portal vein to the peribiliary plexus are veins of drainage, and they are probably the route along which infection extends from the ducts to involve the larger intrahepatic branches. Portal-hepatic venous shunts of greatly varying calibre develop in the scars, and the portal components of the majority of these have their origin in the peribiliary plexus. Importantly, in sections of specimens of liver obtained during or shortly after acute exacerbations the vessels in the scars commonly show the histological appearance of acute pylephlebitis. We believe that these portal-hepatic shunts are the source of the pulmonary microemboli and that they account for the ease with which the causal organisms, even early in acute exacerbations, gain access to the right heart.

Summary

In a consecutive series of 728 patients with recurrent pyogenic cholangitis 15 (2.1%) developed pulmonary hypertension. However, the incidence among those with a history of frequent acute exacerbations for more than eight years was 7.6%. At laparotomy, which in 14 antedated the development of the pulmonary hypertension, all were found to have greatly scarred livers and all had stones in the intrahepatic and extrahepatic ducts.

The findings at necropsy on 3 of the 15 patients were consistent with the pulmonary hypertension being due to repeated pulmonary microembolism. It is concluded that the emboli had their origin in vessels within the liver, and it is suggested that the vessels concerned were the portal-hepatic venous shunts within scars. The portal components of these shunts have been shown to be mainly derived from the peribiliary plexus, and the shunts have been found commonly to show the histological changes of acute pylephlebitis.

It would appear that, before the introduction of antibiotics, metastatic pulmonary abscesses were a not infrequent complication of pyogenic cholangitis. Subsequent to their introduction this complication has become distinctly uncommon. It is thought possible that if the exacerbations of cholangitis in those who developed pulmonary hypertension had not been treated with any antibiotic, metastatic pulmonary abscesses would have developed instead.

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B.C.G. Vaccination of Children against Leprosy in Uganda: Results at End of Second Follow-up

J. A. KINNEAR BROWN,* C.M.G., M.D., B.SC., D.T.M.; M. MARY STONE,† S.R.N., S.C.M.; IAN SUTHERLAND,‡ M.A., D.PHIL.

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A controlled trial of B.C.G. vaccine in the prevention of leprosy was begun in the Teso district of Eastern Uganda in September 1960. By September 1962 17,397 children, more than 80% of whom were under 10 years of age, had been included. All those included were related to or had been in contact with known leprosy patients; all had been examined and found to be free of skin lesions due to leprosy.

The great majority of the children had either negative reactions to an initial Heaf tuberculin test or Grade I or Grade II positive reactions, and all these children were allocated alternately to an unvaccinated group and a B.C.G.-vaccinated group. Those in the vaccinated group were given a single dose of freeze-dried vaccine, prepared by Glaxo Laboratories Ltd. from the Copenhagen substrain of B.C.G. Those with Grade III or Grade IV positive reactions at the initial test (1,096 children) were all left unvaccinated. No B.C.G. vaccine has been given subsequently to any of these children, whether they were vaccinated or left unvaccinated at the time of intake.

In the course of the first follow-up of 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 were reported during the period of one to three years since entry, the incidence of these early manifestations of the disease among the vaccinated children being one-fifth of that among the corresponding unvaccinated group (Kinnear Brown and Stone, 1966).

While the first follow-up was in progress a further 1,926 young children, nearly all of whom were aged 2 years or less and had been born into the trial families since the initial intake, were admitted to the trial without tuberculin testing, and were allocated alternately to the unvaccinated and the B.C.G.-vaccinated groups. The purpose of this subsidiary intake was to increase the numbers of very young children under study, so as to permit in due course a more precise assessment of the efficacy of vaccination soon after birth.

The second follow-up of all the participants in the main intake (and the first follow-up of those in the subsidiary intake) began in July 1964 and ended in March 1966. The present report gives the results of the trial at the end of this second follow-up. Full details of the plan and conduct of the trial were given by Kinnear Brown and Stone (1966).

