Apparently mutants produced destructive disease in animals on deficient diet, those which were silicotic, and at least two species of normal animals. In people, they sometimes caused lesions at the site of administration and of regional lymph nodes, as well as other organs, and death in at least a few cases. Calmette repeatedly warned that no living organism capable of producing tubercles in animal tissues should be administered to people.

If methods of preventing mutation in cultures have been or can be devised, there is no assurance that it will not occur after the living organisms are introduced into human tissues.

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LONG-TERM EFFECTIVENESS OF B.C.G. VACCINATION OF INFANTS IN CLOSE CONTACT WITH INFECTIOUS TUBERCULOSIS

BY

JOHN LORBER, M.D., M.R.C.P.
Reader

AND

PEGGY C. MENNEER, M.B., Ch.B.
Tuberculosis Research Assistant

Department of Child Health, University of Sheffield

It has been demonstrated many times that B.C.G. vaccination can prevent tuberculosis. For example, Aronson *et al.* (1958) vaccinated 1,557 American Indian children 20 years ago and left 1,457 as controls. The incidence of tuberculosis in that community was high at the time these vaccinations were done. Twenty years later they were able to account for over 99% of both groups, and found that 104 (6.7%) of the vaccinated subjects had died. Tuberculosis was responsible for 0.8% of the deaths. Of the controls, 150 (10.4%) died, including 4.7% from tuberculosis. The excess of deaths in the control group was entirely due to deaths from tuberculosis. Hyge (1947) observed an epidemic of tuberculosis in a school in Denmark. Of 94 tuberculin-negative children who were exposed to an infectious school teacher, 41 developed tuberculosis; whereas of 106 B.C.G.-vaccinated children who were exposed to the same infection, only two developed the disease. The Medical Research Council (1956) conducted a large-scale controlled trial on adolescent boys and girls. It was found that the annual incidence of tuberculosis in the initially tuberculin-negative unvaccinated group was 1.94 per 1,000, whereas in the B.C.G.-vaccinated group it was only 0.37 per 1,000.

Present Investigation

In this country there have been no reports so far about the long-term effectiveness of B.C.G. vaccination in contacts. We have therefore decided to review the results of B.C.G. vaccination in all the 267 children who attended our contact clinic, and who were under the age of 2 years when they were vaccinated with B.C.G. between October, 1949, and October, 1952. All of those who had been in contact with an active case of tuberculosis were segregated for six weeks after the initial negative tuberculin test. They were then retested and when a second negative result had been obtained were immediately vaccinated with 0.1 ml. of the liquid Danish B.C.G., given intradermally over the left deltoid. A further period of segregation followed for six weeks, or for a longer period if by then tuberculin conversion had not taken place. In the case of newborn infants in potential contact with a case of tuberculosis the initial tuberculin tests were omitted. These were vaccinated at birth with 0.2 ml. of B.C.G. and segregated until tuberculin conversion was demonstrated. After tuberculin conversion all were allowed to return home, irrespective of the condition of the index case.

The children were then seen at approximately annual intervals, or more often if required At the end of the third year and annually thereafter the tuberculin tests

were repeated and radiographs of the chest were taken. A number of children left the district and were transferred to other chest clinics for the parents' convenience, and we have lost trace of others. For the purpose of this survey we made a special effort to trace and examine as many of these as possible.

Results

Between the summer of 1957 and the spring of 1958 we were able to trace 261 of the 267 children who had been vaccinated five or more years earlier. As Table I shows, three had died of non-tuberculous illnesses (consisting of leukaemia in two and paralytic poliomyelitis in one). Ten others were alive and well

TABLE I.—*Follow-up of Contacts Who Had Been Vaccinated with B.C.G. During Infancy Between October,* 1949, *and October,* 1952

	No.	%
Total vaccinated	267	100
Died of tuberculosis	0	0
,, ,, other causes	3	1·1
Untraced Emigrated	4	1·5
Untraced No information	2	0·7
Known alive and well; refused to be examined	10	3·7
Seen and examined in 1957–8	248	92·9

and were seen by our health visitors; they were going to school, but their parents refused to attend with them for examination and did not agree to tuberculin-testing. The remaining 248 (92.9%) were seen, examined, and tuberculin-tested, and radiographs of the chest were obtained in 235 of them. Of the six children untraced, four were known to have emigrated, and we have no information about the remaining two, five years after their vaccination.

