

## Further Notes on the Incidence of Leprosy in Hong Kong Children Living with a Lepromatous Parent<sup>1</sup>

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Three years ago we reported a study (3) of the subsequent incidence of leprosy in 66 Hong Kong families in which a total of 177 children had been exposed to leprosy by living at home with at least one parent who had lepromatous leprosy. The children were enrolled in the study only if they had received no chemoprophylaxis, had been under age 12 at the time they were first exposed, and had been seen periodically for at least three years thereafter in the Special Skin Clinics for contact examinations. The lepromatous parents had been new admissions to the clinics during 1954-1960, had had histologic and clinical confirmation of active lepromatous leprosy, had received no therapy prior to admission, and were placed on sulfone therapy as outpatients as soon as they were diagnosed. This study showed that by the summer of 1967 the 109 children (cohort A) who had been exposed *prior to* the initiation of sulfone therapy in the parents had given rise to ten cases of leprosy. By 1967 no cases appeared in the 68 children born into these families *after* the parent had been started on sulfone therapy. Of these 68 children, 42 (cohort B) had been born while the parents were still bacteriologically positive, while the remaining 26 children (cohort C) had been born after the parents had become bacteriologically negative.

The difference between the 9% incidence of leprosy in cohort A and the 0% incidence in cohort B was only of a borderline zone of statistical significance because of the small number of cases involved. However the concordance of this observation with the

well-known morphological changes seen in *M. leprae* within a few months after the initiation of sulfone therapy, plus the mouse foot-pad evidence provided by Shepard, Levy, and Fasal (1) of the loss of reproductive ability of *M. leprae*, as tested in the mouse foot-pad, in lepromatous patients within 90 days after the initiation of sulfone therapy, gave considerable combined support to the hypothesis that a lepromatous patient loses his ability to transmit the disease to others shortly after sulfone therapy is begun, even though his skin still contains many irregularly staining bacilli when examined either by smear or by biopsy. The confidence generated by this combination of human, morphological, and mouse foot-pad data lies in the statistical proposition that the combined probability of the concordance of several *independent* sets of observations is equal to the *product* of the probability of each of these separate sets of observations.

The study summarized above was subsequently criticized on the following grounds:

1. Some of the children included in the statistical analysis had been followed for only seven years after exposure, therefore some cohort B children might yet develop leprosy.
2. The method of age adjustment between cohort A (the older siblings, most of whom were first exposed sometime *after* infancy) and cohort B (the younger siblings, *all* of whom were exposed at birth) introduced a small bias in favor of the hypothesis.
3. The use of BCG in the children was an uncontrolled variable in this study.

The purpose of this current report is to respond to the above three criticisms by:

1. adding three more years of observation (through the summer of 1970), and
2. presenting alternative ways of analyzing the data.

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## METHODS AND RESULTS

In the summer of 1970 the Special Skin Clinic records of the 177 children were again examined, and their status between 1967 and 1970 was abstracted. Only one new case of leprosy had appeared. The onset of his disease was in January, 1968, just before his tenth birthday. He was in cohort A by virtue of having been exposed to his father during the first month of his life (in 1958 in China), after which the father had come alone to Hong Kong and had been started on sulfone therapy in April, 1958, for widespread, active lepromatous leprosy. The son was not again exposed to the father for five years, at about the time the father's skin smears became negative.

No new case has been discovered in cohort A since early 1968, and only one new case since early 1967. Since ten out of the eleven cases in cohort A had their onset

in less than ten years after initial exposure, an arbitrary dotted line has been drawn in Table 1 to indicate that once a child has been observed for ten years or more after his initial exposure his risk of subsequently developing leprosy is sufficiently low ( $1/69=1.4\%$ ) to be considered as approaching that of the general public (vs. the 0-10 year risk of  $10/108=9.3\%$ ). The possible approaches to statistical analysis of these data are presented in the discussion below.

Table 2 shows the maximum incubation period observed in the eleven cases tabulated against the age of the child at the time he was first exposed.

This distribution shows a mean incubation period<sup>3</sup> of seven years and a median incubation period of six years, thus confirming the belief that if any cases were going to appear in cohort B, some would have appeared by 1970, when 32 out of the

TABLE 1. Distribution of 177 children by the number of years observed<sup>a</sup> after their first exposure to a lepromatous parent, by kind of exposure, and by subsequent incidence of leprosy (Hong Kong, 1954-1970).

