World Health Organisation Technical Report Series, No. 88. Vaccination against Tuberculosis. (Sixth Report of the Expert Committee on Tuberculosis.) October, 1954.

This report is short but of such interest that we here reprint the report in full.

BASIC PRINCIPLES.

Before starting a detailed discussion, the committee wished to express its opinion that enough convincing evidence was available for it to agree on the following fundamental points:—

(1) A specific resistance develops following a natural primary tuberculosis infection.

(2) A specific resistance to tuberculosis can be induced by artificial means (vaccination).

VACCINATION WITH BCG.

VACCINES.

The committee considered the problem whether real differences in fact exist between strains of BCG used for vaccines in different parts of the world. Experience with vaccines produced in various laboratories makes it evident that there are appreciable differences in the allergy-producing qualities of vaccines and in the degree of regional glandular reactions which they provoke. These variations are particularly evident in oral vaccination when results obtained

with the strain of BCG used for the vaccine which is now being prepared in a number of laboratories in Latin America are compared with those obtained with strains used in some other laboratories. The committee felt that further studies were necessary to determine whether these differences in results are due to variations in methods of production and administration of the vaccine and to the characteristics of vaccinated populations or whether strains actually differ biologically. The committee recommended that the multiplication of BCG vaccine production centres should be discouraged.

The importance was stressed of producing vaccines with good keeping qualities, i.e. vaccines which could be kept for a considerable period of time and still be used with good effect. In this regard the committee felt that the freeze-drying process offered great hopes. However, it was recognized that there were appreciable variations between freeze-dried vaccines prepared in different laboratories using different methods. On the basis of evidence which is available at present and until further investigations are carried out, the committee did not feel able to recommend a more general use of freeze-dried vaccines even though these may offer certain advantages.

The committee considered studies made on the keeping qualities of liquid vaccines. There was suggestive evidence that liquid vaccine might maintain its allergy-producing power for a considerably longer period than was hitherto believed, particularly if it was adequately protected from light, even during the process of manufacture, and kept at a low temperature. In this connexion, the committee felt that it was important to carry out further laboratory investigations on the fundamental qualities of vaccines (with particular reference to methods for viable counts, and the relation of the survival of the bacilli to the protective value in animals), and that the results of such experimental work be correlated with the effects of vaccination in man.

The final appreciation of the value of a vaccine should be based on its ability to produce increased resistance—and not only allergy—in laboratory animals as well as in man.

TECHNIQUES OF ADMINISTRATION.

Extensive discussion took place concerning oral BCG vaccination.

Dr. de Assis presented data derived from his wide experience of oral vaccination by large repeated doses, including that in children exposed to heavy risk of environmental infection (" vaccinacao concorrente "). The opinion of the committee was favourably influenced by his report that this type of oral vaccination could be carried out without inconvenience even in tuberculin

reactors. There is, however, evidence that not every vaccine is suitable for this purpose. The committee felt that, on the basis of present evidence, it would be premature for it to recommend that this method be generally adopted. In view, however, of the apparent practical advantages of oral vaccination by large doses, the committee wished to make a strong recommendation that this procedure be carefully investigated further. Such studies should include comparisons in animals between this and other methods of vaccination. Although the committee realized that comparative studies between this form of oral vaccination and intradermal methods of vaccination in man would be most difficult and expensive, it wished to recommend that the WHO Tuberculosis Research Office (TRO) be requested to undertake the responsibility for these studies and that adequate financial support be given to this Office for this purpose.

The committee felt that, meantime, parenteral methods should be preferred for general use, but that, in situations where vaccination of the newborn and infants is desirable because the risk of infection is high and where for practical reasons the parenteral route cannot be used, oral vaccination should be recommended, provided that the particular vaccine and method chosen in each case have been shown not to give undue complications.

Reviewing previous recommendations for mass vaccination campaigns, the committee reaffirmed that intradermal vaccination was a satisfactory method.

The committee believed that when a mass vaccination campaign was carried out in a country, only one method of vaccination should be used, so as to avoid possible confusion among vaccines of different concentrations. It recognized that in some cases it might be desirable to carry out individual vaccination by more than one method for experimental or other purposes. In such instances, adequate security precautions must be taken—for example, by using markedly different containers for the different strengths of vaccine.

EFFECTS OF VACCINATION.

