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LIVE ATTENUATED POLIOVACCINE*

A REVIEW

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INTRODUCTION

An immense amount of research into the nature and epidemiology of poliomyelitis has been carried out during the last 30 or so years. This followed the discovery that poliomyelitis is due to infection with a specific virus and that a condition similar to that of paralytic poliomyelitis in man may be induced in monkeys by inoculation of their central nervous system with infective material. As a result of this research it soon became evident to many that the only hope of effectively controlling the disease lay in the development of an efficient vaccine.

Attempts were made by Brodie in 1934 and Kolmer in 1935 to prepare a poliovaccine, similar to that of rabies vaccine. They used suspensions of infected monkey nervous tissue in which the virus particles had been inactivated by chemical agents. It was not until 1949, however, when Enders *et al.*[1] published their studies on the artificial growth of poliovirus in high titre on monkey kidney-tissue culture, that the production of poliovaccine became a reasonably feasible proposition. This discovery was of fundamental importance in the development of poliovaccine. Also of basic importance was the work of Bodian *et al.*[2] who showed that there were 3 distinct immunological types of poliovirus. The Typing Committee of the National Foundation of Infantile Paralysis of the USA then proved that, although there were numerous strains of poliovirus which differed greatly in their virulent properties, each strain belonged to one or other of the 3 types. This work made it clear that any effective vaccine would have to be trivalent. It then had to be decided what type of vaccine should be produced — a living attenuated or a dead inactivated vaccine.

On general principles, many authorities believed that the best hope of developing a really effective prophylactic agent against poliomyelitis lay in the production of a live vaccine. Live poliovaccine is, however, attended by two possible dangers, viz. (1) the vaccine virus may not be sufficiently attenuated and so may cause paralytic disease in unduly susceptible persons; and (2) the vaccine virus, being excreted from the alimentary tract of those vaccinated, might be passed on to others and, gaining in virulence by such passage, might ultimately produce paralytic disease in them.

At that stage it was obvious that several years of very careful and intensive research would have to be carried out before a live attenuated poliovaccine, the safety of which to the individual and the community could be guaranteed beyond all doubt, could be produced. It thus seemed that the development of a 'dead' vaccine would be the quickest answer to this urgent problem. There could be little doubt of the safety of such a vaccine, though there might be doubt as to its probable efficacy.

SALK VACCINE

Salk then developed his formalin-inactivated vaccine. This was soon conclusively proved, by the now famous large-scale field trials carried out in the USA during 1954, not only to be safe but to be 60 - 70% effective in preventing paralytic poliomyelitis. Following the report by Francis[3,4] of these trials, a mass vaccination campaign was immediately started in America. However, this campaign soon experienced a very serious setback due to a number of paralytic cases unexpectedly occurring among vaccinated people. These were later proved to be due to contamination of some of the batches of vaccine with live virulent virus. An immediate official investigation was carried out and it was shown that the method of inactivation of the vaccine virus was not foolproof, as was first thought, and that the safety tests which had been used were inadequate.

After more stringent control of the processing of the vaccine had been introduced and more elaborate safety tests enforced, a mass vaccination campaign again slowly proceeded. Since then many millions of children have been successfully inoculated with Salk vaccine throughout the world and the vaccine has proved to be the safest and most innocuous vaccine in routine use today. Moreover, its potency has been so improved that a 90% immunity to paralysis may be expected after 3 or more properly-spaced injections. There can thus be no doubt whatever about the great success of the Salk vaccine. Inactivated vaccine, however, has its limitations and there are a number of authorities who still believe that the final conquest of poliomyelitis will be achieved by a live vaccine.

LIVE VACCINE

One of the most important discoveries of the immortal Louis Pasteur was the rationale for the production of live vaccines. These vaccines are composed of living micro-organisms, the virulence of which for a particular species of animal has been attenuated by such means as passage through resistant animals of another species. This attenuation causes them to lose their ability to produce serious disease in the original animal species but allows them to retain their ability to provoke a protective immunity. Infection with such attenuated micro-organisms induces subclinical disease, so that the organisms multiply in the tissues and, by sustained antigenic stimulation, produce an effective immunity in a natural way. Thus it is that the most efficient viral vaccines are smallpox and yellow-fever vaccines, both of which are composed of living attenuated organisms. As natural immunity to paralytic poliomyelitis, which lasts throughout life, is normally acquired by subclinical infection with wild strains, there is every theoretical hope that live poliovaccine will produce a relatively solid and lasting immunity.

