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MEDICAL EDUCATION IN TUBERCULOSIS

Technical Education is designed mainly on utilitarian basis. Both the general and social medical education must, therefore, take into account the prevalence of diseases, background of social and environmental conditions, financial and technical resources of the country, and be modified accordingly. The under and post-graduate education in Tuberculosis must be designed in this context to equip students for general and special services.

Tuberculosis in India is widely prevalent both in urban and rural areas. A substantial bulk of general practice consists of this disease. The country has a "Tuberculosis Control Programme" in which intelligent co-operation of general practitioners is a necessity. For these reasons the under-graduate training in Tuberculosis should be comparatively more important than in developed countries. For proper conduct of the control programme different kinds of specially trained medical personnel are also necessary. For such a training competent teachers are vitally needed.

We are of the opinion that the load of this training cannot be light in under-graduate study as the problem of tuberculosis is very important. We are also of the opinion that the training should be on chest diseases as a unit with tuberculosis as the most important part, as knowledge of tuberculosis is essential for learning other chest diseases and vice versa. Practical and clinical training should not be limited to the clinics, hospitals and laboratories but field practice in community control should also be provided. Obviously, the teacher-in-charge must be a specialist on the subject of Tuberculosis and Chest Diseases having a clear and comprehensive knowledge of epidemiology, control measures etc. and not only of clinical medicine. Medical colleges should therefore appoint teachers in the subject with academic designations.

In post-graduate education the diploma and degree courses should also be on "Tuberculosis and Chest Diseases", the former to train responsible officers to man the clinics and hospitals, and the latter for higher type of teachers. Besides these, there should be courses to train personnel to man routine clinic and hospital services, refresher courses for them and also for general practitioners. Education for the latter and the former can also be

extended through simple, well-written and attractive literature. There could be many other ways for extending medical education in Tuberculosis.

It is obvious that for all post-graduate education, adequate basic undergraduate training is the corner stone. This is the mainstream of education. Banks are to be dressed for local modifications and canals for specialised educations are to be cut according to the needs. In doing so the Universities, the Medical Council, the Medical Colleges, and organisations like the Tuberculosis Associations will all be involved. We, therefore, feel strongly that a competent and authoritative committee of educationists on the subject should be appointed by the Government and the Universities jointly to consider the subject from all angles, formulate policies, set curricula and recommend measures for implementation of various types of this education.

A COLD STAINING METHOD FOR TUBERCLE BACILLI USING CHLOROFORM

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Introduction

Of the various methods of staining acid-fast organisms, the Ziehl-Neelsen (ZN) technique is the best known and is in vogue in most laboratories in the world. In this method, the basic fuchsin-phenol stain is heated to higher temperature in order to stain tubercle bacilli in few minutes before decolorisation with mineral acids and alcohol, and counter-staining with methylene blue. It is believed, that the success of the method depends partly on the heat employed, which renders the bacilli, permeable to aqueous dyes. Various attempts have been made to develop a cold staining method for tubercle bacilli as for other organisms. Kinyoun (1915) used higher concentrations of basic fuchsin and phenol for cold staining. Desbordes et al (1952, 1960) claimed favourable results by using anionic surface-active detergents. Tax Thiam Hok (1962) used Kinyoun's carbol-fuchsin and combined the steps of decolorisation and counter-staining (Gabbets 1887) and reported that this method was 'quicker than the complex ZN method and also superior. This last method was tried in our laboratory but did not give satisfactory results

The difficulty in staining tubercle bacilli is believed to be related to the complex surface structure which contains a large amount of unsaponifiable wax, Andersen (1932). Any staining technique which can counteract the influence of this wax could, therefore, be expected to give better results. As this wax is soluble in chloroform, cold staining using chloroform was tried. This method has been compared with the conventional ZN method in the present investigation.

2. Methods

2.1 Conventional Ziehl-Neelsen (ZN) Method

(a) Preparation of Stain:

One gram of basic fuchsin was dissolved in 5 grams of warm phenol and 10 ml. of absolute alcohol was added to the fuchsin-phenol mixture. The solution was diluted with 90 ml. of distilled water and filtered.

(b) Technique of Staining:

1. Smears were stained with carbol-

- fuchsin for 5 minutes, heating twice in this period.
2. Washed in tap water and decolorised twice with 25% sulphuric acid, 2-1/2 minutes each time.
3. Decolorised with 70% alcohol or methylated spirit for 2 minutes.
4. Counter-stained with 0.1% methylene blue for 10 seconds and washed in tap water and dried.

2.2 Cold Staining (CS) Method Using Chloroform

(a) Preparation of Stain:

One gram of basic fuchsin was dissolved in 5 grams of warm phenol. To this, 0.25 ml. of chloroform in 5 ml. of absolute alcohol was added to dissolve basic fuchsin completely. Then remaining 5 ml. of alcohol were added and finally diluted with 90 ml. of distilled water and then filtered.

(b) Technique of Staining:

Same procedures as for ZN method except that the stain on smear was not heated.

In many of the studies, it is a routine practice to examine smears first by fluorescence microscopy (FM) and superimpose ZN stain on the same smear after removing Potassium Permanganate by Oxalic acid 5% solution in cold and washing in water. For part of the material in the present study also, this procedure has been followed for both ZN and CS methods.

2.3 Grading of Smears

- Negative : No acid-fast bacilli seen in 5 minutes examination of smears.
- Actual Number : One to 100 bacilli seen in 5 minutes examination.
- +
- ++
- : More than 100 bacilli seen in 5 minutes examination.
- : Masses of bacilli seen in many fields.

The counting of actual number of bacilli upto 100 was adopted for the present study so that the 2 techniques can be compared with

regard to the ability to detect smears with small number of bacilli only. Though such a detailed analysis was made, the results are presented for 3 groups only, namely; 1-10, 11-30 and 31-99 bacilli.

2.4 Routine Examination

Besides the two methods of microscopy under study, fluorescence microscopy (FM) and culture were done as a routine for each specimen. The results were graded as follows:

Grading of FM:

Negative	: No bacilli seen in 2 minutes examination.
(+)	: 1 to 3 bacilli seen in 2 minutes examination.
+	: 1 to 5 bacilli seen in most fields.
++	: More than 5 bacilli in most fields.
+++	: Masses of bacilli.

Grading of Culture:

Negative	: No growth in 8 weeks incubation.
Actual Number	: Less than 20 colonies seen in culture slope.
+	: 20 to 100 colonies.
++	: More than 100 colonies, but discrete.
+++	: Confluent growth.

3. Material

Triplicate smears were made from 186 specimens and smears of each were stained by ZN, CS and FM methods. In order to include smears of all grades in sufficient number and in shorter time, single smears of 343 specimens previously examined by FM were divided randomly into 2 subsamples and stained by ZN and CS methods respectively. The staining of these sub-samples were carried out after removal of potassium permanganate from smears prepared for FM. To investigate whether the use of pre-stained FM smears influences results of superimposed ZN and CS methods, one set of smears from 264 specimens stained and examined by FM, were randomised for staining by either methods. Duplicate smear of each specimen, unstained by fluorescent technique was paired with the first smear and stained by the same method.

Tables 1 & 2 show correlation between duplicate smears examined by ZN and CS methods respectively. For both methods, the correlation between the two smears is of a very high order. Disagreement regarding positivity was observed in only 8 smears, both in tables 1 and 2, and constituted only about 6% of the total examined. Differences observed were minor and of an order that could be expected by repetition of either method. This shows that use of smears pre-stained by fluorescent technique does not influence the results of either ZN or CS method. Therefore, while comparing the latter methods with culture or FM, the results of all smears stained by any one method have been combined. Thus, ZN results were available for 490 specimens and CS for 486. Culture was not done for 2 specimens in each group and culture contaminated for 5 in the former group and 7 in the latter.

All the smears were examined by an experienced technician and always under same magnification of X 500. Before examination all the smears were given random numbers so that the technician examining the smears had no knowledge of different methods of staining employed for the smears.

4. Findings

The results of examination of duplicate smears from 186 specimens by ZN and CS methods are shown in Table 3.

It may be seen that the 2 methods show a high degree of correlation with 75% of the figures along the diagonal of identical grading and that only 16 (8%) are positive by one method and negative by the other.

Of the 8 smears positive by CS method alone, 7 (87.5%) were confirmed by culture, whereas only 3 (37.5%) of the 8 smears positive by ZN method alone were confirmed. The difference is statistically significant ($P < 0.05$). This indicates that those positive by CS method alone are likely to be real cases, whereas those positive by ZN method alone may include some false positive cases.

The extent to which culture negatives occur among different grades of positivity under ZN and CS methods could also be compared from the random sub-samples which were subjected to either of these methods (Table 4).

It can be seen that the percentage of such probably false positives is less under CS method for each degree of positivity, particularly among smears showing 1 to 10 bacilli. The difference was statistically significant ($P < 0.05$). The total difference, however, just

TABLE 1

Correlation between I and II smear by ZN method according to different grades of smears

Grading	II smear						Total	
	Neg.	1—10	11—30	31-99	+	++		
I smear	Neg.	97	2	1	1	—	—	101
	1—10	2	—	1	—	1	—	4
	11—30	2	1	1	—	12	—	7
	31—99	—	—	—	—	33	—	6
	+	—	—	2	1	11	1	15
	++	—	—	—	—	1	—	1
Total		101	3	5	6	18	1	134

TABLE 2

Correlation between I and II smear by CS method according to different grades of smears

Grading	II smear						Total	
	Neg.	1—10	11-30	31—99	+	++		
I smear	Neg.	95	1	—	1	—	—	97
	1—10	2	—	—	—	11	—	4
	11—30	312	—	1	—	—	—	7
	31—99	—	1	—	21	—	—	4
	+	1	—	—	—	7	3	11
	++	—	—	—	—	—	2	2
Total		101	3	2	59	—	5	125*

* 5 slides were broken.

failed to attain statistical significance at the 95% confidence level. It may be mentioned that in these two sub-samples, the percentage of positives which are not confirmed by culture. To understand the extent to which false positives are obtained by any method of microscopy, it would be more realistic to judge also on the basis of other methods of microscopy. For this, 186 specimen results were available for 3 methods, namely ZN, CS and FM. Culture did not confirm 14 specimens in which at least one of the microscopy method gave positive

Both tables 3 and 4 indicate that comparatively the ZN method gives a higher grading of smears than CS method.

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TABLE 3

Correlation between CS and ZN methods for 186 duplicate smears
CS method

	Grading	Neg	1—10	11—30	31—99	+	++	Total
ZN method	Neg	86	6	1	1	—	—	94
	1—10	7	7	1	—	—	—	15
	11—30	—	2	7	2	1	—	12
	31—99	1	2	3	2	3	—	11
	+	—	1	—	7	31	2	41
	++	—	—	—	—	6	7	13
	Total	94	18	12	12	41	9	186

TABLE 4

Culture negatives among different grades of smear positives by ZN and CS
methods

Grading of smear	ZN method			CS method		
	Total Positive	Not confirmed by culture	Percentage not confirmed	Total Positive	Not confirmed by culture	Percentage not confirmed
1-10	36	9	25.0	50	3	6.0
11—30	40	4	10.0	40	3	7.5
31—99	33	1	3.0	30	—	—
+	92	1	1.1	80	—	—
++	21	—	—	12	—	—
Total	222	15	6.7	212	6	2.8

results. There were 5, which were positive by CS method and of these 4 were positive by the other two methods also. Among 9 positive by ZN method, 4 were positive by the other two and one by FM alone, leaving 4 which were not supported by other two methods. FM also showed 4 positives which were considered negative by both the other methods. Thus a positive result under CS method seems to be more reliable than positive results from the other two methods among culture negatives also. This indicates that CS may be superior to both ZN and FM methods, unless it misses a large proportion of true cases.

Among the culture negative cases, there was only one case which was positive by both ZN and FM, but missed by CS method. The number of cases missed by each method out of culture positives among 186 specimens for which all 4 examinations have been done is shown in Table 5.

CS method compares quite favourably with FM method both in terms of cases missed by that method alone and total cases missed. There is also an indication, that it may be superior to the ZN method in this respect also.

The larger material using different random sub-samples for CS and ZN methods (Table 6)

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TABLE 5

Culture positives among 186 specimens missed by CS, ZN and FM methods either alone or in combination with the others

Missed by	Total	Alone	By one more method	By other methods also
CS	13	2	4	7
ZN	17	5	5	7
FM	12	2	3	7

TABLE 6

Smear negatives by ZN, CS and FM methods of microscopy among different grades of culture positives

of culture	Culture positive	ZN method		Culture positive	CS method	
		Negative by ZN	Negative by FM		Negative by CS	Negative by FM
<20	48	28 (58.3)	16 (33.3)	40	18 (45.0)	10 (25.0)
+	95	19 (20.0)	9 (9.5)	101	25 (24.7)	7 (6.9)
++	74	—	1 (1.3)	81	2 (2.5)	—
+++	37	—	—	29	—	—
Total	254	47 (18.5)	26 (10.2)	251	45 (17.9)	17 (6.8)

(Figures in parenthesis are percentages to the culture positives of each grading).

indicates that these two methods may give more false negative than FM, but does not differ between themselves in this respect.

The percentage of culture positives not detected by FM is slightly more in the material under ZN method than under CS method but the difference is not statistically significant. The proportion of cultures with less than 20 colonies also does not differ much for the 2 groups of the specimens. Thus the 2 groups again appear to be similar and the differences noticed may not be attributed to any difference in the distribution of positives among them.

The above findings show that the CS method is atleast as good as the other two methods. There is some indication that the method is superior in giving less number of false positives, but valid conclusions in this respect could be

drawn only from larger data for which each of the 3 methods of microscopy and culture examinations have been done on the same specimens.

It was also observed that there was a fairly high degree of correlation between culture gradings and smear gradings by either ZN or CS method. Further, ZN detected 81.5% of culture positives and CS 82.5%.

Discussion

In developing and evaluating any method for staining of tubercle bacilli, both theoretical and practical aspects have to be considered. The usual theoretical considerations are that the method should,

1. enable uniform entry of stain through the surface barrier of the bacilli so that

- its morphology is brought out clearly,
2. not destroy the acid-fastness of the organism, and
 3. provide, by counter-staining, a suitable background against which the bacilli can be seen so distinctly that chances of missing them are reduced.

To this may be added a fourth important consideration viz., whether the method could eliminate the appearance of atleast non-pathogenic acid-fast organisms and thereby provide a more specific staining of pathogenic tubercle bacilli.

The failure of normal staining procedures in the case of acid-fast organisms is believed to be due to their complex surface structure which contains a large amount of unsaponifiable wax. In the conventional ZN method this barrier was most probably overcome, temporarily atleast, by applying heat while staining. In the cold staining method developed by Kinyoun and used by Tax Thiam Hok no attempt was made to increase the permeability of the surface barrier, but a more concentrated solution of the basic dye was used. Theoretically, such a concentrated stain is less likely to penetrate the barrier as freely as a more dilute solution. As the wax is known to be chloroform soluble, in the CS method, chloroform is used to render the surface of bacilli more pervious to the basic dye and stain the bacilli uniformly.

The acid-fastness of the bacilli is believed to be due to the presence of a lipid in the surface structure and the resistance of the bacilli to decolorisation has been found to increase with the amount of the acid-fast lipid in the bacilli (Darzin 1932). This is soluble in chloroform, but in actual practice cannot be removed completely by using chloroform. It is estimated that the chloroform soluble lipid fraction is 11.03% (Anderson 1927, 1941 and 1943) in the human tubercle bacilli and the low concentration of chloroform used in the CS method is unlikely to deplete the lipid fraction to a level at which any substantial decolorisation can take place.

Both ZN and CS methods used have the same procedure for counterstaining and as such provide the same type of background for demonstration of the bacilli under the microscope. The superimposition of these staining techniques on prestained fluorescent smear which is followed in this laboratory by first removing the potassium permanganate, provides a better counterstained background for the bacilli.

It has been observed in the present study that the CS method gives less number of false positives than ZN and FM methods. The reasons for this are not clear. However, some ex-

planations are possible based on the finding (loc. cit) that the resistance of the bacilli to decolorisation increases with the amount of acid-fast lipid in the bacilli. Thus the human bacilli are comparatively more acid-fast than other bacilli and saprophytes. This fact may affect the three methods differently. Two modes of action may be considered possible:

1. Larger quantities of stain may be taken up by the organisms when subjected to heat under ZN method. The comparatively less acid-fast organisms will lose some stain during decolorisation, but those stained under ZN method may still retain sufficient stain to be clearly visible under the microscope. This might also be a possible reason for the grading of smears under ZN method being generally higher than under CS method. However, this cannot explain why false positives are more under FM than CS method as the amount of stain taken up may be the same in both (lesser than under ZN as there is no heating). But the smaller concentration of acid used in FM method may not decolorise the less acid-fast bacilli to such an extent as in the CS method where higher concentration of acid is used.
2. With the use of chloroform, the acid-fast lipid fraction of the surface may be altered or reduced and thereby reduce the acid-fastness of each type of organism. It is likely that those acid-fast organisms with less amount of this lipid are more affected and get decolorised easily. Such organisms are probably not detected under CS method.

Either of the above explanations, if true, will indicate that the comparatively less acid-fast organisms are more likely to be discriminated by the CS method than ZN and FM methods and to that extent the CS method may be more specific. Preliminary investigation of *Mycobacterium phlei*, known to have chloroform soluble acid-fast lipid concentration of 4.98% (loc. cit) (c.f. 11.03% inhuman type), grown in liquid culture and stained by both ZN and CS methods showed that there was distinct difference. Only occasional bacillus here and there had taken stain by the CS whereas bacilli had taken uniform and deep staining by ZN method. This aspect is being further studied with acid-fast saprophytes. The false positives under FM method could probably be reduced by increasing the strength of acid for decolorisation if the first mode of action is true.

The theoretical considerations discussed above are sufficiently encouraging to expect better and reliable results by CS method. The section on findings showed that this method was atleast as good as ZN and FM methods and even indicated that it may be better than the other two as it gives less false positives. It also appears to be superior to ZN method with respect to false negatives also. Before accepting the latter conclusions it would be necessary to study larger material wherein all the three methods of staining and culture examination of the same specimens have been done.

There is no appreciable difference between ZN and CS methods in the cost and no difference in the time taken for staining. It may be mentioned here that the cold staining method suggested by TaxThiam Hok takes slightly less time but the cost is approximately trebled.

Under CS method, preparation of stain is as simple as under ZN method. Staining technique is simpler because heating, which requires certain amount of precision, is eliminated. It is easy to train para-medical staff of general health facilities in the new method, as for ZN as is being done now under the National Tuberculosis Programme, India. Further attempts are being made to simplify the method, make it cheaper by reducing the concentrations of chemicals required and to increase the speed. Even slight improvements in any of these may be worthwhile for large scale application and would make the method more acceptable for mass case-finding and the National Tuberculosis Programme.

Summary

A cold staining (CS) method using chloroform was compared with the conventional Ziehl-Neelsen (ZN) and fluorescence microscopy (FM) for evidence of tubercle bacilli in sputum smears. The reliability of these methods was judged on the basis of culture results and agreement among themselves. The CS method was found to be as efficient as the ZN method in detecting different gradings of culture positives.

False positives under the method were significantly lower than by ZN or FM microscopy. Some possible explanations for the relatively less number of false positives under CS method have been discussed.

Preparation of stain for cold staining is simple and in the procedure of staining, heating, a much too precise step in ZN method for large scale application, is eliminated.

To reduce false positives in FM, further investigation has been suggested employing increased strength of mineral acid for decolorisation.

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**A CONTROLLED STUDY OF THE INFLUENCE OF SEGREGATION OF
TUBERCULOUS PATIENTS FOR ONE YEAR ON THE ATTACK RATE
OF TUBERCULOSIS IN A 5-YEAR PERIOD IN CLOSE
FAMILY CONTACTS IN SOUTH INDIA***

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In 1956-57, a controlled study was undertaken at the Tuberculosis Chemotherapy Centre, Madras (1959), to compare the efficacy of treatment at home and treatment in sanatorium for one year with a standard regimen of isoniazid plus PAS; the response to treatment in the home series was almost as satisfactory as that in the sanatorium series (Tuberculosis Chemotherapy Centre, Madras, 1959). Subsequently, all the patients were managed almost entirely on a domiciliary basis. Of the patients with bacteriologically quiescent disease at one year, about one quarter received maintenance chemotherapy with isoniazid alone for two years, another quarter received isoniazid alone for one year and the rest received no specific chemotherapy; the relapse rates in the home and the sanatorium series over a 4-year period of follow-up have also been reported to be similar (Dawson et al., 1966¹). Patients with an unsatisfactory response in the first year and those who had a bacteriological relapse in the second or subsequent years were usually retreated with reserve regimens, first with streptomycin plus pyrazinamide and, if this was ineffective, with cycloserine plus ethionamide. Considering *all* patients originally admitted to the home and sanatorium study, it was found that the proportion of patients with bacteriologically quiescent disease at five years was practically the same in the two series (Dawson et al., 1966¹). These studies have firmly established the value of domiciliary chemotherapy for *tuberculous patients* in the Madras community.

As part of the same investigation, it was decided to study the risk of contracting tuberculosis for *contacts* of patients treated at home and for contacts of patients segregated in sanatorium during the first year of treatment. The attack rates of tuberculosis during the first two

years did not suggest any special risk to the contacts of patients treated at home (Andrews et al., 1960; Ramakrishnan et al., 1961a). The present report gives the findings for the contacts for the whole 5-year period.

The great majority of patients in the chemotherapy study came from the lowest income groups in Madras city. Living conditions were poor, the majority of the homes being overcrowded, and the nutritional standards low (Tuberculosis Chemotherapy Centre, Madras, 1959; Ramakrishnan et al., 1961 b. 1966¹.) It was under these conditions that the patients lived and their contacts were exposed to the risk of infection.

Definitions used in this report

The index case was defined as the first member of the family suffering from pulmonary tuberculosis to be registered at the Centre.

Close family contacts were defined as those related by blood or marriage and living, cooking and feeding in the same hut or house (or portion of the house) as the index case for at least the three months immediately prior to the start of treatment. The contacts of patients treated at home are termed "home contacts" while those of patients treated during the first year in sanatorium are termed "sanatorium contacts".

