The conditions of the trial, it could not be concluded that BCG had been effective in the prevention of leprosy, but that present results have suggested that BCG raises the level of general resistance to invasion by *M. leprae*, plays a role in the development of apparent or self-healing cases, rather than the more severe forms of the disease, and prevents relapse of the self-healed cases.

Dr. Bees reported preliminary results of the investigation of the prophylactic value of BCG vaccination planned by the Uganda government, and conducted by the Leprosy Committee of the British Medical Research Council. The first progress report of this large-scale trial of BCG vaccination against leprosy in children, was published by J. A. K. Brown and M. M. Stone in the *British Medical Journal* early in 1966.

The trial in Uganda, based on large experimental and control groups, was carried out on 16,301 tuberculin-negative children, more than 80 per cent of whom were under ten years of age, and all of them contacts of known leprosy patients. The BCG-vaccinated group consisted of 8,149 children and the nonvaccinated group of 8,152 children. At the first follow-up, 107 cases of leprosy were discovered, 89 of them (11.0 per 1,000) among 8,071 unvaccinated children, and, in contrast, 18 or 2.2 per 1,000 among 8,091 BCG vaccinated children.

The results thus far obtained indicate that BCG vaccination of children in eastern Uganda has conferred substantial protection against early tuberculoid leprosy for a period of one to three years. Vaccination before and during the incubation period appeared to be effective regardless of the age of the children. It was concluded, therefore, that the preliminary results of the Uganda trial indicate that BCG vaccination is worth considering in a leprosy control program.

The participants in the Tokyo Conference felt that an important field for future study is the prophylactic effect of BCG vaccination against lepromatous leprosy. It is expected that the first results of the WHO trial in Burma, where the lepromatous rate is high, will be available for study by the end of 1967.

The Conference also discussed the subject of laboratory investigation of the value of BCG vaccination. Dr. C. C. Shepard, reporting on studies in the mouse, stated that an effect "appears to have been exerted at two times. one, early, against the newly inoculated bacilli, and the other later, by suppressing growth at some lower plateau value."

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**Chemoprophylaxis and BCG Vaccination Against Leprosy**

Recent large and well-controlled studies of chemoprophylaxis and BCG vaccination have encouraged the hope that these two procedures will be of significant value in the prevention of leprosy. In a survey to learn the prophylactic value of DDS against leprosy, Dharmendra and his colleagues, with associated teams of medical and paramedical workers, examined 203-234 persons. Five hundred and eighty-five child contacts (0-14 years of age) of leprosy patients completed prophylactic DDS treatment and remained under observation for two and a quarter years. 291 in the prophylactic DDS group and 294 in a control group receiving a placebo.

The report has been widely read and its significant data need not be repeated here. Figures thus far available indicate a substantial reduction in the incidence of leprosy in the group given DDS. This reduction, calculated as 0.99-0.848, or 31.5 per

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1 Received for publication June 17, 1966.
cent is attributable to chemoprophylaxis if the groups are strictly comparable, particularly as to the bacteriologic status of the index cases (145 were bacteriologically negative although classified as lepromatous). Maximum prophylactic activity was found within seven to 15 months after treatment (DDS, 4 cases, and controls, 18 cases). On the basis of an incubation period of three or four years for tuberculoid leprosy, chemoprophylaxis should also be credited with aborting preexistent leprosy infections. Of 29 cases in the untreated children, only two (6.9%) were indeterminate, with some likelihood of turning lepromatous; the rest were tuberculoid and of minimal extent, with a very high expectancy of healing spontaneously. The possible value of prophylactic DDS therapy against lepromatous leprosy has, therefore, not been measured by this study thus far.

Leprosy rates in contacts of lepromatous patients are four to six or more times higher than for noncontacts, but it is also a fact that even among children only about 30% per cent of all leprosy cases in endemic areas are traceable to contact with a known "open" case. If prophylactic DDS therapy were 50% per cent effective, as in the Madras study, a reduction of only half of 30 per cent in total incidence should be expected if chemoprophylaxis is limited to known contacts in the population. To be an effective control measure chemoprophylaxis must be applied to the general population and not limited to contacts; if so, however, administering DDS tablets twice a week indefinitely may not prove practicable as compared, for example, to a single BCG vaccination.