Early Research

Because of the great promise offered by a living poliovaccine, certain research workers of vision have devoted

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all their efforts towards the development of such a vaccine and have refused to be deviated from their task by the apparently great success of the 'dead' vaccine. Foremost among these workers has been Koprowski. In the late 1940s[5] he attenuated selected strains of poliovirus by serial passage through rodents. By inoculation of the central nervous system of monkeys with these virus strains he proved that they had become attenuated, in that their ability to produce progressive lesions in the monkeys was greatly diminished. Such biological tests on monkeys, though they have certain obvious defects, are still the best laboratory means of distinguishing between virulent and avirulent strains. Eventually, feeling confident that his attenuated strains had lost their ability to cause paralytic disease in Man, he fed a suspension of infected cotton-rat brain to a 6-year-old boy. This was in February 1950, and it is the first recorded case of the use of live polio-vaccine in Man. The boy developed an intestinal infection with the virus but showed no signs of disease and gradually produced specific neutralizing antibodies in his blood. The experiment, therefore, appeared to be successful and soon 20 subjects were fed vaccine without any ill effects.

Since these initial and most important experiments by Koprowski, an immense amount of research on live polio-vaccine has been carried out by him and by other workers. Other methods of attenuating poliovirus have been developed, such as the adaptation of certain strains to the developing chick embryo. Tissue culture has been of the greatest help in studying and propagating various strains, and the plaque technique of Dulbecco,[6] whereby the progeny of individual virus particles may be isolated, has proved invaluable in the selection and purification of strains.

Many of the strains selected have had to be discarded because, on monkey test, they have proved to be insufficiently avirulent. Others, again, have had to be discarded because, though they have been proved to be avirulent, they have also lost some of their important specific antigenic properties.

Later Research

As a result of much meticulous and time-consuming laboratory work and intensely studied small-scale experiments on humans in closed communities, confidence was soon obtained in the safety of several live poliovaccines. This enabled the Expert Committee on Poliomyelitis of the World Health Organization to advise in 1957 that a stage of development in these vaccines had now been reached where large-scale studies on humans were justified in those countries where suitable epidemiological conditions prevailed.

MAIN LIVE-VACCINE STRAINS

Three different sets of carefully selected attenuated strains were then used for large-scale experiments, viz. (1) the Koprowski strains, (2) the Cox strains, and (3) the Sabin strains. Each of these strains has been named after its originator.

These 3 sets of strains, though all regarded as safe and antigenically potent, have shown considerable differences in their neurovirulent properties as tested in monkeys. The Sabin strains have, however, been shown consistently by such tests to be the most avirulent.

1. Koprowski Strains

The first large-scale experiments with live poliovaccine were conducted with the Chat (Type I) strain of Koprowski in the Belgian Congo, commencing in 1957.[7] By early 1959 some 46,000 African children under the age of 5 years had been vaccinated in Leopoldville. The vaccine used appeared to be perfectly safe in that it caused no cases of paralytic poliomyelitis or other complications among the vaccinated subjects or their contacts. The immunity response, as shown by the development of specific antibodies in the serum of the vaccinated children, was, however, somewhat disappointing. Only about 60% gave positive reactions as compared with 90 - 95% obtained in studies with the Chat strain elsewhere. This partial failure was attributed to interference with the vaccine by other enterovirus infections which are common in children living in a tropical and unhygienic environment. When a poliomyelitis epidemic occurred in Leopoldville shortly after the vaccination campaign had commenced, the vaccine appeared to have proved of definite protective value. Of 99 paralytic cases with 4 deaths in this epidemic, 89 cases occurred in non-vaccinated children. However, it has been considered that the numbers involved were too small to allow of a proper statistical evaluation. This experience in the Congo strongly suggests that the live-virus vaccine used was of definite protective value. Also, there was no evidence to indicate that the vaccine was unsafe either for the individual or the community.

