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A controlled study of the effect of a domiciliary tuberculosis chemotherapy programme in a rural community in south India

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To study the efficacy of a domiciliary drug-therapy programme in the control of tuberculosis in a rural community, an investigation was set up in 1958 under the auspices of the Indian Council of Medical Research in 12 towns with populations ranging from 6000 to 25000, all within 160 km of Madanapalle (Andhra Pradesh). The prevalences of bacillary and radiological cases of pulmonary tuberculosis in adults (aged 15 yr or more) were estimated in each town by carrying out a base-line random sample survey in 1959; also, the prevalences of tuberculous infection in all school children aged 5 to 9yr were estimated. These three indices of prevalence were used to rank the 12 towns and then randomly allocate them into two comparable groups of 6 towns each, designated as 'treatment' and 'control' towns. In treatment towns, intensive case finding was undertaken by means of 2 X-ray surveys (survey I during 1960-61 and survey II during 1962-64) covering all adults, sputum examinations by microscopy and culture when indicated, and periodic follow up of all 'suspect' cases with X-ray and sputum examinations. All bacillary cases were offered domiciliary treatment for one year with isoniazid and PAS in the 3 treatment towns (selected at random) and with isoniazid alone in the other 3 towns. Of 148 2cases eligible for treat- at ment in the 6 treatment towns, 15 per cent refused treatment and 29 per cent discontinued chemotherapy prematurely. In the control towns, no special facilities for diagnosis or treatment were introduced, and patients were left to the routine treatment facilities available locally. A tuberculosis prevalence survey (survey III) covering all adults was carried out in all 12 towns during 1965-68, and this was followed by a random tuberculin sample survey during 1966-69.

The overall results of treatment at the end of one year were: (i) among cases initially positive by microscopy, 10 per cent died, 33 per cent remained sputum-positive and 57 per cent became sputum-negative in INH-PAS towns, the corresponding percentages for INH towns being 15, 48 and 37 per cent respectively; (ii) among cases initially positive by culture only, 6 per cent died, 26 per cent remained sputum-positive and 68 per cent became sputum negative in INH-PAS towns, the corresponding percentages for the INH towns being 7, 38 and 55 per cent respectively.

All the bacillary cases (treated or untreated) were followed up and their status at the end of 5 yr was 40.4 per cent dead, 18.2 per cent sputum-positive and 41.4 per cent sputum-negative. Sputum status at one year had considerable prognostic value. Of 532 sputum-negative cases at one year, 18 per cent were dead, 16 per cent sputum-positive and 66 per cent sputum-negative 5 yr afterwards, whereas the corresponding percentages for the 379 sputum-positive cases at one year were 56, 20 and 24 respectively.

There was an interval of about 2½ yr between survey I and survey II and about 4 yr between survey II and survey III in the 6 treatment towns. The prevalence of bacillary cases in these surveys was age-standardised, considering separately cases found by microscopy and cases found by culture only. The mean prevalence of cases positive by microscopy in the 6 treatment towns was 6.81 per thousand in survey I and it decreased significantly ($P < 0.01$) to 5.01 in survey II and 4.83 in survey III. Change of culture technique during the course of the investigation complicated the interpretation of prevalences of culture-positive cases.

Between the 1959 base-line survey and the resurvey in 1965-68, the prevalence of smear-positive tuberculosis decreased from 5.92 per thousand adults to 4.78 in the 6 treatment towns, and similarly from 5.72 to 4.21 in the 6 control towns. The prevalence of 'culture only-positive' cases was 3.85 and 2.44 per thousand adults in the treatment and control towns respectively at the base-line survey and (with the more sesnsitive culture technique) 4.92 and 4.82 per thousand adults at the resurvey in 1965-68. Lastly, the tuberculin survey in 1966-69 did not reveal any significant differences between the treatment and the control towns.

The inability of the domiciliary treatment programme to make an impact on the prevalence of tuberculosis in the rural community around Madanapalle is a finding that has considerable significance in the context of the tuberculosis control programme in India; the reasons for the failure aud its implications are discussed.

Before the discovery of modern antibiotics effective in tuberculosis, the traditional methods of combating tuberculosis were considered to be isolation of the infectious cases in hospitals, sanatoria or special colonies (for persons with chronic disease) and the use of BCG vaccination. These methods were used quite extensively before World War II in Western countries but were not applied on any significant scale in the developing countries, including India. While it was possible in the countries in the West to provide a sufficient number of hospital beds to admit the majority of the infectious cases, it was quite impossible to adopt such a procedure in a country of the size of India. Although the number of beds reserved for tuberculous patients has increased in the post-war period from 30,000 to 43,000, it is very small considering the size of the country and the bacillary cases running into millions. In 1948, BCG vaccination was introduced by the Government of India with the assistance of the World Health Organization (WHO). After a preliminary pilot study conducted by the Union Mission Tuberculosis Sanatorium at Madanapalle (Andhra Pradesh),which showed that BCG vaccination in Indian children did not cause any serious or harmful local reactions[1,2], BCG vaccination was introduced on a country-wide scale in 1949 by the Central Government assisted by the International Tuberculosis Campaign, WHO and UNICEF. In the course of a few years, BCG vaccination teams were operating in all the states in India.

At Madanapalle, the initial pilot study of the immediate effect of BCG vaccination led to the setting up of a Field Research Station under the Government of India, Health Ministry, and the WHO Tuberculosis Research Office with a view

to study the epidemiology of tuberculosis, particularly trends or changes in the prevalence and incidence of tuberculosis if modern control methods were applied.

Reports on the results obtained during the first five years were published in 1960[3] and studies on the protective effect of BCG vaccination in the Madanapalle Study Population were reported between 1960-1973[3'4'6'8].

Modern anti-tuberculosis drugs were introduced in India in 1946 when streptomycin became available. Para-aminosalicylic acid (PAS) followed in 1949 and isoniazid in 1952. It became soon evident that these three drugs represented very potent chemotherapeutic agents which could produce marked improvement in pulmonary tuberculosis patients by reducing and eliminating the bacilli from the expectorate. Whereas streptomycin and PAS were quite expensive and might cause certain complications, isoniazid was capable of rendering a high percentage of tuberculous patients sputum-negative even when given alone. The breakthrough in the widespread use of isoniazid came when the Tuberculosis Chemotherapy Centre (of the Indian Council of Medical Research) at Madras, showed that isoniazid in combination with PAS was able to render about 90 per cent of bacillary cases of tuberculosis sputum-negative, even if the patients continued to live under ordinary, simple home conditions (Tuberculosis Chemotherapy Centre, Madras, 1959)[9]. The demonstration of the fact that chemotherapy under home conditions was as effeetive as chemotherapy in hospital led very soon to the idea that chemotherapy, particularly with isoniazid, if used on a mass scale, could be a powerful factor in the control of tuberculosis. However, the Madras investigation which had compared home with institutional treatment was conducted under very special conditions for the purpose of ensuring reliable research results. Could these highly encouraging results also be acclaimed under ordinary working conditions ? If they could, a very valuable tool in the control of tuberculosis would have been found.

There was, therefore, a need to try under normal working conditions, how far it would be possible to use home treatment to influence or make an impact upon the tuberculosis problem by reducing the prevalence and possibly also the incidence in a particular community. The matter was discussed with experts in the Government and the WHO. It was agreed that such an investigation should be carried out as closely as possible to that which could be expected by a Government clinic. It was stressed that the financial outlay should not exceed what would be considered reasonable for such a clinic. The use of streptomycin was ruled out as it would involve placing a nurse in the various localities and providing for regular supervision by medical officers who would have to be responsible for such treatment. Further, PAS which at that time was considered the common companion drug to isoniazid was frowned at because of its cost and reputation of causing unpleasant side effects. There was general agreement that isoniazid was the drug of choice, particularly in doses large enough to be effective but not so large that they would cause toxic complications. As some experts insisted upon a two drug regimen and others on one drug (isoniazid alone), it was decided to

examine both possibilities under similar conditions. So the two regimens finally decided upon were isoniazid alone and isoniazid plus PAS.

Although the aim was to carry out the investigation as if it had been done by a Government clinic, it was unavoidable that certain deviations would arise. For instance, in order to detect almost all bacillary cases in a community, surveys by mobile X-ray units were to be employed and the investigation had at its disposal the well established bacteriological laboratory at the U.M.T. Sanatorium with access to culture work and drug sensitivity tests. It was also recognised that situations would arise where the Research Unit would soon know which cases yielded cultures that were resistant to isoniazid or other drugs, but as such information would not be available to other centres with no access to culture work, the Research Unit should not change for that reason, the type of regimen.

It was then decided by the Government of India as well as the WHO to let the investigation be carried out by the Madanapalle Field Research Unit, a part of the Union Mission Tuberculosis Sanatorium (UMTS), Arogyavaram. A special Project Committee* was set up to decide upon a protocol for the investigation and to supervise and advise the Unit during the conduct of the investigation.

Aim and design of the study

The immediate aim was to see if it was possible to organize home treatment so that the results would be comparable or nearly comparable to those obtained at the Tuberculosis Chemotherapy Centre, Madras, so that a high percentage of the patients treated would obtain sputum conversion within 12 months. The distant aim was to see if it would be possible through home treatment with simple drug regimens to reduce the prevalence of tuberculosis significantly. In other words, the aim was to compare two policies, namely intervention or non-intervention in the control of tuberculosis in a community. This required therefore the setting up of a programme where the prevalence in two comparable communities could be compared before and after a period of implementation of free domiciliary drug therapy programme in the one but not in the other community. The study was designed as follows :

Twelve towns ranging in population from 6,000 to 25,000 and all lying within reach of Madanapalle *i.e.* within a distance of 160 km were chosen. To start with, a base-line sample survey was carried out in 1959 covering samples of 20-25 per cent of the adult population (children below 15 yr being excluded). After a complete census in the selected

*Members of the Project Committee of the Tuberculosis Research Project, Madanapalle, February 1959: Dr C.G. Pandit, Director, ICMR; Dr P. V. Benjamin, Adviser-in-Tuberculosis, Directorate General of Health Services, Government of India; Dr E. J. T. McWeeney, Representative of WHO; Dr Halfdan Mahler, WHO; Dr K. S. Sanjivi, Madras; Dr K. T. Jesudian, Medical Superintendent, U.M.T. Sanatorium Arogyavaram; Sri K. K. Mathen, Asst. Professor of Statistics, All India Institute of Hygiene and Public Health, Calcutta, the Director of Medical Services, Andhra Pradesh; and Dr J. Frimodt-Moller, Director, Tuberculosis Research Project, Madanapalle.

samples, X-ray examination by means of mobile X-ray units was carried out and followed by bacteriological examination of the cases which had radiological signs of lung pathology. In order to obtain an unbiased estimate of the prevalence of X-ray positive cases of tuberculosis, all the 70 mm X-ray films from the sample survey in the 12 towns were read by an independent assessor. In addition to X-ray survey, another survey based upon tuberculin testing by Mantoux's tests was carried out among children in the two lowest grades of all the schools, *i.e.* in the age groups 5-9 yr.

The results of the base-line survey were expressed in the form of the three prevalence indices : (i) number of cases of bacillary tuberculosis per 1000 population; (ii) number of cases of radiologically active or probably active tuberculosis per 1000 population; and (iii) reactors to tuberculin among the small school children (expressed in per cent). These results were passed on to a senior statistician who ranked the 12 towns according to the degree of prevalence of tuberculosis and then divided them by random allocation into two comparable groups of 6 towns each. One group became the 'treatment' group and the other the non-treatment 'control' group. The former group was further subdivided randomly into two groups of three towns each, in one of which the treatment was to consist of isoniazid and PAS, and in the other of isoniazid alone.

The X-ray survey was thereupon resumed in the 6 'treatment' towns and all the residual populations which had not been examined by X-ray previously were now examined so that a full survey would be carried out. All cases who showed presence of bacilli in the sputum either by microscopy and culture or only by culture were offered free treatment for 12 months by fortnightly drug issues.

When the first full survey had been completed, another full survey was again carried out in the 6 'treatment' towns, and new patients detected and anyone who had presented with symptoms during the interval between surveys were given the same type of treatment already used in the towns, where the patients lived. Lastly, after completing survey II, a third and final survey was carried out in the 6 'treatment' towns and this time the 6 'control' towns were also included in the survey which constituted in their case, the first full resurvey, the previous one being the base-line sample survey of 1959.

While the last survey was being done, a tuberculin survey was carried out (1966-69) in random sample blocks in each of the 12 towns.

The outcome of the study *i.e.* its final results, was based upon comparisons of the mean prevalences of tuberculosis of the various groups representing such items as treatment *versus* non-treatment, 2-drug *versus* one drug towns, males-females-both sexes, initial sputum findings (microscopy *versus* culture only), bacillary drug sensitivity to isoniazid, follow-up results *etc.*

It may be noted that, according to the design of the study, the sampling units were not patients within towns, but the towns themselves. It follows that comparisons between treatment and control

groups must be based on the means of the prevalences in individual towns. In view of the smallness of the degrees of freedom for these comparisons, the differences between the treatment and control groups would have to be substantial for being labelled as statistically significant. Details on methods of statistical analysis used have been given in the accompanying paper by Dr S. Radhakrishna.

Selection of towns : A number of small towns between 6,000 and 25,000 in population and situated in Chittoor, Cuddapah and Anantapur districts of Andhra Pradesh, and in Kolar District of Mysore State, all within a distance of 160 km or so of the Madanapalle Tuberculosis Research Centre, were selected for the trial (Fig. 1). The total population was about 120,000-140,000.

In selecting the towns the principle was that they should be neither too small nor too large, not too heterogenous with regard to the type of population nor the population too fluctuating. Therefore, large district headquarter towns or towns with railway junctions with staff given to frequent transfers, or towns with temples attracting large crowds of pilgrims several times a year, were excluded. Further, the towns were not so far away that they could not be handled from Madanapalle as the centre of operations. It was unavoidable that many roads leading to these towns

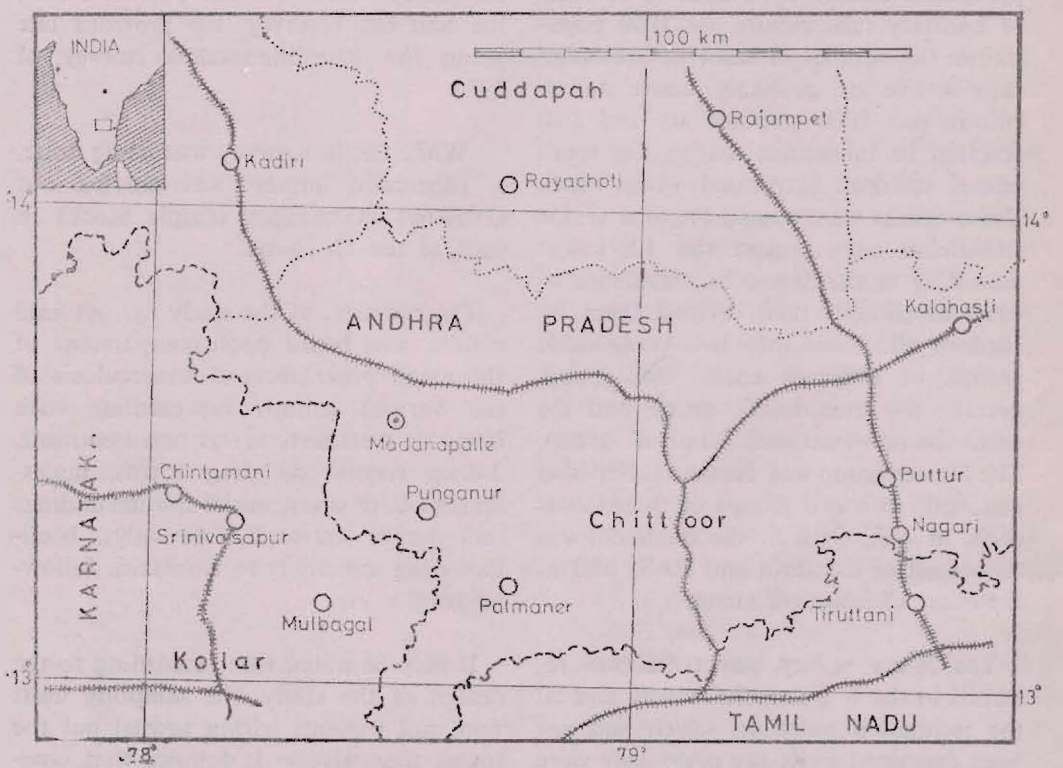

Fig. 1 — Map showing the 12 towns selected for the study.

were of the second or third degree, so the staff had to travel through rivers, thinly populated areas or jungles. During the monsoon season when the rivers were often impassable, detours of many miles had to be done.

List of towns showing distance from Madanapalle :

	Population	*Distance, km*
Andhra Pradesh :		
Rayachoti	10,700	68
Rajampet	9,300	145
Kalahasti	18,000	145
Puttur	8,000	169
Nagari	6,600	163
Tiruttani*	10,000	182
Kadiri	20,300	80
Punganur	11,300	18
Palmaner	6,900	56
Karnataka state :		
Chintamani	14,400	64
Srinivasapur	6,600	58
Mulbagal	9,000	80

*Later transferred to Tamil Nadu

Time schedule : The calendar periods in which the different surveys were carried out in the 'Treatment' and 'Control' towns are given in Table I.

Bacteriological examinations : These examinations were done after the X-ray examinations in the Surveys and they were confined to persons selected on the basis of lesions seen on X-ray films. They consisted of (i) two smears for microscopy, (ii) two laryngeal swab cultures (from 1959 till 1964 and then abandoned), and (iii) a sputum culture from a specimen collected overnight or on the spot when taking laryngeal swab cultures or by pooling the specimens if obtained both ways.

Bacteriological methods

Isolation of tubercle bacilli from expectorates : The standard method used in the UMTS Laboratory for purposes of homogenisation and decontamination when culturing sputa for tubercle bacilli was for many years 6 per cent sulphuric acid. Equal amounts of expectorates and sulphuric acid were mixed and kept in the incubator for 20 min, then cen-

TABLE I — (a) CALENDAR PERIODS OF THE THREE CONSECUTIVE SURVEYS IN THE 6 'TREATMENT TOWNS'

Towns	Survey I*	Survey II	Survey III
Kadiri	1960, March — Aug.	1962, Jan. — July	1965, Sept. — '66 Apr.
Rajampet	1960, March — July	1962, Jan. — Nov.	1966, July — '67 Jan.
Chintamani	1960, July — '61 Jan.	1962, Dec. — '63 Sep.	1966, Dec. — '67 Nov.
Tiruttani	1960, Aug. — Dec.	1963, Jan. — July	1967, July — '68 Feb.
Palmaner	1960, Nov. — '61 March	1963, Sep. — '64 Jan.	1967, Dec. — '68 May
Kalahasti	1961, Apr. — Dec.	1963, Sep. — '64 Oct.	1968, Apr. — '69 Jan.

*Note : — 'Survey I' relates to the survey of the remaining portion (75-80%) of the towns not covered by the 1959 Sample Survey.

(b) MEAN INTERVALS INMONTHS BETWEEN SURVEYS

Towns	Intervals in months		
	Survey I- Survey II	Survey II- Survey III	Survey -I Survey III
Kadiri	22.5	44.5	67.0
Rajampet	27.5	49.5	77.0
Chintamani	30.5	49.0	79.5
Tiruttani	30.0	54.5	84.5
Palmaner	34.0	51.5	85.5
Kalahasti	31.5	53.0	84.5
Means	29.3	50.3	79.7

(c) CALENDAR PERIODS OF 'SURVEY III' OF THE 6 'CONTROL' TOWNS

Towns	Survey III
Rayachoti	1965, May — August
Srinivaspur	1966, March — July
Mulbagal	1966, August — December
Nagari	1967, March — June
Puttur	1967, November — '68 March
Punganur	1968, May — October.

trifuged, decanted and the sediment neutralised with a drop of sodium hydroxide. The sediment was then inoculated into two tubes of Lowenstein-Jensen medium.

As it had been observed for some time that a number of specimens positive by microscopy had failed to grow by culture, it was suspected that the sulphuric acid concentration was too strong and might kill the bacilli. It was then decided in 1964 to change over from 6 per cent sulphuric acid to 4 per cent sodium hydroxide; after centrifugation the sediment was now neutralised with a drop of nitric acid. It was soon found that the change meant a great improvement in the culture technique. The smear positive specimens rarely failed to grow by culture and the number of positive cultures from specimens negative by smear showed a much higher number of positive cultures than before. To get a numerical expression of the advantage obtained by the new method, a special study was made in 1966.

Over a period of several months, all routine specimens obtained in the field were divided into two equal aliquots of which one set was treated with sulphuric acid and the other with sodium hydroxide. The culture bottles were given code numbers so that neither the technician nor the bacteriologist who read the culture bottles would know which method had been used. The results obtained are shown in Table II. The sulphuric acid method produced 66 and the sodium hydroxide method 139 positive cultures whereas only 48 of the same specimens were positive by microscopy. Of the 48 specimens, 33 or 69 per cent only were positive by culture when using sulphuric acid, whereas all 48 specimens were positive when NaOH was used. Evidently 15 of 48 specimens positive by smear and treated with sulphuric acid had failed to grow. The difference in yield is equally striking when noting that among the specimens negative by microscopy, only 33 cultures were obtained when using H_2SO_4 against 91 obtained when NaOH had been used. Of the 91, 33 were positive by both methods and 58 positive by NaOH but negative by H_2SO_4. Table II (b) compares the results by culture with the number of bacilli noted in the specimens which were positive by microscopy. When the smears showed +++ or ++, the number of positive cultures were nearly the same. Of 34 specimens showing 1+ bacilli by microscopy, only 20 gave growth with sulphuric acid against growth

TABLE II — EFFICACY OF MICROSCOPY, CULTURES BY H_2SO_4 AND CULTURES BY NaOH IN DEMONSTRATING TB IN 650 SPUTUM SPECIMENS

(a)

Microscopy	Culture (H_2SO_4)	Culture (NaOH)	Specimens No.
+	+	+	33
+	+	—	0
+	—	+	15
+	—	—	0
—	+	+	33
—	+	—	0
—	—	+	58
—	—	—	511
			650
+			48
	+		66
		+	139

(b)

Result of microscopy TB	No.	Positive by culture H_2SO_4 No.	NaOH No.	Gain by NaOH No.
+++	3	3	3	—
++	11	10	11	1
+	34	20	34	14
—		33	91	58
Total positives	48	66	139	73

in all 34 cases treated with NaOH. The advantage obtained by switching over to sodium hydroxide from sulphuric acid was even more striking when it was noted that over and above the 48 specimens positive by microscopy, the sodium hydroxide method produced 91 positive cultures against only 33 by the sulphuric acid method*.

Drug sensitivity tests : The minimal inhibitory drug concentration (MIC) was defined as the lowest concentration of the drug which inhibited growth of 20 or more colonies. Drug resistance was defined either by the MIC itself or by the ratio of the MIC of the test strain to the MIC of the standard laboratory strain 'H37 Rv'; this ratio is called the 'resistance ratio'. In the case of isoniazid, 'resistant' strains were defined as strains with an MIC of 5 mcg isoniazid per ml or more; 'doubtfully resistant', if the MIC was 1 mcg per ml. 'streptomycin resistance' was defined as strains with a resistance ratio (RR) of 8 or more, and 'doubtfully resistant', if the RR was 4. 'PAS resistance' was defined as strains showing an RR of 8 or more; 'doubtfully resistant' if it showed an RR of 4.

All cultures of *M. tuberculosis* were tested, as a matter of routine for drug sensitivity to isoniazid, streptomycin and PAS. However, in the present report, only the isoniazid results have been included.

Doubtfully resistant strains : For the purpose of the present analysis all cultures classified as 'doubtfully resistant to isoniazid' have been counted as 'resistant to isoniazid'.

*The present investigation began in 1959 and concluded in 1968. The improvement in culture technique took place early in 1964. The Sample Survey and Survey I were done with the old culture technique. The change took place in the midst of Survey II while Survey III was done wholly with the new method. This has an important bearing upon the estimates of the prevalence and inicdence of tuberculosis at different points in time during the investigation.

The implications of this decision can be gathered from the following observations :—(*i*) Analysing the results of all routine sensitivity tests carried out in the Research Laboratory in the months of March 1965, 1966 and 1967, it was found that of 551 cultures examined 61.3 per cent were INH-sensitive, 31.8 per cent INH-resistant and 6.9 per cent 'doubtfully resistant to INH'. By adding the doubtfully resistant strains to the resistant, the latter was increased from 31.8 per cent to 38.8 per cent, *i.e.* an increase of 18.9 per cent, in other words, of the strains now classified as INH-resistant, about one-fifth would be 'doubtfully resistant to INH' and four-fifths INH-resistant; (*ii*) As for the consistency of demonstrating strains 'doubtfully resistant to INH', an analysis of repeat INH sensitivity tests on cultures noted as 'doubtfully resistant to INH' carried out between March 1, 1965 and February 28, 1966 showed that of 107 repeat tests, 14 cultures were classified as INH-sensitive, 75 as 'doubtfully resistant' to INH and 18 as INH-resistant'. The original classification was therefore confirmed in 70.1 per cent while 16.8 per cent were found to be resistant and only 13.1 per cent of the strains were classified as INH-sensitive.

The merging of strains 'doubtfully resistant to INH' with INH-resistant strains appears justified as the chance of strains classified as resistant being really sensitive is of the order of 2 to 3 per cent only.

The preliminary base-line sample survey, 1959

The main purpose of this survey was to assess the initial size of the tuberculosis problem. It was also intended to provide criteria for allocating the towns to the three treatment groups outlined in the protocol *viz.* (*i*) towns in which the only drug issued would be isoniazid, (*ii*) towns in which isoniazid as well as PAS would be given; and (*iii*) towns where no treatment would be given. On the advice of Dr K. K. Mathen, Professor of Statistics and member of the Project Committee, it was decided that the sampling fraction should be 20 pre cent except for towns with populations of less than 8,000 where it should be 25 per cent.