A single-infection family was defined as a family with only one infectious member, namely the index case, at the prevalence survey.

A multiple-infection family was defined as a family with one or more infectious members, *in addition to the index case*, at the prevalence survey.

1. Plan and Conduct of the contact study

The plan of the contact study, the routine for the initial and follow-up examinations of the close family contacts and the procedures adopted when a radiographic abnormality was found have already been described in detail (Andrews et al., 1960; Ramakrishnan et al., 1961a). Briefly, the contacts were to be examined by radiography and tuberculin testing at the start of treatment for the index case, and were to be followed routinely by serial radiography and tuberculin testing for a 5-year

* From the Tuberculosis Chemotherapy, Centre, Madras-31j India. The Centre is under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organization and the Medical Research Council of Great Britain.

¹ This paper is also published in the *Bulletin of the World Health Organization*.

¹ The radiograph nearest to a set examination (and not nearer to any other set examination) was regarded as that due for that examination. About 75% of the radiographs were taken within two weeks of the set date.

period. The first contact was admitted to the study in September 1956 and the last one in September 1957.

First Examination of contacts

Each contact was to have the following standard investigations initially :

(a) a full-plate postero-anterior radiograph of the chest;

(b) an intracutaneous tuberculin (Mantoux) test with 5 tuberculin units (TU) of purified protein derivative in 0.1 ml of solution on the left forearm. (Batch RT 22 without Tween 80 (Magnusson et al., 1958) was used throughout.) The greatest diameter of palpable induration after 2-3 (occasionally 4) days was measured in millimetres.

Follow up examinations of contacts

(a) A radiograph was to be taken at 3-monthly intervals during the first year and at 6-monthly intervals in the subsequent four years.

(b) At first the rule was to perform a tuberculin test with 5 TU, 3-monthly in the first year and 6 monthly in the second year, until an induration of 5 mm occurred, when further testing was stopped. This level of induration was soon changed to 10 mm and shortly afterwards to 20 mm, for reasons given by Andrews et al. (1960). From the third year, the procedure was to perform tests only annually, but for *all* contacts, irrespective of the indurations at previous tests.

In addition to the set examinations, contacts were frequently observed during the regular home visits by health visitors, and patients were encouraged to bring their contacts to the Centre if the latter were ill. When a radiographic abnormality appeared for the first time, the procedure was to set up a culture of at least one overnight sputum specimen or a pair of laryngeal swabs and to order further full-plate radiographs as indicated, which was seldom at intervals of more than one month. Further, after the first few months of the study, contacts showing changes in tuberculin sensitivity suggesting a recent infection were to have a full-plate radiograph taken 4-6 weeks later, and this was to be repeated at similar intervals for several months before returning to the normal routine.

Specific antituberculosis chemotherapy

Antituberculosis chemotherapy was usually not started unless bacteriological confirmation

of the diagnosis was obtained; exceptions were made in the case of infants or young children who were clinically ill, or where lesions were large, disseminated or showed rapid progression.

Independent assessment of the findings

Dr. J. Frimodt-Moller, who was the independent assessor for this study, made the assessment for the attack rates of tuberculosis in the third, fourth and fifth years, following the same procedure as for the first two years (Andrews et al., 1960; Ramakrishnan et al., 1961a). Throughout his assessments, he was unaware of whether an individual contact under review was related to a patient treated at home or in sanatorium in the first year, nor was he aware at any time of the radiographic and bacteriological progress of individual index cases.

The assessor had earlier scrutinized all the radiographs taken in the first and second years for the purpose of determining the attack rate during this period. At the current assessment, the object of which was to define the attack rates in the third, fourth and fifth years, he was shown the radiographs taken at the initial examination and at 24 months, together with *all* the films taken in the third, fourth and fifth years. He first assessed each series either as normal or abnormal. Next, he reviewed the *full* radiographic series (for the whole 5-year period) of those he had called abnormal and classified them as follows:

- (a) normal;
- (b) non-tuberculous abnormality;
- (c) doubtfully tuberculous abnormality;
- (d) active tuberculosis.

The assessor was then presented with the full radiographic series of certain groups of contacts and asked to review them in the light of relevant bacteriological, clinical (including the results of tuberculin tests) and pathological data obtained in the third, fourth and fifth years. These contacts were selected on the same basis as described by Ramakrishnan et al. (1961a); however, on account of the difficulties involved in interpreting the results of tuberculin tests undertaken over a period of several years changes in tuberculin sensitivity were not considered as grounds for selection.

The assessor also reviewed the radiographic series of all the new births in the 5-year period. Finally, for all the contact cases of active tuberculosis diagnosed during the five years, he described the first lesion, each subsequent increase and the maximal extent, with particular reference to the date of each; he then summarized the course of the disease in each case.

II. RESULTS

Population under study

As a result of the present assessment, there were certain minor changes in the prevalence (Table 1) and the attack rates of tuberculosis in the first two years (Table 2) reported by Ramakrishnan et al. (1961a). These changes arose because the assessor had more extensive

TABLE 1

Prevalence Findings in the 1961 Report a and Revised Figures for the Present Report

	Figures in 1961 report ^a	Revised figures (present report)
Total close family contacts	693	693
No initial radiograph	21	21
Doubtfully tuberculous abnormality, present initially	4	5
Active tuberculosis, present initially	49	50
Tuberculosis of doubtful activity, present initially	2	2
Inactive tuberculosis, present initially	11	12
Population at risk in the first year :		
In single-infection families	606	603
In multiple-infection families	530	528
	76	75

^a See Ramakrishnan et al. (1961a). For definition see page 10

information at the current assessment. For example, a radiographic series that he had reported as doubtfully tuberculous earlier could be reclassified as clearly non-tuberculous or definitely tuberculous in the light of subsequent information; conversely, the presence of a calcified focus in the later years could sometimes be traced back to a small lesion in a series that had previously been reported as normal.

The assessor identified one more contact with active tuberculosis and one more with inactive tuberculosis in single-infection families in the prevalence survey, and one more with a

doubtfully tuberculous abnormality in multiple-infection families. Consequently, the population at risk of developing tuberculosis decreased from 530 to 528 in single-infection families and from 76 to 75 in multiple-infection families.

As in earlier reports, in order to make a pure comparison between the infectivity of home index cases and that of sanatorium index cases, the attack-rate of tuberculosis has been studied separately for contacts in single-infection families and for those in multiple-infection families. As a result of the current assessment, there were certain additions to the figures quoted by Ramakrishnan et al. (1961a). Thus, in single-infection families (Table 2), five more cases of active tuberculosis (3 home, 2 sanatorium) were diagnosed in the first year and two (1 home, 1 sanatorium) in the second; further, one more contact (home) was detected with a doubtfully tuberculous abnormality in the first year and two more (both sanatorium) in the second year. (The only addition in the multiple-infection families was a contact (home) with active tuberculosis in the first year.)

Findings in single-infection families

The population at risk of developing tuberculosis in single-infection families is set out in Table 2, and shows a steady decline in numbers over the years which is due to the removal of contacts who developed tuberculosis or a doubtfully tuberculous abnormality and contacts who died.

Comparability of the two groups

In an earlier report (Andrews et al., 1960), it was shown that the two groups of contacts were similar initially in respect of a number of characteristics—namely, age, sex, family size, and results of radiographic examinations and tuberculin tests. In this report, it is therefore necessary to compare only the intensity of radiography, tuberculin-testing and bacteriology in the two series during the 5-year period of follow-up.

Table 3 shows that in both series of contacts the coverage was very high at all the set radiographic examinations, and particularly so at the yearly examinations, when extra efforts were made to ensure attendance of the contacts. Thus, 92.8% of the home contacts and 94.8% of the sanatorium contacts had a radiograph at 12 months, 92.6% and 94.7% at 24 months, 97.3% and 97.9% at 36 months, 99.5% and 97.8% at 48 months and 99.0% and 98.2%, respectively, at 60 months.

Table 4 sets out, separately for the two series of contacts, the average number of radiographs taken each year, whether they were

TABLE 2

Population at risk single-infection Families in the first and second years (earlier figures^b and revised), and in the third, Fourth and fifth years

Year of observation	Population at risk	Earlier figures (1961 report ^a)			Revised figures (present report)		
		Home contacts	Sanatorium contacts	Total	Home contacts	Sanatorium contacts	Total
		256	274	530	256	272	528
First	Active tuberculosis	9	18	27	12	20	32
	Doubtfully tuberculous abnormality	1	0	1	2	0	2
	Non-tuberculous death	7	1	8	7	1	8
	Population at risk	239	254	494	235	251	486
Second	Active tuberculosis	3	4	7	4	5	9
	Doubtfully tuberculous abnormality	0	1	1	0	3	3
	Non-tuberculous death	4	4	8	4	4	8
Third	Population at risk		—		227	239	466
Fourth	Population at risk	—	—		215	229	444
Fifth	Population at risk	—	—		211	224	435

^a See Ramakrishnan et al. (1961a).

For definition see page 10

taken at the set examinations or at extra examinations; it also gives the corresponding information for tuberculin tests and culture examinations. (Examinations undertaken at or after the start of treatment have not been included.) The findings show that the intensity of investigation was similar in the two series throughout the 5-year period, apart from a slight suggestion that the home contacts were studied rather more intensively bacteriologically.

Attack rate of tuberculosis among the contacts

Table 5 gives the attack rates, year by year, for the home and the sanatorium contacts, according to whether the induration to the initial 5 TU test was 0-4 mm (presumed tuberculin-negative), or 5 mm or more (presumed tuberculin-positive). This division of the population into uninfected and infected contacts is not entirely satisfactory for an area such as

South India, where low-grade tuberculin reactions, presumably due to infection with mycobacteria other than tubercle bacilli, are common (Frimodt-Moller et al., 1961). However, evidence from tuberculin tests in the contacts and their index cases has revealed no better criterion of tuberculous infection (Andrews et al., 1960).

Considering the initially tuberculin-negative contacts, 9 (10.5%) of the home and 10 (11.5%) of the sanatorium contacts developed active tuberculosis in the 5-year period. In both series, the majority of the cases—namely, seven in each series—occurred in the first year, three and six, respectively, occurring in the first 3 months. In subsequent years, only sporadic cases occurred in both series. Considering next the initially tuberculin-positive contacts, 15 (9.4%) of the home contacts and 28 (15.8%) of the sanatorium contacts developed tuberculosis in the 5-year period, a non-significant difference

TABLE 3
Percentages of Home and Sanatorium contacts with radiographs taken at the 12 set examinations during the five years

Year	Months after admission to study	Home contacts		Sanatorium contacts	
		Total surviving ^b	Percentage radiographed	Total surviving ¹	Percentage radiographed
First	3	252	91.7	272	91.2
	6	250	87.6	271	86.7
	9	250	86.8	269	88.8
	12	249	92.8	269	94.8
Second	18	231	90.5	247	84.2
	24	230	92.6	247	94.7
Third	30	224	94.6	238	89.5
	36	223	97.3	237	97.9
Fourth	42	214	98.1	228	97.8
	48	214	99.5	228	97.8
	54	207			
Fifth	60	207	98.6	224	97.3
			99.0	223	98.2

^a Among the population at risk for the year.

TABLE 4
Intensity of examination of the home and sanatorium contacts during the five years

	First year		Second year		Third year		Fourth year		Fifth year	
	Home	Sana-torium	Home	Sana-torium	Home	Sana-torium	Home	Sana-torium	Home	Sana-torium
Average number of radiographs	4.3 ^a	4.5 ^a	2.4	2.3	2.3	2.2	2.2	2.2	2.1	2.1
Average number of 5 TU tests	2.0 ^a	1.9 ^a	1.3	1.2	1.1	1.1	1.0	0.9	0.8	0.9
Percentage of total contacts	21	20	17	15	14	15	9	8	9	6
Contacts with one or more cultures	3.3	3.3	2.3 ¹	1.9	2.2	2.2	3.0	3.1	2.8	2.0
Average number of cultures										
Total contacts	256	272	235	251	227	239	215	229	211	224

^a Excluding the initial examination.

TABLE 5
Cases of active tuberculosis during the five years in the home and sanatorium contacts

Diameter of induration to initial 5 TU test (mm) ^a	Contact group	First year			Second year		Third year		Fourth year		Fifth year		Five-year period							
		Population at risk (A)	Contacts who developed active tuberculosis		Population at risk	Contacts who developed active tuberculosis	Population at risk	Contacts who developed active tuberculosis	Population at risk	Contacts who developed active tuberculosis	Population at risk	Contacts with developed active tuberculosis								
			1-3 months	4-12 months										No.	%	No.	%	No.	%	No.
0-4	Home	86	3	4	7	8.1	71	0	0.0	69	1	1.4	64	1	1.6	63	0	0.0	9	10.5
	Sanatorium	87	6	1	7	8.0	80	1	1.2	73	2	2.7	71	0	0.0	70	0	0.0	10	11.5
5 or more	Home	159	1	4	5	3.1	153	4	2.6	147	4	2.7	140	1	0.7	139	1	0.7	15	9.4
	Sanatorium	177	8	5	13	7.3	163	4	2.5	158	7	4.4	150	2	1.3	146	2	1.4	28	15.8

^a There were 19 contacts (11 home, 8 sanatorium) with no initial 5 TU test result; none developed active tuberculosis during the five years.

($P>0.1$). The higher attack rate in the sanatorium contacts was most conspicuous in the first year, when 13 (7.3%) of them developed tuberculosis, as compared with 5 (3.1%) in the home series ($P>0.1$); of these cases, eight and one, respectively, occurred in the first 3 months.¹ In subsequent years, cases continued to occur in both groups, although there was a decline in the number in the last two years; thus in the home and sanatorium groups combined, there were 8 (2.5%) cases in the second year, 11 (3.6%) in the third, 3 (1.0%) in the fourth and 3 (1.1%) in the fifth year.

Table 6 presents the attack rate of tuberculosis during the five years according to the dia-

TABLE 6
Attack rate of tuberculosis during the five years according to induration to tin¹ initial 5 TU test

Diameter of induration of initial 5 TU test (mm)	Home			Sanatorium		
	Total contacts	Contacts who developed active tuberculosis		Total contacts	Contacts who developed active tuberculosis	
		No.	%		No.	%
0-4	85	9	10	87	10	11
5-9	70	8	11	63	13	21
10-14	39	3	8	55	9	16
15 or more	50	4	8	59	6	10

meter of the induration to the initial 5 TU test. There was no clear association in either series. Thus, the proportions of home contacts who developed tuberculosis were 10%, 11%, 8% and 8% corresponding to indurations of 0-4, 5-9, 10-14 and 5 5 mm or more, respectively; the corresponding proportions for the sanatorium contacts were 11%, 21%, 16% and 10%, respectively.

The associations between sex, age and attack rate of tuberculosis over the 5-year period are

¹ In the families contributing to this comparison, there were 11 home as compared with 5 sanatorium contacts who had active tuberculosis at the prevalence survey. If these cases (apart from one home contact who was initially tuberculin-negative) are added to those developing in the first 3 months, there were 11 home and 13 sanatorium contacts with positive reactions to 5 TU initially, who were either found to have active tuberculosis when the index case started treatment or else manifested the disease within 3 months; thus the disparity between the home and the sanatorium series largely disappears.

presented in Table 7 and in the—figure overleaf. The attack rate was high in contacts aged less than 5 years, both in the males (22%) and in the females (28%), and (not tabulated here) in home contacts (17%) and sanatorium contacts (33%). Thus, contacts under the age of 5 years constituted a particularly vulnerable group. Considering all age-groups, 34 (12.9%) of the male contacts developed tuberculosis as compared with 28 (10.6%) of the female contacts.

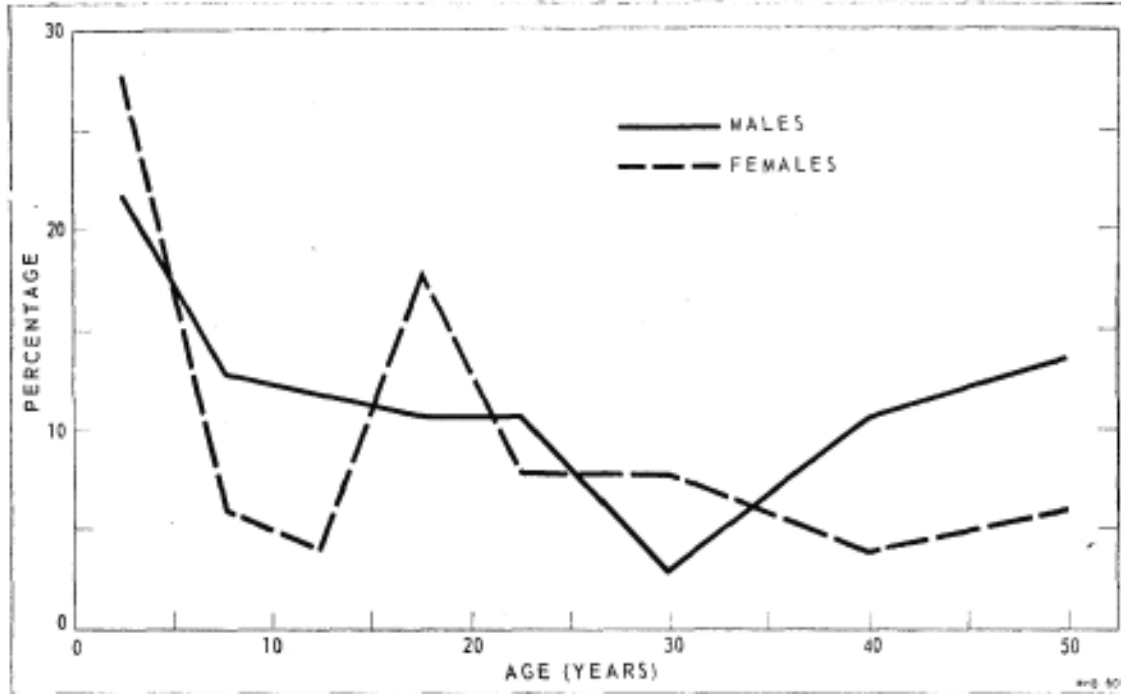
TABLE 7

Attack rate of tuberculosis during the five years in the home and sanatorium contacts, according to age and sex

Sex	Estimated age on admission (years)	Total contacts	Contacts who developed active tuberculosis	
			No.	%
Male	Less than 5	54	12	22
	5-14 15-24 25-34 35 or more	87	11	13
		46	5	11
		37	1	3
		40	5	12
	Total	264	34	12.9
Female	Less than 5	47	13	28
	5-14 15-24 25-34 35 or more	76	4	5
		41	5	12
		36	3	8
		64	3	5
	Total	264	28	10.6

Forms of active tuberculous lesions. Table 8 sets out the forms of all the 62 active tuberculous lesions that developed during the five years. In all, 54 cases (22 homes, 32 sanatorium) were classified as having primary or post-primary type disease and 8 (2 home, 6 sanatorium) as having adult-type disease. The former included 3 cases (1 home, 2 sanatorium) of tuberculous meningitis and 2 (both sanatorium) of miliary pulmonary tuberculosis (all 5 occurring in contacts aged under 5 years, in the first 2 years of follow-up), 3 cases (2 home, 1 sanatorium) of pleural effusion and 22 cases (8 home, 14 sanatorium) of progressive primary

ATTACK RATE OF TUBERCULOSIS DURING THE FIVE YEARS IN THE CONTACTS, ACCORDING TO AGE AND SEX



disease. It will be noted that there was a greater number of disseminated lesions in the sanatorium series.

Results of bacteriological examinations. Cultures were examined from 55 (21 homes, 34 sanatorium) of the 62 contacts who developed tuberculosis during the 5-year period, and

found to be positive on at least one occasion in 16 (6 homes, 10 sanatorium). Tests of sensitivity to streptomycin were undertaken on the first positive culture for 14 contacts and to isoniazid for 15. The cultures were sensitive to both drugs in 11, isoniazid-resistant but streptomycin-sensitive in 2 and isoniazid-sensitive but

TABLE 8

Forms of tuberculous lesions developing during the five years in the homes and sanatorium contacts

Contact group	Total with active tuberculous lesions	Adult-type disease	post-primary type disease	Form of primary or post-primary type disease					
				Tuberculous meningitis	Miliary pulmonary tuberculosis	Pleural effusion	Progressive primary	Simple primary	Other
Home	24	2	22	1	0	2a	8	9	26
Sanatorium	38	6c	32	2d	2	1	14e	12	1f

a Includes one case with a progressive primary complex.

b One of these had a tuberculin conversion associated with a positive sputum culture and a doubtfully tuberculous radiographic abnormality, while the other had *lupus verrucosus cutis*.

c Includes one case with an intra-pulmonary lesion and a pleural effusion.

d Both with a pulmonary lesion.

e Includes one case with spinal tuberculosis, and one with a lobar lesion and pleural effusion.

f Tuberculous adenitis.

streptomycin-resistant in 1. The culture that was tested for isoniazid sensitivity but not for streptomycin sensitivity was isoniazid-sensitive. There was no evidence that any of the three contacts with resistant cultures had been infected by their index cases.

Doubtfully tuberculous lesions developing during the five years

The independent assessor classified 13 contacts (7 home, 6 sanatorium) as having developed a doubtfully tuberculous abnormality during the 5-year period; despite careful scrutiny of all the relevant data (radiographs, tuberculin test results, bacteriological findings and clinical notes) during this period, he was unable to identify with certainty the etiology of any of these lesions. The lesions first appeared in the first year in two contacts (both home) in the second in three (all sanatorium), in the third in three (all home), in the fourth in three (1 home, 2 sanatorium) and in the fifth in two (1 home, 1 sanatorium). Of these 13 contacts, 7 (3 home, 4 sanatorium) were tuberculin-negative initially; a tuberculin conversion by the 10-mm criterion (fully tuberculous either before or at the time the doubtfully tuberculous abnormality developed in three of these—namely, two home contacts (aged 3 and 9 years) and one sanatorium contact (aged 2 years).