Live-virus vaccine composed of Koprowski strains has also been employed in Poland.[8] This vaccine was used only on a small number of subjects in 1958 but since 1959 it has been employed on a mass scale, so that nearly a million children were vaccinated by the end of the year. Only Types I and III strains were used and no Type II. The results appeared to be most promising, but a detailed report of the efficacy and safety of live poliovirus as used in Poland is still awaited.

More recently a report has been published by Pagnano *et al.*[9] on the routine use of live-virus vaccine composed of all 3 types of the Koprowski strains. This was given to 850 normal children, aged from 1½ months to 6 years. They were mainly Negroes, from a low-income group, living in Philadelphia, USA. One, 2 or 3 types of vaccine were fed at monthly intervals. Of the children under 6 months of age, 91 - 100% had a significant antibody response and, in children over 6 months, who had no antibodies before vaccination, there was a significant rise in titre in 84 - 100%. Serologically, therefore, the vaccine was efficacious; it also appeared to be safe in that no case of poliomyelitis occurred in a vaccinated child or in his household.

Thus the evidence available concerning the Koprowski strains is that they are safe and effective for use in live-virus vaccine but the results of the mass trials in Poland must be awaited before a final opinion is given. Perhaps these strains will prove as safe as, and possibly more effective than, the Sabin strains.

2. Cox Strains

The Cox strains of poliovirus have been used in live vaccine on a large scale in recent years in Latin America (Colombia, Nicaragua and Costa Rica).[10] In these countries different programmes have been followed. In some cases monovalent feedings of all 3 types have been given separately at intervals of 3 - 4 weeks, while in other cases trivalent vaccine has been fed either once only, or twice at an interval of 8 weeks between doses. In Colombia, among 7,000 children who were fed with 3 successive doses of the 3 types of vaccine, 91% responded serologically to Type I, 72% to Type II and 87% to Type III, while those with antibodies showed a booster effect from the vaccine. Serologically, therefore, the vaccine appeared to be efficacious.

In Nicaragua vaccine was fed to children during a Type II epidemic and it appeared to be of value in preventing paralytic cases. In Costa Rica, where the vaccine was used during an epidemic, the attack rates among the vaccinated and non-vaccinated were 7 and 100 per 100,000 of population respectively.

Thus in the Latin American countries the Cox type of vaccine appears to have been effective, though there is little information about its safety.

Cox vaccine was recently used in large-scale field trials in Florida, USA, and it was learnt at the Copenhagen congress, that, though the incidence of paralytic poliomyelitis had decreased in Florida during the last 5 years, several unexpected cases had occurred in young adults in association with this trial. The development of paralytic complications does not depend solely on the virulence of the invading virus but also on the susceptibility of the host. It appears that the person who reaches early adult age without having acquired an immunity is the one most likely to suffer nervous-system lesions after a poliomyelitis infection. The question, therefore, arises whether the cases were due to the vaccine virus and, if so, whether this virus had gained an enhanced virulence by passage through the vaccinated children.

It was also reported at the congress that Cox trivalent vaccine had recently been used in West Berlin in the face of an epidemic. Over 250,000 children, representing about half the preschool children of the city, had been fed the vaccine. Following this, 34 cases of poliomyelitis were notified of which 23 were in the vaccinated children. Were any of these cases due to the vaccine?

It may well be that none of the cases occurring in Florida or West Berlin were due to the attenuated-vaccine virus but that all were due to virulent wild strains, i.e. the infections were purely coincidental with the vaccine campaigns. Whenever vaccinations are carried out there is always the possibility of coincidental infections occurring. This is inevitably so if there is a contemporaneous epidemic. These incidents in Florida and West Berlin cannot, however, be ignored. The problem of safety can only be solved by extensive epidemiological investigations which include elaborate laboratory studies. An answer to these important questions must, therefore, be postponed until such investigations have been completed and reported in detail.