The method followed in drawing the samples was as follows :—

A team consisting of a doctor and 4-5 clerks visited the towns and made a study of the outlay of the towns and noted the number of households in each block, or definable cluster of houses, by preparing sketches of the different parts of the town. These sketches were then fitted together at headquarters by a draughtsman as pieces in a jig-saw puzzle to form a large map of the town. The map was then reproduced as a blue print measuring about 60 × 80 cm. In the case of Kalahasti, the largest town, 3 maps had to be made to cover the whole town. Although the maps were by no means made to scale, estimates of the distances were arrived at by letting a jeep run up and down the main street a couple of times to measure the diameter of the town. Thereafter, the blocks of the map were encircled with red corresponding to not less than 20 and not more than 40 households per block. In some cases the blocks were so crowded with families that they had to form a special stratum containing over 40 house-

holds per block. The blocks were numbered in serial order and samples of either 20 or 25 per cent, were drawn by consulting a table of random numbers. Thereafter, a complete census was taken of the persons living in each of the sample blocks selected. When the census was over, the mobile X-ray unit visited the town, halting in different places according to the convenience of the staff and the local population. The different localities were visited until about 90 per cent of the eligible residents had been X-rayed. The Research Unit had at its disposal two mobile X-ray units. As there was some difference in the quality of the X-ray films, the two X-ray units were interchanged so that each town was served equally by the two units.

All persons aged 15 yr aud more were eligible for X-ray examination. Children below 15 were therefore excluded. The skiagrams were read independently by two doctors who were experienced in X-ray interpretation. All cases showing radiological evidence of pulmonary pathology according to either one or both readers were then visited by a team from the Laboratory. Sputum was collected for microscopy and culture and two laryngeal swab cultures were made on the spot. The sputum and the cultures were kept in portable refrigerators from the time of collection till they had been brought back to the Laboratory at the UMT Sanatorium. Smears for direct microscopy were prepared and examined either in the field or at headquarters.

The sample survey began in Kadiri in May 1959 and was followed by surveys at Rayachoti and Rajampet in Cuddapah district, Srinivasapur and Mulbagal in Kolar District and from October 1959 by surveys in Tiruttani, Nagari, Puttur and Kalahasti in Chittoor District. Finally, Palmaner and Punganur were examined in December so that the sample survey was completed by the end of 1959. The bacteriological examinations continued, however, during the first two months of 1960.

The number of blocks in the two strata is shown in Table III. Stratum I contains 20-40 households and Stratum II contains more thau 40 households. In 8 towns, the sampling fraction was 20 per cent and in 4 towns with populations of 8,000 and less, it was 25 per cent. Table IV shows the number of households counted at the time of drawing the maps of the towns. It also shows the resulting sampling fraction varied from 17.7 to 21.6 in the group where it was inteuded to be 20 per cent and from 24.1 to 25.9 in the group of small towns where it was 25 per cent. The last column indicates the number of persons living in the sample blocks as found by the survey teams when they carried out the census of the sample blocks. The estimates of population living in all the blocks are shown in Table V, along with the official census populations in the 12 towns as found in the Census of India 1951 Report. From the Census of India Reports for 1951 and 1961, the annual growth rate has been estimated and from this again the populations in 1959. Comparing these estimates there was a fairly close agreement in most of the towns except in Kadiri and Rayachoti where the populations of the Sample Survey were 60.6 and 69.3 per cent only. The discrepancies are due to our teams not covering the whole official municipality area when carrying out the sample survey.

TABLE III — 1959 SAMPLE SURVEY. NUMBER OF BLOCKS IN STRATUM I (20-40 HOUSEHOLDS) AND STRATUM II (MORE THAN 40 HOUSEHOLDS)

Towns	Stratum I blocks		Stratum II blocks		Total blocks	
	Total	Sample	Total	Sample	Total	Sampling fraction (%)
Kadiri	81	16	14	3	95	20
Rayachoti	90	18	6	1	96	20
Rajampet	81	17	11	2	92	21
Chintamani	100	20	7	2	113	19
*Srinivasapur	41	11	3	1	44	27
Mulbagal	74	16	3	1	77	22
Tiruttani	53	15	6	1	59	27
*Nagari	40	10	6	2	46	26
*Puttur	41	13	9	2	50	30
Kalahasti	155	31	17	4	172	20
*Palmaner	44	11	11	3	55	25
Punganur	57	11	19	4	76	20

*Sample fractions 25%, the remainders 20%

TABLE IV — 1959 SAMPLE SURVEY. SAMPLING FRACTION AND NO. OF PERSONS LIVING IN THE SAMPLE BLOCKS

Towns	Households in		Sampling fraction	Persons living in sample blocks
	All blocks no.	Sample blocks no.	(%)	No.
Kadiri	3714	658	17.7	2519
Rayachoti	2863	572	20.0	2116
Rajampet	2699	519	19.2	2158
Chintamani	3283	654	19.9	3436
Srinivasapur	1236	307	24.8	1695
Mulbagal	2064	425	20.6	2478
Tiruttani	2022	436	21.6	1730
Nagari	1457	366	25.1	1726
Puttur	1711	422	24.1	2137
Kalahasti	5116	1053	20.6	4615
Palmaner	1828	473	25.9	2075
Punganur	2523	478	18.9	2211

TABLE V — COMPARISON OF TOWN POPULATIONS ACCORDING TO CENSUS OF INDIA AND THE 1959 SAMPLE SURVEY

Towns	Census 1951	Annual growth rate (%)	Estimated population 1959	1959 survey All blocks	
				No.	%
	(a)	(b)	(c)	(d)	(e)
Kadiri	20,354	1.79	23,458	14,218	61
Rayachoti	10,655	4.61	15,281	10,591	69
Rajampet	9,281	2.29	11,124	11,222	101
Chintamani	14,411	3.15	18,469	17,248	93
Srinivasapur	5,978	1.31	6,634	6,824	103
Mulbagal	9,025	2.87	11,318	12,034	106
Tiruttani	9,925	0.39	10,239	8,023	78
Nagari	6,567	2.01	7,700	6,871	89
Puttur	7,989	2.35	9,620	8,664	90
Kalahasti	17,921	3.97	24,470	22,422	92
Palmaner	6,884	3.66	9,178	8,019	87
Punganur	11,284	2.04	13,263	11,646	88
				Mean	88.2

*Estimated from sample blocks

Prevalence of bacillary pulmonary tuberculosis : Table VI summarizes the work done and gives the results for males and females respectively in each of the 12 towns. The coverage obtained at the time of X-ray examination was close to 90 per cent ranging from 89 to 94 per cent for males and from 86 to 93 per cent for females. As children below 15 yr of age were excluded from the Survey, the eligible persons are those who were 15 yr of age or older, and the persons selected for bacteriological examination of the expectorates are those who had shown signs of pulmonary pathology according to either one or both of the two local readers. Among those selected for bacteriology, the coverage by sputum examinations was on average 88 per cent for males and 92 per cent for females, ranging from 83 to 94 per cent for males and from 80 to 100 per cent for females.

In estimating the bacillary prevalence per 1000 adults, due regard was paid to the fact that the coverage by X-ray or bacteriology was not complete. Assuming that the persons not X-rayed or examined bacteriologically were absent because of circumstances unrelated to tuberculosis, the number of bacillary cases which should have been found if all had been examined was calculated for each sex and age-group, and the sum of these was divided by the total eligible males or females and multiplied by 1000 giving prevalence rates per 1000 (Tables VI and VIA). The procedure employed is arith-

TABLE VI — PREVALENCE OF BACILLARY PULMONARY TUBERCULOSIS IN MALES AND FEMALES PER 1000 'ADULTS'

Town	Males						Females					
	X-ray		Bacteriology		Bacillary cases		X-ray		Bacteriology		Bacillary cases	
	Eligible No.	Examined* %	Selected No.	Examined %	No.	Rate per 1000[a]	Eligible No.	Examined* %	Selected No.	Examined %	No.	Rate per 1000[a]
Kadiri	736	92	104	86	8	14	715	89	60	95	3	5
Rayachoti	668	90	91	87	12	23	587	88	44	82	0	0
Rajampet	700	94	74	88	13	22	706	90	56	95	3	5
Chintamani	1067	91	76	83	2	3	993	91	64	83	5	7
Srinivasapur	500	94	54	85	4	10	514	90	39	95	2	5
Mulbagal	733	92	77	84	3	5	690	91	54	80	1	2
Tiruttani	534	89	77	91	7	16	553	88	46	93	0	0
Nagari	543	90	98	91	5	11	519	90	46	98	3	7
Puttur	678	93	106	94	8	13	654	91	72	90	6	11
Kalahasti	1524	92	210	92	33	25	1491	93	132	98	13	10
Palmaner	597	89	51	84	4	9	598	92	34	91	1	2
Punganur	651	91	62	85	2	4	704	86	36	100	3	5
Mean		91.4		87.5				89.9		91.7		

*Persons with films containing technical errors are excluded
[a]see text for the method of calculation

metically equivalent to multiplying the probability that an X-rayed person is selected for bacteriological examination with the probability that a bacteriologically examined case produces a positive finding.

The prevalence per 1000 adults varied among males from 3 in Chintamani to 25 in Kalahasti, showing a large variation.

The prevalence rates among females were much lower than among the males. In two of the towns no bacillary cases were found, the samples being too small. The highest prevalence rate of 11 per 1000 females was found in Puttur town.

Prevalence of radiologically positive cases of tuberculosis : Although all the X-ray films taken at the Sample Survey had been read by two readers and selection of cases for bacteriological examination had been based upon their readings, it was possible that they could have been biased as they would know from which towns the X-ray pictures came. All the 70 mm X-ray pictures were therefore submitted to an expert, Dr Wallace

TABLE VI A — BASE-LINE SURVEY 1959 PREVALENCE OF BACILLARY TUBERCULOSIS PER 1000 ADULTS AMONG MALES AND FEMALES

Town	Males ‰	Females ‰
Kadiri	13.9	4.9
Rayachoti	22.9	0.0
Rajampet	22.4	5.0
Chintamani	2.5	6.7
Srinivasapur	10.0	4.6
Mulbagal	5.3	2.0
Tiruttani	16.2	0.0
Nagari	11.3	6.6
Puttur	13.4	11.2
Kalahasti	25.4	9.6
Palmaner	8.9	2.0
Punganur	04.0	5.0

Fox, the then Director, Tuberculosis Chemotherapy Centre, Madras. The films (about 17,000) were taken to Madras for study by him. The films were not read in serial order but in a random order so that possible changes in his interpretation would be equally distributed over the whole range of films regardless of the towns.

The classification used by the independent assessor was the one adopted by the Survey Teams which conducted the National Tuberculosis Survey of the Indian Council of Medical Research in the years 1955 to 1958. The origin of this classification and the definition of the different categories are described in a previous communication[3].

The cases selected for bacteriological examinations by the local readers and the independent assessor were distributed as follows :—

Reader	Number	Cases with TB
Selected by the independent assessor alone	352*	
By the independent assessor as well as local readers	1033	132
By the local readers alone	730	4
	2115	136

*Not examined bacteriologically

Of the 2115 cases selected, 1763 had been selected by the local readers and 1385 by the independent assessor; common to the independent assessor and the local readers were 1033. In this group 132 cases were found to be bacteriologically positive. Among the 730 selected only by the local readers, 4 showed presence of bacilli. The 352 cases selected by the independent assessor only were not examined bacteriologically as his reading took place after the field work of the Sample Survey had been completed. It is, therefore, not known how many bacillary cases would have been found had they been examined.

The cases selected by the independent assessor according to the 5 main categories were distributed as follows :—

	No.	%
A. Probably non-tuberculous	181	13
B. Probably tuberculous but inactive	79	6
C. Probably tuberculous and possibly active	614	44
D. Probably tuberculous and probably active	406	29
E. Etiology uncertain	105	8
Total	1385	100

Whereas the independent assessor considered 13 per cent as probably non-tuberculous and 8 per cent too uncertain to be classified, 79 per cent were thought to be probably of tuberculous origin; 73 per cent were considered to be either possibly or probably active tuberculosis. The distribution of the two main groups, C and D, have been merged together for the purpose of working out a suitable index enabling the ranking of the 12 towns according to prevalence of tuberculosis. This is shown in Table VII. The prevalence ranged from 3.9 per cent in Palmaner to 9.1 per cent in Kalahasti.

Prevalence of tuberculin reactors among school children aged 5-9 : In order to provide a third index of the prevalence of tuberculosis in the towns, children in the first two grades of all the schools in the 12 towns were given Mantoux tests with 1 T.U. of the PPD tuberculin Rt23 (+Tween 80). Table VIII summarizes the work done and gives the mean percentage of children showing indurations measuring 6 mm or more in cross diameter, on the 2nd, 3rd or the 4th day. Of 4052 children whose tests were read, 630 showed scars resembling those following a BCG vaccination. They have been excluded.

In most of the towns, reasonably good cooperation was obtained but in some of the towns the school headmasters were non-cooperative as they thought the parents might object to the tests thinking that they were actually BCG vaccinations. At the time of the survey, there was a newspaper campaign against the introduction of BCG vaccination.

Frequency distributions of the

TABLE VII — 1959 SAMPLE SURVEY, PREVALENCE OF RADIOLOGICALLY POSITIVE CASES (CATEGORIES C AND D) ACCORDING TO THE INDEPENDENT ASSESSOR

Town	Males			Females			Both sexes
	X-rayed*	C & D		X-rayed*	C & D		C & D cases
	No.	No.	%	No.	No.	%	(%)
Kadiri	671	51	7.6	637	26	4.1	5.9
Rayachoti	601	68	11.3	514	24	4.7	8.3
Rajampet	658	55	8.4	632	26	4.1	6.3
Chintamani	968	50	5.2	905	48	5.3	5.2
Srinivasapur	469	28	6.0	460	20	4.3	5.2
Mulbagal	676	38	5.6	626	22	3.5	4.6
Tiruttani	475	33	6.7	488	23	4.7	5.8
Nagari	486	49	10.1	465	20	4.3	7.3
Puttur	631	49	7.8	593	39	6.6	7.2
Kalahasti	1403	170	12.1	1389	83	6.0	9.1
Palmaner	534	25	4.7	553	17	3.1	3.9
Punganur	589	40	6.8	607	16	2.6	4.7

*Films with technical errors are excluded

TABLE VIII — 1959 SAMPLE SURVEY, MANTOUX TESTS WITH PPD-RT23 (1 TU + TWEEN 80) OF CHILDREN IN AGE GROUPS 5-9 YR

Towns	Schools	Student strength standards I & II	Children tested	Tests read	BCG scar seen	Persons without BCG scar	Reactors*
	No.	No.	No.	No.	No.	No.	%
Kadiri	10	538	523	445	129	316	23
Rayachoti	8	673	385	338	7	331	15
Rajampet	8	660	328	273	56	217	21
Chintamani	8	1020	701	646	144	503	18
Srinivasapur	7	503	301	251	51	200	13
Mulbagal	8	644	438	361	92	269	7
Tiruttani	3	308	186	160	12	148	3
Nagari	4	390	236	205	19	186	16
Puttur	4	484	259	228	2	226	19
Kalahasti	16	1459	739	643	105	538	22
Palmaner	3	455	247	202	7	195	6
Punganur	5	720	344	300	6	207	12

*Persons with reactions (indurations) measuring 6 mm or more in transverse diameter

diameters of indurations to the Mantoux tests are given in Fig. 2.

Randomisation of the 12 towns into three treatment groups : The results of the Sample Survey were submitted to Dr K. K. Mathen of the All India Institute of Public Health and Hygiene, Calcutta. The three indices *viz.* (*i*) the prevalence of bacillary cases per 1000 adults, (*ii*) radiologically active cases per 1000 and (*iii*) the tuberculin reactors among young school children in per cent are shown in Table IX. The wide range between the lowest and highest prevalences and the close correlation between the three indices are shown in Fig. 3. The diagram to the left shows the correlation between the 12 town prevalences of the bacillary cases and the radiologically active cases and the right side shows the correlation between

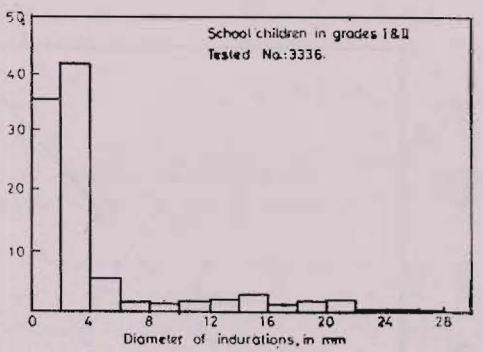

Fig. 2 — Histogram showing the percentage frequency distribution of 3336 school children in grades I and II according to the diameter of Mantoux induration.

the bacillary cases and the tuberculin reactors among the small school children. On the basis of these data, Dr Mathen ranked the towns in the following descending order :—

(1) Kalahasti, (2) Rayachoti, (3) Puttur,

TABLE IX — INDICES OF TUBERCULOSIS PREVALENCE USED IN THE RANDOMISATION OF THE 12 TOWNS (BOTH SEXES)

Town	Cases per 1000 adults (15 yr+)		School children (5-9 yr)
	Radiologically active cases	Bacillary cases	% tuberculin reactors
Kadiri	58	9	23
Rayachoti	83	13	15
Rajampet	62	14	21
Chintamani	52	4	18
Srinivasapur	52	7	13
Mulbagal	46	4	7
Tiruttani	57	8	3
Nagari	73	9	16
Puttur	71	12	19
Kalahasti	89	17	22
Palmaner	39	5	6
Punganur	47	5	12

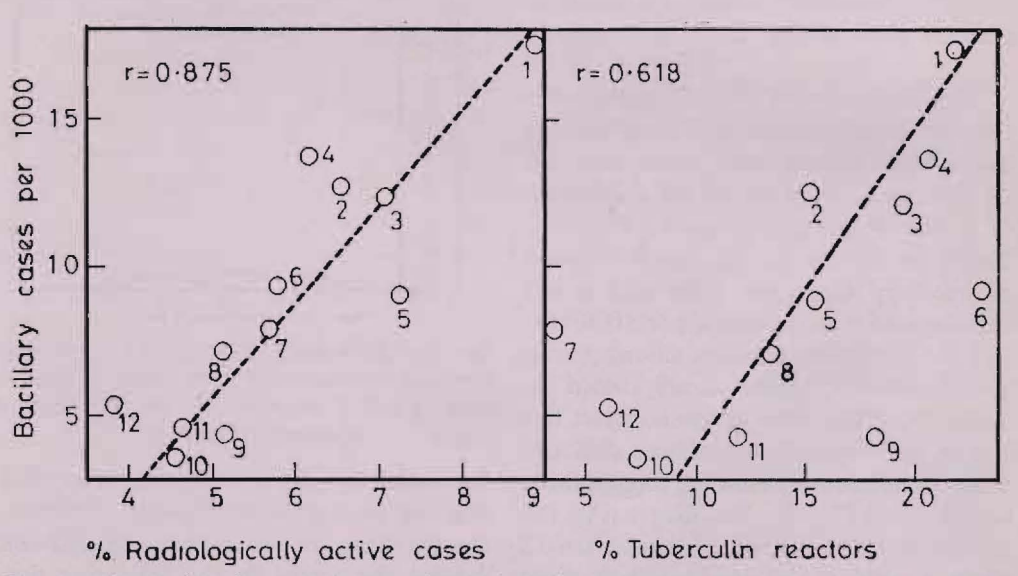

Fig. 3 — Correlations between the prevalence of bacillary cases per 1000 and (i) the percentage of radiologically active cases and (ii) the percentage of tuberculin reactors.—The numbers indicate the rank of the 12 towns as stated on p 17.

TABLE X — PREVALENCE OF BACILLARY TUBERCULOSIS AT START OF STUDY IN 6 'TREATMENT' AND 6 'CONTROL' TOWNS

Treatment towns*			Control towns	
	Prevalence of bacillary tuberculosis (per 1000 adults)			Prevalence of bacillary tuberculosis (per 1000 adults)
Kalahasti	17.4		Rayachoti	12.6
Kadiri	9.4	Mean 10.7	Puttur	12.3
Palmaner	5.3		Nagari	9.0
Rajampet	13.6		Srinivasapur	7.2
Tiruttani	7.9	Mean 8.7	Mulbagal	3.7
Chintamani	4.5		Punganur	4.6
Mean	9.7		Mean	8.2

*The 3 treatment towns listed attop received INH + PAS and the remaining 3 towns received INH alone.

(4) Rajampet, (5) Nagari, (6) Kadiri, (7) Tiruttani, (8) Sreenivasapur, (9) Chintamani, (10) Mulbagal, (11) Punganur, and (12) Palmaner.

The 12 towns were then divided by random allocation into two groups (Table X) of which the 6 formed the 'Treatment towns' and the other 6 the 'Control towns'. The 'Treatment towns' were further sub-divided, at random, into two groups of which the patients in Kalahasti, Kadiri aud Palmaner would receive isoniazid and PAS and the patients in Rajampet, Tiruttani and Chintamani, isoniazid only.

Domiciliary drug therapy

When the allocation of the 12 towns to the three experimental groups *viz.* (*i*) treatment with isoniazid-PAS ,(*ii*) treatment with isoniazid and (*iii*) the no treatment or the 'control' group, had been done, the main investigation was taken up. Whereas no further action was taken in the 6 'control' towns, the 6 'treatment' towns were surveyed one by one. Survey I began in March 1960 and the towns were examined in the same order as during the Sample Survey the previous year. The sample blocks already examined were not re-examined but the cases then detected plus any new ones presenting with symptoms were registered as patients due for treatment. The 75-80 per cent blocks not examined previously were now covered by a house-to-house census followed by X-ray examination of all the persons except children below 15 yr of age. The X-ray pictures were studied by two doctors and all persons with signs of pulmonary pathology—whether tuberculous or non-tuberculous—were referred for bacteriological examination. This was done in the same way as described under the Sample Survey, except that from the beginning of 1964 when the change in the culture technique was introduced, the setting up of 2 laryngeal swab cultures was discontinued.

In each of the six towns a house was rented which became the sub-centre or branch office of the Madanapalle Research Unit. It served as office and provided quarters and kitchen facilities for the staff who attended to the fortnightly clinics held on the same premises, and for the X-ray and laboratory staff whenever they visited the towns. The clinics were held on special week-days every fortnight. The team consisted of a nurse or a public health nurse or a social worker, one or two paramedical workers or clerks and

a driver. A doctor from the Madanapalle Centre visited the clinics once a month and saw the patients, particularly the new ones, and informed them about the diagnosis based on the X-ray and bacteriological examinations, and explained the need for their treatment for a period of at least one year. History was taken, case sheets filled in, body weights recorded and detailed instructions given as to how the patients should take the drugs at home during the fortnight till the next clinic was held. The Medical Officer saw not only the new patients but also those who were irregular in attending the clinics or stayed away from the drug issues.

With regard to follow up examinations by X-ray and bacteriology, in addition to the first X-ray examination done as part of the survey, a second miniature X-ray photograph was taken of all cases referred for bacteriological examinations, so that the diagnosis could be supported by comparing the two skiagrams. No case was considered eligible for treatment unless the bacilli had been demonstrated either by microscopy or by culture (or both) but in case where no bacilli were found a decision was taken whether they should be followed up or not. The rolls containing the survey X-ray films were not cut but kept in serial order for later reference, whenever necessary. All follow-up films including the one taken at the time of the first bacteriological examination were cut and mounted on special cards so that they could be easily handled, examined and filed away in special envelopes which would also hold pictures taken at subsequent follow up examinations. The case sheets and the mounted small X-ray films in the envelopes were carried in handy trays in the jeeps to the sub-centres whenever the doctors visited the clinics. In addition to treated cases, persons showing pulmonary pathology on the survey films but who had negative sputum were followed-up together with the treated cases; some would develop into bacillary cases, others might not require further follow up and this was therefore discontinued. A control study of prophylactic drug treatment of radiologically positive, sputum-negative cases was reported in 1965[5].

The treatment consisted of isoniazid 300 mg for a patient weighing 45 kg *i.e.* 6.7 mg per kg and was adjusted for patients weighing more or less. Isoniazid was made up in special, fairly large pink tablets so that they looked different from the isoniazid tablets ordinarily bought in chemists' shops. The PAS was issued as granulate of sodium para-amino-salicylate, and was given in doses of 10 g for a patient of 45 kg and adjusted for persons weighing more or less. The PAS issued was the same brand which was ordinarily obtainable at the chemists' shop. The drugs were issued free of charge.

Follow up examinations : In the first year, patients under treatment or under observation were re-examined every three months by X-ray and sputum examinations, in the second year by X-ray twice a year and sputum examinations every quarter and in the third year (and thereafter) by X-ray once a year and sputum examinations twice a year. Should the patients suffer a relapse and treatment be resumed they were re-examined as often as in the first year.

All bacillary strains isolated by culture were tested for sensitivity to isoniazid,

streptomycin and PAS, and from 1964 tested for niacin, and when required submitted to other identification tests.

Hospitalization was not used except in very special cases such as haemoptysis, spontaneous pneumothorax or massive pleural effusions. After the first year of treatment patients with strains of bacilli which had developed drug resistance were offered hospital treatment with second line drugs, provided special funds could be found for their purchase. A few cases who failed to respond to second line treatment were referred to the UMT Sanatorium for lung resection.

Material : The total number of bacillary cases encountered in the 6 towns from the time of the 1959 Sample Survey till Survey III had been completed were 1781 (Table XI). Deducting 176 who were admitted so late that they did not have one year of observation, 1605 cases were available for analysis; of these, 123 died or moved out of the towns before they were contacted for treatment; 1482 cases were offered treatment, of which 1266 accepted and 216 refused.

Extent of disease and cavitation : All the bacillary cases encountered from 1960 in Survey I till 1968 in Survey III have been classified with regard to extent of disease and presence of cavities as seen on the X-ray picture *i.e.* the first follow-up picture taken at the time of the initial bacteriological diagnosis. The classification was done by the senior author at two sittings two years apart. In order to check if any change had taken place in his interpretation of the films with regard to the extent of disease and cavitation, 50 films were selected at random from the first batch and mixed with the second batch. When the two sets of independent readings of the sample films were compared, a certain change was noted but it was not considered to be of importance, so the results of the two readings were merged. All the entries on the card on which the small 70 mm picture was mounted were covered up so that it was not possible to know when and where the X-ray pictures had been taken nor to which treatment group the patients belonged. The lesions were classified according to the system used for the classification of the patients seen at the

TABLE XI — NUMBER OF BACILLARY CASES DIAGNOSED AND TREATED

Towns	Number diagnosed	Cases with observation period of < 1 yr	Number died or moved out	Number available for treatment	Treated No.	Treated %
Kadiri	417	21	18	378	351	93
Palmaner	100	5	4	91	86	95
Kalahasti	640	86	56	498	403	81
Rajampet	299	7	20	272	240	88
Chintamani	164	2	11	151	117	77
Tiruttani	161	55	14	92	69	75
Total	1781	176	123	1482	1266	85

Tuberculosis Chemotherapy Centre, Madras (1960). The extent of disease was subdivided into six groups *viz.*: Trivial (a very small lesion), Slight (a few infiltrations), Limited (lesions smaller than the area of the right upper lobe), Moderate (lesions covering an area larger than corresponding to the right upper lobe but less than the area of one lung), Extensive (lesions involving an area greater than one lung) and Gross (all lung fields involved). With regard to cavities they were subdivided into four groups *viz.* nil, slight, moderate and extensive.