Examinations during the Second Follow-up

The procedures for visiting the eitelas (the rural population units), for identifying the participants in the trial and for examining them for signs of leprosy were the same during the second follow-up as they were during the first (Kinnear Brown and Stone, 1966). In particular, the arrangements for placing a piece of adhesive paper on *every* child on the site where a

* Senior Consultant (Leprosy), Uganda.
† Nursing Sister Special Duties, Kumi-Ongino Leprosy Centre, Uganda.
‡ Member, Statistical Research Unit, Medical Research Council, London.
Reprints may be obtained from Dr. J. A. Kinnear Brown, "Sonning," Leicester Road, Hale, Cheshire, England.

vaccination would have been made, covering any scar which happened to be there, together with the allied precautions to ensure an independent assessment of the leprosy lesions, without any bias from knowledge of the vaccination (or tuberculin) history, have not changed.

The total number of children due to be examined during the second round of visits was 19,096—namely, the 17,397 of the main intake and the 1,926 of the subsidiary intake, minus the 227 deaths recorded during the period of the first follow-up. Of this total it was found during the second follow-up that 103 children (0.5%) had died (62 from the main intake, and 41 from the subsidiary intake) and a further 1,621 (8.5%) were not examined. Thus, in all, 91.5% of the 19,096 children were seen and examined for leprosy during the second follow-up.

The proportion not examined (8.5%) was greater than that during the first follow-up (4.1%), partly because there was more movement of participants within the district and partly because it was not practicable, at the end of the second follow-up, to make special visits to the various areas to examine participants missed at routine earlier visits, as was done at the end of the first follow-up. However, 367 of the 718 absentees during the first follow-up were seen and examined during the second, and so it is likely that many of the 1,621 absentees during the second follow-up will also be seen and examined at later follow-up visits.

Cases of Leprosy Developing after Intake and up to End of Second Follow-up

Of the total of 19,323 participants in the main and subsidiary intakes combined, 154 had had lesions of doubtful origin on intake and were included in the standard allocation procedure. The findings in this small group are given separately in the next section.

A total of 165 cases of leprosy were discovered by the end of the second follow-up among the other 19,169 participants, none of whom had shown any signs of leprosy at their intake examination. In addition a number of these children had been noted as having suspicious lesions at a follow-up visit, but no definite diagnosis could be made. By now some of these children have been seen again during the *third* follow-up, which is still in progress, and in seven it has become clear that the lesions noted earlier were due to leprosy. These seven therefore represent additional patients, giving a total so far of 172 developing by the end of the second follow-up.

Table I shows the distribution of these 172 cases according to their tuberculin and vaccination status on entry. Considering first all those with tuberculin grades O to II at the main intake, together with the very young children in the subsidiary intake, who were not tested, there were 143 cases among the unvaccinated children, representing an incidence of 15.8 per 1,000, and 19 among the vaccinated children, or 2.1 per 1,000, which is less than one-seventh of the incidence in the unvaccinated group. The possibility that this difference could have 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 87%.

Among those with grade III or grade IV positive reactions on entry, none of whom were vaccinated, there were 10 cases, or 9.3 per 1,000 children. No case of leprosy had developed by the end of the second follow-up among the very young children admitted during the subsidiary intake, whether they were vaccinated or not.

Table I also gives the findings separately for those initially tuberculin-negative, and those with Grade I and Grade II positive reactions. The percentage reduction in leprosy incidence attributable to vaccination was similar for each of these groups.

Table II shows the percentage reduction in leprosy incidence according to the age of the child at intake; the reduction did not appear to depend upon the age at vaccination.

