Papers and Originals

B.C.G. Vaccination of Children Against Leprosy: First Results of a Trial in Uganda

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The original observation of Fernandez (1939) in Argentina that conversion to lepromin positivity occurs in a large proportion of lepromin-negative children following B.C.G. vaccination has been confirmed by many workers, both in South America—for example, Rosenberg *et al.*, 1950—and in other parts of the world, in particular in Nigeria (Lowe and McNulty, 1953) and in Uganda (Kinnear Brown and Stone, 1959a). (Lepromin is a suspension of killed human leprosy bacilli. There are two types of positive reaction which may be observed when a standard amount is injected intradermally—namely, an early hypersensitivity reaction at about 48 hours (the Fernandez reaction) and a late reaction presenting as a nodule at about three to four weeks (the Mitsuda reaction). In leprosy patients the Mitsuda reaction is regarded as having the greater prognostic value.) Moreover, it has been shown that individuals found to be lepromin-positive are less likely to develop leprosy subsequently than those found to be lepromin-negative, and that a smaller proportion of the cases developing in those initially lepromin-positive are of the more serious lepromatous type of the disease (Dharmendra and Chatterjee, 1955). Taken together these findings suggest the possibility, originally advanced by Fernandez (1939), Ginés and Poletti (1945), and Chaussinand (1949), that B.C.G. vaccination, known to be highly effective against tuberculosis (see, for example, Medical Research Council, 1956, 1959, 1963), might confer some protection against leprosy, which is also caused by a mycobacterium.

A few small studies of B.C.G. vaccination against leprosy have been made since 1955, and are discussed later in this report, but because of their smallness and other limitations they have not been generally accepted as demonstrating whether B.C.G. vaccination is of value in preventing this disease. For several years efforts have been made by the Leprosy Committee of the Medical Research Council in London to establish a large-scale trial which would yield scientifically acceptable results, and this has also been urged by successive W.H.O. Expert Committees on Leprosy (World Health Organization, 1953, 1960). The investigation reported here, which started in 1960, was the first large-scale trial to be established. The plans were submitted by the Uganda Government in 1959 to the Leprosy Committee of the Medical Research Council, and close scientific contact with this committee has been maintained. A preliminary report, describing the initiation of the investigation, has already appeared (Kinnear Brown and Stone, 1963).

Plan and Conduct of the Trial

Extensive surveys of the prevalence of leprosy in the general population were made throughout Uganda between 1952 and 1959 (Kinnear Brown, 1952, 1955, 1957, 1959), and these provided background information essential for planning the

investigation. Patients with lepromatous leprosy formed only a small proportion of the total, amounting to about 8% of patients of all ages in Eastern Uganda. The surveys had also shown that, as in other countries, the prevalence rate steadily increased with age among children, reaching a peak in Uganda in the age group 10 to 14 years. It was therefore decided that the effects of B.C.G. vaccination should be studied in children, and preferably in young children, since the effectiveness of vaccination might well depend on whether or not it preceded natural infection with leprosy bacilli. It was, however, impracticable to undertake the trial entirely in the group least likely to have been infected—namely, children aged less than, say, 1 year—because of the difficulty of obtaining adequate numbers, and it was therefore agreed to concentrate on those aged up to 10 years (but not to turn away older children if they presented themselves for admission), and to swell the numbers of the very young children by a secondary intake, in the course of the follow-up, of children born since the main intake period.

It was also decided to undertake the trial in relatives and contacts of known leprosy patients (whether their disease was lepromatous or non-lepromatous) rather than in the general population, though this increased the chance that an infection with leprosy bacilli might have preceded the vaccination. This decision was reached partly because an analysis of the prevalence of leprosy found in the general population surveys (9 per 1,000 at ages under 15 in Eastern Uganda) indicated that it would be necessary to admit very large numbers of children to the trial from such a population to obtain a definite answer on the value of vaccination, whereas smaller numbers would suffice if there was a greater risk of exposure to the disease, coupled with a greater genetic disposition (Kinnear Brown, 1955, 1957, 1959), and partly because it would be very much easier in a long-term investigation to obtain and keep the co-operation of child relatives and contacts of known cases than of children in the general population. It was not possible to undertake the trial only in relatives and contacts of patients with lepromatous leprosy, as had originally been hoped, since many of these were unmarried, or had small families, and the numbers would not have been adequate.

It was recognized that the incidence of leprosy in the vaccinated children must be compared with the incidence in a similar but unvaccinated group, and that this comparison would not be valid unless those suitable for vaccination were assigned at random to the vaccinated and unvaccinated groups. Because of the possibility of adverse reactions to B.C.G. vaccine in some of the children who had already been infected with tubercle bacilli, it was decided to make tuberculin tests on all children on entry to the investigation, using a multiple-puncture (Heaf)

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technique, and not to vaccinate any of those with strong positive reactions (Grade III or IV). Those with negative reactions (Grade O), or with weak positive reactions (Grade I or II), would be assigned at random to the vaccinated and unvaccinated groups, since it was known from a survey in 1958 (World Health Organization, 1959) that in Uganda, as in many other countries, weak positive reactions were common and could be attributed to infections with some organism antigenically related to, but not identical with, the tubercle bacillus.

In the early stages of the intake in some of the eitelas (rural population units) the children also had an initial depot lepromin test (Kinnear Brown and Stone, 1959a, 1959b, 1959c, 1960). This was later discontinued because extra visits to the villages were needed for reading the results, both before and after vaccination, and this was unduly protracting the intake. In all, about one in eight of the children in the trial was given a lepromin test, and because of this small proportion the results of these tests will not be examined in the present report.