Non-tuberculous pulmonary lesions developing during the five years

The assessor reported one or more non-tuberculous radiographic abnormalities during the 5-year period in 76 contacts (40 home, 36 sanatorium). The first (or only) abnormality appeared in the first year in 28 contacts (13 home, 15 sanatorium), in the second in 14 (9 home, 5 sanatorium), in the third in 18 (8 home, 10 sanatorium), in the fourth in 8 (4 home, 4 sanatorium) and in the fifth in 8 (6 home, 2 sanatorium). Thus, the incidence was broadly similar in the home and sanatorium contacts during each of the five years of follow-up.

Incidence of tuberculin conversion during the five years

Throughout the period of study, tuberculin tests were given at the Centre by the clinic nurses and the great majority were also read in the Centre by them. To avoid bias, which might have resulted if the reader was aware of the findings of previous tests at the time of reading the current test, the standard procedure was to record the result of each test on a

separate card and subsequently to transfer the result to the contact's record sheet.

As in the earlier reports (Andrews et al., 1960; Ramakrishnan et al., 1961a), the principal definition of tuberculin conversion was an increase in induration of at least 10 mm at any subsequent 5 TCJ test from an initial induration of 0-4 mm; a second and slightly less restrictive definition was an increase of at least 8 mm at any subsequent test. A subsidiary approach consisted in identifying the two groups of contacts who had an induration of 5-7 mm to the initial test and who showed an increase of 10 mm or more, or an increase of 8 mm or more, at any subsequent test.

On the basis of these criteria, it was reported that the incidence of tuberculin conversion was very similar for the home and the sanatorium contacts during the first two years (Ramakrishnan et al., 1961a). This conclusion was confirmed by the findings over the 5-year period. Thus, 39% of 83 home contacts and 45% of 87 sanatorium contacts with indurations of 0-4 mm initially showed tuberculin conversion by the 10-mm criterion, and 46% and 48%, respectively, by the 8-mm criterion. In contacts with indurations of 5-7 mm initially, the conversions by the 10-mm criterion were 52% for the home and 59% for the sanatorium contacts, and by the 8-mm criterion, 74% and 77%, respectively.

Association tables were prepared separately for the home and the sanatorium contacts, relating the induration to the initial 5 TU test to the indurations at one year and at five years. These also showed that tuberculous infections had occurred no more frequently in the home contacts than in the sanatorium contacts. The results are not tabulated here.

Further evidence regarding the relative risk of infection in the two series may be obtained by examining the results of tuberculin tests in infants born during the first year, when the index cases of sanatorium contacts were isolated. Of 12 infants born into the families of the home series and who had at least one tuberculin test, 4 showed an induration of 5 mm or more to 5 TU on one or more occasions, as compared with 2 of 6 in the sanatorium series. The corresponding proportions for the total births during the 5-year period were 15% of 68 and 15% of 54, respectively.

In summary, the risk of infection, as assessed by changes in tuberculin sensitivity, was similar for the two groups of contacts.

Deaths

During the five years, there were 22 (8.6%) deaths among the 256 home contacts, as com-

pared with 12 (4.4%) among the 272 sanatorium contacts; the difference between the two series borders on statistical significance ($P=0.07$). All the deaths were reviewed by the independent assessor, who was provided with all the available data—radiographic, bacteriological and clinical (including tuberculin test results). He classified four (1 home, 3 sanatorium) of them as due to tuberculosis. Of these, two (home, 1 sanatorium) were due to tuberculous meningitis, in children aged 4 years and 1 year, respectively, and occurred in the second and first years, respectively. A third (sanatorium), a male aged 75, died of a massive effusion in the first year, and the fourth (sanatorium), a female aged 30, died in the third year with a positive sputum and cavitated pulmonary disease. All four were tuberculin-positive at the initial examination.

Of the remaining 39 contacts (21 home, 9 sanatorium) who died, many had not been seen by a doctor during the terminal illness, and autopsies were not performed on any of them. Consequently, clinical details regarding deaths had often to be gathered from relatives (occasionally after a lapse of months), and were frequently incomplete and inconclusive. On the available evidence, the independent assessor did not regard any of them as due to tuberculosis.

Of these 30 deaths, eight (7 home, 1 sanatorium) occurred in the first year, nine (5 home, 4 sanatorium) in the second, six (4 home, 2 sanatorium) in the third, two (1 home, 1 sanatorium) in the fourth and five (4 home, 1 sanatorium) in the fifth year. The age at death was 5 years or less in 15 contacts (11 home, 4 sanatorium), including 4 (all home) aged under 1 year; of these, 12 died with symptoms of diarrhoea and vomiting which were frequently associated with marasmus and dehydration, while in the remaining 3, death was due to smallpox, bronchopneumonia and drowning, respectively. None of these contacts had an induration of 5 mm or more to the initial 5 TU test; however, in three (all home), in whom death had been ascribed to gastroenteritis, the induration was 5 mm or more at the last test before death, two showing a conversion by the 10-mm criterion.

Of the remaining 15 deaths (10 home, 5 sanatorium), five were ascribed to heart failure, two to cerebral catastrophes, two to hepatic failure, and one each to pulmonary embolism, typhoid, dysentery, post-vaccinal encephalitis, *status epilepticus* and complications following a fractured femur. An induration of less than 5 mm to the initial 5 TU test was recorded in four contacts (all home); of these, two had an induration of 5 mm or more

at the last test before death, including one (whose death followed a fractured femur) who showed a conversion by the 10-mm criterion. In all, 3 (all home) of 19 contacts (15 home, 4 sanatorium) with an induration of less than 5 mm to the initial 5 TU test had a conversion by the 10-mm criterion at the last test before death, but none had evidence of active tuberculosis.

In summary, there is no firm evidence that these deaths were related to tuberculous infection; however, there is no simple explanation for the finding of a greater number of deaths among the home contacts.

Births

There were 72 births in the home families and 57 in the sanatorium families during the five years. Of these contacts, 11 (15%) and 12 (21%), respectively, died, including one (home) who had an induration of 10 mm to 5 TU at three months before death followed by no induration at two subsequent tests. On the basis of the available evidence, the independent assessor considered that none of the deaths was due to tuberculosis. Of the 61 home and 45 sanatorium contacts who were alive at five years, one (born in the fifth year) and none, respectively, had developed active tuberculosis and three (1 born in the first year and 2 in the second) and one (born in the third year), respectively, had developed doubtfully tuberculous abnormalities. Tuberculin tests were undertaken in 68 of the home contacts and 54 of the sanatorium contacts; the results have been described earlier.

Findings in Multiple-Infection Families

In all, 75 contacts with no initial evidence of tuberculosis (apart from calcification in seven cases) were excluded from the main comparison because they came from multiple-infection families of these, 39 were from the home series and 36 from the sanatorium series. The two series were distributed similarly in terms of sex, initial 5 TU test results and family size, and were investigated with similar intensity by radiography and tuberculin testing over the 5-year period. However, the home series had rather more contacts under the age of 5 years (28%) than the sanatorium series (17%) and, further, there was some evidence that the intensity of bacteriological investigations was rather greater proportion of the contacts had calcification initially in the sanatorium series (14%) than in the home series (5%).

In the first year, six (15%) of the 39 home contacts developed active tuberculosis, as com-

pared with none of the 36 sanatorium contacts; the six contacts were aged 9 months, 2, 3, 4, 22 and 32 years, and included two who were tuberculin negative initially. In subsequent years, no cases of tuberculosis developed in the home contacts, as compared with two in the sanatorium contacts (both tuberculin-positive initially), one in the second year and one in the fourth year. One home contact (with an induration of 15 mm to the initial 5 TU test), as compared with none of the sanatorium contacts, developed a doubtfully tuberculous lesion; this was in the first year.

Considering the tuberculin test result, seven of the home and nine of the sanatorium contact had an induration of 0-4 mm to the initial 5 TU test. During the 5-year period, four of the former and five of the latter had a tuberculin conversion by the 10-mm criterion, and five and six, respectively, by the 8-mm criterion. Of nine home contacts with an induration of 5-7 mm initially, five had conversion by the 10-mm criterion as did two of four sanatorium contacts; the numbers who had a conversion by the 8 mm criterion were seven and three, respectively.

There were four deaths (3 home, 1 sanatorium) in the 5-year period and all were classified as non-tuberculous by the independent assessor.

There were 19 births (12 home, 7 sanatorium) during the 5-year period. Of these, one (sanatorium) developed tuberculosis in the third year, two (1 home, 1 sanatorium) died from non-tuberculous causes and two (1 home, 1 sanatorium) developed an induration of 5 mm or more to the 5 TU test.

Consolidated findings for contacts in single-infection and multiple-infection families

In all, 295 home contacts and 308 sanatorium contacts were exposed to the risk of developing tuberculosis over the 5-year period. Of these, 30 (10.2%) home contacts developed tuberculosis, as compared with 40 (13.0%) sanatorium contacts, including 10 and 12, respectively, with at least one positive culture. A doubtfully tuberculous abnormality was reported in eight (2.7%) home and six (1.9%) sanatorium contacts. There were 25 deaths (8.5%) in the home contacts, as compared with 13 (4.2%) in the sanatorium contacts, a difference which just attains statistical significance ($P=0.05$); however, only one and three, respectively, were classified as due to tuberculosis by the independent assessor. Tuberculin conversion occurred with similar frequency in both series. Thus, in initially tuberculin-negative contacts, 36 (40%) in the home series

and 44 (46%) in the sanatorium series had a conversion by the 10-mm criterion, and 43 (48%) and 48 (50%), respectively, by the 8-mm criterion.

During the 5-year period, there were 84 births in the home families and 64 in the sanatorium families. Of these, 12 (14%) home and 13 (20%) sanatorium died, none from tuberculous causes. One contact in each series developed active tuberculosis, and three and one, respectively, developed a doubtfully tuberculous abnormality. An induration of 5 mm or more to 5 TU was observed in 14% of the home contacts and 15% of the sanatorium contacts.

In summary, both the risk of infection and the risk of developing tuberculosis over the 5-year period were similar for the home contacts and the sanatorium contacts,

III. Discussion

The present report gives information on the attack rate of tuberculosis during a 5-year period among the close family contacts of patients with newly diagnosed infectious pulmonary tuberculosis who came from a poor, overcrowded section of a large urban community in South India. The index cases were, on diagnosis, allocated at random to treatment with isoniazid plus PAS for one year either at home or in sanatorium (Tuberculosis Chemotherapy Centre, Madras, 1959). Subsequently, about half the patients with bacteriologically quiescent disease at one year received maintenance chemotherapy with isoniazid alone for one or two years (the rest receiving no specific chemotherapy) while patients with bacteriologically active disease and those who had a bacteriological relapse were prescribed reserve regimens (Dawson et al., 1966). As a result of the random allocation in the first year, the close family contacts (all of whom had been living, feeding and cooking with the patients for at least the three months immediately prior to diagnosis) were divided into "home contacts" and "sanatorium contacts". None of these contacts was given BCG vaccination or chemoprophylaxis, as the aim of the present study was to assess whether there was any special risk to the home contacts which might indicate the use of these preventive measures; instead, they were all followed by an intensive routine of supervision.

The main comparison is between 256 home and 272 sanatorium contacts in families in which the only source of infection at the prevalence survey had been the index case. The two groups of contacts were similar at this time in respect of sex, age, family size and

results of initial radiographic examinations and tuberculin tests. Further, there were only minor differences in the intensity of subsequent investigations by bacteriology, radiography and tuberculin testing in each of the five years. A particularly high coverage by radiography was achieved, a coverage which actually increased in the later years; thus, the proportion of contacts who had a radiographic examination was 94% at one and at two years 98% at three years and 99% at four and at five years. The attack rates of tuberculosis in the study are therefore based on exceptionally comprehensive radiographic information. Further, in order to avoid bias, they have been based on assessments of the radiographic series and other relevant data by an experienced independent assessor who was unaware throughout, for any individual contact under review, of the identity of Index case (home or sanatorium) or his response to treatment.

Over the 5-year period, 10.5% of 86 home contacts who were tuberculin-negative on admission to study developed tuberculosis, as compared with 11.5% of 87 sanatorium contacts, the attack rates in the first year being 8.1% and 8.0%, respectively. Among the initially tuberculin-positive contacts, 9.4% of 159 home and 15.8% of 177 sanatorium contacts developed tuberculosis, the attack rates in the first year being 3.1% and 7.3%, respectively. Thus, the home contacts were at no special risk of developing tuberculosis, either over the whole 5-year period or, indeed, even in the first year, when the infectious index cases were under treatment at home.

The sanatorium contacts were exposed to the risk of contracting tuberculosis from two sources. First, from the index case before the diagnosis of tuberculosis had been made and before the patient had been segregated in sanatorium and, secondly, from some other source in the urban community in which the family lived (approximately 90% of the patients were non-infectious when discharged from sanatorium at the end of the first year). The home contacts were exposed to both these risks and, *in addition*, to the risk of continued contact with the index case during treatment in his own home from the outset.

Information on the relative importance of these three sources of infection is provided by the findings of the present study. Of the total of 62 cases that arose in the 5-year period among the home and the sanatorium contacts, no less than 32 occurred in the first year, 18 of them in the first 3 months. These 18 included six of the seven cases that occurred in the first year among the sanatorium contacts who were tuberculin-negative initially and whose index cases had been segregated within a few days of

diagnosis. This strongly suggests that these 18 contacts had already been infected and were incubating the disease when treatment was started for the index case, although the disease (and in nine contacts even the sensitivity to tuberculin) became manifest only afterwards. Further, the finding that, despite the segregation of the index cases of the sanatorium contacts for a year, the attack rate in the first year in the initially tuberculin-positive sanatorium contacts was higher than in the tuberculin-positive home contacts also suggests that infection had occurred before the diagnosis of the index case, and that the isolation was effected too late to influence the risk to the contacts. Thus, it is clear that the major part of the risk to the contacts of developing tuberculosis had occurred before the diagnosis of the index cases, the great majority of whom had presented with symptoms at chest clinics; it therefore follows that an early diagnosis of tuberculosis can be expected to play an important role in preventing cases of tuberculosis arising in close contacts.

Cases of tuberculosis occurred sporadically after the first year in initially tuberculin-negative contacts—two in the home series and three in the sanatorium series—and might well have been due to exposure to an urban community with a high prevalence of tuberculosis. (The national sample survey of tuberculosis in India, Indian Council of Medical Research, 1959) showed that the prevalence of active and probably active tuberculosis in those aged 5 years or more ranged from 1.5% to 2.1% in six large cities.) However, the possibility that one or more of the cases in the home contacts may have arisen from exposure to the index case during his treatment at home cannot be excluded.

Considering next the contacts who were initially tuberculin-positive, cases continued to emerge in both the home and the sanatorium series in the second and subsequent years. However, there was some evidence of a decline in the incidence in the last two years. Thus, considering both the home and sanatorium series combined, there were 18 cases in the first year, 8 in the second, 11 in the third, 3 in the fourth and 3 in the fifth.

It is noteworthy that of the 62 cases, 40 were under the age of 15 years, including 25 under the age of 5 years. Further, a number of lesions in the contacts under 5 years of age were serious and included three cases of tuberculous meningitis, two of miliary pulmonary tuberculosis and one of spinal tuberculosis with a pulmonary lesion (five of the six occurred in sanatorium contacts). The attack rate for the 5-year period was 25% in contacts

under 5 years of age, 9% in those aged 5-14 years and 8% in those aged 15 years or more; the corresponding rates for the first year were 18%, 4% and 3%, respectively. These findings suggest that there is scope for chemoprophylaxis in close family contacts, which has been reported to be effective by Ferebee & Mount (1962) and Ferebee (1964). However, any such measure must necessarily be fitted into the over-all tuberculosis programme for the country, and be given a lower priority than the treatment of index cases (Fox, 1964), particularly in developing countries with limited resources.

There is now evidence of the protective value of BCG in tuberculin-negative subjects in India (Frimodt-Moller, Thomas & Parthasarathy, 1964). In the present study, all 19 (11%) cases of tuberculosis in initially tuberculin-negative contacts were aged 8 years or under, and 5 of these occurred in the second or subsequent years. This suggests that there is scope for BCG vaccination among initially tuberculin-negative contacts, particularly in children.

Although the main serial assessment of the contacts was radiographic, tuberculin testing was used as a subsidiary measure of infection. Tuberculin conversion has been defined for the purpose of this study in several ways, the principal definition being an increase in diameter of induration of 10 mm or more from an initial induration of 0-4 mm, to 5 TU. The observed incidence of such conversions during the 5-year period was 39% of 83 home contacts and 45% of 87 sanatorium contacts, including 25% and 23%, respectively, in the first year—finding which do not indicate any special risk to the home contacts. These figures, as well as others based on less restrictive definitions, are useful for making valid comparisons between the risk of infection among the home contacts and the sanatorium contacts. However, for reasons stated below, the comparisons themselves are not very precise nor do the figures above measure the true infection rates in the two series. First, a high incidence of non-specific reactions, presumably due to infection with mycobacteria other than tubercle bacilli, has been reported in South India (Frimodt-Moller et al., 1961). Secondly, there is evidence from the USA (S.H. Ferebee, personal communication, 1964) and South India (Raj Narain et al., 1966) that repeated tuberculin testing enhances allergy to tuberculin. Thirdly, the magnitude of the error of the tuberculin test is such (Raj Narain et al., 1966) that it was not unusual in this study to find that contacts who had a tuberculin "conversion" had low indurations repeatedly

at subsequent tests. Lastly, it is possible that variations in standards of tuberculin testing and reading could have occurred during the period of follow-up, resulting, for example, in a systematic over-reading of the test indurations at the later stages. However, in the present instance, information is available concerning the standards of tuberculin testing and reading over the 6-year period of study (that is, the 1-year period of intake plus the 5-year period of follow-up); this is in the form of distributions of 5 TU test results in newly diagnosed index cases and their close family contacts on admission to various studies at the Centre during the period. These showed that, despite numerous changes in the personnel giving and reading the tests, there was no real variation in standards, apart from a slight tendency for smaller reactions to be recorded in the last 9 months of the 6-year period of study (unpublished data).

The present report is the last of a series of nine publications concerning an investigation of the role of ambulatory chemotherapy for pulmonary tuberculosis, which was initiated at the Tuberculosis Chemotherapy Centre, Madras, nearly 10 years ago. These have shown, from the point of view both of the patients (Tuberculosis Chemotherapy Centre, Madras, 1959; Velu et al., 1960; Devadatta et al., 1961; Ramakrishnan et al., 1961b, 1966; Dawson et al., 1966) and of their contacts (Andrews et al., 1960; Ramakrishnan et al., 1961a), the high degree of effectiveness of well-organized domiciliary chemotherapy. Further, the striking level of co-operation, both of the patients and of their close family contacts for the five years, is an important finding, not only for long-term field research in other diseases in India, but for the general field of social inquiry also.

IV. Summary

1. In a controlled study undertaken in South Indian families to assess the value of domiciliary treatment of pulmonary tuberculosis for one year as compared with sanatorium treatment, there were 693 close family contacts—that is, relatives living, cooking and feeding with the infectious patients for at least the three months immediately prior to diagnosis. The great majority of the families came from the lower income groups in Madras city and their living conditions and dietary standards were poor.

2. The contacts were followed by serial radiography and tuberculin testing, and, where necessary, bacteriological examinations, to determine the attack rate of tuberculosis during a 5-year period.

3. The main comparison is among contacts in families in which the only source of infection initially was the index case. In these "single-infection" families, there were 256 contacts of patients treated at home (home contacts) and 272 contacts of patients isolated in sanatorium in the first year (sanatorium contacts). In subsequent years, all patients were followed up at home.

4. The two groups of contacts were similar initially in respect of age, sex, family size, radiographic findings and tuberculin test results; further, they were followed with similar intensity by radiography and tuberculin testing throughout the five years. The coverage by radiographic examination was very high, the proportion of contacts examined being 94%, 94%, 98%, 99% and 99% at 1, 2, 3, 4 and 5 years, respectively.

5. All the radiographic series, together with bacteriological and clinical information (including tuberculin test results), were reviewed by an independent assessor, who was unaware throughout of the identity (home or sanatorium), or the progress, of the index case of any individual contact under review.

6. During the 5-year period, there were 34 deaths (22 home, 12 sanatorium) of which four (1 home, 3 sanatorium) were classified by the independent assessor as due to tuberculosis.

7. Tuberculosis developed during the 5-year period of follow-up in 24 (9.4%) home and 38 (14.0%) sanatorium contacts, including 12 (4.7%) and 20 (7.4%), respectively, in the first year; of these, 4 and 14, respectively, occurred in the first 3 months.

8. In all, 8 cases (2 home, 6 sanatorium) were classified as having adult-type disease and the remaining 54 as having primary or post-primary disease; the latter included three cases (1 home, 2 sanatorium) of tuberculous meningitis and two cases (both sanatorium) of miliary pulmonary tuberculosis, all in contacts under 5 years of age.

9. The attack rate of tuberculosis over the 5-year period in initially tuberculin-negative contacts was 10.5% in the home series and 11.5% in the sanatorium series, including 8.1% and 8.0%, respectively, in the first year; the corresponding figures for initially tuberculin-positive contacts were 9.4% and 15.8% over the 5 year period, and 3.1% and 7.3% in the first year.

10. The attack rate in contacts under the age of 5 years was 24.8% as compared with 8.7% in those aged 5 years or more.

11. An increase in the induration of at least 10 mm at any subsequent 5 TU test from an initial induration of 0-4 mm was observed

in 39% of the home and 45% of the sanatorium contacts.

12. The findings in this report, together with those published previously for patients, demonstrate that ambulatory treatment of patients with pulmonary tuberculosis is practicable and effective, and safe for the close family contacts.

