Genetic factors in leprosy: a study of children in Uganda

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SUMMARY

A group of 20990 children in Uganda was examined for leprosy over a period of 8 years. There was no evidence that the incidence of leprosy varied according to a child's genetic relationship to a leprosy patient, once allowance had been made for the grade of physical contact.

INTRODUCTION

The prevalence of leprosy in different parts of Uganda in the 1950s was surveyed by Kinnear Brown (Brown, 1955, 1957, 1959). He suggested that the differences in prevalence which he found were not entirely explained by environmental factors such as climate and the degree of mixing between individuals. The higher rates were found in comparatively small groups of people who had limited outside contact. The lower rates were found among larger sections of the population, where there was more mobility, and where marriage was not confined to a restricted circle. These observations led Kinnear Brown to postulate that inherited constitutional differences in susceptibility might also play an important part in the spread of leprosy (Brown, 1955).

The setting up by Brown of a controlled trial of BCG vaccination against leprosy in Uganda in the 1960s (Brown & Stone, 1966; Brown, Stone & Sutherland, 1968) provided him with the opportunity to collect a substantial body of data bearing directly on the role of genetics in leprosy. The child participants in the trial were selected as being in contact with or related to a known leprosy patient, and particular care was taken to assess the precise genetic relationship between the child and the index patient, as well as (inevitably less precisely) the degree of physical contact. It was thus possible to study, in a large group of children, the prevalence and incidence of leprosy according to both the degree of genetic relationship and the degree of physical contact with an index case.

SUBJECTS AND METHODS

In 1960 a controlled trial of BCG vaccination against leprosy was set up in Eastern Uganda. Details of the trial methodology, and results concerning BCG vaccination and the relation between tuberculin status and the development of leprosy have already been reported (Brown & Stone, 1966; Brown *et al.* 1968).

The trial was undertaken in children who were related to or had been in contact

with known leprosy patients. It was expected that these children, by virtue of their greater exposure and possibly greater genetic disposition, would run a higher than average risk of developing leprosy. Eligible children were identified by local health staff, and the diagnosis of each index patient was confirmed by an assistant from a leprosy treatment village. Children were also traced from lists of patients known to have been treated in the leprosy villages during the previous 10 years. It was expected that almost all the eligible children in the area would be included in this way.

A total of 19 014 children entered the trial in the main intake period between mid-1960 and mid-1962, and a further 1976 children were included during the first follow-up visit, starting in late 1962. The latter group consisted mainly of children who had been born into the trial families since the main intake.*

When a child was registered for the trial, the child's name, age and sex, and the names of the natural parents were recorded, and details of any leprosy patient(s) in contact with or related to the child were also noted. The details of each index patient consisted of his or her name, the type of leprosy (lepomatous/non-lepomatous), whether treatment was being received, the genetic relationship of the patient to the child, and the amount of physical contact between them. Care was taken to find the exact genetic relationship between the patient and the child: since the society is polygamous this required detailed description. Full information on all leprosy patients known to be related to or in contact with the child was recorded, to a maximum of four such patients.

Children in the main intake were examined twice by the visiting team. At the initial examination each child was examined for leprosy and other skin lesions, and was given a tuberculin test. At the second examination the tuberculin test was read, and alternate eligible children received BCG vaccination (Brown & Stone, 1966). A child was deemed to be eligible for vaccination if there were no leprosy lesions, and if the result of the tuberculin test was negative, or positive in Grades I or II. In the subsidiary intake the children were seen once only. There was no tuberculin testing, and every alternate child received BCG vaccination.

The children were followed over a period of 8 years, and examined for signs of leprosy at approximately two-year intervals. At the first follow-up examination a check was made on the details of contact and relationship for some children, where possible discrepancies had been found between the records for the same family.

Groupings of contact and relationship

At the time of the trial, as now, the great majority of the population of Uganda lived in segregated family units. Each family homestead was set in the middle of its own farmland, and there was no grouping into villages. As the distance to the next house was commonly at least half a mile, it was likely that any leprosy infection in childhood was the result of contact within the family, rather than outside it.

* Some children were excluded from the study of BCG vaccination for reasons connected with the tuberculin testing and the vaccination (Brown & Stone, 1977). They are however, included here.

Table 1. *Distribution of number of index cases according to child's closest genetic relationship with a patient*

Closest genetic relationship	No. of children with				Total
	1 index case	2 index cases	3 index cases	4 or more index cases	
1	4279* (84.1)†	679 (13.3)	122 (2.4)	10 (0.2)	5090 (100)
2-4	8304 (93.4)	488 (5.5)	91 (1.0)	11 (0.1)	8894 (100)
5 or more	6677 (96.7)	188 (2.7)	42 (0.6)	0	6907 (100)
Not known	39 (95.1)	0	2 (4.9)	0	41 (100)
Total	19299 (92.2)	1355 (6.5)	257 (1.2)	21 (0.1)	20932 (100)

* Total children.

