It is a pleasure to thank Sir Russell Brock, not only for his outstanding work in developing these direct operations, but for allowing and even encouraging me to judge the success of his results ; also Dr. Charles Baker for his help and for the inclusion of some of his patients; and Mr. Holmes Sellors and Mr. Ian Hill for operating on some and for keeping me so well informed about what they had done. I also thank Drs. S. S. Suzman, Geoffrey Reynolds, and D C. Deuchar for help at different stages in the follow-up of so many patients for up to ten years, and Drs. Deuchar, R. J. Shephard, and L. Brotmacher and the registrars at the National Heart Hospital for the results of catheterization.

REFERENCES

Bedford, D. E. (1956). *Proc. roy. Soc. Med.*, 49, 314.
Campbell, M. (1957). *Lancet*, 1, 111.
—— (1948). *Guy's Hosp. Rep.*, 97, 1.
—— and Deuchar, D. C. (1953). *Brit. med. J.*, 1, 349.
—— —— and Brock, R. (1954). Ibid., 2, 111.
Marquis, R. M. (1956) *Brit. med. J.*, 1, 819.
Peacock, T. B., (1866). *On Malformations of the Human Heart*, 2nd ed. Churchill, London.
Potts, W. J., Gibson, S., Berman, E., White, H., and Miller, R. A. (1955). *J. Amer. med. Ass.*, 159, 95.
White, B. D., McNamara, D. G., Bauersfeld, S. R., and Taussig, H. B. (1956). *Circulation*, 14, 512.
White, P. D., and Sprague, H. B. (1929). *J. Amer. med. Ass.*, 92, 787.
Wood, P. (1956). *Diseases of the Heart and Circulation*, 2nd ed. Eyre and Spottiswoode, London.

VACCINATION AGAINST POLIOMYELITIS WITH LIVE VIRUS VACCINES

4. A REVIEW OF THE PRESENT POSITION

BY

G. W. A. DICK, M.D., D.Sc., F.R.C.P.Ed.
Professor of Microbiology

AND

D. S. DANE, B.A., M.B., B.Chir.
Lecturer in Microbiology

The Queen's University, Belfast

In a report recently published by the World Health Organization (1958), the Expert Committee on Poliomyelitis strongly recommended that controlled field trials of live attenuated poliovirus vaccines should be carried out. The committee suggested suitable circumstances and populations for the trials and specified the strains of virus which it considered should be used. Trials are now in progress in many parts of the world, and a preliminary report of one of them has already been published (Courtois, Flack, Jervis, Koprowski, and Ninane, 1958). The purpose of this review is to give the reader who is unfamiliar with the subject some idea of the progress that has been made in the development and testing of attenuated poliomyelitis vaccines.

The possible advantages of living attenuated poliovirus vaccines over formalinized vaccines (Salk type) are that they can be given by mouth, that they are cheaper to produce, and that they may give a better immunity. They certainly give a broader type of immunity which will for a time prevent or modify subsequent infection of the alimentary tract with poliovirus. This is in contrast to the immunity at present produced by vaccination with formalinized vaccines which does not modify subsequent alimentary infection, at any rate to the same degree. The difference in the immunity produced by the currently available formalinized vaccines and attenuated virus vaccines is important because the use of attenuated virus vaccines in a community might interfere with the natural spread of virus, and so far there is no evidence that formalinized vaccine is capable of doing this (Langmuir, 1957 : Fox, 1957a, 1957b).

In the last few years there have been a number of small laboratory-studied trials of attenuated poliovirus vaccines, and there has been much progress in their development (Sabin, 1957a, 1957b), but the rapid emergence of a successful formalinized vaccine in 1955 removed some of the urgency which might have led to their earlier trial in the field. This delay allowed time for cautious progress, which may have been a good thing because attenuated poliovirus vaccines have certain novel features not previously encountered in human vaccines.

The poliovirus strains incorporated in current living vaccines developed by Sabin (1957b), by Cox and his associates (see da Silva, McKelvey, Bauer, Prem, Cooney, and Johnson, 1957), and by Koprowski (1957) have all been grown in monkey-kidney-tissue culture and selected for their comparative lack of neurotropism when inoculated into the C.N.S. of monkeys in large amounts. The vaccine viruses are given orally and cause an inapparent infection. They multiply in the alimentary tract like natural polioviruses, and the vaccinated subjects develop an immunity which is probably similar to that following an infection with one of the less invasive naturally occurring strains.

