy, chemoprophylaxis, epidemiology and such other facets which are useful for planning and execution of anti-tuberculosis work in India. It was suggested that the Association should supplement whatever the Indian Council of Medical Research, the Government of India and other organisations were doing.

6. Voluntary Effort

(a) Every State TB Association should set up a Pilot Project on the general lines of the one operating in the Tumkur District of Mysore State. State Associations must also organise Seminars and group Discussions on Tuberculosis Control. It was suggested that Honorary Secretaries of the State Tuberculosis Associations should personally study the working of the Tumkur Project with a view to initiating similar projects in their own States.

(b) The Committee reiterated its previous recommendations that all State Associations should have full-time paid staff, and where Government officials were associated with them as Chairman or Honorary Secretaries, they should employ suitable non-officials as Secretary or Organising Secretary or Joint Secretary so that non-official work such as Seal Sale Campaign can be intensified.

(c) The Committee recommended that the State TB Associations should establish District and Taluk Tuberculosis Associations, wherever they did not exist and utilise their funds expeditiously by initiating social service programmes, health education activities, pilot projects, etc.

7. Basic Training of Personnel of Teams for Tuberculosis Programme

The Committee felt that it would be advisable for Demonstration and Training Centres to speed up the basic training of personnel for teams in their concerned States, so that adequate number of technical personnel are available to organise the programme. Their training should be so orientated as to enable them to be eventually leaders in community control of tuberculosis.

8. Quantum of Training for Under-Graduates

The Committee suggested that the Tuberculosis Association of India may organise a group discussion/Seminar as early as possible by inviting among others, Professors of Medicines and of Tuberculosis from the Universities of Bombay, Delhi, Madras, Calcutta,

Amritsar, Patna, Lucknow and Andhra Pradesh to consider this matter.

9. Blue-print of Tuberculosis Control Work in India

The Committee strongly recommended that a blue-print giving detailed suggestions on all aspects of tuberculosis control work in India should be prepared on the lines of the Eighth Report of the World Health Organisation Expert Committee.

10. Tuberculosis Control

Since tuberculosis continued to be the largest public health problem in India tuberculosis Control work should receive the highest priority and every one found to be suffering from tuberculosis should be effectively treated.

11. Case-finding Programme

The country's economy does not warrant elaborate and expensive methods of case finding like mass X-ray of general population. An easy and effective method will be to have all patients with continuous cough attending the out-patient department of medical institutions investigated by systematic sputum examination in a special "Cough Clinic". All those who are found to have positive sputum should be immediately treated. Suspicious cases with negative sputum should be sent for X-ray examination.

12. Training of Technicians

Training of technicians for tuberculosis control work should receive the immediate attention of the Central and State Governments and Tuberculosis Associations.

13. BCG Vaccination

All new-borns should be BCG vaccinated. It was recommended that the Government should consider combining the programmes of BCG vaccination with small pox vaccination and utilise the services of the staff engaged in small pox vaccination programme also for BCG vaccination.

14. Institutional Assessment

Periodical reviews of the activities and achievements of important institutions like the Tuberculosis Chemotherapy Centre, Madras, National Tuberculosis Institute, Bangalore and Tuberculosis Training and Demonstration Centres in the country should be undertaken and the results of reviews and investigations made available to tuberculosis institutions in

the country through the Tuberculosis Association of India.

It was also recommended that newer methods of tuberculosis control like the District Control Programme should be submitted to periodic assessment by an Expert Committee appointed by the Government of India.

15. Host Factor

The Committee recommended that basic and fundamental research should be encouraged to establish the relationship of various biochemical host determinants in the human body which are responsible for development of tuberculosis following infection by tubercle bacilli. This, in the opinion of the Committee, would be necessary to safeguard against disease.

17. District Tuberculosis Centres

The Committee noted the statement of the Adviser in Tuberculosis, Government of India, that inspite of speedy development of District Tuberculosis Programme and the availability of UNICEF assistance, as many as 51 districts in India do not have tuberculosis clinics. The Committee strongly urged that all the State Governments should be moved to take early steps to provide tuberculosis services in every district in their respective States.