The area chosen for the trial was the district of Teso, in the Eastern Region of Uganda, which has an area of 4,649 square miles and a population (1959 census) of 453,474, including 154,466 children under 16 years of age. The general leprosy prevalence in the area, according to the original surveys, was 25 per 1,000 population of all ages, and this is about twice the average value for the whole of Uganda. The area had the advantage that all parts were accessible from the leprosy settlement at Kumi-Ongino, which could therefore be used as a base for the investigation, and the area appeared to be large enough to yield adequate numbers of children for the inquiry.

Preliminary calculations could be only approximate, because the general population surveys gave no reliable information on the expected incidence of leprosy in a group of children related to or in contact with patients (especially since many of the patients were by the time of the trial receiving specific treatment for their leprosy), nor on the level of migration or other losses from observation during the follow-up. They did, however, indicate that it would be desirable to admit several thousand children to the investigation to be reasonably sure of detecting a moderate effect from B.C.G. vaccination, if it occurred, in the course of a follow-up period which was envisaged as continuing for at least five years. It was recognized also that even larger numbers would be needed if the investigation was to give more detailed information—for example, on whether any benefit from B.C.G. vaccine depended on the age at vaccination, or on the degree of contact with the leprosy patient. It was therefore decided to admit as many children to the trial as possible from the Teso district. As explained in the Appendix, the information obtained in the early part of the intake was used to check the adequacy of the numbers admitted up to that time, and the final total of participants from Teso appears to be ample to answer the more detailed points as well as the general question of the effect of B.C.G. vaccination in leprosy.

Main Intake

Each county in Teso has a leprosy assistant in charge of a treatment village, and a health inspector with auxiliary staff. In each eitela the health staff and chiefs completed a form for each child believed to be related to a patient, the latter being seen by the leprosy assistant to confirm the diagnosis. The leprosy assistant had a list of lepromatous patients in each of his eitelas who had been treated at the Kumi-Ongino leprosy settlement during the previous 10 years, and his own list of patients of all types who had attended at his own treatment village. These lists enabled children to be traced who might otherwise have been missed. Each record included the age and sex of the child, the type of leprosy in the index case, whether this case had been treated or not, the relationship of the index case to the child, and the degree of contact.

Although it was explained that this was an attempt to prevent leprosy in those in contact with the disease, it was not easy to dispel the idea that this was a new treatment. In the beginning, therefore, some children appeared with obvious disease who were not related to or in contact with the index case, and were excluded, but eventually the children were registered in their natural family groups without any loading with unconnected patients.

Two visits were made to each eitela; at the first the children were examined for leprosy and tuberculin-tested. At the second, a week later, the tuberculin test was read, and alternate eligible children were given B.C.G. vaccine.

At the first session each child was given a serial number, and was photographed with a parent or other adult near relative, the serial number being included on the photograph to assist identification. (If the child was small the photograph of the relative was quite as useful for identification as that of the child.) A careful examination of the child was made by one or both of us, usually with a leprosy assistant, and the size, position, and other details of any skin lesion, whether due to leprosy or not, were noted on the child's record for future reference. In some instances it was uncertain whether or not a lesion was due to leprosy; the use of local applications to skin lesions is common and a great hindrance to correct diagnosis. Each child was then given a Heaf multiple-puncture tuberculin test; concentrated P.P.D. tuberculin (State Serum Institute, Copenhagen) was used, and was stored in a refrigerator until required.

At the second visit the tuberculin tests were read. The children were not seen in the order of their serial numbers but just as they came, and each alternate child with a negative, Grade I, or Grade II result, who was free from leprosy, was vaccinated. Children with skin lesions due to leprosy, or with lesions of doubtful aetiology, were not eligible for vaccination, since B.C.G., like other inoculations, may precipitate reactions in leprosy patients (Wade, 1960). (In the early stages some children with doubtful lesions were alternated for vaccination, until it was realized that this was inadvisable.) Alternate allocation to the vaccinated and unvaccinated groups was chosen as the simplest practical method of random allocation in the field, and no particular difficulties were experienced in applying it. Routine batches of freeze-dried B.C.G. vaccine (Glaxo) were used throughout; they were stored in a refrigerator until required. A dose of 0.1 ml. of the reconstituted vaccine (slightly reduced for small babies) was given by intradermal injection. The site of vaccination was over the deltoid muscle, or in small babies near the inferior angle of one of the scapulae. The left arm was used in some eitelas, the right arm in others. Different arms were used, so that, if a child should ever be seen casually—that is, not at an organized follow-up—it would not be immediately obvious whether any visible scar was caused by B.C.G. vaccination, smallpox vaccination, or trauma. An identity card for the child, together with a print of the photograph, was presented to the child or the adult relative, and these were usually treasured and produced spontaneously at the follow-up.

The district is rural, and the population scattered, and each eitela had to be visited separately by the investigators to examine, tuberculin-test, and vaccinate the children. In the eitela the work, from choice and often of necessity, was undertaken almost entirely in the open. Frequently there was little shade, but it is an advantage to examine for leprosy in full daylight. If there was no natural screen to give older children some privacy during the examinations, an artificial screen was erected. Vaccinations were performed in a convenient near-by hut or other building to protect the vaccine from sunlight.

The intake began in September 1960 and continued until September 1962. The work was seriously interrupted by extensive and unprecedented floods in 1961, but, in all, more than 17,000 children were included.

Further Tuberculin Tests

A number of eitelas were revisited one or two years after the visit for the main intake, and the participants, whether vaccinated or not, were given a further tuberculin test. The purpose of this was to provide a check that the potency of each batch of vaccine used was satisfactory under field conditions, as judged by the development of tuberculin sensitivity following vaccination.