Complications. It was accepted that any method and any vaccine may give a certain percentage of complications, including suppurative adenitis. One should aim at using a vaccine which would give the smallest number of complications and yet produce satisfactory allergy. The committee wished to stress that small abscesses at the site of vaccination healing within two months, or non-suppurative regional adenitis of moderate degree, should not be considered as complications.

Tuberculin allergy. Testing after vaccination should be carried out with the same test that is used for selection of subjects

to be vaccinated. In order to see in mass vaccination programmes whether satisfactorily high and constant levels of allergy are maintained, periodic quantitative tests should be carried out in samples of vaccinated subjects. Such post-vaccination testing should be expressed not merely by stating the percentage of reactors but by using a quantitative method of measurement such as, for example, that adopted by the WHO Tuberculosis Research Office (frequency distribution of the diameter of induration measures in millimetres).

Since these sample checks might be affected by possible variations among batches of vaccine produced in a given laboratory, the committee felt that regular tests should also be performed on each batch, whenever practicable or else periodically, to assess the level of allergy conferred by the vaccine when properly handled and administered. In this connexion, the committee felt that satisfactory periodic checks of mass vaccination work could be achieved by the use of special assessment teams such as those now working for WHO in several areas.

The committee stressed again the importance of using standardized preparations of tuberculin, and, since the biological assay of newly prepared tuberculins against the International Standard presents great difficulties the committee strongly recommended that a single large batch of PPD of standard potency be prepared, which would be sufficient to meet the need for a considerable number of years and which should be made internationally available for the purpose of Mantoux testing.

Protection. The committee was provided with information on the large-scale control trials at present being undertaken in the U.S.A. and Great Britain designed to assess the degree of protection given by BCG vaccination in different sections of the population in these two countries. The committee was also informed by Dr. Palmer of two studies designed to obtain from mass vaccination campaigns some information on the protective value of BCG (the national vaccination roster in Finland and the tuberculosis index in Denmark). The committee looked forward to the results that might be achieved through these studies.

The committee felt that for the assessment of the protective value of BCG vaccination in man there was, more than ever, a need for studies of morbidity. The present apparent dissociation between tuberculosis mortality and morbidity gave support to this view.

The committee also stressed the necessity of reaching international agreement on a definition of tuberculosis morbidity, and the importance of having bacteriological evidence in the diagnosis of tuberculosis disease.

The committee felt that, where conditions are favourable, countries should be encouraged to maintain central or regional vaccination rosters so that records might be kept of cases of tuberculosis occurring in vaccinated individuals.

SELECTION FOR VACCINATION.

Tuberculin and tuberculin tests. The Expert Committee on Tuberculosis at its fifth session had recommended " that the WHO Tuberculosis Research Office be requested to investigate the question of which dosage of tuberculin should be used in surveys for determining the level of tuberculosis infection in the country."[1]

Dr. Palmer summarized for the committee the results of studies which had been carried out in this connexion. These supported the view that the use of a single test of 5 tuberculin units (TU) was satisfactory and practical for selecting individuals for vaccination. Moreover, much experience that had now been accumulated in the field on the use of a single 5-TU screening test had shown that this dose could be used without inconvenience in mass programmes. The committee therefore recommended that in mass vaccination programmes a single Mantoux test of 5 TU continue to be used, and that the arbitrary definition of a tuberculin reactor continue to be based on the presence of an induration of 5 mm or more in diameter at the end of three days.

Selection of groups. The committee recommended that, before undertaking a mass BCG programme in an area, preliminary surveys should be made. In most cases in would be necessary to determine the levels of natural tuberculin sensitivity and the prevalence of tuberculosis in a particular area; in some it might be important also to study more general social and demographic aspects, such as stability or movement of population, industrial development, etc.

In areas with a stable population and low incidence of tuberculosis infection, the relative needs of different public-health programmes should be considered, and priorities established, before embarking upon a mass vaccination campaign.

The committee recommended that, in areas with a high prevalence of tuberculosis, mass vaccination should cover all age-groups from 1 year to that in which 80%-90% reactors to tuberculin are found. Although in such areas vaccination of the newborn would be highly desirable, it was believed that this group would usually best be dealt with outside the mass vaccination programme.

In areas with a low and decreasing tuberculosis prevalence,

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[1] Wld. Hlth. Org. techn. Rep. Ser. 1951, 32, 10.

where mass vaccination of the whole population is not carried out, the selection of age-groups for vaccination should be determined in accordance with the epidemiology (including age distribution) of the disease in those areas.

REVACCINATION.