Tuberculin Tests.—The method of tuberculin-testing the 248 who were followed up was largely guided by convenience (Table II). In the large majority the initial test was the tuberculin jelly test, which was applied by the health visitor in the child's home and the results of

TABLE II.—*Results of* 248 *Tuberculin Tests Performed in* 1957–8 *on Children Vaccinated in* 1949–52

		No.	%
Total positive		243	98·0
Jelly	128		
Mantoux (10 or 100 T.U.)	36		
Heaf	79		
Total negative		4*	1·6
Mantoux (10 or 100 T.U.)	3		
Heaf	1		
Not read		1	0·4

* Revaccinated.

which were read by one of us at the contact clinic. If the result was negative, intradermal or percutaneous tests were used. The latter were the primary tests on those who attended without having had a tuberculin jelly test at home. Of the 248 tested, 243 (98%) were tuberculin-positive, four were tuberculin-negative, and one failed to attend for reading of the test. The four negative reactors were revaccinated, and they responded with a typical primary B.C.G. lesion like tuberculin-negative children.

Radiographs of Chest.—These were obtained in 235 of the 248 patients followed up for five years, and were normal in 232 (Table III). There were only 3 (1.2%) children in whom tuberculous lesions were found and

TABLE III.—*Results of* 235* *Radiographs of Chest of Children Seen in* 1957–8

Result	No.	%
Normal	232	98·8
Calcified lesions	3	1·2

* In 13 cases radiographs were not taken.

which led to pulmonary and hilar calcification. One of these children never had any symptoms suggestive of tuberculosis or of respiratory disease, and his pulmonary lesion was a minute calcified focus. The other two were subject to recurrent cough. Clinically their infection was mild, and neither patient required anti-tuberculous chemotherapy. Their case histories are given in full.

Case 1

The patient was first seen at the age of 4 months as a contact of her grandfather, who had chronic old-standing pulmonary tuberculosis and was being admitted to a sanatorium the next day. He was sputum-positive. The infant was well and tuberculin-negative. She remained tuberculin-negative to 100 T.U. of old tuberculin (Mantoux) up to September, 1952, eight weeks after separation from contact. She was then vaccinated with B.C.G. A tuberculin-jelly test six weeks later was positive. The B.C.G. produced the usual small lesion. An ulcer had been present at the site of the vaccination, but it had healed by the time she was seen for a conversion test. There had been no further contact with the grandfather, who remained in the sanatorium until this time. Later he was discharged from the sanatorium and frequent contact was resumed. The child remained in good health up to one year after vaccination. She did not keep subsequent appointments, but was seen eventually four and a half and again five and a half years after vaccination. She was said to have been quite well, but on more detailed inquiry it appeared that she was subject to recurrent cough, causing much loss of time from school. On physical examination she was in excellent condition and had no abnormal signs. She weighed 44 lb. (20 kg.) at the age of 6 years. The tuberculin-jelly test was positive. Radiographs of her chest showed a well-calcified primary complex in her left upper lobe, with a segmental collapse (Fig. 1).

Meanwhile her grandfather had died of tuberculosis in 1955. There were no other cases of known tuberculosis in the family.

Comment.—It is possible that this infant contracted tuberculosis when contact was resumed with her infectious grandfather, in spite of a successful conversion following B.C.G. vaccination. Alternatively,

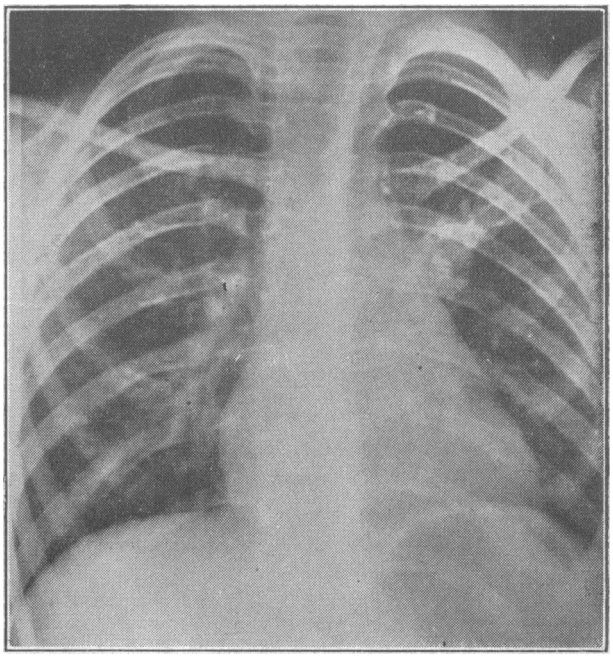

FIG. 1.—Case 1. Partial collapse of left upper lobe with calcified complex.