Follow-up

It is intended to revisit all the eitelas periodically for a number of years, and to examine all the participants for signs of leprosy. The first series of follow-up visits began in May 1963 and lasted until May 1964. The second began in July 1964 and is still in progress. For a variety of practical reasons, such as the weather (many eitelas cannot be reached during the rainy season), and in order not to overburden local staffs, the eitelas were visited in a different order during the first follow-up from that at intake, but this is of no particular consequence.

The procedure in each eitela was as follows: A group of about 12 to 20 children was collected together, either by the health inspector calling out names from a register, which gave no information on tuberculin-test results or vaccination, or by a direct check of identity cards and photographs, as they were presented by the children, against the same register. There was thus no particular order in which the children were examined for skin lesions. Each child's identification was confirmed, the date was stamped on the back of the field record for the child, and a piece of adhesive paper was placed on *every* child on the site where a vaccination would have been made, covering any scar which happened to be there. The paper was applied by a different person at each session. The main purpose of the paper was to conceal from those examining the skin subsequently for leprosy lesions whether a participant had been vaccinated or not. It was, however, generally accepted by the children and their relatives that the paper was a means of recognizing which children had been checked in for examination, and for this it was also useful.

A thorough first examination of each child for skin lesions was carried out by leprosy assistants working some 50 yards from where we sat checking in new arrivals, but within our view. Two of these leprosy assistants were permanently attached to the team, and the third was brought in from the local treatment village. Their duty was to call attention to any skin lesion of whatever kind (though they were quite capable of distinguishing leprosy from other lesions). Sometimes the assistants examined singly, sometimes two together. Periodically and unexpectedly one of us examined the children or watched what the assistants were doing. There was no opportunity for the assistants to discover whether a particular child had been vaccinated or not, even had they had any reason to do so, partly because of this general oversight of their activities, partly because of the adhesive paper, and partly because the children themselves could not have given reliable information if asked. (For example, quite apart from simple failure to remember, there is no specific word in Teso for vaccination, any scar under the plaster might be due to some cause other than B.C.G. vaccine, and tuberculin-testing and vaccination are often confused.) One of us (M.M.S.) is familiar with the local language and would readily have noticed any unusual questioning or procedure on the part of the leprosy assistants. Their initial screening may therefore be accepted as not having been influenced by knowledge of the vaccination or tuberculin status of the child.

The children with skin lesions were then referred to us for a final examination and diagnosis, usually about half an hour after the initial identification check. The adhesive paper was still in place, and this examination also was therefore not

influenced by knowledge of the vaccination or tuberculin status of the child. We examined separately, gave our agreed diagnosis aloud, and then asked the health inspector to trace the field record. The description of the skin lesions, and the diagnosis, were entered on the back of the field record without referring to any of the vaccination or tuberculin details on the front.

In view of the continuous long-term nature of the project it was impracticable to use a separate leprosy consultant as an assessor. The follow-up procedure described above was devised to permit us to make independent assessments of the leprosy lesions despite our administrative involvement, without any bias from knowledge of the vaccination or tuberculin history.

It was open to the parents of any child developing skin lesions, or in whom lesions of doubtful aetiology became more definite, to apply for the child's admission to the Kumi-Ongino leprosy settlement. There the medical superintendent made his own diagnosis and assessed the need for treatment. A number of the trial children applied for admission in this way, and this has provided a valuable independent check of our diagnostic standards. In two instances there was a slight difference of opinion on the need for early treatment, and for these two patients the medical superintendent's decision was accepted.

In the main the forms of leprosy seen at intake and during the follow-up have been early, and many of these, from past experience, were expected to resolve spontaneously. It was therefore the general policy to observe the course of the lesions without treatment. It should, however, be made clear that whenever treatment was thought to be necessary it was recommended, and parents were not discouraged from seeking a second opinion at the leprosy settlement if they wished to.

Progress of the Trial

Number of Children

The total number of children registered for the trial during the main intake was 19,079, and 1,292 have been excluded from all the analyses during the follow-up. These comprise 894 who, though tuberculin-tested, did not attend the vaccination session, 42 who were unwell at this session, 218 children from a few eitelas visited at the very beginning of the intake, when the vaccination and alternation procedures were still being tried out, and 138 who had lesions of doubtful aetiology and who were not alternated for vaccination. A further 390 children who had leprosy lesions at intake are considered only in an analysis of the progress of these lesions since intake. The other analyses of results all relate to the remaining 17,397 children (see Table I), of whom 8,152 were tuberculin-negative, or tuberculin-positive in Grade I or II, and were left unvaccinated; 8,149 had the same tuberculin status and were given B.C.G. vaccine; and 1,096 were tuberculin-positive in Grade III or IV and were not eligible for vaccination. The great majority of the children (14,024 or 80.6%) were aged under 10 years at intake, and these included 1,361 (not shown separately in the Table) who were aged under 1 year.

TABLE I.—Numbers of Children Admitted during Main Intake, According to Tuberculin Status (after Exclusions)

Age (Years)	Tuberculin Status			Total Children
	Negative (Grade O) or Positive (Grade I or II)		Positive (Grade III or IV)	
	Unvaccinated	Vaccinated		
0—	1,367	1,306	10	3,683
2—	1,592	1,521	62	3,175
4—	1,633	1,663	144	3,440
6—	1,281	1,283	188	2,752
8—	882	933	159	1,974
10—	570	596	156	1,322
12—	498	484	176	1,158
14—	251	284	110	645
16 or more	78	79	91	248
All ages	8,152	8,149	1,096	17,397

Prevalence of Leprosy at Intake

From the point at which it appeared that the intake was not being loaded with unrelated leprosy patients the prevalence of leprosy among the entrants was 26 per 1,000 (364 patients among 14,188 children), compared with 9 per 1,000 among the general child population aged under 15 years in the original surveys in Eastern Uganda (Kinnear Brown, 1955). This finding shows the value of having undertaken the investigation in children related to or in contact with leprosy patients.

