Section of Neurology

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Vaccination against Poliomyelitis

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Poliovirus Vaccines and the Control of Poliomyelitis

Seven years' experience of immunization against poliomyelitis has not entirely resolved the controversy which surrounds this subject. Nevertheless, it is time that opinion was based on the weight of evidence now accumulated rather than on personal views.

Poliovirus Vaccines

Inactivated vaccine: Vaccine prepared from monkey kidney tissue culture infected with poliovirus, processed, filtered and formolized according to Salk's formula has been used on millions of children and adults in various countries from 1955 onwards. In Britain the vaccine was varied only by the substitution of a different Type 1 strain of virus for the original virulent Mahoney virus but much American vaccine has been used as well. Some 19,000,000 persons in England and Wales completed a primary course of two doses. 17,000,000 received a third dose and 4,000,000 had had a fourth dose by September 1963. Throughout its use, manufactured inactivated vaccine has carried the risk of failing to pass the safety test for determining the presence of residual living virus. Only in the one episode in 1955 was such incompletely inactivated vaccine known to have been given, however, and this was in the notorious Cutter incident recently redescribed by Nathanson & Langmuir (1963). Hundreds of American cases of poliomyelitis occurring within twenty-eight days of the injection of inactivated vaccine have since been faithfully recorded by the US Health Department through its surveillance scheme (Langmuir 1958). These cases have not shown the features of the cases of inoculation poliomyelitis of 1955 when the incubation period averaged eight days, there was a coincidence of paralysis in the inoculated limb and cases occurred after certain batches of vaccine. In Britain, cases of poliomyelitis and of various neurological disorders have also occurred within twenty-eight days of the injection of inactivated vaccine.

Safety tests, including tests for wild monkey virus, were thus the main basis for reliance upon the inability of Salk vaccine to produce ill effects. Yet, as is now known, many of the earlier batches of vaccine must have contained a contaminating virus known as SV_{40} which resists formolization (Sweet & Hilleman 1960). This virus can only be revealed by cultivation in tissue cultures prepared from cercopithecus monkeys and thus it has been screened out from all vaccine released for use since 1960. The fact that it will, when injected into suckling hamsters, produce tumours (Rabson & Kirschstein 1962) and that it can induce the so-called malignant transformation of tissue cultures *in vitro* (Koprowski *et al.* 1962) has caused considerable alarm. It was at first thought that the virus could not infect after oral use in man because antibodies against it were found in children receiving inactivated vaccine intramuscularly, but not in those receiving oral vaccine (Magrath *et al.* 1961). However, SV_{40} virus has been recovered in the USA from the fæces of children to whom oral vaccine was given (Melnick & Stinebaugh 1962) and when given intranasally to volunteers it induced subclinical infection with antibody formation (Morris *et al.* 1961). Fortunately, epidemiological enquiries designed to reveal a possible carcinogenic effect in man of inactivated vaccine which might contain SV_{40} have been negative (Fraumeni *et al.* 1963). The story is important as an indication that safety tests are only valid for agents which are known and not against the unknown ones.

Apart from safety, however, a major drawback of inactivated vaccine is its inability to protect the alimentary tract from infection by virus acquired by natural contagion or given in the form of attenuated virus. There is universal

Table 1
Advantages and disadvantages of Salk vaccine

Advantages	*Disadvantages*
Killed-controllable. Unable to cause disease	May contain unknown viruses in an active state. 'Accidents' possible
Can be incorporated into mixed vaccines (e.g. diphtheria, whooping-cough)	Antibody response less good in mixtures
Excellent 'booster' for waning antibodies	Poor stimulus in antibody-negative persons. Therefore multiple doses necessary
Widespread use shown to lessen risk of disease and lower epidemicity. Protects central nervous system 80%	Does not protect alimentary tract. Degree of herd immunity low, therefore outbreaks in unprotected persons continue
Use during epidemics 'safe', i.e. cannot be blamed	Cannot control epidemics because of time-lag after inoculation

agreement that at least the commercially-available inactivated vaccines used in many millions of children have failed to prevent alimentary infections and have thus permitted the circulation of wild poliovirus in the community to continue. The very satisfactory figure of 80% protection against paralytic disease (Langmuir 1961) tends to conceal the facts that vaccinated persons can still be infected and that unvaccinated persons in the community remain fully susceptible. Outbreaks of poliomyelitis have been experienced in well-vaccinated countries such as the USA and Canada in 1959, and Australia and New Zealand in 1962. The Hull epidemic in 1961 occurred after the completion of a course of immunization by two or more injections in 50% of the most susceptible children under 5 and 80% of those aged 5–14 years of age.

Dick and his colleagues (1961) believe that vaccine which is more concentrated than that used formerly can limit alimentary infection because of the enhanced antibody response thereby produced. This effect of high antibody levels in the serum on the quantity of excreted virus was confirmed by Howe (1962) in a study of cases of Type 1 poliomyelitis and their family contacts. Table 1 summarizes my own views of the advantages as well as the disadvantages of the inactivated vaccine. It would certainly be foolish to deny the contribution which this vaccine has made to the control of poliomyelitis.