she might have been infected by an unknown person, possibly before the vaccination took effect.

Case 2

This child was 18 months old when she was first seen on account of contact with her tuberculous mother, who was admitted to a sanatorium the same day. The mother had had a cough for three months, and five weeks before her admission to the sanatorium was found to have pulmonary tuberculosis. Her children were then taken to the paternal grandmother. The mother had not seen this infant for three weeks prior to the baby's first visit to the clinic. The baby was then well and tuberculin-negative. Six weeks later she was negative to 100 T.U. of old tuberculin and was vaccinated with B.C.G. A further 10 weeks later she was positive to tuberculin jelly, and her B.C.G. lesion was a typical 12-mm. papule with a central crust on it. The mother was kept in hospital until conversion had taken place, and was then discharged home and contact was resumed.

The child remained well, but when seen at a routine visit three and a half years after vaccination she had a cough associated with rales in her chest. A radiograph of her chest then showed partial collapse of her left lower lobe as well as a round lesion in the right upper lobe and enlargement of the right hilum (Fig. 2). This lesion was consistent with a recent primary tuberculous infection. She was given a course of sulphadimidine, but, although her cough improved during the next two weeks, there was no significant change either in the physical signs or in the *x*-ray appearances. She was admitted for investigation, and for more energetic treatment with intramuscular penicillin, postural drainage, and physiotherapy. The physical signs disappeared, but her radiological lesions persisted. During her stay in hospital three consecutive gastric washings were cultured for tubercle bacilli and were inoculated into guinea-pigs, all with negative results.

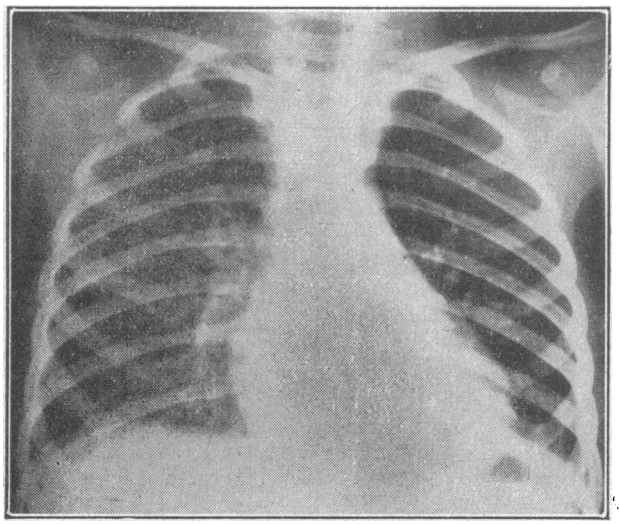

FIG. 2.—Case 2. Partial collapse of left lower lobe, a round lesion in right upper lobe, and enlargement of right hilum.

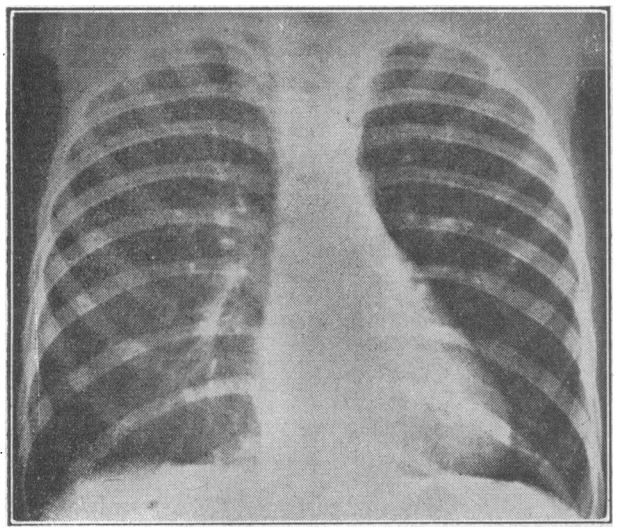

FIG. 3.—Case 2. Calcified shadow in right upper lobe, scattered calcifications in lower half of left lung, and partial collapse of left lower lobe.

