PRESENT SITUATION WITH FORMALIN-KILLED POLIOMYELITIS VACCINE*

BY

J. KNOWELDEN, M.D., D.P.H.

Lecturer, Department of Medical Statistics and
Epidemiology, London School of Hygiene
and Tropical Medicine

In recent years the attitude of the profession to prophylaxis has become far more sophisticated—it has been realized that if a prophylactic is introduced widely before its performance has been fully tested it may be exceptionally difficult to assess how well it works subsequently. Over fifty years ago, for example, the adoption of typhoid vaccination by the British Army without adequate evidence of protection provoked one of the most acrimonious correspondences ever to be conducted in the columns of the *British Medical Journal*, between Almroth Wright, the champion of the vaccine, and Karl Pearson, who pleaded for proper assessment of its effect. Precise information on the performance of this prophylactic in the field has waited on a study sponsored by W.H.O. in Yugoslavia only a few years ago (Cvjetanović, 1957). On the other hand, before the recently developed Salk vaccine was accepted for general use in North America in 1955, a controlled field trial had been carried out (Poliomyelitis Vaccine Evaluation Center, 1955).

North American Field Trial

The 1954 field trial of Salk vaccine was in two parts—in the first, the “observed control study,” children in the second grade of school were vaccinated and their subsequent attack rates for poliomyelitis were compared with those of children in the first and third grades of the same schools. There are serious objections to this method of assessment. In the second part, the “placebo control study,” volunteer children in the first, second, and third grades were allocated at random—just over 200,000 to receive Salk vaccine, and very nearly the same number to receive injections of a solution of similar appearance which should have had no influence on immunity to poliomyelitis. As the parents, children, and observers did not know which material an individual child had received the subsequent assessment provided an unbiased measure of the vaccine's performance.

In this placebo control study in the period May 1 to December 31, 1954, the paralytic attack rate in the vaccinated was 16 per 100,000, compared with 57 per 100,000 in the controls. The incidence in the vaccinated was only 28% of that in the unvaccinated, or, put another way, the vaccine was 72% effective against paralytic disease.

A small quantity of vaccine prepared in this country had been used in tests of antigenicity in adult volunteers. In view of the occurrence of cases of poliomyelitis in the U.S. associated with some commercial batches of vaccine released early in the summer of 1955, further use of formalized vaccine was abandoned for the time in Great Britain. Subsequently the Medical Research Council Committee on Safety Tests of Poliomyelitis Vaccine recommended that vaccine distributed in this country

should not contain the virulent type 1 Mahoney strain used in the American vaccine and adopted up to that time elsewhere. By the winter of 1955–6 further batches of British vaccine were prepared containing the less virulent Brunenders strain as the type 1 component.

Medical Research Council's Trial

The Poliomyelitis Vaccine Committee of the Medical Research Council, reviewing the situation in consequence, considered that two questions needed answering urgently. (1) It was important to know first of all whether the substitution of the Brunenders strain for the Mahoney strain had reduced the capacity of the vaccine to protect against type 1 infection. (2) The American field trials had given evidence of protection in children 6–9 years of age only, with a slight suggestion of less protection in the youngest of this group. It was therefore also important to know whether formalized vaccine would protect younger pre-school children who have the highest rates of paralytic poliomyelitis in this country and are possibly subject to a different epidemiological background from that of American children. Consequently the Medical Research Council was invited to plan for an assessment of the protective effect of the vaccine which was to be issued in 1956 as part of the Health Departments' poliomyelitis vaccination programme in England, Wales, and Scotland.

It was impossible to set up a placebo control similar to that in the United States two years earlier. However, in the situation of shortage of vaccine, an assessment was made based on poliomyelitis occurring among about 150,000 children 1½–9½ years of age who received vaccine compared with that occurring among over 1,500,000 children of the same age who registered for vaccine but for whom none was then available (Medical Research Council, 1957b). The selection of whom to vaccinate from those registered was made according to month of birth—November for those born in 1947–50, roughly 5½–9½ years, and March and November for those born in 1951–4, roughly 1½ to 5½ years.

In the period July 1, 1956, to January 31, 1957, vaccinated children aged 5½–9½ years had only 16% of the paralytic poliomyelitis in registered unvaccinated children of the same age; for the younger group (1½–5½ years) the vaccinated had only 20% of the paralytic poliomyelitis in the unvaccinated. The apparent protection was 84% in the older group, 80% in the younger. I must emphasize here, *apparent* protection. Although the difference in rates achieved formal significance in both age groups, the number of cases was so small that no precise estimate of degree of protection could be made: in the younger group the true degree of protection could have been as little as 39%, and in the older only 6%. In the American trial, however, where the epidemics were more severe, the estimate of 72% protection was more precise, and at worst the true protection was unlikely to be less than 61%.