Living attenuated poliovirus vaccines: From 1952 until now poliovirus vaccine prepared from strains of virus which have been attenuated by propagation in experimental animals or in tissue cultures have been used in small trials, large-scale trials and for the immunization of entire countries. The advantages claimed for these oral vaccines are summarized in Table 2, which also mentions disadvantages. There is no doubt that oral vaccines can infect the alimentary tract, produce antibodies and protect against reinfection by the same serological type of virus as that given on the first occasion. The duration of such protection is still unknown. To produce immunity all three virus types must be given, at the same time or separately. Interference by one type of virus with successful infection by another type of poliovirus occurs under conditions of vaccine administration and so does interference by other viruses which inhabit the alimentary tract. Multiple doses of trivalent vaccine are therefore necessary. Interference can be used to advantage by mass vaccination with oral vaccine during outbreaks of disease in order to break the chain of transmission of wild poliovirus through uninfected susceptibles. Vaccine viruses may be excluded from the alimentary tract in persons already infected naturally or may replace wild virus in the intestine only (Gelfand 1963). In such persons already incubating poliomyelitis, vaccine may not alter the course of the illness. When paralysis develops, however, the excreta may only yield viruses derived from the vaccine strains.

The problem of determining the source of infection in cases of poliomyelitis occurring within a few days of administration of oral vaccine may therefore be insoluble. It is made particularly difficult because of the fact that during alimentary infection the vaccine virus deviates or mutates in its properties. Some of these, such as a capacity to grow in tissue cultures kept in a more acid medium than normal or a capacity to grow at 40° C, which are the properties of wild poliovirus but not of the vaccine strains, may be re-acquired

Table 2
Advantages and disadvantages of living oral (attenuated) vaccine

Advantages	*Disadvantages*
Produces infection of alimentary tract, antibodies and resistance to reinfection	Prolonged excretion, possible contact infection. Immunity type-specific, therefore multiple doses. 8–20% reinfection possible
Interferes with natural infection, therefore use during epidemics possible	Mutation of virus during infection, therefore possible risk to individual (1: 1,000,000) or contacts. Blame likely for cases during epidemics
Best in antibody-negative persons	Cannot 'take' and immunize in babies under 3 months of age
Boosts previous immunity if it 'takes'	Antibody response unpredictable if it does not 'take'. Interference by natural enteroviruses
Reduces incidence to zero after mass use	Duration of protection unknown

Table 3
Vaccine-associated cases of paralytic poliomyelitis 1962 and 1963

		No. of cases	Time interval in days				Virus recoveries					
							Polioviruses			Cox-		
			1–7	8–15	16–28	>28	1	2	3	ECHO	Other	None
Received oral vaccine	1962	11	7	2	2	–	6	2●	2●	1	–	1
(within 28 days)	1963	3	1	1	1	–	–	–	1	–	1	1
Household contact	1962	8	2	2	4	–	3	–	2	–	–	2■
(within 60 days)	1963	3	–	1	1	1	1	–	–	1	–	1
Total		25	10	6	8	1	10	2●	5●	2	1	5■

●Includes one patient excreting both Types 2 and 3 ■Plus one patient not examined

almost fully by the viruses excreted in the fæces. Other properties, such as close antigenic affinity to the homologous vaccine virus and inability to cause paralysis in monkeys inoculated intracerebrally or intraspinally, are altered only to a certain degree. It is nevertheless true that it is impossible to prove virologically that the illness could not have been due to the vaccine virus unless the illness is due to a virus antigenically distinct from the vaccine strain. This happened during the Hull Type 1 epidemic in 1961 (Ministry of Health 1963) when only Type 2 virus vaccine was used and when paralytic cases of poliomyelitis continued to occur for some days after mass use of vaccine. All but one of 21 cases whose onset of illness occurred after administration of vaccine yielded Type 1 virus in the stools. The patient excreting Type 2 virus in the stools on admission to hospital experienced an onset of paralysis two days after vaccine administration, so that it is exceedingly unlikely that the Type 2 vaccine virus was the cause of the illness.

In spite of the many theoretical advantages of oral vaccines the stumbling block remains that the vaccine has been blamed for causing poliomyelitis. The only answer to this problem is strict surveillance. Both in the USA and in England and Wales surveillance is maintained on each case of paralytic disease notified as poliomyelitis. Galbraith (1963) described the English scheme in detail to the European Symposium of Poliomyelitis held in Stockholm in September 1963. The responsibility for initiating action rests on the Medical Officer of Health, who reports to the Public Health Laboratory Service giving details of the vaccination history and of any members of the household who have received oral vaccine. Full clinical reports and laboratory findings are compiled. A watch has been kept to see whether cases of paralytic disease occurring within twenty-eight days of administration of oral vaccine exhibit similar features to those noted in the USA in 1962. Some cases occurred during 1962 in both the USA and Canada in association with mass use of monovalent vaccine which were reported to have been caused by vaccine viruses. There were thus 7 of 23 reported cases following Type 1 vaccine and 11 of 22 cases following Type 3 vaccine which were regarded by the US Surgeon-General's committee as being 'compatible' with causation by vaccine (US Department of Health, Education and Welfare 1962). Thirteen of the 18 cases thus suspected were in adults and the onset of illness averaged fifteen days from the date of administration of oral vaccine.