After this admission the family removed from the district, and the child was not seen again until three years later, when they returned to Sheffield. The child had had no illnesses meanwhile, but her cough persisted. It now became known that her paternal grandmother, who looked after her while the mother was in the sanatorium, also had pulmonary tuberculosis. This was not known at the time she was in charge of the baby.

The child now had persistent rales over her left lower lobe, and the radiograph of her chest showed a calcified shadow in the right upper lobe, scattered calcifications in the lower half of the left lung, and partial collapse of the left lower lobe (Fig. 3). At this time the mother became ill again, and was readmitted to the sanatorium with tuberculous laryngitis and a cavity in her right lung.

Comment.—It is probable that this child was infected by her grandmother during the pre-allergic phase. It is possible, however, that she was infected either by her mother or by the grandmother after tuberculin conversion following the B.C.G. vaccination.

The Index Cases

In order to assess the protective value of B.C.G. in these children it is clearly necessary to know the nature of the contact with tuberculous persons. All of these were household contacts (Table IV). The parents were the "index" cases in 116 (47%), the grandparents in 31 (12.4%), and other persons in 101 (40.6%). The fact that more than half the index cases were not members of their immediate family reflects the overcrowding and poor living conditions of these families during the period under review.

TABLE IV.—*Index Cases and Their Subsequent Progress*

	No.	%
Principal potential source of infection:		
Mother	65	26·2
Father	51	20·8
Grandparents	31	12·4
Other relatives of household contacts	101	40·6
Condition at time of vaccination:		
"Active"	202	81·4
"Inactive"	46	18·6
Condition at time of this survey:		
Died of tuberculosis	39	15·7
Still active tuberculosis	28	11·3
Quiescent	170	68·5
Not known	11	4·4

More than four-fifths of the index cases were considered to have active tuberculosis at the time the children came under our care. The remainder were "inactive" in the sense that they had negative sputum. We know from past experience, however, that "inactive" cases may well cause fatal infection in children (Briggs, Illingworth, and Lorber, 1955). During the period of observation 39 (15.7%) of the index cases ended in death from their tuberculosis after variable periods of fluctuating fortune; 28 (11.3%) had either been persistently active or were considered to be in the

active stage again at the time of this review; and 170 (68.5%) were no longer active. We have no information about the last 11.

Conclusions and Summary

As there was enough evidence available by 1949 that B.C.G. was of value in the prevention of tuberculosis, it would have been ethically indefensible to withhold B.C.G. vaccination from any of our contact babies and so study comparable series of unvaccinated controls. Consequently, there is no absolute evidence that B.C.G. vaccination prevented tuberculosis in any. Nevertheless, the fact that from such a particularly unfavourably situated group of infants none died of tuberculosis, and only two developed symptoms which could possibly be attributed to tuberculous infection, suggests that the vaccinations were of value. It is more definite and satisfactory to record the prolonged effectiveness of the vaccination as judged by the persistence of the positive tuberculin reaction in 98% of the cases for five years or more.

267 children aged 2 years or less who were in close household contact with cases of tuberculosis and who remained tuberculin negative six weeks after segregation from contact were vaccinated with B.C.G. between October, 1949, and October, 1952. Of these, 261 were traced five years or more after vaccination. There were no deaths from tuberculosis; only two had minor clinical symptoms associated with tuberculous lung lesions which healed by calcification, and one other had a calcified lung lesion. There were only four who reverted and became tuberculin negative. In contrast, of the "index" cases 39 (15.7%) died of their tuberculosis and 28 (11.3%) still had active disease at the time of this review.

As there were no comparable controls it cannot be shown conclusively that B.C.G. vaccination prevented tuberculosis in this group of infants. Nevertheless the results are highly suggestive that this, in fact, was the case.