A BCG trial conducted in eastern Uganda2 has brought out many facts of importance besides an empiric knowledge of the practical value of BCG in preventing the onset of leprosy. Among numerous noteworthy findings was an apparent lack of association between reactivity to tuberculin and susceptibility to leprosy, as shown in a study of attack rates among 9,152 unvaccinated children, in relation to their initial tuberculin status. The children were not lepromin-tested, but numerous studies have reported an existing close positive correlation between reactions to lepromin and to tuberculin, particularly in children. In view of this cross relationship, some association might have been expected between attack rates and the tuberculin status of the children irrespective of age, although in theory this could be limited to lepromatous leprosy. Tuberculin reactivity increases with age in children, as with that to lepromin. The negative tuberculin reactors (Grade 0) were appreciably younger than those with weakly positive reactions (Grade I & II), and the strong (Grade III and IV) reactors were probably essentially older children. This lack of association between attack rates for tuberculoid leprosy and reactivity to tuberculin could thus not have been due to the age-constitution of the groups.

Study of age-specific attack rates for the two matched groups of vaccinated and unvaccinated children of tuberculin grades 0, I and II showed that attack rates were highest at 10-15 years and lowest at 0-5 years in the unvaccinated children. Differences between vaccinated and unvaccinated groups were equally appreciable at all childhood ages, so that BCG must have conferred definite protection from tuberculoid leprosy on all the children, irrespective of age at vaccination and antecedent tuberculin sensitivity.

The prophylactic value of BCG in leprosy was predicated solely on its acknowledged faculty of inducing lepromin positivity on top of specific positivity to tuberculin. As is known, lepromin reactivity is associated with relative resistance to leprosy, because, except in childhood, healthy persons and tuberculoid cases are equally lepromin-positive, while lepromatous cases are lepromin-negative. On the basis of lepromin reactivity alone, BCG vaccination might be expected to prevent lepromatous leprosy, but not tuberculoid leprosy.

The Uganda results suggest, however that BCG confers substantial protection against tuberculoid leprosy. If the groups

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are comparable, the 80 per cent reduction in tuberculous leprosy is attributable entirely to BCG vaccination. Furthermore, it appears that BCG not only prevented but actually aborted already pre-existing infections in the vaccinated group. Such a conclusion would be logical if we allow an incubation period (for tuberculous leprosy) of three or four years in the children, since the period between vaccination and reexamination averaged only 26 months and could range from eight to 44 months.

Reactivity to lepromin was not taken into account, but attack rates were much higher in the older children than in the younger ones. Tuberculous leprosy certainly may develop in previously lepromin-positive individuals, including children. It has not been established that tuberculous leprosy occurs only among lepromin-negative. As is shown, lepromin reactivity is nonspecific, may occur in the absence of leprosy, and increases sharply with age in children. Under the conditions prevailing in Cebu in the Philippines, for example, large groups of children 6-9 years of age were already found 75 to 91 per cent Mitsuda-positive at the 5 mm. level, but only 22 per cent tuberculin-positive to 5 TU PPD, and 25 per cent positive to 10 TU PPD. Not all of the unvaccinated children developing tuberculous leprosy in the Uganda study could have been lepromin-negative originally, especially the older ones and the tuberculin reactors; they could have been lepromin-positive and/or tuberculin-positive at the outset. If this premise is accepted, BCG vaccination confers protection or immunity against leprosy that is not completely related to or dependent on lepromin reactivity, as has been theorized. The value of BCG vaccination against lepromatous leprosy was not shown in the Uganda study; no instances of lepromatous or prelepromatous leprosy were observed among the secondary cases.

The World Health Organization4 has inquired into the possibility of prospective trials in Cebu (by the Leonard Wood Memorial) or elsewhere to confirm or add to the important results of the Madras DDS and Uganda BCG studies.

The island of Cebu is 150 miles long and 20 miles wide; the population is 1,600,000. On 30 April 1966, 1,865 "active" leprosy cases, including 208 lepromatos or borderline and 1,157 tuberculous or indeterminate cases, were registered in this province. Actual prevalence, active cases only, is 1.5/1,000 for total leprosy and 0.4/1,000 for lepromatous and borderline leprosy; the known total prevalence, however, was as high as 19/1,000 in Cordova and Talisay, highly endemic foot in Cebu. The 708 available index cases are not expected to yield more than 700 child contacts, a number insufficient for a good prophylaxis study.