Attenuated poliovirus vaccines, like any other vaccines, require testing in the field for safety and effectiveness, both to the individuals vaccinated and to the community as a whole. For reasons of clarity these different aspects are considered separately.

Safety to the Vaccinee

The safety of attenuated poliovirus vaccines to vaccinees has been assessed both by direct clinical observation and, indirectly, by studying alterations which may occur in the character of the vaccine virus after multiplication in the human host.

To the best of our knowledge no illness definitely attributable to the use of attenuated poliovirus vaccines has so far been reported among thousands of persons who were observed carefully after vaccination in different trials with several different attenuated virus vaccines. This is a most encouraging fact, but we must bear in mind that nearly all natural poliomyelitis infections are mild or inapparent, especially with types II and III poliovirus, and that many of the people vaccinated in these trials have either been immune before vaccination or have been selected in a manner which has been far from ideal.

The indirect assessment of safety is made by testing the properties of the virus excreted by vaccinees. While there is a wide spectrum of monkey neuropathogenicity among naturally occurring or *wild* polioviruses, markedly neurotropic strains have always been recovered from the faeces of paralysed patients. If the excreted vaccine virus remains considerably less neurotropic for monkeys than wild polioviruses, which have been isolated from the faeces of paralytic cases, then it is usual to presume that the vaccine virus will do no harm to the vaccinee.

So far only one vaccine virus has been shown to change greatly in its neurotropism after growth in the human gut (Dane, Dick, Connolly, Fisher, and McKeown, 1957). This was the rodent-adapted TN type II poliovirus (Koprowski, Norton, Jervis, Nelson, Chadwick, Nelsen, and Meyer, 1956), and there is general agreement that it is unsuitable for further trial (Dick and Dane, 1957 : World Health Organization, 1958). All the other vaccine viruses which have been grown in monkey-kidney tissue culture and have been tested have shown some change towards greater neurotropism, but these changes have been insufficient to cause anxiety for the safety of vaccinees. If safety for the individuals receiving vaccine were all that was required of a vaccine, then there would be few problems in planning progressively larger trials of the currently available attenuated strains, though opinions would vary on the relative importance of direct clinical assessment and the indirect laboratory

study of excreted virus; and they would also vary on the degree of neurotropism theoretically permissible in the attenuated virus.

Unfortunately the vaccine viruses now undergoing trials have been shown on numerous occasions to spread from vaccinees to their associates. Spread has not always occurred, but neither does it always occur with natural poliovirus infections. Because of this ability to spread by contact infection we have to consider carefully the safety of the vaccine viruses to the community in which they are used.

Safety to the Community

The spread of a poliomyelitis attenuated vaccine virus from vaccinees to their contacts was first demonstrated by Koprowski *et al.* (1956) with SM type I virus. His subjects in this trial were incontinent institutional children. Later we demonstrated that SM virus could spread in a normal household (Dick, Dane, Fisher, Connolly, and McKeown, 1957). With the more recently developed attenuated polioviruses spread of virus from vaccinees to their contacts has been shown (Paul, Horstmann, Melnick, Niederman, and Deutsch, 1957; da Silva *et al.*, 1957; Smorodintsev, Drobishevskaya, Gorev, Ilienko, Kluchareva, and Kurnosova, 1958; Smorodintsev, personal communication). To date no significantly greater change towards neurotropism has been reported for virus recovered from infected contacts than has been observed in the excreted virus of some vaccinees. This finding is satisfactory, but the number of observations has necessarily been limited by the number of monkeys which are required for this type of test.

The basic problem we have to consider is the safety of the virus which is excreted by vaccinees and which will probably spread to other members of the community. As stated earlier, there is a broad spectrum of neurotropism among wild polioviruses. From the evidence so far published we do not consider that the virus excreted by some vaccinated subjects in recent trials can be differentiated from the less neurotropic strains of wild poliovirus. This opinion is based on our own interpretation of results from other laboratories, and we realize that not everyone will agree with it. Further work may show that there has been an irreversible change in the vaccine virus and that the excreted viruses are in fact unlike wild polioviruses and are never likely to change sufficiently to become dangerous. At the moment we consider that the irreversibility of the change is not proved.