† Percentage.

The family compound was arranged so that there was one house for the father and a separate house for each of his wives. It was common for there to be two wives, each having her own children living with her while they were young. However it was not unusual for the children to live with the other wife periodically.

Four main grades of contact with an index patient could be distinguished: house, compound, occasional or 'visiting' contact, and none. The last arose, for example, where a relative with leprosy had died some years before the birth of the child. Visiting contact was readily assessed, as this applied only where the patient did not live in the same compound as the child, but visited it occasionally. House and compound contact were less easily distinguishable, and probably changed from time to time. Where it was impossible to say whether a child's contact with a patient was of house or of compound type, this was recorded as house/compound contact.

The genetic relationship of a leprosy patient to the child was recorded exactly. As noted above, this required careful description in order to distinguish family members who were *genetically* related to the child from those who were not. For example, a child's 'uncle' could be a true brother of either of the child's true parents, or the husband of a sister of either parent, or some male relative of the father's 'other wife'. Generally, in only the first case was there a genetic relationship. For the purposes of analysis, the relationships were grouped according to the degree of consanguinity. Thus the father, true mother, and full brothers and sisters were grouped as being relatives of degree one, the half-brothers and half-sisters of the child, and the full brothers and full sisters of the true parents were grouped as degree two, and so on. Relationships of degree five or more, and 'of no genetic relationship' (such as the father's 'other wife' and her relatives) were grouped together.

To summarize for analysis the genetic relationship and degree of contact for

children with more than one index case, the closest genetic relationship and the grade of the closest contact were used. These may or may not have referred to the same index patient. It was also noted in such a case that the child had multiple contact. The distribution of children according to the number of index cases is shown in Table 1. It may be seen that only 7·8% of children had multiple contact.

Where a child had *any* relationship or contact with a case of lepromatous leprosy, the child was described as having lepromatous contact, whether or not this was the closest relationship or contact. About 7% of the children had such contact, a proportion consistent with the results of earlier surveys (Brown, 1959), in which 8% of leprosy patients in eastern Uganda were found to have lepromatous leprosy.

Method of analysis

The effect of genetic relationship was studied in two ways: first by examining the *prevalence* of leprosy amongst the children at intake to the trial according to genetic relationship with an index case, and then by examining the *incidence* with respect to this factor as the trial progressed. Other variables taken into account were the age of the child, the type of leprosy in the index case(s), the grade of physical contact, and the number of index patients.

RESULTS

Children at intake

During the main and subsidiary intakes 20 990 children were registered for the trial. The majority (17 043 or 81%) were under 10 years of age, including 4 477 (21%) who were under two years of age. On entry to the trial a total of 390 children were found to have leprosy lesions, and 138 were noted as having lesions of doubtful aetiology. Some of the lesions classed as 'doubtful' on entry were later confirmed to be leprosy, giving a total of 429 children who were considered to have had the disease at intake.

As the trial progressed it was found that 58 children were neither in contact with nor related to a known leprosy patient. After excluding these from the present study there remained 20 932 children, of whom 411 were considered to have had leprosy at intake.

Variations in the prevalence of leprosy according to genetic relationship

No cases of leprosy were found amongst the children under two years of age, nor amongst the children in the subsidiary intake. These children were therefore excluded from the analyses of prevalence at intake, leaving 16 093 children, of whom 411 (26/1000) had leprosy lesions.

It was found that, amongst the 1 202 children related to or in contact with a case of lepromatous leprosy, the crude prevalence rate of leprosy was 38/1000, compared with 25/1000 amongst the other children (Table 2). After standardization by the indirect method for the distributions of age, number of index cases (one or more than one), degree of closest genetic relationship and grade of closest contact with a patient, these rates were 38·5/1000 and 24·5/1000 respectively. The

Table 2. *Prevalence of leprosy in children aged two years or more at intake to the trial according to the number of index cases and the type of leprosy in those cases*

No. of index cases and type of leprosy in those cases		No. of children aged ≥ 2 years	Children with leprosy		
			No.	Rate per 1000 (crude)	Rate per 1000 (stand.)*
One case	Lepromatous	991	30	30	31.2
	Non-lepromatous	13 831	306	22	22.9
	Total	14 822	336	23	23.5†
Two or more cases	≥ 1 Lepromatous	211	16	76	69.1
	0 Lepromatous	1 024	58	57	38.2
	Total	1 235	74	60	42.3†
All	≥ 1 Lepromatous	1 202	46	38	38.5‡
	0 Lepromatous	14 855	364	25	24.5‡
	Not known	36	1	28	—
	Total	16 093	411	26	25.5

* Standardization by indirect method for age, degree of closest contact, and degree of closest genetic relationship with an index case.