For individuals and groups especially exposed to tuberculosis, the committee considered it important that the vaccination be controlled by a tuberculin test 2-3 months after the vaccination had been made, and that individuals found to be non-reactors to tuberculin at this time have the vaccination repeated. Period retesting should be made later on and every individual found to be a non-reactor should be revaccinated.

For the mass campaigns, retesting should be made of sample groups to establish the effect of vaccination in terms of degree of allergy induced. The results of these " spot checks " should permit a decision as to whether or not the whole vaccinated population should be retested and non-reactors revaccinated.

VACCINATION WITH THE VOLE BACILLUS.

The committee heard with great interest a statement by Dr. Wells, who summarized the experience available to date, and described control trials in man which were being carried out to determine the possible advantages of the vole bacillus compared with other available antigens. Dr. Wells expressed the opinion that it was premature at this stage to recommend wide application of this vaccine.

The committee felt that these trials and further experimental work should be followed with close attention.

VACCINATION WITH KILLED BACILLI.

Dr. Giovanardi presented the experiments and experience in Italy with the formalin-killed tubercle bacilli (" anatubercolina "). The experimental work included a comparison with BCG in animals and in humans and showed that the degree of resistance and allergy produced by this vaccine in animals and the allergy produced in man were inferior to those produced by BCG.

It was felt that the general application of this method could not be recommended at this stage, but the committee would follow with interest further experimental work on killed tubercle bacilli.

PLACE OF VACCINATION IN THE PUBLIC-HEALTH PROGRAMME.

The committee discussed the integration of BCG vaccination into the tuberculosis-control programme and into the general public-health services of a country.

It was felt that in countries where a large-scale BCG-vaccination campaign was envisaged, its organization should not be left to tuberculosis centres but should be co-ordinated centrally or regionally and made part of the general public-health programme. The mass campaign should make use of all appropriate public-health facilities and institutions, while the tuberculosis centres would concentrate their efforts on the vaccination of particularly exposed individuals and groups.

THE WORK OF WHO.

The committee heard a statement from the Secretary, who outlined the principles which were at the basis of WHO's work in BCG vaccination and tuberculosis control. The Secretary described to the committee how WHO was attempting to stimulate, lead and co-ordinate international co-operative efforts. In carrying out this task, WHO was trying to build its programme on a solid and scientific foundation, and in this connexion the guidance and help of the Tuberculosis Research Office was essential. Without basic and field research it would not be possible for materials, procedures, and methods to be critically assessed and compared before being put into general use. Moreover, with TRO's help in the planning of field work, a high degree of comparability of data could be achieved, which would permit of sound evaluation of programmes.

The committee fully agreed that research was most necessary if satisfactory field work were to be carried out. Among the important problems needing elucidation were: the comparison of oral vaccination by large repeated doses with other methods; the value of freeze-dried vaccines (in this regard the committee understood that studies were being carried out by the BCG Pilot Station in Paris); and the effectiveness of BCG vaccination, especially in areas of high tuberculosis prevalence.

The committee was much impressed by the value and the amount of work which had already been achieved by the Tuberculosis Research Office, and expressed the hope that the activities of this Office would continue and expand and that it would be given all possible support. Some of the problems mentioned above might suitably be undertaken by the Tuberculosis Research Office.

The committee heard with interest and appreciation that the United Nations Children's Fund, which had given so much assistance already to mass vaccination work, had extended its support to research activities.

BCG AND LEPROSY.

Dr. de Assis presented his views to the committee on the role of BCG vaccination in the prevention of leprosy. The committee

also considered the report of the Joint Meeting of Leprologists and Phthisiologists held in September 1953 under the auspices of the British Tuberculosis Association's Research Committee. The committee also noted with interest the opinions expressed by the WHO Expert Committee on Leprosy in its first report.[2]

The committee did not feel qualified to take a decision in this matter which, it felt, was not within its field of competence. It believed, however, that the mass BCG-vaccination campaigns, conducted against tuberculosis with the assistance of WHO in countries where leprosy is endemic, might perhaps be used by leprologists to study the possible value of BCG vaccination in the prophylaxis of leprosy. The committee did not know whether the conditions under which BCG programmes are conducted at present would allow any valid conclusions to be drawn regarding leprosy. Were it not possible to do so, and should certain changes in the organization of BCG campaigns permit that data be more easily obtained, the committee felt that such changes might be considered, provided that they did not interfere with the correct execution of a mass campaign against tuberculosis.

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[2] See Wld. Hlth. Org. techn. Rep. Ser. 1953, 71, 13.