It is a pleasure to acknowledge and thank the help given by the chest physicians of Sheffield and many other areas; Dr. Llywellyn Roberts, the Medical Officer of Health of Sheffield, and his health visitors; and Dr. Marion C. Taylor, principal school medical officer of Sheffield, without whose help it would have been impossible to secure such a full follow-up; Professor R. S. Illingworth for his criticism; and the Tuberculosis Research Fund of the University of Sheffield for its grant to one of us (P. C. M.).

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The second edition of Colonel Sir R. N. Chopra's *Indigenous Drugs of India* has been largely rewritten by the original author in collaboration with I. C. Chopra, K. L. Handa, and L. D. Kapur. In its preparation account has been taken of the considerable accumulation of relevant literature since the appearance of the first edition in 1933. This is a very useful reference book, carefully documented and fully indexed. It is published by Dhur and Sons Ltd., 15, Bankim Chatterjee Street, Calcutta, 12 (pp. 816+xxxii; 1958. £5 5s.).

"B.C.G. SARCOIDOSIS"

BY

PHILIP ELLMAN, M.D., F.R.C.P.

Consultant Physician in Diseases of the Chest, North-east Metropolitan Hospital Board, and the Chest Unit, Plaistow Hospital, London

AND

LESLIE G. ANDREWS, M.B., D.C.H.

Registrar, Chest Unit, Plaistow Hospital, London

Since the earliest major contributions on sarcoidosis were made (Hutchinson, 1875–8; Besnier, 1889; Boeck, 1899, 1905; Schaumann, 1914; Jüngling, 1919) the aetiology has been much debated. Hutchinson (1898), in his study of the disease, thought the cause "may not improbably be a tuberculous affection and one of the lupus family." A large school of thought believes sarcoidosis to be a group of granulomatous diseases of known distinct aetiology—for example, tuberculosis, histoplasmosis, brucellosis, berylliosis—or to be idiopathic. Scadding (1950, 1956b) recommended the use of the terms "tuberculous sarcoid," "histoplasma sarcoid," "beryllium sarcoid," etc., whilst idiopathic cases belong to the tuberculous group passing through an unusual phase of tuberculosis. In latter years cases of sarcoidosis occurring in patients previously given B.C.G. vaccination have been recorded in the literature (Larsen, 1950; Löfgren and Lundbäck, 1952; Törnell, 1954; Pfisterer *et al.*, 1954; Ganguin, 1956; Birkhäuser, 1957; Fried and Genz, 1958). The term "B.C.G. sarcoidosis" is being applied to these cases. We record here a further case of histologically proved sarcoidosis occurring in a girl given B.C.G. vaccination seven years previously.

Case Report

In December, 1950, when the patient was 14 years old, she was vaccinated with Danish B.C.G. as a Mantoux-negative school-leaver. She was subsequently followed up under the Medical Research Council Tuberculosis Vaccines Clinical Trial by skin-sensitivity testing and chest *x*-ray examinations (see Table).

Results of Follow-up

Date	Skin Test (Same Batch of Old Tuberculin was used throughout except on 2/9/57 and 1/9/58)	Chest *X*-Ray Examination
1/12/50	Negative 1/100	Normal
7/12/50	*B.C.G. vaccination*	
26/2/51	Positive 1/3,000 (10 mm.)	,,
8/7/52	—	,,
18/11/53	Positive 1/3,000 (7 mm.)	,,
16/2/55	Negative 1/3,000 Positive 1/100 (12 mm.)	,,
15/5/56	Positive 1/3,000 (14 mm.)	,,
23/7/57	Negative 1/3,000	Reticular mottling right upper and mid-zones and left upper zone
2/9/57	Negative 1/1,000	Reticular mottling of whole of right lung and left upper and mid-zones
12/9/57	,, 1/100	
1/9/58	Heaf test positive	Normal

In July, 1957, her Mantoux reaction (1/3,000) had become negative, and reticular mottling had appeared in the right upper and mid-zones and left upper zone of her chest *x*-ray picture. In September she was admitted to Plaistow Hospital Chest Unit under the care of one of us (P. E.).

The patient was asymptomatic. On examination small cervical and scalene glands were palpable and the liver edge was felt one fingerbreadth below the right costal margin. The spleen was just felt on inspiration. The results of further investigations were: haemoglobin, 12.6 g./100 ml.