More than prevalence, a sound knowledge of incidence (attack rates) is essential in planning prophylaxis trials, particularly in determining the minimum numbers of children needed to guarantee significant results. Aside from the disparity in total numbers of child subjects (355 in Madras and 17,243 in Uganda), there are other striking dissimilarities between the Madras and Uganda prophylaxis trials, as shown by the following data:

(a) Madras DDS study, 1962-1965, untreated control group: 27 tuberculous and two indeterminate cases developed in 294 child contacts of "open" and formerly open index cases; the attack rate was 99/1,000 in 25 years, or 44/1,000 per year. (Known prevalence in Madras 21/1,000; 86 per cent of all cases tuberculous.

(b) Uganda BCG study, 1962-1964, unvaccinated control group: 89 tuberculous cases developed in 8,671 child contacts or relatives of predominantly tuberculous index cases; the attack rate was 11/1,000 over an average period of 26 months or 5/1,000 per year. (Known prevalence in Uganda 25/1,000; 92 per cent of all cases tuberculous.)

With allowances for differences in clinical type of index cases, frequency of examinations, tuberculin reactivity, etc., attack rates presumably may range from 5/1,000 yearly in Uganda to 44/1,000 yearly in Madras among children with the highest

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4 Letter from L. M. Boechli, April 13, 1966.
leprosy risk available for each area. Incidentally, judged solely from the Uganda and Madras findings, BCG vaccination, with an attributed percentage reduction in incidence of 11.0-2.2 per thousand or 80 per cent appears to be a more effective prophylactic measure than DDS (treatment); the latter presumably accomplished a reduction in incidence of 99.0-48.0 per thousand or only 51.5 per cent.

Incidence figures for leprosy in Cebu, available for comparison, were obtained during a 15 year follow-up of the population of Cordova and Talisay from 1935 to 1950, in the course of three successive surveys and population examinations. These showed average annual attack rates in childhood (0-14 years), estimated somewhat differently by a modified life-table method, of 11.7 leprosy cases per 1,000 children per year among contacts of lepromatous patients, 1.9/1,000 among contacts of purely tuberculoid patients, and only 1.0/1,000 in the general noncontact population. On the basis of these attack rates it would appear impracticable to conduct a prophylaxis trial in Cebu with any expectation of securing significant results. Not enough contacts of lepromatous cases are available and attack rates for children in the general population are too low, even in highly endemic foci in the province.

Data on average annual attack rates for all forms of leprosy with respect to age and household exposure to lepromatous and nonlepromatous cases show that out of 273 leprosy cases developing in the entire population of Cordova and Talisay from 1935 to 1950, only 88 cases, or 32.3 per cent, occurred among contacts of known leprosy patients of either type of the disease. These figures support the contention that any prophylactic measure limited to contacts only would not be likely to prove effective in the control of leprosy.

—R. S. Guinto

### Antagonism Among Diseases

The question of antagonism among diseases has intrigued physicians, especially those philosophically inclined, for centuries. Opinions on the subject have been based largely on clinical or epidemiologic impression, and relatively rarely on statistically controlled observation.

The evidence for an antagonistic effect of one disease upon another has rested largely on judgments on the prevalence of two diseases in a given locality. At one time, for example, it was believed that a "mutual exclusiveness" existed between typhoid fever and malaria. Persons long resident in malarious regions were believed to have lost an originally natural susceptibility to typhoid fever (1). The original, and certainly quite uncontrolled observations leading to this concept, were made in Algiers and Italy. Hirsch cited many later reports from other countries, including the United States, supporting the hypothesis of such an antagonism.

Most of such concepts have been abandoned in the light of later study. Indeed, as far as typhoid fever and malaria were concerned, physicians in the United States, at the time of the Civil War, believed loosely in the existence of a combination of the two diseases. All this was before the advent of specific concepts of the etiology of the two diseases based on later knowledge from bacteriology and parasitology.

Yet in more recent times other antagonisms among microbial diseases, resting on a more readily established foundation, have been recognized, e.g., that between malaria and the dementia paralytica of cerebral syphilis. However, in this case,