Results of Tuberculin Retesting

The results of the tuberculin retests in a sample of children given each batch of B.C.G. vaccine are not reported in detail here, but they gave no indication that any of the batches used was technically unsatisfactory.

Examinations During First Follow-up

During the first follow-up (Table II) it was found that 227 children (1.3%) had died since intake, and a further 718 (4.1%) were not examined.

TABLE II.—Numbers of Children who were Found to Have Died, or were Absentees from Examination, during First Follow-up

Age in Years at Intake	Total Children	Deaths		Absentees	
		No.	%	No.	%
0—	3,683	125	4.7	67	2.5
2—	3,175	46	1.4	97	3.1
4—	3,440	27	0.8	111	3.2
6—	2,752	9	0.3	99	3.6
8—	1,974	7	0.4	93	4.7
10—	1,322	5	0.4	66	5.0
12—	1,158	4	0.3	95	8.2
14—	645	1		66	
16 or more	248	3	0.4	24	10.1
All ages	17,397	227	1.3	718	4.1

Of the deaths 125 were in children aged under 2 years on admission to the trial; 49 of these deaths occurred in the vaccinated group, compared with 74 in the corresponding unvaccinated group. This difference is just significant at the 5% level; if it represents a real contrast in mortality and not an unusual chance fluctuation it may reflect a reduction in tuberculosis mortality in these young children as a result of B.C.G. vaccination. In those aged 2 or more on admission the numbers of deaths during the first follow-up were similar in the vaccinated and unvaccinated groups.

The absentee rate of 4.1% was much lower than expected in view of the length of time between the intake and the follow-up, which varied from one to three years in different eitelas, the average interval being about two years. Table II shows that the absentee rate was least among the youngest children; it was 2.5% for those aged under 2 on admission and rose to 10.1% for those aged 14 or more on admission. The main reasons were family removals, migration in connexion with employment and education, and the marriage of older girls. Those who had moved were often seen and examined in a different eitela from that in which they entered the trial, and, if so, they were not included among the absentees. Some of the absentees from the first follow-up have already been seen during the incomplete second follow-up, and have therefore not been lost from observation.

Thus in all more than 94% of the original 17,397 children were seen and examined for leprosy during the first follow-up.

Subsidiary Intake

During the first follow-up a further 1,926 children (including 979 aged less than 1 year) were admitted to the trial without

tuberculin testing, and alternate children were given B.C.G. vaccine. These children were mainly those born since the intake into the trial families. No findings on these additional children can be presented until they have been examined during further visits to the eitelas.

Results at End of First Follow-up

Progress of Leprosy Patients Discovered at Intake

Table III summarizes the findings at the first follow-up in the 390 leprosy patients discovered at intake. After excluding 47 patients whose progress could not be assessed at the first follow-up because their lesions were obscured by local treatment, or who had been treated before the intake, or who were absent, 45% of the remaining 343 had extending lesions or had been admitted to treatment, 27% had stationary, and 29% had resolving or apparently healed lesions.

TABLE III.—Progress at First Follow-up of Leprosy Patients Found at Intake

Status at First Follow-up	No. of Patients	%*
Patients admitted to treatment	57	17
Lesions extending	96	28
Lesions stationary	92	27
Lesions resolving	71	21
Lesions resolved	27	8
Lesions obscured by local treatment	9	—
Patients treated before intake	4	—
Patients absent at first follow-up	34	—
Total	390	—

* Of the total of 343 in the first five categories.

Cases of Leprosy Developing after Intake

Of the 17,397 participants 154 had had lesions of doubtful aetiology at intake, and had been examined in eitelas at which it was still the policy to allocate them alternately (if in Grade O, I, or II) to the vaccinated and unvaccinated groups (see above). The findings in this small group are given separately in the next section.

By the end of the first follow-up a total of 100 cases of leprosy had been discovered among the other 17,243 participants, none of whom had shown any signs of leprosy at their initial examination. In addition, a number of these children were noted as having suspicious lesions at the follow-up, but no definite diagnosis could be made at the time. By now some of these children with suspicious lesions have been seen again during the second follow-up, which is still in progress, and in 16 it has become clear that the lesions noted earlier were due to leprosy. These 16 therefore represent additional cases of leprosy arising during the period of the first follow-up, giving a total so far of 116 cases developing during this period.

As would be expected in a population consisting of children, the lesions seen represented early forms of the disease. In individual cases they ranged from a single lesion, perhaps 1 in. (2.5 cm.) in diameter, either flat or raised, to several lesions of this or larger size, with or without nerve enlargement or tenderness. They were nearly all tuberculoid lesions. This type of disease usually takes many years to develop, by stages of regression and exacerbation, and does not reach an advanced stage with crippling until adult life.

Table IV shows the distribution of these 116 cases according to the tuberculin and vaccination status on entry. Considering first those who were tuberculin-negative or tuberculin-positive in Grade I or II at intake, there were 89 cases among the unvaccinated children, representing an incidence of 11.0 per 1,000 children, and 18 among the vaccinated children—namely, 2.2 per 1,000, which is one-fifth of the incidence in the unvaccinated group. The possibility of this difference having occurred by chance is remote (less than one in a million). The

percentage reduction in the incidence of leprosy in the vaccinated group, compared with the corresponding unvaccinated group, was thus 80%. Among those who were positive in Grade III or IV, none of whom were vaccinated, there were 9 cases or 8.3 per 1,000 children.