3. Sabin Strains

The Sabin strains were developed by Dr. A. B. Sabin of the University of Cincinnati, USA and, as previously mentioned, have proved to be the most avirulent on monkey testing of the 3 sets of live-virus strains used in present-day live poliovaccine production. Laboratory evidence, therefore, suggests that they should be the safest strains for the preparation of vaccines.

After intensively studied small-scale experiments on humans in the USA and the USSR, the USSR Ministry of Health, being impressed by the harmlessness and efficacy of these Sabin strains as shown by these experiments, authorized their use in large-scale experiments with live virus vaccine in the republics of the USSR during 1959.[8] Starting with the Republic of Estonia where there had been a recent epidemic, some 15 million persons under the age of 20 years were soon fed with the vaccine. So successful did this experiment prove that it was decided in future to abandon Salk vaccine and to switch over completely to live vaccine. Thus, during the first half of 1960, another 60 million persons were fed this vaccine in Russia, as well as several million persons in Eastern European countries.

Live virus composed of Sabin strains has also been used in Mexico and in Singapore.

At the Fifth International Poliomyelitis Congress held in Copenhagen (26 - 28 July 1960) detailed reports of all these experiences with Sabin-type vaccine were given.

Russian Trials

In the Russian trials there was no control group as in the American field trials of 1954 with Salk vaccine. The Russian campaign was a mass one and the vaccinations were purely voluntary. The response of the population was remarkably good. Serological surveys, to determine the prevaccination immunity of the population, were carried out and an effective surveillance programme was put into operation. In Tashkent the vaccine was given in the face of an epidemic. The vaccine was administered in a liquid form or in candy and it was shown that the candy kept well at 4°C. for more than a month. Six different schedules of feeding were used by the Russians.[11] The Sabin-recommended schedule of first feeding Type I, then Type III and finally Type II at monthly intervals appeared to be superior to feeding trivalent vaccine. A schedule of Type I followed by Types II and III and then by Types I, II and III, so that each person received 2 feedings of each type, appeared to give the best results. However, if vaccine was given at monthly intervals, the difference between the different schedules appeared to be negligible. If a poliomyelitis epidemic is imminent 2 feedings of trivalent vaccine are probably best. With shortened intervals between feedings the viruses tended to interfere with each other and, in particular, Type II interfered with the 'takes' of the other types. Because of occasional interference by other enteroviruses, it is also thought advisable to carry out feedings during the winter months.

In their experience the Russians[12] claimed that the vaccine proved to be completely harmless and to have shown no reversion to a virulent state. They noted no local or systemic reactions to the vaccine and they claimed that the epidemiological effectiveness of the live Sabin vaccine substantially exceeded that of Salk vaccine. Unfortunately, since there was no control group, the incidence of paralytic poliomyelitis in vaccinated and unvaccinated persons could not be compared. The overall incidence of the disease, however, in comparison with the incidence over the last 5 years, showed a dramatic fall. The serological responses compared favourably with those obtained by Salk vaccine. One month after feeding, $\frac{2}{3}$ - $\frac{3}{4}$ of those vaccinated developed antibodies, and this proportion became even higher after 3 months.

The Russian delegates to the Copenhagen congress also stressed the cheapness of the vaccine and the great ease with which a mass campaign employing live-virus vaccine could be rapidly carried out.

By means of compulsory vaccination of all the population at risk under strict government supervision, the Ministry of Health hopes to eliminate the reservoir of wild pathogenic strains in Russia and so liquidate the disease.

Sabin was in close liaison with the Russian Ministry of Health during the trials and appeared to be much impressed by the efficiency with which the campaign was carried out.

Dr. D. Horstmann,[8] Associate Professor of Preventive Medicine and Pediatrics of Yale University School of Medicine, USA, visited Russia, Poland and Czechoslovakia in 1959 in agreement with the ministries of health of these countries and on behalf of the WHO, to evaluate the results of these vaccination programmes. She states in her report that surveillance in Russia was very efficient and she considered that, under the system adopted, it was most unlikely that any paralytic cases were missed. She concluded that the attenuated live vaccines used in these large-scale experiments appeared to have been safe both for the individual and the community. She also felt that the fall in the incidence of paralytic poliomyelitis indicated that the vaccine was effective though, because of the absence of controls, it was difficult to gauge its effectiveness accurately.