† Additional standardization for proportion with a lepromatous contact.

‡ Additional standardization for proportion with multiple contact.

difference between the standardized rates was statistically significant ($P = 0.02$, Cochran's method of comparison) (Cochran, 1954).

There were 1235 children who were related to or in contact with more than one index case. In these children the crude prevalence rate was 60/1000, compared with 23/1000 in children related to or in contact with only one known index case (Table 2). The standardized rates (indirect method, for age, closest genetic relationship, closest contact, and lepromatous/non-lepromatous contact) were 42.3 and 23.5/1000 respectively. The rate for children with more than one index case was significantly higher ($P < 0.001$).

Table 3 shows the distributions of closest genetic relationship and closest physical contact with a patient. About one quarter of the group of children had house contact, and the great majority of these (92%) had a first-degree relative with leprosy. Of the rest of the group, about one-third had compound contact, and two-thirds had visiting contact. The genetic relationship for these children was generally of degree two or more.

The closest degrees of contact and genetic relationship for the children found to have leprosy are also shown in Table 3, together with the standardized prevalence rates these represent. Any interpretation of these rates must take into account the possibility that some bias may have arisen, because of the way in which the children who were eligible for the trial were identified. There was an obvious difficulty in ensuring that *all* the children with only a weak genetic relationship and distant contact were included. It thus seems probable that some of these children were missed, particularly those who were free of leprosy symptoms, and so the recorded prevalence rate in this group may be higher than the true value.

In looking for an effect of genetic relationship on the prevalence rates, attention had thus to be limited to the children in house or compound contact. Since nearly

Table 3. *Prevalence of leprosy in children aged two years or more at intake to the trial according to closest genetic relationship and closest contact with a leprosy patient*

Degree of closest contact		Degree of closest genetic relationship						All
		1	2	3	4	≥ 5	Not known	
House	Total	3 577	161	30	6	96	0	3 870
	Lep.*	121	4	1	1	1	—	128
	Rate†	(29·9)	(27·6)	—	—	—	—	(29·6)
House/ compound	Total	100	2	0	0	0	0	102
	Lep.	15	0	—	—	—	—	15
	Rate	—	—	—	—	—	—	(52·7)
Compound	Total	303	1 667	560	169	1 266	9	3 974
	Lep.	7	35	14	2	20	0	78
	Rate	(15·4)	(21·0)	(27·0)	(13·6)	(16·8)	—	(19·6)
Visiting	Total	42	1 811	1 397	684	3 978	17	7 929
	Lep.	2	38	31	10	95	0	176
	Rate	—	(21·8)	(22·8)	(16·5)	(26·7)	—	(24·0)
None	Total	2	110	66	10	20	4	212
	Lep.	1	6	3	1	2	0	13
	Rate	—	—	—	—	—	—	(70·7)
Not known	Total	0	0	0	0	0	6	6
	Lep.	—	—	—	—	—	1	1
All	Total	4 024	3 751	2 053	869	5 360	36	16 093
	Lep.	146	83	49	14	118	1	411
	Rate	(30·1)	(23·0)	(24·9)	(18·3)	(24·2)	—	(25·5)

* Children with leprosy.

† Per thousand, standardized by indirect method for age, lepromatous contact and multiple contact.

all the children with house contact had a first-degree relative with leprosy, it was not possible to look for an independent effect of relationship within this group. For children in compound contact, Table 3 shows that there was possibly some difference in prevalence according to the degree of closest genetic relationship with a patient, the prevalence apparently decreasing as the relationship became more distant. However, any such effect must have been small, if indeed it existed at all.

Children during follow-up

The children in the main intake were followed for a period of about 8 years, and each child who could be found was examined for signs of leprosy after average times of 2, 4, 6 and 8 years. The children admitted to the trial while the first follow-up was in progress (subsidiary intake) were followed for about 6 years.

