RECENT ADVANCES IN B.C.G. VACCINATION

By K. NEVILLE IRVINE, D.M.Oxon.

Adviser in B.C.G. Vaccination to the Oxford Regional Hospital Board

The history of B.C.G. up to 1948 has been dealt with elsewhere (Irvine, 1949); an article in this Journal covered the years 1949-51 (Irvine, 1952): this paper is intended to summarize the work that has been carried out in the years 1952-54.

Safety

For the first time two cases of progressive tuberculosis resulting from B.C.G. vaccination have been reported. The first was a seven-year-old Danish boy who was given B.C.G. intracutaneously in a batch of 30 children; the vaccinations ran a normal course in the other 29. This boy began to ail within two weeks of vaccination and became progressively worse; he eventually died after two years from cachexia with generalized tuberculosis. An organism identified as B.C.G. was grown from the lungs, liver, spleen, kidneys and mesenteric glands; none of the laboratory animals inoculated developed progressive tuberculosis (Meyer, 1954). The second was a Norwegian youth, aged 19, who was vaccinated intracutaneously in 1948: in 1949 he developed a glandular abscess and in 1950 an abscess of the chest wall from which 'tubercle bacilli of the B.C.G. type' were grown: despite chemotherapy he developed a lung infiltration in 1951 and caries in a rib and clavicle: in 1952 a cavity was found in the right kidney and spinal caries with paraplegia developed: in 1953 emaciation became extreme and he died. At autopsy a generalized infection with an organism identified as B.C.G. was found; none of the many animals inoculated developed progressive tuberculosis (Thrap-Meyer, 1954). In neither of these cases was any increase in the virulence of B.C.G. found: both boys must have had a complete absence of resistance to any tubercle bacillus and would presumably have succumbed rapidly to a virulent infection.

This brings the number of deaths resulting from B.C.G. vaccination up to three; the third case (Despieres *et al.*, 1951) was reported in the previous article. As over a hundred million persons have now been given B.C.G. (Saenz *et al.*,

1954), these three deaths, though disturbing, do not materially affect the safety of the vaccine. Vaccination against smallpox, which is regarded as a safe and desirable procedure, caused 4 deaths in the period 1940-49 in England and Wales alone (Registrar-General, 1949).

Efficacy

Little fresh light has been thrown on the problem during the last three years. No report of the M.R.C. trial on school children has yet been published. Olsen (1953) has reported a further decline of tuberculosis in the island of Bornholm and described the protection given by B.C.G. vaccination in a small epidemic outbreak of tuberculosis. The Final Report of the International Tuberculosis Campaign (1953) records the vaccination of nearly 17 million persons, but gives little statistical information. Sams (1954) reports nearly 53 million vaccinations between 1945 and 1952 on Japanese under the age of 30; the tuberculosis mortality rate in Japan fell from 282.2 per hundred thousand in 1945 to 82.1 in 1952 and practically the whole of the drop occurred in this under-thirty age-group.

Present Policy

Now that the vaccination of nurses, medical students and contacts is being routinely carried out in this country, the Ministry has released B.C.G. for use on thirteen-year-old school children. This is a broadening of the original policy of vaccinating only those individuals who are specially exposed to infection, to include a complete age-group that is entering a period of life when the risk of tuberculosis is high. The advantage of selecting this particular age is that most children will be under observation for some months before leaving school; the disadvantage is that part of the period of protection will be wasted before the child goes out into the world.

This extension to school children may mean nearly half a million additional vaccinations a year. This is beyond the capabilities of the overworked Chest Physician, and Medical Officers of

Health are already training School Medical Officers as vaccinators. The original five sessions, with two prevaccination and one postvaccination test, are cumbersome for such numbers and attempts are being made to simplify the procedure.

Tuberculin Testing

For nurses, medical students, and contacts, the Ministry has supplied dilutions of Old Tuberculin for Mantoux testing: for school children, dilutions of P.P.D. are being issued. Up to the present it has been thought that dilutions of O.T. and P.P.D. ran mathematically parallel, but Seibert and DuFour (1954) have shown that the first strength P.P.D. (0.0002 mg.) is *more* sensitive than its official equivalent in O.T. (1/10,000) and the second strength P.P.D. (0.005 mg.) is *less* sensitive than its equivalent 1/40 O.T. If this is confirmed there will have to be some readjustment of standards.

