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Attack Rate of Tuberculosis in a 5-Year Period Among Close Family Contacts of Tuberculous Patients under Domiciliary Treatment with Isoniazid plus PAS or Isoniazid Alone*

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This report from the Tuberculosis Chemotherapy Centre, Madras, considers the risk, over a 5-year period, to close family contacts of sputum-positive patients treated at home for 1 year with a standard regimen of isoniazid plus PAS or one of 3 regimens of isoniazid alone. The attack rate of tuberculosis in the contacts did not appear to be influenced by the treatment received by the patients in the first year or by the duration in the S-year period for which the patients had (1) positive sputum smears, (2) positive cultures, or (3) isoniazid-resistant cultures. Further, over half the cases of tuberculosis developed in the first year, many of these being in the first 3 months. These findings confirm the conclusions reached from an earlier study, namely, that the major risk to the contacts is from exposure to the infectious patient before diagnosis, and that the risks from the other possible sources of infection (the patient during treatment and the urban environment of Madras) are, in comparison, small.

A previous report from this Centre (Kamat et al., 1966) presented information on the attack rate of tuberculosis among close family contacts of newly diagnosed infectious patients who were treated for 1 year with a standard regimen of isoniazid plus PAS, either at home or in sanatorium. Over a 5-year period of follow-up, there was no evidence of any special risk to the contacts resulting from the treatment of patients at home as compared with the isolation of patients in sanatorium for a year, the major risk in both series having occurred from exposure to the patients *before* the diagnosis was made. and the treatment commenced.

Another report from this Centre (Ramakrishnan et al., 1961b) presented information on the risk of contracting tuberculosis over a 1-year period among a further group of close family contacts of infectious patients, all of the patients having been treated at home with a standard regimen of isoniazid plus PAS or one of 3 regimens of isoniazid alone. Although the 4 regimens differed widely in the proportions of patients that they rendered non-infectious (Tuberculosis Chemotherapy Centre, Madras, 1960), they did not influence the attack rates in the 4 series of contacts in the first year. The present report describes the findings over a 5-year period of follow-up, and considers the relative importance of the 3 sources of infection to the contacts-namely, (1) the urban environment of Madras; (2) the patient before diagnosis; and (3) the patient during treatment and, in particular, the risk to the contacts from prolonged exposure to patients with isoniazid-resistant cultures, The contacts in the present study came from the same community as those in the earlier study (Kamat et al., 1966), the families living in poverty-stricken and overcrowded conditions (Tuberculosis Chemotherapy Centre, Madras, 1959; Andrews et al., 1960; Ramakrishnan et al., 1966).

DEFINITIONS

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

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[1] Deceased.

Close family contacts were defined as those persons who were related to the index case by blood or by marriage, and who had been living in the same hut or house and using the same kitchen as the index case for at least the 3 months immediately preceding the start of treatment (or from birth, in the case of infants less than 3 months of age).

TREATMENT AND PROGRESS OF THE INDEX CASES DURING THE 5-YEAR PERIOD

The index cases, all of whom had positive sputum cultures on admission (and almost always positive smears as well), had been allocated at random to one of 4 chemotherapeutic regimens for the first year. The regimens and the dosage schedules (which depended on the body-weight) have been fully described in a previous report (Tuberculosis Chemotherapy Centre, Madras, 1960). For patients weighing 100 lb (45.4 kg), the details were as follows:

Regimen	*Drugs and daily dosages*
PH	200 mg of isoniazid plus 10 g of sodium PAS, given together in cachets in 2, divided, doses
HI-1	400 mg of isoniazid in a single dose
HI-2	400 mg of isoniazid in 2, divided, doses
H	200 mg of isoniazid in 2, divided, doses

The mean daily dosage of isoniazid at the start of chemotherapy was 4.6 mg/kg of body-weight for the PH series, 8.7 mg/kg for the HI-l and the HI-2 series and 4.5 mg/kg for the H series. The mean daily dosage of PAS (for the PH series) was 0.23 g/kg.

Treatment was changed during the first year if there was definite radiographic deterioration or serious clinical deterioration or major drug toxicity, the reserve regimens employed being streptomycin plus pyrazinamide (SZ) or streptomycin plus PAS (SP), followed, if necessary, by cycloserine plus ethionamide (CE) or cycloserine plus thioacetazone (CT).

Of the patients with bacteriologically quiescent disease at 1 year, about a quarter (selected at random) was prescribed maintenance chemotherapy with isoniazid alone until the end of the third year and another quarter (also selected at random) until the end of the second year, while the rest were not prescribed any further chemotherapy. Patients with a clear-cut bacteriological relapse in the second or subsequent years were re-treated with the PH regimen if the cultures at that time were isoniazid-sensitive; if, however, the cultures were isoniazid-resistant, the patients were treated with the SZ or the SP regimen followed, if necessary, by the CE or the CT regimen.

Patients who had bacteriologically active disease at 1 year continued to receive the *initially* allocated chemotherapy in the second year unless a definite radiographic deterioration occurred. If it did, or if the patient still had bacteriologically active disease at the end of 2 years, treatment was changed as above.

Another report (Evans et al., 1969) has described the progress of the patients (index cases) over a 5-year period. The mean duration of infectivity, as assessed by *smear* positivity (based on monthly examinations in the first 2 years and 3-monthly examinations subsequently), was 4.1 months for the PH patients, 5.4 months for the HI-1, 7.7 months for the HI-2 and 9.5 months for the H patients. The corresponding averages for infectivity as assessed by *culture* positivity were 6.8, 7.9, 11.0 and 13.6 months.

PLAN AND CONDUCT OF THE CONTACT STUDY

The plan of the contact study and the procedures employed have been described earlier (Ramakrishnan et al., 1961b) and are only briefly summarized in this report.

It must be emphasized that at no stage of the study was BCG or chemoprophylaxis used. However, as described below, all contacts were followed by an intensive routine of supervision.

Initial examination

Each contact had the following investigations initially:

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

(2) An intracutaneous tuberculin (Mantoux) test on the left forearm with 5 tuberculin units (5-TU test) of a purified protein derivative in 0.1 ml of solution, batch RT 22 without Tween 80 (Magnusson et al., 1958) being used. The greatest diameter of palpable induration after 2 or 3 (occasionally 4) days was recorded.

Follow-up examinations

A radiograph was taken at 3-monthly intervals in the first year and at 6-monthly intervals in the subsequent 4 years. In the early stages of the study, a 5-TU test was undertaken at 3-monthly intervals during the first year and at 6-monthIy intervals

thereafter, provided the induration resulting from every one of the previous tests had been less than 20 mm. Subsequently, tests were performed annually for all contacts, irrespective of the results of the previous tests.

In addition to the set examinations, contacts were frequently observed during the regular home visits by health visitors and, if ill, were encouraged to attend the Centre; at such attendances, extra radiographic examinations and tuberculin tests were undertaken if the physicians considered them necessary. If a radiographic abnormality appeared at *any* examination, a culture of at least 1 overnight sputum specimen or a pair of laryngeal swabs was set up, and a radiograph was taken about a month later. Contacts showing changes in tuberculin sensitivity suggesting a recent infection had a radiograph taken 4-6 weeks later.