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THE DIET, PHYSICAL ACTIVITY AND ACCOMMODATION OF PATIENTS WITH QUIESCENT PULMONARY TUBERCULOSIS IN A POOR SOUTH INDIAN COMMUNITY*†

A Four-Year Follow-up Study

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& S. RADHAKRISHNA

A previous communication from the Tuberculosis Chemotherapy Centre, Madras, presented the results of a study of the influence of diet on the response to treatment of patients with pulmonary tuberculosis receiving a standard combination of antituberculosis drugs for one year (Ramakrishnan et al., 1961). The dietary study was undertaken in the course of a controlled comparison of treatment at home with treatment in sanatorium for a year with isoniazid plus PAS in patients who were drawn from a malnourished poverty-stricken section of the community in Madras City (Tuberculosis Chemotherapy Centre, 1959). It was found that the response to treatment was not influenced by the diet during the year; thus, the difference between the home and the sanatorium series in the proportion of patients whose disease attained bacteriological quiescence at one year was small even though the diet of the patients treated at home was clearly inferior in terms of total calories, total and animal proteins, fats, several of the vitamins and phosphorus, an inferiority which was further accentuated by the much greater physical activity of the patients in the home series.

All the patients in the home series and in the sanatorium series who had bacteriologically quiescent disease at one year have subsequently been followed up for four years. Their diet was assessed on two occasions in the second year and two in the third year, in order to study the relationship between diet and the occurrence of bacteriological relapse. However, because there were few bacteriological relapses, the present report is principally concerned with the diet, physical activity and accommodation of patients in whom bacteriological quiescence was maintained throughout the four years of follow-up.

1. General Plan and Conduct of the Study

The patients in the present analysis

An earlier report (Tuberculosis Chemother-

* From the Tuberculosis Chemotherapy Centre, Madras-31, India. The Centre is under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organization and the Medical Research Council of Great Britain.

† This paper is also being published in the *Bulletin of the World Health Organization*.

rapy Centre, 1959) has described the progress during a year of chemotherapy with isoniazid plus PAS of 163 patients with extensive pulmonary tuberculosis. These patients had presented themselves at local chest clinics because of symptoms and, in most cases, had received no antituberculosis chemotherapy (two patients had received up to two weeks of chemotherapy). They were allocated at random to treatment for one year at home or in sanatorium and, at the end of the year, 130 patients had attained bacteriologically quiescent disease. Of these, three (all home patients) have been excluded from the present study; one died of carcinoma of the oesophagus in the 15th month, another died suddenly in the 17th month of anontuberculous condition and the third refused to co-operate in the dietary assessments. There remain 127 patients in the present study of whom 57 had been treated at home and 70 in sanatorium in the first year. Of these patients, 63 (30 home, 33 sanatorium; received a placebo, calcium gluconate (500 mg a day in one tablet), in the second year; 63 (26 home, 37 sanatorium) received isoniazid (150, 175 or 200 mg a day, depending on the body-weight); and one received isoniazid plus PAS. In all except three patients the allocation was made at random. Of the 63 patients who received the placebo in the second year, 58 had quiescent disease at two years and therefore received the placebo in the third year also. Of the 63 patients who received isoniazid in the second year, 61 still had quiescent disease at two years, and, of these, 31 received the placebo in the third year and 30 isoniazid, the treatment being allocated at random for all except one patient. All patients with quiescent disease at three years received the placebo in the fourth year and all with quiescent disease at four years received no medicament in the fifth year.

General management and routine investigations

The management of patients in both series has already been reported in detail in earlier reports (Tuberculosis Chemotherapy Centre, 1959; Velu et al., 1960; Devadatta et al., 1961). Briefly, the patients in the home series were treated in their own homes from the beginning, with clinic supervision. The patients in the sanatorium series were treated in sanatorium for one year, after which they continued their

treatment in their own homes, with clinic supervision. All the patients in both series attended the clinic monthly in the second year and once in every three months in the third, fourth and fifth years. Their examinations at each attendance included a chest radiograph and weight measurement, and a record was kept of the patient's physical activity and occupation. In the second year, an overnight specimen of sputum or a pair of laryngeal swabs was examined by culture for tubercle bacilli and, thereafter, a minimum of two cultures was examined every three months.

Dietary assessments

Dietary assessments were performed on admission to treatment, at some time between 6 and 12 months, and at 18, 24, 30 and 36 months. All the assessments were made by one of us (K.R.). The method of conducting the dietary assessments, reported in detail earlier (Ramakrishnan et al., 1961), was as follows:

All the patients were carefully interrogated and, sometimes, other members of the family were also questioned to elicit precise information on the amounts of different articles of food consumed by the patient and the various members of the family in the course of the day. It is usually possible to make a fairly accurate assessment of an individual's dietary intake by assessing the total quantity of food consumed by the whole family and, on the basis of adult equivalents (Aykroyd, Patwardhan & Ranganathan, 1951), calculating the proportion of food consumed by the individual. This method has been used by the Nutrition Research Laboratories of the Indian Council of Medical Research (Pasricha, 1958, 1959). However, most of the patients in the present study were seriously ill when treatment was originally started (Tuberculosis Chemotherapy Centre, 1959) and had little or no appetite so that they were consuming very much less than their normal intake of food (Ramakrishnan et al., 1961). In such circumstances, the adult equivalent method would give misleadingly high values; therefore, the patients were asked to express, with the aid of standard vessels, the actual quantities of food they ate. The adult equivalent was applied only for items like oil, dhal (pulses) and sugar, where it is difficult to express the actual quantity consumed. Special articles of diet consumed by the patient alone—for example, eggs or fruit—were also taken into consideration in calculating the dietary intake of the patient. Since the above procedure was used for all the pretreatment assessment, it was used for all the subsequent dietary assessments also, so as to maintain comparability.

The reliability of this oral questionnaire technique was confirmed in a comparison with the weighment method, both in the home patients and in the sanatorium patients (Ramakrishnan et al., 1961).

Definitions of bacteriologically quiescent and bacteriologically relapsed disease

Bacteriologically quiescent disease

(a) *At one year.* A patient's disease was classified as bacteriologically quiescent if all the cultures for at least the last three monthly examinations (that is, those at 10, 11 and 12 months) were negative.

(b) *During the four-year period of follow-up.* Patients who yielded only negative cultures, or an isolated positive culture among a series of negative ones, were considered to have bacteriologically quiescent disease throughout the four-year period of follow-up.

Bacteriologically relapsed disease

If a patient yielded two or more positive cultures in a period of six months, the disease was considered to have relapsed bacteriologically. In the second year this meant two or more positive cultures in seven consecutive monthly examinations. In the subsequent years, when two cultures were examined every three months, this meant two or more positive cultures in three consecutive examinations—for example, at 27, 30 and 33 months.

Plan of the report

Section II gives the relapse rates in the four-year period of follow-up, separately for the home and the sanatorium series. Section III considers in detail the diet, weight changes, physical activity, occupation and accommodation of the patients whose disease remained bacteriologically quiescent throughout the four-year period of follow-up. The findings for the home and the sanatorium series are presented separately, because there were large dietary differences between the two series in the first year. The corresponding details for the small numbers of patients whose disease relapsed bacteriologically are presented in section IV. Section V considers the role of chemotherapy in the prevention of relapse, section VI is the discussion and section VII the summary.

II. Relapse Rates in the Four-Year Period of follow-up

Home series

Of the 57 patients in the home series, 5 (9%) had a bacteriological relapse in the 15th,

16th, 22nd, 27th and 57th months, respectively. Thus the great majority of patients had quiescent disease throughout the four-year period of follow-up.

Sanatorium series

Of the 70 patients in the sanatorium series, 7 (10%) had a bacteriological relapse in the 13th, 14th, 15th, 17th, 18th and 54th months, respectively. As in the home series, the great majority of patients maintained quiescent disease throughout the four-year period of follow-up.

III. Patients with bacteriologically quiescent disease throughout the four-year period of follow-up

Home series

*Dietary intake:*¹

The intake of the main dietary factors at the five assessments in the first three years after admission to the study is set out in Table 1 for the 52 patients in the home series who had quiescent disease throughout the follow-up period.

Calories. The total daily intake was less than 1800 calories in 37% of the patients at the assessment in the first year, in 38% at 18 months, and in 54%, and 36% 39% at 24, 30 and 36 months, respectively. At each of the five assessments, about one-fifth of the patients had a daily intake of 2600 calories or more.

Proteins. The total daily protein intake was less than 50 g in 50% of patients at the assessment in the first year, in 58% at 18 months, and in 62%, 54% and 65% at 24, 30 and 36 months, respectively. The data for animal protein intake have not been tabulated here, but a large majority of the patients had a daily intake of less than 20 g—namely, 77% at the assessment in the first year, 92% at 18 months, 90% at 24, 94% at 30 and 92% at 36 months. The proportions with a daily intake of less than 10 g of animal protein

were 42% 37%, 46%, 58% and 65%, respectively.

Fats. Only a small proportion of patients had a daily intake of fats of 40 g or more at any of the five assessments and the intake was less than 20 g in 63% of the patients during the first year, in 56% at 18 months, and in 65%, 66% and 65% at 24, 30 and 36 months, respectively.

Carbohydrates. A considerable majority of the patients at each of the five assessments had a daily intake of 300 g or more of carbohydrates; the proportion who had 400 g or more was 50% during the first year, 48% at 18 months, 42% at 24, 50% at 30 and 51% at 36 months.

In summary; the intake of the proximate principles (proteins, fats and carbohydrates) and calories was similar to the five assessments in the first three years.

Minerals and vitamins. The intake of certain minerals—namely, calcium, phosphorus and iron—and of vitamin A, carotene, thiamine, riboflavin, nicotinic acid and ascorbic acid was calculated from the assessments of the diet during the first year only. In view of the fact that the intake of minerals and vitamins is generally associated with that of proteins and fats in the poorer segments of the population (C. Gopalan, personal communication), and because the intake of proximate principles by the patients at each of the various assessments was similar, the intake of minerals and vitamins was not calculated for the later periods, but was presumed to be of the same order as in the assessment undertaken during the first year. The calculations here are based on the mineral and vitamin contents of uncooked foodstuffs and, as such, the results do not take into account loss in cooking. The findings are described below, but have not been tabulated in this report.

Calcium. The daily intake of calcium was less than 1 g in 41 (79%) of the patients, 15 (29%) receiving less than 0.5 g a day. However, 79% of the patients chewed betel leaves to which slaked lime had been added; this additional source of calcium has not been taken into account in the calculations.

Phosphorus : The daily intake of phosphorus was less than 1 g in 21 (40%) of the patients and between 1 g and 1.5 g in 23 (44%).

Iron : The daily intake of iron was less than 20 mg in 25 (48%) of the patients, between 20 and 30 mg in 17 (33%) and 30 mg or more in 10 (19%).

Vitamin A : The intake of vitamin A was

¹ The daily allowances recommended by the Nutrition Advisory Committee of the Indian Council of Medical Research for adults in all types of work are 45-55 g of protein, 1 g of calcium, 20-30 mg of iron, 3000-4000 IU of vitamin A, 1-2 mg of thiamine and 50 mg of ascorbic acid. The amount of fats recommended as "probably desirable" is 45-60 g, of riboflavin is 1500 µg and of nicotinic acid is 4-19 mg. The rest of the diet is to be composed of carbohydrates, the calorific value of which, together with that of proteins and fats, should amount to 2000-2400 for sedentary workers, 2300-2800 for those engaged in moderately strenuous work and 3000-3900 for those doing heavy work (Aykroyd, Gopalan & Balasubramanian, 1963).

TABLE I

Dietary intake of patients in the home series who had bacteriologically quiescent disease throughout the four-year period of follow-up

Dietary intake	Time of assessment									
	During the first year		18 months		24 months		30 months		36 months	
	No.	%	No.	%	No.	%	No.	%	No.	%
Calories:										
Less than 1400	5	10	9	11	9	17	9	78	10	20
1 400-1799	14	27	11	21	19	37	9	78	10	20
1 800-2199	12	23	14	27	8	75	15	30	11	22
2 200-2599	10	19	6	12	5	70	9	78	10	20
2 600 or more	11	21	12	23	11	27	8	76	10	20
Total proteins (g):										
Less than 30	3	6	5	10	5	70	8	16	7	14
30-39	10	19	13	25	11	27	6	72	11	22
40-49	13	25	12	23	16	31	13	26	15	29
50-59	13	25	9	11	10	79	15	30	7	14
60-69	6	12	1	13	7	73	3	(5	1	14
70 or more	7	13	6	12	3	6	5	70	4	8
Fats (g):										
0-9	13	25	14	27	12	23	16	32	13	25
10-19	20	38	15	29	22	42	17	34	20	39
20-29	1	13	14	27	11	27	11	22	10	20
30-39	1	13	6	12	7	73	6	72	4	8
40-49	2	4	1	2	0	0	0	0	2	4
50 or more	3	6	2	4	0	0	0	0	2	4
Carbohydrates (g):										
Less than 200	3	6	2	4	1	2	3	6	3	6
200-299	5	10	9	17	11	27	7	14	7	14
300-399	18	35	16	31	18	35	15	30	15	29
400-499	11	21	14	27	10	79	13	26	14	27
500 or more	15	29	11	21	12	23	12	24	12	24
Total patients	52	700	52	700	52	700	50*	100	51‡	100

* Excluding two patients who were not assessed.

‡ Excluding one patient who was not assessed.

TABLE 2
Weight change in the patients with bacteriologically quiescent disease throughout the four-year period of follow-up

Period (months)	Home series				Sanatorium series			
	Males		Females		Males		Females	
	No. of patients weighed*	Average weight change (lb)†	No. of patients weighed††	Average weight change (lb)†	No. of patients weighed*	Average weight change (lb)†	No. of patients weighed††	Average weight change (lb)†
0-6	34	+ 9.5	15	+ 11.7	36	+ 15.3	26	+ 16.5
6-12	34	+ 1.3	15	+ 1.3	36	+ 2.2	26	+ 7.2
12-18	32	— 0.5	16	— 0.7	37	- 2.4	23	— 4.1
18-24	32	+ 0.2	15	— 1.6	37	— 1.6	22	— 2.3
24-36	34	+ 0.2	14	0.0	37	+ 0.2	24	- 3.8
36-48	33	+ 1.0	15	+ 1.0	36	+ 0.5	21	— 1.6
48-60	32	+ 0.8	16	+ 1.2	36	+ 0.2	21	+ 1.0
0-60	32	+ 13.4	18	+ 12.8	36	+ 13.2	25	+ 14.6

* Excluding patients whose weight assessments were not available at the beginning or at the end of the period.

† 1 lb.=0.45 kg. †† Excluding patients while they were pregnant.

FIG. 1
WEIGHT CHANGES OVER THE 60-MONTH PERIOD, ACCORDING TO SEX OF PATIENTS AND PLACE OF TREATMENT IN THE FIRST YEAR

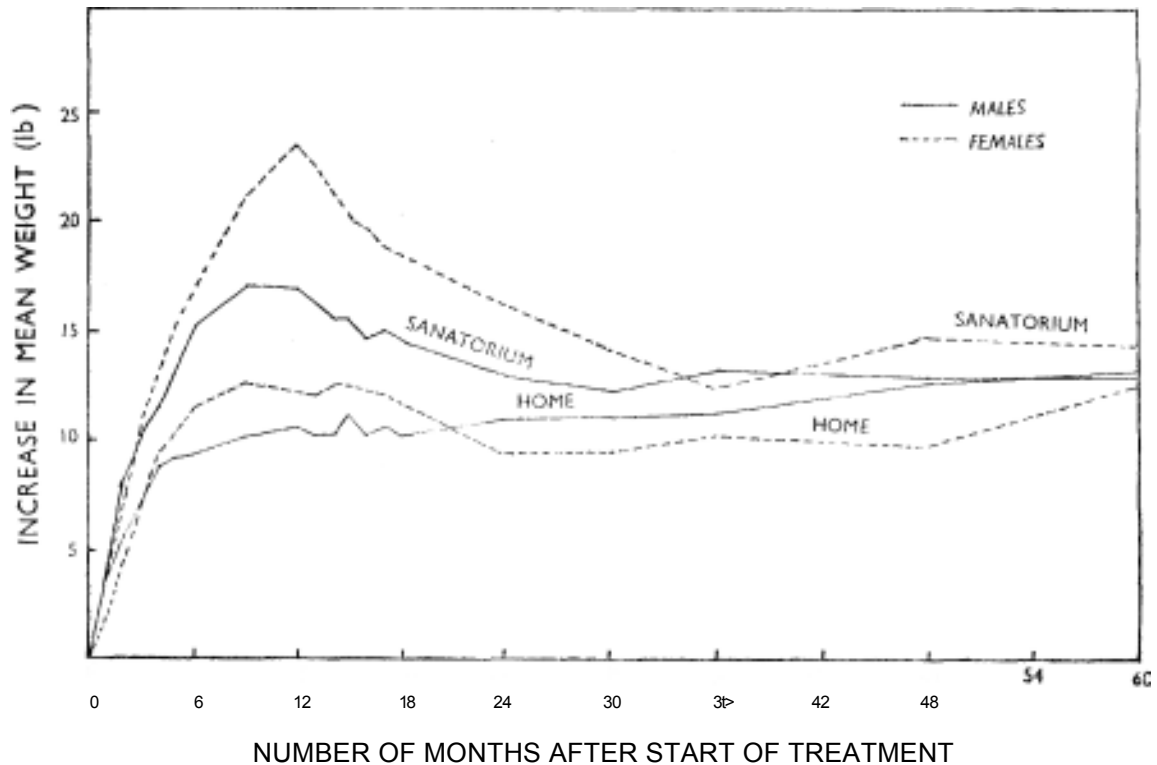


TABLE 3
Physical activity of patients with bacteriologically quiescent disease throughout the four-year period of follow-up

Physical activity	Home series				Sanatorium series				
	At 12 months	At 18 months	At 24 months	At 36, 48 and 60 months	At 12 months	At 13 months	At 18 months	At 24 months	At 36, 48 and 60 months
	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Resting	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Slight	5 10	0 0	0 0	0 0	63 700	9 14	0 0	0 0	0 0
Part-time	22 42	6 12	2 4	0 0	0 0	24 15	9 14	1 2	1 2
Full-time	25 48	46 88	50 96	52 100	0 0	30 45	54 56	62 95	62 98
All patients	52 100	52 100	52 100	52 100	63 100	63 100	63 100	63 100	63 100

less than 1000 IU daily in 50 (96%) of the patients and less than 500 IU in 46 (88%).
Carotene : The daily intake of carotene was less than 1000 IU in 35 (67%) of the patients. Only 6 (12%) had a daily intake of 1600 IU or more.

Thiamine : The intake of thiamine was less than 400IU¹ in 25 (48%) of the patients and more than 600 IU in 10 (19%).
Riboflavine : Less than 500 $\bar{u}g$ of riboflavine daily was received by 48 (92%) of the patients.

Nicotinic acid : The intake of nicotinic acid was less than 15 mg a day in 14 (27%) of the patients, between 15 and 25 mg in 28 (54%) and 25 mg or more in 10 (19%).

Ascorbic acid : The intake of ascorbic acid was less than 25 mg in 14 (27%) of the patients; the great majority—namely, 45 (87%)—had an intake of less than 100 mg a day.

In summary, the patients had, on the average, a diet which was low in calories, in both total and animal proteins and in fats; further, a number of patients had a diet deficient in phosphorus, iron and vitamins. The main dietary constituent was carbohydrates for practically all the patients.

Weight changes

The weight changes are set out, separately for the males and females, in the left-hand side of Table 2 and in Fig. 1.

The males gained, on the average, 9.5 Ib¹ in

¹1 lb=0.45 kg.

the first 6 months and 1.31b in the second 6 months. Thereafter there were only minor changes in weight. Over the five-year period, there was an average increase in weight of 13.41b. The females gained, on the average, 11.7 Ib in the first 6 months and 1.3 Ib in the second 6 months. There was, on the average, a small weight loss in the second year, no change in the third year and a small gain in the fourth and fifth years. Over the five-year period there was an average increase in weight of 12.8 Ib. Thus, for both sexes, the main change in weight occurred in the first 6 months.

Physical activity and occupation

Many of the patients had already returned to their normal occupations during the first year of treatment (Tuberculosis Chemotherapy Centre, 1959) and at 12 months 90% were on part-time or full-time activity (left-hand side of Table 3). At 18 months 88% were undertaking full-time activity and at 24 months 96%. All the patients with quiescent disease were on full-time activity at the assessments at 36, 48 and 60 months.

The main occupation of the home patients in the second year is shown in Table 4. Of the 52 patients, six were unemployed and nine were housewives. The remaining 37 were engaged in a variety of occupations, many in full-time employment in trades which involved long hours of work and considerable physical activity in a humid tropical climate.

Living accommodation

The area of living accommodation per

TABLE 4
Occupation of the Patients in the second year

Occupation	Home series	Sanatorium series
Unemployed	6	2
Housewife	9	18
Craftsman or skilled worker	7	10
Heavy unskilled	10	15
Light unskilled		
Clerical or professional	6	3
Shopkeeper or tradesman	7	9 ^{15 2A} 75 2A
Other	2	2
Total	52	63 55 or

Person for the families of patients in the home series is set out in Table 5. It will be seen that, at the time of admission of the patients to treatment, one was homeless, 75% lived in accommodation with less than 45 ft² per person and 42% in accommodation with less than 25 ft² per person¹. According to the recommendations of the Environmental Hygiene Committee of the Government of India (India, Ministry of Health, 1950), the total floor area of living-rooms should not be less than 50 ft² per person; by this criterion, most of the families were living in overcrowded conditions. Although there were some changes in the accommodation in the first year, these resulted in very little improvement in the area of living space (Tuberculosis Chemotherapy Centre, 1959). Records were not kept of all the details of subsequent changes in accommodation.

Pregnancy

Seven of 16 females of child-bearing age had a total of 12 pregnancies in the five-year period, four starting in the first year, three in the second, one in the third, two in the fourth and two in the fifth year.

Concluding remarks

The diet was not assessed in the fourth or fifth year and complete records were not kept, after the first year, of every change in occupation or of all the details of changes in the area of living accommodation. However, from the available data, it may be concluded that the

¹ 1 ft²=0.09 m².

TABLE 5

Area of living accommodation per person in the families at the time of admission

Area per person* ft ² †	Home series		Sanatorium series	
	No.	%	No.	%
Homeless	1		3	
5-14	5	10	6	10
15-24	17	33	18	29
25-34	11	21	17	27
35-44	6	12	8	13
45-54	5	10	3	5
55 or more	1	13	7	11
Total	52	101	621	100

* For the purpose of calculating the area per person, infants under one year were not counted, each child between one and 10 years counted as half a person, and each member of the household aged 10 years or more counted as one person.