A total of 1682 cases were classified and the material divided into cases who were found to be sputum-positive by microscopy (M+) and those who were microscopically negative but positive by culture (C+). Summarising the findings, the cases positive by microscopy showed very small lesions in 7.2 per cent, limited lesions in 17.7, moderate in 39 and extensive and gross lesions in 36.2 per cent. Correspondingly, cases which were negative by smear but positive by culture showed the following distribution : 26.6, 28.8, 31.4 and 13.3 per cent respectively. It was thus clear that the cases positive by microscopy were generally much more advanced than the cases whose bacilli could be found by culture only.

As for cavities, the group which was positive by microscopy initially, showed moderate and extensive cavitation in 54.2 per cent against only 11.9 per cent in the group which was initially smear negative but positive by culture.

Comparison of 'two-drugs' and 'one-drug' towns with regard to extent of disease and cavities : In Table XII, the first three towns designated 'HP' represent the group in which the patients were given isoniazid and PAS and the last three, the H-group where the treatment consisted of isoniazid only. The means of the percentage distribution of each group are shown in two parts in Table XII. The

TABLE XII — COMPARISON OF TYPES OF CASES FROM 'ISONIAZID-PAS' TOWNS (HP) AND 'ISONIAZID' TOWNS (H)

Mode of detecting bacilli	Treatment policy	Extent of disease			
		Trivial & slight %	Limited %	Moderate %	Extensive & gross
M+	HP	7	17	35	40
	H	5	16	43	36
C+	HP	26	31	32	11
	H	27	27	30	15
		Cavitation			
		Nil %	Slight %	Moderate %	Extensive %
M+	HP	17	30	33	21
	H	16	29	28	26
C+	HP	58	31	7	4
	H	49	35	11	5

first part of the table refers to the extent of disease and the second to cavitation; each has been divided into two sub-groups of which the first one represents the cases initially positive by microscopy (M+), and the second the group in which the patients had been smear negative initially but positive by culture (C+). Whether one considered the extent of disease or cavitation, the distribution in the two groups of towns were broadly similar, Group C+showing slightly more advanced cases in the one-drug group, as compared with the two-drugs group.

Cooperation of the patients

As the survey progressed and more and more patients were admitted to the domiciliary treatment and the issue of drugs went on at regular intervals, it became increasingly clear that a major problem was the difficulty in getting the patients to take their treatment regularly and not to discontinue it prematurely. Some patients preferred to take the treatment from private practioners instead of from the clinic of the Research Unit so that they might avoid publicity or be able to take injection of streptomycin which did not form part of the treatment offered by the Research Unit.

The difficulty in obtaining full cooperation was apparent from the very begining. Excluding patients who died or moved out during the interval between the 'survey' X-ray examination from which a provisional diagnosis was made and until the diagnosis could be confirmed by the demonstration of the tubercle bacilli in the sputum, 84.5 per cent accepted and 15.5 per cent refused treatment (Table XIII). Among the cases whose initial sputum examination was positive by microscopy, 90.5 per cent accepted the treatment and 9.5 per cent refused; among those who were negative by microscopy but positive by culture, 79.5 per cent accepted and 20.5 per cent refused. The former group representing the more advanced cases had evidently a greater urge to be treated than those with less advanced disease who were only positive by culture. The degree of cooperation varied from town to town. In Palmaner and Kadiri 94 and 93 per cent respectively accepted the treatment as against 74 and 77 per cent in Tiruttani and Chintamani. These findings repre-

TABLE XIII — PERCENTAGE OF PATIENTS ACCEPTING DOMICILIARY TREATMENT (BOTH SEXES)

Towns	M+ cases		C+ cases		All cases	
	Total	% treated	Total	% treated	Total	% treated
Kadiri	199	96	179	89	378	93
Palmaner	42	95	49	94	91	94
Kalahasti	207	90	291	75	498	81
Rajampet	140	94	132	83	272	88
Chintamani	65	85	86	72	151	77
Tiruttani	48	83	44	64	92	74
Mean		90.5		79.5		84.5

sent the patients encountered from 1960 to 1968. An apparent change during this period in the attitude of the patients towards acceptance of treatment will be discussed later (p 28).

What happened to the patients who did accept our treatment ? In order to answer this question, statistics have been prepared showing how many of the patients available took treatment month by month until the end of the 12th month. The number of patients who died or moved out of the towns were deducted from each month's quota leaving a balance of cases who were alive and expected to have treatment; the percentages indicate how many of these did have treatment. In Table XIV, the first column headed '0 month' shows the percentage of patients

TABLE XIV — PERCENTAGE OF PATIENTS UNDER TREATMENT OF VARIOUS POINTS IN TIME (BOTH SEXES)

Towns	Cases (No.)	Percentage of patients under treatment at the following points in time (months)				
		0	3	6	9	12
(i) Cases initially positive by microscopy (M+) :						
Kadiri	199	96	92	86	81	78
Palmaner	42	95	90	90	82	74
Kalahasti	207	90	81	74	68	62
Rajampet	140	94	81	75	71	62
Chintamani	65	85	80	72	68	55
Tiruttani	48	83	79	69	65	46
	Mean	90	84	78	73	63
(ii) Cases initially positive by culture only (C+) :						
Kadiri	179	89	79	71	64	57
Palmaner	49	94	83	80	74	67
Kalahasti	291	75	63	55	47	40
Rajampet	132	83	71	62	53	45
Chintamani	86	72	63	50	49	47
Tiruttani	44	64	64	54	50	42
	Mean	79	70	62	56	50
(iii) All cases initially positive (M+ and C+) :						
Kadiri	378	93	86	79	73	68
Palamanet	91	94	86	85	80	70
Kalahasti	498	81	71	63	56	49
Rajampet	272	88	76	68	62	53
Chintamani	151	77	70	59	57	50
Tiruttani	92	74	72	62	57	44
	Mean	85	77	69	64	56

who started treatment (this corresponds to the last column of Table XIII). The decrease in percentages of patients under treatment corresponds to the increase in the rate of defaulters. Details according to males and females and the method of sputum examination by which the bacilli were demonstrated first time are given in Appendix Table II*. A summary for 'both sexes' is given in Table XIV showing the percentage of patients under treatment each quarter. The findings for males and females in each of the six towns are shown in Figures 4 and 5; the former (Fig. 4) corresponds to the towns in which the treatment consisted of isoniazid and PAS and the latter (Fig. 5) to the three towns where only isoniazid was issued.

Generally, a higher percentage of the more advanced cases as represented by the patients whose sputum had been positive by microscopy (M+) accepted treatment than the less advanced patients whose sputum had been positive by culture only (C+). The former accepted treatment in 90 per cent but dropped in attendance by

*Available on request from Shri G. S. Acharyulu Madras.

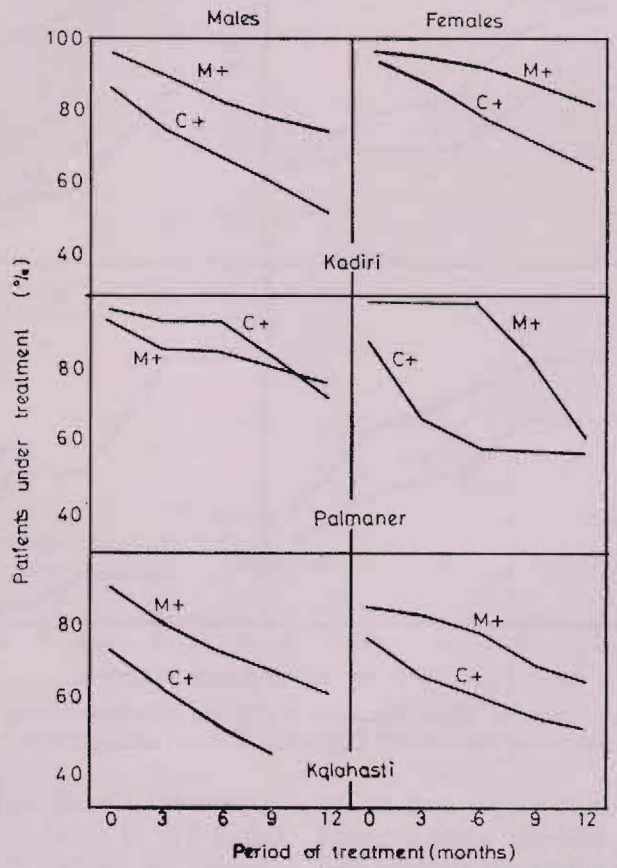

Fig. 4 — Percentage of patients under treatment at different months in INH-PAS towns. M + =TB initially demonstrated by microscopy; C + =TB initially demonstrated by culture only.

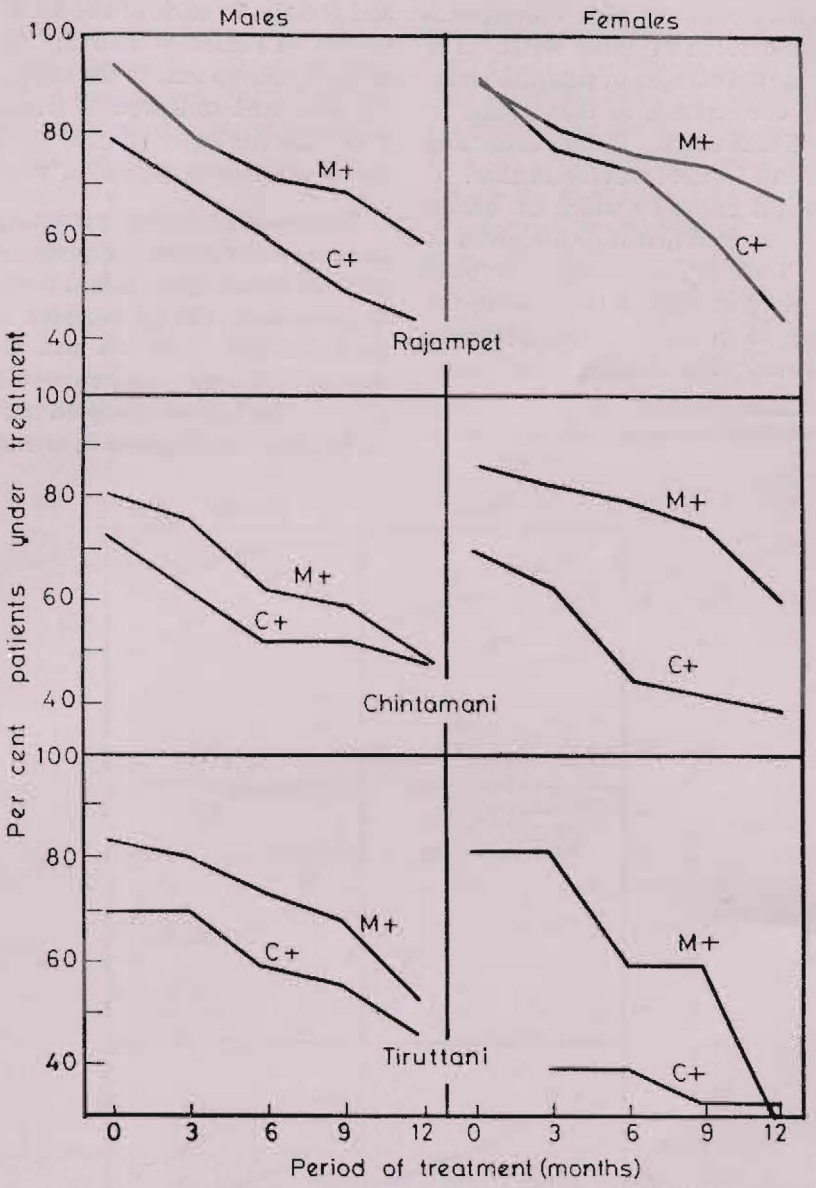

Fig. 5 — Percentage of patients under treatment at different months in the INH towns. M + = TB initially demonstrated by microscopy; C + = TB initially demonstrated by culture only.

nearly 30 per cent to 63 per cent at the end of the year, while the latter accepted treatment in 79 per cent and dropped also by about 30 per cent during the year to 50 per cent. Considering all cases regardless of type of initial sputum examination or extent of disease, the average performance corresponds to 85 per cent accep-

ting treatment, 30 per cent discontinuing treatment prematurely and 55 per cent still continuing treatment at the end of the year.

A summary of the statistical analysis of linear regression is given in Table XV. The first column indicates the mean monthly percentage of patients treated during the year; this mean corresponds closely to the position of the curve at six months. The second column indicates the mean of the four regression coefficients obtained by fitting lines to the four series of percentages for each town. The regression coefficients indicate the mean monthly defaulter rate in per cent. The overall per cent of patients under treatment at six months were 70.7 per cent and the mean defaulter rate 2.3 per cent patients per month. Table XV also shows the result of comparisons bet-

TABLE XV — COOPERATION OF PATIENTS UNDER DOMICILIARY TREATMENT

Items	Patients treated %	Defaulter rate per month %
A. Towns		
Kadiri	81.3	1.93
Palmaner	82.4	2.10
Kalahasthi	66.8	2.32
Rajampet	71.3	2.65
Chintamani	63.7	2.33
Tiruttani	58.8	2.46
Means :	70.7	2.30
B. Comparisons :		
(i) *Sex* :		
Males	70.6	2.34
Females	70.8	2.26
Differences :	—0.2	0.08
(ii) *Method of initial diagnosis* :		
By microscopy	78.2	2.29
By culture only	63.2	2.31
Differences :	15.0**	—0.02
(iii) *Drug regimens* :		
INH-PAS	76.8	2.12
INH	64.6	2.48
Differences :	12.2**	—0.37**
(iv) *Interactions* :		
Sex × diagnosis	5.3**	
Sex × regimens	3.8+	

*Mean of 12 months observation
+ and ** indicate statistical significance at 5% and 1% levels, respectively

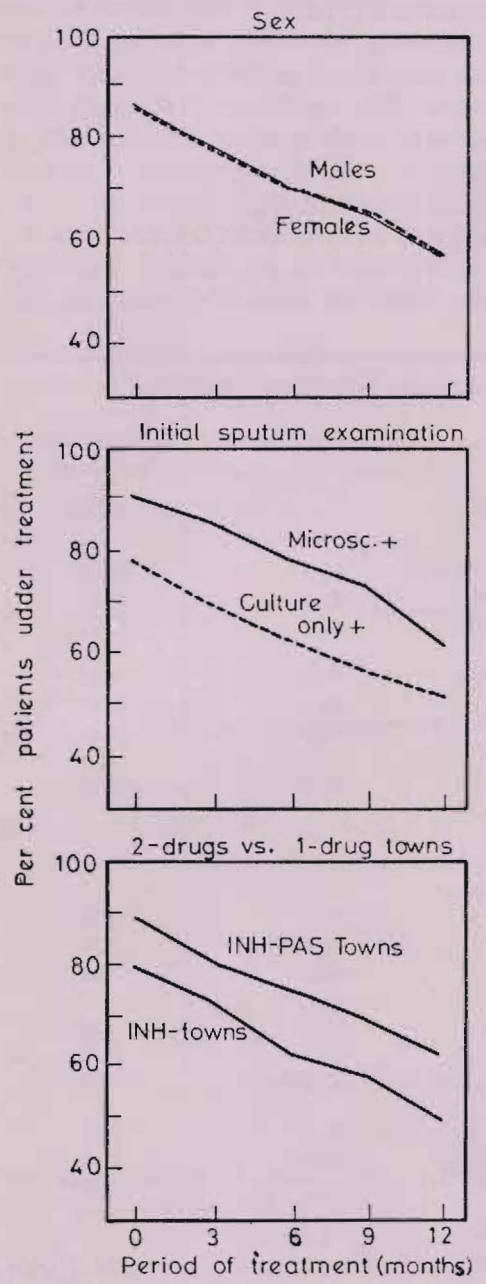

Fig. 6 — Percentage of patients under treatment according to sex, initial mode of diagnosis and drug regimen.

ween the main effects analysed. The same are illustrated in Fig. 6. As for sex, the curves for males and females are practically identical; there is no difference between them. As for the initial sputum examinations, the difference of 15 per cent between the levels of 78 per cent among those positive by microscopy and of 63 per cent among those positive by culture only is highly significant (Table XV and Fig. 6, centre). The curves run parallel indicating the same defaulter rate in the two groups As for the difference between 'drug regimens' (Fig. 6—lowermost) the INH group showed a much poorer response than the INH-PAS group. Not only was the level significantly lower, namely 65 per cent against 77 per cent (Table XV), but the monthly defaulter rate was 2.48 per cent against 2.12 per cent in the INH-PAS towns, the difference being statistically significant.

The findings relating to the patients diagnosed at Surveys I, II and III are shown in Fig. 7, for 4 of the 6 towns; the other 2 had too few cases. The levels of cooperation were distinctly higher at Survey I than at the two subsequent surveys. Taking Kadiri as an example of the 3 two-drug towns and Rajampet of the 3 one-drug towns, the figures show that there was no significant difference between the two towns with regard to the degree of cooperation among patients found at Survey I. The patients belonging to Survey II showed in the two towns a marked fall of the attendance rate, and the patients belonging to Survey III showed another marked fall.

These findings indicate that the degree of cooperation was high at Survey I, less at Survey II and much lower at Survey III. It suggests that the general public came forward with trust and expecta-

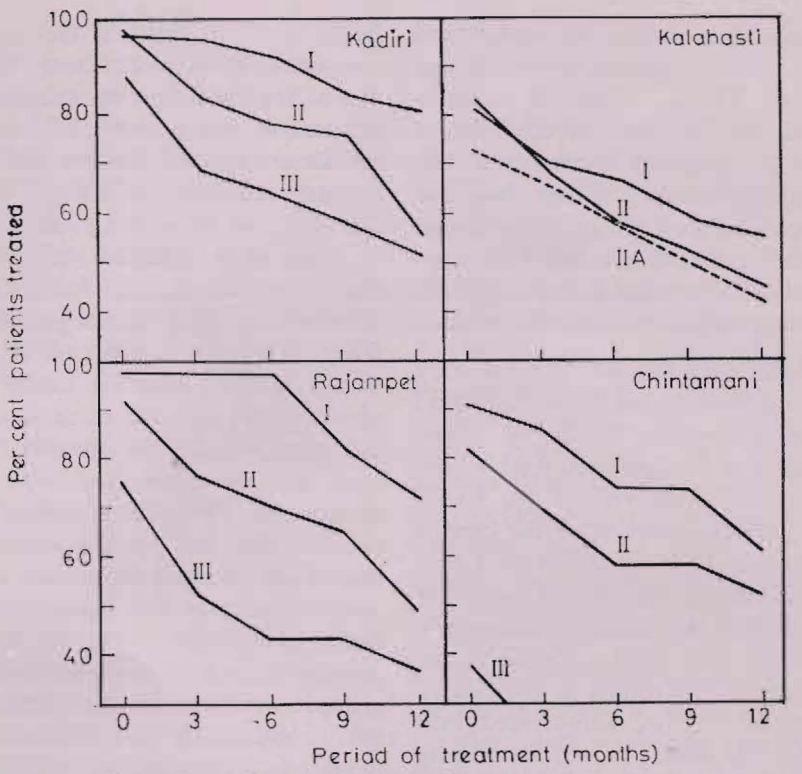

Fig. 7 — Percentage of patients under treatment according to the surveys in which they were initially diagnosed. I, II and III correspond to the surveys in which patients were initially diagnosed. II A corresponds to the interval between surveys II and III.

tion when the treatment programme was new but as time went on and they noted that the results were not satisfactory, they became disillusioned and turned away from our treatment centres. These observations suggest that as the general public had time and opportunity to judge the results of the treatment offered, disillusionment or apathy set in leading to a marked increase of defaulters.

Treatment results*

All patients in the six 'Treatment' towns diagnosed as having bacillary pulmonary tuberculosis were offered treatment either with isoniazid and PAS or isoniazid only. It may be recalled that the treatment given depended upon in which group of towns the patients lived—either in the 1-drug or the 2-drug towns, and that the allocation of treatment regimens was done by randomisation of the towns and not of the individual patients. They were followed up every three months by sputum and X-ray examinations whether they had treatment or not. The results obtained at 9th, 12th and 15 month examinations were consulted and included in the assessment of the case at the end of one year of observation. If any of the sputum examinations at the

*An interim report was given by R. Parthasarthy 1969[10].

9th, 12th or 15th months of examination showed a positive sputum, the result was recorded as 'TB+'. Although streptomycin did not form part of the present treatment programme, it was unavoidable that some patients either had had streptomycin before being admitted to our programme or that they might have supplemented the treatment issued under the present study with streptomycin injections.

The basic data for all the bacillary cases encountered during the investigation are shown in Appendix Table IV*. Each group has been divided according to the initial isoniazid-sensitivity of the bacilli and sub-divided according to the type of sputum examinations by which the bacilli were demonstrated initially. Cases with negative smears but positive cultures are shown under the heading 'Positive by culture only'. The results at the end of one year are further sub-divided into those who had died, moved out, those whose sputum was positive (TB+) and those who were negative (TB−) and, lastly, patients who were alive but for whom bacteriological examinations were not available (NE). The cases still sputum-positive at the end of one year have been divided into isoniazid sensitive and isoniazid-resistant cases plus a small group of cases (N) where sensitivity tests were not done.

When working out the results in per cent, the cases who had moved out during the year have been excluded. The percentage of patients who died or survived is therefore based upon the total number minus those who left. In working out the percentage of patients who had obtained negative sputum or continued to have positive sputum, the assumption has been made that those who were absent for the follow up examinations at the end of one year would have shown the same ratio of positive and negative sputum as those who did get examined. Similarly, in estimating the percentage of cases with isoniazid-sensitive or isoniazid-resistant strains, it has been assumed that the cases who did not get drug sensitivity tests done at the end of the year would have shown the same ratio of sensitive and resistant cases as those who did get tested. The results presented here are therefore reduced to three groups *viz.* the patients who died, the patients who had positive sputum at the end of the year and those who had negative sputum. In the Tables showing the initial sensitivity to isoniazid the sputum positive cases have been divided into two groups: the cases with isoniazid-sensitive bacilli and those with isoniazid-resistant bacilli.

The results of treatment are discussed under three headings : First, the results regardless of the initial isoniazid-sensitivity; second, the results according to the initial type of isoniazid-sensitivity and third, a comparison of the results in the towns where the treatment consisted of isoniazid and PAS and the three towns where only isoniazid was issued.

Results—regardless of isoniazid-sensitivity : The overall findings are shown in Table XVI. Although the results in each of the six 'treatment' towns are available, the discussion is based upon the means only, each town-serving as one experimental unit. Considering 'both sexes' in Table XVI the findings, irrespective of the initial type of sputum examinations, were 9 per cent died, 37 per cent remained

*See foot note on p 25

TABLE XVI — TREATMENT RESULTS (PER CENT) AT THE END OF ONE YEAR ACCORDING TO INITIAL MODE OF DEMONSTRATION OF BACILLI (MEAN OF 6 TOWNS)

	Males			Females			Both sexes		
	Died	TB+	TB—	Died	TB+	TB—	Died	TB+	TB—
M+	13	42	45	11	40	49	12	41	47
C+	5	35	60	10	23	67	6	32	62
All cases	9	39	52	10	33	57	9	37	54

sputum positive and 54 per cent were sputum negative. Dividing the cases into those whose sputa were initially positive by microscopy and those who were positive by culture only, there is a clear difference : the former obtained negative sputum in 47 per cent and the latter in 62 per cent ($P = 0.01$). Further, in the former group 12 per cent died, and 41 per cent had positive sputum while in the latter group 6 per cent died and 32 per cent remained positive.

The main reason for dividing the material into two groups according to the method of sputum examination by which the bacilli were initially demonstrated is the fact that few tuberculosis centres in India are equipped for culture work and they must, therefore, rely upon microscopy alone. The percentage of cases who, to begin with, had positive sputum by microscopy (M+) varied between 46 and 58 per cent with an average of 51 per cent. So, without access to culture facilities (C+) half of the cases would be missed. The Tables in the present report which give the results among cases positive by microscopy initially are, therefore, nearest in line with the results which can be expected from other tuberculosis centres.

In Table XVI, results are shown according to sex. The percentage of females who obtained negative sputum was 57 against 52 among the males. In the groups 'M+' and 'C+', there is a slight advantage to the females.

Cases with strains initially isoniazid-sensitive : The results with regard to initial isoniazid-sensitivity are shown in Tables XVII and XVIII. Table XVII shows that strains with isoniazid resistance were found in 18 per cent when the patients were admitted to the study; among M+ cases in 22 per cent and among C+ cases in 14 per cent. There was considerable variation, the percentage of cases with INH-resistant bacilli in the M+ group reaching as high as 34 per cent in Chintamani but being only 9 per cent in Palmaner. The treatment results are shown in Table XVIII. Cases who either had no cultures done at the initial sputum examination or had cultures but no sensitivity tests done are omitted. In the group M+ 50 per cent of the males and 58 per cent of the females obtained negative sputum. In the group C+ 59 per cent of the males and 73 per cent of the females obtained negative sputum. Considering all positive cases together, 55 per cent among males,

TABLE XVII — PERCENTAGE DISTRIBUTION OF CASES WITH ISONIAZID SENSITIVE (S) AND ISONIAZID RESISTANT (R) STRAINS BEFORE THE START OF TREATMENT

Towns	M+			C+			All cases		
	Cases (No.)	S (%)	R (%)	Cases (No.)	S (%)	R (%)	Cases (No.)	S (%)	R (%)
Kadiri	171	84	16	155	90	10	326	37	13
Palmaner	34	91	9	46	91	9	80	91	9
Kalahasti	171	70	30	213	83	17	384	77	23
Rajampet	123	75	25	108	89	11	231	81	19
Chintamani	47	66	34	61	74	26	108	70	30
Tiruttani	34	79	21	29	90	10	63	84	16
Mean		77	22		86	14		82	18

TABLE XVIII — TREATMENT RESULTS IN PER CENT AT THE END OF ONE YEAR ACCORDING TO THE INITIAL SENSITIVITY OF THE STRAINS TO ISONIAZID (MEAN OF 6 TOWNS)

Initial isoniazid sensitivity	Mode of detecting bacilli	Males			Females			Both sexes		
		Died	TB+	TB—	Died	TB+	TB—	Died	TB+	TB—
Sensitive	M+	10	40	50	11	31	58	10	37	53
	C+	5	36	59	8	19	73	6	31	63
	All cases	8	37	55	10	24	66	8	34	58
Resistant	M+	19	67	14	25	47	28	22	55	23
	C+	10	41	49	10	51	39	13	41	46
	All cases	17	55	28	16	51	33	18	51	31

66 per cent among females and 58 per cent among 'both sexes' obtained negative sputum at the end of one year.