Specific antituberculosis chemotherapy

Chemotherapy was not usually started unless bacteriological confirmation of tuberculosis was obtained. However, exceptions were made for infants and young children who were clinically ill, or where lesions were large, disseminated or showed rapid progression.

Independent assessment of the findings

An independent assessor, Dr J. Frimodt-Møller, made the assessments for the attack rates of tuberculosis in the second, third, fourth and fifth years, adopting the procedures he had followed for the earlier 5-year study (Kamat et al., 1966) and the first year of the present study (Ramakrishnan et al., 1961b). He was unaware throughout of the chemotherapeutic regimen or the bacteriological or radiographic progress of individual index cases.

For the current assessment, Dr Frimodt-Møller was shown the radiographs taken at the initial examination and at 1 year, together with *all* the radiographs taken in the second, third, fourth and fifth years. He first classified each series as normal or abnormal. For the latter, he reviewed the *full* radiographic series over the 5-year period, and reclassified them as follows: (1) normal; (2) non-tuberculous abnormality; (3) doubtfully tuberculous abnormality; (4) active tuberculosis.

Next, the independent assessor reviewed the full radiographic series of certain groups of contacts, selected (as in Kamat et al. (1966)) in the light of relevant bacteriological, clinical and pathological data in the second, third, fourth and fifth years, and modified in a few instances the classification he had previously made on the basis of radiography alone.

RESULTS

Population under study

In all, 1109 close family contacts were admitted to the study. However, 234 were excluded from the comparisons of the attack rates of tuberculosis in the 4 series–namely, (1) 27 contacts with no initial radiograph; (2) 2 contacts who received antituberculosis chemotherapy during the period of follow-up but for whom, in the independent assessor's opinion, there was inadequate evidence on which to make a diagnosis of active tuberculosis; (3) 121 [1] contacts who had an *initial* abnormality classified as active tuberculosis, tuberculosis of doubtful activity, inactive tuberculosis or a doubtfully tuberculous abnormality (and who could not therefore contribute to the attack rate); (4) 84 contacts with at least 1 other infectious (culture-positive) member in the family at the outset of the study (this last group was excluded because it was considered desirable to make as pure a comparison as possible between the 4 series of contacts in terms of exposure to infectious tuberculosis).

After all these exclusions, there remain 875 [1] close family contacts from 291 [1] families–228 from 81 PH, 212 from 66 HI-1, 210 from 65 HI-2 and 225 from 79 H families.

Comparability of the 4 series

The 4 series of contacts were similar on admission to the study in respect of age, sex, family size and the results of radiographic examinations (apart from calcification) and tuberculin testing, as shown in the earlier report (Ramakrishnan et al., 1961b).

Considering next the investigations during the 5-year period of follow-up, the coverage was very high in all 4 series at all the set radiographic examinations (Table 1), and particularly so at the end of each year (range 95 %-100 %) when special efforts were made to obtain a radiograph. Table 2 shows the average numbers of radiographs, tuberculin tests and culture examinations undertaken each year,

[1] This number is slightly different from that given in the earlier report (Ramakrishnan et al., 1961b). on account of changes in the values for the initial prevalence of tuberculosis resulting from the more extensive information available to the independent assessor. The revised findings are: active tuberculosis, 8.1%; tuberculosis of doubtful activity, 0.3 %; inactive tuberculosis, 1.8 %; doubtfully tuberculous abnormality, 0.9 %.

TABLE 1
PERCENTAGES OF CONTACTS WITH RADIOGRAPHS TAKEN AT SET EXAMINATIONS DURING THE B-YEAR PERIOD

Year	Months admission to study	Percentage of contacts who were radiographed [a]			
		PH	HI-1	HI-2	H
First	3	94	94	92	95
	6	93	93	94	91
	9	94	90	91	87
	12	97	96	95	95
Second	18	95	94	96	94
	24	100	98	96	98
Third	30	98	97	97	95
	36	100	99	96	99
Fourth	42	97	96	97	95
	48	98	98	96	95
Fifth	54	94	93	89	89
	60	97	97	96	99
Mean		96	95	95	94
Number of contacts in the comparison		228	212	210	225

[a] Based on the number of surviving contacts from the population at risk for the year.

whether at the set examinations or at additional examinations. The intensity of investigation by radiography and tuberculin testing was similar in the 4 series. However, the intensity of culture examination was higher in the PH contacts.

Attack rate of tuberculosis

Table 3 presents the cases of tuberculosis, year by year, in the 4 series of contacts, according to whether the induration from the 5-TU test *on admission* was 0 mm–4 mm (tuberculin-negative) or 5 mm or more (tuberculin-positive). The criterion for the division of contacts into tuberculin-negative and tuberculin-positive was based on the distributions of tuberculin-test results at this Centre in sputum-positive index cases and their close family contacts on admission to study (Andrews et al., 1960; Ramakrishnan et al., 1961b).

Of the total of 233 initially tuberculin-negative contacts in the 4 series combined, 32 (13.7 %) developed tuberculosis in the 5-year period. Of these, 17 developed the disease in the first year, including 10 in the first 3 months. Considering the individual series, the proportions who developed tuberculosis were 19% of 73 PH, 17% of 53 HI-1, 8% of 53 HI-2 and 9% of 54 H contacts; none of these differences was statistically significant ($P > 0.1$).

Of the 618 initially tuberculin-positive contacts in the 4 series combined, 42 (6.8%) developed tuberculosis in the 5-year period. Of these, 23 developed the disease in the first year, including 8 in the first 3 months. Considering the individual series, the

TABLE 2
INTENSITY OF EXAMINATION OF THE CONTACTS DURING THE I-YEAR PERIOD

Year	Average number of radiographs [a]				Average number of 5-TU tests [a]				Contacts with 1 or more cultures [b]							
									Expressed as a percentage of total contacts				Average number of cultures			
	PH	HI-1	HI-2	H	PH	HI-1	HI-2	H	PH	HI-1	HI-2	H	PH	HI-1	HI-2	H
First	4.4	4.2	4.3	4.2	2.7	2.6	2.5	2.7	30	30	25	28	3.6	3.0	2.9	2.6
Second	2.4	2.3	2.2	2.2	1.0	1.1	1.1	1.2	20	18	11	11	2.7	2.3	2.3	2.4
Third	2.3	2.2	2.2	2.2	1.0	0.9	0.9	0.9	15	11	9	11	2.2	1.8	2.8	3.4
Fourth	2.1	2.0	2.1	2.1	0.8	0.8	0.8	0.9	8	6	6	6	2.8	2.3	2.2	2.4
Fifth	2.0	2.0	2.0	1.9	0.9	0.9	0.9	0.9	6	3	3	5	3.5	2.8	2.8	3.1
S-year period	13.2	12.7	12.8	12.6	6.4	6.3	6.2	6.6	47	44	37	38	4.8	3.8	3.7	4.1

[a] Excluding the examination on admission to study and, for contacts admitted to treatment, examinations undertaken at or after the start of treatment.

