
PROBLEMS IN THE DEVELOPMENT AND USE OF ORAL POLIOVIRUS VACCINE

ALBERT B. SABIN *

I have spent a great part of my life in the pursuit of knowledge about the natural history of poliomyelitis and in the development of vaccines that may give man the power to eliminate this disease as a source of human misery. On this occasion I have, therefore, chosen to present to you not a detailed analysis of isolated observations, which are already available for critical evaluation in the scientific literature, but rather a review of some of the problems that had to be solved and my interpretation of the assembled facts which are the basis for the expectation that poliomyelitis may now be eliminated from many parts of the world.

The following basic facts in the natural history of poliomyelitis are of fundamental importance in guiding our attempts completely to eliminate this disease:

1. Poliomyelitis is primarily an infection of the human alimentary tract — and it is well to recall here that the crucial evidence for establishing this fact became available only a little over 20 years ago.
2. The polioviruses maintain themselves in nature by passing with contaminated feces, directly or indirectly from one susceptible human being to another. Except in unusual circumstances when people have paralysis of deglutition, the virus that is present in the posterior pharyngeal wall is swallowed and is not expelled through the mouth for transmission to others. While polioviruses are readily detected in extrahuman sites, such as flies and reaches which have access to human feces, there is no evidence at the present time, of a cycle of transmission independent of the human alimentary tract.
3. There are only three main immunologically distinct types of poliovirus and not an ever-changing, unmanageably larger number. This important fact, first established only about 12 years ago through the collaborative efforts of many investigators, has survived in the face of many extensive studies by more precise methods in the ensuing years. These later studies, however, did reveal the important fact

* Distinguished Service Professor of Research Pediatrics, University of Cincinnati.
Conferência proferida no dia 28 de agosto na Faculdade de Medicina da Universidade de São Paulo por ocasião do cinquentenário do Centro Acadêmico Oswaldo Cruz.

that some of the newly recognised Coxsackie and ECHO viruses may occasionally produce paralytic disease clinically indistinguishable from poliomyelitis. While the paralytic disease caused by these other enteric viruses fortunately occurs only rarely and is usually, but not always of short duration, it must, nevertheless, be expected to persist even after all the disease caused by the three types of poliovirus has been eliminated by specific vaccination.

4. Naturally acquired immunity can persist a lifetime in the absence of reinfection — a fact that has been established by the studies of Paul and his associates on Eskimos living in prolonged isolation from outside human contact.
5. Natural infection leaves behind it varying degree of intestinal resistance to viral multiplication, which serves to eliminate many people from the chain of transmission of the polioviruses. This important fact was established only during the past 10 years by two types of precise study: a) by observation of long duration on families prior to and following episodes of laboratory recognized natural infection, and b) by quantitative studies on excretion of virus after feeding of various doses of attenuated strains.
6. Not all naturally occurring polioviruses have the same capacity for multiplication in extraneural tissues outside the alimentary tract or the same capacity for damaging the neurones, whose destruction in large numbers is responsible for the paralysis. It was not until the important work of Enders, Weller and Robbins made it possible for us to recognise and measure the activity of polioviruses in cultures of non-nervous tissue, that it became possible to learn so much about the properties of the polioviruses beyond their capacity for damaging the nervous system. These new methods also provided the tools for the selection of the special viral particles, from whose progeny it was possible to prepare the live, attenuated orally administered poliovirus vaccines that now provide us with the means and the hope for the complete elimination of poliomyelitis.

The development of an effective, formalinized virus vaccine by Dr. Salk provided the first means by which many thousands of cases of paralytic poliomyelitis could be prevented. Although killed virus vaccine of adequate potency and in an adequate number of doses can provide protection against paralysis for 90 per cent or more of vaccinated individuals, carefully controlled experimental and field studies have shown that it has no effect on the multiplication of polioviruses in the intestinal tract of the immunized persons. Even the most extensive use of killed virus vaccine, that has been possible to achieve in some places, has not interfered with the continued dissemination of the naturally occurring polioviruses, nor, when these viruses have been especially virulent, with the occurrence of serious epidemics. Such epidemics have occurred in the USA, Canada, Hungary, Israel, Japan most recently in Australia. These epidemics affected the unvaccinated, the inadequately vaccinated, those who have failed to develop immunity even after three or more doses of killed virus vaccine, and those who had lost their immunity

a year or more after vaccination. There is no question that these epidemics would have claimed thousands more victims if it had not been for the beneficial effects of the Salk vaccine among the large number who were adequately immunized with it. But the fact that those who are themselves adequately protected by the Salk vaccine, retain the capacity for disseminating dangerous polioviruses in their own families and communities is one of the most important factors in the continued occurrence of poliomyelitis among highly vaccinated populations.