17. Microscopes and Microscopists

The Committee noted with disappointment that many primary health centres in India did not have microscopes and microscopists and strongly recommended that in view of the present policy of the Government to integrate tuberculosis services with general health services the obvious deficiencies in staff and equipment

in all primary health centres should be immediately rectified. It was recommended that posts of microscopists be created and filled in all primary health centres and microscopes be provided so that sputum case detection can develop throughout the country.

18. The Committee recommended that there should be satisfactory integration of tuberculosis work with the general health services at the peripheral level so that tuberculosis cases are detected in the early stages where they report with symptoms first. The Committee emphasised that effective drug therapy should be provided from all health facilities nearer the homes of patients.

If periodic assessment of District Control Programme reveals that peripheral integration does not work satisfactorily, the question of providing separate TB Control units at the periphery should be seriously considered.

19. The Committee recommended that the Post of Tuberculosis Adviser in the Directorate General of Health Services of the Government of India should be upgraded and designated as Director 'National Tuberculosis Control' so that he can function as the Central executive authority to administer National Control Programmes, in collaboration with the State Governments and not merely in an advisory capacity.

The Committee also recommended that the Directorate should have a board of Honorary Advisers. In order to enable the Tuberculosis Association of India to function as an effective instrument of National policy in regard to tuberculosis, the Committee recommended that it could be called upon to function as the Advisory Board to the Directorate.

NEWS & NOTES

Annual Meetings of the Association

The Twentyninth Annual General Meeting of the Tuberculosis Association of India will be held on 27th April at 11.45 A.M. in the Conference Hall of the Association. Dr. S. Chandrasekhar, the President of the Association, will preside. The Chairman of the Association will be presenting the report on the working of the Association during 1967, and the Honorary Treasurer will be presenting the accounts. The meeting will elect members to the Central Committee as provided for in the rules.

The Conference of the Secretaries of the State TB Associations and Seal Sale Organisations in India will be held in the Conference Hall of the Association at 3.00 P.M. on 26th April and a meeting of the Technical Committee of the Association will meet on 26th April.

National Conference: Bombay

The twentythird National Conference on TB and Chest Diseases was held in Bombay from 7th to 10th January, 1968. Dr. P.V. Cherian, the Governor of Maharashtra, inaugurated the Conference. Dr. R. Viswanathan, Emeritus Professor, Vallabhbhai Patel Chest Institute, was President of the Conference. The Scientific sessions included discussions on "Changing trends in Tuberculosis", "Organisational and Administrative Problems", "Chemotherapy", "Small pox and BCG Vaccination", "Cor pulmonale in pulmonary TB", "Respiratory Allergy" and "Surgery in Tuberculosis" etc.

Seminar in Goa

A seminar on TB was held in Panjim on 13th January, 1968. Mr. Nakul Sen, Lt.-Governor of Goa, Daman and Diu, inaugurated the Seminar. Srimati Indu Sen, President of Goa TB Association, welcomed the delegates. The Seminar was addressed by Shri Bandodkar, Chief Minister of Goa and Shri G.G. Mayenkar, Minister for Health. Over 20 papers covering various aspects of Tuberculosis Control was presented by eminent specialists on the subject.

Seal Sale Award: 1968

The 1968 Trophy for the highest Seal Sale collections will be awarded to TB Association of Madras. This Trophy will be presented at the Annual General Meeting of the Association in April.

Junior Award

The Tuberculosis Association of India gives a cash prize of Rs. 300/- to a Tuberculosis worker, preferably below 45 years of age for an original article not exceeding approximately 6,000 words excluding charts and diagrams on a subject relating to Tuberculosis. *Articles or papers already published will not be considered for this Award.* Papers should be sent in quadruplicate to reach the office of the Tuberculosis Association of India on or before 30th October, 1968.