Singapore Trials

At the congress, Hale[13] reported on his Singapore experience. In 1958 there was a Type I epidemic in this city. He fed 50% of the population at risk, some 200,000 children between the ages of 3 months and 10 years, with live vaccine composed of Sabin Type II strain only. The object of this was to be able to distinguish clearly between paralytic cases due to the epidemic Type I strain and any Type II cases which might have been caused by the vaccine. No cases of Type I paralysis occurred in the vaccinated children between the 8th and the 34th day after feeding. This experiment showed how a harmless intestinal infection by Type II avirulent virus prevented Type I infection from occurring. This was due to the phenomenon of interference, i.e. the Type II virus blocked the receptors and so prevented a Type I infection establishing itself. He concluded that, because of mutual interference between enteroviruses, it is obviously desirable to conduct vaccination campaigns with live poliovirus at times of the year when infection with enteroviruses is minimal.

Mexican Trials

An account was also given at the congress of laboratory and field experience with Sabin strains in 4 Mexican cities.[14] It was noted that interference with other enteroviruses occurred again leading to a certain failure rate. Nevertheless, serological tests on paired sera indicated that the strains

used were highly immunogenic and that the conversion rate for Type I was 84%, Type II, 81% and Type III, 73%. In Mexico City only 17% of the children at risk were immunized and in Guadalajara, 30%.

These proportions were too small to influence the dissemination of wild paralytogenic strains. To banish paralytic poliomyelitis in a community it was calculated that at least 80% of the susceptible population should be vaccinated in the shortest possible time.

In Monterrey and Puebla it was noted that there was a striking difference between the number of expected cases and the number of observed cases in the vaccinated children. This indicated that the vaccine was effective, though conditions did not allow the effective rate to be statistically calculated.

Finally Dr. Sabin[15] gave an inspiring account of the effect of rapid mass immunization of the population of Toluca, Mexico, with live oral vaccine under conditions in which massive enteric infection with other viruses was prevalent. Because of prevailing hygienic conditions in Toluca, all children acquired an immunity at a relatively early age by natural infection with circulating wild viruses. But this was at a cost of many paralytic cases a year. Sabin, in 2 feedings separated by an interval of 6 - 8 weeks, fed all children under 5 years in Toluca with trivalent vaccine. Paralytic cases were brought to a dramatic end. He had artificially produced a herd immunity in a few months which would normally take as many years to acquire by natural means. Later he showed that almost all polioviruses, tame and wild strains, had disappeared from Toluca. The reservoir for poliomyelitis was thus eliminated, and poliomyelitis had been banished from the city by this mass campaign. What has been done in Toluca can be done elsewhere. Sabin stressed that in future in Toluca it would be necessary to immunize all infants below the age of 6 months because they would now have little or no opportunity of acquiring infection by natural means.

Thus it may be concluded that more than 60 million Russians have proved the safety and efficacy of attenuated live poliovaccine composed of Sabin strains, and the city of Toluca has clearly indicated how poliomyelitis may be totally vanquished.

INACTIVATED *versus* LIVE ATTENUATED POLIOVACCINE

Inactivated Salk poliovaccine has proved to be a great success. It is a safe and innocuous vaccine and its use has substantially reduced the incidence of paralytic poliomyelitis. The immunity produced after a full and properly spaced course of treatment with this vaccine is, however, relative, in that it reduces the incidence of paralysis at best by only 80 - 90%.

Live poliovaccine causes a temporary but harmless infection similar to that of the natural disease and, therefore, it is to be hoped that the resultant immunity will be more solid and lasting than that of the Salk vaccine.

Inactivated poliovaccine prevents paralytic complications after infection by stimulating the production of circulating antibodies which intercept the virus particles in their passage in the blood stream from the intestinal tract to the central nervous system. This vaccine does not, however, prevent intestinal infection occurring. Therefore, it does not interfere with the natural circulation of polioviruses in the community or reduce the reservoir of infection.