Our present knowledge of the properties and behavior of the live, attenuated poliovirus vaccines has been laboriously accumulated during the past ten years by the studies of large numbers of investigators in many parts of the world. I hope you will forgive me if at this point I reminisce a little about some of the major steps and problems in the development of the attenuated, oral poliovirus vaccines currently in use in almost every part of the world. At first there was the task of finding by experimental modification and selection of strains of poliovirus of each of the three types that had the least residual activity in the nervous system, the least capacity for multiplication in extraneural tissues outside of the alimentary tract as measured by viremia, and the greatest capacity for multiplication in the intestinal tract. Quantitative studies on monkeys and chimpanzees established that the nervous system of the lower primates, were more susceptible to poliovirus than that of the higher primates, while the reverse was true for the alimentary tract. Thus, it became necessary to extend the studies to human volunteers when it was found that polioviruses that were devoid of paralytogenic activity in chimpanzees multiplied poorly or not at all in the alimentary tract of monkeys, and that amounts of virus that multiplied poorly or not at all in the alimentary tract of chimpanzees, multiplied very well in the intestinal tract of susceptible adult human volunteers. The paralytogenic activity of highly virulent polioviruses when given by mouth to chimpanzees, compared with the incidence of paralysis in human beings during the course of the most severe epidemics on record, was the basis for the assumption that the nervous system of the most highly susceptible human beings was no more susceptible to polioviruses than that of chimpanzees. Thus each strain that was completely avirulent by direct intraspinal inoculation of very large doses in chimpanzees, was then studied for its behavior on feeding to nonimmune adult volunteers. The strains that were finally selected had the least residual activity in the spinal cord of the more susceptible monkeys, and multiplied in the intestinal tract of the human volunteers, with little or no demonstrable viremia, and with the least detectable alteration in neurovirulence of the virus excreted in the stools. The appearance in the stools of some virus particles, that were less attenuated than the virus that was fed as determined by direct inoculation of different amounts of virus in the nervous system of monkeys, was the subject of many extensive studies. With the more desirable strains these altered virus particles appeared rather late during multiplication in the intestinal tract after the individual had already developed specific antibodies. These altered particles, did not have a selective advantage in the intestinal tract, since they often disappeared after continued multiplication, and did not significan-

tly increase in amount or virulence on continued transmission from one person to another. Although it at first seemed that this phenomenon might be due to the fact that the virus that was fed consisted of a genetically mixed population of virus particles, it was found that the progeny of multiply purified single plaques behaved in a similar manner after multiplication in human intestinal tract. Beginning in 1957, extensive studies were carried out with the selected strains on increasingly larger groups of persons in institutions, homes, nurseries, and in cities in different parts of the world where large numbers of susceptible children and adults were in contact with varying and increasing numbers of vaccinated children. All of these studies have led to the conclusion, that the transmission of polioviruses from vaccinated to unvaccinated is not associated with any hazard of acquiring poliomyelitis.

The studies on the multiplication of the vaccine strains in the human alimentary tract revealed many new facts of basic importance to the use of oral vaccines for the control and elimination of poliomyelitis. Thus the vaccine strains multiplied extensively in the intestinal tracts of those without naturally acquired immunity, regardless of whether or not or how much specific antibody they may have, either placentally transmitted or acquired from inoculations of killed virus vaccine. On the other hand in persons with naturally acquired immunity, the vaccine strains multiplied poorly or not at all depending in part on the dose fed — again without reference to the level of demonstrable antibody in the blood. Resistance to reinfection after oral vaccine feeding was as good or better than after naturally acquired infection. The degree of subsequent intestinal resistance to reinfection was found to be independent of the presence of demonstrable antibody in the blood, but depended rather on the extent of initial multiplication in the intestinal tract, which is optimal when each type multiplies separately as long as possible without interference from other viruses.