TABLE I.—*Cases of Leprosy Discovered by the End of the Second Follow-up (March 1966) According to Tuberculin Status and Vaccination Status at Intake*

Tuberculin status at intake (Heaf)	Unvaccinated			B.C.G.-vaccinated			Percentage reduction attributable to vaccination
	Total children	Cases of leprosy		Total children	Cases of leprosy		
		No.	Per 1,000		No.	Per 1,000	
Negative:							
Grade O	2,930	37	12·6	2,844	3*	1·1	92
Positive:							
Grade I	4,867	101	20·8	4,989	16	3·2	85
Grade II	274	5	18·2	258	0	0·0	100
Not tested:							
Subsidiary intake ..	965	0	0·0	961	0	0·0	—
Total	9,036	143	15·8	9,052	19	2·1	87
Positive:							
Grade III	847	8	9·4	—			—
Grade IV	234	2	8·5	—			—
Total:							
(Grades III and IV)	1,081	10	9·3	—			—

* It was recently found that a small number of children had been admitted to the trial twice from different eitelas. They have been retained under the earlier admission unless their status was changed by the later admission—for example, if they were vaccinated on the second occasion. One of the small group that had to be excluded on these grounds has developed leprosy, which explains why this figure is one less than the corresponding total of cases in Kinnear Brown and Stone (1966). No adjustment has yet been made to the totals of children included in the trial, because the eligibility of every child is the subject of a current check.

TABLE II.—*Cases of Leprosy Discovered by the End of the Second Follow-up Among Those Tuberculin-negative, or Positive in Grade I or II, According to Age at Intake and Vaccination Status*

Age in years at intake	Unvaccinated			B.C.G.-vaccinated			Percentage reduction attributable to vaccination
	Total children	Cases of leprosy		Total children	Cases of leprosy		
		No.	Per 1,000		No.	Per 1,000	
0–	2,142	3	1·4	2,115	0	0·0	86
2–	1,770	12	6·8	1,663	2	1·2	
4–	1,630	30	18·4	1,661	4	2·4	87
6–	1,251	29	23·2	1,274	5	3·9	83
8–	870	30	34·5	921	3	3·3	90
10–	561	15	26·7	587	2	3·4	87
12–	490	15	30·6	477	2	4·2	86
14–	247	6	24·3	277	1	3·6	89
16 or more	75	3	40·0	77	0	0·0	
All ages	9,036	143	15·8	9·052	19	2·1	87

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

Of the 154 children with lesions of doubtful origin at intake 81 were tuberculin-negative or positive in Grade I or Grade 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 Grade IV and were not eligible for vaccination.

By the end of the second follow-up 12 (15%) of the unvaccinated group, 11 (19%) 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 appear to have any beneficial effect on leprosy lesions which were already present at the time of vaccination.

Progress of Leprosy Lesions According to Vaccination Status

It is important to know whether, in addition to preventing (to a considerable extent) the development of leprosy lesions, B.C.G. vaccination is able to modify the course of the disease in those who do contract it. Now that the second follow-up has been completed it is possible to investigate this point by analysing the progress, at the second follow-up, of the patients in whom leprosy had developed by the end of the first follow-up, according to their vaccination status.

There were 124 of these patients; the diagnosis was made

In 98* during the first follow-up, in 25 during the second follow-up, and in one during the (incomplete) third follow-up, suspicious lesions already having been noted in these 26 patients during the first follow-up. In the majority of the patients it was possible to classify the natural progress of the lesions between the first and the second follow-up, in the absence of treatment, from the records made at the two examinations, and the findings are shown in Table III. Some patients, usually with more serious lesions, had been admitted to treatment before the second follow-up and have been so classified. However, difficulty was encountered in assessing the progress of some of the lesions, particularly for those patients in whom the diagnosis of leprosy was made only at the second (or third) follow-up. The very factors which had made it difficult to diagnose the lesions initially (which may have included smearing with dye or burning with caustic) also made it difficult to assess how the lesions were progressing by the time that the diagnosis of leprosy became definite; some quite minor change in appearance or thermal anaesthesia may have sufficed to establish the diagnosis. These patients have therefore been grouped as "assessment difficult, and not made" at the foot of Table III, together with a few patients not seen at the second follow-up.