Dr. M.D. Deshmukh Honoured

We are glad to record that Dr. M. D. Deshmukh, Honorary Secretary, Maharashtra Anti-TB Association, has been nominated for F.R.C.P. by the Council of Royal College of Physicians of England.

Eastern Regional Committee

A meeting of members of the Eastern Regional Committee was held in Amsterdam on the 5th of October, 1967. About twenty members were present. The accounts for 1966-67 presented by the Honorary Secretary were adopted. It was suggested that the Committee should fix a quota of contribution for each National Association instead of depending on voluntary contributions from them. A Committee consisting of Dr. Cotter Harvey (Australia), Shri B.M. Cariappa (India), Dr. Yamaguchi (Japan), Dr. Sodhy (Malaysia) and Dr. China Choty (Thailand) was appointed to examine the details. Shri B.M. Cariappa was authorised to take the initiative in this regard.

Invitation to Burma and Indonesia

The Secretariat of the Eastern Regional Committee, Bangkok, has requested the President of the Tuberculosis Association of India to depute Shri B.M. Cariappa, its Secretary-General, to visit Indonesia and Burma to assist their National TB Associations in their activities and also to advise them how voluntary work can benefit the National TB Control Programme.

Chest Diseases Award

The Indian Association for Chest Diseases has instituted a prize of Rs. 200/- to be given to the author of the best article published during the previous year either in Indian or foreign journal on any subject on the special

lity of Chest disease. Those who desire to be considered for this prize may send six copies of their article to the Secretary, Indian Association for Chest Diseases, C/o Silver Jubilee TB Hospital, Kingsway Delhi-9 by not later than 31st July 1968.

Association of Physicians in India

The Association of Physicians in India is giving awards for lecturerships and fellowships. Those interested may kindly contact the General Secretary of the Association, Laud Mansions, 3rd Floor, 21-Queen's Road, Bombay-4.

Conference on Iron Deficiency Anaemia

A national conference on Iron Deficiency Anaemia will be held in Bombay from 15th to 17th November, 1968. The last date for receiving summary of papers is 31.7.68. For further particulars contact, Department of Hematology King Edward Memorial Hospital, Parel, Bombay-12.

Proceeding of the XXII TB Conference

Copies of the Proceedings of the twenty-second conference held in Hyderabad in 1967 are available at a cost of Rs. 20/- including postage from the Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

BOOK REVIEW

The challenge of Tuberculosis 1967 by **J.H.F. Jayasuriya**: pages 208; published by the Ceylon Medical Association for the prevention of Tuberculosis; Printers: Wesley Press Colombo-6, Ceylon. Linen cover Library edition Rs. 10; Hard cover with jacket Rs. 7.50 and Soft cover Rs. 5; postage -/7 cts.

Dr. Jayasuriya F.R.C.S., O.B.E., is a renowned thoracic Surgeon. He has been President of the Ceylon Medical Association and Chairman of the Council of Ceylon National Association for Prevention of Tuberculosis. He is a recipient of the Commonwealth Award of honour from the Chest and Heart Association of Great Britain and a devoted tuberculosis worker and has done service to mankind by writing this book.

The material is presented in a most interesting way and once the reader begins to read he wishes to complete the reading before

leaving it. The chapters include a wide range of subjects like history of Tuberculosis Epidemiology. Elementary and basic knowledge on tuberculosis are presented very well and as applicable to developing countries. The book covers a wide range of subjects like infection resistance, Prevention and Control, tuberculin testing & B.C.G. vaccination etc. Clinical aspects of Tuberculosis find a prominent place. The treatment, rehabilitation are adequately dealt with.

The book is extensively illustrated and the photographs are taken from areas which represent the prevailing conditions in developing countries.

The book will be useful for general medical practitioners, the young specialists, other tuberculosis workers and the intelligentsia as a whole. The book is written in a beautiful easy flowing language and should be a best seller.

Note:—The information on "Essential Knowledge" which was published in the December 1967 issue of the Indian Journal of Tuberculosis was reproduced from the Bulletin of the Ceylon National Association for the Prevention of Tuberculosis.