Interference by other intestinal viruses became another problem for intensive study. Under certain conditions, the multiplication of another virus in the intestinal tract was found to interfere either with the initial inoculation of the vaccine strain or with its multiplication at a high level for a sufficiently long time to produce an adequate antibody response or adequate resistance to reinfection. As regards the interference among the three different types of vaccine virus, the problem was solved by administering the three types separately at intervals of not less than four to six weeks, or by administering a mixture of the three types on two or three occasions. As regards interference by other enteric viruses, it was found that they played no significant role during the winter and spring months in temperate climates in countries like the U.S.A., Britain, Switzerland, Czechoslovakia and Yugoslavia, where ninety-five to one hundred per cent of young children developed antibody to all three types following the feeding of the three types separately or of the trivalent mixture on three occasions. In subtropical and tropical countries, where the prevalence of naturally occurring polioviruses and other enteric viruses has been found to be extraordinarily high among young children during all months of the year, rapid mass feeding of a

mixture of all three types of the vaccine was found to result in a marked suppression of the naturally occurring enteric viruses for a period of about four weeks and an extensive natural transmission of the vaccine strains. This natural transmission of the vaccine strains is, however, so markedly curtailed in about 4 to 6 weeks, that it is necessary to repeat the mass feeding a second time to achieve immunization of ninety per cent or more of the previously non-immune children. This procedure of mass vaccination in tropical countries can thus harmlessly achieve within a few months an immunogenic effect in the child population for which nature requires at least four years and for which nature extracts a varying and sometimes high price in paralysis.

The routine use of oral poliovirus vaccine on a mass scale which began in many countries in 1960 was preceded by the most extensive trials in different parts of the world over a period of three years. In 1957, 1958 and 1959 the tests proceeded step by step on increasingly larger numbers — tests on hundreds were followed by tests on thousands, ten thousands, hundred thousands and finally in the spring of 1959 on millions. In all of these preliminary trials fifty per cent or more of the population remained unvaccinated to study the effects of the spread of the vaccine strains to the unvaccinated. Trials were carried out in countries with large numbers of susceptible adults as well as in countries where almost all persons over five years of age are immune. In all of these trials it was evident that the spread of the vaccine strains to unvaccinated susceptible children and adults, and the resulting immunization by contact, was without harmful effects — a fact that has been amply confirmed by extensive subsequent experience in many countries. The remarkable international collaboration, without reference to political orientation of countries, was particularly gratifying because it showed how barriers can be overcome when people decide to work together on a common goal of importance to all mankind. I particularly wish to mention here the great contribution of the first excellent mass trial on 144,000 children in Czechoslovakia at the end of 1958 and the subsequent excellent studies on millions of children in the Soviet Union in 1959. The large numbers of susceptible adults in Estonia, Latvia and Lithuania provided data of special importance that were lacking before. The official acceptance of the vaccine in the United States in August, 1960, followed studies with all three types in the American cities of Cincinnati, Ohio and Rochester, New York, on a total of about three hundred thousand children in the spring of 1960, and further large scale tests in different cities were carried out in 1961 before licensure of the commercially produced vaccines.

The extensive laboratory tests that were carried out during the Cincinnati study in the spring of 1960 showed that vaccination of about seventy-five per cent of the pre-school children with all three types and of the school children with type one was capable of breaking the chain of transmission not only of type one but of all three types of poliovirus after an initial extensive dissemination of the vaccine strains in the community. Similar studies in Czechoslovakia and Hungary, where more than ninety per cent of the children were vaccinated in 1960, showed

a similar suppression of dissemination of polioviruses and with it a suppression of paralytic disease caused by polioviruses. In Rochester, New York, where as a result of improper organization only twenty per cent of the pre-school children received the type one and type three oral vaccines in May and June of 1960, there was evidence that the spread of naturally occurring type one poliovirus which was previously present in the community was not prevented. In Mexico, where the incidence of naturally occurring polioviruses is much higher, the administration of oral vaccine to only twenty to fifty per cent of the pre-school children during the field trials of 1959 did not significantly alter the dissemination of polioviruses and the disease continued to occur among the non-immune portions of the population the following year.

Since the first mass use of the oral vaccines in 1960, it is estimated that almost two hundred and fifty million people in all parts of the world have received the vaccine both in emergency anti-epidemic programs as well as in routine immunization programs. These mass programs have not been without problems of interpretation of the significance of a great variety of concurrent disease. When hundreds of thousands or millions of people are simultaneously given a vaccine or a drink of water or anything else, it must be expected that the various diseases which afflict human beings will continue to occur in the subsequent days, weeks, and months. And yet the tendency for *post hoc propter hoc* reasoning is so great, that almost everything under the sun — both good and bad — has been blamed on the vaccine during these mass campaigns. The most difficult to answer are those who ask whether you can with absolute certainty *exclude the possibility* that a certain event or a certain illness, particularly one that occurs only rarely, is not related to the vaccination. It is obvious that diseases which occur without any reference to vaccination will have a similar frequency also after vaccination. Controlled studies have been carried out in many places to determine especially whether the oral vaccines produce fever, systemic symptoms, or any sort of illness, and these have invariably shown the same frequency among non-contact, unvaccinated persons as among the vaccinated. Of particular interest have been diseases that are associated with various forms of paralysis that are known to have a variety of causes other than the polioviruses — among these one may mention particularly infectious polyneuritis and disseminated, perivenous encephalomyelitis. Although it should hardly be necessary to stress this point, it must, nevertheless, be emphasized that these diseases which occur irregularly in different places and different times, without any reference to vaccination, must also be expected to appear among some of the millions of persons who receive the oral poliovirus vaccine, or for that matter anything else. During the very careful clinical and virologic surveillance that we carried out in Cincinnati in 1960 after the administration of oral vaccine to about one hundred and eighty thousand children under 19 years out of a total population of about eight hundred and fifth thousand, we encountered 3 fatal cases of infectious polyneuritis (or polyradiculitis as some call it), and it so happened that all of them occurred in persons who did not receive the vaccine, had no intimate