† 1 ft²=0.9 m².

‡ One patient, a nun who was living in a dormitory, has been excluded.

dietary intake and accommodation were stable throughout the period of follow-up.

In summary, most of the patients in the home series with bacteriologically quiescent disease at one year had achieved this state, and maintained it throughout the period of follow-up, despite a deficient diet, unfavourable living accommodation, little rest and an early return to their normal occupations, which, frequently, were arduous.

Sanatorium Series

Dietary intake*

The dietary intake at the five assessments in the first three years after admission to the study is set out in Table 6 for the 63 patients in the sanatorium series who had quiescent disease throughout the follow-up period.

Calories. The total daily intake was 1800 calories or more in 98% of the patients at the assessment in the first year, during which time they were in sanatorium. There was a decline in intake after discharge from sanatorium;

TABLE 6
Dietary intake of patients in the sanatorium series who had bacteriologically quiescent disease throughout the four-year period of follow-up

Dietary intake	Time of assessment									
	During the first year		18 months		24 months		30 months		36 months	
	No.	%	No.	%	No.	%	No.	%	No.	%
Calories:										
Less than 1,400	0	0	16	25	17	27	12	20	10	76
1,400-1,799	1	2	14	22	15	24	10	76	16	26
1,800-2,199	16	25	17	27	11	17	17	25	10	76
2,200-2,599	33	52	7	77	10	76	9	75	13	27
2,600 or more	13	21	9	14	10	76	13	27	13	27
Total proteins (g):										
Less than 30	0	0	8	13	11	77	7	77	7	77
30-39	0	0	16	25	14	22	12	20	17	27
40-49	0	0	13	21	15	24	18	50	8	75
50-59	3	5	10	76	8	75	9	75	14	25
60-69	19	30	8	13	7	77	3	5	12	79
70 or more	41	65	8	75	8	75	12	20	4	6
Fats (g):										
0-9	0	0	15	24	18	29	14	25	14	25
10-19	0	0	17	27	19	50	18	50	17	27
20-29	0	0	10	75	12	79	11	18	12	79
30-39	0	0	7	11	5	8	6	70	14	25
40-49	4	6	10	76	4	6	6	70	2	5
50 or more	59	94	4	6	5	8	6	70	3	5
Carbohydrates (g):										
Less than 200	0	0	5	8	3	5	3	5	1	2
200-299	1	2	20	52	17	27	12	20	12	79
300-399	43	68	17	27	21	55	15	25	19	57
400-499	18	29	13	27	13	21	15	25	14	25
500 or more	1	2	8	75	9	14	16	26	16	26
Total patients	63	100	63	100	63	100	61*	100	62†	100

* Excluding two patients who were not assessed.

† Excluding one patient who was not assessed.

thus, the proportion with an intake of 1800 calories or more was 52% at 18 months, 49% at 24, 64% at 30 and 58% at 36 months.

Proteins. All the patients had a total protein intake of 50 g or more at the assessment undertaken while they were in sanatorium. After discharge, the proportion with an intake of 50 g or more decreased, being 41% at 18 months, 37% at 24, 39% at 30 and 48% at 36 months. Considering the intake of animal protein (not tabulated here), all the patients had at least 60 g a day during the first year, 28(44%) having 50 g or more. In contrast, after discharge from sanatorium, most patients had less than 20 g, the proportions being 71%, at 18 months, 83% at 24, 84% at 30 and 84% at 36 months; the proportions of patients who received less than 10 g were 46%, 52%, 49% and 50%, respectively.

Fats. During the first year all (100%) of the patients received 40 g or more of fats—as compared with only 22% at 18 months, 14% at 24, 20% at 30 and 8% at 35 months. At every assessment after discharge from sanatorium, a substantial proportion of patients had less than 20 g of fats—namely, 51% at 18 months, 59% at 24, 52% at 30 and 50% at 36 months.

Carbohydrates: Nearly all the patients (97%) had a daily carbohydrate intake of between 300 and 500 g while at sanatorium, 30% having an intake of 400 g or more. After discharge from sanatorium, there was greater variability in the intake of the patients. On the average, the intake in the second year was about the same as that in sanatorium, but in the third year it was slightly higher; the proportions of patients receiving 400 g or more were 33%, 35%, 51% and 48% at 18, 24, 30 and 36 months, respectively.

In summary, during the first year, when the patients were in sanatorium, they had an adequate and well-balanced diet in terms of calories, proteins, fats and carbohydrates. On discharge from sanatorium, however, there was a sharp decline in the take of calories, proteins and fats.

Minerals and vitamins. The intake of minerals and vitamins has been calculated for the assessment in sanatorium in the first year and that at home at 18 months but is not tabulated here. Calculations for the later assessments (at 24, 30 and 36 months) have not been undertaken for the reasons stated earlier (page 4).

Calcium: At the assessment undertaken during the first year, 57(90%) of the patients had a calcium intake of 1 g or more, as compared with 12(19%) patients at the assessment

at 18 months. It has not been possible to make allowance for the consumption of betel with slaked lime, a practice which is believed to have been more common after the patients' discharge from sanatorium.

Phosphorus: All the patients had a phosphorus intake of 1 g or more a day while in sanatorium, the great majority—namely, 50 (79%)—receiving 1.5 g or more a day. At 18 months, the corresponding figures were 23 (37%) and 6 (10%), respectively.

Iron: Of the 63 patients, 33 (52%) had an iron intake of less than 20 mg a day at the assessment in sanatorium and 29 (46%) received between 20 and 25 mg. At 18 months the corresponding figures were 44 (70%) and 10 (16%), respectively.

Vitamin A: Only one patient had a vitamin A intake of less than 1500 IU daily while in sanatorium; he received 1450 IU. A large majority—namely, 54 (86%)—received between 1500 and 2500 IU daily. At the assessment at 18 months, 60 (95%) of the patients had an intake of less than 1000 IU daily, 50 of them receiving less than 500 IU.

Carotene: The daily intake of carotene was between 600 and 1000 IU in 42 (67%) of the patients at the assessment in sanatorium and 1000 IU or more in 20 (32%). At the assessment at 18 months, 32 (51%) had less than 600 IU, 11(17%) received 600 and 1000 IU, and 26 (32%) received 1000 IU or more.

Thiamine: During the first year, 43 (68%) of the patients had a thiamine intake of 600 IU or more and no patient received less than 400 IU. At 18 months the corresponding figures were 4 (6%) and 34 (54%), respectively.

Riboflavine: During the first year, 62 (98%) of the patients had a riboflavine intake of 1500 µg or more daily; at 18 months, all (100%) received less than 1500 µg, 53 (84%) receiving less than 500 µg daily.

Nicotinic acid: At the assessment in sanatorium the intake of nicotinic acid was less than 15 mg a day in only 4 (6%) of the patients, the remaining 58 (94%) having an intake of between 15 and 25 mg a day. At 18 months, 32 (51%) had less than 15 mg a day, 28 (44%) had 15-25 mg and 3 (5%) had 25 mg or more

Ascorbic acid: At the assessment in sanatorium the intake of ascorbic acid was less than 25 mg in only 3(5%) of the patients; the majority—namely, 37 (59%)—received between 25 and 50 mg. At 18 months, the corresponding figures were 21 (33%) and 16 (25%), respectively.

In summary, while in sanatorium, the majority of patients had an intake of more

than 2000 calories a day, the diet containing substantial amounts of fats and proteins (particularly of animal origin) as well as carbohydrates, and being adequate in the mineral and vitamin content. On discharge from sanatorium there was a sudden drop in caloric intake mainly due to low fat and protein intakes. There was also a decline in the intake of phosphorus and vitamins.

Weight changes

The weight changes are set out in the right-hand side of Table 2 and in Fig. 1, separately for the males and females.

The males gained, on the average, 15.3 lb. in the first 6 months and 2.2 lb in the second 6 months. In the second year, there was a moderate loss in weight, but little change subsequently; over the five-year period, the average gain in weight was 13.2 lb. The females gained, on the average, 16.5 lb in the first 6 months and 7.2 lb in the second 6 months. However, there was a substantial loss of weight in the second year and also losses in the third and fourth year. Even so, over the five-year period there was an average gain of 14.6 lb.

Physical activity and occupation

While in sanatorium, all the patients had very limited physical activity (Tuberculosis Chemotherapy Centre, 1959) and, even at the end of the year, the longest they were allowed up was four hours a day. On discharge from sanatorium, they experienced an immediate and major increase in their physical activity and, at 13 months, 86% were on part-time or full-time activity (Table 3, right-hand side). At 18 months, 86% were on full-time activity, as were 98% at 24, at 30, at 48 and at 60 months.

The main occupation of the sanatorium patients in the second year is shown in Table 4. Of the 63 patients, two were unemployed and 18 were housewives. The rest were in full-time employment in a variety of trades which often involved long hours of work and considerable physical activity.

Living accommodation

Throughout the first year, the patients were nursed in well-ventilated and spacious wards in the sanatorium, which was in a rural area. On discharge from sanatorium, they returned to their over-crowded homes. A detailed study was made of the accommodation which the families of the sanatorium patients occupied at the time of diagnosis of the disease; the results are set out, in Table 5. It will be seen that 5% of the patients were homeless and that a further 79% were living in accommodation which provided less than 45 ft² per person, 39%

having less than 25ft² per person. For all practical purposes this represents the accommodation to which the patients returned on discharge from sanatorium since very little change in the standards of accommodation of the family took place in the first year.

Pregnancy

Nine of 25 females of child-bearing age had a total of 11 pregnancies in the five-year period, four beginning in the second year, one in the third, four in the fourth and two in the fifth. One of the last two terminated in an abortion.

Concluding remarks

Details of dietary intake in the fourth and fifth years and of accommodation after the first year were not available, but it may be concluded from the available data that the dietary intake and accommodation were stable throughout the period of follow-up.

In summary, the patients had ample rest for the whole of the first year, good accommodation and an adequate diet, and it was under these conditions that their disease attained bacteriological quiescence. On discharge from sanatorium at the end of the year, there was a marked increase in physical activity and usually a rapid return to the normal occupation. There was a return to overcrowded accommodation and a sudden decline in the dietary intake, and both the diet and accommodation remained unfavourable for the rest of the five years. Even so, the patients maintained bacteriological quiescence of their disease throughout the period of follow-up.

IV. Patients Whose Disease Relapsed Bacteriologically

As already mentioned, 5 (9%) of the 57 patients in the home series had a bacteriological relapse as did 7 (10%) of the 70 patients in the sanatorium series. For these patients, the findings of the dietary assessments undertaken prior to the relapse, the maximum weight gain, the weight gain at the time of the relapse, the weight change in the six months immediately prior to the relapse, the physical activity at the time of relapse, the occupation and information on the living accommodation are given in Table 7.

Home series

One patient (P34) showed a declining dietary intake (Table 7) at 18 and at 24 months and had a relapse in the 27th month. A second patient (PI54), who showed a fairly stable dietary intake at all five assessments, had a relapse in the 57th month. A third patient

TABLE 7
Summary of findings up to the time of relapse in the patients whose disease relapsed bacteriologically

Serial No.	Month of relapse	Dietary assessments before relapse (cf. Table 1 for home series and Table 6 for sanatorium series)										Maxi- mum weight gain (lb)*	Weight change in 6 months prior to relapse (lb)*	Physical Activity at time of relapse (cf. Table 3)	Occupation at time of relapse (cf. Table 4)	Area of accom- moda- tion per person (ft ²)* (cf. Table 5)	
		During the first year			At 18 months	At 24 months	At 30 months	At 36 months	Calories								
		Calories	Proteins	Fats	Carbo- hydrates (g)	Calories	Calories	Calories	Calories	Calories							
Home series																	
P 34	27	3 607	78	55	690	2 814	1 937	—	—	—	6	3	+ 1	Full-time	Office boy	71	
P154	57	2 204	64	21	417	1 739	2 285	1 995	1 992	—	27	10	- 6	Full-time	Housewife	33	
P163	22	1 529	31	8	480	1 766	—	—	—	—	16	12	- 11	Full-time	Housewife	27	
P178	15	2 800	89	45	423	—	—	—	—	—	19	17	+ 5	Full-time	Accountant	38	
P182	16	1 591	40	10	227	—	—	—	—	—	36	29	+ 9	Part-time	Housewife	31	
Sanatorium series																	
P19	54	2 250	65	53	375	1 693	2 253	—	2 079	—	7	0	- 8	Full-time	Cycle shop assistant	16	
P60	17	2 056	62	54	328	—	—	—	—	—	12	7	- 6	Full-time	Dhobi	16	
P90	18	2 936	92	71	479	—	—	—	—	—	16	6	- 8	Full-time	Housewife	13	
P132	14	2 438	67	54	418	—	—	—	—	—	36	35	- 6	Full-time	Housewife	67	
P159	15	2 343	79	75	404	—	—	—	—	—	28	12	- 16	Full-time	Housewife	15	
P181	13	2 360	73	60	421	—	—	—	—	—	21	20	- 2	Full-time	Farmer	116	
P191	14	2 194	73	62	348	—	—	—	—	—	26	19	- 7	Full-time	Unemployed	50	

* 1 lb = 0.45 kg.

* 1 ft² = 0.9 m².

(P163) showed a slight increase in dietary intake at 18 months, which was four months before she had a relapse. The remaining two patients (P171 and P182) had a relapse at 15 and 16 months, respectively, and so had only one dietary assessment. There is no suggestion that these five patients were at a special dietary disadvantage in comparison with the patients who had quiescent disease throughout the period of follow-up (Table 1), nor that their occupations, physical activity and accommodation were particularly unfavourable.

Three patients had gained weight and two had lost weight in the six months immediately prior to the relapse; all five weighed more at the time of the relapse than at the time of their admission to the study.

All three females of child-bearing age became pregnant, two of them before they had a relapse. One of these two became pregnant in the ninth month, had residual cavitation at one year, received calcium in the second year and had a relapse at 22 months (she became pregnant again in the 41st month); the other became pregnant in the 13th and in the 40th month, and had a relapse at 57 months. The third started a pregnancy 14 months after the relapse.

Sanatorium series

The assessments of the patients in the sanatorium series, which are presented in the lower part of Table 7, show features similar to those of the patients in the home series.

It will be noted that all seven patients lost weight (average loss, 7.6 lb) in the six months immediately preceding the relapse, which occurred between 12 and 18 months in six of them. (It is of interest that, during this period, about 70% of the sanatorium patients whose disease remained quiescent throughout also lost weight, the average loss being 3.4 lb for the whole group and 7.0 lb for those who actually lost weight.)

There were three females of child-bearing age of whom two became pregnant on one or more occasions. One, who had residual cavitation at one year and received isoniazid in the second year, became pregnant in the 16th month and had a relapse at 18 months. The other started pregnancies two and 11 months after the relapse, both terminating in abortion.

Timing of the relapses in the two series

Three of the five patients in the home series and six of the seven in the sanatorium series had a relapse in the second year. Of these, the relapse occurred early —i.e., between 12 and 18 months — in two patients in the home

series and all six in the sanatorium series. This finding suggests that relapse in some of the sanatorium patients might have been due to one or more of the factors associated with the return of the patients to the home environment at the end of the year—namely, clearly inferior diet, markedly increased physical activity, early resumption of normal occupation and return to very overcrowded living accommodation.

V. The Role of Chemotherapy in the Prevention of Relapse in the Two Series

As already mentioned, the patients with bacteriologically quiescent disease at one year were allocated at random either to a placebo, calcium gluconate, or to isoniazid in the second year. The relapse rates are given in Table 8, separately for cavitated and non-cavitated disease at one year. It will be seen that whereas chemotherapy with isoniazid in the second year did not apparently reduce the number of relapses among the patients with cavitated disease at one year, it prevented *any* relapse among the patients with non-cavitated lesions at one year, irrespective of whether they had been treated in the first year at home or in sanatorium. Thus, even if relapse in individual patients may result from environmental stresses acting on the disease there is evidence that continuation therapy with isoniazid alone can prevent such relapse in patients without residual cavitation. In patients with residual cavitation at one year, there is evidence from another study (Great Britain, Medical Research Council, 1962) that continuation chemotherapy with a combination of isoniazid and PAS can prevent about 80% of the relapses.

VI. Discussion

Earlier papers from the Centre (Tuberculosis Chemotherapy Centre, 1959; Ramakrishnan et al., 1961) reported on the role of diet, physical activity and accommodation in the response to treatment of patients with pulmonary tuberculosis. These factors had been studied in a comparison, based on random allocation, of two groups of patients, all of whom had received a standard oral regimen of isoniazid plus PAS for one year. One group was treated at home in overcrowded and unfavourable accommodation, had a bare subsistence diet and little rest, and returned early to work. The other group was treated in sanatorium in large airy wards and received a good diet and ample rest during the whole year. Despite the differences in the environmental factors in the two groups, the patients

TABLE 8

Bacteriological relapses in the four-year period of follow-up

Place of treatment in first year	Treatment during the second year	Patients with bacteriologically quiescent disease throughout follow-up period	Patients with bacteriologically relapsed disease	Month of bacteriological relapse
Home	Calcium Isoniazid	Patients with cavitation at 9 9	one year 1 1*	22 15
Sanatorium	Calcium Isoniazid	8 10	0 3	— 13, 15, 18
Both series	Calcium Isoniazid	17 19	1	12, 13, 15, 15, 18
Home	Calcium Isoniazid	Patient without cavitation 16 18	at one year 3 0	16, 27, 57 —
Sanatorium	Calcium Isoniazid	21 24	4 0	14, 14, 17, 54 —
Both series	Calcium Isoniazid	37 42	7 0	14, 14, 16, 17, 27. 54, 57 —

* Misclassified at 12 months as having bacteriologically active disease and so continued to receive isoniazid plus PAS.

treated at home fared almost as well, in terms of the attainment of bacteriological quiescence at one year, as the patients treated in sanatorium (Tuberculosis Chemotherapy Centre, 1959). In a study, also based on random selection, in Ghana, Bell (1960) compared in-patient and out-patient treatment for three months with a daily injection of streptomycin-isonicotinic acid hydrazide. He found no difference in the response to treatment between the two series even though the out-patients had received an inferior diet, had not been restricted in their physical activity and had been permitted to continue work if they felt well enough to do so.

The present report is based on patients admitted to the home and sanatorium study mentioned above, and gives information on the diet, physical activity, occupation and

living accommodation of the patients with bacteriologically quiescent disease throughout the four-year period of follow-up, as well as for those whose disease relapsed bacteriologically during this period. This information is of particular interest as the environment of the patients in the home series during the period of follow-up was similar to that in the first year in terms of diet, accommodation, physical activity and occupation; thus, their diet was the "poor South Indian" diet (Patwardhan, 1952; Dakshinamurti & Devadatta, 1956), the accommodation overcrowded and a number had arduous occupations and long hours of work. Even so, the great majority of the 57 patients—namely, 52 (91%)—maintained bacteriologically quiescent disease throughout the four-year period of follow-up. The environmental background of the patients in the sana-

torium series in the first year is in sharp contrast. They had a good diet and ample rest in large airy wards and gained, on the average, a very considerable amount of weight during the year. At the end of the year they were discharged from sanatorium to their overcrowded accommodation and, at the same time, not only suddenly received a markedly inferior diet but also returned to full physical activity; in the majority of instances, they had resumed their normal occupations within a few weeks after discharge. Not surprisingly, there was a moderate loss of weight in these patients in the second year, particularly between 12 and 18 months. However, despite all these sudden changes in the environment, the great majority of the 70 sanatorium patients—namely, 63 (90%)—had bacteriologically quiescent disease throughout the four-year period of follow-up. Thus bacteriological quiescence of the disease, whether it had been attained under treatment at home or under the much more favourable conditions in sanatorium, was stable and even the sudden environmental changes in the sanatorium series did not disturb quiescence in the *great majority* of patients.

It is relevant that six of the seven patients in the sanatorium series who had a bacteriological relapse, as compared with two of the five in the home series, had it between 12 and 18 months, suggesting that the sudden stresses of returning to the home environment may have been responsible for the relapse in some of these six sanatorium patients. There are, however, good reasons for believing that most of the relapses in *both series* could have been prevented by chemotherapy in the second year. Thus, in the combined home and sanatorium series, not one bacteriological relapse occurred among the 42 patients who had no residual cavitation at one year and received (as a result of random allocation) isoniazid in the second year (22 of these patients received isoniazid in the third year also), as compared with seven among the 37 patients on the placebo, calcium gluconate (three of these seven relapses occurred between 12 and 18 months in patients in the sanatorium series). Chemotherapy was therefore capable of overcoming all subsequent disadvantageous environmental factors in patients with no residual cavitation at one year. Although isoniazid alone at the dosage used did not apparently influence the relapse rate in the patients with residual cavitation, evidence from another study (Great Britain, Medical Research Council, 1962) suggests that combined chemotherapy with isoniazid plus PAS might have done so.

It may be concluded that the earlier study (Ramakrishnan et al., 1961) and the present

study together have shown that the diet, the amount of rest and the type of accommodation of patients—traditionally factors of importance in the treatment of patients in the pre-chemotherapy era—are, at most, of minor importance not only in the immediate response to treatment (Ramakrishnan et al., 1961), but also in the occurrence of relapse (present report), *if effective chemotherapy is administered for an adequate period of time*. Bacteriological quiescence of the disease at one year, as produced by chemotherapy, has proved to be stable in the great majority of patients, irrespective of the environmental background in which the chemotherapy was administered.

Finally, it must be stressed that this study has been concerned with the importance of various environmental factors in the response to treatment of patients receiving effective chemotherapy for active pulmonary tuberculosis, and in the occurrence of relapse among such patients. The findings provide no information on the effect of diet, physical activity and living accommodation on the susceptibility of the individual to tuberculosis, on the spread of the disease in the community or on the progression of the disease in *undiagnosed or diagnosed but untreated or inadequately treated cases*.