TABLE IV.—Cases of Leprosy Discovered in course of First Follow-up according to Tuberculin and Vaccination Status at Intake

Tuberculin Status at Intake (Heaf Grade)	Unvaccinated		B.C.G.-Vaccinated		Percentage Reduction Attributable to Vaccination
	Total Children	Cases of Leprosy Per No. 1,000	Total Children	Cases of Leprosy Per No. 1,000	
Negative: Grade O ..	2,930	20 6.8	2,844	4 1.4	79
Positive: Grade I ..	4,867	64 13.1	4,989	14 2.8	79
Grade II ..	274	5 18.2	258	0 0.0	100
Total (Grades O-II)	8,071	89 11.0	8,091	18 2.2	80
Positive: Grade III	847	7 8.3	—	—	—
Grade IV ..	234	2 8.5	—	—	—
Total (Grades III-IV) ..	1,081	9 8.3	—	—	—

Table IV gives the findings separately for those initially tuberculin-negative, those with Grade I and those with Grade II positive reactions. The percentage reduction in leprosy incidence in the vaccinated compared with the unvaccinated group was similar for each grade of initial tuberculin sensitivity.

The percentage reduction in leprosy incidence in the vaccinated group is shown, according to the age of the child at intake, in Table V. The percentage reduction did not appear to depend upon the age at vaccination.

TABLE V.—Cases of Leprosy Discovered in course of First Follow-up among Those Tuberculin-negative, or Positive in Grade I or II, according to Age and Vaccination Status

Age in Years at Intake	Unvaccinated		B.C.G.-Vaccinated		Percentage Reduction Attributable to Vaccination
	Total Children	Cases of Leprosy Per No. 1,000	Total Children	Cases of Leprosy Per No. 1,000	
0— ..	1,366	1 0.7	1,306	0 0.0	74
2— ..	1,588	7 4.4	1,518	2 1.3	90
4— ..	1,623	19 11.7	1,654	2 1.2	90
6— ..	1,251	17 13.6	1,274	6 4.7	65
8— ..	870	20 23.0	921	3 3.3	86
10— ..	561	10 17.8	587	1 1.7	90
12— ..	490	10 20.4	477	3 6.3	69
14— ..	247	3 12.1	277	1 3.6	82
16 or more	75	2 26.7	77	0 0.0	82
All ages ..	8,071	89 11.0	8,091	18 2.2	80

It will be noted from Table V that the attack rate of leprosy, in the absence of vaccination, rose from a very small figure in young children to a level of about 20 per 1,000 at the age of 8 years, this level persisting throughout the remainder of childhood. The gradient in attack rate with grade of tuberculin sensitivity, shown in Table IV, from 6.8 per 1,000 for those initially negative to 18.2 per 1,000 for those initially in Grade II, appears to be largely explicable in terms of age, the children initially in Grade II being on average substantially older than those initially tuberculin-negative. A fuller examination of the influence of initial tuberculin sensitivity on the incidence of leprosy will be made in a later report.

Development of Leprosy in Those with Lesions of Doubtful Aetiology at Intake

Of the 154 children just referred to, with lesions of doubtful aetiology at intake, 81 were tuberculin-negative, or positive in Grade I or II, and were left unvaccinated; 58 had the same

tuberculin status and were given B.C.G. vaccine; and 15 were tuberculin-positive in Grade III or IV, and were not eligible for vaccination. The disparity in numbers in the first two groups has arisen by chance within the scheme for alternate allocation of all eligible participants to these two groups as they presented themselves, and does not indicate a breakdown of that scheme.

By the end of the first follow-up 9 (11%) of the unvaccinated group, 9 (16%) of the B.C.G.-vaccinated group, and 5 (33%) of the tuberculin-positive (Grade III or IV) group had developed confirmatory signs of leprosy. Thus B.C.G. vaccination did not show any beneficial effect on incipient leprosy lesions.

Discussion

Previous Studies

There have been a few previous investigations in which the incidence of leprosy in children given B.C.G. vaccine has been contrasted with that in unvaccinated children, but in none of these, as far as we are aware, were the vaccinated and unvaccinated groups established by random allocation. De Souza Campos (1953) noted the appearance of 10 cases of leprosy (0.6%), none being lepromatous, during a period of about one year among 1,658 contacts (of all ages) given B.C.G. vaccine in Brazil, compared with 179 cases (5.4%), 47 being lepromatous, among 3,329 unvaccinated contacts observed during the same period. Fernandez (1955) observed 83 child contacts of lepromatous leprosy patients in Argentina for varying periods—in most for more than five years: 28 had been given B.C.G. vaccine, and 55, of whom 32 were tuberculin-positive initially, were left unvaccinated. Nine (32%) of the vaccinated contacts, 10 (43%) of the tuberculin-negative unvaccinated group, and 13 (41%) of the tuberculin-positive unvaccinated group, developed leprosy. The only lepromatous cases were 3 of the 10 in the tuberculin-negative unvaccinated group. The incidence was least in the vaccinated group, but the differences between the groups were not large.