Table 4 shows the numbers of children at each visit who were followed up to that time, excluding those who had been found to have leprosy at a previous examination. A child was considered to be followed up to the time of a specific visit if he or she was present for examination either at that time, or at a later visit. A child was considered to have leprosy at the time of a follow-up visit either

Table 4. Cases of leprosy discovered at each follow-up examination according to tuberculin and vaccination status at intake

		Follow-up examination											
		1			2			3			4		
Initial tuberculin and vaccination status	Intake total healthy children†	With* leprosy		Total	With* leprosy		Total	With* leprosy		Total	With* leprosy		Total
		No.	Per 1000‡		No.	Per 1000‡		No.	Per 1000‡		No.	Per 1000‡	
Negative or positive grades I-II													
Unvaccinated	8268	103	13	7795	54	7	7322	30	4	6057	14	2	6057
BCG-vaccinated	8128	22	3	7761	6	1	7393	10	1	6095	4	1	6095
Positive grades III-IV													
Unvaccinated	1073	10	10	999	2	2	935	2	2	719	2	3	719
Total (main intake)	17469	135	8	16555	62	4	15650	42	3	12871	20	2	12871
Not tested (subsidiary intake)													
Unvaccinated	—	0		956	0		914	1	1	792	2	3	792
BCG-vaccinated	—	0		952	0		907	0		810	0		810
Total (subsidiary intake)	—	0		1908	0		1821	1	1	1602	2	1	1602
Grand total	17469	—		18463	62	3	17471	43	2	14473	22	2	14473

* Definition in text.

† Excluding those for whom either closest genetic relationship or closest contact was unknown.

‡ Crude rate.

if leprosy was discovered then, or if suspicious lesions were first found at that time and later confirmed to be leprosy. There were 6 children who were absent for a particular follow-up examination, but were present and showing leprosy symptoms at the next. These are included in the table as if they were healthy at the time of the former examination. Children who had leprosy at entry to the trial or, in the case of children in the main intake, who were absent for the initial tuberculin testing, are not included in the table. The remaining children are grouped according to their tuberculin status on entry, and according to whether or not they received BCG vaccination. Both of these factors have already (Brown *et al.* 1968) been shown to be related to the development of leprosy during the period of follow-up.

At the first follow-up examination, 17048 (97.6%) of the 17469 leprosy-free children admitted to the trial during the main intake were present. Including the children admitted to the trial in the subsidiary intake, the percentage follow-up achieved at each of the next three examinations was 95.0%, 89.9% and 74.4% respectively. Some children were known to have died between visits, these deaths being mainly before the first follow-up examination amongst children aged two years or less on intake. The absentee rate, excluding deaths, was highest amongst the oldest children. This was mainly because of migration in connection with employment, education and marriage.

The crude prevalence rates of leprosy found at each follow-up visit in children who were healthy at the previous visit are shown in Table 4. These may be considered to be estimates of the two-year incidences of leprosy between the visits.

Leprosy during the follow-up period according to genetic relationship

The distribution of the children developing leprosy during the follow-up period according to closest genetic relationship with an index case at intake is shown in Table 5. When interpreting the differences in the rates between the genetic relationships, allowance must be made for the amount of physical contact that the children had with leprosy patients. From Table 3 it may be seen that about 89% of the children having a first-degree relative with leprosy were in house contact with the patient, compared with less than 5% in house contact for the other genetic relationships. Because of the small numbers of children in house contact whose closest genetic relationship was not of degree one, it was impossible to distinguish an independent genetic component for the children in house contact. The only children for whom a genetic effect might have been distinguishable were those with only either compound or visiting contact.

Table 6 shows the rates of leprosy found amongst the children with compound or visiting contact, according to the closest genetic relationship, at each follow-up examination. The rates are standardized for age, tuberculin and vaccination status at intake, lepromatous and multiple contact. The results of all the follow-up examinations are combined by summation in the 'Total' column.

It may be seen that, for the children with compound contact, there was no evidence of a trend of decreasing incidence with decreasing genetic relationship. For the children with visiting contact, the summed rate for those having only a

Table 5. Cases of leprosy discovered at each follow-up examination according to closest genetic relationship with a patient at intake

Degree of closest genetic relationship	Follow-up examination											
	1			2			3			4		
	Total children	With leprosy*		Total children	With leprosy*		Total children	With leprosy*		Total children	With leprosy*	
		No.	Rate†		No.	Rate†		No.	Rate†		No.	Rate†
1	4123	58	12.7	4383	23	5.1	4115	21	4.2	3358	9	2.3
2	4010	27	6.9	4439	16	3.6	4191	4	1.0	3534	4	1.2
3	2208	15	6.8	2406	5	2.1	2304	5	2.4	1928	2	1.1
4	975	6	7.1	1088	3	3.1	1038	2	2.2	877	2	2.7
5 or more	5732	29	5.3	6147	15	2.4	5823	11	2.0	4776	5	1.1
All	17048	135	7.9	18463	62	3.4	17471	43	2.5	14473	22	1.5

* Definition in text.