VII. Summary

1. A study was undertaken of the diet, physical activity, occupation and living accommodation of 127 South Indian patients with pulmonary tuberculosis whose disease had attained bacteriological quiescence after one year of treatment with isoniazid plus PAS.

2. During the first year, 57 of the patients had been treated at home and 70 in sanatorium. As a result of random allocation procedures at one year and at two years, about a quarter of the patients were prescribed isoniazid alone for two years, another quarter were prescribed isoniazid for one year and the remainder were prescribed no specific chemotherapy. All patients have been followed up to the end of five years.

3. Dietary assessments were undertaken on admission to treatment, at some time between 6 and 12 months, and at 18, 24, 30 and 36 months; all the assessments were made by the *same* assessor, who used the oral questionnaire technique.

4. Of the 57 patients treated at home in the first year, 5 (9%) had a bacteriological relapse, as compared with 7 (10%) of the 70 patients treated in sanatorium. There was no suggestion that the patients who had a relapse were at a special dietary disadvantage in com-

parison with those who had quiescent disease throughout, nor were there any appreciable differences in the occupations, physical activity and living accommodation. However, there was some evidence that the stresses of suddenly returning to the home environment may have been responsible for some of the relapses in sanatorium patients.

5. The 52 patients in the home series who maintained quiescent disease throughout the period of follow-up did so under conditions usually considered to be adverse. Thus, they had throughout a predominantly carbohydrate diet which was low in calories, total and animal proteins, fats, phosphorus, iron and vitamins. Further, about three-fourths of them lived in overcrowded accommodation (less than 45 ft² per person), and nearly all were usually on full-time activity in occupations which were often arduous and involved long hours of work.

6. The 63 patients in the sanatorium series who maintained quiescent disease throughout the four-year period did so despite suddenly being subjected to the stresses of a return to the home environment - namely, inferior diet, increased physical activity and overcrowded accommodation - after a year in sanatorium during which they had received an adequate and well-balanced diet, had undertaken very limited physical activity and had been nursed in well-ventilated and spacious wards.

7. It may be concluded that, despite adverse environmental conditions, bacteriological quiescence attained by the administration of effective chemotherapy for one year has proved to be stable over four years in the great majority of patients.

8. This study does not provide information on the influence of environmental factors on the susceptibility of the individual to tuberculosis, on the spread of the disease in the community or on the progression of disease in untreated or inadequately treated cases.

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*Annex***DETAILS OF THE LIVING ACCOMMODATION
OF THE PATIENTS**

In order to give a clearer picture of the type of accommodation occupied by the patients in this study, the photographs of three typical houses—two interior views (Fig. 2 and 4) and one exterior view (Fig. 3)—are reproduced in this annex. For this purpose, the houses of the patients' families were classified into three

groups, according to the area of living accommodation available per person: namely, less than 25 ft² (2.3 m²), 25-44 ft² (2.3-M m²) and 45 ft² (4.2m²) or more (see Table 5); from each of these three groups, one house has been selected for reproduction here.



FIG. 2

PATIENT No. T1248: ACCOMMODATION WITH LESS THAN 25 FT² PER PERSON

Brick and tile house, occupied by three families.

Accommodation occupied by patient and family- Two rooms, a verandah/kitchen and a common court yard; water tap and lavatory shared with the other two families; no electricity. Total floor area, 115 ft² (10.7 m²).

Family composition: Patient, husband, two children (aged 2 and 6 years), and four adults in laws.

FIG. 3

PATIENT No. TI487: ACCOMMODATION WITH 25-44 FT PER PERSON

Brick and thatch house, occupied by four families.

Accommodation occupied by patient and family: One room and a kitchen; water tap and lavatory shared with the other three families; no electricity. Total floor area, 182 ft² (16.9 m²).

Family composition: Patient, husband, four sons (aged 1, 5, 15 and 18 years) and two daughters (aged 10 and 18 years).



FIG 4

PATIENT No. TI003 ACCOMMODATION WITH 45 FT² OR MORE PER PERSON

Brick and tile house, occupied by six families.



Accommodation occupied by patient and family: One room, a kitchen, a verandah and a common courtyard; water tap and lavatory shared with the other five families; no electricity. Total floor area, 278 ft² (25.8 m²).

Family composition: Patient, mother, brother, sister-in-law and nephew (aged 1 year).

SOME OBSERVATIONS ON THE DRUG COMBINATION OF INH + THIA CETAZONE UNDER THE CONDITIONS OF DISTRICT TUBERCULOSIS PROGRAMME

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Introduction

Isoniazid (INH) and Thiacetazone (TSC) combination, following recent trials in East Africa and India (East African Trials, 1960 & 1968 Sikand, 1963) has been considered as a possible choice of regimen for domiciliary treatment in Tuberculosis Programmes. Other studies (Hinshaw et al, 1950) have demonstrated a high degree of toxicity to Thiacetazone when 200 mgms dosage was used. The efficacy of the combination when a smaller dose of thiacetazone is used and the ease of intake make the combination a suitable choice under the conditions of District Tuberculosis Programme (DTP) (Piot, 1962).

While studies mentioned above were essentially clinical trials it was considered desirable to conduct a study on the acceptability of the drug combination under the conditions of DTP.

Acceptability of a drug or a drug combination by the patients is a function of several factors; chief among which are the clinical efficacy, incidence of unpleasant side effects, relief of symptoms, ease of intake and free availability. Whereas these factors determine the acceptability of drug or a drug combination, it is difficult to identify the factors independently and evaluate the role played by these independent factors. As such, acceptability can broadly be denned in terms of the proportion of patients completing the major period of treatment.

While 'acceptability' refers to the intake of drug or drug combination by the patients, 'applicability' has a broader concept. The main factors that influence applicability, though not in the same priority, are the cost of the drug combination and acceptability. While defining applicability it is desirable to fix the priorities as it is likely that no single drug or drug combination will satisfy all the requirements mentioned above, to the maximum. A study planned to observe the applicability of INH -f TSC combination with special reference to acceptability and toxicity, is herewith reported.

2. Material and Methods

2.1 The study was conducted in Tumkur District, Mysore State. 150 patients from Tumkur Town and some nearby villages were

discovered during a mass casefinding investigation, of whom 127 were included in the study. Except for one patient all others were treated in their homes on ambulatory chemotherapy. The 127 patients included in the study were prescribed 300 mgms of INH and 150 mgms of TSC in a single tablet to be taken once a day usually after the evening meal. Initial supply of the drugs were made to the patients after necessary motivation and subsequent supplies made to the patients or their representatives attending for drug collection at monthly intervals. The age, sex and geographical distribution of patients is shown in table 1.

2.2 Initial bacteriological & radiological status of the study population:

Table 2 shows the initial bacteriological and radiological status of the 127 patients.

2.2.1 Bacteriological status

Out of 127 patients, 123 had their sputa examined of whom, 43 were positive, 22 both by direct microscopy and culture, 16 by culture alone and 5 by direct smear only (culture could not be done).

Of the 33 culture positive patients, 20 had organisms sensitive and the other 18 resistant to INH (Drug sensitivity status to other drugs is not reported).

2.2.2 Radiological status:

Of the total 127 patients, 5 were judged to be suffering from pleurisy with effusion or hilar adenitis (one of these was sputum positive) and 122 from adult type of pulmonary tuberculosis, 42 of whom were not examined. The extent of disease and cavitory status are shown in the table.

2.3 Re-examination:

Check up with sputa and/or X-ray examinations were arranged on completion of one year after the initiation of treatment. Of the 127 patients put on treatment only 98 were available for re-examination at one year; 93 had both sputa and chest X-ray examinations, 3 had only sputum examinations. Of the remaining 29, who could not be examined 19 had died, 5 migrated and 5 refused re-examination.

TABLE 1

Age and sex distribution of cases put on treatment—TSC

Age	Male			Female			Total		
	Urban	Rural	Total	Urban	Rural	Total	Urban	Rural	Total
10—19	5	—	5	5	—	5	10	—	10
20-29	11	—	11	11	2	13	22	2	24
30 -39	12	3	15	11	—	11	23	3	26
40-49	15	7	22	6	1	7	21	8	29
50+	14	16	30	7	1	8	21	17	38
Total	57	26	83	40	4	44	97	30	127

TABLE 2

Initial bacteriological and radiological status and sensitivity to INH of cases put on thiacetazone

Radiological status		Sputum positive			Smear Neg.			Total
Cavity	Number of lung zones involved	Resistant	Sensitive	Smear + Cul. not done	Cul. negative	Cul. examined	Not not examined	
No cavity	1—2	1	6	1	29	13	3	53
	3-4	3	3	1	12	5	—	24
	5-6	—	—	—	—	—	—	—
Cavity	1—2	1	2	—	1	1	—	5
	3-4	5	7	1	4	5	1	23
	5-6	8	1	2	4	2	—	17
Pleural effusion and) Hilar Adenitis)		—	1	—	4	—	—	5
Total		18	20	5	54	26	4	127

2.4 Excluded from Final Analysis:

For the purposes of presentation of findings, 24 patients (19 dead and 5 migrated) are excluded from analysis. Among these, 10 were sputum positive, 7 of whom were resistant to INH.

3. Findings

3.1 The pattern of drug collection:

Pattern of drug collection in terms of the

amount of drugs collected by the patients in each quarter after initiation of treatment was studied. It was seen that only about 50% of the total patients put on treatment collected drugs upto 10 months or more.

Table 3 shows the drug collection among different categories of patients viz., sputum positive and negative disease, cavitory and non-cavitory disease, males and females, younger and older age groups and by their residential status. It is seen that drug collection for a

TABLE 3

Drug collection regularity by disease status before treatment, sex, age and residence

Character-	Drug collection in months			Character-	Drug collection in months		
	Total	Upto nine months	Ten months or more		Total	Upto nine months	Ten months or more
	Number	%	%		Number	%	%
Sputum negative	67	52	48	Male	65	52	48
Sputum positive	32	47	53	Female	38	50	50
Non cavitory	70	54	46	(10 -39) Yrs.	48	48	52
Cavitory	33	45	55	40+Yrs.	55	55	45
Up to 2 zones	53	49	51	Rural	27	44	56
3 zones or more	50	54	46	Urban	76	54	46

period of 10 months or over was lowest among patients with sputum negative radiological disease and highest among patients with cavitory sputum positive disease, though these differences are not statistically significant.

It is likely that because of the small number of patients no clear cut pattern of drug collection emerges. Further it may be pointed out that in a service programme it is not possible to assure consumption of drugs among those who collect. It is presumed that patients who take pains to collect drugs also consume the same.

3.2 Changes in sputum and radiological status at one year among sputum positive patients:

3.2.1 Changes in sputum status:

Sputum changes at one year among sputum positive patients are shown in Table 4.

Of the 43 sputum positive patients intaken in the study 28 were available for subsequent check up by sputum. Of the 28 patients, 14 became sputum negative and the other 14 continued to remain positive. Of those that converted, only one was initially INH resistant while of those who continued to remain positive 9 were initially resistant.

Of the 15 sputum positive patients not re-examined 10 were due to deaths, 1 due to migration, and the remaining 4 could not be examined.

3.2.2 Radiological Changes:

Of the 43 sputum positive cases, both initial and subsequent radiological findings were available for 30 patients. Out of these, 22 had a favourable radiological response. Of the 11 initially INH resistant patients 6 and of the 16 initially sensitive to INH, 13 showed radiological improvement. Cavity closure was observed among 11 of the 18 with cavities initially. Radiological improvement was marked among the drug sensitive patients but was also considerable among the resistant patients.

3.3 Changes in sputum and radiological status among sputum negative patients at one year:

3.3.1 Changes in sputum status:

Of the 67 sputum negative patients, 64 had their sputa re-examined at one year, 56 of whom remained negative and 8 became positive (6 sensitive and 2 resistant to INH). Sputa of 5 of these 8 were not cultured initially,

TABLE 4

Post treatment sputum status among initially sputum positive cases with their INH sensitivity

Pre-treatment sensitivity status	Post Treatment sputum status				Total
	Sputum negative	Sputum	Positive	Not examined	
		Sensitive	Resistant		
Sensitive	10*	3	—	3	16*
Resistant	1	—	9	1	11
Not known	3	1	1	—	5
Total	14*	4	10	4	32*

* Includes one pleural effusion.

This table excludes dead and migrated cases.

remaining 3 were negative by both direct smear and culture.

3.3.2 Radiological changes:

Of the total 64 sputum negative cases re-examined at one year, 50(78%) showed favourable radiological response 10 remained stationary and only 4 deteriorated. It was seen that among sputum negative cases, the post treatment radiological improvement is not influenced by the presence of cavity or the extent of disease.

3.4 Changes as related to drug collections:

Full range distribution of patients by number of months for which the drugs were collected in relation to the bacteriological and radiological changes at one year were studied in detail, but because of small numbers the full range distribution is not presented. The drug collection has arbitrarily been divided into two categories viz, those who collected for 9 months or less and those who collected for 10 months and more.

3.4.1 Bacteriological changes as related to drug collection among initially sputum positive patients:

Table 5 gives the pattern of drug collection among 32 initially sputum positive patients according to their initial and post treatment status.

Of the total 32 sputum positive patients 17(53%) collected drugs for 10 months or more.

Among these, 17 patients, 7 were converted. Of the remaining 10, 6 were initially resistant to INH and continued to remain positive resistant and the sputa of 4 patients could not be examined.

Whereas the conversion rates are higher in the sensitive than in resistant patients, even among the sensitive patients the conversion rates are not related to the drug collection. Though based on few cases, it is seen that, patients when treated with this drug combination, inspire of their irregular short duration of treatment do not excrete drug resistant organism subsequently,

3.4.2 Radiological changes as related to drug collection among initially sputum positive patients :

Of the sputum positive patients, 17 collected drugs for 10 months or more of whom 13 showed radiological improvement. Of the 15 who collected drugs for 9 months or less 9 were judged to have improved radiologically.

Among the 8 sputum positive sensitive patients radiological improvement was observed in 7 patients even when treatment was taken for 9 months or less while the 4 resistant patients collecting the drug for the same duration, one patient showed radiological improvement. While patients who are initially resistant have a tendency to continue treatment for a longer duration, patients who are initially drug sensitive do not continue prolonged treatment probably because they improve early even with less treatment.

TABLE 5

Initial and post treatment sensitivity status according to drug collection among sputum positive patients after Thiacetazone treatment

Initial INH sensitivity	Drug collection/Post treatment sputum status								Total
	Negative		Sensitive		Resistant		Not examined		
	Upto nine months	Ten months or more	Upto nine months	Ten months or more	Upto nine months	Ten months or more	Upto nine months	Ten months or more	
Sensitive	5	5	3	—	—	—	—	3	16
Resistant	1	—	—	—	3	6	—	1	11
Culture not examined	1	2	1	—	1	—	—	—	5
Total	7	7	4	—	4	6	—	4	32

This table excludes dead and migrated.

3.4.3 *Bacteriological change! as related to drug collection among initially sputum negative patients:*

Among the 67 cases, 64 had both initial and post treatment sputum examinations. Of the 64 cases, 8 were sputum positive at the end of one year (Refer 3.3.1). Of these 8, 4 collected drugs for 10 months or more and the rest for 9 months or less. All the 4 who had treatment for 10 months or more had considerable radiological improvement, the other 3 did not improve radiologically and one was not X-rayed. Of the 56 who continued to remain sputum negative, 26 collected drugs for 10 months or more and the rest for 9 months or less.

3.4.4 *Radiological changes as related to drug collection among initially sputum negative patients:*

Among the 67 sputum negative patients 35 had collected drugs for 9 months or less. Of these 24 (69%) improved; from the remaining 32 patients who collected drugs for 10 months or more 26 (81%) improved. The number of patients collecting drugs for 10 months and more is almost equal to that who collected for 9 months or less. Though the proportion registering improvement among those who collected drugs for 10 months or more is higher, the observed difference is not statistically significant.

3.5 *Deaths:*

Of the 127 patients admitted in the study,

19 died 10 of whom were sputum positive and 9 sputum negative.

The overall death rate was of the order of 15%. Death rates among sputum positive and negative were 23% and 11% respectively. Among the sputum positive cases, 4 deaths were in the first quarter, 5 in the second and 1 in the third and among the sputum negative 4 in the first quarter, 3 in the second and 2 in the fourth.

It is seen that about 40% deaths among sputum negatives as well as among positive occurred in the first quarter.

Causes of death among patients initiated on treatment could not be ascertained, as the conditions of the district tuberculosis programme under which the study was undertaken, is usually devoid of the facilities for detailed and careful followup. However, in none the death could be attributed to the toxicity of TSC as no deaths were observed in those who developed side effects. Moreover among 23 patients who were not treated with thiacetazone 5 (22%) died. As in these cases the deaths were due to causes other than TSC, similarly in the group treated with TSC the deaths were probably due to causes other than TSC toxicity. On the basis of a review of the initial X-ray of 'dead' patients, with a view to subjectively assess the cause of death, it can be surmised that 10 of the 19 patients who died could have died as a result of pulmonary tuberculosis, 9 of whom were sputum positive. It is likely that other 9 deaths were due to causes other than pulmonary tuberculosis.

3.6 Side effects :

As the study was under normal working conditions of a tuberculosis programme, regular supervision of drug intake and laboratory clinical examinations to elicit the side effects if any, of INH or thiacetazone were not practicable.

Here it is pointed out that all patients who had developed major side effects would have been missed had it not been for the fact that active search was made by the home visiting staff for tracing those who did not return to collect their monthly drug supply. This was done basically to elicit the reasons for defaulting.

During the first motivation, the patients were told to report back if they experience some unpleasant symptoms and to see the Medical Officer of the Tuberculosis Centre, Tumkur. At each monthly collection, the patient or the relative of the patient who came to collect the drugs was questioned indirectly for any of the side-effects. Further if the patients defaulted they were given a home visit within one week of the default and the reasons for default noted. Thus absence of any such complaints was presumed preliminary as absence of any side effects.

In all, 23 patients complained of possible side effects 5 of them were considered to have major side effects and 18 as minor. Some had more than one side effect.

The most common complaint possibly attributable to drugs due to which patients interrupted or discontinued treatment are shown in Table 6.

TABLE 6

Number of patients experiencing different types of side effects

Complaint	Number of patients
Giddiness	14
Skin rashes or itching	9
Vomiting	8
Localised or generalised oedema	3
Petechial Haemorrhages	3
Exfoliative Dermatitis	2
Soreness of the mouth	1

The complaints are placed in the order of priority of occurrence in numbers and not of

severity. The occurrences were not related to age, sex or weight of the patients.

Among the 5 patients with side effects that can be considered as major, two males had exfoliative dermatitis, one aged 58, sputum negative and the other aged 52, sputum positive. When the patients noticed the side effects they themselves stopped the drugs and both cases were treated with anti-histamines as soon as they were contacted by the DTC Home-visiting staff.

The patient aged 55 became very ill after a month of starting the drugs; he felt burning sensation all over the body and sore throat. This was followed by peeling off of the skin all over the body including those of hands and feet. The patient took 2 months to recover completely.

The second patient, a male aged 52 heralded symptoms with pain all over the body which started within one month of treatment. The patient discontinued treatment for a short while. He resumed treatment after 2 weeks and 2 months after the resumption of treatment he again felt pain all over the body, which was followed by peeling off of the skin. The peeling was much milder than that in the other patient described above and healed early after the stoppage of treatment. Similar unusual skin reactions have been reported from Mombasa, Kenya (Harland, 1962).

Other 3 patients, considered to have major side effects, had generalised petechial haemorrhages. One was 75 years of age, another 41 and the third 65, all the three being males. In them the side effects were first noticed, 15 days, 2 months and 7 months respectively after starting treatment. In all these three patients symptoms subsided soon after the withdrawal of drugs and treatment with anti-histamines.

In any of the patients, no investigations for liver function or blood changes could be carried out due to lack of facilities. These patients were treated with INH alone, after recovery from side effects.

Minor side effects were noticed in 18 other patients, most common being giddiness and vomiting. One of the 18 patients died after six weeks of withdrawing the drugs and death could not be attributed to the drug. Most of the patients recovered shortly after withholding the drugs. Treatment with INH and thiacetazone was restarted in 7 and continued upto one year period, 8 stopped treatment and 2 were put on INH alone.

In other group of 50 patients, put on treatment with INH and thiacetazone in the same area, not included in the present study, one

female patient aged 25 had severe exfoliative dermatitis within a month of starting the drugs. She felt giddiness and started bleeding from the nose, followed by peeling off layers of skin all over the body (Fig. 1). The patient was very ill and it took nearly 2 months to heal.



4. Discussion

The investigation reported is not a clinical controlled trial, where all the factors except those under study are kept under control. Controlled trials are planned under experimental conditions. The results of clinical trials are not reproducible under service conditions. Whereas in a clinical trial, the patients admitted to study are a group, selected on various criteria, in a routine tuberculosis programme all kinds of patients of tuberculosis will have to be provided relief. The present study on the acceptability and applicability of INH in combination with Thiacetazone was undertaken in the conditions simulating a routine 'District Tuberculosis Programme' where most of the factors were, by design, not under control.

A drug regime, to be applicable in tuberculosis control programme on a countrywide basis in a developing country, should satisfy several conditions as listed earlier. The above study, carried out with the objective to define the applicability of INH and thiacetazone for

ambulatory domiciliary treatment programme, though small, has shown that considering the therapeutic efficacy only, the drug combination satisfactory for application in such programmes. A second important factor viz., cost is also quite favourable. Treatment of one year will cost about Rs. 34/- for the drugs only, as against Rs. 175/- if INH and PAS are used (DGHS).

An observation of great importance coming out from the study is the presence of side effects. Though INH, PAS and streptomycin or a combination of any of these drugs are not entirely free from side effects, the frequency and severity of side effects rarely prohibit their large scale use under un-supervised condition in the DTP in rural areas. Blood changes of serious nature are reported when patients were treated with INH...TSC (Pines, 1964). In the study reported, 5 patients developed serious side effects possibly attributable to thiacetazone. It is not claimed that this indicates an incidence of 4% toxicity wherever such regimens are applied, but the finding does not exclude the presence of serious toxic reactions. Other studies (Sikand, 1963 & Menon, 1965) have indicated an almost complete absence of serious side effects among those that were followed up. One of the differences between those studies and the present one is that in their studies thiacetazone was split into two daily doses whereas a single daily dose has been used in this study. The possibility that this factor is responsible for the severe side effects cannot be overruled.