The live vaccine causes a temporary intestinal infection which lasts for several weeks and which not only stimulates the production of circulating antibodies but, as shown by many workers, also induces a local intestinal resistance so that the subject cannot be reinfected. As the polioviruses normally exist only in the gastro-intestinal tract of Man, mass vaccination of all susceptible members of a community with live vaccine must eliminate the reservoir of infection. That poliovirus may thus be banished has been proved by the experience of Toluca, Mexico. Live poliovaccine not only protects the individual from poliomyelitis infection but, when mass vaccination is carried out, it also protects him and the community by preventing infections from being acquired. This is obviously a matter of great public-health importance. To achieve total banishment of polioviruses from a community, it has been estimated that at least 80% of the population at risk should be successfully immunized with live vaccine, as previously mentioned. This is a practical proposition that may readily be achieved.

Because passively transferred antibodies from the mother neutralize the circulating antigens, it has not been found practical to immunize infants effectively below the age of 6 months with inactivated vaccine. Such infants, however, may be successfully immunized with live vaccine.

A good immunity to paralytic poliomyelitis takes several months to achieve with present-day inactivated vaccine, but protection from poliomyelitis infection may be obtained in little more than a week by use of a live vaccine. Thus an epidemic may be rapidly aborted by the prompt use of such a vaccine.

An annoying disadvantage of any parenterally administered agent is the occurrence of allergic complications. Inactivated vaccine is given by injection and, although the Salk vaccine is almost a pure aqueous suspension of formalinized virus particles, it may contain traces of antibiotics or monkey-kidney protein from the culture media in which the virus was grown. On occasion, these substances may induce allergic reactions in sensitized persons. As live poliovirus is fed by mouth, these complications should be eliminated by its use.

In all public-health measures to be applied on a large scale, economic questions are of great importance. Here live poliovaccine has the advantage over the inactivated form in that it is much cheaper to produce. Because the potency of the inactivated vaccine used up to this time has not been as high as desired and because several injections must be given to obtain a good immune response, attempts have been made to produce a more concentrated form of the vaccine. These attempts have been successful and concentrated vaccine which gives a satisfactory antibody response after only 2 injections has been experimentally produced.[16] Salk himself,[17] at the recent Copenhagen congress, optimistically prophesied that it may be possible to produce so highly potent a concentrated vaccine in the near future that only 1 injection would be necessary to produce an adequate immunity. A concentrated vaccine must be purified to eliminate possible serious contamination with monkey-kidney protein or other undesirable antigenic materials, which may accumulate in the concentrated vaccine in significant amounts. It is thus to be expected that concentration and purification of these new inactivated vaccines will add considerably to the cost of their production.

Inactivated vaccine must at present be administered by a series of injections, whereas the live virus is simply fed to children in the form of a syrup or candy — a far cheaper procedure and one which should allow of far easier coverage of the population. True, the live vaccine

must be kept continuously at low temperature until immediately before its administration; otherwise it may rapidly lose potency. This means that it must be transported packed with dry ice in suitably insulated containers and then stored at low temperature until used. It is best stored in a 'deep-freeze' but may be stored in the freezing compartment of a domestic refrigerator for up to a month without undue loss of potency. These difficulties in the transportation and storage of live poliovaccine may make it impractical for private medical practitioners to deal with individual cases. Periodic mass vaccination campaigns, carried out by public-health authorities, can readily overcome all these difficulties.

There is no danger today of inactivated vaccine, which has been properly processed and subjected to routine safety tests, being contaminated with live micro-organisms. Micro-organisms which may contaminate live vaccine can also be readily excluded and their absence proved by suitable testing. Special difficulties, however, arise in respect of 2 contaminants, viz. (1) poliovirus particles of enhanced virulence, and (2) 'simian agents'.