In its earlier campaigns the I.T.C. attempted to use two prevaccination tuberculin tests; it soon became apparent that this was impracticable. An attempt was then made to use a single Mantoux 10 T.U., but too many fierce reactions resulted in some countries. A Mantoux 5 T.U. was finally chosen as the universal standard pre- and post-vaccination I.T.C. test. This may be an adequate prevaccination test to exclude active tuberculosis, but it is inadequate for detection of the weak post-vaccination allergy; the Ministry of Health (1953) recommends a Mantoux 10 T.U. for this country. In the Oxford Region, where research into the duration of allergy is being carried out, all persons are still tested to a Mantoux 100 T.U. so that a similar test may justifiably be used at their follow-up. This is admittedly open to the criticism that some persons who should have been vaccinated may have been excluded by a non-specific or pseudo-reaction to this strength; the work of Bates *et al.*, (1951) and Edwards and Palmer (1953), show that in some tropical countries this non-specific factor is so prevalent that the 100 T.U. is quite unreliable. Whether these pseudo-reactions are due to the presence of some saprophyte has not yet been demonstrated, but Zettergren *et al.*, (1952), have found a mycobacterium balnearia in swimming pools, infection with which will produce a positive tuberculin reaction in man. There is, however, no evidence to suggest that non-specific reactions to a Mantoux 100 T.U. are common in this country.

Clearly some 'one-shot' prevaccination test is highly desirable. Unless non-specific reactions are found to be common in this country, there is no reason why a test of the sensitivity of a Mantoux 100 T.U. should not be used; the use of the Mantoux 100 T.U. itself as a one-shot test is

precluded by the fact that severe reactions would occur in sensitive persons. The original Pirquet test and its modification, the Adrenalin-Pirquet, are only of about equal sensitivity to the Mantoux 10 T.U. The reliability of the jelly test and its flourpaper modification introduced by Dick (1950) is upheld by Lendrum (1951), but more recently doubt has been thrown on it by Coles (1952), Frew *et al.*, (1953), and Caplin *et al.*, (1954); in any case its use is restricted to children.

A new tuberculin test has recently been devised by Heaf (1951), which gives promise of being the ideal one-shot test. The test is performed with a special instrument which automatically stabs six needles into the skin to a standard depth through a film of adrenalinized O.T.; P.P.D. 2 mg./ml. in 25 per cent. glycerine (without adrenalin) may also be used (Heaf, 1953). The reaction, which is read on the third day, varies from a small papule at the site of each puncture up to a solid plaque of induration. Its sensitivity appears to be only a little less than that of the Mantoux 100 T.U. (Irvine, 1955), but it may safely be given without a preliminary test; the worst reaction I have seen was an induration of 30 mm. in diameter with six discrete 3 mm. vesicles over the puncture marks. No skill is required to give this test as the Heaf 'gun' is automatic. As the reaction fades slowly it may be found possible to read it at several days; this would form a useful 'market day' test for country chest clinics where the test could be given and read at the weekly clinic which is usually held on market days.

Though Foley and Parrot (1953) still defend their practice of vaccinating without tuberculin testing, it is generally agreed that a prevaccination test is essential, but there is considerable argument as to whether the postvaccination test could not be omitted. In the first 5,000 persons of all ages vaccinated in the Oxford Region a conversion rate of 99.9 per cent. was found; in view of this is the time and expense involved in conversion testing warranted? For school children the answer would appear to be 'No,' provided that a high conversion rate is confirmed in this age-group; the M.O.s.H. in the Oxford Region are working together as a voluntary research team to test this statistically. On the other hand for nurses and medical students, who are bound to come in contact with open tuberculosis, there can be no justification for omitting to check that each individual has converted.

Variations in the Vaccine

Pierce and Dubos (1954) have shown that there is considerable variation between the fresh vaccines produced at different centres. Edwards and Palmer (1953) have demonstrated that

exposure to direct tropical sunlight will kill fresh B.C.G. in half an hour; at the latitude of Great Britain it would take an hour. Even if shaded from direct sunlight, the glare from a tropical sky has a similar effect in four hours. Room temperature has little deleterious effect on fresh B.C.G. provided it does not reach 20°C. (68°F.); rapid deterioration occurs at 30°C. (86°F.). Other interesting findings are reported in this W.H.O. monograph.

The variation between the freeze-dried vaccines produced at different centres is so great that W.H.O. (1954) has as yet been unable to recommend their general use. As van Deinse (1951) points out, up to 95 per cent. of the organisms are destroyed during the process of freeze-drying by some of the methods used.