† Rate per 1000 standardized by indirect method for age, tuberculin and vaccination status at intake, lepromatous and multiple contact.

Table 6. *Standardized* rates of leprosy during period of follow-up according to degree of contact with a patient at intake*

Closest contact and genetic relationship	Follow-up examination				Total	Mean no. of children followed per examination
	1	2	3	4		
House contact						
All	12.7	5.2	4.6	2.1	24.6	3934
House/compound contact.						
All	0.0	0.0	0.0	0.0	0.0	76
Compound contact						
1	11.4	0.0	0.0	3.0	14.4	239
2	6.1	5.3	1.1	0.7	13.2	1824
3	3.2	2.9	1.7	1.8	9.7	605
4	6.5	5.8	0.0	7.2	19.4	195
5 or more	6.6	3.5	2.2	1.8	14.1	1330
All	6.3	4.1	1.4	1.7	13.5	4193
Visiting contact						
1	0.0	0.0	0.0	0.0	0.0	31
2	7.5	2.0	1.1	1.9	12.4	1931
3	8.0	1.9	2.7	0.8	13.5	1488
4	5.8	2.5	2.8	1.7	12.8	779
5 or more	5.0	2.2	2.0	0.9	10.1	4167
All	6.2	2.1	2.0	1.2	11.4	8396
No contact						
All	14.6	4.0	0.0	0.0	18.7	264
All	7.9	3.4	2.5	1.5	15.2	16864

* Rates per 1000, standardized by indirect method for age, tuberculin and vaccination status at intake, lepromatous and multiple contact.

distant genetic relationship (degree 5 or more) with a leprosy patient was lower than that for children having a closer relationship (degree 2 to 4), but again there was no convincing evidence of an overall trend.

DISCUSSION

Various workers have reported observations consistent with a genetic influence on susceptibility to leprosy. In 1848 Daniellsen and Boeck (Daniellsen & Boeck, 1848) noted a tendency for some families to have a high concentration of leprosy cases. More recently Beiguelman (Beiguelman, 1972) showed that, in families in an endemic area, the recurrence of leprosy cases was non-random. He also demonstrated a familial association in the type of leprosy manifested, whether lepromatous or tuberculoid, as had previously been found by Dungal and Spickett (quoted in Spickett, 1964).

Several studies of twin pairs have been reported (Spickett, 1962; Mohamed-Ali & Ramanujam, 1966; Chakravarti & Vogel, 1973). The results indicate a high degree of concordance for both leprosy and type of leprosy in identical, but not in non-identical twins. Unfortunately all these studies are open to the possibility of

an ascertainment bias, by which the concordance of identical twins could easily be overestimated.

Differences in susceptibility to leprosy between separate racial groups have been cited as evidence for the action of a genetic component (Brown, 1959; Spickett, 1964). However, differences in the amount of contact with the disease are also sufficient to account for such variation. More convincing are the racial differences in the relative prevalence rates of lepromatous and tuberculoid leprosy (Spickett, 1964).

Another approach to the question has been in attempts to relate the incidence of leprosy to various genetically controlled determinants. These have included studies of blood group, atypical enzymes, G6PD deficiency, taste sensitivity to phenylthiourea, and HLA antigens (Beiguelman, 1972; Vogel, 1968; Thomas & Job, 1972; De Vries *et al.* 1976; World Health Organization, 1970). The results are in some instances controversial, but together they point towards a definite genetic influence on susceptibility to leprosy.

The present study aimed to examine the occurrence of leprosy in a large group of children with differing family (genetic) histories of leprosy, to see if the effect of a genetic factor could be shown. The data on family history and degree of exposure to the disease were necessarily limited, but should have been sufficient to reveal any important genetic influence. That such an influence was not shown was due partly to the difficulty of distinguishing genetic from environmental effects for many of the children. However, for the children for whom the effects *could* be separated, *no* evidence of a genetic factor was found. Thus the conclusion is that, if a genetic component of susceptibility existed, its influence was small. The large apparent differences according to genetic relationship may therefore be attributed to the differing degrees of physical contact.

In this study it was unfortunately not possible to examine the occurrence of leprosy in only those children with a lepromatous contact, since the numbers were small. Since the ability to develop lepromatous leprosy may be a genetically transmitted character (Beiguelman, 1972; Newell, 1966), it would be of interest to study this in a population with a higher proportion of lepromatous cases.

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