Convit (1956) vaccinated a group of 584 persons of German stock in Venezuela with B.C.G. in 1950, and left another group of 522 unvaccinated; 239 of the first group and 101 of the second were aged under 10 years. Both groups were observed until 1955, by which time 3 (0.5%) of the vaccinated and 25 (4.8%) of the unvaccinated subjects had developed leprosy (their ages were not stated). There were 6 lepromatous cases, all in unvaccinated subjects. The two groups were evidently not established by random allocation, and they differed substantially in age-distribution. It is therefore not possible to be certain that the two groups were exposed to the same risks of contracting the disease, although this was stated to have been the case. The contrast in morbidity (and also in type of disease) was nevertheless impressive. Chatterjee *et al.* (1958) compared the incidence of leprosy in child contacts vaccinated with B.C.G. in a W.H.O. anti-tuberculosis campaign in South India in 1953 with that of child contacts who had not been vaccinated. Of 678 vaccinated children 5 (0.7%) had leprosy, whereas of 1,651 unvaccinated children 283 (17%) had leprosy, including 15 lepromatous cases. Again there was an impressive difference in type of disease as well as in incidence, but, as with the other investigations, there can be no certainty that the two groups had been exposed to the same risks of contracting the disease. Yanagisawa (1958) observed a total of 248 children in Japan, divided into tuberculin-negative vaccinated and unvaccinated groups, and a tuberculin-positive unvaccinated group, for more than 12 years after close contact with leprosy had been broken. The proportions developing leprosy were 5.1% of the B.C.G.-vaccinated group, 47.2% of the negative unvaccinated group, and 1.5% of the tuberculin-positive group; there were no differences between the groups in type of lesion.

Present Study

Because the present study was based on an effectively random allocation of the subjects with Grade II positive reactions (or less) to the vaccinated and unvaccinated groups, these two groups can be regarded as alike on entry to the investigation, apart from their vaccination status, and as exposed to the same risks of contracting leprosy subsequently. Moreover, the two groups have been followed similarly, and no bias has been allowed to enter into the assessment of the cases of leprosy developing among them. The difference in the incidence of the disease in the vaccinated and unvaccinated groups may therefore be attributed directly to the vaccine, and at the present stage of the follow-up it may be concluded that B.C.G. vaccination of children in Eastern Uganda has conferred substantial protection against early forms of leprosy for a period of one to three years.

This finding, strongly hinted at, though it could not be regarded as established, by the earlier inquiries, is remarkable from several points of view. In the first place the percentage reduction in the incidence of leprosy in the vaccinated compared with the unvaccinated group was 80%, which is closely similar to the corresponding reduction of 82% in the incidence of tuberculosis in schoolchildren in Britain in the first two and a half years after B.C.G. vaccination (Medical Research Council, 1956). It is surprising to find that B.C.G. vaccine, which is derived from an attenuated strain of bovine tubercle bacilli, appears to protect as effectively against leprosy, which is caused by a different mycobacterium, as against tuberculosis. However, this is in line with recent experimental work, which showed an almost complete suppression of multiplication of leprosy bacilli in the footpads of B.C.G.-vaccinated mice (Shepard, 1965).

Secondly, the percentage reduction in incidence appears to be the same whether the initial tuberculin status was negative, positive (Grade I), or positive (Grade II). The causes of low-grade tuberculin sensitivity in Eastern Uganda are not known, but whatever they may be the presence of such sensitivity to tuberculin does not appear to alter the reduction in leprosy incidence to be expected from B.C.G. vaccination.

Thirdly, and perhaps most surprisingly, the percentage reduction in leprosy incidence is apparently independent of the age of the child when vaccinated. A proportion of the older children will already have been infected with leprosy bacilli at the time of vaccination, and in such circumstances vaccination might have been expected to be less effective. In this connexion it is of interest that Yanagisawa (1958) commented that his results showed a beneficial effect of B.C.G. vaccination in a situation in which it was highly probable that infection with leprosy bacilli had preceded the B.C.G. vaccination in all the children receiving it. However, in the small group of participants with suspicious lesions initially, who were included in the random allocation process in the early stages of the intake for the present study, vaccination did not reduce the incidence of leprosy. There must therefore be some stage in the development of clinical leprosy, following infection with leprosy bacilli, after which vaccination is no longer able to modify or arrest the process. Indeed, there is a suggestion from the figures that in some individuals vaccination may even have stimulated the development of the disease, and it is relevant that two of the other 18 vaccinated participants who developed leprosy (Table IV) dated the first signs of their disease to the weeks immediately following the vaccination. If widespread B.C.G. vaccination is being undertaken in an area where leprosy is endemic, it would therefore be wise to screen the older children and to withhold vaccination from those with incipient leprosy lesions as well as those with obvious disease.

It must be emphasized that the forms of leprosy seen so far, both in the vaccinated and the unvaccinated groups, have been early, and some may resolve spontaneously. (Of the leprosy lesions detected at intake 8% had resolved completely one to

three years later, and a further 21% appeared to be resolving at that time.) It is thus possible that the early types of leprosy skin lesion in children represent a natural immunological response to infection with leprosy bacilli, and vaccination may have done no more than modify this response to a first infection. It is therefore of particular importance to follow the trial children for some years to see how these lesions evolve. If a greater proportion of the lesions in the unvaccinated children resolve than in the vaccinated children, the final conclusion on the value of B.C.G. in leprosy may well be substantially altered. As mentioned above, the prevalence of leprosy in Uganda increases to a peak at ages 10 to 14 years, and it would be valuable to follow the trial children at least until the age of 15 years, if this proves to be practicable.