Type of exposure	Number of years <sup>a</sup> from first exposure to most recent examination					Total
	4-5	6-7	8-9	10-11	12-20	
Cohort A (exposed before parent started Rx)	6 defectors <sup>b</sup> 4 cases	11 <sup>b</sup> 2 cases	13 <sup>b</sup> 4 cases	27 contacts <sup>c</sup> 0 cases	41 <sup>c</sup> 1 case	98 children 11 cases
Cohort B (exposed after Rx but parent still bact. positive)	6 <sup>b</sup> 0 cases	4 <sup>d</sup> 0 cases	5 <sup>d</sup> 0 cases	11 <sup>c</sup> 0 cases	16 <sup>c</sup> 0 cases	42 children 0 cases
Cohort C (exposed after parent bact. negative)	6 <sup>d</sup> 0 cases	8 <sup>d</sup> 0 cases	7 <sup>d</sup> 0 cases	4 <sup>c</sup> 0 cases	1 <sup>c</sup> 0 cases	26 children 0 cases
	22	25	29	42	59	177 children

<sup>a</sup> The number of years that elapsed between the time of first exposure of the child and the time of: 1) the onset of leprosy, or 2) the most recent Skin Clinic examination of those who have not developed leprosy.

<sup>b</sup> defector = a child who had not developed leprosy when last seen and who is old enough to have been examined for at least 10 years, but who failed to do so because of death, out-migration, or non-cooperation.

<sup>c</sup> contact = a child who has been seen over a period of at least 10 years since exposure, but who has not developed leprosy.

<sup>d</sup> either a defector or a child who has had "incomplete" follow-up, being too young to have been seen for 10 years.

TABLE 2. Distribution of 11 cases of leprosy in children by age at time of first exposure and length of maximum incubation period (Hong Kong, 1954-1970).

		Number children Cohort A	Years from 1st exposure to onset of leprosy										Total cases	
			≤3	4	5	6	7	8	9	10	11	12		≥13
Age of child at first exposure to leprosy	0	25				1			1					2
	1	9		1					1					2
	2	9												0
	3	11		1					1					2
	4	7		1										1
	5	12				1						1		2
	6	7		1				1						2
	7	10												0
	8	9												0
	9	5												0
	10	3												0
	11	2												0
		109	0	4	0	2	0	1	3	0	0	1	0	11 cases

42 children in that cohort had been observed for at least eight years. It also confirms the observation made in the 1967 study that the 29 children in cohort A who were first exposed at ages 7-11 have produced no cases of leprosy (vs. the 2.9 cases expected from the performance of the remaining 80 children in cohort A). There is no evidence in this distribution of any strong correlation between the age of the child at the time of exposure and the incubation period in that child.

#### DISCUSSION

In the original paper summarizing the data to 1967 a distribution was made of the 177 children by cohort, by number of years of observation, and by subsequent incidence of leprosy. In that table it was indicated that none of the children in cohort A who had been observed for less than seven years had developed leprosy, and a confusing statement was made in that paper that "children observed less than seven years

should not be considered at risk (in the context of the statistical evaluation of incidence), since follow-up is too brief." This is a misleading statement that arose from counting the cases that were discovered early (after 4-6 years observation) as belonging to the sub-cohort of children that has continued to stay under observation, rather than becoming defectors. It was a confusing way of trying to say that only certain children were going to be considered in the statistical analysis, those children that fall to the right of the dotted lines in Table 1 in this paper (1970 data). Table 1 in this paper (1970 data) puts the data into a less ambiguous context by defining the concept of a "defector," as well as defining the concept of a child who has had "incomplete" follow-up, who may be handled statistically the same as a "defector," even though he is still coming in regularly for his examinations.