[b] For contacts admitted to treatment, examinations undertaken at or after the start of treatment have been excluded.

TABLE 3
CASES OF ACTIVE TUBERCULOSIS DURING THE 5-YEAR PERIOD ACCORDING TO TUBERCULIN SENSITIVITY ON ADMISSION [a]

Diameter (mm) of induration from 5-TU test on admission	Contact series	Total no. of contacts	Contacts who developed tuberculosis in:									
			First year				Second year	Third year	Fourth year	Fifth year	Total for 5-year period	
			1–3 months	4–12 months	Total No.	Total %					No.	%
0–4 (tuberculin-negative)	PH	73	3	4	7	*10*	3	4	0	0	14	*19*
	HI-1	53	4	2	6	*11*	0	0	2	1	9	*17*
	HI-2	53	2	1	3	*6*	0	1	0	0	4	*8*
	H	54	1	0	1	*2*	3	0	0	1	5	*9*
	All series	233	10	7	17	*7.3*	6	5	2	2	32	*13.7*
5 or more (tuberculin-positive)	PH	150	1	5	6	*4*	2	1	0	I	10	*7*
	HI-1	153	1	5	6	*4*	3	1	0	0	10	*7*
	HI-2	151	3	3	6	*4*	3	1	1	1	12	*8*
	H	164	3	2	5	*3*	2	2	1	0	10	*6*
	All series	618	8	15	23	*3.7*	10	5	2	2	42	*6.8*

[a] There were 24 contacts (5 PH, 6 HI-1, 6 HI-2, 7 H) with no initial 5-TU test result: of these, 3 developed tuberculosis, 1 (HI-1) in the second year and 2 (both PH) in the third year.

attack rates were very similar, namely, 7 % of 150 PH, 7% of 153 HI-1, 8% of 151 HI-2 and 6% of 164 H contacts.

Further analyses showed that the substantial difference in attack rates between the initially tuberculin-negative and the initially tuberculin-positive contacts (13.7% as compared with 6.8%) was due largely to the fact that the proportion of contacts aged less than 5 years (a very vulnerable group) was considerably higher in the former category (see page 343).

Forms of tuberculous lesions

Table 4 sets out the forms of the tuberculous lesions in 77 contacts who developed tuberculosis during the 5-year period (including 3 who did not have a tuberculin test result on admission). In all, 67 cases (22 PH, 18 HI-1, 13 HI-2, 14 H) were classified as having primary or post-primary type disease and the remaining 10 (4 PH, 2 HI-1, 3 HI-2, 1 H) as having adult-type disease.

Three contacts developed grave tuberculous lesions. One *initially tuberculin-negative* contact (H, aged 3 years) developed tuberculous meningitis in the 19th month (the index case had all sputum smears negative from the 2nd month onwards and all cultures negative from the 4th month onwards), and 2 *initially tuberculin-positive* contacts (1 HI-l aged 17 years, 1 H aged 2 months) developed miliary tuberculosis (with a positive culture) in the 22nd and the 1st month, respectively. All 3 contacts were successfully treated with antituberculosis drugs.

Results of bacteriological examinations

Cultures were set up from sputum specimens or laryngeal swabs for 70 (22 PH, 20 HI-1, 15 HI-2, 13 H) of the 77 contacts who developed tuberculosis during the 5-year period, and were positive on at least 1 occasion in 29 (11 PH, 7 HI-1, 6 HI-2, 5 H). Tests of sensitivity to isoniazid and streptomycin were undertaken on the first positive culture for 27 contacts, and to streptomycin alone in 1; none of these contacts had received antituberculosis drugs up to this time. The cultures were sensitive to both drugs in 19 (7 PH, 4 HI-1, 5 HI-2, 3 H), isoniazid-sensitive but streptomycin-resistant in 1 (H), isoniazid-resistant but streptomycin-sensitive in 3 (1 PH, 1 HI-1, 1 HI-2) and resistant to both the drugs in 4 (3 PH, 1 HI-1). The 28th contact (HI-1) had a streptomycin-sensitive culture.

TABLE 4
FORMS OF TUBERCULOUS LESIONS DEVELOPING DURING THE C-YEAR PERIOD

Contact series	Total no. of contacts with active tuberculous lesions	Adult-type disease	Primary or post-primary type disease	Form of primary or post-primary type disease					
				Tuber-culous meningitis	Miliary pulmonary tuberculosis	Pleural effusion	Pro-gressive primary	Simple primary	Other
PH	26	4	22	0	0	3	13	5	1 [a]
HI-1	20	2	18	0	1	1	10	5	1 [b]
HI-2	16	3	13	0	0	1 [c]	7	4	1 [d]
H	15	1	14	1	1	2	5	3	2 [e]
All series	77	10	67	1	2	7	35	17	5

[a] Abnormal radiographic series, classified as pneumonia by the independent assessor; however, the contact produced 2 positive cultures.
[b] Normal radiographic series and 2 positive cultures.
[c] With a progressive primary complex.
[d] Normal radiographic series and 1 positive culture.
[e] One had enlarged hilar glands and a lung lesion, and a calcified focus in the other lung on admission; the other had a normal radiographic series and 1 positive culture.

Attack rate of tuberculosis in relation to age, sex and tuberculin sensitivity on admission

Table 5 relates the attack rate of tuberculosis during the 5-year period to the age of the contacts on admission to the study. Amalgamating all the 4 series (as there were no important differences in attack rates between them), the attack rate was very high in contacts aged less than 5 years [1]– namely, 20% of 147–as compared with 7% of 728 in contacts aged 5 years or more, a highly significant difference ($P<0.001$). Among the latter contacts, the attack rates were broadly similar in the 5-14 years, 15-24 years, 25-34 years, 35-44 years and 45 years or more age-groups.

Further analyses (not tabulated here) showed that, among contacts aged less than 5 years, 20% of 59 males developed tuberculosis as compared with 19% of 88 females. The corresponding proportions in those aged 5 years or more were 6% of 320 and 7 % of 408. Thus, there was little difference between the sexes in the attack rates over the 5-year period.

Table 6 presents the attack rate of tuberculosis during the 5-year period according to the age and tuberculin sensitivity *on admission.* Considering first the contacts aged less than 5 years, the attack rate

TABLE 5
ATTACK RATE OF TUBERCULOSIS DURING THE 5-YEAR PERIOD ACCORDING TO AGE ON ADMISSION

Age on admission (years)	Total contacts	Contacts who developed tuberculosis	
		No.	%
Less than 5	147	29	*20*
5-14	254	21	*8*
15-24	147	11	*7*
25-34	120	5	*4*
35-44	107	6	*6*
45 or more	100	5	*5*
Total	375	77	*8.8*

was 18 % of 110 for those with an induration of 0 mm–4 mm (tuberculin-negative) as compared with 23 % of 35 for those with an induration of 5 mm or more (tuberculin-positive); this is a non-significant difference ($P = 0.7$). The corresponding proportions for contacts aged 5 years or more were 10% of 123 and 6% of 583, respectively, again a non-significant difference ($P=0.2$). Thus, in neither of the age-groups was there any association between tuberculin sensitivity on admission to the study and the attack rate of tuberculosis. However, when both age-groups were combined, the attack rate in the tuberculin-

[1] The proportions of contacts aged less than 5 years were similar in the 4 series, both among the initially tuberculin-negative and the initially tuberculin-positive contacts.