association with vaccinated persons, and had no poliovirus in their stools. By mere chance, of course, the opposite could have happened and did happen in other places. On the basis of all the accumulated information in various countries there is now no justification for regarding various neurologic manifestations that are only rarely encountered among persons who have received the oral vaccines as anything but coincidental.

The experience of the past three years have already given us an indication of the requirements for obtaining the best results with the oral vaccines, although it is obvious that much remains to be learned in the coming years. There is now no doubt that epidemics of poliomyelitis can be quickly aborted by the mass use of oral vaccine. To achieve the best results it is necessary to start early when only a few cases indicate that an epidemic may develop rather than after many cases have already appeared and the population is widely seeded with the epidemic virus. The optimum results are also obtained when vaccine of the same type as that responsible for the outbreak is used. Organization for mass administration should and can be rapid, and the vaccine should and can be administered to the maximum possible number of susceptibles within a few days rather than over a period of many weeks. The people must be told to expect some cases of the disease among vaccinated persons chiefly because they were already infected before receiving the vaccine, but that the vaccine can quickly protect those who had not yet been infected.

But it is better to prevent epidemics than to undertake emergency procedures for stopping them after needless cases of paralysis and death have occurred. Programs for the elimination not only of epidemics but of all paralytic disease caused by the polioviruses involve two phases:

1. Community-wide oral vaccination preferably during the winter and spring months of the year of at least seventy-five per cent of the most susceptible age groups, regardless of how many doses of killed-virus vaccine they may have had with special emphasis on the pre-school children, who are the most important disseminators of the polioviruses. The purpose of this first phase is not only to immunize those who are not immune, but also to create enough resistant intestinal tracts to break the chain of transmission of the polioviruses and thereby to protect also those in the family and community who failed to receive the vaccine.

2. Continuing immunization with oral vaccine of the oncoming generations of children during their first year of life as part of their regular medical care.

Experience in many different parts of the world has now shown that the first phase of such programs can be accomplished with great success wherever the public health authorities or the medical societies have provided the leadership for organizing the communities in a concerted effort to make the vaccine available within a brief period of time to all people without reference to their ability to pay. The extraordinary success that can be achieved in reaching the major part of large populations on a single Sunday has been amply demonstrated by the remar-

kable community programs developed by medical societies in the United States in 1962. It is now quite clear that properly performed community programs, utilizing all three types of the vaccine, can within a few months achieve a most marked or complete cessation of transmission of polioviruses and an elimination of paralytic disease caused by polioviruses. However, the extent to which systematic on-going programs with oral poliovirus vaccines are successfully put in operation for the new generations of children will determine how well poliomyelitis will stay eliminated. Where killed virus vaccine, which has practically no effect on the dissemination of polioviruses, will be used for one portion of the oncoming child population and the oral vaccines for another, or wherever improved methods for reaching most of the newborn children during their first year of life will not be developed, many children will be immunized but complete elimination of poliomyelitis will not be achieved. It may be predicted that in communities that have had satisfactory initial mass immunization programs but have failed to develop adequate programs for oral vaccination of most of the children during their first year of life, poliomyelitis will within a few years again become a threat to the unimmunized and inadequately immunized children and adults.

In oral poliovirus vaccines we now have remarkable tools for the attempted eradication of poliomyelitis within a short time in many parts of the world. However, only the optimum utilization of present knowledge and continued long-range studies and careful observations under different epidemiologic conditions, will teach us what may be needed for complete and lasting victory. Therefore, it would be well to remember Sir Francis Drake's admonition: "Grant us to know that it is not the beginning, but the continuing of the same until it is thoroughly finished, which yieldeth the true glory"