Cases with strains initially isoniazid-resistant : The percentage of 'resistant' cases who obtained sputum conversion (Table XVIII) is only about half of that obtained by the cases who had isoniazid-sensitive strains, and the percentage of patients who died or remained sputum positive are about twice as high as obtained by the cases with isoniazid-sensitive strains. There is no significant difference between males and females.

Although the prognosis of patients with isoniazid-resistant bacilli is clearly worse than that of cases who started with isoniazid sensitive bacilli, the present results are not quite as unfavourable as might have been expected. As already mentioned, the patients living in the 'treatment' towns were not prevented, if they so wished, from taking other drugs in addition to the drugs issued by our

treatment centres. They were at liberty to purchase themselves streptomycin, PAS or other drugs. This may partly explain why the results of treatment in patients with isoniazid-resistant strains are better than expected.

Isoniazid-sensitivity of the bacilli isolated by culture at the end of one year : When considering 'both sexes' who initially had isoniazid-sensitive bacilli, it will be seen from Table XIX that the cases remaining positive in spite of treatment are almost equally divided among those with isoniazid-sensitive and isoniazid-resistant bacilli, namely 18 and 15 per cent respectively. This by itself is unusual when the results are compared with what is usually seen among hospitalised patients who get their drugs under supervision. Such cases who continue to have positive sputum will ordinarily have a high percentage of isoniazid-resistant bacilli only, (Tuberculosis Chemotherapy Centre, Madras 1960)[11]. The finding of a high percentage of isoniazid sensitive strains at 12 months is a direct indication of the irregular and inadequate treatment they had received.

There is a difference in the proportion of isoniazid-sensitive and isoniazid-resistant strains among the M+ and C+ cases. The M+ group showed at the end of one year, one-third with sensitive and two-thirds with resistant bacilli as against three-fourths sensitive and one-fourth resistant among the latter. The difference is undoubtedly due to M+ cases being more advanced and more regular in taking the drugs than C+ cases.

The patients who initially had isoniazid-resistant strains and who continued to be sputum-positive at the end of the year, had still isoniazid-resistant bacilli in 96 per cent while 4 per cent had isoniazid-sensitive bacilli.

Comparison of treatment results in 'INH-PAS' and 'INH' towns : The mean

TABLE XIX — ISONIAZID SENSITIVITY RESULTS AT THE END OF ONE YEAR AMONG CASES WITH ISONIAZID SENSITIVE STRAINS INITIALLY (BOTH SEXES)

Towns	M+ cases			C+ cases			All cases		
	Cases treated	INH sens. at 1 yr		Cases treated	INH sens. at 1 yr		Cases treated	INH sens. at 1 yr	
	No.	Sens. %	Res. %	No.	Sens. %	Res. %	No.	Sens. %	Res. %
Kadiri	144	14	18	140	23	7	284	19	13
Palmaner	31	3	17	42	17	0	73	11	7
Kalahasti	119	20	16	177	20	7	296	20	11
Rajampet	92	15	32	96	23	16	188	19	24
Chintamani	31	15	30	45	28	13	76	23	20
Tiruttani	27	8	34	26	27	4	53	18	18
Mean%		13	24		23	8		18	15

results for the three towns in each group are shown in Table XX. Considering first 'both sexes' in the M+ group, negative sputum was obtained in 57 per cent in the 'INH-PAS' group against 37 per cent only in the group which received only isoniazid; the difference of 20 per cent is statistically significant. In the C+ group, 68 per cent obtained negative sputum in the INH-PAS group as against 55 per cent in the group who received only isoniazid; the difference of 13 per cent is also statistically highly significant.

Considering males and females separately, both sexes on INH-PAS fared better than those on INH alone; the difference was highly significant among the males but the females showed significant difference only when all the positive cases (M+ and C+) are considered together.

Table XXI shows the results according to the initial isoniazid-sensitivity. Considering first the cases with isoniazid-sensitive bacilli, the percentage who continued to be isoniazid-sensitive until the end of the year was nearly the same whether they belonged to the INH-PAS or INH group, or belonged to the microscopically positive group, to the culture-positive group or to 'all positive'. On the other hand, the percentages of isoniazid-resistant bacilli at the end of the year were nearly twice as high in the 'INH' treated group than in the 'INH-PAS' group. Considering for example the 'all positive' group (M+ and C+), 10 per cent in the INH-PAS group were resistant as compared with 20 per cent in the INH group, the difference being statistically highly significant. It is evident that the chance of patients who received two drugs developing resistant bacilli was less than that among patients who received only one drug; expressed another way, the chances of developing isoniazid-resistance were nearly twice as high in the 'INH' towns than in the 'INH-PAS' towns.

As for the cases who had resistant bacilli initially (Table XXI), the difference

TABLE XX — COMPARISON OF TREATMENT RESULTS IN PER CENT WITH INH-PAS (PH) AND INH (H) ALONE BASED ON MEANS IN 3 TOWNS

Mode of detecting bacilli initially	Result at 1 yr	Males		Females		Both sexes	
		PH	H	PH	H	PH	H
M+	Died	12	14	6	16	10	15
	TB+	33	51	34	46	33	48
	TB—	55	35	60	38	57	37
C+	Died	5	6	7	13	6	7
	TB+	27	43	24	22	26	38
	TB—	68	51	69	65	68	55
All	Died	8	10	7	15	8	11
	TB+	30	47	28	37	29	44
	TB—	62	43	65	48	63	45

TABLE XXI — COMPARISON OF ISONIAZID SENSITIVITY RESULTS IN PER CENT AT THE END OF ONE YEAR IN 'INH-PAS' AND 'INH' TOWNS (BOTH SEXES)

Initial isoniazid sensitivity	Mode of detecting TB initially	Treatment groups							
		INH-PAS				INH			
		Died	TB+		TB—	Died	TB+		TB—
			S	R			S	R	
Sensitive (S)	M+	10	12	17	61	10	13	32	45
	C+	5	20	5	70	7	26	11	56
	All	7	17	10	66	9	20	20	51
Resistant (R)	M+	11	3	51	36	34	0	56	9
	C+	20	6	30	44	6	0	47	47
	All	16	4	42	38	20	0	56	24

between the two-drugs and one-drug groups was not statistically significant although the latter did show a higher percentage of isoniazid-resistant bacilli at the end of the year than the former.

Treatment results—if findings by the culture method were omitted : As has been pointed out above several times, tuberculosis clinics in India do not ordinarily have laboratories with culture facilities. In the treatment results presented above, both microscopy and cultures were used to determine the results at the end of one year. What would the results have been, if the cultnre method had not been available at all ?

Of the cases (both sexes) reported positive in Table XVI, the 41 per cent in the group 'M+' which showed positive sputum can be divided into two : 28 per cent which were positive by microscopy and 13 per cent which were positive by culture only *i.e.* about two-thirds were positive by microscopy and one-third by culture. (Of the other group, 'C+', the 32 per cent sputum positive cases consisted of 13 per cent who were positive by microscopy and 19 per cent who were positive by culture only). If the cases which were positive by the culture method only are excluded as they would have to be if the culture method had not been available, the treatment results would necessarily appear more favourable. Thus, in group M+ the mean percentages for 'died', 'TB+' and 'TB—' were 12, 41 and 47 per cent, respectively. If the cases who were positive by culture only at the end of one year are ignored, the results would have been 12, 28 and 60 per cent, respectively.

Five years' follow up

For the purpose of the present follow-up study, all cases in the 6 'treatment' towns were amalgamated excluding only those who had less than one year of observation. From the number of cases at risk at the beginning of each observa-

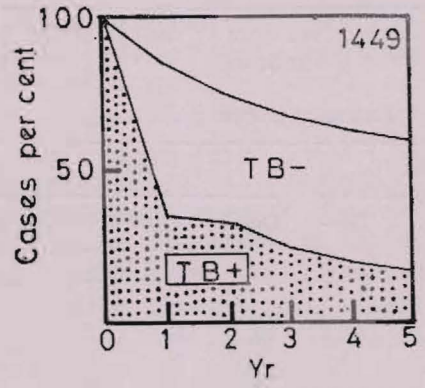

Fig. 8 — Five years follow up. No. of patients observed is indicated in the corner.

tion year, those who moved out of the town have been deducted; those who died have been deducted from the number at risk in the following observation year. The cases who survived have been divided into two groups according to the results of the sputum examinations by microscopy and/or culture in the proportion found within each observation year assuming that those who were not examined bacteriologically would have had the same ratio of sputum positives and negatives as those who were examined. Figs 8–12 show three zones of which the uppermost indicates the percentage of cases who died, the second those who were sputum-negative and the third those who remained sputum-positive. The uppermost curve represents the survivors.

Of all 1449 cases encountered, whether accepting treatment or not, a 5-year follow up showed that 40.4 per cent had died, 18.2 per cent were alive but had a positive sputum and the remaining 41.4 per cent had a negative sputum (Table XXII). Considering the 1154 cases who received treatment, the corresponding proportions were 35.5 per cent, 19.7 per cent and 45.1 per cent, respectively. Although these results are better than those in patients who received no treatment, it was discouraging to find that as much as one-fifth of the treated cases continued to have a positive sputum

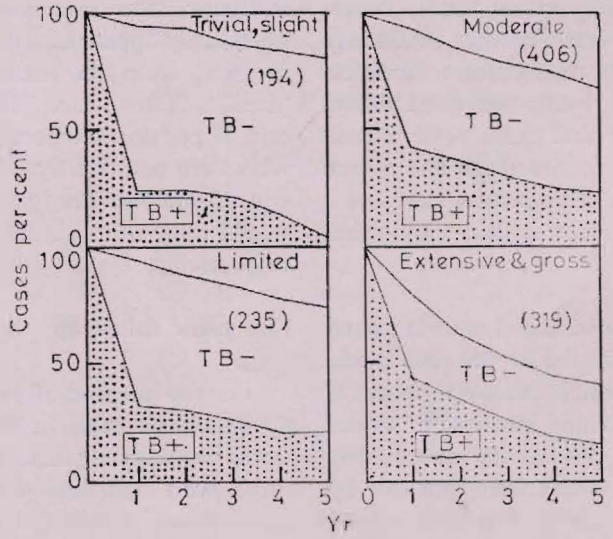

Fig. 9 — Five years' follow up according to initial extent of disease.

even after 5 years, thereby continuing to be a public health risk to the community.

There were 295 patients who did not accept the treatment from our clinics. At 5 yr, 60 per cent had died, 13 per cent had positive sputum and 27 per cent had negative sputum.

The 1154 cases who accepted treatment have been analysed with regard to the initial extent of the disease as seen on the pre-treatment X-ray photograph. As seen from Fig. 9 and Table XXIII the rate of survivors decreased as the extent of disease increased so that whereas 80 per-cent were alive at 5 yr among those who had only very small lesions ('trivial' and 'slight'), only 42 per cent were alive of those who had far advanced disease ('extensive' and 'gross'). The adage from the years when chemotherapy was not yet available that the prognosis was better the earlier the patients reported for treatment, is still valid.

In Fig. 10, the cases treated have been divided according to age groups as well as according to the method of the initial sputum examination. The graphs on the left side correspond to the cases whose sputum were positive by microscopy(M+) and those on the right to those who were negative microscopically but positive by

TABLE XXII — FIVE YEAR FOLLOW UP OF ALL DETECTED CASES (PER CENT) AND ALL TREATED CASES PER CENT IN THE 6 TREATMENT TOWNS

Year of observation	All detected cases (1449)*			All treated cases (1154)*		
	Died	TB+	TB—	Died	TB+	TB—
1	14.6	35.8	49.6	9.6	37.6	52.8
2	23.7	32.1	44.2	18.2	33.5	48.3
3	31.1	24.9	44.0	25.4	27.2	47.3
4	36.2	19.9	43.9	31.0	21.2	47.7
5	40.4	18.2	41.4	35.5	19.7	45.1

*Cases found up to the end of Survey III only are included in this analysis

TABLE XXIII — FOLLOW UP STUDY OF 1154 TREATED CASES (PER CENT) ACCORDING TO THE INITIAL EXTENT OF DISEASE

Year of observation	Trivial and Slight (194)			Limited (235)			Moderate (406)			Extensive and Gross (319)		
	Died	TB+	TB—	Died	TB+	TB—	Died	TB+	TB—	Died	TB+	TB—
1	5	22	73	5	32	63	6	42	52	20	46	34
2	6	23	71	11	31	58	13	38	48	37	36	28
3	12	21	67	16	28	56	20	30	50	47	27	26
4	15	16	68	21	21	57	25	26	49	55	18	27
5	19	12	69	24	22	54	32	25	44	58	17	25

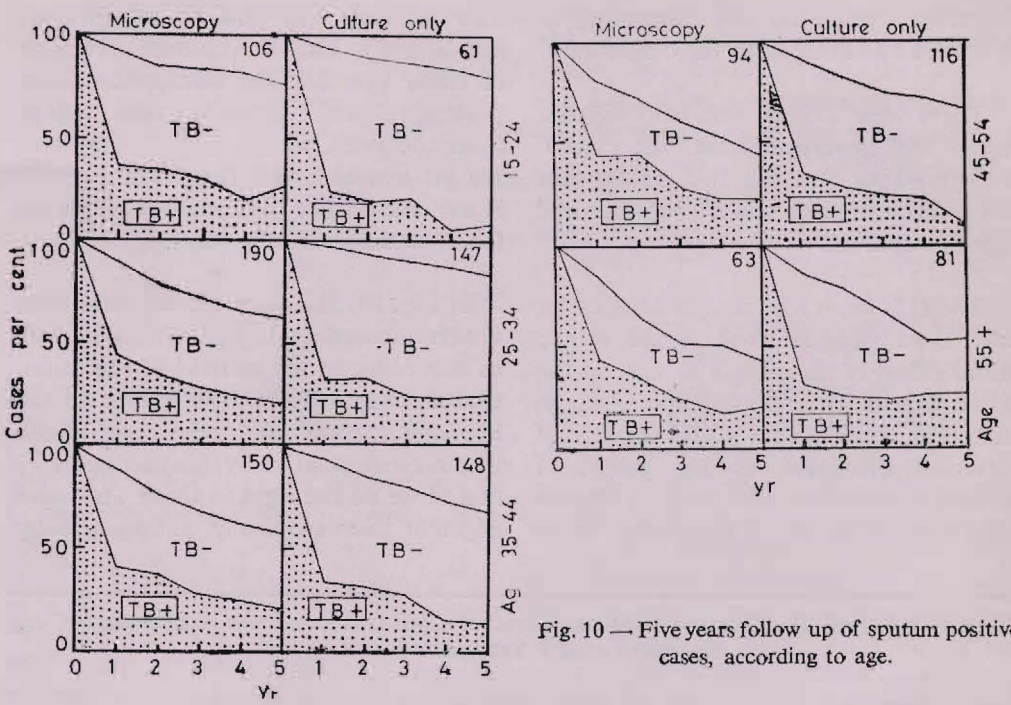

Fig. 10 — Five years follow up of sputum positives cases, according to age.

culture (C+). As pointed out earlier, the former group corresponds to the more advanced cases and the latter to the less advanced. It is, therefore, not surprising that the percentage of survivors in the group 'positive by culture only' is higher than among those whose sputum was positive by microscopy. With regard to the influence of age the percentage of patients who had died at 5 yr were highest at the age 45-54 and 55+. However, this merely corresponds to the normal increase with age in the mortality from all causes.

The cases treated have been divided into those whose bacilli were sensitive to isoniazid at the start of treatment and those whose bacilli were resistant. Fig. 11 and Table XXIV show at one year a marked difference between the two groups, as the isoniazid-sensitive group turned sputum negative in 58 per cent as against 27 per cent only among the cases with isoniazid-resistant bacilli. This difference of 31 per cent became smaller in subsequent year, and at 5 yr the proportions negative were 46 per cent in the isoniazid-sensitive group and 41 per cent in the isoniazid-resistant group. The decrease can be explained partly by higher mortality among the isoniazid-resistant cases, and partly by the special efforts made by the Research Unit to give treatment with second-line drugs in hospital from the second year onwards, with funds raised from charitable sources or from the patients themselves. It may be added that it was possible to obtain sputum conversion in about 40 per cent of cases who had persistently excreted isoniazid-resistant bacilli.

Fig. 12 and Table XXV show a 5-year follow up of cases according to whether the sputum was negative or positive at the end of one year. There is very marked difference between the two groups. Thus, 82 per cent of the sputum-negative cases were alive at 6 yr, including 66 per cent who were still sputum-negative. In contrast, only 44 per cent of the sputum positive cases were alive at 6 yr, including only 24 per cent who were sputum negative. This finding underlines the great prognostic advantage of obtaining negative sputum during the period of initial treatment.

TABLE XXIV — FOLLOW UP OF 1086 TREATED CASES ACCORDING TO INITIAL ISONIAZID SENSITIVITY OF BACILLI

Year	INH sensitive (887)			INH Resistant(199)		
	Died %	TB+ %	TB— %	Died %	TB+ %	TB— %
1	8	34	58	18	55	27
2	16	32	52	30	42	28
3	22	28	50	38	26	36
4	27	22	51	44	19	37
5	32	22	46	44	14	41

TABLE XXV — FIVE YEARS FOLLOW UP OF 911 CASES ACCORDING TO THEIR BACTERIOLOGICAL STATUS ONE YEAR AFTER STARTING DOMICILIARY TREATMENT

Year	Sputum negative (532)			Sputum positive (379)		
	Died %	TB+ %	TB— %	Died %	TB+ (3) %	TB— %
2	3	17	79	18	66	16
3	7	19	74	32	45	23
4	11	13	76	40	38	22
5	14	17	70	48	28	24
6	18	16	66	56	20	24

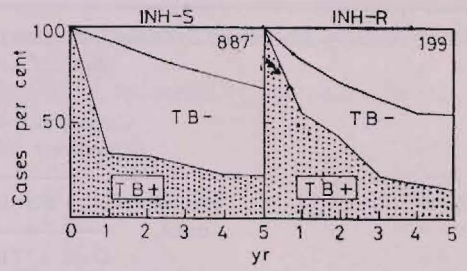

Fig. 11 — Five years follow up by initial isoniazid sensitivity.

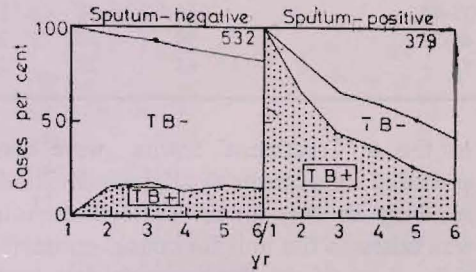

Fig. 12 — Five years follow up—Bacteriological status at one year. No. of patients observed is indicated in the corner.

In Table XXVI the follow up results at 5 yr have been shown according to the age of the patient at the time of starting treatment. The influence of age on deaths is clearly brought out, also the differences in prognosis of patients who had positive sputum by microscopy, as compared with those detected by culture only.

Mortality

At the 1959 base-line Sample Survey, 20-25 per cent of the populations in the 12 towns were enumerated; the remaining 75-80 per cent of the populations in the 6 towns which were selected as 'Treatment Towns' were enumerated during 1960-61, the two stages being combined to form prevalence Survey I. Surveys II and III

TABLE XXVI — STATUS AT 5 YEARS (PER CENT) RELATED TO AGE AND MODE OF DEMONSTRATION OF BACILLI ON ADMISSION

Age (yr)	Cases positive by microscopy (M+)				Cases positive by culture only (C+)			
	No. of cases	Status at 5 yr			No. of cases	Status at 5 yr		
		Died %	TB+ %	TB— %		Died %	TB+ %	TB— %
15-24	106	25	26	49	61	21	9	70
25-34	190	38	21	41	147	14	26	60
35-44	150	42	21	37	148	30	14	56
45-54	94	55	22	23	116	32	11	57
55 +	63	58	20	22	81	46	17	37

in the 6 'Treatment' towns were also preceded by a census of all the individuals residing in the towns. The household was taken as the unit for census enumeration. Apart from the common data such as family name, house address and religion, data regarding name, sex, relationship within the household, residential status and approximate year of birth were obtained, and entered in the census files for each individual enumerated in the census. At the time of Surveys II and III, the relevant files from the previous census were also consulted by the census clerks. If the families had continued to stay in the same house as in the previous census, there was no difficulty in obtaining the information about persons present in the previous survey but absent in the present survey. If the families had shifted the places of residence from one house to another within the town either in the same locality or in a different locality, they could still be traced. If they had left the towns, no further information could be obtained. Of those who were present at the earlier census but not present at the next census, reasons such as death and emigration were noted down. The emigration rate per year varied between 4 and 6 per cent and was nearly the same for the two sexes. With regard to age, the emigration rates were found to be a little lower in the higher age groups *i.e.* from 45 yr and above. The highest emigration rates were observed among females in the age group 15 to 24 yr.

The average annual death rates per 1000 due to all causes are given in Table XXVII. As mentioned in our previous report[3] it was not possible to obtain enough data to determine the infant mortaliy. Children who were born and died between two censuses were usually not recorded The estimate of deaths in the age groups 0–14 are therefore minimum rates. Combining all age-groups, the rate of death from all causes shows considerable variation, ranging from 12.3 in Rajampet to 8.3 in Chintamani, a difference of about 33 per cent.

Deaths among tuberculosis patients aged 15 yr or more are shown in

TABLE XXVII — AVERAGE ANNUAL DEATH RATES PER 1000 DUE TO ALL CAUSES

Age group	Kadiri	Palmaner	Kalahasti	Rajampet	Chintamani	Tiruttani
Males						
0 —	7.4	4.8	4.6	4.6	7.3	6.6
15 —	2.7	4.4	4.8	5.7	3.2	4.7
25 —	3.7	4.5	9.1	9.2	4.1	5.3
35 —	8.3	5.7	16.5	13.4	6.4	16.7
45 —	22.5	14.9	28.8	27.0	12.2	22.0
55 +	44.3	56.5	67.3	63.5	49.8	61.7
All males	9.4	9.1	13.1	13.0	9.0	12.8
Females						
0 —	9.2	6.0	5.8	4.9	5.7	6.4
15 —	3.9	4.8	5.7	8.8	4.2	4.4
25 —	4.9	3.5	6.2	6.6	2.9	5.1
35 —	6.0	4.0	8.0	8.0	4.9	10.2
45 —	12.3	8.6	15.4	19.0	12.9	16.2
55 +	37.2	42.1	51.9	55.4	42.9	55.0
All females	9.2	7.8	10.4	11.6	7.6	10.3
All	9.3	8.4	11.8	12.3	8.3	11.6

Table XXVIII. Considering both sexes combined, the overall death rate ranged from 45 in Palmaner to 234 in Rajampet giving a five-fold variation. The rates among males were particularly high at Kalahasti and Rajampet, the estimates of which are found to be more than 300 per 100,000. The death rates increased, especially among males, after the age of 45 yr. It should, however, be borne in mind that not all deaths among tuberculous patients were due to tuberculosis and that, deaths from other causes, inculded in the above rates, are likely to vary appreciably with age.

Table XXIX presents deaths with or due to tuberculosis as a percentage of all deaths. It is worth noting that, both in Kalahasti and Rajampet, this proportion is very high among males aged 25-54 yr, namely 1 in 4 to 1 in 5, which is particularly depressing when effective modern anti-tuberculous drugs were available for the treatment of tuberculosis. Considering all the six towns together, the proportionate mortality from, or with, tuberculosis is highest in males aged 25-44 yr, and females aged 25-34 yr.

The incidence of deaths from all causes, and deaths from or with tuberculosis are presented for the 6 towns combined (based on arithmetic means) inTable XXX according to age. Fiducial limits at the 95 per cent level are also given, and it is readily seen that mortality has been estimated with rather wide margins.

TABLE XXVIII — ANNUAL DEATH RATES PER 100,000 AMONG PATIENTS WITH TUBERCULOSIS*

Age group	Kadiri	Palmaner	Kalahasti	Rajampet	Chintamani	Tiruttani
Males						
15-24	38	0	81	91	0	62
25-34	61	43	238	175	51	91
35-44	194	52	342	342	18	235
45-54	397	109	604	599	92	267
55 +	452	140	851	783	56	537
All males**	162	53	324	315	36	204
Females :						
15-24	12	38	35	80	52	20
25-34	63	19	88	169	111	82
35-44	72	0	132	138	49	0
45-54	61	112	112	204	23	130
55 +	102	47	51	210	62	103
All females**	52	37	81	150	93	60
Both Sexes	108	45	202	234	50	132

*Deaths among cases with present and previous bacillary pulmonary tuberculosis.
**Children less than 15 yr of age are omitted.

TABLE XXIX — DEATHS AMONG CASES OF TUBERCULOSIS AS PERCENTAGE OF DEATHS DUE TO ALL CAUSES

Age group	Kadiri	Palmaner	Kalahasti	Rajampet	Chintamani	Tiruttani	Mean of 6 towns
Males							
15-24	14.3	0.0	16.9	16.1	0.0	13.0	10.0
25-34	16.7	9.5	26.1	19.1	12.5	17.2	16.8
35-44	23.4	9.1	20.7	25.5	2.9	14.1	16.0
45-54	17.6	7.3	21.0	22.2	7.5	16.7	15.4
55 +	10.2	2.5	12.6	12.3	1.1	8.7	7.9
Females							
15-24	3.0	8.0	6.1	9.1	12.2	4.5	7.2
25-34	12.8	5.6	14.1	25.7	38.5	16.1	18.8
35-44	12.0	0.0	16.5	17.2	10.0	0.0	9.3
45-54	5.0	13.0	7.3	10.7	1.8	8.0	7.6
55 +	2.8	1.1	1.0	3.8	1.5	1.9	2.0

TABLE XXX — AVERAGE DEATH RATES PER 1000 IN THE 6 'TREATMENT' TOWNS

Age	Deaths from all causes		Deaths from orwith tuberculosis*	
	Per 1000	95% fiducial limits	Per 1000	95% fiducial limits
A. Males :				
0 —	5.9	4.5- 7.3	..	..
15 —	4.3	3.1- 5.4	0.45	0.4-0.89
25 —	6.0	3.4- 8.6	1.10	0.27-1.93
35 —	11.2	5.9-16.4	1.97	0.51-3.43
45 —	21.2	14.4-28.1	3.61	1.25-5.97
55 +	57.2	48.0-66.4	4.70	1.29-8.11
15-55 +	14.17	10.34-18.00	1.82	0.59-3.05
All	11.1	8.9-13.3		
B. Females :				
0 —	6.3	4.8- 7.9	..	..
15 —	5.3	3.4- 7.2	0.40	0.14-0.65
25 —	4.9	3.3- 6.4	0.89	0.36-1.41
35 —	6.9	4.4- 9.3	0.65	0.01-1.20
45 —	14.1	10.3-17.9	1.07	0.42-1.72
55 +	47.4	39.4-55.5	0.96	0.32-1.60
15-55 +	11.32	8.57-14.07	0.91	0.47-1.34
All	9.5	7.8-11.1		
Both sexes :				
15-55 +	12.78	9.59-15.97	1.29	0.51-2.07
All	10.3	8.4-12.2		

*Deaths among cases with present or previous bacillary pulmonary tuberculosis.