In the present study when patients defaulted from collecting the drugs, at least one home visit was paid to each defaulter. It was during these home visits that information on patients who died, migrated or experienced any side effects, was available. None of the five patients who developed severe side effects reported by themselves at the District Centre. Instead they took treatment elsewhere and tried to avoid attending the district centre. It was only through careful interrogation of the relatives that the facts about the side effects and treatment elsewhere were discovered. It is stressed that in the absence of such active efforts all the cases of severe side effects could have been missed leading to a belief that the drug combination was absolutely free from major side effects.

In a District Tuberculosis Programme, treatment in rural areas refers to drug distribution and defaulter control by the Primary Health Units and dispensaries under the supervision of the District Tuberculosis Centre. At these institutions, facilities for very frequent examinations of patients or complex laboratory investigations to elicit and confirm the presence

of toxic reactions are not and will not be feasible, for a considerable time. If, when under such circumstances, toxic side effects of serious nature occur and quickly progress, not these might lead to serious doubts in the minds of doctors administering the drugs, but also the efforts required to identify them will not be in consonance with the application of such therapy. In short, it may be said that if at 4% incidence of drug toxicity, 2000 patients treated in a district might give rise to 80 cases of serious side effects which will need identification and adequate care thereby enhancing the overall cost of treatment. The time and effort invested in the identification of such cases, in addition to adding to the cost the programme, likely in itself to be out of consonance with the principles of domiciliary treatment. Further such serious toxic reactions in some patients might contribute to enhance irregularity and even permanent drug default in other patients.

In the light of the above consideration though INH and thiacetazone combination as a single daily dose appears to be therapeutically efficient for mass application, the incidence of side effects appears to be high. Whether the side effects were due to the use of the single dose regimen can only be found in comparative study designed for the above purpose. Use of the combination in the tuberculosis programmes, will necessitate a reasonably good treatment organisation. Two basic requirements of such an organisation would be, satisfactory initial and subsequent motivations of patients put on this regimen as regards the probable side effects, the vigilance of the treating physicians to suspect and identify them in the initial stages and the availability of basic facilities to take care of the same when they occur.

5 Summary

127 patients both from semi-urban and rural areas representing a normal population of patients in a district programme were included in the study, 43 of whom were sputum positive and for 38 of whom INH sensitivity results are available. Of these 38 patients, 18 were resistant and the rest sensitive to INH. In all 41% (52 patients) collected drugs for a period of 10 to 12 months. The drug collection was not related to initial disease status, but compared to INH sensitive patients, INH resistant patients took treatment for longer duration.

The sputum conversion at the end of one year was of the order of 50% among all survivors; initiated (excluding dead and migrated) on treatment. Among those who were drug sensitive, examined at one year, the conversion rate was 63%.

Favourable radiological response was seen in 74% of patients started on INH+TSC and

examined at one year (excluded dead and migrated). The radiological improvement was better among those who collected drugs for a longer period than among those who collected for a shorter period.

23 patients developed 'side effects' presumably due to thiacetazone. Of these, 5 can be considered as major and the rest as minor side effects. Consequence of the side effects must be borne in mind while using the drug combination under District Tuberculosis Programme condition.

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ROLE OF SURGERY IN PULMONARY TUBERCULOSIS IN INDIA TODAY

GODREJ S. KARAI

(National Medical Institute, Calcutta.)

In the management of Pulmonary Tuberculosis, Surgery has an important and well-defined role to play, which, rather than suffer limitation with the advent of chemotherapy, has enhanced its effectiveness when staged carefully. Chemotherapy has made Resection and other procedures safe and effective weapons that have largely displaced the limited scope of the older operations of Thoracoplasty and Phrenic Paralysis.

Born of the prospect of physically removing every bit of tuberculous tissue under cover of chemotherapy, the initial enthusiasm went so far as to deserve the ridicule of being labelled "pimple excision", but tubercular surgery settled down to lobar, segmental or total excision and achieved a virtual cure of the disease in a much shorter time than before. It was soon realized that end-results were best when an adequate preoperative course of chemotherapy had controlled the bacillary population to render the sputum negative. Smaller foci in the lung tissue left behind, or stabilized contralateral disease did not break down as feared. Quick re-expansion of the residual lung insured against the unwanted broncho-pleural fistula. Complications were fewest where the organisms retained sensitivity to at least two of the three drugs in common use.

The commonest conditions and best indications were, cavities persisting after adequate chemotherapy, or temperamental and unstable residual lesions, bronchiectatic segments of larger areas of collapse from parenchymatous infiltration fibrosis or proximal endostenosis. Associated pleural fibrosis, empyema or bronchopleural fistula made the surgery more difficult technically. Judged from all over India, the results varied in degree, but were comparable with Western figures and compatible with local conditions. The overall mortality from surgery varied from 4% to 12%. The morbidity was higher in cases with positive sputum, and for bronchopleural fistula a rate of between 5% to 14% prevailed according to the case-selection and the proportion of sputum-positive material in the series.

As experience with the effects of chemotherapy increased over the years, three significant findings began to influence the role that surgery plays in pulmonary tuberculosis today.

1. Of certain lesions being submitted to surgery, a larger number were now

found to be controllable with chemotherapy alone and could be managed conservatively.

- II. In the average group of cases a small percentage does not strictly respond with the expected behaviour and leads to unstable lesions or progressive deterioration.
- III. There is a group where undetected or inefficiently treated disease progresses to virtual destruction of lung value functionally and physically. The common term "destroyed lung" covers these deficiencies.

Briefly stated, the modified surgical attitude towards this influence can be summed up as :

Surgery appears to be necessary where chemotherapy fails to achieve adequate control, yet the extent of the lesion is within resectable limits. In these cases certain lesions may persist owing to mechanical reasons or endobronchial changes and maintain a source of positive sputum. Drug resistance may have no small part in this local interplay between tissue and the bacillus. Finally, the lung may have become clearly functionless. Most of these cases have got past the toxicity phases, and are usually well except for the social danger from their positive sputum. Others have cough and expectoration within reasonable limits, but have become negative. Still others have marked symptoms of recurrent or large haemoptyses, some develop empyema, some suffer from the effects of a bronchopleural fistula. These last, must be offered surgery where compatible ; according to one's evaluation of the individual case, the sputum-negative cases need not be so; the sputum-positive cases must be advised surgery.

Surgery must offer its service where the patient's symptomatic condition can be relieved, where his social intermingling is a danger to others, where a destroyed and functionless lung is an undesirable affair.

Perhaps this summing up adequately covers the general surgical indications governing most thoracic surgeons in India today. Exceptions will be found, and there will be certain other conditions requiring surgery, such as failed thoracoplasty, removal of plumbage, simple decortication, or decisions concerning the controversial "open negative cavities". Under these circumstances, the operation of Thoracoplasty is again coming into favour as a means

of obtaining conversion of the sputum rather than obtaining excision of the tuberculous tissue. This occasion arises when the distribution of the lesions may mean excessive removal of pulmonary tissue or the surgeon may envisage a safer and less extensive removal with lower fistula-risk under conditions of negative sputum. Often having achieved conversion of sputum, it may even be permissible to keep the case under chemotherapy and observation; many attain stability of control thereby and need no further surgery.

This trend toward conservative surgery arises also when one is faced with the problems raised by the Chronic Drug-Resistant Sputum-Positive Destroyed Lung. Quite a formidable proposition, but judgment can be used here. Mortality rises to almost 22%, fistulation to 15%, rehabilitation time is extended to over one year, but a final salvage rate of about 80% in those surviving is the only consolation to this arduous programme of surgery. Conservatism is only called for in this group when one sees the patient as being unsuitable physically and mentally for this long programme of surgery which may be called for. Putting them under prolonged, almost permanent chemotherapy regime with INAH will convert at least 33%, and perhaps also render the excreted bacilli innocuous in the remainder.

If conservatism finds favour here, there are some, but rare instances where salvage in the form of Bronchus-ligation may help closure of massive cavities which have been otherwise regarded as hopeless.

In a review such as this one may question whether in India this problem has found adequate solution, and if not, determine what future role surgery can play in the wider management of pulmonary tuberculosis.

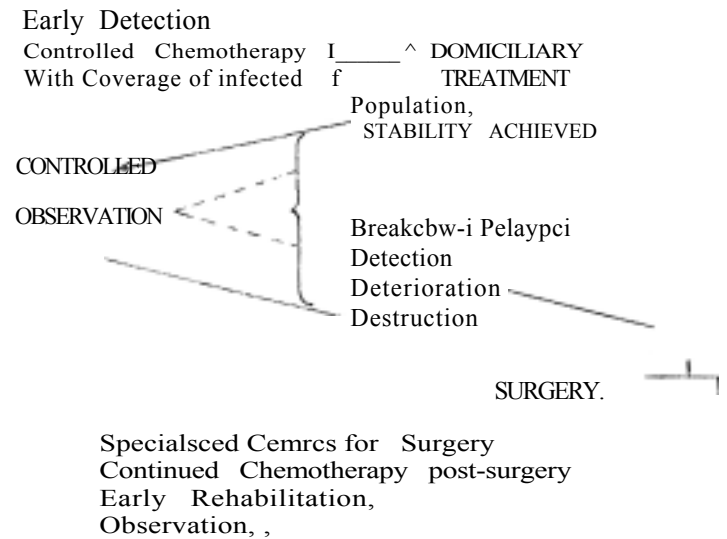
It is clear we have not reached adequacy in the solution of this problem, neither in bed-capacity, nor in the number of surgical centres dealing with this work. There is, however, future hope in this direction if the problem is approached in the perspective offered today by

the effects of chemotherapy. To date, there are no new or material advance in surgical technique over the last ten years, but there have been advances in the chemotherapeutic approach and in the methods of its administration. "Secondly, while chemotherapy can with widespread distribution reach a larger number of the tuberculous population, the number of surgical beds among them is few and far between.

The solution, it seems, would lie in two directions which are complementary to each other. If the total dimension of the problem can be reduced the target can be made easier. To this end.

- i. Surgery should concentrate only on those cases where chemotherapy has failed. Referral must not be delayed till chemotherapy has lost its effectiveness.
- ii. Surgery should itself be concentrated in centres where they are equipped with the high standards required of this form of work, and be judiciously spread out over the country regionally.

Schematically placed the approach would look like this.



PLACE OF SURGERY IN THE TREATMENT OF PULMONARY TUBERCULOSIS WITH SPECIAL REFERENCE TO DOMICILIARY TREATMENT

J. A. THOMPSON WELLS, R. M. SAHA TAHABILDAR, MRS. G. R. SAHA TAHABILDAR,
E. A. K. TEWARI and J. RAO SAMUEL
(Madar Union Sanatorium, Ajmer)

The acceptance of the principle of domiciliary treatment of pulmonary tuberculosis on a national scale has resulted in a sharp decline in the utilisation of beds for tuberculosis in Sanatorium throughout India. Certain criteria have been laid down for the admission of a patient and this includes:

1. Haemoptysis
2. Empyema with or without broncho-pleural fistula
3. Patients with bacilli resistant to first line drugs
4. Patients in need of surgery
5. Other reasons, social, economic, public health etc.

Almost all hospitals for tuberculosis have empty beds and some hospitals are faced with the problem of survival. Fortunately those with facilities for surgery do not have such a bleak future.

Two questions come to mind :

1. What part can hospitals with facilities for surgery play in the National Programme for the treatment of tuberculosis ?
 2. What changes in the surgery of tuberculosis have taken place or are taking place as a result of the widespread use of drugs?
1. The senior author has repeatedly stated that surgery plays a small but extremely important part in the treatment of tuberculosis and has stressed that every effort should be made to utilise facilities for this type of treatment to the fullest extent so that the residual pool of infection may be further reduced by treating cases of this nature.

There is a suggestion, and it is an excellent one, that there should be regional centres set up for the surgical treatment of tuberculosis. Unfortunately this has resulted in the establishment of rival institutions in some regions, where as other regions, are without any facilities for surgery. Since the State has assumed the responsibility of seeing to the health of the Nation, it would seem reasonable for the Government to see that where adequate facilities for thoracic surgery exist, the hospitals concerned should be recognised as the regional centre for cases requiring thoracic surgery and

all other efforts to duplicate these facilities stopped, so that the money, including foreign exchange, effort and personnel may be put to good use in establishing facilities where they do not exist. The Central Government should make it clear to the State Governments and all other Government agencies that the aim of the Government and voluntary institutions is the same—the relief of suffering. Therefore no two institutions should be planned where adequate facilities already exist and existing facilities used to the full. By this I do not mean directives but specific actions. The need to conserve money is great at the present time and this can be a small but important contribution. With the establishment of these regional centres for thoracic surgery the surgeon should be a member of a committee that sits once a month along with the staff of the District Clinic to study and review the case histories and x-rays of those patients who may need surgery. We would like to emphasise that surgery when indicated should be done early in the course of the disease when the bacilli are still sensitive to the drugs being used and it should not be put off till resistant strains have emerged. In most cases the optimum time for surgery is after six months of treatment with antimicrobial drugs, however, some cases may require surgery after three months and others after nine months, this periodic revaluation of cases will enable the District Clinic to achieve maximum results from the resources available. It is necessary for the State Government and the Centre to reserve beds in institutions both Government and Private for this purpose only. In this way empty beds will be put to good use.

2. We have analysed all the cases of tuberculosis operated upon in the last five years and find that there have been some interesting and significant changes in the surgical treatment of tuberculosis as shown in the accompanying tables. These relate to the following procedure:

- A. Pulmonary Resections and Decortication
- B. Thoracoplasties
- C. New forms of treatment.

(A) Pulmonary Resections

Pulmonary resections continue to be the most frequent operation performed for pulmonary tuberculosis. The indications for surgery at the present time include:

1. A destroyed lung or lobe
2. Persistent cavities in spite of adequate chemotherapy, especially if the sputum is positive
3. Tuberculous bronchiectasis
4. Tuberculous broncho stenosis
5. Carcinoma of the lung complicating tuberculosis
6. Possibly open healed cavities following adequate chemotherapy.

On studying the tables appended to this paper, it will be noticed that there is no significant change in the number of pneumonectomies performed each year. Lobectomies are the commonest operation and further analysis reveals the right upper lobe to be the commonest lobe removed.

There has been a definite decrease in the number of segmental resections performed. Complications following this type of surgery are high and the saving of a segment does not justify the increased morbidity.

During this period we have treated 29 cases of tuberculous empyema, 20 of these cases had a decortication alone or along with some form of resection. 16 of these patients had good results, two indifferent results and one patient died. 5 pleuro-pneumonectomies were also performed for tuberculous empyema and a destroyed lung. 4 of these patients have been cured. One patient still has a broncho-cutaneous fistula. Of the remaining 4 patients, two were cured with a thoracoplasty and drainage.

(B) Thoracoplasty:

On studying the tables we find that the number of primary thoracoplasties performed in the last two years have increased and we also find that more ribs may be resected in a single stage. In 32 patients 5, 6 or 7 ribs were removed in the 1st stage. There is no significant morbidity from this type of operation. There has been one death which might have been avoided as the patient died from Asphyxia due to inhaled vomitus.

(C) Other forms of surgical treatment:

In recent years bronchial ligation has been advocated as a means of converting a positive

sputum into a negative one in patients with disease too far advanced or too extensive for conventional methods of surgery. There have been several surgeons in India who have tried this procedure but they have not been very encouraged by the results.

At the International Chest Diseases Conference held in Delhi in 1963, Kano advocated the operation of casectomy for patients who had a tuberculoma or a blocked cavity. He reported excellent results with very few complications. We have been performing this operation in cases in which it is indicated either alone or in combination with a resection. The results of our experience are included in the tables and we are very satisfied with the procedure so far.

The Japanese surgeons have also had good results with Cavernostomy but in India, no one has reported any experience with this operation though I feel it does have a place in the treatment of pulmonary tuberculosis.

Conclusions:

1. The adoption of domiciliary treatment has not diminished the need for surgery.
2. A Pulmonary resection is the operation of choice with a lobectomy being the operation most frequently performed.
3. Tuberculous empyemas that do not respond to drugs and aspirations should be referred early for surgery. A decortication, with the resection of a lobe or a pleuro-pneumonectomy can be performed safely and with excellent results. In longer standing cases a thoracoplasty may be needed.
4. Primary thoracoplasties are being done more frequently and one stage 5 or 6 rib operations can be performed provided the patients condition permits. The collapse obtained is excellent and the results promise to be as good as when a thoracoplasty is staged.
5. Casectomy is a useful operation for blocked cavities and tuberculomas. The complications are few and healthy lung is conserved. This operation should be performed when indicated either alone or in combination with a resection.

TABLE I
Resections for pulmonary tuberculosis
 (430 operations on 427 patients)

	1961	1962	1963	1964	1965	Total
Pneumonectomy	20	16	21	22	21	100
Pleuro-pneumonectomy	1	0	3	2	0	6
Lobectomy	26	40	41	63	34	204
Lobectomy + Casectomy	0	0	9	3	4	16
Lobectomy -f Segmentectomy	3	4	6	4	3	20
Segmentectomy	20	14	10	4	6	54
Segment + Casectomy	0	0	1	2	1	4
Decortication + Lobectomy	1	4	8	4	0	17
Decortication + Segment	0	4	3	0	0	7
Lobe + fusion spine	1	0	0	0	0	1
Segment + fusion spine	0	0	1	0	0	1
Total	72	82	103	104	69	430
Total	72	82	102	103	68	427
Unilateral TB	65	54	57	62	39	277
Bilateral TB	6	23	42	37	29	137
TB. with Empyema	0	0	2	4	0	6
Pul. TB+TB spine	1	0	1	0	0	2
TB Bronchiectasis	0	5	0	0	0	5

TABLE 2 *Complications—Resection
for Pul. TB*

	1961	1962	1963	1964	1965	Total	%
Broncho-pleural fistula	1	1	1	0	1	4	.93%
Empyema+Broncho-pleural fistula	4	2	9	8	8	31	7.2%
Empyema	1	1	2	0	2	6	1.3%
Atelectasis	0	1	0	4	0	5	1.1%
Wound infection	12	4	0	4	5	25	5.8%
Gastric dilatation	7	0	0	3	0	10	2.3%
Spread	0	0	0	1	3	4	.93%
Hemiplegia	0	0	0	2	0	2	.4%
Death	3	1	1	5	2	12	2.7%
Surgical emphysema	*0	0	0	1	1	2	.4%
Paralysis of Recurrent laryngeal nerve	0	0	0	2	0	2	.4%
Auricular fibrillation	0	0	1	0	0	1	2 o/ ...- /o
Streptococcal Pneumonia	1	0	0	0	0	1	.2%
Total	29	10	14	30	22	105	24.4%

TABLE 3

Thoracoplasty

(80 operations on 56 patients)

	1961	1962*	1963 ^t	1964	west	Total
No. of patients	5	5	6	17	23	56
No. of 1st stage	5	6	6	17	23	56
No. of 2nd stage	1	3	3	4	12	23
	6	9	9	21	35	80

* In 1962, 1 patient had 1st stage left, the right being done in 1961.

^t In 1963, 1 patient had 2nd stage plombage

^t In 1965, 1 patient had a 2nd stage thoracoplasty. The 1st stage was done in 1964.

Analysis of first stage thoracoplasty

	1961	1962	1963	1964	1965	Total
Plombage	—	—	1	—	1	2
3 ribs	1	1	—	—	—	2
4 ribs	1	2	2	6	11	22*
5 ribs	2	2	1	8	3	16
6 ribs	1	1	2	2	8	14
7 ribs	—	—	—	1	—	1
	5	6	6	17	23	57
* 2 patients had one stage 4-rib thoracoplasty operation						
<i>Complications:</i> 1 wound infection following plombage						
<i>Deaths:</i> 1 from Asphyxia following a 6 ribs thoracoplasty Remainder were all discharged as sputum improved, much improved or arrested with negative						

TABLE 4
Casectomy

	No. of patients	No. of operations	pre of sputum		Specimen		Results			
			+ve changed	— ve	+ve	— ve	Good	Fair	Worse	Un- changed
Casectomy	8	9	9	5	4	5	3	—	1	
Decortication+Case	1	1	1		1	1	—	—	—	
Casectomy + Lobe	15	16	2	14	6	8	15	1		
					(2 not taken)					
Segment with Casectomy	4	4	4	22	4	—	—	—		
	28	30	2	28	13	15	25	4	—	

Good: Healing by linear scar, sputum negative by concentration method.
Fair: Lesion smaller, sputum negative *No change:* Lesion somewhat improved, sputum negative *Worse:* Lesion larger or sputum converted from negative to positive or both.

TABLE 5 *Tuberculous
empyema*

Decortication	g
Decortication with resection	1\
Decortication with excision mediastinal glands	1
Pleuropneumonectomy	5
Thoracotomy	j
Drainage & thoracoplasty	2
Conservative treatment	1
	29

Results of surgery:

	<i>Good</i>	<i>Fair</i>	<i>Poor</i>		<i>Died</i>
Decortication	7	1	—	1 =	9
Decortication with resection	7	2*	2	—	= 1 1
Pleuro-pneumonectomy	4	—	1		— — 5
Thoracoplasty	2	—	—	—	= 2
	20	3	3	1 =	27

* These two patients had apical spaces which obliterated after thoracoplasty and the results were good.

	1961	1962	1963	1964	1965	Total
Decortication	0	3	5	0	1 =	0
Thoracoplasty	1	0	0	0	1 =	2
				0	2 =	11

Programme of the Twentysecond Tuberculosis and Chest Diseases Workers' Conference—Hyderabad—3rd to 6th February, 1967.

FIRST DAY

Friday, 3rd February, 1967.