If we accept that excreted vaccine polioviruses are similar to wild avirulent polioviruses, then how safe are they? Because neurotropic strains of virus have always been isolated from paralytic cases we may presume that the avirulent wild strains are probably safe provided that they are stable and cannot change to a more neurotropic form. Unfortunately there is little information on the stability of wild polioviruses, and for this reason we have been attempting to discover more about the problem by comparing the monkey neurotropism of polioviruses isolated from the faeces of paralytic patients and their close contacts. This method of approaching the problem is open to the criticism that, however carefully one may select a case and a contact, there is never absolute proof that both were infected with the same virus strain. The results of tests on three pairs of viruses are shown in the Table. Faecal virus was given one passage in monkey-kidney-tissue culture and then inoculated intracerebrally into rhesus monkeys in various amounts.

Comparison of the Monkey Neurotropism of Viruses Excreted by Paralysed Children and their Contacts

Serial Letter of Pair	Initials of Children	Type of Infection	Monkeys Paralysed when Inoculated with the Following TCD_{50} of Virus				
			10^6	10^5	10^4	10^3	10^2
A	D.D.	Paralytic.. ..	3/3*	3/3	3/3	1/3	0/3
	P.B.	Asymptomatic ..	1/3	1/3	0/3	0/3	—
B	J.A.	Paralytic.. ..	—	—	3/3	3/3	3/3
	R.Y.	Asymptomatic ..	3/3	3/3	3/3	—	—
C	W.N.	Paralytic.. ..	—	—	2/2	—	—
	K.S.	Minor illness ..	—	—	2/2	—	—

The techniques used in these tests are fully described elsewhere (Dane, *et al.*, 1957).
* Denominator = number of monkeys inoculated. Numerator = number of monkeys paralysed.
— Indicates not tested.

With two pairs (B and C) the viruses isolated from both the contact and the paralytic case were probably equally neurotropic. But in pair A, though the virus from the paralytic case (D.D.) was highly neurotropic, the virus from the contact (P.B.) was only slightly neurotropic and fell into the group of naturally occurring avirulent strains. The virus from P.B. resembled in monkey neurotropism (as judged by intracerebral inoculation) the virus excreted by subjects vaccinated with SM 100 type I poliovirus vaccine (Dick *et al.*, 1957; Koprowski *et al.*, 1956) and by subjects vaccinated with more highly attenuated poliovirus strains in a recent Minnesota trial (da Silva *et al.*, 1957). If other currently used vaccine viruses had been subjected to the same type of trial that was conducted at Minnesota similar results might have been obtained.

We do not consider that the small piece of circumstantial evidence we have given above is in any way conclusive proof that wild polioviruses are unstable in their neurotropism, but we do think that these preliminary results might serve as a reminder to those planning attenuated vaccine trials of the sort of problems they have to face in evaluating vaccine safety.

The W.H.O. Expert Committee on Poliomyelitis (World Health Organization, 1958), in its review of present knowledge about live poliovirus vaccines and in its recommendations for trials, virtually ignores the problem of spread. It points out "that preliminary tests on attenuated polioviruses in the hands of several investigators have failed to reveal signs of illness or other harmful effects in the vaccinees *or their associates*" (our italics). Apart from this one oblique reference to spread there is no indication to the reader that it might be important. Whether the committee considered the spread of these vaccine viruses potentially dangerous or not, it was odd that it dismissed the whole problem with such brevity. The uncontrolled spread of poliomyelitis vaccine virus in a community must either be beneficial or potentially dangerous. If spread is dangerous this will be discovered only if field trials are planned with the object of answering this most important question. If spread is beneficial then it would be useful to know this. A new concept in the use of attenuated virus vaccines might be evolved which could be of great value in combating such diseases as influenza, mumps, and measles.

Effectiveness in the Vaccinee

The ultimate test of the effectiveness of attenuated poliovirus vaccines must await controlled field trials if these are in fact possible. In the meantime it seems reasonable to judge likely effectiveness by measuring the levels of neutralizing antibody in vaccinated subjects.