Pool of Infectious Cases

In order to study the effect on the community as a whole, two approaches have been made : (i) to compare the prevalence of bacillary cases in the 6 towns at three points in time *viz.* at Surveys I, II and III which took place at the beginning, the middle and at the end of the investigation, and (ii) to study the prevalence year by year of cases proved to be infectious and to note whether there was any change due to the treatment programme. The second approach will be discussed first.

All patients with bacteriological evidence of pulmonary tuberculosis during the period from 1960 to 1968 have been entered as 'Cases on the Register' in Appendix Table VII*. Cases who were removed from the community by death

*See foot note on p. 25

or by emigration were struck off the re-register the following year. All cases whether treated or not, should have had at least one bacteriological sputum examination each year. Those who were not examined bacteriologically in a year were noted as 'Not examined'.

The definition of cases entered as 'sputum positive' in a particular year required that they should have been positive either by microscopy or by culture, or by both, at least once during that particular year. This stipulation does not exclude that cases could have been examined many times during a particular year and have shown bacilli more often than once. The definition here given indicates simply that such a person, at least once during the year, was known to have excreted bacilli which could have transmitted the disease to his or her contacts.

The sputum positive cases (as just defined) have been divided into three categories designated as A, B and C. Category A refers to patients diagnosed as bacillary cases for the first time in the particular calendar year. Category B corresponds to patients initially diagnosed as bacillary cases during the previous calendar year, and category C comprises patients who were diagnosed any time earlier than the previous year. As long as a patient once diagnosed as a case of bacillary tuberculosis continued to reside in the town, he or she would continue to appear on the Register. As such, any patient or ex-patient would continue to be carried forward from year to year and would be classified each year as being either 'sputum positive', 'sputum negative' or 'not examined' according to the results of the sputum examinations in that particular year.

In order to simplify the argumentation, bacillary cases in category A have been called 'new' cases and bacillary cases in categories B and C have been added together under the designation 'old' case. Although this group (B, C) is a mix-up of cases with illnesses of varying duration, the great majority had one factor in common *viz.*, that if their treatment had been effective they should not have been there but appeared in the group designated 'sputum negative'.

Results : The diagrams shown in Fig. 13 illustrate well the composition of the cases on the Register with regard to the sputum results and the different categories since 1960 when Survey I began till 1968 when Survey III ended. The uppermost curve indicates the total number of cases (per 1000 adults) on the Register. It starts with the cases diagnosed at the time of Survey I and increases from year to year mainly owing to the accumulation of the patients who turned sputum-negative and were keeping well. The second curve from above indicates the number of patients who were examined within each calendar year. The zone between the two curves indicates the patients who were 'Not examined'. The following zone corresponds to cases whose sputum was found to be TB-negative; the third curve-(second from below)—corresponds to the total number of cases who had bacilli in the sputum at least once in a particular calendar year. They are divided into two zones, the upper one representing the 'old' and the lower one the 'new' cases who were diagnosed for the first time in the

particular year, *i.e.* category A. The prevalence of 'new' bacteriologically positive cases and the prevalence of 'old' bacteriologically positive cases as shown in Fig. 13 are entered in Table XXXIII.

Fig. 13 shows in a striking manner the variation in prevalence of tuberculosis among the six 'Treatment' towns. High prevalence was found in Kalahasti, Rajampet and Kadiri and relatively low

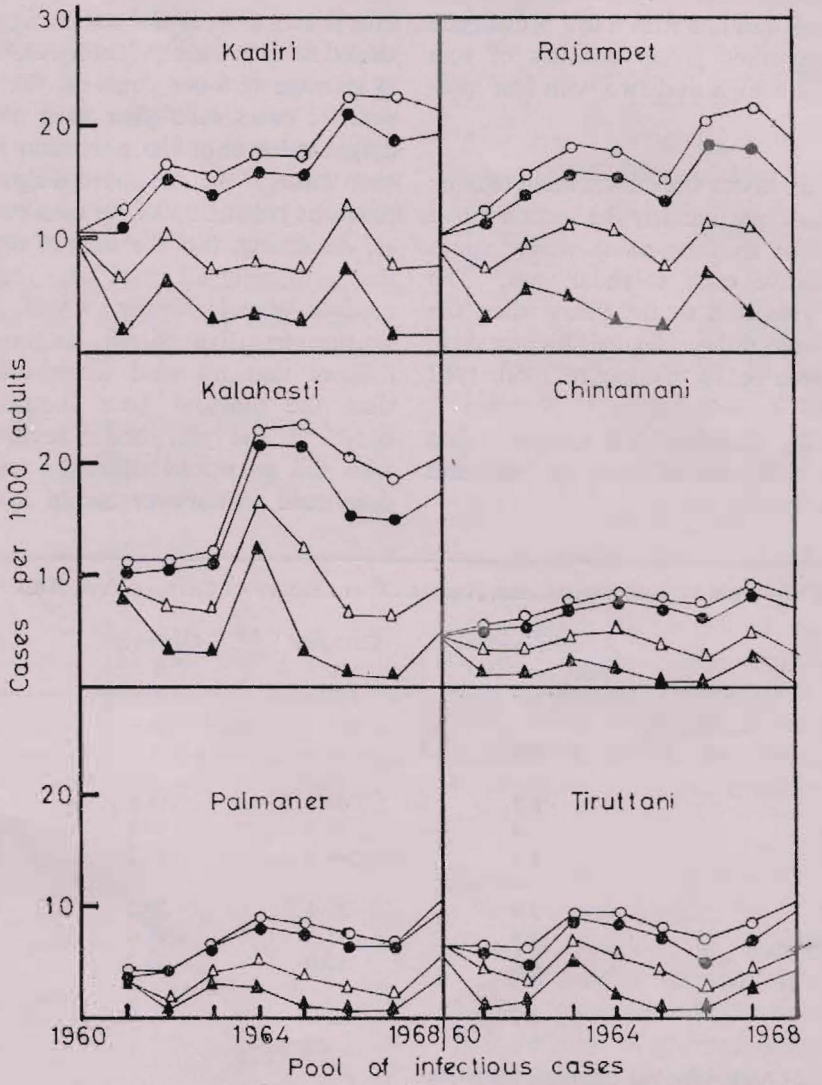

Fig. 13 — Pool of infectious cases.

○—○ Total registration
●—● No. examined
△—△ TB+(old)
▲—▲ TB+(New)

prevalence in Palmaner, Chintamani and Tiruttani. The three towns on the left side of the graph correspond to the group of patients treated with isoniazid and PAS and the three on the right side to the group who received only isoniazid; therefore, the former contains two towns with a high and one with a low prevalence while the other group consists of one town with a high and two with low prevalence.

In all six towns the curves have two or three peaks, particularly the second curve from below showing cases whose sputa were positive each calendar year. The peaks correspond to the years when the surveys were done. Kadiri, for instance, shows three peaks, namely in 1960, 1962 and 1965 corresponding to Surveys I, II and III. Kalahasti was examined first time in 1961, second time in 1964 and lastly in 1968.

The inter-relationship of categories A, B and C is brought out in Table XXXI. It gives the average number of sputum positive cases per 1000 adults per year. In order to be able to calculate the rates, the populations present in each town each calendar year were estimated by interpolation from the census figures obtained at each survey. Table XXXI shows in average 42.6 per cent of the sputum positive cases each year were new cases diagnosed within the particular calendar year while 17 per cent were diagnosed the previous year and 40.4 per cent even earlier. Assuming, for the sake of argument, that ordinarily all cases who respond to modern chemotherapy would become sputum negative within six months, it follows that no case diagnosed earlier than the previous year should excrete bacilli in the year under review; those who did so would either be cases who continued to harbour bacilli in spite of

TABLE XXXI—POOL OF INFECTIOUS CASES, AVERAGE DISTRIBUTION OF CATEGORIES A, B & C* (1960-68)

Towns	Sputum positive cases per 1000 adults per year (=100%)	Category A (%)	Category B (%)	Category C (%)
Kadiri	8.7	40.2	16.1	43.7
Palmaner	3.4	50.0	14.7	35.3
Kalahasti	8.9	44.3	17.3	38.4
Rajampet	9.9	39.4	20.2	40.4
Chintamani	3.8	31.6	18.4	50.0
Tiruttani	4.6	50.0	15.2	34.8
Mean	6.5	42.6	17.0	40.4

*Initial bacteriological diagnosis done :—

(i) the same year	Category A
(ii) the previous calendar year	Category B
(iii) earlier than the previous calendar year	Category C

TABLE XXXII — POOL OF INFECTIOUS CASES, MEAN SPUTUM POSITIVE CASES PER 1000 ADULTS PER YEAR SHOWING PERCENTAGE DISTRIBUTIONS OF 'NEW' AND 'OLD' CASES

Towns	Males			Females		
	Mean TB+ per 1000	New (A) %	Old (B+C) %	Mean TB+ per 1000	New (A) %	Old (B+C) %
Kadiri	6.00	37	63	2.32	48	52
Palmaner	2.07	48	52	0.99	54	46
Kalahasti	6.95	42	58	2.00	50	50
Rajampet	7.58	39	61	1.80	43	57
Chintamani	2.36	32	68	1.36	35	65
Tiruttani	3.43	41	59	1.07	58	42
Mean %		39.8	60.2	—	48.0	52.0

TABLE XXXIII — POOL OF INFECTIOUS CASES, BACILLARY CASES PER 1000 ADULTS IN EACH OF THE SIX TREATMENT TOWNS ACCORDING TO THE CATEGORIES (NEW) A AND (OLD) B+C (BOTH SEXES)

Year	Kadiri	Palmaner	Kalahasti	Rajampet	Chintamani	Tirnttani	Mean
New cases (A) :							
1961	1.9	3.3	8.1	2.9	1.2	0.8	3.03
62	6.3	0.9	3.0	5.8	1.1	1.3	3.07
63	2.0	3.0	2.6	4.8	2.1	5.1	3.27
64	3.3	2.4	12.7	2.7	1.5	1.8	4.07
65	2.1	0.9	2.9	2.0	0.3	0.4	1.43
66	7.5	0.4	0.8	7.5	0.4	0.4	2.83
67	1.5	0.3	0.6	3.6	2.8	2.6	1.90
68	1.5	3.7	4.7	0.8	0.3	4.0	2.50
Mean	3.24	1.86	4.43	3.76	1.21	2.05	2.76
Old cases (B+C) :							
1961	4.1	—	0.8	4.3	1.9	3.3	2.88
62	4.0	0.5	4.0	4.1	2.0	1.9	2.75
63	4.8	1.0	3.9	6.8	2.3	2.1	3.48
64	4.6	2.4	3.7	8.1	3.3	3.6	4.28
65	4.6	2.7	9.4	5.6	3.4	3.7	4.90
66	5.5	2.0	5.3	4.4	2.0	1.7	3.48
67	5.9	1.5	5.5	7.6	2.0	1.6	4.02
68	5.6	1.5	3.6	5.4	2.8	1.9	3.47
Mean	4.89	1.66	4.52	5.79	2.46	2.48	3.65

their treatment or be relapse cases. Of the cases diagnosed during the previous year, those detected as early as on January 1st and re-examined as late as on December 31st of the present year would theoretically have an observation period of two years, while cases diagnosed on December 31st the previous year would have had an observation period of only one day if the check-up examination took place on January 1st in the calendar year under review. Assuming that the intake of new cases was equally distributed during the year and assuming also that no case would remain positive after the end of the first six months of treatment, the cases in category B should not contain more than 50 per cent with bacilli in the sputum while 50 per cent should be sputum-negative. Adding the 50 per cent of category B (that is 8.5 per cent) to the 40.4 per cent in category C, it may be estimated that of all the patients having positive sputum, 49 per cent or about half are due to failure of the treatment programme.

The six diagrams in Fig. 13 have been combined in Fig. 14 to show the means of observations (for both sexes) from all the six towns. The lowermost zone represents category A or 'new' cases, while the zone just above it represents categories B+C or 'old' cases. Table XXXII shows the distribution according to males and females. Among males, 60 per cent belong to categories B and C and among females 52 per cent, the difference being statistically significant ($P < 0.02$).

The sputum-positive cases have also been divided according to the method by which the bacilli were found within each calendar year. Fig. 15 shows the cases whose sputum was positive by microscopy and those positive by culture only. The curves represent the means of the observations in the 6 towns. The high peak in 1964 coincides with Survey II and the introduction of the improved culture technique. It is noteworthy that almost half of the cases (43 per cent) would have been missed had the culture method not been available. Dividing

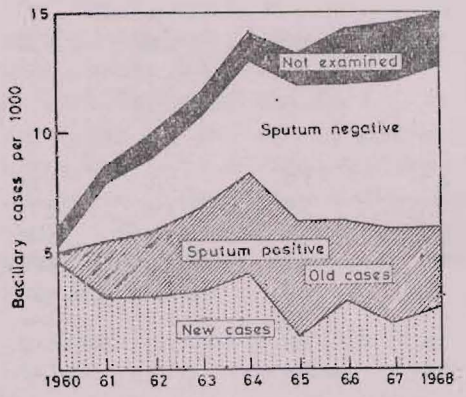

Fig. 14 — Pool of infectious cases.—Means of 6 treatment towns.

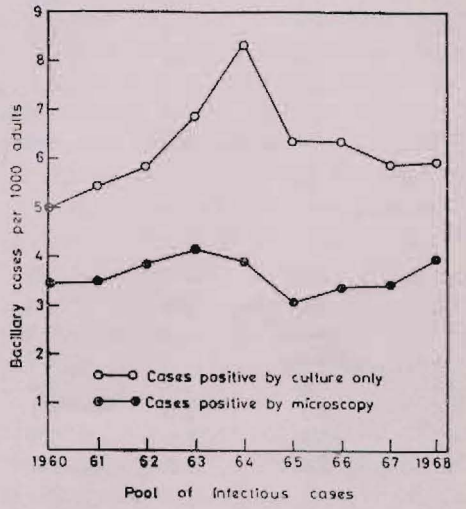

Fig. 15 — Pool of infectious cases. in different years.

the two groups into 'new' and 'old' cases, Fig. 16 shows that the cases whose sputa were positive by microscopy contained a majority of old cases, namely in average 61 per cent 'old' and 39 per cent 'new' cases. The cases which were found by culture (upper half of Fig. 16) were almost equally divided into 'new' cases (49 per cent) and 'old' cases (51 per cent). Fig. 16 also shows that among the cases positive by microscopy there appears to be from 1960 (or 1961) till 1968 a decrease of 'new' cases while there is an increase of 'old' cases.

From Fig. 14 it is seen that even if the findings in 1960 are disregarded there appears to be a slight downward trend in the rate of 'new' cases as against slight increase of the 'old' cases; therefore, the ratio of 'old' cases to 'new' cases tends to increase during the observation period.

Isoniazid sensitivity : In the same way as a case with a single positive sputum result in a particular calendar year was defined as a positive case despite perhaps many possible negative sputum results earlier or later during the same year, an isoniazid-resistant case in the 'Pool of infectious cases' indicates that isoniazid resistant bacilli were demonstrated at least once during that calendar year. It follows that it might happen that some patients in category A—the' new' cases—who were admitted with isoniazid-sensitive bacilli could have developed isoniazid resistance before the year was completed; they would be classified as resistant. Therefore, the rates of isoniazid resistant cases under category A will not correspond to the true incidence of isoniazid resistance among newly-admitted cases.

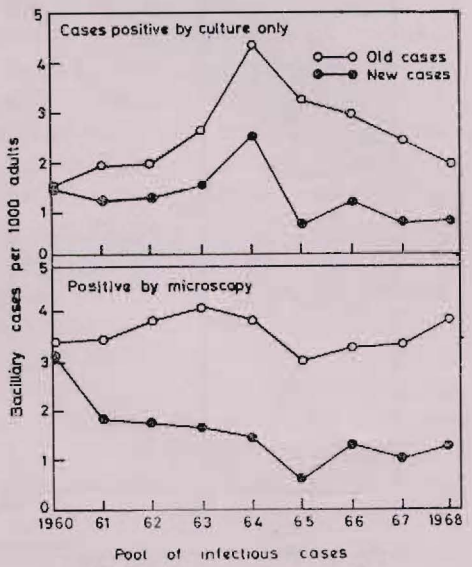

Fig. 16 — Pool of infectious cases.

From Table XXXIV it will be seen that of the average bacillary prevalence of 6.38 cases per 1000 adults, 62 per cent (3.93 per 1000) was isoniazid-sensitive and 38 per cent (2.45 per 1000) was isoniazid-resistant. Most of the isoniazid resistant cases, namely 1.87 (76 per cent) of 2.45, were from the 'old' cases (B and C groups). Indeed, among the 'old' cases, approximately half, namely 1.87 (52 per cent) of 3.61, were isoniazid-resistant. Further, among old cases positive by microscopy, the proportion was even higher *i.e.* 1.35 (61 per cent) of 2.22. This high proportion of resistance, arising in a community where the treatment programme is far from satisfactory, raises serious problems in an active tuberculosis control programme.

One-drug versus two-drugs towns : A comparison of the findings in the 3 towns where the treatment offered consisted of isoniazid only and the 3 towns where it

TABLE XXXIV — POOL OF INFECTIOUS CASES, ANNUAL MEAN RATES OF BACILLARY CASES PER 1000 ADULTS FROM 1961-68 IN THE 6 TOWNS ACCORDING TO ISONIAZID-SENSITIVITY AND 'CATEGORIES' AND METHODS OF SPUTUM EXAMINATION

Category		INH-S		INH-R		Total	
			%		%		%
'New' (A)	M+	1.03	72	0.39	28	1.42	100
	C+	1.16	86	0.19	14	1.35	100
	All	2.19	79	0.58	21	2.77	100
'Old' (B+C)	M+	0.87	39	1.35	61	2.22	100
	C+	0.87	63	0.52	37	1.39	100
	All	1.74	48	1.87	52	3.61	100
Total		3.93	62	2.45	38	6.38	100

Note : — INH-S = Isoniazid-sensitive strains.
INH-R = Isoniazid-resistant strains.
M+ = Sputum positive by microscopy.
C+ = Sputum positive by culture only.

consisted of isoniazid and PAS is given in Table XXXV. The total rate of sputum positive cases is rather higher in the INH-PAS towns than in the INH towns; this may be because the INH-PAS group contains 2 towns with high and one town with low prevalence, whereas the INH group contains one town with high and two with low prevalence.

Considering isoniazid sensitivity test results, Table XXXV shows that the INH towns had a higher percentage of INH resistant cases than the INH-PAS towns, namely 45 per cent against 31 per cent. Among the 'old' cases, the corresponding proportions were 59 per cent and 43 per cent. The differences are borne out clearly in Fig. 17. These findings suggest that treatment with isoniazid only was associated with higher

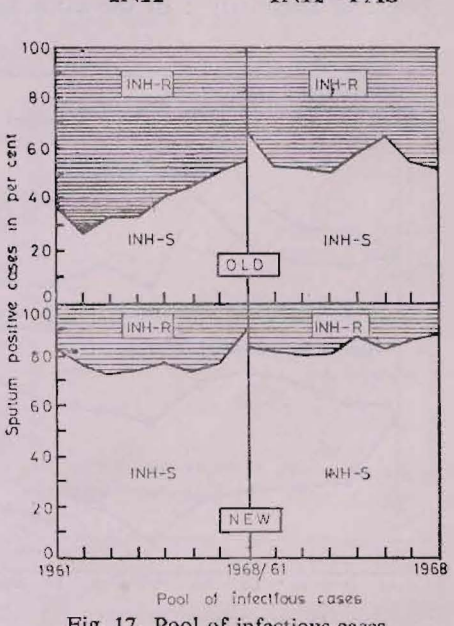

Fig. 17. Pool of infectious cases (ref. Table XXXV)

TABLE XXXV — POOL OF INFECTIOUS CASES, MEAN ANNUAL RATES OF CASES PER 1000 IN 2-DRUGS AND 1-DRUG TOWNS RESPECTIVELY SHOWING PER CENT DISTRIBUTION OF STRAINS SENSITIVE AND RESISTANT TO ISONIAZID ACCORDING TO THE REGIMEN AND CATEGORY

Town regimens	Category	Sputum positive cases per 1000	INH-S (%)	INH-R (%)
INH-PAS	New (A)	3.18	83	17
	Old (B+C)	3.64	57	43
	All positive	6.82	69	31
INH	New (A)	2.34	77	23
	Old (B+C)	3.58	41	59
	All positive	5.92	55	45

proportion of isoniazid-resistant cases as compared with treatment with isoniazid plus PAS.

Three prevalence surveys

The six 'Treatment' towns were examined three times : Survey I in 1960-61, Survey II in 1962-64 and Survey III in 1965-68. (A detailed time-table is given in Table I). The average interval between the surveys were 29 months from Survey I to Survey II and 50 months from Survey II to Survey III; altogether from Survey I to Survey III, the average interval was 80 months. The time-table does not include the base-line sample survey done in 1959 but covers the period spent on examining the remaining 75-80 per cent blocks of the 6 'Treatment' towns not covered in 1959. However, in the Tables showing the results of the three surveys, the results obtained in the sample blocks are included under Survey I. The 6 'Control' towns were examined during Survey III together with the 6 'Treatment' towns.

Table XXXVI gives a summary of work done at the three Surveys. The term 'persons eligible' stands for adults aged 15 yr and above. Children below 15 yr account for the difference between the total population and the persons eligible. The average attendance rates at the X-ray examinations at the three surveys were 88, 80 and 82 per cent, respectively. The corresponding rates for the examinations of cases selected for sputum examinations were 84, 89 and 88 per cent. The increase from survey to survey in total population and number of eligible persons reflects the population growth. As for the 'control' towns examined at Survey III, the coverage by X-ray and bacteriological examinations were 85 and 93 per cent respectively.

Basic data: Appendix Table X*presents, in detail, the findings at the three surveys for each sex and age groups, the number of persons eligible, number examined by X-ray and among these the number of

*See foot note on p 25

TABLE XXXVI — SUMMARY OF WORK DONE AT SURVEYS, I, II AND III

Town	Year(s)	Duration of survey (months)	Total population	X-ray		Bacteirology		Bacillary cases
				Eligible* No.	Examined (%)	Selected No.	Examined (%)	No.
Survey I (1960-61) :								
Kadiri	1960	6	16543	9814	90	820	87	89
Palmaner	1960-61	5	8812	5156	91	275	81	18
Kalahasti	1961	9	23364	15229	83	1068	89	144
Rajampet	1960	5	10835	6983	90	740	82	65
Chintamani	1960-61	7	17438	10400	90	608	85	48
Tiruttani	1960	5	9079	5839	87	413	84	36
Survey II (1962-64) :								
Kadiri	1962	7	18390	10805	76	580	90	57
Palamaner	1963-64	5	10479	6186	90	333	90	23
Kalahasti	1963-64	14	25548	16814	82	1396	88	221
Rajampet	1962	11	10686	6857	74	469	84	60
Chintamani	1962-63	10	18767	11139	72	543	88	36
Tiruttani	1963	7	10282	6621	85	551	91	32
Survey III (1965-68) (*A*) *Treatment towns* :								
Kadiri	1965-66	8	20438	12267	84	721	92	107
Palmaner	1967-68	6	12148	7471	86	380	89	28
Kalahasti	1968-69	10	29741	19052	84	1268	87	168
Rajampet	1966-67	7	12182	7811	78	527	88	92
Chintamani	1966-67	12	20682	12772	80	477	90	47
Tiruttani	1967-68	9	12617	8035	83	371	82	51
Survey III (1965-68) (*B*) *Control towns* :								
Rayachoti	1965	4	16236	9517	89	929	96	113
Srinivasapur	1966	5	7968	4610	84	211	90	23
Mulbagal	1966	5	14587	8127	82	337	93	33
Nagari	1967	4	7786	4783	88	285	94	41
Puttur	1967-68	5	10212	6299	84	430	93	59
Punganur	1968	6	16677	10084	82	469	92	53

*Persons aged 15 yr and above

persons who on account of their X-ray findings as determined by two independent readers were selected for bacteriological examinations. Then follows the number whose sputa were examined, and finally, the number who were found to excrete tubercle bacilli as demonstrated either by microscopy (M+) or if the microscopic examinations were negative by culture (C+).

Prevalence rates : Tables XXXVII-XXXVIII give the rates of cases with bacillary tuberculosis per 1000 adults by

TABLE XXXVII — AGE-STANDARDISED PREVALENCES OF BACILLARY TUBERCULOSIS (PER 1000 ADULTS) IN THE 6 TREATMENT TOWNS IN THE 3 SURVEYS. MICROSCOPY POSITIVE CASES (M +)

Town	Males			Females			Both sexes		
	S I	S II	S III	S I	S II	S III	S I	S II	S III
Kadiri	12.1	7.6	6.0	4.3	4.4	3.3	8.3	6.0	4.7
Palmaner	6.6	1.6	5.1	1.2	1.0	0.7	3.9	1.3	2.9
Kalahasti	13.3	9.7	9.8	4.3	3.7	3.0	8.8	6.7	6.4
Rajampet	13.2	17.0	11.4	6.7	2.7	2.9	9.9	9.8	7.1
Chintamani	3.0	2.4	3.6	4.4	2.3	1.2	3.7	2.3	2.5
Tiruttani	10.3	6.6	8.5	2.2	1.2	2.5	6.2	3.8	5.5
Mean	9.78	7.49	7.40	3.86	2.55	2.3	6.81	5.01	4.83
P.value*	SI-SII	0.1-0.2			0.08			<0.01	
for the contrast	SI-SIII	0.05			0.05			<0.01	

*Based on a weighted mean change between surveys (for details, see the accompanying paper).