Other Large-scale Trials

Apart from this uncertainty attached to the short period of observation it would be unwise to conclude that the present results will necessarily apply in other areas. As indicated above, only 8% of the leprosy patients in Eastern Uganda can be classed as having lepromatous leprosy. Lepromatous leprosy, being bacteriologically positive, is usually regarded as the principal source of infection; the other main type of the disease, tuberculoid leprosy, is usually bacteriologically negative and was once thought to be relatively uninfected (the other two types, "borderline" and "indeterminate," are less common and are unstable; they usually evolve into one of the two main or "polar" types). However, there appears to be an imperfectly understood tendency for leprosy to be particularly widespread in communities in which the proportion of lepromatous cases is small (Guinto *et al.*, 1954; Kinnear Brown, 1959). Thus the findings in Uganda will not necessarily be valid in a community with a different proportion of lepromatous cases or a different total prevalence, and for this reason the results of the three other large-scale trials of B.C.G. vaccine in leprosy, which are currently in progress, will be of great interest and importance (no results have so far been reported). These trials are in Malaya (McFadzean and Singh, 1960), where the proportion of lepromatous patients was about 70% of the total patients; in New Guinea (Russell *et al.*, 1964), where the corresponding proportion is about 10%; and in Burma, under W.H.O. auspices (World Health Organization, 1964), where about 70% of the patients have the lepromatous form of the disease.

The present results are clearly only preliminary, and a longer period of observation will be needed before it is possible to make a full evaluation of the effects of B.C.G. vaccination in leprosy. It is hoped that future reports on this investigation will also include more detailed analyses of the influences of initial tuberculin and lepromin sensitivity, and the degree of contact and relationship of the participants with the index case.

Summary

A controlled trial of B.C.G. vaccine in the prevention of leprosy started in the Teso district of Eastern Uganda in September 1960. By September 1962 17,397 children, more than 80% of whom were aged under 10 years, had been included. All were relatives or contacts of known leprosy patients.

Those with negative reactions to an initial Heaf tuberculin test, or with Grade I or Grade II positive reactions, were allocated alternately to an unvaccinated group (8,152 children) and a B.C.G.-vaccinated group (8,149 children). Those with Grade III or Grade IV reactions (1,096 children) were all left unvaccinated, as were children who already had skin lesions due to leprosy.

In the course of the first follow-up of all the participants, between May 1963 and May 1964, more than 94% of the children were seen and examined for leprosy. A total of 116 cases of leprosy had developed during this period of about two years since intake. The incidence in the unvaccinated children was 11.0 per 1,000, and in the vaccinated children 2.2 per 1,000, which is one-fifth of the incidence in the absence of vaccination. Among those positive in Grade III or IV and left unvaccinated the incidence was 8.3 per 1,000. The reduction in leprosy incidence in the vaccinated group did not appear to depend on the grade of initial tuberculin sensitivity (negative, Grade I or Grade II) nor on the age of the child at intake.

The results so far establish that B.C.G. vaccination has conferred substantial protection against early forms of leprosy in Uganda for a period of about two years. Since these early forms may resolve spontaneously, it is of particular importance to follow the trial population for some years to see how these lesions evolve, as well as to study the further incidence of the disease. About 8% of leprosy patients in Eastern Uganda have lepromatous leprosy, and it would be unwise to conclude that the present results will necessarily apply in other parts of the world, where the proportion of patients with lepromatous leprosy may be as high as 70%.

From 1960 to April 1963 this work was financed directly by the Uganda Government, with a grant from what is now the Ministry of Overseas Development. Since April 1963 the direct costs have been supplemented by the same Ministry, and a grant has been made to one of us (J. A. K. B.) by the Medical Research Council. The Uganda Government and the Teso District Council have throughout supplied the services of the medical and health staff in Teso district. During these investigations, as well as in the preliminary work before they began, the Church Missionary Society has met the full cost of one of us (M. M. S.). We would like, therefore, to express our gratitude to the Uganda Government, the Teso District Council, the Medical Research Council, and the Church Missionary Society for their support for the investigation. We wish, at the same time, to acknowledge the co-operation of the Board of Governors of the Kumi-Ongino leprosy settlement and the medical superintendent, Dr. J. M. Lea, for allowing the work to be based on the settlement. Our thanks are due also to all the leprosy assistants, particularly to Mr. Okapel and Mr. Okwi; to the medical and health staff for their assistance and interest, often in circumstances that have not been too easy; and to Mr. R. A. Adnitt, of the British Leprosy Relief Association, the treasurer of the settlement.

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APPENDIX. Use of Information on the Prevalence of Leprosy at Intake to Estimate the Incidence of Leprosy in the Course of the Trial

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By the end of 1961 information on the prevalence of leprosy at intake had been obtained from a total of 4,542 child relatives and contacts of leprosy cases. (Children examined in the etelas in which the intake appeared to have been loaded with unrelated patients were not included in this total.) The information was used in the following manner to estimate the expected incidence of leprosy in the course of the trial.

Table A gives the findings in these 4,542 children according to age, and shows the general tendency for the prevalence to rise until the age of 15. A straight line was "fitted" to the prevalence rates to describe their upward trend, the standard statistical technique of weighted regression being used; this straight line provided an adequate fit to the data and there was no indication of curvature. The figures were therefore consistent with a steady increase in the prevalence rate of leprosy from zero at birth to a figure of over 60 per 1,000 at the age of 15 years, the increase amounting to 4.62 per 1,000 for each year of age.

TABLE A.—Prevalence of Leprosy among 4,542 Children at Intake Examination, according to Age

Age (Years)	Total Examined	Cases of Leprosy	
		No.	Prevalence per 1,000
0—	633	0	0
2—	810	2	2
4—	934	13	14
6—	749	16	21
8—	546	30	55
10—	345	17	49
12—	309	13	42
14—	165	10	61
16 or more	51	2	39
All ages	4,542	103	23

If it is assumed that the population of child contacts is "stationary"—that is, not changing in total size or age distribution—and that the risk that they will contract leprosy is also not changing, then the increase in the prevalence of leprosy from one year of age to the next may be taken as a minimum estimate of the annual incidence of the disease. (The true annual incidence of leprosy is likely to exceed this estimate, since a proportion of the cases, having developed, will from past experience resolve spontaneously and so not contribute to the prevalence at the next year of age.) Subject to those assumptions, therefore, the estimated

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annual incidence of leprosy in this population of child contacts, in the absence of vaccination, was 4.62 per 1,000 children per year.