TABLE 6
ATTACK RATE OF TUBERCULOSIS DURING THE I-YEAR PERIOD ACCORDING TO AGE AND TUBERCULIN SENSITIVITY ON ADMISSION [a]

Age on admission (years)	0 mm-4 mm induration from 5-TU test on admission (tuberculin-negative)			5mm or more induration from 5-TU test on admission (tuberculin-positive)		
	Total no. of contacts	Contacts who developed tuberculosis		Total no. of contacts	Contacts who developed tuberculosis	
		No.	%		No.	%
Less than 5	110	20	*18*	35	8	*23*
5 or more	123	12	*10*	583	34	*6*
Total	233	32	*13.7*	618	42	*6.8*

[a] Excluding 24 contacts who did not have a 5-TU test result on admission.

negative contacts (13.7%) was twice as high as that in the tuberculin-positive contacts (6.8 %); this difference is due largely to the fact that the proportion of contacts aged less than 5 years, a very vulnerable group (see above), was considerably higher in the former (47 %) than in the latter (6 %).

Attack rate of tuberculosis in contacts related to bacteriological findings in index cases

Table 7 relates the attack rates of tuberculosis in the 4 contact series to the bacteriological findings in the corresponding index cases *after the start of treatment.* There were substantial differences between the 4 contact series in the mean durations of exposure to index cases with (1) positive sputum smears, (2) positive cultures and (3) isoniazid-resistant cultures (the mean durations of exposure to index cases with isoniazid-sensitive cultures were low and similar in the 4 series). However, there was no evidence that these differences were associated with the attack rates. For instance, among initially tuberculin-negative contacts, the attack rates were similar in the PH and the HI-1 series, even though the mean durations of exposure for the latter were about 2 or 3 times as high as those for the former; again, although the mean durations of exposure for the HI-2 and the H contacts were broadly similar to those for the HI-1 contacts, the attack rates in the HI-1 contacts were about twice as high.

In Table 8, the influence of bacteriological findings in the index cases (after the start of treatment) on the development of tuberculosis in the contacts is analysed more directly. The findings are presented separately for the initially tuberculin-negative and for the initially tuberculin-positive contacts, but amalgamating the 4 series (PH, HI-1, HI-2 and H) as there were no statistically significant differences between them in the attack rates. Again, there was no evidence that longer exposures to patients with (1) positive sputum smears, (2) positive cultures or (3) isoniazid-resistant cultures had resulted in higher

TABLE 7
ATTACK RATES OF TUBERCULOSIS IN THE 4 CONTACT SERIES RELATED TO BACTERIOLOGICAL FINDINGS IN INDEX CASES DURING THE 5-YEAR PERIOD[a]

Diameter (mm) of induration from 5-TU test on admission	Contact series	Total no. of contacts	Attack rate of tuberculosis (%)	Mean duration of exposure (months) to index cases with:			
				Positive smears	Positive cultures	Isoniazid-sensitive cultures	Isoniazid-resistant cultures
0–4 (tuberculin-negative)	PH	73	*19*	2.3	4.7	2.3	2.4
	HI-1	53	*17*	5.7	9.1	2.2	6.9
	HI-2	53	*8*	6.2	9.8	1.8	8.0
	H	54	*9*	5.1	8.8	2.4	6.4
5 or more (tuberculin-positive)	PH	150	*7*	3.0	5.1	2.5	2.6
	HI-1	153	*7*	5.0	7.4	2.0	5.4
	HI-2	151	*8*	7.9	11.1	1.6	9.5
	H	164	*6*	8.6	12.5	2.1	10.4

[a] For contacts who developed tuberculosis or died, the bacteriological findings in the index cases have been consideredup to the time of diagnosis or death.

TABLE 8

ATTACK RATE OF TUBERCULOSIS IN CONTACTS RELATED TO DURATION OF EXPOSURE TO INDEX CASES WITH POSITIVE SMEARS, POSITIVE CULTURES AND ISONIAZID-RESISTANT CULTURES DURING THE 5-YEAR PERIOD

Bacteriological state of index case	Duration of exposure (months)	0 mm-4 mm induration from 5-TU test on admission (tuberculin-negative)			5 mm or more induration from 5-TU test on admission (tuberculin-positive)		
		Total no. of contacts	Contacts who developed tuberculosis		Total no. of contacts	Contacts who developed tuberculosis	
			No.	%		No.	%
Smear-positive	Nil	16	3	*(19)* [a]	35	2	*6*
	Under 3	151	25	*17*	333	24	*7*
	3–	30	0	*0*	138	10	*7*
	12-60	36	4	*11*	112	6	*5*
Culture-positive	Under 3	118	21	*18*	262	20	*8*
	3–	67	7	*10*	196	14	*7*
	12-60	48	4	*8*	160	8	*5*
Isoniazid-resistant	Nil	137	24	*18*	322	24	*8*
	Under 3	24	1	*(4)* [a]	39	2	*5*
	3-	29	3	*10*	110	9	*8*
	12-60	43	4	*9*	147	7	*5*

[a] Parentheses indicate that the percentage is based on fewer than 25 observations.

attack rates. Similar analyses (not tabulated here) relating the durations of exposure in the first year and in the first 2 years to the attack rates in the 5-year period were undertaken and yielded the same conclusion. (As the duration of exposure to index cases with isoniazid-sensitive cultures was less than 6 months for over 95% of the contacts, there was little scope for studying the influence of this duration on the attack rate of tuberculosis.)

Relationship between isoniazid sensitivity test results of contacts and index cases

Table 9 relates the isoniazid sensitivity of the first positive culture isolated from the contacts to the results of isoniazid sensitivity tests on cultures produced by the corresponding index cases up to the time of diagnosis of tuberculosis in the contacts. Considering the initially tuberculin-negative contacts, the first positive culture was isoniazid-sensitive for 7 contacts. Of these, 5 had been exposed only to isoniazid-sensitive cultures from their index cases. A sixth had a tuberculin conversion (as defined on p. 345) and a radiographic abnormality at 18 months, and produced a positive culture at 25 months; her index case had had isoniazid-sensitive cultures on admission, and negative cultures persistently from the 1st month onwards, apart from a single positive culture (isoniazid-resistant) at 7 months. The seventh contact had a tuberculin conversion at 12 months, a radiographic abnormality at 19 months and a positive culture at 21 months; her index case had had isoniazid-sensitive cultures on admission, but had persistently produced isoniazid-resistant cultures between 2 and 17 months.