TABLE XXXVII-A — MEAN DISTRIBUTION IN PER CENT OF BACILLARY CASES IN THE 12 TOWNS AT SURVEY III ACCORDING TO SEX AND AGE

Age (yr)	Males (%)	Females (%)	Ratio M : F
15 —	7.6	4.8	1.5 : 1
25 —	16.5	5.5	3.0 : 1
35 —	21.4	5.8	3.7 : 1
45 —	15.9	2.9	5.5 : 1
55 +	16.8	3.4	4.9 : 1
Sub total	77.6	22.4	3.5 : 1
Total	100.0	100.0	

sex. Assuming that the reasons for incomplete coverage at the time of the sputum examinations were unconnected with tuberculosis, an adjustment has been made giving an estimate of cases which would have been detected if all persons selected for sputum examinations had been examined. Similarly, in estimating the prevalence of the bacillary cases for all males and females in each town an adjustment has been made for incomplete coverage at the time of the X-ray examination. These adjustments have been taken into consideration when estimating the variance of the estimate at each survey based upon the sex and age group.

As the main purpose of the investigation was to compare the results obtained in the six towns in which home treatment was offered to the cases of bacillary tuberculosis, with the six comparable towns in which no clinics were set up or any special treatment offered, and since the former group *i.e.* the 'Treatment' group itself was divided into two groups of three towns each where the treatment consisted of isoniazid-PAS in one group and of isoniazid alone in the other group, the basic comparisons have been between the mean prevalence rates obtained from survey to survey in the different groups concerned. By applying this principle the towns have been given equal weightage although they differed in the size of populations. Had the analysis been based

TABLE XXXVIII — AGE-STANDARDISED PREVALENCES OF BACILLARY TUBERCULOSIS (PER 1000 ADULTS) IN THE 6 TREATMENT TOWNS IN THE 3 SURVEYS. CASES POSITIVE BY CULTURE ONLY (C+)

Town	Males			Females			Both sexes		
	S I	S II	S III	S I	S II	S III	S I	S II	S III
Kadiri	4.9	2.3	9.7	1.6	0.8	2.7	3.3	1.6	6.3
Palmaner	1.0	3.9	2.6	0.4	2.7	1.9	0.7	3.3	2.2
Kalahasti	5.8	16.0	9.5	2.3	6.1	1.5	4.0	11.0	5.5
Rajampet	1.9	5.9	14.9	2.1	1.9	4.0	2.0	3.9	9.4
Chintamani	2.1	3.2	3.5	2.3	1.8	1.8	2.2	2.5	2.6
Tiruttani	5.1	3.3	4.4	0.0	1.8	2.5	2.5	2.5	3.5
Mean	3.46	5.75	7.44	1.47	2.52	2.4	2.47	4.13	4.92
P-value*	SI-SII	>0.2			0.2			>0.2	
for the contrast	SI-SIII	0.1			0.2			0.06	

*Based on a weighted mean change between surveys (for details, see the accompanying paper).

on simple summation the larger towns or those with high prevalence of tuberculosis would have unduly dominated over the smaller towns or those with low prevalence.

General observations : Appendix Table XI* gives the prevalence rates of bacillary tuberculosis according to sex and age. The same are shown in Fig. 18 which covers Survey I and II, and Fig. 19 which shows the findings at Survey III in the 6 'Treatment' and the 6 'Control' towns. In the two sets of graphs the towns have been arranged according to the degree of prevalence starting from above with the towns with high prevalence and ending below with those with low prevalence.

There is a marked uniformity in the results obtained from survey to survey. Not only do the towns keep their rank according to prevalence but also the shape of the curves are remarkably consistent from survey to survey.

Two main observations stand out prominently : The great difference in prevalence between males and females and the high rates of tuberculosis among elderly males. Considering the ratio of cases among males to cases among females, the mean percentage distribution for the 12 towns at Survey III was 76.3 per cent males and 23.7 per cent females giving a ratio M/F of 3.2/1. This represents the general picture. There were however exceptions, *e.g.* in Chintamani, the females were at Survey I in preponderance, namely 57 per cent as against 43 per cent males; at Survey II the opposite was observed, namely 58 per cent males and 42 per cent females, and at Survey III the findings were 71 per cent males and 29 per cent females, which is more in keeping with the general ob-

*See foot note on p 25

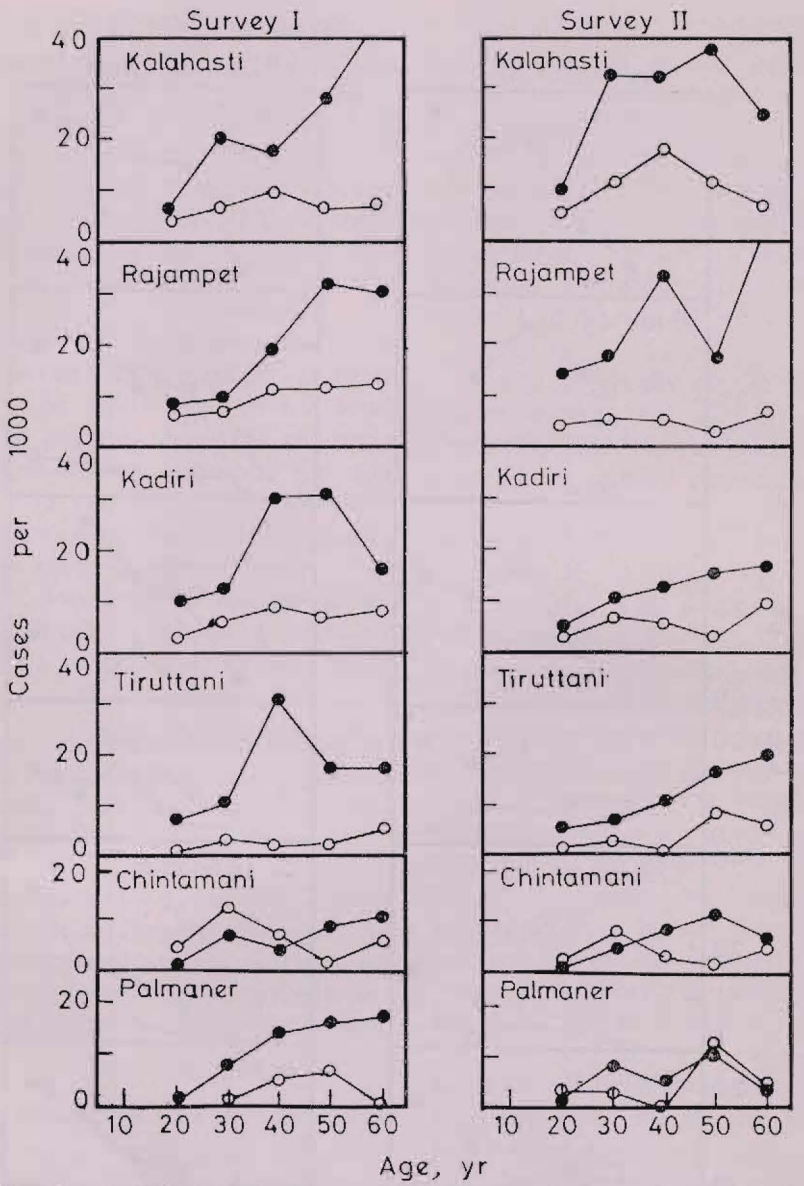

Fig. 18 — Prevalence of bacillary cases by sex and age in Surveys I and II in the 6 'treatement' towns.

servations. However, in Nagari, at Survey III, the prevalence rates were 18.4 in males and 2.3 per 1000 in females *i.e.* 89 per cent males for 11 per cent females, or a ratio of 8/1. As for exceptionally high rates of prevalence it will be noted that in Kalahasti at Survey I, males in the age group 55+ showed a prevalence of over 40 per 1000, or 1 person in 25. Similar rates were found in Rajampet

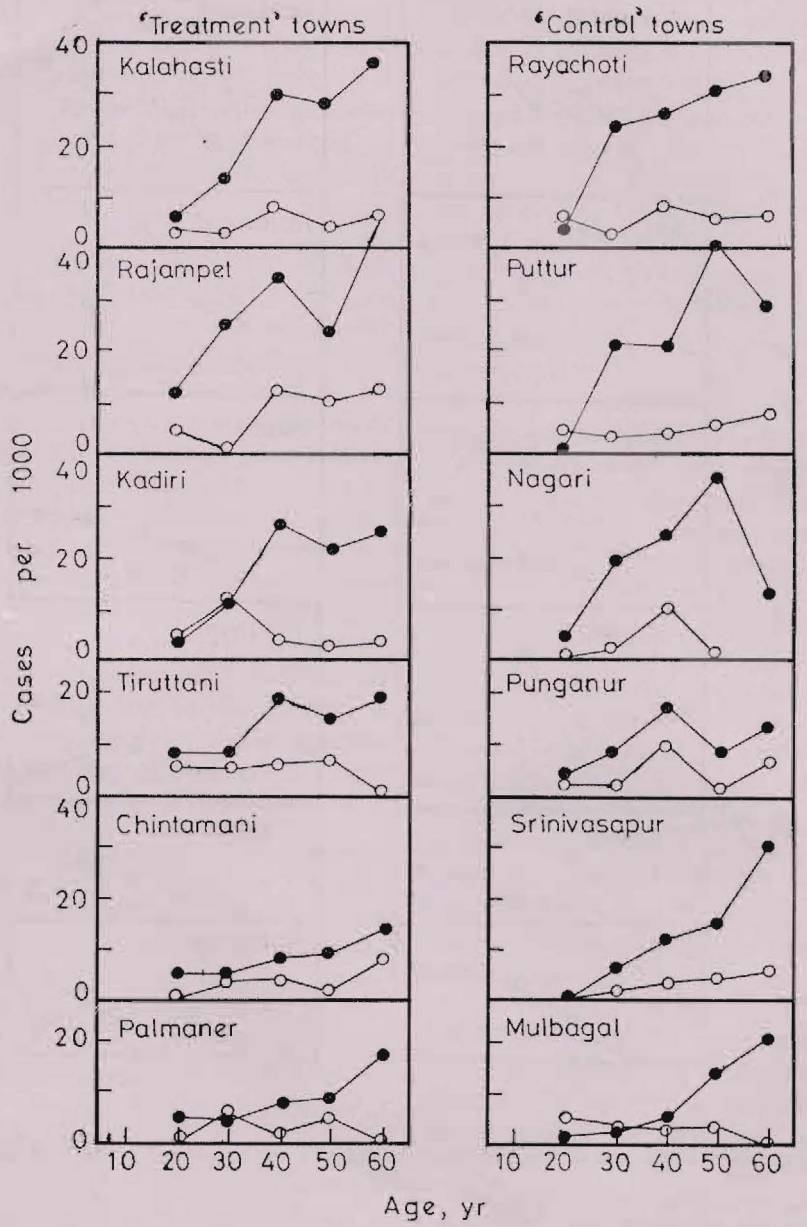

Fig. 19 — Prevalance of bacillary cases by sex and age in Survey III (1965–68) in the treatment and control towns.

at Survey II and in Puttur at Survey III in the age group '45-54'. However, the number of persons in the community reaching the age of 50 to 60 may not be high, so an estimate has been made of the distribution of male and female cases in the community taking the average of the 12 towns examined at Survey III, as shown in Table XXXVII-A.

Of every 100 bacillary cases, 77.6 were males and 22.4 females, giving a ratio M/F of 3.5/1. Half of the total number of bacillary cases (54 per cent) were found among males in the age group of 35 and above and one-third (33 per cent) were found among males in the age group of 45 and above. The ratio M/F was 1.5/1 in the age group 15-24, thereafter increasing steadily through 3:1 to 5.5:1 in the age group 45-54.

To sum up, the main sources of infection in the community are dominated by the male patients and among these again by males aged 35 and above.

Mean changes in prevalence between surveys in the 6 *'Treatment' towns* : All prevalences quoted are age-standardised, the Standard Population being the pooled population from the 3 surveys in each town.

The comparisons between the Surveys are based upon the means of the observations in the six towns. For instance, in Survey I (Table XXXVII) the mean for males positive by microscopy was 9.78 while at Survey II, it was 7.49 and at Survey III, 7.40. The mean differences between the prevalences of the first and the second, and the first and the third survey have been calculated and their *P*-values are shown in Tables XXXVII to XXXIX. In the present example, the difference between Survey I and Survey II of males with sputum positive by microscopy was 2.29. It was satatistically not significant as the *P*-value was 0.1, while the difference between Survey I and Survey III *viz.* 2.38 had a *P*-value of 0.05, indicating a significant decrease from Survey I to Survey III.

The main results of the three prevalence surveys are shown in Tables XXXVII to XXXIX. Considering first the cases whose sputum examinations were positive by microscopy, there was a decrease in mean prevalence from Survey I to Survey II and especially Survey I to Survey III. This applies to males as well as females and also to 'both sexes'. Considering—'both sexes'—there was a significant decrease among the cases whose sputa were positive by microscopy (M+) from 6.81 at Survey I to 5.01 at Survey II and to 4.83 at Survey III. In cases whose sputa were positive by culture only (C+), there was for males as well as for females, an increase in the prevalence from Survey I to Survey II and from Survey I to Survey III. Considering 'both sexes' the mean prevalence rose from 2.47 at Survey I to 4.92 per 1000 at Survey III. This increase of 2.45 per 1000 was almost significant at the 5 per cent level, the *P* value being 0.06. As the rates among the cases positive by microscopy showed a decrease and the cases positive by culture only an increase, it is not surprising that when added together, the total results show no important changes from survey to survey. For 'both sexes', total prevalences at Surveys I, II and III were 9.28, 9.14 and 9.76 (per 1000 adults).

TABLE XXXIX — AGE-STANDARDISED PREVALENCES OF BACILLARY TUBERCULOSIS (PER 1000 ADULTS) IN THE 6 TREATMENT TOWNS IN THE 3 SURVEYS. ALL CASES (M+ AND C+)

Town	Males			Females			Both sexes		
	S I	S II	S III	S I	S II	S III	S I	S II	SIII
Kadiri	17.0	9.9	15.7	6.0	5.2	6.0	11.6	7.6	11.0
Palmaner	7.7	5.5	7.7	1.7	3.8	2.6	4.7	4.6	5.1
Kalahasti	19.1	25.7	19.4	6.6	9.8	4.5	12.8	17.7	11.9
Rajampet	15.1	22.9	26.2	8.8	4.6	6.9	11.9	13.7	16.5
Chintamani	5.2	5.6	7.1	6.7	4.1	3.0	5.9	4.9	5.1
Tiruttani	15.4	9.8	12.9	2.2	3.0	5.1	8.8	6.4	9.0
Mean	13.26	13.24	14.85	5.33	5.07	4.67	9.28	9.14	9.76
P-value*	SI-SII	>0.2			>0.2			>0.2	
for the contrast	SI-SIII	>0.2			>0.2			>0.2	

*Based on a weighted mean change between surveys

The decrease in prevalence from Survey I to Surveys II or III of the cases positive by microscopy is considered to indicate a real decrease which is not likely to be due to changes in the technique. On the other hand, the increase in the prevalence in the C+ group is considered to be due to the improvement in the bacteriological technique which took place in 1964 when the homogenizing agent used at the time of setting up primary cultures was changed from 6 per cent sulphuric acid to 4 per cent sodium hydroxide.

Comparison between mean prevalence rates in the three 'INH-PAS' towns and the three 'INH' towns: The results are given in Tables XL and XLI. The 3 towns where the treatment consisted of isoniazid and PAS, were Kadiri, Palmaner and Kalahasti and the towns where the treatment consisted of isoniazid only, Rajampet, Chintamani and Tiruttani. In the 'INH-PAS' group, the cases with sputum positive by microscopy showed among the males a statistically significant decrease from Survey I to Survey II and among females from Survey I to Survey III. The cases which were positive by culture only, showed an increase from Survey I to Survey II or Survey III but the difference among males or females did not reach significant levels. However, when both sexes were taken together, the cases microscopically positive (M+) showed appreciable decrease from Survey I to Survey II ($P < 0.01$) and from Survey I to Survey III ($P = 0.09$). With regard to the cases positive by culture only (C+), there was an increase from 2.68 at Survey I to 4.67 at Survey III which is almost significant ($P = 0.06$). Turning to the INH-towns, the trend observed among the 2-drugs towns were also noted among them but none of the changes reached significant levels.

The changes from Survey to Survey observed in the 'INH-PAS' towns have

TABLE XL — AGE-STANDARDISED MEAN PREVALENCE OF BACILLARY TUBERCULOSIS IN 3 INH-PAS AND 3 INH TOWNS

	Survey	Mean prevalence (per 1000 adults) of bacillary TB cases					
		Males		Females		Both sexes	
		INH-PAS	INH	INH-PAS	INH	INH-PAS	INH
M +	I	10.69	8.87	3.30	4.42	7.01	6.62
	II	6.34	8.66	3.06	2.04	4.70	5.32
	III	6.99	7.82	2.32	2.23	4.65	5.01
C +	I	3.90	3.02	1.45	1.49	2.68	2.25
	II	7.37	4.12	3.20	1.85	5.28	2.98
	III	7.29	7.60	2.02	2.76	4.67	5.17
All positive	I	14.59	11.90	4.75	5.91	9.69	8.87
	II	13.71	12.78	6.26	3.89	9.98	8.31
	III	14.27	15.42	4.35	4.99	9.33	10.19

TABLE XLI — COMPARISONS BETWEEN INH-PAS TOWNS AND INH TOWNS*

	Treatment policy	Weighted mean change in bacillary prevalence (per 1000 adults)					
		Survey I minus Survey II			Survey I minus Survey III		
		Male	Female	Both sexes	Male	Female	Both sexes
M +	INH-PAS	4.35	0.24	2.29	3.75	0.97	2.36
	INH	0.30	2.32	1.40	0.99	2.17	1.58
	P	0.1—0.2	0.07	0.2	0.1—0.2	0.2	0.2
C +	INH-PAS	—3.46	—1.74	—2.59	—3.39	—0.57	—1.99
	INH	—1.10	—0.36	—0.73	—4.57	—1.26	—2.91
	P	0.2	0.2	0.2	0.2	0.2	0.2
All positive	INH-PAS	0.88	—1.50	—0.29	0.32	0.40	0.37
	INH	—0.86	2.0	0.58	—3.52	0.92	—1.28
	P	0.2	0.2	0.2	0.2	0.2	0.2

*Based on weighted, age-standardised, mean changes between surveys in the 3 INH-PAS towns and in the 3 INH towns.

been compared with the corresponding changes observed in the 'INH' towns (Table XLI) but in none were the differences statistically significant.

Isoniazid sensitivity : All cultures isolated were, as a matter of routine, examined for drug sensitivity towards isoniazid, streptomycin and PAS (Tables XLII and XLIII). In this report only the results of isoniazid sensitivity tests are presented. The distribution of isoniazid-sensitive and resistant strains in the 12 towns according to survey, sex and method of demonstrating the bacilli is shown in Appendix Table XII*. In a few cases cultures were obtained but drug sensitivity tests were missing or the tests not done. Assuming that these cases would have shown the same ratio of sensitive to resistant cases as found among those for which the results are available, the mean prevalence rates for cases with INH-resistant strains are shown in Table XLII. The mean prevalences of the six towns according to sex and method of demonstrating the bacilli are also found in Table XLII as well as the *P*-values for mean changes between surveys. Whereas the previous comparisons among cases whose sputa were positive by microscopy showed a decrease in prevalence from Survey I to Survey II and Snrvey III, the present comparisons show among males an increase from Survey I to Survey II and from Survey I to Survey III. However, in none were the changes statistically significant. With regard to cases positive by culture only (C+), there was an increase from Survey I to the other surveys (Table XLII), and in case of females there was a significant increase from 0.12 at Survey I to 0.94 per 1000 at Survey II. Considering the positive cases irrespective

*See foot note on p 25

TABLE XLII — AGE-STANDARDISED MEAN PREVALENCE OF ISONIAZID-RESISTANT STRAINS IN THE 6 TREATMENT TOWNS IN THE 3 SURVEYS

	Sex	Mean prevalence (per 1000 adults) of INH-res. strains			P-value* for the following contrast	
		S I	S II	S III	SI - S II	SI - S III
M +	Males	1.42	3.09	2.31	0.1	0.2
	Females	1.23	1.35	0.72	0.2	0.2
	Both sexes	1.33	2.23	1.50	0.1	0.2
C +	Males	0.66	1.22	1.37	0.2	0.2
	Females	0.12	0.94	0.53	0.03	0.2
	Both sexes	0.39	1.08	0.94	0.08	0.1
All positive cases	Males	2.13	4.27	3.68	0.1	0.2
	Females	1.30	2.32	1.23	0.03	0.2
	Both sexes	1.71	3.30	2.43	0.04	0.2

*Based on a weighted mean change between surveys

of method of diagnosis, there were satistically significant increases from Survey I to Survey II, in males from 2.13 to 4.27 per 1000, in females from 1.30 to 2.32 and in 'both sexes' from 1.71 to 3.30 per 1000.

The treatment programme and the changes in prevalence : Comparing the results of the three prevalence surveys conducted in the 6 'Treatment' towns, it was found that even though the total prevalence of bacillary tuberculosis showed no essential change from Survey to Survey, the study of special factors such as the method of demonstrating tubercle bacilli in the sputum either by microscopy or by culture, or the division of the material into isoniazid-sensitive and isoniazid-resistant cases, did reveal further changes in the prevalence of the more advanced type of cases (M+) as compared with the less advanced(C+), and isoniazid-sensitive cases as compared with isoniazid-resistant cases. The question arises to which extent could the active treatment programme in the 6 'Treatment' towns started at the time of Survey I have been responsible for the changes and how much could be due to other causes ? In order to understand better the currents or cross currents which could have been set in motion by the active treatment programme the significance of the observations described in the preceding paragraphs have been summarised in Table XLIII. This table summarises in a more lucid way the main changes observed. Equalling the observations at Survey I with 100 per cent, the corresponding prevalences at Survey II and Survey III are shown as percentages of the rates of Survey I.

Whether the changes from Survey-I to Survey II, or from I to III were an

TABLE XLIII — SUMMARY OF CHANGES IN PREVALENCE BETWEEN SURVEYS (BOTH SEXES COMBINED)

	Survey	M +			C +			All positive cases		
		Prevalence*	%**	Change from Survey I	Prevalence*	%**	Change from Survey I	Prevalence*	%**	Change from Survey I
Bacillary TB	I	6.81	100		2.47	100		9.28	100	
	II	5.01	74	—26	4.13	167	+67	9.14	99	— 1
	III	4.83	71	—29	4.92	200	+100	9.76	105	+ 5
INH-sensitive strains	I	5.48	80		2.08	84		7.57	82	
	II	2.78	41	—39	3.05	124	+ 40	5.84	63	—19
	III	3.33	49	—31	3.98	161	+ 77	7.33	79	— 3
INH-resistant strains	I	1.33	20		0.39	16		1.71	18	
	II	2.23	33	+13	1.08	44	+ 28	3.30	36	+18
	III	1.50	22	+2	0.94	38	+ 22	2.43	26	+ 8

*Arithmetic mean of age-standardised prevalences in the 6 individual towns. (per 1000 adults)
**Computed by taking as base (100%) the prevalence of bacillary tuberculosis at Survey I

increase or decrease, they were similar for males and females. It is therefore justified to confine the following considerations to 'both sexes' only. The material in Table XLIII has been subdivided according to the method of sputum examination, and the results of drug sensitivity tests.

Considering first the group of cases positive by microscopy (M+), the prevalences at Survey II and Survey III were only 74 per cent and 71 per cent of that found at Survey I. With regard to the C+ group, which deals with cases positive by culture only, there is at Survey II an increase of 67 per cent and at Survey III an increase of 100 per cent over the prevalence at Survey I. As mentioned earlier, this increase is ascribed to the improvement in culture technique which took place in 1964, during Survey II. As for 'all cases', the decrease observed in group M+ is offset by the increase in group C+, so that the percentages observed at Surveys II and III are very similar to that at Survey I.

Table XLIII describes also cases with INH-sensitive-strains. Group M+ shows a much lower prevalence at Survey II and Survey III than was seen when considering the results regardless of drug sensitivity. Thus, the drop was from 80 per cent to 41 per cent at Survey II and from 80 per cent to 49 per cent at Survey III. As for the 'C+' group, there is an increase of 40 per cent from Survey I to Survey II and of 77 per cent from Survey I to Survey III; with regard to the group 'all positives', the percentages had decreased from 82 at Survey I to 63 at Survey II, and to 79 at Survey III.

It is obvious that the changes from Survey I to Survey II and from Survey I to Survey III are quite different when dealing with cases having INH-sensitive strains, and when no attention is paid to INH sensitivity. The reasons for the lower prevalences among INH-sensitive cases than among 'all cases' is clearly the omission of the isoniazid-resistant cases from the total positives. Turning now to cases with INH-resistant strains—there is in Group M+ an increase from 20 per cent at Survey I to 33 per cent at Survey II and in Group C+ an increase from 16 per cent to 44 per cent. Such a marked increase is not likely to be due to the improved culture technique alone, but must be due also to isoniazid-resistant strains which have emerged between Survey I and Surveys II and III.

The six 'Control' towns : In pursuance of the original design of the experiment, 6 of the 12 towns examined by the sample survey in 1959 were, by random allocation, made 'Treatment towns' and other 6 were set aside as 'Control towns'. When Survey III was started in 1965, the Control Towns were also included in the Survey. The findings at the base-line survey* (20-25 per cent sample) and at the resurvey (total population survey) in 1965 are presented for the 6 'treatment towns' and 6 'Control towns' in Table XLIV, separately for M+ cases, C+ cases and all positive cases. Considering the mean prevalences, it can be readily seen that there was a de-

*That the findings in the 20-25 per cent random sample survey were typical of the prevalence in the total base-line population is evident from the fact that, in the 6 treatment towns, the correlation coefficient between the sample survey prevalence and the population survey prevalence was very high, namely 0.9.

crease in the prevalence of M+ cases in both the 'Treatment towns' and the 'Control towns'. Also, there was an increase in the prevalence of C+ cases in both the Treatment towns and the Control towns, which is, in all likelihood, due to the introduction of an improved culture technique during the course of the study.

Formal statistical comparisons have been made in Table XLV for both sexes combined, employing a method of weighted averages (for further details of statistical methods, see the accompanying paper). It is seen that there is no evidence that the Treatment Towns showed larger decreases in the prevalence of tuberculosis than the control towns.