B.C.G. Vaccination

New books on this subject have been produced by Griesbach (1954), Irvine (1954) and Mande (1954). Intracutaneous vaccination still remains the method of choice; in this country there is no option, as the vaccine supplied by the Ministry is only suitable for this purpose. The public are becoming used to the weeping local lesion which is its main disadvantage, while the advantages of this method are becoming more apparent to the medical world. Though multiple-puncture usually leaves no scar, when it does the result is a white rosette 1½ in. in diameter which enlarges as the infant grows. After scarification the site must be left untouched to dry for 15 minutes, which raises difficulties of organization in children's clinics; the subsequent duration of allergy appears to be shorter than with the intracutaneous method.

De Assis's (1953) 'concomitant' oral vaccination in Brazil has attracted much notice recently. Six doses of 100 mg. B.C.G. are given by mouth at monthly intervals from birth; for older infants the dose is doubled. Conversion is said to take place usually about the eleventh week, but the subsequent doses may completely desensitize the infant so that at the end of six months it has reverted to negative. It is claimed that this desensitization to a state of 'iathergy' is accompanied by further increase in resistance; this is in accord with Birkhaug's work on guinea-pigs (1940). De Assis has followed this theory to its logical conclusion and produced iathergy in natural positive reactors by oral B.C.G.; he claims that this increases their resistance. Latterly he has dispensed with all prevaccination tuberculin testing and gives these repeated oral doses indiscriminately to all children; no ill effect other than a transitory gastro-intestinal upset has been reported.

W.H.O. (1954) has pointed out that all strains of B.C.G. are not equally suitable for this procedure. When oral B.C.G. was tried in the Netherlands on 1,814 infants, the results were disastrous; cervical adenitis occurred in 64 cases—half of which ultimately suppurred—and chronic middle ear infection occurred in 19 cases from 7 of which B.C.G. was grown (Hammelburg 1953).

The discovery that B.C.G. vaccination produces a positive lepromin reaction has raised the hope that it may also prove effective against leprosy (Lowe and McNulty, 1953); no evidence is yet available on this point. Vaccination of lepers appears to have no effect on the course of the disease.

Complications

B.C.G. is at last being accepted for what it is—a tubercle bacillus of very low virulence. Only in the two cases mentioned above has it been reported as producing progressive tuberculosis. Lupus of the skin around the vaccination site has been reported in six cases (Marcusson, 1954). Zammit-Tabona (1952) has described 17 cases of phlyctenular conjunctivitis following B.C.G. Apart from these, no new complications have been reported. Le Melletier and Cassar (1951) have made a critical study of enlarged hilar shadows following B.C.G. and have enumerated their causes.

Gaisford and Griffiths (1954) have made some interesting observations on the avoidance of glandular abscesses in infants. They have shown that there is a direct relationship between the dose and the incidence of abscesses. They have also shown that in infants a glandular abscess is much commoner after vaccination on the leg than on the arm; this has been confirmed by our work in the Oxford region. Any extra burden on the regional glands within six months of B.C.G. vaccination may produce a late glandular breakdown; vaccination should not therefore be given above the level of the insertion of the deltoid where the drainage is partly to the supraclavicular glands, or the sudden load of an upper respiratory infection on these glands may produce a breakdown; for a similar reason no smallpox vaccination or injection should be given in the same arm during this period. In view of this latter finding it would appear logical to make the use of the right arm a standard procedure for all B.C.G. vaccinations thus leaving the traditional injection arm free for other inoculations.

The Vole Vaccine

Work on the vole vaccine has been progressing steadily over the last three years; a compact and

comprehensive survey of the present position has been given by Wells and Wylie (1954). They have found that the vaccination of man or animals with vole vaccine by any of the standard routes gives rise to a higher and more lasting tuberculin sensitivity than with B.C.G. In guinea-pigs the resistance following vole vaccination outlasts the sensitivity, while after B.C.G. the resistance drops only a little slower than the allergy (Wells and Wylie, 1952). Hall and Wylie (1952) have demonstrated that the allergy in man seven weeks after vole vaccination is greater than after B.C.G. Animal experiments show that the higher level of sensitivity produced by the vole vaccine is accompanied by a higher level of resistance to tuberculous infection.