Considering next the 2 initially tuberculin-negative contacts with an isoniazid-resistant infection, one had an index case who had produced only isoniazid-sensitive cultures. The other had an index case who had isoniazid-sensitive cultures on admission but repeatedly produced isoniazid-resistant cultures for 14 months prior to the appearance of the radiographic abnormality in the contact, a finding which

TABLE 9

ISONIAZID SENSITIVITY TEST RESULTS OF CONTACTS RELATED TO THOSE OF CORRESPONDING INDEX CASES [a]

Contacts			Index cases		
Diameter (mm) of induration from 5-TU test on admission	Isoniazid sensitivlty of first positive culture	No.	Isoniazid sensitivity during the period of exposure of the contacts		
			Sensitive only	Sensitive and resistant	Resistant only
0–4 (tuberculin-negative)	Sensitive	7	5	2	0
	Resistant	2	1	1	0
5 or more (tuberculin-positive)	Sensitive	12	7	3	2
	Resistant	5	2	2	1

[a] Excluding 1 contact (isoniazid-sensitive) with no 5-TU test on admission: the index case had produced only isoniazid-sensitive cultures

suggests that the contact was, in all probability, infected by the index case during the latter's treatment.[1]

Finally, considering the initially tuberculin-positive contacts, 12 had isoniazid-sensitive infections and 5 had isoniazid-resistant infections. Assuming that the infections had occurred *before* the diagnosis of the index cases, the findings suggest that of the 5 contacts with a resistant infection, only one is likely to have been infected by the index case,[1] who, in this instance, had primary isoniazid resistance on admission to the study.

Doubtfully tuberculous or non-tuberculous pulmonary lesions

The independent assessor classified 8 contacts (I PH, 1 HI-1, 2 HI-2, 4 H) as having developed a doubtfully tuberculous abnormality during the 5-year period, 1 (HI-2) in the first year, 2 (1 PH, 1 H) in the second, 2 (1 HI-1, 1 H) in the third, 2 (1 HI-2, 1 H) in the fourth and 1 (H) in the fifth year. Of these, 4 (1 in each series) were initially tuberculin-negative; a tuberculin conversion (as defined below) occurred before the development of the radiographic abnormality in 2 of them, 1 (PH) aged 4 years and the other (H) aged 23 years.

One or more non-tuberculous radiographic abnormalities during the 5-year period were reported in 76 contacts, namely, 31 (14%) PH, 20 (9 %) HI-1, 12 (6%) HI-2 and 13 (6 %) H contacts.

[1] The findings of streptomycin sensitivity tests (not presented here) support this conclusion.

Changes in tuberculin sensitivity

Among the initially tuberculin-negative contacts (that is, contacts with an induration of 0 mm-4 mm resulting from the 5-TU test on admission), 56% of 73 PH, 43 % of 53 HI-1, 58 % of 53 HI-2 and 52% of 54 H showed a tuberculin conversion, i.e., an *increase* in induration of at least 10 mm at *any* subsequent 5-TU test in the 5-year period. None of the differences between the series was significant ($P \geq 0.2$).

Over the 5-year period, the mean induration for the initially tuberculin-negative contacts increased by 5.8 mm in the PH series, 5.6 mm in the HI-1, 5.0 mm in the HI-2 and 4.3 mm in the H series; again, none of the differences was significant ($P \geq 0.3$).

Deaths

In all, 32 contacts died during the 5-year period– namely, 11 (5 %) of 228 PH, 9 (4%) of 212 HI-1, 6 (3 %) of 210 HI-2 and 6 (3 %) of 225 H contacts. An autopsy was not performed on any of them. Indeed, many of them had not been seen by the Centre's physicians during the terminal illness, and consequently the clinical details often had to he obtained from relatives and were seldom complete. In these circumstances, and in the conditions that prevail in Madras, it is very difficult to be sure of the cause of death; however, considering all the available evidence (radiographic, bacteriological and clinical, including the results of tuberculin tests), the independent assessor did not regard any of the deaths as definitely due to tuberculosis.

Of the 32 contacts who died, 14 (5 PH, 3 HI-1, 3 HI-2, 3 H) were initially tuberculin-negative. The results of subsequent 5-TU tests in these contacts are obviously of interest. Of the 14 contacts, 5 (2 PH, 1 HI-1, 2 HI-2) were under 1 year of age on admission and had no induration from the 5-TU test on admission, or indeed from the last test before death (apart from 1 contact who had a l-mm induration). Seven contacts (2 PH, 2 HI-1, 1 HI-2, 2 H) were aged between 1 and 5 years; of these, 2 (both PH, and with no induration from the 5-TU test on admission) were tuberculin-positive at the last test before death, the indurations being 10 mm and 28 mm, respectively. The 2 remaining contacts (1 PH, 1 H) were aged 38 and 30 years; both were tuberculin-positive at the last test, the indurations being 9 mm and 11 mm, respectively.

Of the 14 initially tuberculin-negative contacts who died, 1 (PH), aged 1½ years on admission, had developed tuberculosis (an intrapulmonary primary lesion) in the 3rd month, which was associated with a positive culture; the lesion had regressed without chemotherapy but the contact died of gastroenteritis in the 13th month. Of the 18 initially tuberculin-positive contacts who died, 1 (PH), aged 45 years, had developed tuberculosis (a pulmonary infiltration) at 36 months which persisted, and died of an undiagnosed illness in the 60th month; no sputum specimens from this contact were examined.

Births

There were 61 births in the PH families, 57 in the HI-1, 57 in the HI-2 and 56 in the H families during the 5-year period, of whom 8 (13 %) PH, 11 (19 %) HI-1, 8 (14%) HI-2 and 10 (18%) H died-very similar rates. On the available evidence, which was rather limited (page 345), the independent assessor did not regard any of these deaths as definitely due to tuberculosis.

Of the contacts who died, 1 (HI-2), born in the 11th month, had developed tuberculosis with a positive culture at 36 months; the lesion resolved without chemotherapy but the contact died of gastroenteritis in the 56th month. Two others (1 HI-1, 1 HI-2) were tuberculin-positive at the last test before death (the indurations being 14 mm and 6 mm), but they had no radiographic abnormality; they died of gastroenteritis and typhoid fever, respectively. The index cases of all 3 contacts had become culture-negative before the contacts were born, and continued to be culture-negative.

Of the contacts surviving at 5 years, 3 (1 PH, 2 HI-1) had developed primary tuberculosis and 4 (1 PH, 2 HI-1, 1 H) had developed doubtfully tuberculous lesions. The index cases of these 7 contacts had all become culture-negative before the contacts were born, and all except 1 continued to be culture-negative (the exception produced positive cultures at 18 and 19 months and only negative cultures thereafter; the corresponding contact (PH) developed tuberculosis at 45 months).

Tuberculin tests were undertaken in 53 PH, 52 HI-1, 55 HI-2 and 53 H new-born contacts during the 5-year period and yielded an induration of 5 mm or more on 1 or more occasions in 17%, 23 %, 24 % and 17 %, respectively.