Table XLVI presents the mean prevalence of bacillary tuberculosis, the mean prevalence of isoniazid-sensitive strains, and the mean prevalence of isoniazid resistant strains in the Treatment Towns and the Control Towns, according to sex and the method of sputum examination. From the findings in this table, Table XLVI-A is derived, which shows rather concisely the proportion of

TABLE XLIV — PREVALENCE OF BACILLARY TUBERCULOSIS IN 6 'TREATMENT' AND 6 'CONTROL' TOWNS AT BASE-LINE SURVEY* (1959) AND AT RE-SURVEY** (1965-68), BOTH SEXES COMBINED

Town	Prevalence of bacillary tuberculosis (per 1000 adults)					
	M+		C+		All positive	
	Base-line survey	Resurvey	Base-line survey	Resurvey	Base-line survey	Resurvey
Treatment towns :						
Kadiri	4.3	4.6	5.1	6.3	9.4	10.3
Palmaner	3.2	2.9	2.2	2.1	5.4	5.0
Kalahasti	10.0	6.4	7.6	5.5	17.6	11.9
Rajampet	10.3	6.9	3.4	9.4	13.7	16.3
Chintamani	3.2	2.5	1.3	2.7	4.5	5.2
Tiruttani	4.5	5.4	3.4	3.5	7.9	8.9
Mean	5.92	4.78	3.85	4.92	9.77	9.70
Control towns :						
Rayachoti	11.2	5.5	1.0	8.0	12.2	13.5
Srinivasapur	6.0	2.1	1.2	4.5	7.2	6.6
Mulbagal	1.8	1.5	1.9	3.7	3.7	5.2
Nagari	5.6	5.5	3.4	4.6	9.0	10.1
Puttur	7.9	6.7	4.4	5.1	12.3	11.8
Punganur	1.8	3.9	2.7	3.0	4.5	6.9
Mean	5.72	4.21	2.44	4.82	8.16	9.03

*Based on a 20-25% random sample of the population.
**Based on a population survey (Survey III).

TABLE XLV—CONTRASTS BETWEEN 6 'TREATMENT' TOWNS AND 6 'CONTROL' TOWNS IN CHANGES IN BACILLARY PREVALENCE OF TUBERCULOSIS

		Weighted mean change* in bacillary prevalence (per 1000 adults)	
		Treatment towns	Control towns
Both sexes	M +	1.12	1.37
	C +	—1.05	—2.39
	All cases	0.14	—0.91
Males	M +	1.84	1.74
	C +	—1.91	—5.00
	All cases	—0.02	—3.19
Females	M +	0.30	0.71
	C +	—0.29	0.24
	All cases	0.03	1.00

*Prevalence at Baseline survey (1959; 20-25% random sample) minus prevalence at Resurvey (1965-68, Survey III).
P value in all cases 0.2.

isoniazid-resistant strains in the treatment towns and the control towns. Although there is a slight suggestion, especially in the C+ cases, that the prevalence of isoniazid resistant strains is higher in the Treatment towns than in the Control towns, none of the differences was statistically significant.

Comparison of the mean prevalence of the 12 *towns at the Sample Survey in* 1959 *with the mean prevalence obtained at Survey III,* 1965-68 : The result of this analysis is presented as a series of correlation diagrams, and summarised with mean values in Table XLVII. In Fig. 20, the two uppermost diagrams indicate the cases whose sputa were positive by microscopy, the middle the cases positive by culture only and the lower most all the cases whether positive by microscopy or by culture. The three diagrams to the left represent the males and the other three the females. The diagrams bear out strikingly the modest role played by the females as against the almost domineering role of the males. The distribution of town prevalence rates among the females show no correlation between the two survey results in any of the three diagrams. Turning to the males in the topmost diagram (cases positive by microscopy) 7 of the 12 town prevalences are situated in the right triangle below the diagonal; the diagonal itself indicates towns having the same prevalence at both surveys. The decrease among males in mean prevalence from the first to the last survey was not significant ($P > 0.2$). The middle diagram which shows the town prevalences based upon the male cases negative by microscopy but positive by culture, 9 points are found in the left upper triangle, *viz.* 3 'Treatment' towns and all 6 'Control' towns. It indicates that the prevalence had increased between the Surveys, and this change was significant (P=0.01). The distribution of the town prevalences in the lowermost diagram points to a strong positive correlation ($r = 0.84$); the position of 8 towns to the left of the diagonal suggests a modest increase in mean prevalence but this was not statistically significant.

The three diagrams in Fig. 21 refer to 'both sexes'. In the group 'positive by microscopy', 8 points (4 'treatment and 4 'control' towns) are found below the diagonal, indicating a decrease in the mean prevalence; this decrease was nearly significant (P=0.07) The middle diagram shows the prevalences in the

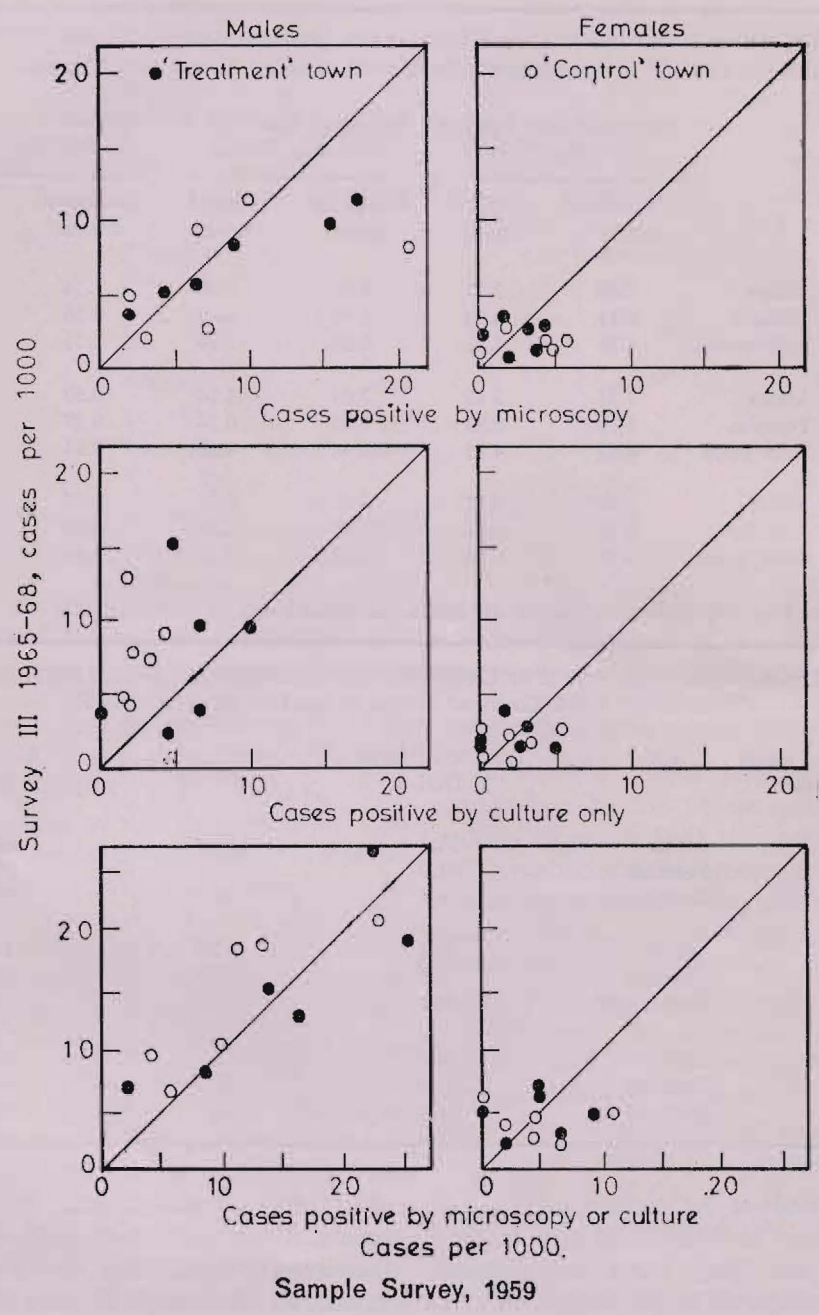

Fig. 20 — Correlation diagrams showing the town prevalences of bacillary cases in the 1959 sample survey and survey III (1965–68) separately for males and females

TABLE XLVI — PREVALENCE OF BACILLARY TUBERCULOSIS, ISONIAZID-SENSITIVE STRAINS, AND ISONIAZID-RESISTANT STRAINS* AT RE-SURVEY (1965-68) IN 'TREATMENT' TOWNS AND 'CONTROL' TOWNS

		Prevalence (per 1000) of bacillary TB.		Prevalence (per 1000) of INH-scns. strains		Prevalence (per 1000) of INH-res. strain	
		Treatment towns	Control towns	Treatment towns	Control towns	Treatment towns	Control towns
M+	Males	3.66	3.27	2.52	2.30	1.14	0.98
	Females	1.13	0.93	0.76	0.64	0.36	0.29
	Both sexes	4.79	4.21	3.29	2.94	1.51	1.27
C +	Males	3.71	3.89	3.03	3.54	0.68	0.35
	Females	1.21	0.93	0.95	0.74	0.27	0.19
	Both sexes	4.92	4.82	3.98	4.28	0.94	0.54
All cases	Males	7.37	7.17	5.55	5.84	1.82	1.33
	Females	2.33	1.86	1.71	1.38	0.63	0.48
	Both Sexes	9.71	9.03	7.26	7.22	2.45	1.82

*Based on arithmetic means of prevalenees in individual towns at Survey III (1965-68).

TABLE XLVI-A — MEAN PERCENTAGE OF CASES WITH ISONIAZID-RESISTANT BACILLI (INH-R) IN THE 6 'TREATMENT' AND 6 'CONTROL' TOWNS AT THE LAST SURVEY (1965-68)

Method of initial sputum exam.	Sex	Treatment towns % INH-R	Control towns % INH-R	All towns % INH-R
M +	Males	31.1	30.0	30.8
	Females	31.9	31.2	31.7
	Both sexes	31.5	30.2	30.8
C +	Males	18.3	9.0	13.6
	Females	22.3	20.4	21.4
	Both sexes	19.1	11.2	15.3
All cases	Males	24.7	18.5	21.2
	Females	27.0	25.8	26.4
	Both sexes	25.2	20.2	22.7

group 'positive by culture only'. Here 10 points (4 'treatment' and all 6 'control' towns), are lying above the diagonal. This corresponds to an increase in mean prevalence which is just statistically significant ($P=0.04$). The lowermost diagram relates to all cases regardless of method of sputum examinations. Of the 12 points, 8 are slightly above the diagonal thereby indicating that the mean prevalence showed a slight increase ($P > 0.2$).

It is of interest that there is such a marked agreement between the findings

TABLE XLVII — CHANGES IN MEAN PREVALENCE OF 12 TOWNS BETWEEN BASE-LINE SURVEY (1959) AND RE-SURVEY (1965-68)

Initial bacteriological examination	Sex	Mean prevalence per 1000 adults		*P*-value*
		Base-line survey	Re-survey	
M +	Males	8.89	6.94	0.2
	Females	2.63	2.06	0.2
	Both sexes	5.83	4.50	0.07
C +	Males	4.13	7.58	0.01
	Females	2.16	2.15	0.2
	Both sexes	3.14	4.87	0.04
All positives	Males	13.02	14.52	0.2
	Females	4.79	4.21	0.2
	Both sexes	8.97	9.37	0.2

*Based on a weighted mean coverage between surveys.

at the base-line Sample Survey in 1959 and the Re-survey done in 1965-68 ($r=0.855$; $P=0.001$). It underlines the value of a sample survey in ascertaining the level of tuberculosis prevalences in selected communities. As the 1959 sample survey of the 12 towns was carried out in the course of six months only by means of two mobile-X-ray units, each with its own trained staff, such sample surveys provide a valuable tool in assessing the size of the tuberculosis problem and in indicating which sectors of the populations present the greatest risk of tuberculosis. This type of information will be helpful either in setting up treatment facilities or in identifying the areas which offer the greatest risk of exposure to infection. It may also be noted that the observations made at the base-line Sample Survey with regard to the ranking of the 12 towns were still valid 6-9 years later.

Tuberculin sample survey 1966-69

In 1964 a special investigation was undertaken by the Madanapalle Tuberculosis Research Unit to study the role of mycobacteria of different types in producing skin sensitivity and disease in man*. As part of this investigation a Tuberculin Sample survey was carried out in the 12 towns which formed the basis for the present investigation. The block size was fixed at 50 households and as the average size of an Indian family is 5.0-5.5, there were about 250 persons per block.

Excluding persons who had died, moved out, were out of station or disabled, and excluding children below the age of two

*The Study was supported by a grant from the US PL-480 Funds and carried out in cooperation with Tuberculosis Research Program, National Communicable Diseases Centre, Washington Office, US Public Health Service.

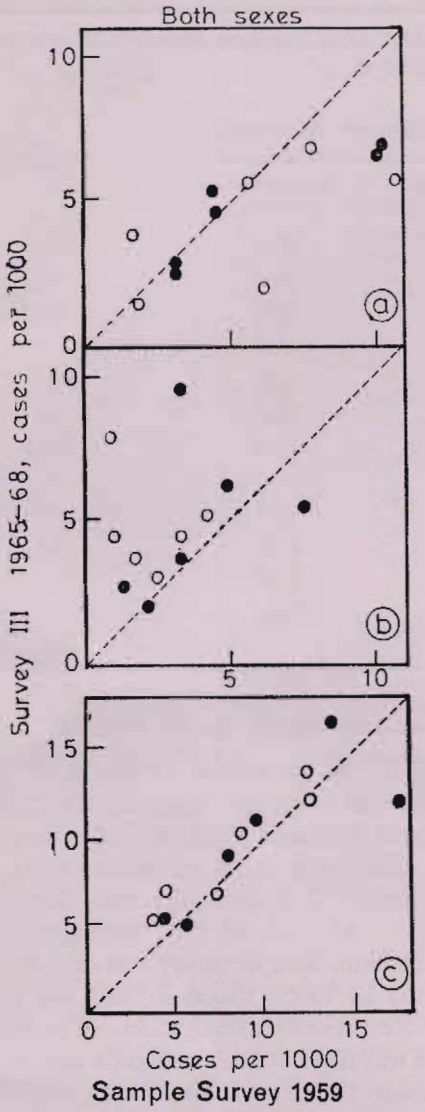

Fig. 21 — Correlation diagram of town prevalences at sample survey (1959) and survey-III (1965–68) for 'both sexes'. *a*: microscopically positive. *b*: cases positive by culture only and and *c* : all positives

years, the number of persons to be tested (Table XLVIII) varied from 1500 to 1800 (in Kalahasti 2400**). The coverage ranged from 56 to 91 per cent with a mean of 72 per cent. The tests were carried out by a trained health visitor who gave the injections as well as read the tests. Injections were given on the first three days of the week and the readings done on the last three. The reactions were therefore normally read at 72 and sometimes at 96 h. The tests were given in the homes. It took about six weeks to complete the testing in a town.

The Mantoux tests were carried out with two PPD antigens namely Standard Tuberculin or PPD-S and PPD-G, an antigen derived from the scotochromogenic strain 'Gause'. The PPD antigens were prepared and delivered in ready made solutions at the Tuberculosis Research Laboratory, Chamblee, Georgia. They were kept in a refrigerator until used. The ampoules were issued to the health visitor under code numbers so that she would not know what product she was testing. Decoding at headquarters was done after covering each town. Doses of PPD-S corresponded to 5 Tuberculin Units (without addition of Tween 80). The dose of PPD-G was adjusted so that the nitrogen content of the two products was the same. The two tests were given in random order on the volar aspect of either forearm. The size of the reactions to the Mantoux tests was indicated by measuring the cross diameter of the indurations in mm. After reading the tests the shoulders of each person were examined for presence of BCG vaccination scars.

For the purpose of the present report the sample populations have been analysed according to age groups but not separately for males and females. Only the results

**In Kalahasti the sample included 15 blocks.

TABLE XLVIII — COVERAGE BY TUBERCULIN TESTING AT TUBERCULIN SAMPLE SURVEY (1966-69)

Town	Persons* living in the sample blocks	Died, moved out or absent	Available for testing (a)	Tested		Tested and read		
				No. (b)	% of (a)	No.	% of (b)	% of (a)
Treatment towns								
Kadiri	2207	717	1490	1044	70	882	84	59
Palmaner	2234	554	1680	1406	84	1336	95	79
Kalahasti	3109	720	2389	1733	72	1546	89	65
Rajampet	1922	273	1649	921	56	781	85	47
Chintamani	2269	580	1689	1315	78	1204	92	71
Tiruttani	1990	365	1625	1222	75	1144	94	70
Control towns								
Rayachoti	2431	436	1995	1303	65	1273	98	64
Srinivasapur	2473	642	1831	1323	72	1210	91	66
Mulbagal	2590	641	1949	1351	69	1227	91	63
Nagari	2083	457	1626	1390	85	1304	94	80
Puttur	1975	444	1531	1387	91	1263	91	82
Punganur	2383	624	1759	1414	80	1332	94	76

*Children below 2 yr of age are excluded.

of tests done with PPD-S are given here whereas the comparable tests with PPD-Gause were reported in 1969[7].

The number of persons living in the sample blocks (excluding children below two years) is given in Table XLVIII together with the number available for testing, the number tested and the number whose reactions were read. Table XLIX shows the total number tested and read in all the sample blocks of each town and the percentage of persons whose indurations measured 8 mm or more; they are divided according to age groups. Fig. 22 shows the frequency distribution of the percentage of reactors according to the size of the induration among 2371 children in the age group 5-9 yr from the sample blocks in the 12 towns when tested in 1966-69.

Results : Fig. 23 shows the mean percentage of reactors according to age in the 6 'Treatment' towns and the 6 'Control' towns at the 1966-69 Sample Survey.

The prevalences of reactors to PPD-S tuberculin in the 'Treatment' and 'Control' towns are shown in Table L. There are noticeable differences in the younger age groups. At the age of 2-4 yr the percentage of reactors was 9.6 in the 'Treatment' towns and 4.5 in the 'Control' towns i.e. about twice as high in the 'Treatment' towns as in the 'Control' towns, and at 5-9 yr it was 18.2 per cent in the 'Treatment' towns and 13.9 per cent in the 'Control' towns; but neither of these differences were statistically significant.

TABLE XLIX — TUBERCULIN SAMPLE SURVEY (1966-69) — MEAN PERCENTAGE OF REACTORS TO PPD-S (≥ 8 MM) ACCORDING TO AGE

Town	Age group in years																	
	2-4		5-9		10-14		15-19		20-24		25-34		35-44		45-54		55+	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Kadiri	98	8	124	20	140	35	72	65	42	73	145	71	120	82	73	83	68	77
Palmaner	185	3	213	8	203	17	133	20	95	36	180	59	137	52	103	58	87	63
Kalahasti*	152	11	233	26	190	42	157	56	110	63	268	82	217	79	118	74	95	80
Rajampet	66	20	89	34	76	46	64	60	41	59	151	82	136	84	81	82	77	76
Chintamani	196	6	213	12	178	26	129	40	74	40	147	56	127	66	71	65	69	69
Tiruttani	119	9	141	9	117	38	103	44	104	54	218	66	156	69	105	69	81	65
Rayachoti	123	8	214	19	196	40	109	51	94	64	222	69	131	77	95	79	89	71
Srinivasapur	176	3	235	11	213	15	89	37	63	44	149	51	120	71	91	66	74	54
Mulbagal	175	1	236	7	239	19	108	22	71	30	137	53	113	65	77	61	71	60
Nagari	146	8	194	16	182	37	103	53	97	59	197	66	181	71	127	70	77	78
Puttur	129	3	225	14	193	31	91	65	82	46	207	66	177	74	93	76	66	63
Punganur	192	3	248	16	176	26	107	38	105	60	207	62	139	71	84	48	74	57

*Data based on 15 sample blocks.

Note : — The number in each age group indicates the total number of persons tested (excluding BCG vaccinated).
The per cent in each age group indicates the reactors to PPD-S.(Percentage)

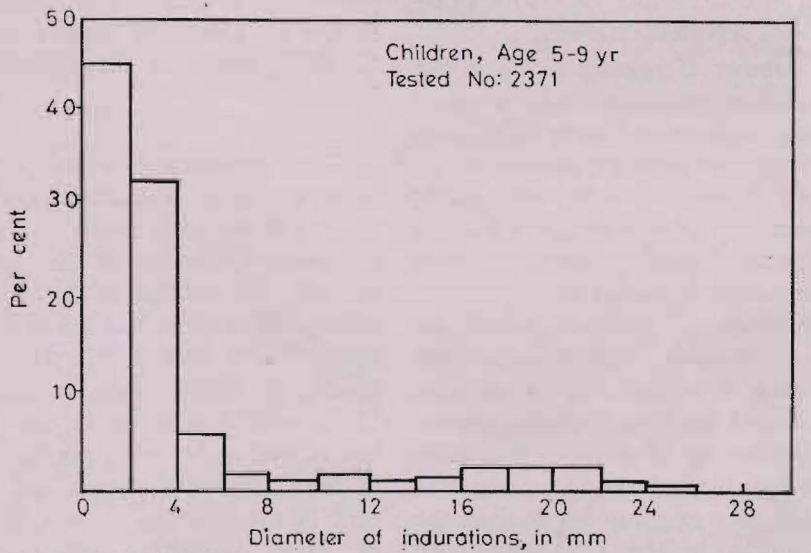

Fig. 22 — Histogram showing the percentage frequency distribution of 2371 children, age 5—9 years, at Sample Survey 1966–69 according to size of induration to Mantoux tests.

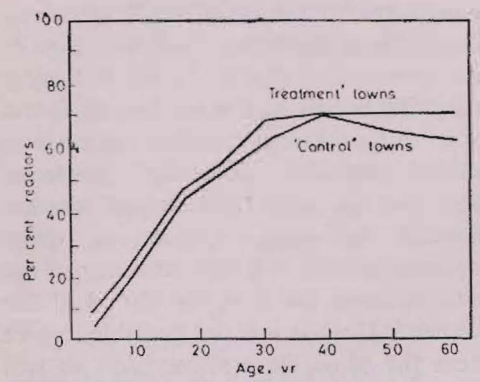

Fig. 23—Mean percentage of reactors to Mantoux tests in 'Treatment' and 'Control' towns respectively at Sample Survey 1966-69.

TABLE L—TUBERCULIN SAMPLE SURVEY(1966-69)—COMPARISON OF MEAN PERCENTAGES OF TUBERCULIN REACTORS (⩾ 8MM) IN THE 'TREATMENT' AND 'CONTROL' TOWNS

Age group	Treatment towns	Control towns	*P*-value
2-4	9.6	4.5	0.09
5-9	18.2	13.8	>0.2
10-14	34.1	28.0	>0.2
15-19	47.5	44.3	>0.2
20-24	54.2	50.4	>0.2
25-34	69.6	61.4	=0.2
35-44	71.9	71.4	>0.2
45-54	71.8	66.7	>0.2
55 +	71.3	63.6	=0.1
All ages	48.0	40.3	>0.2

General discussion

Before drawing the main conclusions, it may be well to recall the aim and purpose of the investigation. Being impressed with the results obtained by the Tuberculosis Chemotherapy Centre (TCC), Madras, by home treatment in converting 86 per cent of advanced bacillary cases of pulmonary tuberculosis to bacteriologically quiescent cases in comparison with the 92 per cent obtained by one year's treatment in hospital of a similar group of patients, the present experiment was designed to try out home treatment under ordinary working conditions in India and to see whether it would be possible to render a high majority of all the existing bacillary cases sputum-negative within a year. If as much as 90 per cent of such patients could really be rendered non-infectious in a year, it would stand to reason to expect that a definite reduction in the tuberculosis prevalence and incidence would occur. Repeated prevalence surveys should therefore reveal significant decreases in the prevalence of the disease, and after some time the annual incidence should also come down.

In paying attention to 'ordinary working conditions', it was stipulated that the introduction of domiciliary drug therapy should be carried out with as little expenditure as possible and not more than could reasonably be expected of Government tuberculosis clinics. Further, attention should be paid to the fact that Government tuberculosis clinics were equipped with limited facilities for diagnosis and in particular that they would not have access to laboratories for isolation of tubercle bacilli by culture or for carrying out drug sensitivity tests. At the same time the sponsors of the investigation were aware that scientific facilities as available at the Madanapalle Centre with its mobile X-ray units and well developed laboratory, were necessary in order to maintain a close observation on the course of the investigation, supervising the medical aspects and not least, it was thought the investigation would be able to

benefit from the prestige earned by the parent Institution (the Union Mission Tuberculosis Sanatorium) through 40 years or more of service to the general public of the area.

As time went on, it became clear that the intentions and principles initially set up could not be wholly maintained. The fact that the Research Unit had at its disposal mobile X-ray units which could detect the majority of the existing bacillary cases within a short time and would include cases which could only be diagnosed as bacillary cases because of isolation by culture, introduced deviation beyond the scope of ordinary Government clinics. Although the teams which issued the drugs to patients in the different towns and the technicians handling the X-ray unit and manning the laboratory were recruited from among the local public and had been trained in the Institution itself, the administration and the statistical set-up were on a higher level than is normally found in Government clinics and district health centres. With regard to the issue of drugs they were given free of charge and strictly within the stipulations drawn up in the protocol. Although the Research Unit had access to the information obtained by the drug sensitivity tests, this information was not made use of to make changes in the drugs used as such information would not be available in ordinary Government clinics. So the intention was, in relation to patients, to act as any Government clinic should do but at the same time applying the facilities and know-how of a research centre.

The present investigation was carried out under conditions which differed in many ways from those of the Tuberculosis Chemotherapy Centre, Madras. Firstly, there was no selection of cases but every one with bacilli in the sputum as found either by microscopy or by culture was offered treatment. Secondly, the treatment was the same regardless of whether patients had drug-sensitive or drug-resistant bacilli. Thirdly, as many of the patients lived far from the Centre of the Research Unit, it was not possible to give them the same close supervision as was possible at Madras; neither was it possible to carry out regular home visits and check the amount of drug kept in the homes nor to examine the urine for presence of isoniazid or PAS. Further, it was the policy of the Research Unit not to insist that patients should discard any other treatment they might be receiving when picked up by the Unit nor did the Unit forbid patients from taking additional drugs if they wished to or were so advised by their local doctors. The contribution to the community made by the Madanapalle Unit was not to replace existing facilities but to supplement them with whatever special service it could give in terms of free and efficient diagnosis, cheap and, hopefully, effective drug regimens and a reasonable good follow up service.