11.00—11.15 A.M.	Welcome Address by the State Health Minister and Chairman, Reception Committee.
11.15—11.30A.M.	Inauguration/Address by Governor of Andhra Pradesh.
11.30—11.45A.M.	Address by the President, Tuberculosis Association of India.
11.45—11.55 A.M.	Presentation of Award. Presidential Address by Dr.
11.55—12.30A.M.	Khushdeva Singh.
12.30—12.45A.M.	Review of tuberculosis work in India by Dr. N. L. Bordia, Adviser-in-Tuberculosis, Government of India and Honorary Technical Adviser, Tuberculosis Association of India.
12.45-12.55 A.M.	Vote of thanks.
12.55— 1.00P.M.	National Anthem.
1.00— 2.30P.M.	LUNCH BREAK.
2.30— 4.00 P.M.	Symposium on: "PREVALENCE OF DRUG RESISTANCE" and "CLINICAL SIGNIFICANCE OF DRUG RESISTANCE"
	Moderator: Dr. J. Frimodt-Moller
	Members : Dr. R. Parthasarathy Dr. K.G. Kulkarni Dr. S. P. Pamra
	Dr. P. R. J. Gangadharam Dr. Raj Narain Dr. S.P. Tripathy Dr. P. Kotaiah TEA BREAK.
4.00- 4.15 P.M.	Special lecture by Dr. K. N. Rao on "Health and Economic Development" •
4.15— 5.00P.M.	SECOND DAY

Saturday, 4th February, 1967.

9.30-11.00 A.M.

Session on "B.C.G. VACCINATION (Direct Vaccination) and "TYPE OF TUBERCULOSIS DEVELOPING AMONG B.C.G. VACCINATED PERSONS AND THE COURSE OF DISEASE AMONG THEM"

Chairman : Dr. N. L. Bordia

Members:

1. National Tuberculosis Institute, Bangalore.
2. Directorate of Public Health, Andhra Pradesh, Hyderabad.
3. The New Delhi TB Centre, New Delhi.
4. Dr. M. L. Mehrotra, Agra.
5. Dr. B. N. M. Barua, Directorate General of Health Services.

11.00—11.15 A.M.	TEA BREAK
11.15— 1.00P.M.	Symposium on “TUBERCULOSIS IN INDUSTRY” Chairman : Dr. M. N. Rao Members: (to be selected by the Chairman)
1.00— 2.30 P.M.	LUNCH BREAK
2.30- 3.30 P.M.	Panel discussion on: “TREATMENT DEFAULT: ADMINISTRATIVE, ORGANISATIONAL AND SOCIOLOGICAL CONSIDERATIONS” Chairman : Dr. D. Banerjee Members: (to be selected by the Chairman)
3.30— 3.45 P.M.	TEA BREAK
3.45— 4.15P.M.	Presentation of paper by the receipt of the junior award and discussion.
4.15— 4.35 P.M.	Papers on : 1. “Some aspects of pulmonary tuberculosis in the armed forces”— by Lt.—Col. J. C. Chatterjee DISCUSSION
4.35— 4.55 P.M.	2. “Clinical aspects of Broncho-pulmonary candidiasis”— by Dr. S. C. Chakravarty DISCUSSION
4.5:— 5.15P.M.	3. “Results of 150 resections of pulmonary diseases” by Dr. O. P. Mital. DISCUSSION

THIRD DAY

Sunday, 5th February, 1967

9.30—11.00 A.M.	Papers on “ECONOMICS OF HEALTH” Chairman: Dr: K.N. Rao Members: Dr. D.R. Nagpaul Dr. D. Banerjee Dr. K.C. Patnaik Shri H.R. Sharma
11.00-11.15 A.M.	TEA BREAK
11.15 A.M.—1.00 P.M.	Papers on: 1. Intermittent (once weekly) Chemotherapy for tuberculosis—by the Tuberculosis Chemotherapy Centre, Madras. 2. Thiacetazone plus INH <i>versus</i> PAS plus INH in the treatment of children sufferins from tuberculosis—a controlled study — by TB Hospital, Mehrauli, Delhi.

3. Five Year Follow-up of primary pleurisy with effusion —
by the New Delhi TB Centre.
4. Intensive Therapy followed by once weekly regimen—
by TB Centre, Agra.
5. Some aspects of relationship between drug collection
and drug consumption under domiciliary treatment—
by the National TB Institute, Bangalore.
6. Toxicity of Thiacetazone with 200 mgm daily dosage —
by Dr. Jaswant Singh, Patiala.

1.00-2.30 P.M.

LUNCH BREAK

2.30—4.00 P.M.

Symposium on “EMERGENCIES OF CHEST
PRACTICE”

Moderator: Dr. B.K. Naik

Members: Dr. H.B. Dingley—

“Spontaneous
Pneumothorax—
a review of 60
Cases”

“Acute Respiratory Embarrassment”
Haemoptysis Lt.—Col. S.N. Chak—
“Injuries of the

Chest”

4.00 - 5.00 P.M.

DISCUSSION

FOURTH DAY

Monday, 6th February, 1967

9.30 A.M. — 1.00 P.M.

(A) PLENARY SESSION

(Chairman, Standing Technical Committee to preside)
Presentation of reports by Chairman of different
Symposia and other sessions.

(b) BUSINESS SESSION

(c) VOTE OF THANKS

3.00 P.M.

MEETING OF THE STANDING TECHNICAL COMMITTEE.

TEN PRECEPTS

Ten precepts to assist physicians (particularly those lacking seniority) to avoid what may become dangerous habits and to keep the always possible error to a minimum :

1. There is no better way to clinical adeptness than getting one's hands dirty.
2. Strive to make a diagnosis of a condition that is relievable.
3. A period of observation is sometimes the only way to arrive at a correct diagnosis.
4. If a diagnosis of an unusual condition is made, it is apt to be wrong.
5. Do not interfere with an improving state, particularly if diagnosis is uncertain.
6. A wary use of drugs is wise policy.
7. The laboratory is no substitute for clinical acumen.
8. Do not perform a laboratory test unless you are prepared to get from it all the information that is in it.
9. Know thyself. 10. To err is human, to learn

S.S.P.

(Excerpt from an article in the 'Archives of Internal Medicine' (Chicago) August 1965, 116—164 by C. D. Aring).

NEWS & NOTES

Conference of TB & Chest Diseases Workers Hyderabad

The twenty-second Conference of Tuberculosis and Chest Diseases Workers in India will be held in Hyderabad from 3rd to 6th February, 1967. Shri Fattom Thanu Pillai, the Governor of Andhra Pradesh will inaugurate the conference.

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

Dr. K.N. Rao, Director-General of Health Services, Government of India and Chairman of the Association will deliver a public address on "Economics of Health" at the Conference.

The inaugural session of the four-day conference will be held in the "Rabindra Bharati", Hyderabad and the Scientific sessions in the Osmania Medical College, Hyderabad. About 500 delegates from all over the country are expected to participate in the conference, a detailed programme of which is being published elsewhere in the Journal.

Dr. K. Somayya, Honorary Secretary, Tuberculosis Association of Andhra Pradesh, Barkatpura, Hyderabad is in-charge of various programmes of the Conference.

Maharashtra State TB & Chest Diseases Workers Conference

The fifth Maharashtra State TB & Chest Diseases Workers' Conference was held in Bombay from 25th to 27th November, 1966. The Conference was inaugurated by the Governor of Maharashtra, Dr. P.V. Cheria at Patkar Hall of S.N.D.T. College and was presided over by Shri Homi J.H. Taleyarkhan, Minister for Housing and Tourism, Government of Maharashtra. Shri Vartak, Deputy Minister for Health also attended the conference.

The Scientific session was presided over by Dr. S.S. Ugrankar and inaugurated by Dr. S.V. Joglekar, Dean of K.E.M. Hospital. Papers on TB Control Plan highlighting the part which various organisations can play in it was discussed in the conference. This was followed by reports of the district control programmes of Nagpur, Aurangabad, Nadiad, Nasik, Latur and Poona.

The plenary session formulated specific

recommendations and submitted to the TB Advisory Board of the Maharashtra Government.

Mysore State TB & Chest Diseases Workers Conference

The Second Mysore State TB & Chest Diseases Workers' Conference will be held in Mangalore on 14th & 15th January, 1967.

Seminar on Tuberculosis: Madras

A Seminar on the control of Tuberculosis was organised by the Tuberculosis Association of Madras in the Madras Medical College Hall on 10th & 11th August, 1966. The Seminar was organised to discuss anti-TB measures to be taken in the city and other urban areas in Madras State. It was inaugurated by Mrs. Jothi Venkatachalam, Minister for Health, Government of Madras. Presiding over the second day's discussion, Dr. K.N. Rao, Director-General of Health Services, Government of India and Chairman, Tuberculosis Association of India noted with regret that TB control programme was not making enough progress because of lack of cooperation between medical practitioners and the Government. The Seminar concluded after appointing a Standing Committee to go into the details of personnel required, the organisation required, the number of basic health workers needed and the problem of coordinating the work of doctors and medical personnel for the control of Tuberculosis in the State.

TB Seal Design—1967

Simple and attractive designs are invited for the TB Seals for the 18th Seal Sale Campaign. A prize of Rs. 500/- will be awarded to the best design submitted. For details write to the Secretary-General, Tuberculosis Association of India, New Delhi.

1967 Health Visitors Course

The Tuberculosis Health Visitor's Course conducted by this Association will commence in the New Delhi TB Centre on 3rd January, 1967. About 20 students are expected to undergo the one year training course.

International TB Conference

The 19th International Tuberculosis Conference Under the auspices of the International Union Against Tuberculosis will be held in

Amsterdam (Netherlands) from the 3rd to 7th October, 1967. Details can be had from the Office of the Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

Chest & Heart Conference, Eastbourne, 1967

The Chest and Heart Association, London, will be holding a Chest and Heart Conference at Eastbourne from 4th to 7th April, 1967. The Conference will be open to doctors and non-medical workers in the chest and heart field. The conference will include a number of sessions devoted to scientific and clinical matters.

Membership—IUAT, Paris

The Tuberculosis Association of India has to appoint on the International Union Against Tuberculosis, Paris, Ordinary Members from India for the year 1967. All members will receive free of cost, Bulletins, 'T' Magazine, etc., published by the Union. For details please write to the Secretary-General, Tuberculosis Association of India, 3, Red Cross Road, New Delhi-1.

Appointment of Miss T.K. Adranvala

Miss T.K. Adranvala, has been appointed by the World Health Organization (WHO) as Nurse Adviser to the WHO Nursing Education Project in Kathmandu, Nepal. The purpose of this project is to establish a Division of Nursing in the Directorate of the Nepal Health Services to co-ordinate nursing activities in the country; to consult on the operation of a basic nursing school to prepare qualified nurse midwives for health services; to upgrade nursing services in Bir Hospital in Kathmandu and to improve the clinical field for student nurses.

Trained in Nursing Education from the Royal College of Nursing in London and in Nursing for Hospital Administration from the University of London, Miss Adranvala had held the post of Nursing Adviser to the Directorate General of Health Services, Government of India, New Delhi from 1948 to 1966. She is an ex-vice-president of the International Council of Nurses and a member of the WHO Expert Committee on Nursing.

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ABSTRACTS

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A Four Year Clinical Investigation of Ethambutol in Initial and Re-treatment Cases of Tuberculosis

Marjorie M. Pyle, Karl H. Pfuete, Maurice D. Peariman, J. De La Huerga and Ralph H. Hubble.

Amer. Rev. Resp. Dis; 1966, 93, 428.

Ethambutol was used in 145 cases of extensive, bacillary pulmonary tuberculosis including 43 re-treatment cases and 102 not previously treated. There were 136 males and 9 females. The average known duration of disease in re-treatment cases was 7.6 years.

In 35 re-treatment cases Ethambutol was the only drug used and there was sputum conversion (negative by culture) in 54% in 3 months. Ethambutol resistant strains (to 5 microgram per ml) were isolated in 37.5% of the cases which were unconverted. In most of them the bacterial resistance first appeared between 3rd and 5th month of treatment, the shortest period being 2.5 months in one case. Radiologically, 2/3rd of the patients in this group showed no improvement after 3 months treatment. At 6 months, moderate or marked improvement was seen in nearly 20% of the cases.

In previously untreated patients Ethambutol was given in combination with INH or with both streptomycin and INH. Tubercle bacilli disappeared from the sputum (by culture) within 6 months in 100% of the cases. No instance of bacterial resistance occurred in any case. Marked radiological improvement was seen in 74% of the cases where INH alone was the companion drug and in 93% where both INH and streptomycin were given.

The dosage of Ethambutol used ranged from 15 to 50 mg per kg. body weight, the total amount usually being given once a day. With the dosage of 40 to 50 mg per kg., 2 of the 6 patients suffered visual toxicity. With a dosage of 20 to 30 mg per kg, 3 of the 117 patients suffered similar but less severe visual toxicity. In all cases vision returned to pre-treatment level when the drug was discontinued. There were no other toxic effects and no hypersensitivity reaction. It may be possible to

virtually eliminate the potential visual toxicity by further reduction in dosage and by checking the patient's serum concentration to avoid excessive levels.

S.P.P.

Comparison of Ethionamide with Isoniazid in Original treatment cases of Pulmonary Tuberculosis

William S. Schwartz Amer. Rev. Resp. Dis; 1966, 93, 685.

United States Veterans Administration carried out a controlled clinical trial of the efficacy of ethionamide in previously untreated bacillary patients of pulmonary tuberculosis excreting sensitive bacilli. Ethionamide in combination with one gm. streptomycin daily (112 patients) was compared to daily streptomycin and INH schedule (124 patients). The dose of ethionamide was 0.5 gm. twice a day. The patients in both series were comparable. 39.2% of the patients did not complete the treatment in the ethionamide group due to toxicity as against 11.3% only in the streptomycin/INH group. The main toxic reactions to ethionamide were gastro-intestinal disturbances, nausea, vomiting and anorexia. Jaundice developed in one patient and 10 others had abnormal liver function tests. The response to treatment in terms of cavity closure and sputum conversion was almost identical in both schedules. Ethionamide containing drug schedules are not recommended for previously untreated patients because of high toxicity.

S.P.P.

Employment and Clinical Follow Up of 532 Tuberculosis Patients Discharged from 1951 to 1954.

Morris W. Lambie, & Kenneth A. Dening. Diseases of the Chest; 1966, 49, 352.

Follow up information on employment and clinical status was obtained for 532 adult male patients discharged from Veterans Administration Sunmount Hospital during 1951-1954. Of

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the 490 who were inactive at the time of discharge, 421 (86%) subsequently started working. The work was full time in 380. Those who did not go back to work had to begin with a higher percentage of far advanced disease, longer hospitalization, longer previous duration of disease and were generally older and had disabilities due to causes other than tuberculosis.

Relapse or probable relapse was found in 9% of those who did not go back to work, 17% of those who did part time work and 2% who were doing full time work. Relapses were seen more often in older patients. The study tends to show that work does not lead to relapse even when the work requires a high degree of physical exertion, even when pulmonary tuberculosis has been far advanced provided the definitive treatment has been good and adequate.

S.P.P.

Long-term Results of BCG Vaccination in the Southern United States.

G.W. Comstock & C.E. Palmer. Amer.

Rev. Resp. Dis; 1966, 93. 171.

The controlled trial of BCG Vaccination, involving 64,136 persons over the age of 5 years was started in Muscogee County USA in 1950. During 14 years of observation, almost 3/4th of the tuberculosis problem arose among the group of initial reactors who were not eligible for vaccination. Among the initial non-reactors (to 5 TU of RT 19-20), vaccination accounted for a reduction in tuberculosis of only 14%. The net reduction in the entire study population was thus less than 5%.

Although tuberculosis appear to be most common among persons with small amount of subcutaneous fat and those in inadequate housing, there was no indication that either of these factors could account for lack of effectiveness of BCG vaccination.

S.P.P.

Chimioprophylaxie des tuberculoses primaires de l'enfant et de l'adolescent en France

A Lotte, F. Hatton, S. Perdrizet & A. Rouillon. Bull. Wld. Hlth. Org. 1964, 31, 223-245.

A large scale long-term trial was started in France in 1953 with the object of assessing the efficacy of early treatment with drugs in preventing the occurrence of post-primary tuberculous manifestations and to determine the

effect of secondary chemoprophylaxis on the annual incidence of disease.

All the 4,992 persons (more than 90% were children below the age of 14) who were included in this study had either been infected less than a year earlier without radiological or clinical evidence of disease or they had radiological evidence of disease following a recent infection. Allocation to the Treatment and Observation groups was not at random. Those under the surveillance of physicians favouring chemoprophylaxis were given INH and PAS for a minimum of 6 months and formed the Treatment Group (2,018 persons). Similarly those who were under the supervision of physicians not in favour of chemoprophylaxis were left alone and were designated as the Control Group (2974 persons). The two groups were however found to be comparable in respect of age, sex, origin (urban or rural), socio-economic status and length of standing of the infection but differed markedly in one respect i.e. the proportion of persons with severe initial lesion was considerably higher in the treated group than in the control group.

The results so far have shown that chemoprophylaxis is particularly effective during the two years immediately following the first infection. The treatment was successful in reducing the frequency of post-primary manifestations of disease especially among persons who had radiological evidence of disease. During the 5 years observation period, 6.3% in the controlled group as compared to 1.5% in the treated group developed fresh disease. Whether this advantage will continue in the long run has yet to be ascertained.

S.P.P.

A New Method for Establishing the Diagnosis of Pleural Disease—Parasternal Lymph Node Biopsy

Hugh E. Burke & J.A.S. Wilson

A New Method for Establishing the Diagnosis of Pleural Disease.

J.A. Wilson, Jean Beland & Hugh Burke

Amer. Rev. Resp. Dis; 1966, 93, 201 and 209

Parasternal and/or para-aortic lymph node biopsy offers a simple and effective means for establishing the nature of some pleural effusions of obscure aetiology. The value of this examination is based on the possibility of bacteria and/or tumour cells being carried to the parasternal and para-aortic lymph nodes from the pleural space through the lymphatics.

S.P.P.

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Management of Undiagnosed Pleural Effusions in Positive Tuberculin Reactors

Cliffton W. Arrington, Joseph A. Hawkins, Joel H. Richert and Alan R. Hopeman
Amer. Rev. Resp. Dis; 1966, 93, 587.

The value of open pleural biopsy is stressed as against needle biopsy. Nearly 50% of the cases of 'Idiopathic' pleurisy showed granulomatous pleural reaction on open biopsy. Of the 18 cases where both open biopsy and needle biopsy were carried out there were 9 cases of positive open biopsy, in 3 of which the needle biopsy gave negative results. The authors conclude that though needle biopsy of the pleura is a useful procedure, failure to find granulomatous pleuritis even after multiple biopsies does not exclude tuberculosis.

S.P.P.

A Factor in the Etiology & Pathogenesis of Pulmonary Emphysema

O.C. Brantigan, M.B. Kress, & R.B. Goco
Dis. of the Chest; 1966, 49, 491

Pulmonary embolism occurs in from 1.5 to 25 per cent of routine necropsies and it is often found in the absence of a history of venous thrombosis. Pulmonary embolism is difficult to diagnose accurately without necropsy or operative evidence of emboli. It appears that death may occur suddenly, slowly, or not until repeated episodes of embolism occur and then death may be in part the result of pre-existing disease. There may be complete recovery after pulmonary emboli without demonstrable evidence of sequela. Many conditions may develop between death and complete recovery. The clinical course and pathogenesis of pulmonary emphysema are influenced by pulmonary emboli. Pulmonary emboli may be the cause of localised, lobar, or unilateral pulmonary emphysema. Pulmonary emboli may also be the cause of bullae in generalized pulmonary emphysema.

S.P.P.

A Two Year Follow up of Patients with Quiescent Pulmonary Tuberculosis following a year of Chemotherapy with an intermittent (twice weekly) Regimen of Isoniazid plus Streptomycin or a daily regimen of Isoniazid plus P.A.S.

V. Nazareth, S. Devadatta, C. Evans, Wallace Fox, B. Janardhanan, N.K. Menon, S. Radhakrishna, C.V. Ramakrishnan, H. Stott, S.P. Tripathy.

Tubercle, Lond; (1966), 47, 178.

Under domiciliary conditions 65 SHTW

(Twice Weekly high dosage isoniazid plus Streptomycin) and 53 PH (Standard daily regimen of Isoniazid plus P.A.S.) were followed after having attained bacteriologically Quiescent disease at one year. All cases were followed up for a period of two years.

Of these, cases were allocated at random to treatment with second year with isoniazid alone or with placebo. No patient was prescribed anti-tuberculosis drugs for the third year.

There were five deaths (four SHTW, one PH) in the 2nd year and all died from non-tuberculous causes. All were with negative cultures in the second year and for at least six months immediately before death.

A bacteriological relapse occurred in five (8%) SHTW and six (12%) PH patients.

An isolated positive cultures was produced by 17% of the SHTW and 27% of the PH patients.

Four of the SHTW patients had a relapse with Streptomycin and Isoniazid sensitive cultures and four of the PH patients with Isoniazid-sensitive cultures.

It is concluded that bacteriological quiescence following a year of thrice weekly isoniazid plus streptomycin is at least as stable over a two-year period of follow up as that attained following a year of a standard daily oral regimen of Isoniazid plus P.A.S.

H.B.D.

Reversion to Drug Sensitivity in Tubercle Bacilli. *Seheila M. Stewart: Tubercle, Lond., (1966), 47, 190.*

Reversion to bacterial sensitivity following known resistance was demonstrated in two out of 46 patients with Streptomycin-resistance cultures and in 14 out of 62 with Isoniazid-resistant cultures. No case of reversion was detected in 41 patients with P.A.S.-resistant cultures. All patients had been off therapy for at least three months, the mean period of treatment for the three drugs being 21.7, 16.1 and 2.2 months respectively.

Reversion to Isoniazid sensitivity occurred most frequently in patients treated for six months or less, in those who had been off treatment for more than 12 months and in those whose bacilli were only of low degree of resistance.

H.B.D.

TO BE OUT SHORTLY

A comprehensive book on
TUBERCULOSIS

by

Tuberculosis Association of India Edited
by prominent TB workers in India

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This publication is primarily intended to serve as a text-book for post-graduate medical students, but will also be most useful for general practitioners, and serve as a reference book for undergraduate students.

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