It is most important that the final vaccine should contain no virus particles that differ from the original attenuated strains. Before any batch of vaccine is issued it is, therefore, necessary to carry out elaborate biological tests on an adequate number of monkeys to ensure that it is composed only of attenuated poliovirus particles. Recently, tests based on genetic markers have also been elaborated to differentiate between virulent and avirulent strains, but the exact value of these tests is still to be accurately determined.

'Simian agents' are viruses of monkey origin which are frequently found as contaminants in monkey-kidney tissue cultures and, therefore, are extremely difficult to keep out of poliovaccines. Their presence in cell cultures used for the preparation of inactivated virus is of no real consequence, since they are 'killed' in the processing, but there has been doubt as to their significance in cultures used to prepare live vaccine. These agents have been fairly extensively studied in recent years and, though not fully classified, most of them appear to be quite harmless and incapable of causing disease in Man or experimental animals. Theoretically they should be excluded from live poliovaccine but whether it is necessary or practical to do so is a matter of some doubt. Certainly some of the live vaccines employed in Russia and elsewhere were contaminated with one or other of these agents and no ill-effects were observed in the many millions vaccinated. The question of excluding them from vaccine may thus appear to be more of academic than practical interest. Furthermore, any remote danger is minimized by the fact that the vaccine is given by mouth and not by injection. As was pointed out in Copenhagen, if the great Jenner had been hampered in his work by all sorts of remote theoretical considerations, many years would have elapsed before smallpox vaccine was put into practical use and countless more people would have died unnecessarily of this foul disease as the result of such delay. Thus, though every endeavour should be made to exclude contamination of live poliovaccine with these agents, their possible presence in the vaccine may not prove to be of any real consequence.

Inactivated vaccine affects only the individual to whom it is administered, but live poliovaccine is excreted for several weeks in the stools of those vaccinated and so may be passed on to others. From an epidemiological study of live virus in a small community, Paul[18] was struck by the great ease and speed of intrafamily spread of the vaccine virus; he also found evidence to show that extra-family spread occurred. The use of live poliovaccine represents a radical departure from previous orthodox practice in preventive medicine in that the vaccine becomes spread beyond the original vaccinated population. In this way others become involuntarily infected and immunized.

Some authorities consider that this is an added advantage in that it keeps the vaccine virus circulating in family and small social groups until all susceptible members become infected and immunized. Others see something immoral in this involuntary vaccination of persons. To let a tame strain of virus loose in a community in competition with wild and virulent strains and so diminish the hazards of normal natural immunization, which may lead to death or the permanent crippling of children, cannot be reasonably looked upon as an immoral procedure in this modern age. The main fear that the vaccine virus may gain significantly in virulence in its passage from person to person, and so become a danger to the community, seems to have been completely negated by the experience gained in more than 60 million Russian subjects and several million other children in whom the Sabin strains were used.

It will thus appear clear that live poliovaccine composed of Sabin strains, and probably Koprowski strains, is safe and effective and offers many advantages, from a public health point of view, over inactivated poliovaccine.

THE POSITION IN SOUTH AFRICA

Inactivated Poliovaccine

Following the serious postwar epidemic of poliomyelitis in South Africa, a large sum of money was raised by generous public subscription to establish a National Foundation to fight poliomyelitis. This money was invested in the South African Poliomyelitis Research Foundation laboratories at Rietfontein, under the directorship of Dr. James Gear, with the main objective of developing a vaccine against poliomyelitis. The result is that South Africa is one of the leading countries in the world in this field. Thus, when the famous field trials of 1954 were being conducted in the USA, the South African Poliomyelitis Research Foundation laboratories had already prepared a large amount of inactivated poliovaccine. This vaccine was made available shortly after its release in America so that South Africa was one of the first countries to have ample stocks of vaccine and was able to launch a vaccination campaign well before many of the most important countries of Europe. South African inactivated poliovaccine proved to be a great success — it was safe and no accidents were recorded. Its potency as judged by laboratory tests and serological assays in susceptible children, compared most favourably with that of any vaccine produced elsewhere. This vaccine has been responsible for a great reduction in the incidence of paralytic poliomyelitis in South Africa.