TABLE III.—*Progress at the Second Follow-up of Leprosy Lesions Found at the First Follow-up*

Natural progress of lesions at second follow-up	Negative (Grade O) or Positive (Grade I or II)				Positive (Grade III or IV)	
	Unvaccinated		B.C.G.-vaccinated		Unvaccinated	
	No. of cases	%	No. of cases	%	No. of cases	%
Patients admitted to treatment before second follow-up	19	21	7	44	0	0
Lesions extending	40	43	1	6	5	83
Lesions stationary	11	12	1	6	1	17
Lesions resolving	14	15	5	31	0	0
Lesions resolved	8	9	2	13	0	0
Total with information on progress	92	100	16	100	6	100
Assessment difficult, and not made	4	—	0	—	3	—
Patients absent at second follow-up	3	—	0	—	0	—
All patients	99	—	16	—	9	—

Of the 114 first-round patients for whom assessments of progress were available 92 had been tuberculin-negative or positive in Grade I or II at intake and were left unvaccinated, and 59 (64%) of these either had extending lesions at the second follow-up or had been admitted to treatment, compared with 8 (50%) of the 16 patients with similar tuberculin status who were B.C.G.-vaccinated and five of the six patients who had been positive in Grade III or Grade IV at intake and were not vaccinated. The lesions were resolving or had resolved in 22 (24%) of the unvaccinated and 7 (44%) of the B.C.G.- vaccinated group. There is a slight tendency for untreated lesions to progress or to come under treatment less frequently, and to regress more frequently, in the B.C.G.-vaccinated patients than in the corresponding group of unvaccinated patients, but with the numbers currently under study the differences could well be due to chance.

Attack Rate of Leprosy among Unvaccinated Children According to Tuberculin Status at Intake

The variations in the leprosy rates in unvaccinated children with different levels of tuberculin sensitivity (Table I) suggest that the natural incidence of leprosy may depend in some way on the tuberculin status of the child. However, the incidence of leprosy also varies with age (Table II), and those with negative tuberculin reactions were on average younger than those with positive reactions. For a valid assessment it is therefore necessary first to adjust the incidence rates in the various tuberculin status groups to allow for the differences in their age distribution, and this was done by the method of indirect standardization. The adjusted rates are shown in Table IV. There was a fall in the incidence of leprosy with increasing tuberculin sensitivity, from a rate of 21.3 per 1,000 among those tuberculin-negative at intake to a rate of 6.8 per 1,000 among those with Grade IV positive reactions initially. This trend attains statistical significance at the 1% level. Those with weak degrees of naturally acquired tuberculin sensitivity therefore appear to be protected against the subsequent development of leprosy to a small extent, and those with strong degrees of natural sensitivity to a greater extent. This natural protection, however, does not appear to be as great as that conferred artificially by B.C.G. vaccination. The adjusted incidence of leprosy among those with Grade III or IV positive reactions (7.1 per 1,000) was less by 66% than the adjusted incidence among those with negative tuberculin reactions, whereas the percentage protection from vaccination among those with negative tuberculin reactions initially was 92% (Table I).

TABLE IV.—*Attack Rates of Leprosy in Unvaccinated Participants by the End of the Second Follow-up, According to Tuberculin Grade on Entry, Adjusted for Differences in Age-distribution of the Children Between the Grades by the Method of Indirect Standardization*

Tuberculin status at intake (Heaf)	Total unvaccinated children	Cases of leprosy		
		No.	Crude rate per 1,000	Adjusted rate per 1,000
Negative: Grade O	2,930	37	12·6	21·3
Positive:				
Grade I	4,867	101	20·8	17·9
Grade II	274	5	18·2	13·5
Grade III	847	8	9·4	7·2
Grade IV	234	2	8·5	6·8
All grades	9,152	153	16·7	16·7