Contacts from families with more than one source of infection initially

It will be recalled (p. 339) that 84 contacts were excluded from the main comparisons because there was at least 1 other infectious member in the family (that is, besides the index case) at the start of the study. Of these, 8 (10%) developed tuberculosis during the 5-year period, as compared with 77 (9 %) of 875 contacts from families in which the index case was the only source of infection initially. The proportions who developed tuberculosis were 18% and 14 %, respectively, in initially tuberculin-negative contacts, and 8 % and 7%, respectively, in initially tuberculin-positive contacts.

DISCUSSION

This report presents information on the attack rate of tuberculosis during a 5-year period among close family contacts of patients with newly diagnosed infectious pulmonary tuberculosis, who came from a poor, overcrowded section of a large urban community in South India. The patients (index cases), all of whom were treated on an ambulatory domiciliary basis, were allocated at random to treatment in the first year with a standard daily regimen of isoniazid plus sodium PAS (PH) or one of 3 daily regimens of isoniazid alone-namely, a moderate dosage in a single dose (HI-1), the same moderate dosage but in 2, divided, doses (HI-2), and a low dosage in 2, divided, doses (H). During the 5-year period, the average number of months of smear positivity was 4.1 for the PH patients, 5.4 for the HI-1 patients, 7.7 for the HI-2 patients and 9.5 for the H patients, and the averages for culture positivity were 6.8, 7.9, 11.0 and 13.6 months, respectively.

Considering families with only 1 infectious member (namely, the index case) at the start of the study,

there were 875 close family contacts at risk of developing tuberculosis; as a result of the random allocation of the index cases, these were divided into 228 PH, 212 HI-1, 210 HI-2 and 225 H contacts. Since the main aim of the present study was to assess whether there was any extra risk to the contacts of patients treated with isoniazid alone, when compared with the contacts of patients treated with isoniazid plus PAS, neither BCG vaccination nor chemoprophylaxis was employed; instead, all the contacts were followed by an intensive routine of supervision.

The 4 groups of contacts were similar on admission in respect of sex, age, family size and the results of tuberculin testing and radiographic examination (apart from calcification). They were followed up by chest radiography with a high and similar intensity, by tuberculin testing with a similar intensity, and, where indicated, by bacteriological examinations as well. The attack rates are therefore based on exceptionally comprehensive information. Furthermore, they have been determined by an experienced *independent* assessor, who was unaware of the treatment or the bacteriological or radiographic progress of the index case of any individual contact under review.

The findings over the 5-year period of follow-up demonstrate that the contacts of patients treated with isoniazid alone were at no greater risk of developing tuberculosis than the contacts of patients treated with isoniazid plus PAS. Thus, considering initially tuberculin-negative contacts, 19 % of 73 PH contacts developed tuberculosis during the 5-year period, as compared with 17 % of 53 HI-1, 8 % of 53 HI-2 and 9% of 54 H contacts; none of the differences was statistically significant (P> 0.1). The corresponding proportions in initially tuberculin-positive contacts were 7 % of 150 PH, 7 % of 153 HI-1, 8% of 151 HI-2 and 6% of 164 H.

When an infectious index case is treated at hone, cases of tuberculosis arising in the close family contacts can be attributed to infection from one of 3 sources, namely, (1) the index case before diagnosis, (2) the index case during treatment, or (3) other sources in the environment. An earlier study from the Centre, in which half the index cases, selected at random, were isolated in sanatorium for 1 year and treated with a standard regimen of isoniazid plus PAS while the other half was treated with the same regimen but at home, had shown that the major risk to the close family contacts was from exposure to the index case before diagnosis (Andrews et al., 1960; Ramakrishnan et al., 1961a; Kamat et al., 1966). In that study, the prevalence of active tuberculosis on admission was high,[1] namely, 50 (7.4%) of 672. Further, of 62 cases that developed during the 5-year period, no less than 32 (52%) occurred in the first year, including 18 (29 %) in the first 3 months. Also, evidence was available from initially tuberculin-negative contacts of sanatorium patients which strongly suggested that the cases arising in the first 3 months were due to infection from the index cases before diagnosis (Kamat et al., 1966). The findings in the present study confirm the conclusion drawn from the earlier one. Thus, the prevalence of active tuberculosis on admission was again high,[1] namely, 88 (8.1%) of 1082. Further, of 32 initially tuberculin-negative contacts who developed tuberculosis during the 5-year period, as many as 17 (53%) did so in the first year, including 10 (31%) in the first 3 months; the corresponding numbers for the 42 initially tuberculin-positive contacts who developed tuberculosis were 23 (55 %) and 8 (19%), respectively. Similar findings have been reported from a rural area in Kenya. The prevalence of radiographically active tuberculosis was found to be 9.8 % [2] in 397 household contacts of smear-positive index cases (WHO Tuberculosis Chemotherapy Centre, Nairobi, 1961). Further, it has been reported by Egsmose, Ang'awa & Poti (1965) that in a follow-up over a period of 2-4 years of untreated household contacts of smear-positive index cases, tuberculosis developed in 13 initially tuberculin-negative and in 5 initially tuberculin-positive contacts, of whom 10 and 4, respectively, developed the disease in the first 6 months.[3]

Considering next the risk of contracting tuberculosis from the urban environment, there was a marked decline in the yearly attack rates over the 5-year period, and relatively small numbers of

[1] Among contacts aged 5 years or more, the prevalence of active tuberculosis was 6.8% of 541 in the earlier study and 7.2% of 890 in the present study. These proportions are considerably higher than the prevalence (of active or probably active tuberculosis) of 1.5%-2.1 % in the general Indian population aged 5 years or more living in large cities (Indian Council of Medical Research, 1959).

[2] Among contacts aged 6 years or more in the Kenya study, the prevalence of active tuberculosis was 9.1 % of 317, which is considerably higher than the prevalence of 1.7% of 3117 observed in a random sample survey of the general population aged 6 years or more (WHO Tuberculosis Chemotherapy Centre, Nairobi, 1961, Appendix Table 4).

[3] These numbers were deduced from Appendix Tables 1 and 2 (Egsmose, Ang'awa & Poti, 1965), defining development of tuberculosis as the development of a pulmonary lesion or the excretion of viable tubercle bacilli, or both.

cases occurred in the fourth and fifth years. Thus, the numbers, year by year, were 17, 6, 5, 2 and 2, respectively, for initially tuberculin-negative contacts, and 23, 10, 5, 2 and 2, respectively, for the initially tuberculin-positive contacts. Since it is unlikely that a sharp decline in the risk from the environment occurred during the course of this study, these findings suggest that the urban environment of Madras could not have been an important source of infection. However, there is other evidence which indicates that the urban environment did constitute some risk. Thus, of 231 contacts born into the families during the 5-year period, 4 developed primary tuberculosis despite their index cases having become culture-negative by the time they were born.