The statistical testing of the difference in incidence between cohort A and cohort B could be conveniently done by using the Chi-square test with Yates' correction for small numbers (as was done in the 1967 paper), but the zero incidence in cohort B sets up a situation where the Yates' correc-

<sup>3</sup> This incubation period is close to the 8.5 year mean and 8 year median observed by Worth and Hirschy (4) in a study of 203 Hawaiian children exposed to a lepromatous parent and followed through periodic examinations for many years thereafter.

tion is probably too severe. An alternative (and probably more accurate) method would be to use the "exact test" for a 2-by-2 table<sup>(2)</sup> as suggested by one of the critics of the 1967 paper<sup>4</sup>. With either method, one might use all of cohort A and cohort B, adjusting for neither length of follow-up nor age at time of initial exposure:

cohort A = 11 cases out of 109 children.  
vs. cohort B = 0 out of 42.  
Chi-square (Yates') = 3.20,  
p  $\cong$  .07;  
"exact test" p = .024

One might also adjust for length of follow-up and age at exposure (as was done in the 1967 paper) by including only those children to the right of the dotted line in Table 1.

cohort A = 11 cases out of 79 children.  
vs. cohort B = 0 out of 27.  
Chi-square (Yates') = 2.83,  
p  $\cong$  .09;  
"exact test" p = .032

In either situation the "exact test" gives us considerable confidence (either 2.4% or 3.2% level) that cohort B's zero incidence is not just by chance. We see that the adjustments for follow-up and for age at exposure do not alter the statistical results materially. We also see that the Yates' correction is not appropriate in this case.

The issue of BCG as an uncontrolled variable was mentioned in the original paper, and should be recapitulated here. It is not possible to get a reliable BCG history for the 177 children in this study. The BCG usage patterns in Hong Kong during the past 20 years make it highly probable, however, that most of the children in cohort A (all born before 1960) received BCG for the first time at the age of school entry, about age 7. Many (perhaps up to half) of the children in cohort B (mostly born between 1950 and 1965) received BCG at birth, and of the remainder, those who were found to be tuberculin negative at school entry (probably about 40-50%)

did receive BCG at about age seven. Most of cohort C (mostly born after 1960) received BCG at birth. A study<sup>(5)</sup> is now being carried out using Hong Kong leprosy data to examine the relationship between BCG usage and childhood leprosy incidence. This study should be finished within the next year or two.

In conclusion, another three years of observation of these Hong Kong children have allowed enough of them to pass over the ten year follow-up mark to give statistical reliability to our hypothesis that compulsory segregation of lepromatous patients is unwarranted. If, once they start treatment, they no longer transmit the disease to their own infants (most of whom sleep in the parental bed in Hong Kong), what public health menace could they be?

## RESUMEN

En 1968 se informó sobre un estudio que se hizo de 66 familias de Hong Kong que tenían por lo menos uno de los padres lepromatosos en tratamiento domiciliario. Se identificaron en estas familias 70 niños que habían sido examinados regularmente durante un mínimo de siete años. Otros tres años de observación de estos niños de Hong Kong han permitido que una cantidad suficiente de ellos hayan sobrepasado la marca control de diez años, lo que permite dar validez estadística a nuestra hipótesis de que la segregación compulsiva de los pacientes lepromatosos no se justifica. Si una vez que han empezado su tratamiento ya no transmiten la enfermedad a sus propios hijos (la mayor parte de los cuales duermen en la cama de los padres en Hong Kong), que amenaza para la salud pública pueden ser?

## RÉSUMÉ

En 1968, on a publié une étude se rapportant à 66 familles de Hong-Kong qui comprenaient au moins un membre lépromateux traité au domicile. Dans ces familles, on a identifié 70 jeunes enfants qui avaient été examinés régulièrement au cours d'une période s'étendant sur sept ans au moins. On a poursuivi l'observation de ces enfants de Hong-Kong pendant trois années. Ceci a permis à un nombre suffisant d'entre eux d'atteindre dix années de surveillance, de manière à fournir une base statistique à notre hypothèse qui veut que la ségrégation obligatoire des malades lépromateux ne se justifie point. Si les malades lépromateux, une fois qu'ils ont commencé le traitement, ne trans-

<sup>4</sup> K. Lance Gould, then EIS officer stationed in Hawaii from the Communicable Disease Center, Atlanta, Georgia.

mettent plus la maladie à leurs propres enfants (dont, à Hong-Kong, la plupart partagent le lit de leurs parents), quelle menace pourraient-ils donc encore représenter pour la santé publique?

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