Discussion

The trial of B.C.G. vaccination against leprosy in children in Uganda has now been taken a stage further. The follow-up of the main intake of 17,397 participants has been extended from an average period of 26 months since entry to 44 months; in addition the 1,926 young children comprising the subsidiary intake, who were included during the first round of follow-up visits, have now been followed for an average period of 18 months. In all, 91.5% of the participants have been seen and examined for leprosy during the second round of visits. During the follow-up so far 172 cases of leprosy are known to have developed in participants free of any sign of leprosy initially; the total reported earlier by Kinnear Brown and Stone (1966) was 116.

The effectively random allocation of participants with negative or weak positive tuberculin reactions to the B.C.G.-vaccinated and unvaccinated groups, and the similar subsequent observation of these two groups, by methods designed to avoid bias, have ensured that the difference in incidence of leprosy in the B.C.G.-vaccinated group and the corresponding unvaccinated group may be attributed directly to the vaccine. The percentage reduction in leprosy incidence attributable to vaccination over the average period of follow-up of three and a half years was 87%, compared with 80% during the first two years. There is thus no indication of any waning of efficacy of the vaccine.

It must, however, be reiterated that the forms of leprosy seen so far, in both the vaccinated and the unvaccinated groups, have been early, and some may resolve spontaneously. Of leprosy lesions noted during the first round of visits, 9% had resolved and a further 17% were resolving without treatment at the second round of visits about 18 months later. Further, there is no firm indication so far that the lesions differ in their subsequent progress in the vaccinated and unvaccinated patients. However, it is important to know whether the lesions which have resolved will remain so, and for this it will be necessary

* The difference from the figure of 100 given by Kinnear Brown and Stone (1966) is a result of more recent information on eligibility of the participants, which is the subject of a current check.

to continue to observe the children in this trial for several years.

Particular interest attaches to the association now shown between the degree of initial tuberculin sensitivity of the unvaccinated child and the subsequent natural incidence of leprosy. Weak natural tuberculin sensitivity (Grade I or II positive reactions) appears to indicate a slight protection against the subsequent development of leprosy, and strong natural tuberculin sensitivity (Grade III or IV positive reactions) a greater degree of protection (though not as great as that conferred by B.C.G. vaccine). The interpretation of this finding is complicated because the natural sources of tuberculin sensitivity in children in the tropics and subtropics may include leprosy bacilli and other mycobacteria as well as tubercle bacilli. A provisional interpretation does, however, seem possible by contrasting the present findings for leprosy with those for tuberculosis.

It has been shown in guinea-pigs (though not as yet directly in man) that the protective efficacy of B.C.G. vaccination against *tuberculosis* is less among those with previous non-tuberculous mycobacterial infection (which in man usually results in a weak sensitivity to human tuberculin) than among those not so infected, because the former group have already acquired a partial protection against tuberculosis from other mycobacterial infection (Palmer and Long, 1966). However, it was found by Kinnear Brown and Stone (1966), and is confirmed in the present report, that the degree of protection from B.C.G. vaccination against *leprosy* is similar for those with weak tuberculin sensitivity at intake and for those who were tuberculin-negative at intake. This finding therefore suggests that whatever sources of low-grade tuberculin sensitivity there may be in Eastern Uganda they do not confer any special protection against leprosy infection.

Further, a primary infection with tubercle bacilli (if it does not progress to clinical disease) confers an enhanced resistance to later infection with tubercle bacilli, and B.C.G. vaccination is believed to confer little or no additional protection against *tuberculosis* in such already infected subjects. However, it was found by Kinnear Brown and Stone (1966), and is confirmed in the present report, that the degree of protection from B.C.G. vaccination against *leprosy* is independent of the age of the child. Though all these children were clinically free of leprosy lesions on entry to the present study, it would be expected that a substantial proportion, especially among the older children, would nevertheless already have been infected with leprosy bacilli before entry. The lack of association between protection and age might therefore indicate that, in contrast to tuberculosis, a first infection with leprosy bacilli confers no special protection against later infection with leprosy bacilli.