The incidence of lupus at the site of multiple-puncture vaccination is considerably higher than with B.C.G.; in view of the different virulence of these two organisms, this was to be expected. These 'lupoid reactions' had always been associated with secondary infection in low-grade mental deficients who had scratched their vaccinations with filthy hands (Wylie *et al.*, 1954). Recently, however, Frew (1954) has reported cases in normal children; this has called a halt to multiple-puncture vole vaccination, pending the report of the M.R.C. trial. Meanwhile intracutaneous vole vaccination, which had been becoming increasingly popular, is being intensively studied.

Future Policy

The duration of allergy after vaccination has not yet been proved, but on the available evidence one must assume that roughly 80 per cent. of persons will still be positive at five years, after which the reversion rate may be high. To protect children only through their teens is not enough; some method of retesting young men and women of 18 to 20 years must be evolved. The only part of the Tuberculosis Service that has easy access to this age-group is the Mass Radiography Unit. As the incidence of the undiscovered case drops, there may come a time when the M.R.U. will no longer be an economic proposition. Would it not be a far-sighted policy for them to copy the Norwegian M.R.U.s and incorporate tuberculin testing and B.C.G. vaccination in their units?

B.C.G. vaccination in the bush is impracticable without a reliable freeze-dried vaccine; active steps must be taken to solve the problem of standardization. Intensive research into concomitant vaccination and the possible protective effect of B.C.G. against leprosy must also be carried out.

Finally, should all infants be vaccinated at birth? This is a most difficult question to answer. On the one hand such a mass vaccination

would largely eliminate tuberculous meningitis: on the other hand this is the age-group in which the greatest skill is required and in which—despite the greatest skill—the incidence of glandular abscesses is highest. Lorber (1954) has shown what can be done without mass vaccination by the vigorous pursuit and vaccination of all infant contacts, which amount to only 1 per cent. of the total number of infants. Despite the difficulties, this is a question that cannot be shelved indefinitely.

Summary

A review is given of the main advances in B.C.G. and vole vaccination over the last three years. The extension of B.C.G. vaccination to school children has caused a demand for a simplification of procedure. In particular a 'one-shot' tuberculin test is a necessity; it is suggested that the Heaf multiple-puncture test may be the answer. The possibility of omitting conversion testing is discussed.

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Excised portion of ileum with tumour at its centre.

any peritonitis during this period. Permission for post-mortem could not be obtained.

Pathological report on the specimen (Dr. J. W. Shackle) reads: 'This is a very cellular malignant tumour with many mitoses and some areas of necrosis. Apparently a reticulum-celled sarcoma.'

Comment

Wilkie (1953), who has thoroughly reviewed the available literature, reported a case in which perforations occurred on three occasions, but the total number of cases reported presenting with a perforation still appears to be less than 20. An exact figure is difficult to obtain because of the lack of differentiation between reticulum-celled sarcomas and lymphosarcomata. Frank, Miller and Bell (1942) review 361 cases of sarcoma of the small intestine and stress the rarity of perforation. They draw attention to a number of other case reports in which perforation occurred, but in at least one of these the growth was a

lymphosarcoma. Lewis (1939), who collected six cases from the literature, added one of his own, but this also was reported as a lymphosarcoma. Joergenson and Weibel (1951), who review 100 small intestinal tumours, do not mention reticulum-celled sarcoma as a separate entity. They do, however, stress the very poor prognosis of this condition. Hindmarsh (1951) found 11 previous cases of perforated small intestinal sarcomata in the literature and added a further case, but again this is reported as a lymphosarcoma. Recovery followed emergency laparotomy and resection, which was followed by deep X-ray therapy. Williams and Fodden (1946) report an unusual case of a reticulum-celled sarcoma causing diverticulosis of the jejunum in a woman of 70.

The case reported here is remarkable for certain features. No case in this advanced age-group appears to have been previously reported. As far as could be ascertained, the lesion was solitary without any ascertainable spread. The perforation was of considerable size and yet it failed to give rise to any gross peritonitis. There is little doubt on histological grounds that the tumour here reported was a reticulum-cell sarcoma.

Summary

A further case of perforation of a reticulum-celled sarcoma of the small intestine is reported. The patient appears to have been considerably older than in any other previous report, and the lesion appears to have been solitary.

Acknowledgments

I am very grateful to Miss G. M. Barry for permission to publish this report, to Dr. J. W. Shackle for the pathological report, and to Dr. L. W. Proger for the photograph.

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