Turning lastly to the risk from exposure to the index case during treatment, this study provides particularly valuable evidence since the 4 chemotherapeutic regimens employed had widely different efficacies. Considering first the findings in initially tuberculin-negative contacts, the group more likely to be affected by differences in the duration of exposure to infectious index cases, the attack rates were similar for the PH (19%) and the HI-1 contacts (17%), although the mean durations of exposure for the latter were appreciably higher, namely, 5.7 months for smear positivity and 9.1 months for culture positivity, as compared with 2.3 months and 4.7 months, respectively, for the PH contacts. Furthermore, the HI-2 and the H contacts, despite having mean durations of exposure that were fairly similar to those of the HI-l contacts, had appreciably lower attack rates, namely, 8 % and 9 %, respectively. Considering next the initially tuberculin-positive contacts, the attack rates in the 4 series were similar although there were substantial differences between them in the mean durations of exposure, a finding readily explained as break-down to active disease among contacts who had already been infected. Finally, amalgamating all 4 series, there was no evidence, either in the initially tuberculin-negative contacts or in the initially tuberculin-positive contacts, that a longer duration of exposure to index cases with positive sputum smears or with positive cultures during treatment carried a higher risk of contracting tuberculosis. These findings suggest that exposure to the index case during treatment is, like exposure to the urban environment of Madras, a relatively unimportant source of risk. They do not, however, mean that it constitutes no risk. In this context, it will be appreciated that, in this study, exposure to the infectious (culture-positive) index case during treatment largely meant exposure to patients with isoniazid-resistant cultures.

The risk to contacts from prolonged exposure to index cases with isoniazid-resistant cultures is of great interest from the epidemiological point of view. In this study, there was no evidence that contacts with a longer duration of exposure to patients with isoniazid-resistant cultures had a higher attack rate. For instance, among initially tuberculin-negative contacts, the mean durations of such exposure were 2.4 months in the PH series, 6.4 in the H, 6.9 in the HI-1 and 8.0 in the HI-2 series, and the corresponding attack rates were 19%, 9%, 17% and 8%. Further, amalgamating the initially tuberculin-negative contacts in the 4 series, the attack rates were 18 % of 137 in those who were never exposed to index cases with isoniazid-resistant cultures, 8 % of 53 in contacts exposed for under 12 months and 9% of 43 in contacts exposed for 12-60 months. This finding raises the possibility that isoniazid-resistant strains of tubercle bacilli have a low virulence in man, as in the guinea-pig (Barnett, Bushby & Mitchison, 1953; Barry, Conalty & Gaffney, 1953; Middlebrook & Cohn, 1953; Steenken & Wolinsky, 1953) and in the monkey (Schmidt, 1956). There is also a possibility that isoniazid-resistant strains are less infectious to contacts than isoniazid-sensitive strains. Thus, Raj Narain et al. (1967) reported, over an l&month period of follow-up (on average), a 15-mm increase in induration resulting from the inoculation of 1 TU (PPD RT 23 with Tween 80) in 12.1% of 488 contacts exposed to index cases with isoniazid-sensitive cultures initially, as compared with 5.6% of 89 contacts exposed to index cases with isoniazid-resistant cultures initially ($P = 0.1$), including 8.6 % and 4.5 %, respectively, with a 20-mm increase ($P=0.3$).

Attempts are sometimes made to determine possible sources of infection from the results of drug-sensitivity tests, that is, by employing drug-resistance as a microbial marker characteristic (Brander, Aho & Patiala, 1968; Steiner et al., 1968). It is important to appreciate the limitations of such attempts. For instance, for any contact-index case pair, there are 3 possible modes of infection. First, the index case may have infected the contact (or vice versa). Secondly, both may have been infected from a common source (that is, both are really contacts of a third party). Thirdly, the index case may have been infected from one source and the contact from another. In the present study, of 77 contacts who developed tuberculosis during the 5-year period,

29 had a positive culture, and of these 7 had an isoniazid-resistant infection. A consideration of the time sequence of infection and the results of isoniazid sensitivity tests in these contacts and their index cases suggested that the index case might have been the source of infection in 2 instances. the infection taking place before diagnosis of the index case in one (the index case had primary isoniazid resistance) and after the commencement of treatment in the other (the index case had acquired isoniazid resistance). However, even in these 2 instances, it is not possible to exclude the possibility that both the contact and the index case were infected from a common source.

It is noteworthy that of 77 contacts who developed tuberculosis during the 5-year period, 50 (65 %) were under 15 years of age, including 29 (38 %) under the age of 5 years. (Further, of 3 contacts who developed a serious lesion, namely, miliary tuberculosis or tuberculous meningitis, 2 were under 5 years of age and the third was aged 17 years.) The attack rate over the 5-year period was 20% of 147 in contacts under 5 years of age, 8% of 254 in those aged 5-14 years and 6% of 474 in those aged 15 years or over (including 11 %, 4% and 3 %, respectively, in the first year). These proportions are similar to those found in an earlier study, namely, 25 % of 101, 9 % of 163 and 8 % of 264, respectively (Kamat et al., 1966), and confirm that there is scope for chemoprophylaxis in close family contacts, especially in those under 5 years of age. In view of the finding that chemoprophylaxis with daily isoniazid is highly effective in family contacts (Ferebee & Mount, 1962; Ferebee, 1964; Egsmose, Ang'awa & Poti, 1965), and in keeping with current trends of supervised intermittent administration of drugs to tuberculous patients (Tuberculosis Chemotherapy Centre, Madras, 1964, 1970; Poole & Stradling, 1965, 1969; Dawson, 1966; Chaulet et al., 1967; Sbarbaro & Johnson, 1967), a double-blind study is being undertaken at this Centre to determine the chemoprophylactic value of fully supervised, twice-weekly, high-dosage isoniazid in close family contacts aged less than 5 years. However, it must be emphasized that any chemoprophylactic measure must necessarily be fitted into the over-all tuberculosis programme for the country and be given a lower priority than the treatment of patients, particularly in developing countries with limited resources (Fox, 1964).

Considering the findings in initially tuberculin-negative contacts in this study and the earlier one (Kamat et al., 1966), the attack rate of tuberculosis was high in both studies, namely, 14% of 233 and 11% of 173, respectively. Furthermore, about half the cases (15 of 32) in the present study and about a quarter (5 of 19) in the earlier study occurred in the second or subsequent years. Finally, about 90 % of the cases in the present study (29 of 32) and all the 19 cases in the earlier study developed in contacts aged less than 10 years on admission. These findings suggest that there is considerable scope for BCG vaccination of initially tuberculin-negative contacts, particularly children aged under 10 years.

Although the main serial assessment of the contacts was based on radiographs, tuberculin testing was also used as a measure of infection. The incidence of tuberculin conversion (defined as an *increase* of 10 mm or more from an initial induration of 0 mm–4 mm) was 57% in the PH contacts, 43% in the HI-1, 58 % in the HI-2 and 52% in the H contacts–findings which do not indicate any enhanced risk of infection to the contacts of patients treated with isoniazid alone. Although these proportions are useful for making valid *comparisons* between the risks of infection in the 4 series, it must be emphasized that, for reasons stated elsewhere (Kamat et al., 1966), they are not accurate measures of the *infection rates* in the 4 series.