Live Poliovaccine

The South African Poliomyelitis Research Foundation laboratories have also been to the fore in the production of live attenuated poliovaccine, composed of Sabin strains. Several million doses have been produced and subjected to all the recommended laboratory safety tests with success. With the permission of the Colonial Office of Great Britain, 200,000 doses of this vaccine have recently been used in Mauritius to combat a poliomyelitis epidemic there. Unfortunately the vaccine was administered only towards the end of the epidemic so that its efficacy cannot be fairly judged. It was, however, proved safe, since no significant ill-effects occurred. More than a million doses of this vaccine have also been used recently in Kenya; again without any reported ill-effects, but also too recently to judge its efficacy. As, however, it is composed of Sabin strains, there is every reason to believe that it will prove as efficacious as this type of vaccine has proved elsewhere. Two million doses of this vaccine have now been released by the Minister of Health for use in South Africa. This is being done on the recommendation of the Public Health Virological Advisory Committee which is perfectly satisfied as to the safety of the vaccine. This recommendation of the South African Committee is given added confidence by the fact that, within a few days of its making its recommendation, the Federal Public Health Department of the USA authorized the release of live poliovaccine, of Sabin strains only, in the USA.

The first batch being released in South Africa is monovalent Type I vaccine because the most likely type to cause any cases of poliomyelitis this summer is this one. By using this vaccine now it is hoped to prevent paralytic cases in the vaccinated communities. Batches composed of the other types will be released later for use next winter. It is recommended that all Europeans up to the age of 30 years and all non-Europeans up to school-leaving age be fed with this vaccine whether or not they have received previous inoculations with inactivated vaccine. The racial differentiation is made because serological evidence indicates clearly that non-European children acquire a natural immunity at a much earlier age than do the European.

The public money invested in the South African Poliomyelitis Research Foundation is thus about to pay another handsome dividend to the country. Once again this Foundation has proved that it is an institution of which South Africa can be justly proud.

CONCLUSIONS

The development of live poliovaccine marks another important milestone in the continual advance of preventive medicine. Not only does it promise to protect the individual against paralytic poliomyelitis but, employed for the mass vaccination of communities, it also promises to banish poliomyelitis altogether. This question of mass vaccination is most important from a public-health point of view. Langmuir[19] has shown that, in communities in which only part of the susceptible population is adequately vaccinated, although paralytic poliomyelitis is reduced among those vaccinated, outbreaks have become more intense among the unvaccinated. This change for the worse he attributes to some basic change in the ecology of the polioviruses and he thinks that this altered epidemiological pattern may be attributed to the widespread but incomplete use of vaccine. It is, therefore, most desirable, if live poliovaccine is to be employed in the Union of South Africa, that an attempt should be made to immunize all persons at risk throughout the country. With the live vaccine this should be a more feasible proposition than it is with inactivated vaccine.

In certain favoured countries, the bulk of the population at risk has been immunized with inactivated vaccine with very good results. In Denmark[20] it was reported that 99% of the population between 9 months and 14 years had been immunized, 93% between 15 and 19 years, and 85% between 20 and 39 years. As a result, only 10 cases of poliomyelitis were reported in that country last year. It will, therefore, be readily understandable if such countries adopt a conservative attitude towards the use of live poliovaccine. In the countries where virtually everybody at risk has been successfully immunized by inactivated vaccine, there would seem to be little point in suddenly changing horses in midstream and also, perhaps, in wasting large unissued stocks of vaccine.

In South Africa the position is rather different since there is still a large proportion of unimmunized susceptible children — children who may not be readily reached by repeated inoculations with inactivated vaccine but who may be more readily reached by the simpler process of feeding with live vaccine. Most important, however, is the promise that with a mass campaign to cover the whole country, poliomyelitis may finally be banished as smallpox has been banished. In conclusion, it must be stressed that, once we have embarked on this course, there can be no turning back. If polioviruses are banished from the environment, no child will be able in future to acquire a natural immunity by normal and accidental infection. Feeding of all newborn children with live vaccine at the earliest age then becomes essential for, should they grow up without an immunity and the polioviruses return, disaster will inevitably follow.

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