Information from Trials

In both American and British studies, therefore, significant protection against paralytic disease was shown. In both, however, the position with regard to non-paralytic disease was equivocal. For all so-called non-paralytic illnesses there was scarcely any difference in rates between vaccinated and unvaccinated in illnesses in either study. Dr. Galpine has rightly warned us of

*Read to the Section of Medicine at the Annual Meeting of the British Medical Association, Birmingham, 1958.

the unsatisfactory nature of a purely clinical diagnosis of non-paralytic poliomyelitis. If, then, we consider only aseptic meningitis in which there was laboratory confirmation by isolation of virus, both American and British studies show smaller attack rates for vaccinated than for unvaccinated children. However, the differences are nothing like as great as for paralytic illness and nowhere near approach significance. It looks, therefore, as if formalized vaccine may offer little protection against non-paralytic poliomyelitis. Furthermore, various studies in the United States show that Salk vaccine may produce little if any immunity to alimentary infection (Lipson, Robbins and Woods, 1956; Paul, Horstmann, Melnick, Niederman, and Deutsch, 1957; Fox, Gelfand, LeBlanc, and Rowan, 1958). Not only are vaccinated people as liable to infection as unvaccinated but the duration of excretion and the quantity of virus in the stools appear to be unmodified. Such vaccinated people are themselves as effective sources of infection to their associates as if they had never been vaccinated. In these respects artificially acquired immunity induced by killed virus vaccine differs from immunity derived from natural infection.

From this it follows that, however extensive our programme using killed-virus vaccine, we are unlikely to reduce the reservoir of poliovirus in the community. Even if formalized-virus vaccine produced lasting immunity to the paralytic complication of poliovirus infection, the programme would have to be maintained indefinitely, and to be successful would have to include a high proportion of those at risk. In this respect we should remember particularly the position of young adults going abroad—for example, in the armed Forces or Colonial Service—and the young parent with children of school age.

Number and Spacing of Injections

The 1954 field trials in North America used a course of three injections with an interval of one week between the first and second and of four weeks between the second and third injections. The British programme uses a two-injection course with an interval of three to four weeks. The antibody responses to such courses appear to be similar, and quite early the short interval between first and second injections was abandoned in North America, where the recommendation is now that, after the primary course of two injections at an interval of one month, a third injection should be given six or more months later. This recommendation finds support in the serological trials carried out by the M.R.C. Biological Standards Control Laboratory and their associates. These workers showed that in nearly all volunteer children who had no detectable antibody before inoculation the course of two doses produced an antibody response to all three types of virus (Medical Research Council, 1957a). After the second injection a decline in antibody levels occurred, especially marked for types 1 and 3. Nevertheless, a third injection 8 to 11 months after the primary course produced a booster response to all three types of virus to reach levels far higher than after the second injection (Medical Research Council, 1957c). Even when the interval between the second and third injections was extended to 18 months the same sort of booster response was seen (Medical Research Council, 1958).

The case for a third injection would seem clear on this evidence. Nevertheless we have no idea whether the

booster antibody response to a third injection would be mirrored by additional protection against paralytic disease. There has been no rigid assessment of the degree of clinical protection since the three-injection course was adopted in North America, and in Britain the evidence is serological only because three injections have been given only to small experimental groups. Similarly, although antibody levels fall after vaccination we do not know whether there is a corresponding loss of protection. Both the British and the American assessment included a period of seven months only after vaccination. We have no direct evidence from the field, then, on which we can decide how long vaccination protects. We do not know what is the optimum antibody level we should try to maintain, or even whether there is such a fixed optimal level.

Conclusions

The facets of this problem on which we have sound information are those in which planned investigations have been made. We know from the field trials that formalized vaccine containing either Mahoney or the less virulent Brunenders type 1 component protects against paralytic disease, but probably does not prevent alimentary infection. We know that in Britain protection was afforded to both pre-school and primary-school-age children. We know from serological studies that older children and adults respond to vaccination in much the same way as younger children, but at the other end of the scale a recent paper gives evidence suggesting that the response of infants may be inadequate because of maternally transmitted antibody (Perkins, Yetts, and Gaisford, 1958). We know from the surveillance programmes in countries using killed-virus vaccines that no major catastrophe has occurred since the Cutter incident, although we cannot say categorically that no one has been infected with live virus.

On the other hand, we do not know how long the protection against paralytic disease lasts after primary vaccination with two doses. We do not know whether protection will be appreciably greater after a third injection or whether its duration will be prolonged. We do not know how best to use antibody responses in man to estimate his immunity to paralysis.

It may be impossible to set up the investigations which would fill these gaps in our knowledge. Certainly it must become more difficult to obtain this information the longer we use vaccine. We need this precise knowledge if we are going to formulate an intelligent vaccination programme. It would be a pity if we have to take important decisions in ignorance because we had not even tried to find out.

REFERENCES

- Cvjetanović, B. B. (1957). *Amer. J. publ. Hlth*, **47**, 578.
 Fox, J. P., Gelfand, H. M., LeBlanc, Dorothy R., and Rowan, D. F. (1958). *Ibid.*, **48**, 1181.
 Lipson, M. J., Robbins, F. C., and Woods, W. A. (1956). *J. clin. Invest.*, **35**, 722.
 Medical Research Council (1957a). *Brit. med. J.*, **1**, 366.
 — (1957b). *Ibid.*, **1**, 1271.
 — (1957c). *Ibid.*, **2**, 1207.
 — (1958). *Ibid.*, **1**, 1206.
 Paul, J. R., Horstmann, Dorothy M., Melnick, J. L., Niederman, J. C., and Deutsch, J. (1957). In *Cellular Biology. Nucleic Acids and Viruses*, edited by T. M. Rivers. *Spec. Publ. N.Y. Acad. Sci.*, **5**, 141.
 Perkins, F. T., Yetts, R., and Gaisford, W. (1958). *Brit. med. J.*, **2**, 68.
 Poliomyelitis Vaccine Evaluation Center (1955). *Amer. J. publ. Hlth*, **45**, No. 5, pt. 2.