The present report and previous reports from this Centre (Dawson et al., 1966; Kamat et al., 1966; Evans et al., 1969) have shown that it is possible to follow both patients and their close family contacts over a period of 5 years with almost 100% success, provided that (1) the families are carefully selected as being *bona fide* local residents and regarded as co-operative, (2) the follow-up is carefully planned and (3) the facilities are adequate (Tuberculosis Chemotherapy Centre, Madras, 1959, 1960; Andrews et al., 1960; Ramakrishnan et al., 1961b). This is an encouraging finding, not only for long-term research in chronic diseases but for the general field of social inquiry also. However, it must be emphasized that in developing countries with limited financial and organizational resources, long-term follow-up of contacts has little or no place in a *service programme* (see *Tubercle (Edinb.)*, 1967).

In conclusion, the findings in the present study and those in a previous 5-year study of the risk to close family contacts (Kamat et al., 1966), together with the findings of 5-year studies of the index cases (Dawson et al., 1966; Evans et al., 1969), have firmly established that, even where the environmental background is very unfavourable, ambulatory domiciliary treatment of patients with pulmonary tuberculosis is practicable and effective, and carries little risk to close family contacts.

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RÉSUMÉ

INCIDENCE DE LA TUBERCULOSE, PENDANT UNE PÉRIODE DE 5 ANS, CHEZ DES SUJETS VIVANT EN CONTACT FAMILIAL ÉTROIT AVEC DES MALADES TRAITÉS À DOMICILE PAR L'ASSOCIATION ISONIAZIDE-PAS OU PAR L'ISONIAZIDE SEUL

On a entrepris une étude contrôlée en vue d'évaluer l'efficacité respective d'un traitement type comportant l'administration quotidienne d'isoniazide et de PAS (schéma PH) et de trois traitements par l'isoniazide seul donné quotidiennement soit à dose modérée en une prise unique (schema HI-1), soit à la même dose mais en deux prises séparées (schema HI-2), soit à faible dose également en deux prises distinctes (schéma H). On a relevé de trés nettes différences entre ces traitements en ce qui concerne le nombre de malades rendus non contagieux: le schéma PH et, à un degré moindre, le schéma HI-1 se sont montrés les plus actifs, les schémas HI-2 et H étant les moins efficaces.

On a inclus dans cette étude l'observation pendant 5 ans de 1109 personnes faisant partie de la famille des malades et vivant en contact intime avec eux; elles ont fait l'objet d'examens radiologiques et d'épreuves tuberculiniques répétés et, si nécessaire, d'examens bactéiologiques. Aucun de ces contacts n'a été vacciné par le BCG et aucun n'a bénéficié de la chimioprophylaxie. Les groupes familiaux étudiés appartenaient à la classe indigente et vivaient dans des quartiers surpeuplés de Madras (Inde).

Les comparaisons ont porté essentiellement sur des contacts (228 PH, 212 HI-1, 210 HI-2 et 225 H) exposés à l'origine à une source unique de contagion familiale représentée par le cas indice (premier membre de la famille atteint de tuberculose pulmonaire enregistré au Centre de Chimiothérapie de la Tuberculose, Madras); 234 contacts ont été exclus de l'enquête pour diverses raisons.

Au moment où a débuté le traitement des cas indices, les quatre séries de contacts présentaient des caractéristiques similaires en ce qui regarde le sexe, l'âge, l'importance numérique de la famille, les données radiologiques (compte non tenu des calcifications pulmonaires) et la sensibilité à la tuberculine. Au cours des 5 années d'observation, tous les contacts ont bénéficié dans une mesure identique d'investigations radiologiques et d'épreuves tuberculiniques. La proportion des contacts contrôlés radiologiquement a été particulièrement élevée, notamment lors des examens annuels (95-100%). Toutes les données radiographiques, bactériologiques et cliniques (y compris les résultats des épreuves tuberculiniques) relatives aux contacts ont été vérifiées par un examinateur indépendant, non informé du traitement appliqué au cas indice et de l'évolution de ce dernier.

Pendant les 5 années d'observation ont été reconnus atteints de tuberculose 32 contacts initialement tuberculino-négatifs, soit 19% de 73 PH, 17% de 53 HI-1, 8% de 53 HI-2 et 9 % de 54 H ainsi que 42 contacts initialement tuberculino-positifs, soit 7% de 150 PH, 7 % de 153 HI-1, 8% de 151 HI-2 et 6% de 164 H. Sur les 32 contacts tuberculino-négatifs, 17 ont contracté la maladie pendant la 1re année, dont 10 dans les trois premiers mois; pour les 42 contacts tuberculino-positifs, les chiffres correspondants ont été de 23 et 8 respectivement. Chez les 77 contacts atteints de tuberculose (ce total comprenant trois sujets non soumis à l'épreuve tuberculinique), la maladie a évolué dans 10 cas (4 PH, 2 HI-1, 3 HI-2 et 1 H) selon le type observé chez l'adulte; dans 67 cas (22 PH, 18 HI-1, 13 HI-2 et 14 H), les manifestations ont été du type primaire ou postprimaire, deux patients (1 HI-1 et 1 H) étant atteints de tuberculose miliaire et 1 (H) de méningite tuberculeuse.

La culture a été positive, une fois au moins, chez 29 contacts (11 PH, 7 HI-1, 6 HI-2 et 5 H) et on a recherché, pour 27 d'entre eux, la sensibilité des bacilles à l'isoniazide et à la streptomycine. La 1re culture positive était sensible aux deux médicaments dans 19 cas (7 PH, 4 HI-1, 5 HI-2 et 3 H), sensible à l'isoniazide mais streptomycino-résistante dans 1 cas (H), résistante à l'isoniazide mais sensible à la streptomycine dans 3 cas (1 PH, 1 HI-1 et 1 HI-2) et résistante aux deux médicaments dans 4 cas (3 PH et 1 HI-1).

L'incidence de la tuberculose a été de 20% au-dessous de 5 ans (147 contacts), de 8% dans le groupe d'âge 5-14 ans (254 contacts), de 7% dans le groupe d'âge 15-24 ans (147 contacts) et de 5% chez les 327 contacts âgés de 25 ans ou plus. On n'a obtenu aucune preuve que cette incidence était fonction de la durée pendant laquelle, en 5 ans d'observation, le cas indice a été *a)* positif à l'examen direct des crachats, *b)* positif à la culture ou *c)* a fourni une culture résistante à l'isoniazide.

Cette étude montre que, sur une période de 5 ans, les

sujets vivant en contact familial étroit avec un malade traité à domicile par l'isoniazide seul ne risquent pas davantage de contracter la tuberculose que les contacts de malades traités par l'association isoniazide-PAS. Elle confirme aussi que le principal risque couru par les contacts est celui d'une contamination par le cas indice intervenant avant que le diagnostic ait été pose, et que les risques resultant d'une exposition à d'autres sources de contagion (cas indice en cours de traitement, milieu urbain de Madras) sont, par comparaison, faibles.

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