In the trials where virus grown in monkey-kidney-tissue culture has been used the proportion of vaccinees developing neutralizing antibody has usually been over 90%, and the levels of antibody appear to have been satisfactory. With the TN type II rodent-adapted virus we found that a smaller proportion of children developed antibody (77% of 124), but the *levels* of antibody in children who did so were broadly similar to those reported following vaccination with viruses grown in tissue culture. Information about the persistence of neutralizing antibody comes mainly from trials with strains of vaccine virus no longer in use. Our own follow-up study on children vaccinated with TN type II virus (Dane, Dick, Briggs, and Nelson, 1958) is open to this criticism, but we consider that the results obtained with TN type II virus are likely to be at least as good as, or better than, those which will be found with the less virulent current vaccine viruses that do not undergo such a marked change after growth in the human gut. We found that about two months

after vaccination 77% of children had developed neutralizing antibody at levels comparable to that found by others following two injections of formalinized virus (Report, 1957a), and that in a proportion of the children there was a marked decline in antibody level over the next year, which again was like that reported after two injections of formalinized virus (Report, 1957b).

Very high levels of neutralizing antibody have been shown to develop following a third booster injection of formalinized vaccine (Report, 1957b), and it is doubtful whether refeeding with live virus vaccines would have such a marked effect. Furthermore, in view of the alimentary resistance to reinfection which follows vaccination with live virus vaccine, it would be difficult to predict whether or not, or when, reinfection would occur. This does not mean that refeeding would not be a possible way of maintaining immunity induced by live virus vaccines, but only that certain problems would arise which have not arisen with formalinized vaccine.

The alimentary resistance to reinfection which follows vaccination with live virus is often presumed to be some sort of local gut immunity. Little is known about the nature of this immunity or how long it will last, and, although it is of obvious benefit to the individual vaccinee, it may have more far-reaching consequences to the community as a whole.

Effectiveness to the Community

The resistance or comparative resistance of people vaccinated with live attenuated polioviruses to reinfection with these viruses gives hope that they will be similarly resistant to infection with wild polioviruses. If this proves to be the case, then there is a real chance that wild polioviruses might disappear from a community where sufficient numbers had been vaccinated with live virus vaccines. This does not appear to have happened in the U.S.A. following the use of formalinized vaccine, but until a high proportion of the susceptibles in a country have been adequately vaccinated with potent formalinized vaccine the possibility that the elimination of polioviruses from a community can be achieved with this type of vaccine cannot be excluded. Experimentally, Howe (1957) has shown that there was a significant reduction in the amount of virus excreted by chimpanzees fed a virulent strain of poliovirus if they had previously been vaccinated with formalinized virus. Poliovirus infection in chimpanzees is characterized by a greater pharyngeal multiplication than occurs in man, and for this reason a direct comparison may not be valid.

Use and Testing of Current Attenuated Strains

There appear to be four possible uses of attenuated poliovirus vaccines. They could be used (*a*) instead of formalinized vaccines; (*b*) to supplement formalinized vaccines; (*c*) to halt epidemics; and (*d*) in countries whose financial resources do not permit the use of formalinized vaccines.

In the first case, it seems unlikely that any country with the finances available to undertake a vaccination programme using formalinized vaccines would use, or switch to, attenuated virus vaccines until it has been shown that they are as safe as, or safer than, formalinized vaccines and produce as good or better levels of immunity.

In the second case, attenuated virus vaccines might be used to supplement formalinized vaccines in the hope of eliminating wild viruses from the community. Before undertaking such a programme one would like to know whether virulent polioviruses may not in fact be largely eliminated from communities which are efficiently immunized with potent formalinized vaccines. Enough time has not elapsed from the introduction of formalinized vaccines, and sufficiently thorough immunization has not yet been achieved to answer this question.

The use of attenuated vaccines to control epidemics at the present time involves the employment of a contagious virus whose safety and effectiveness during non-epidemic periods has been inadequately studied. It cannot be predicted how avirulent viruses would behave if they were introduced into a community in which conditions are ripe for an epidemic, and in many areas it would be difficult to organize voluntary immunization of a whole population as was done recently in Africa (Courtois *et al.*, 1958). The problems involved in attempting to evaluate the results of vaccinating a community during an epidemic are great enough to deter some authorities from introducing a largely unproved vaccine in this manner.