As for the lessons to be drawn from the present investigation, the most important of these was the difficulty in obtaining the full co-operation of the patients. Already at the initial stage 10-20 per cent preferred to have treatment from other sources or no treatment at all. Of the 80-90 per cent patients who accepted the treatment, many defaulted prematurely so at the end of first year only about 65 per cent of those who started still conti-

nued to take treatment. Even among those who collected their drugs at the fortnightly clinics of the Unit, the intake of drug was often irregular and faulty. The high proportion of patients who continued to excrete isoniazid-sensitive bacilli after 12 months of treatment indicates the inadequacy of the drug intake.

There are several reasons for the unsatisfactory co-operation and the relatively high rate of defaulters. First, many patients did not wish it to be known that they were afflicted with tuberculosis; so they desisted from attending the clinics or resisted the visits of our staff to their homes. If the jeep belonging to the Research Unit with "M.T.R.U." conspicuously painted on it stopped in front of a house, all the neighbours would believe that there was a case of tuberculosis in the house. Second, in certain cases propaganda directed against the work of the Unit was carried out by local medical practitioners who feared they would lose their patients. Third, in spite of repeated explanations and admonitions, many patients did not grasp the seriousness of their illness and being tied down by their daily work on which their meagre earnings depended, they could not find time to go to the clinics to get their drugs but would either send a messenger to fetch the drugs or abstain from the drug issues altogether. The fact that drugs were issued free of charge, made some patients believe that the matter was not of any consequence.

A serious hindrance to establishing trust and confidence in the type of treatment offered was undoubtedly that many advanced cases failed to respond to the treatment. As time went on, the public lost faith in the treatment. The attendance at the drug issues became therefore less and less as time went on. In some sections of the 'treatment' towns, the people resisted openly the carrying out of the repeated surveys pointing to the failure of saving a number of their sick people who had advanced tuberculosis when detected during Survey I.

It would be tempting to attribute the decrease in prevalence from Survey I to Survey III observed among smear-positive cases to the active treatment programme which began in 1960 and was carried on till 1965-68. However, the inclusion of the 'control' towns in the 1965-68 Survey—the third for the six 'treatment' towns and the first full survey for the six 'control' towns—has provided a new dimension to the interpretation of the results observed in the six 'treatment' towns. Comparing the prevalence observed in the 12 towns at the time of the 1959 base-line Sample Survey with the results obtained 6-9 years later at the resurvey, it was seen that the decrease in prevalence of tuberculosis observed in the six 'treatment' towns was similar to that observed in the six 'control' towns.

There was an increase in the prevalence of cases positive by culture only which was observed in both groups of six towns. It is thought to be due to the change and improvement in the culture technique introduced in 1964. However, the decrease in the prevalence observed among the microscopically positive cases, it is thought, represents a general decrease in the prevalence of tuberculosis in that part of India where the investigation took place.

The observation that the treatment programme has left no impact on the prevalence of tuberculosis in the six 'treatment' towns seems surprising. However, varions reasons can be given. One may consider, for instance, the limited response of the public to the different phases of the programme. Assuming a coverage of 90 per cent at the X-ray survey, and 90 per cent at the bacteriological examination, it would appear that only 81 per cent of all the bacillary cases had been detected. But it is to be noted that a number of cases were later found to be TB positive among persons with chest X-ray lesions suggestive of tuberculosis as a result of periodical sputum examinations. So it is reasonable to assume that 90 per cent of the existing cases in the community were detected by means of surveys and follow up examinations. If, of the known cases, only 80 per cent acepted the treatment, only 80 per cent of the 90 per cent or 72 per cent of the existing cases could benefit from the treatment programme. Recalling tbat only about 50 per cent obtained negative sputum at the end of one year of treatment, only 36 per cent of all the existing cases had been rendered sputum-negative by the efforts of the Unit. Adding to this, the fact that follow up examinations of such cases for another four years showed that of those who had obtained negative sputum at the end of the first year, 31 per cent had either died or relapsed while 69 per cent had survived and remained sputum-negative, the total effect of the treatment programme had been to ensure that only 22 per cent of all the positive cases had become lasting sputum-negative cases. It is, therefore, not surprising that the present treatment programme has not made any impact on the prevalence. Further, the time factor may be considered. The initial base-line survey took place in 1959. The domiciliary treatment programme reached its peak towards the end of 1961 when the survey was over. The last survey (Survey III) was carried out during 1965-68. This allows for only an average period of 4-5 yr during which the treatment programme could exert its effect. Adding to this, that the regimens used were of low efficacy and the response from the public rather poor, it is not surprising in retrospect, that the overall effect was negligible.

When considering the observations regarding the 'pool of infectious cases, it was pointed out that the reason for the continued high level of positive cases year by year was due to the carrying over from one year to another of a high proportion of patients diagnosed more than a year earlier who should normally have turned sputum-negative. From 1960 to 1968, the yearly prevalence of proved bacillary cases stood at a level of 5-7 per 1000 adults—apart from a peak of 8 per 1000 in 1964 when the culture technique was changed. About 3 out of 5 of these cases were due to 'old' cases and 2 out of 5 to 'new' cases. The 'old' cases represented cases diagnosed in the previous calendar year of whom only about half had had sufficient time to turn sputum-negative and half were still positive; to this should be added cases who were diagnosed more than a year earlier and who should have been sputum-negative. It was, therefore, maintained that had the treatment been truly effective, about 85 per cent of the 'old' cases ought to have been rendered sputum negative and thereby eliminated as carriers of infectious tuberculosis. So, deducting 80 per cent

of these old cases from the total number of TB positives, it can be calculated that the 'pool' of infectious case should have been half its present size. The remaining 'pool' would then have consisted mainly of fresh 'new' cases and those who had not yet had time to turn sputum-negative.

It should be realised that any decrease of 'new' cases which could also be designated as 'incidence cases', does necessarily take considerable time. First, there should be time to introduce an active treatment programme and give it a chance to function for some time before a sizeable proportion of the bacillary cases can become sputum-negative. Then there must be time for the persons in the community not yet infected to acquire a primary infection, and for this to develop into a demonstrable tuberculous lesion beginning to excrete bacilli. Assuming the decrease of 'new' cases as shown in Fig. 14 to be genuine (and not due to artificial factors arising from the Investigation itself), the fact that the decrease of the incidence appears to have started already at the beginning of the observation period (in 1960 or 1961) suggests that the factors responsible for this decrease must have been in operation before the present treatment programme began. It is, therefore, suggested that the decrease in the incidence may represent a general decrease in the level of tuberculosis owing to many different factors of which one may be that most Indian patients suffering from tuberculosis somehow do find their way to receive some modern chemotherapy.

Eventhough the inability to demonstrate any community effect of the treatment programme may seem surprising, it would not be correct to condemn domiciliary drug therapy as ineffective in the management of tuberculosis in the community. The fact is that there is no other way in a country of the size of India with its 6-700 million population to treat the millions of its patients who suffer from tuberculosis. The present investigation suggests, however, that the type of programme entrusted to the Madanapalle Unit and adopted by it, was not effective enough. This may apply to the size of the staff and the type of clinics set up but more important than anything else, it applies to the type of chemotherapy offered. No real progress is likely to be achieved unless recourse is taken to issue to the public suffering from tuberculosis effective drug regimens which can cater for patients with drug-sensitive as well as drug-resistant bacilli.

Summary

1. In order to study the efficacy of domiciliary drug therapy as a tool in the control of tuberculosis in a rural community, an investigation was set up in 1958 by the Indian Council of Medical Research, the World Health Organization and the Union Mission Tuberculosis Sanatorium, Arogyavaram (south India). Twelve towns with populations ranging from 6,000-25,000 situated in Andhra Pradesh (8), Karnataka (3) and Tamil Nadu (1), all within 160 km of Madanapalle (Andhra Pradesh), were selected.

2. A base-line sample survey was carried out in 1959 covering 20-25 per cent of the town population excluding children below the age of 15 years. Three indices were obtained : the prevalence of (*i*) bacillary pulmonary tuberculosis, (*ii*) of

radiologically positive cases of presumably active pulmonary tuberculosis and (*iii*) of reactors to tuberculin tests in school children in the two lowest grades (age 5-9 yr). The 12 towns were ranked according to the degree of prevalences and divided by random allocation into two comparable groups of six towns each; one was designated the 'Treatment' towns and the other the 'Control' towns. During 1960-61, the remaining 75-80 per cent of the population in the six 'Treatment' towns were surveyed by X-ray examination of their adult populations followed by sputum examinations by microscopy and culture of cases with radiological signs of pulmonary pathology. At the base-line survey of the 12 towns the coverage by X-ray and bacteriological examinations were for males 91.4 per cent, 87.5 per cent and for females 89.9 and 91.7 per cent respectively. The six 'Control' towns had no further surveys till five to six years later when they were resurveyed together with the six 'Treatment' towns at Survey III.

3. All proved bacillary cases of tuberculosis were offered treatment at home with isoniazid and the sodium salt of para-aminosalicylic acid (PAS) in3 towns and isoniazid alone in the other 3 towns. Drugs were issued for two weeks at fortnightly clinics over a period of 12 months. Of 1482 bacillary cases living in the 6 'Treatment' towns the mean degree of cooperation per town was as follows : patients accepting treatment 85 per cent of which 29 per cent defaulted prematurely and 56 per cent continued till the 12th month (although often irregularly). Among patients whose initial sputum examination was positive by microscopy, 90 per cent accepted, 27 per cent defaulted and 63 per cent continued till the end of the year while among patients who were initially sputum-negative by microscopy and positive by culture only 79 per cent accepted, 29 per cent defaulted and 50 per cent continued till the end of the year.

4. *Treatment results* : As Government tuberculosis clinics do not ordinarily have facilities for setting up culture they must rely upon microscopy, so the present material has been divided into two groups according to the method of sputum examination by which bacilli were found initially : sputum positive by microscopy or by culture only. The former group represents generally more advanced cases than those positive by culture only. At the end of the first year the cases initially positive by microscopy obtained 'negative sputum' in 47 per cent, 'positive sputum' in 41 and 12 per cent had died. The cases initially positive only by culture were negative in 62 per cent, positive in 32 and 6 per cent had died. Considering cases withi isoniazid-sensitive strains : (*a*) microscopically positive : TB—53 per cent, TB+ 37 per cent and died 10 per cent, (*b*) positive by culture only : TB—63 per cent, TB+31 per cent and died 6 per cent. Among patients with strains initially INH -resistant : (*a*) TB — 23 per cent, TB+ 55 per cent and died 23 per cent, and (*b*) 46, 41 and 13 per cent respectively.

5. *Treatment results in 'two-drugs' and one drug' towns* : In the towns where INH and PAS were issued the results were : TB—63 per cent, TB+29 per cent and died 8 per cent. In the other towns where iso- niazid only was

issued the results were 45, 44 aud 11 per cent, respectively.

6. *Five years' follow up* : Of 1449 cases (treated and untreated) at five years, 41 per cent had negatives putum, 18 per cent positive sputum and 40 per cent had died.

The prognosis was closely associated with the initial extent of disease : of 1154 treated cases, those with (*i*) small lesions : TB—69 per cent, TB+12 percent and died 19 per cent; (*ii*) limited lesions : 54, 22 and 24 per cent respectively : (*iii*) moderate lesions : 44, 25 and 32 per cent and (*iv*) extensive disease : 25, 17 and 58 per cent.

7. *Five years' follow up according to the sputum status at the end of the first year of treatment* : Of those who had obtained negative sputum at 12 months, five years later 66 per cent remained sputum negative, 16 per cent had become sputum positive and 18 per cent had died; of those who had positive sputum at 12 months, five years later 24 per cent had negative sputum, 20 per cent positive sputum and 56 per cent had died. A number of the cases who had positive sputum at one year and had isoniazid resistant bacilli had received second-line drugs.

8. *Mortality* : Deaths from all causes for the adult population (15 years and more) were 12.8 per 1000 (95 per cent fiducial limits 9.6-16.0). Deaths among tuberculous patients were 1.29 per 1000 (95 per cent fiducial limits 0.51—2.07).

9. *Pool of infectious cases* : All cases found to have excreted tubercle bacilli at least once in a calendar year constituted the 'pool' for that year. Excluding, in each year, those who had died or moved out, the Register consisted of all cases who had had or had bacillary tuberculosis. The TB-positive cases were sub-divided into (*a*) cases newly admitted 29 per cent, (*b*) cases admitted during the previous year 11.11 per cent and (*c*) cases admitted earlier than the previous year 19 per cent. The two groups (*b*) and (*c*) correspond to more than half the cases with positive sputum. These are cases of which the majority ought to have been sputum negative but remained positive as 'failure' cases of domiciliary drug therapy.

10. Of the sputum positive cases in the 'pool', 62 per cent had INH-sensitive strains and 38 per cent INH-resistant strains. The latter were found mainly in the groups (*b*) and (*c*) ; in fact, 76 per cent of all resistant strains were from 'old' cases.

11. *The 'pool of infectious cases' in 'INH-PAS' and 'INH-towns'* : The sputum-positive cases in the INH-PAS towns consisted of 69 per cent with INH-sensitive and 31 per cent with INH-resis tant bacilli. In the INH towns, cases with INH-sensitive strains were found in 55 per cent and cases with INH-resistant strains in 45 per cent.

12. *Prevalence surveys* : A second full survey of the six 'Treatment' towns was carried out during 1962-64 and a third survey during 1965-68 : Survey III included also the 6 'control' towns in which no action had been taken earlier except for the preliminary Sample Survey in 1959.

Results of the prevalence surveys : age-standardised mean prevalences of bacillary cases in the group with sputum microscopically positive were for Surveys I, II and III 6.81, 5.01, and 4.83 per 1000. The decrease from Survey I to Survey II and from Survey I to Survey III were statistically highly significant. The prevalence of bacillary tuberculosis among the cases with sputum negative by microscopy but positive by culture were 2.47 4.13 and 4.92 per 1000. The increase in this group (statistically not quite significant) is explained mainly by a major improvement in the culture technique introduced in 1964 during Survey II. The decrease observed among the microscopically positive cases is considered to represent a real decrease.

13. Comparing the mean changes in prevalence from Survey I to Survey II and from Survey I to Survey III in the three INH-PAS' towns with those in three 'INH' towns, it was found that none of the differences between such changes attained statistical significance.

14. *Prevalence of cases with resistant strains* : INH-resistant bacilli among 'all positives' showed at Surveys I, II and III rates of 1.71, 3.30 and 2.43 per 1000; the increase from Survey I to Survey II is statistically significant.

15. As all 12 towns had been surveyed in 1959 and again in 1965-68 it was possible to compare the mean changes in prevalence from 1959 to the 1965-68 survey in the 'treatment' and 'control' groups. The mean prevalence in the 6 'treatment' towns at the base-line Survey in 1959 among cases positive by microscopy was 5.92 per 1000 adults ; at the resurvey 1965-68, 4.78. The corresponding findings in the 6 'control' towns were 5.72 and 4.21.

Regarding cases 'initially positive by culture only' the prevalence in the 'Treatment' towns were 3.85 and 4.92 per 1000, and in the 'Control' towns 2.44 and 4.82.

Considering 'all positive cases' the findings were: 'Treatment Towns' 9.77 and 9.70, and in the 'Control Towns' 8.16 and 9.03.

16. A tuberculin sample survey was carried out in the 12 towns in 1966-69. In the age group 2-4 years the mean percentage of reactors in the 'treatment' towns was 9.6 and in the 'control' towns 4.5. In age group 5-9 it was 18.2 and 13.8, respectively. Neither contrast was statistically significant.

17. It is concluded that although there is evidence of a decrease in the prevalence of cases with isoniazid sensitive bacilli, and an increase of cases with isoniazid-resistant bacilli particularly in the towns where the treatment consisted only of isoniazid, the effect of the active case finding and treatment programme has not been able to produce any measurable change in the overall prevalence of tuberculosis between the 'treatment' group and the 'control' group.

The relatively unsatisfactory cooperation on the part of the patients in accepting the treatment, the limited effect of the drug regimens offered and the relatively short time allowed for the effect of the treatment programme to influence the prevalence and incidence may be the reasons for the absence of any clear difference between the 'Treatment' and 'Control' towns.

18. The observation of a decrease in the prevalence of tuberculosis from 1959 to 1968 among cases positive by microscopy is thought to reflect a general decrease of tuberculosis in the Indian community

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Statistical methods employed in analysing the findings of repeated population surveys for tuberculosis in a controlled study of the efficacy of domiciliary chemotherapy in 12 towns in south India

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In the paper entitled "A controlled study of the effect of a domiciliary tuberculosis chemotherapy programme in a rural community in south India", Frimodt-Moller, Acharyulu and Kesava Pillai (1981)[1] have described a controlled study of the efficacy of domiciliary chemotherapy in 12 towns in Madanapalle area, south India. This note describes the statistical methods employed for assessing the significance of (*a*) time trends in the prevalence of tuberculosis, and (*b*) the impact of a community treatment programme, with single or double-drug therapy.

Design of the study

A 20-25 per cent random sample survey was undertaken in 12 towns in the Madanapalle area, to estimate the prevalence of radiologically active or probably active tuberculosis, and the prevalence of bacillary tuberculosis, in persons aged 15 yr or more. Subsequently, 6 of the 12 towns, selected at random, were labelled as 'Treatment' towns. The remaining population in these towns (75-80%) was then surveyed and a treatment programme initiated for all cases of tuberculosis. The treatment consisted of isoniazid plus PAS in 3 towns (again, selected at random) and isoniazid alone in 3 towns. The remaining 6 towns were labelled as 'Control' towns and no special inputs were introduced to supplement the existing facilities.

The population survey was repeated twice in the 'Treatment towns', after approximately $2\frac{1}{2}$ and 7 yr. On the latter occasion, a population survey was also undertaken in the 'Control Towns.'

Changes in the prevalence of tuberculosis in the 6 Treatment towns

The basic data for each Treatment town consisted of the following items of information at each of 3 surveys, for 5 age-groups (15-24, 25-34, 35-44, 45-54 and 55 yr or more) and separately for the two sexes.

Population eligible	N_i	$i = 1, 2, 3, 4, 5$ corresponding to the 5 age-groups above
Population X-rayed	a_i	
No. selected for bacteriological examination (on the basis of X-ray evidence)	b_i	
No. examined bacteriologically	c_i	
No. positive bacteriologically	d_i	

d_1 could be the number of persons with (*i*) positive smear (*ii*) negative smear but positive culture (*iii*) positive result, on smear or culture or both.

Estimation of prevalence, and its variance, in the i^{th} age-group : Denoting $\frac{b_1}{a_1}$ by p_{1i} and $\frac{d_1}{c_1}$ by p_{2i}, the prevalence of tuberculosis in the i^{th} age group is given by $p_i = p_{1i} \times p_{2i}$, on the assumption that the eligible population that was not X-rayed and the eligible population that was not examined bacteriologically are random losses in coverage.

$$\text{Variance of } p_{1i} = \frac{b_1}{a_1}\left(1-\frac{b_1}{a_1}\right)\frac{1}{a_1}\left(1-\frac{a_1}{N_1}\right)$$

and

$$\text{Variance of } p_{2i} = \frac{d_1}{c_1}\left(1-\frac{d_1}{c_1}\right)\frac{1}{c_1}\left(1-\frac{c_1}{b_1}\right),$$

the last term in each expression being the finite population correction term.

$$\text{Variance of } p_i = p_{1i}^2 \text{ var } p_{2i} + p_{2i}^2 \text{ var } p_{1i} + 2\, p_{1i}\, p_{2i}\, r_i \sqrt{\text{var } p_{1i} \text{ var } p_{2i}}$$

where r_1 is the correlation coefficient between the values of p_{1i} and p_{2i} in the 6 towns. (This formula is valid if Var p_{1i} and Var p_{2i} are both relatively small in relation to p_{1i}^2 and p_{2i}^2, a condition that was satisfied by the present data). r_1 was determined for each age-group (after amalgamating the results of the 3 surveys), and found to be homogenous with respect to age. The pooled correlation coefficient (γ) was therefore substituted in the above equation.

These calculations, and indeed all subsequent ones, were undertaken separately for males and for females, and for the three types of positive bacteriological finding (see page 83).

Estimation of change in prevalence between two surveys, and its variance : Considering the combined population from the 3 surveys in a town as the Standard Population (N_i, i = 1 to 5 corresponding to the 5 age-groups) for that town and employing the Direct method of Standardisation (see Radhakrishna and Sutherland, 1962), age-standardised prevalences were computed for each of the 3 surveys ($\bar{P}1$, $\bar{P}2$, $\bar{P}3$).

$$\bar{P}_1 = \frac{\Sigma N_i P_{1i}}{N_i}, \quad \bar{P}_2 = \frac{\Sigma N_i P_{2i}}{N_i} \quad \text{and}$$

$$\bar{P}_3 = \frac{\Sigma N_i P_{3i}}{N_i},$$ where P_{ji} represents the prevalence in the j^{th} survey in the i^{th} age-group. Further, $d_{12} = \bar{P}_1 - \bar{P}_2 = \Sigma N_i(P_{1i} - P_{2i})/\Sigma N_i$, so that variance of $d_{12} = [\Sigma N_i^2(\text{Var } P_{1i} + \text{Var } P_{2i} - 2\, r_{12} \sqrt{\text{Var } P_{1i} \text{ Var } P_{2i}}]/(\Sigma N_i)^2$,

where r_{12} is the correlation coefficient between P_{1i} and P_{2i} (i = 1 to 5) in each town. In the event, the correlations in the 6 towns were homogenous, so that pooled value was used for all the towns.

Statistical significance of changes in prevalence between surveys : Let d_i denote the difference in the age-standardised prevalence between two surveys in town i (i=1 to 6), and σ_{ti}^2 its variance. The variation between the towns in the values of d_i (σ^2) may be considered as made up of two components, one the genuine variation between towns (σ_T^2) and the other the sampling variation within the same town (σ_t^2), i.e. $\sigma^2 = \sigma_T^2 + \sigma_t^2$ Taking the average value of σ_{ti}^2 in the

6 towns as an estimate of σ_t^2 and calculating σ^2 from the 6 values of d_i, σ_T^2 was estimated. The variance of the change in the prevalence in the i^{th} town (assuming that the towns are sampled from a universe of towns) is then given by $\sigma_T^2 + \sigma_{ti}^2$. Taking $\frac{1}{\sqrt{\sigma_T^2 + \sigma_{ti}^2}}$ as the weight (w_i) for d_i, the weighted mean $(\Sigma w_i d_i / \Sigma w_i)$ and its variance $\left\{\left[\frac{6}{\Sigma (w_i)^2}\right] \times [\text{variance between the 6 values of } w_i d_i]\right\}$ were computed, and the ratio of the former to the square root of the latter was tested as a t with 5 degrees of freedom.

Contrasts between 'Isoniazid plus PAS' towns (PH) and 'Isoniazid alone' towns (H)

Change in prevalence from one survey to another		*Variance of the change*	
PH towns	H towns	PH towns	H towns
d_{11}	d_{21}	σ^2_{t11}	σ^2_{t21}
d_{12}	d_{22}	σ^2_{t12}	σ^2_{t22}
d_{13}	d_{23}	σ^2_{t13}	σ^2_{t23}

Denoting the variance between towns allocated to the *same* regimen by σ^2 (4 degrees of freedom), we have $\sigma^2 = \sigma_T^2 + \sigma_t^2$, where σ_T^2 is the genuine variation between towns, and σ_t^2 the variance within towns due to sampling errors. As in above, σ_t^2 was estimated by $\sum_{ij} \sigma_{tij}^2/6$, and σ_T^2 was determined from the above equation. Taking the weight, w_{ij} for each d_{ij} as $\frac{1}{\sqrt{\sigma_T^2 + \sigma_{ti}^2}}$, a weighted one-way analysis of variance was then undertaken to determine the significance of the observed differences between the PH towns and the H towns.

Combining the findings in males and females in each town

If d_M denotes the changes in the prevalence from one survey to another in males and Var d_M its variance, and d_F and Var d_F are the corresponding estimates in females, the consolidated change in both sexes was taken as $\frac{k_M\ d_M + k_F\ d_F}{k_M + k_F}$, where k_M and k_F were the numbers in males and females in the Standard Population (obtained by pooling the numbers in the 3 surveys). Its variance is given by the expression

$$\frac{1}{(k_M + k_F)^2} \{k^2_M \text{ Var } d_M + k^2_F \text{ Var } d_F + 2\ k_M\ k_F\ \gamma_{MF} \sqrt{\text{Var } d_M \text{Var } d_F}\}$$

where γ_{MF} is the correlation between changes in prevalence in males and changes in prevalence in females, over the 5 age-groups. In the event, these correlations were homogenous for the 6 towns, so that the pooled correlation coefficient was computed and used for all the towns.

For assessing the significance of changes from survey to survey and for examining the contrasts between PH and H towns, the procedures described in the two preceding sections were again employed.

Comparison of the 6 Treatment towns with the 6 Control towns

In all 12 towns (6 Treatment, 6 Control), a base-line survey was undertaken on an approximately 20-25 per cent random sample of the population. Denoting by p_i the proportion selected for

bacteriological examination among those X-rayed, and by p_2 the proportion with a positive result among those examined bacteriologically (all age-groups were amalgamated, in view of the smallness of numbers in individual age-groups),

Prevalence of bacillary tuberculosis

$$= p_1 p_2$$

Its variance $= p_1^2 \text{ Var } p_2 + p_2^2 \text{ Var } p_1$

A complete survey was undertaken several years later in all the 12 towns. For each town, the prevalence in the i^{th} age-group, P_i, and its variance were calculated along the lines described on page 84; the pooled correlation coefficient, however, was calculated separately for the Treatment towns and the Control towns. The overall prevalence for the town was then computed as $\Sigma N_i P_i / \Sigma N_i$ and its variance as $\frac{\Sigma N_i^2 \text{ Var } P_i}{(\Sigma N_i)^2}$ where N_i was the resurvey population in the i^{th} age-group in that town.

The difference in prevalence between the two surveys was next obtained, and its variances computed as the sum of the variances of the two separate prevalences. A weighted one-way analysis of variance was then undertaken to compare the mean change in the Treatment towns with that in the Control towns, along the same lines as the comparison between the PH towns and the H towns described earlier.

Both in the base-line survey and in the resurvey, the findings in males and females were combined by taking a weighted average, the weights being the numbers of males and females in the concerned survey. (In the case of the resurvey, the variance of the weighted mean included a covariance term, for determining which the correlation coefficient between the prevalence in males and the prevalence in females (over 5 age-groups) in the re-survey had to be computed). The difference between the surveys was next obtained, and its variance computed as the sum of the two separate variances. A weighted one-way analysis of variance was then undertaken as above.

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