At the time when this estimate was made a total of 4,263 children (all in Grade O, I, or II initially) had been admitted to the unvaccinated group. According to the estimate 98 cases of leprosy would be expected to develop among them during a period of follow-up of five years. It was not known whether the population of child contacts was stationary, but it was suspected that, as a result of the treatment of known cases, the risk of contracting leprosy might be falling. In addition it was uncertain how effectively the participants could be traced for follow-up examinations, and whether it would be possible to continue these for as long as five years. In the circumstances it was safer to assume that perhaps only about half of the above total of 98 cases would develop and be detected in the course of the trial. If, say, 50 cases were found in the unvaccinated group, then it would not be permissible to claim a clear benefit from B.C.G. vaccination unless 25 or fewer cases were found in a randomly allocated vaccinated group of equal size (any lesser difference could be attributed to chance). Since it was important to be able to detect a reduction in leprosy incidence due to B.C.G.

vaccination, if it occurred, which was less than 50%, it was decided to increase the number of participants in the trial, and the intake was continued.

The final total of children in the unvaccinated group (Grade O–II) was 8,152. According to the same estimate of incidence a total of 75 cases of leprosy would have been expected to develop among these children during an average period of follow-up of two years. This may be compared with the total of 77 cases actually found in this group during the period of the first follow-up (the other 12 of the 89 cases shown in Tables IV and V had suspicious lesions which were not confirmed as leprosy until the second follow-up). Because of the various uncertainties and assumptions associated with the incidence estimate, it is clear that the agreement with reality is very much closer than could reasonably have been expected. It suggests, however, that the approach described in this appendix was not unrealistic, and represented a useful method of assessing when the intake to a trial of a prophylactic measure for a chronic disease was sufficiently large, from information obtained in the course of the intake. The approach has been placed on record in the hope that it may be useful to other workers in similar circumstances.

Hypertension and Cerebral Infarction

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Cerebrovascular disease provides many problems, but none is more puzzling than the reversal in the incidence of cerebral infarction and cerebral haemorrhage during the past four decades. Thirty years ago cerebral haemorrhage caused death in three times the number of cases as did cerebral infarction; to-day the latter is in excess of the former. This change has been brought about by a slight fall in the incidence of cerebral haemorrhage and a steep rise in that of cerebral infarction. The immediate explanation that springs to mind is that there has been a change in the fashion of death certification. This explanation is not tenable, however, for Yates (1964) has shown the same reversal to be present in a large series of cases proved at necropsy.

An alternative explanation for this phenomenon is that many hypertensive patients who would formerly have died from cerebral haemorrhage have been prevented from doing so by hypotensive therapy; these patients may have survived only to become the victims of cerebral infarction. Leishman (1963) has indeed provided evidence that hypotensive therapy reduces the mortality from an early stroke due to cerebral haemorrhage but has little influence upon the long-term risk of dying from a stroke associated with the progressive development of atherosclerosis. On the other hand, both Hodge, McQueen, and Smirk (1961) and Marshall (1964) have found that hypotensive therapy reduces the incidence of all types of stroke in hypertensive patients.

The elucidation of this problem is hampered by the considerable gaps in our knowledge of the causes of cerebral infarction. The widespread use of the term "cerebral thrombosis" to describe the clinical picture commonly associated with the pathological lesion of infarction reflects this, for as long ago as 1951 Hicks and Warren pointed out that it is uncommon to find evidence of arterial thrombosis in cases of cerebral infarction, an observation which has been repeatedly confirmed.

Alternative explanations for cerebral infarctions have therefore been advanced; these include occlusion by emboli which have subsequently fragmented, arterial spasm, the failure of collateral supply because of systemic hypotension (Denny-Brown and Meyer, 1957), and stenosis or occlusion of the carotid and vertebral arteries in the neck by atheroma (Hutchinson and Yates, 1957).

The last of these proposed causes of cerebral infarction raises further complex issues. Brice, Dowsett, and Lowe (1964) have shown that a stenosis of the internal carotid artery must reduce the lumen to 2 square millimetres before there is a significant effect upon blood flow. Most stenoses are not of this degree of severity. On the other hand, interference with blood flow may not be the only means by which a stenosis of the carotico-vertebral system produces a cerebral infarction. Gunning, Pickering, Robb Smith, and Ross Russell (1964) have produced good evidence that emboli formed on atheromatous plaques in the neck arteries may be responsible for such lesions. The incrimination of atheromatous lesions of the neck arteries in the causation of cerebral infarction seems possible therefore on two grounds: the stenosis may be sufficiently severe to interfere with blood flow, or it may provide a site for the formation of emboli; it may, of course, do both.

There is, however, a further aspect of carotico-vertebral stenosis which relates to the starting point of this discussion—namely, the reversal in the incidence of cerebral haemorrhage and cerebral infarction during recent decades. Schwartz and Mitchell (1961) have shown that there is an age-dependent factor involved in the causation of strokes which is not related to the state of the arteries in the neck. That this factor may be hypertension is suggested by the necropsy-controlled study of Low-Beer and Phear (1961), in which it was established that patients who die from cerebral infarction have on average a higher blood-pressure than the normal population of the same age and than patients with myocardial infarction.

These various strands of evidence suggest that among the several factors contributing to the genesis of cerebral infarction hypertension holds an important place. It has always been

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