There remains the possibility that live virus vaccines might be used in countries in which formalinized vaccines cannot be afforded. In our opinion carefully conducted trials of attenuated virus vaccines should be undertaken in such countries if there is a genuine need for vaccination, and they should be done during non-epidemic times of the year. The previous epidemic history of poliomyelitis should be available, and should be carefully considered before initiating the trials. Such trials would be the most valuable first step in gaining information in the field, but it must be appreciated that there are great difficulties in planning trials of a vaccine virus which spreads from vaccinees to their contacts. Any trial of safety must take this factor into account and must attempt to evaluate the harm or good which has been achieved by the uncontrolled spread of a living virus. The information so far published about the currently available attenuated vaccines does not suggest that they will necessarily be either dangerous or completely safe. It is important that trials should aim at defining the limits of safety of these vaccines, rather than at sidestepping the possible dangers which accompany the use of a contagious vaccine.

References

Courtois, G., Flack, A., Jervis, G. A., Koprowski, H., and Ninane, G. (1958). *Brit. med. J.*, **2**, 187.

Dane, D. S., Dick, G. W. A., Briggs, Moya, and Nelson, R. (1958). Ibid., **2**, 1187.

—— —— Connolly, J. H., Fisher, O. D., and McKeown, Florence (1957). Ibid., **1**, 59.

Dick, G. W. A., and Dane, D. S. (1957). Ibid., **1**, 70.

—— —— Fisher, O. D., Connolly, J. H., and McKeown, Florence (1957). Ibid., **1**, 65.

Fox, J. P. (1957a). In *Special Publications of the New York Academy of Sciences*, **5**, 152.

—— (1957b). Fourth International Poliomyelitis Conference, Geneva, 1957. In press.

Howe, H. A. (1957). *Amer. J. publ. Hlth*, **47**, 871.

Koprowski, H. (1957). In *Special Publications of the New York Academy of Sciences*, **5**, 128.

—— Norton, T. W., Jervis, G. A., Nelson, T. L., Chadwick, D. L., Nelsen, Doris J., and Meyer, K. F. (1956). *J. Amer. med. Ass.*, **160**, 954.

Langmuir, A. D (1957). In *Special Publications of the New York Academy of Sciences*, **5**, 93.

Paul, J. R., Horstmann, Dorothy M., Melnick, J. L., Niederman, J. C., and Deutsch, Joyce (1957). In *Special Publications of the New York Academy of Sciences*, **5**, 141.

Report to Committee on Laboratory Investigations of Poliomyelitis, Medical Research Council (1957a). *Brit. med. J.*, **1**, 366.

Report to Medical Research Council (1957b). Ibid., **2**, 1207.

Sabin, A. B. (1957a). In *Special Publications of the New York Academy of Sciences*, **5**, 113.

—— (1957b). Fourth International Poliomyelitis Conference, Geneva, 1957. In press.

da Silva, M. M., McKelvey, J. L., Bauer, H., Prem, K. A., Cooney, Marion K., and Johnson, A. (1957). *Univ. Minn. med. Bull.*, **29**, 133.

Smorodintsev, A. A., Drobishevskaya, A. I., Gorev, N. E., Ilienko, V. I., Kluchareva, T. E., and Kurnosova, L. M. (1958). *Second Scientific Meeting of Institute for Poliomyelitis Research of the Academy of Medical Science. Poliomyelitis and Related Illnesses Caused by Enteric Viruses*. State Publishers for Medical Literature, Moscow.

World Health Organization (1958). *Wld Hlth Org. techn. Rep. Ser.*, No. 145.

"The meat arriving at Smithfield Meat Market has presumably been inspected at the time of slaughter in this country or abroad. Evidence of disease which has escaped notice at the primary inspection is nevertheless found; in some cases it has been overlooked, in others it has only become apparent when the carcass is cut up. Condemnations of meat at Smithfield are to a considerable extent due not to disease but to deterioration during transport, decomposition, bone-taint, brine-staining, etc. The total amount of meat delivered at Smithfield Market was 422,607 tons, of which 497 tons were found to be diseased or unsound and were voluntarily surrendered."—From the *Report of the Medical Officer of Health for the City of London for the Year 1957.*