Table 3 shows the details of 25 cases of paralytic poliomyelitis associated with oral vaccine in England and Wales and investigated during 1962 and 1963. I have added to Galbraith's 19 cases a further 6 investigated by Dr D L Miller at Colindale, who is now in charge of the surveillance scheme. Fourteen cases occurred in persons who received trivalent oral vaccine within twenty-eight days of the onset of illness and all but 2 of these were in children aged 6 or less. The other 11 cases occurred among household contacts exposed to vaccine administered to another member of the household within sixty days of the onset of illness. Five of these were adults. The time interval between the onset of illness and the vaccine administration averaged 9·5 days for those who themselves received vaccine and 14·5 days for the household contacts. The greater number of isolations of Type 1 viruses from the stools agrees with the general experience of poliomyelitis in unvaccinated persons in these years. Type 3 was isolated relatively often but this virus persists for longer in the stools than do the other viruses after vaccine has been given (Public Health Laboratory Service 1962). In addition to the available data on cases of poliomyelitis, the surveillance programme has some information on other forms of neurological disorders including encephalitis which have been associated with oral vaccine. It seems too early to attempt to evaluate these cases, which were relatively few in number; but no causal relationship has yet appeared likely. The occurrence of similar cases after Salk vaccine is perhaps an indication that one should be cautious about the possible relationship with oral vaccine.

Experience of Poliomyelitis in 1962 and 1963

The incidence of poliomyelitis in England and Wales during the past seven years is shown in Table 4. Salk vaccine alone was used from 1957 to 1961 except during the Hull mass vaccine administration in 1961. Oral vaccine has replaced Salk vaccine progressively since February 1962 both in primary immunization and for reinforcing doses. Five million persons had received one or more doses of oral vaccine by June 1963, 1,900,000 doses being used for primary courses. In addition to routine immunization, oral vaccine was offered during 1963 to all children and even adults living in the immediate environment or in contact through school with every case of paralytic poliomyelitis. Even though this has doubtless swelled the number of patients whose illness has occurred after vaccine and who were probably incubating the disease when the latter was given, the principle of partial 'blanketing' of the immediate contacts appears to be sound in practice.

Table 4

Poliomyelitis: corrected notifications in England and Wales 1957–63

	No of cases notified per annum						
	1957	*1958*	*1959*	*1960*	*1961*	*1962*	*1963*
Paralytic	3,177	1,419	739	257	707	212	44
Non-paralytic	1,667	575	289	121	169	59	10
Total notifications	4,844	1,994	1,028	378	876	271	54●

●77 cases notified provisionally but diagnosis changed in 30. Reasons for change not accepted in 7

Table 4 shows that the number of cases of poliomyelitis notified and provisionally confirmed in 1963 was a record low total and only about one-fifth of the number in 1962. Yet this record figure occurred in a year when oral vaccine was introduced all over the country in relatively small numbers of persons. This method of using living vaccine actually affords a greater opportunity for spread of excreted virus to contacts than does simultaneous mass immunization. But in our particular setting and with previous experience of polio vaccine, the method has not caused any difficulty.

The experience of poliomyelitis over the last few years has brought one further lesson. In this phase of declining paralytic disease, it is becoming increasingly difficult to recover polioviruses from the fæces. Other enteroviruses are sometimes being recovered, however, and the role of these numerous agents in causing disease of the central nervous system is slowly becoming apparent. Clinical diagnoses and records of illness therefore require the best possible laboratory support. Fortunately the Public Health Laboratory Service is well equipped for this task.

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The Future of Inactivated Poliomyelitis Vaccines

Recently there has been a tendency to dismiss formolin-inactivated poliomyelitis vaccines (Salk vaccine) as being of limited value, out of date and based on the wrong principle. Certainly it is true that Salk vaccine of the potency used in the past in the United Kingdom and North America was considerably less effective than oral vaccine (Sabin vaccine) both in conferring individual protection and herd immunity. Whether the principle of an inactivated poliomyelitis vaccine was wrong is another matter and I wish to defend this principle by presenting some of the evidence which suggests that potent Salk vaccines are capable of giving complete protection to the individual and of profoundly influencing herd immunity.

Individual Protection

Considering the problem of individual protection first, why did the Salk vaccine we used give only 80–90% protection after a course of three injections? The answer is that it failed to stimulate the production of useful levels of neutralizing antibody in a proportion of those who received it. When a potent vaccine is used high levels of antibody are reached after the third or booster dose and this results in a solid and long-lasting immunity against paralytic poliomyelitis. On the other hand, when a vaccine of poor potency is used, no proper secondary response is obtained after the booster dose and this means a less certain and less durable immunity.