There is, however, an alternative explanation for the lack of association between protection and age in those with no clinical leprosy lesions on entry. It may be that the appearance of early leprosy lesions closely follows infection with leprosy bacilli, in which case the proportion of previously infected children among those clinically free of leprosy on entry would be small at each age, and insufficient to affect the level of protection noticeably. A short period between infection and the appearance of clinical leprosy lesions is also suggested by the contrast between the high degree of protection from vaccination among those clinically free of leprosy on entry and the absence of protection among those with lesions of doubtful origin on entry (many of which were subsequently found to be leprosy lesions).

These considerations therefore indicate the possibility that the protection against leprosy associated with natural tuberculin sensitivity, and particularly with strong positive reactions, may be attributable almost entirely to natural infection with tubercle bacilli. The findings of this trial to date are consistent with the interpretation that an artificial attenuated tuberculosis infection (B.C.G.) confers substantial protection against the early forms of leprosy, that natural tuberculosis infection also confers some protection, but that infection with non-tuberculous mycobacteria (other than the leprosy bacillus) confers little or no protection.

The follow-up is continuing. Future reports will include an evaluation of the findings over longer periods of time, as well as detailed analyses of the influences of the degree of contact and relationship of the participants with their index cases.

Summary

A total of 19,169 children, all contacts or relatives of known leprosy patients, and all free of leprosy lesions, were included in a controlled trial of B.C.G. vaccination against leprosy in Uganda, and have now been followed for an average of three and a half years ; 172 cases of early leprosy lesions have so far developed among them.

The great majority of the children were allocated initially by an effectively random process to a B.C.G.-vaccinated and an unvaccinated group ; 94% were seen and examined for leprosy during the first round of follow-up visits, and 91.5% during the second, with suitable precautions in both rounds to ensure unbiased assessments. The percentage reduction in leprosy incidence in the B.C.G.-vaccinated group compared with the corresponding unvaccinated group was 87%. The percentage reduction was similar for those with weak degrees of tuberculin sensitivity initially and for those with negative tuberculin reactions, and did not appear to depend upon the age at vaccination.

Among those who developed leprosy lesions there was a slight tendency for the untreated lesions to progress, or to come under treatment, less frequently, and to regress more frequently, in the B.C.G.-vaccinated patients than in the corresponding group of unvaccinated patients, but the differences could well be due to chance.

The incidence of leprosy in the unvaccinated children varied with their initial sensitivity to tuberculin. Those with negative tuberculin reactions had the highest subsequent incidence of leprosy, those with weak degrees of naturally acquired tuberculin sensitivity the next highest, and those with strong degrees of tuberculin sensitivity the lowest subsequent incidence of leprosy.

The findings of the trial to date are consistent with the interpretation that B.C.G. confers substantial protection against early forms of leprosy, that natural tuberculosis infection also confers some protection, but that infection with non-tuberculous mycobacteria (other than the leprosy bacillus) confers little or no protection.

We are indebted to the Government of Uganda for continuing to sponsor this work, and to the Ministry of Overseas Development and the Medical Research Council for the grants they have made towards the cost. The Uganda Government and the Teso District Administration have enabled us to use their medical and health staff, who have themselves also been most co-operative. The Church Missionary Society has from the beginning taken a great interest in this work, and we are most grateful both to this society and to the Medical Research Council for arranging for the complete secondment of one of us (M. M. S.) for work on this study. We wish, therefore, to express our thanks to the Uganda Government, the Teso District Administration, the Ministry of Overseas Development, the Medical Research Council, and the Church Missionary Society. At the same time we wish to acknowledge the co-operation of the Board of Governors and the Staff of the Kumi Ongino Leprosy Centre.

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