THE YALE JOURNAL OF BIOLOGY AND MEDICINE 58 (1985), 79-90

The Poliomyelitis Story: A Scientific Hegira

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Received December 6, 1984

There is evidence that paralytic poliomyelitis occurred in ancient times, but it was not recognized as a distinct disease until the eighteenth century and did not come into prominence until the late nineteenth century when epidemics began to appear. Outbreaks of increasing size were reported first in the Scandinavian countries, then in the United States and elsewhere, to the surprise and consternation of the medical profession. Poliovirus was first isolated in 1908, but many years of intensive research were required before the epidemiology and pathogenesis of the disease were sufficiently understood to allow preventive measures to be devised. The road to eventual success was complicated by controversies, setbacks, and tragedies, played out and influenced by many powerful personalities. Today there are two effective vaccines. The disease has been virtually eliminated in countries where they have been used extensively, yet in the developing areas of the world recent "lameness surveys" indicate that the incidence of paralytic poliomeylitis is as high as it was during the peak years in the United States in the early 1950s. The challenge now is to use the available vaccines to extend control to the developing countries and eventually to achieve elimination of the disease worldwide.

Physicians today are very much aware of how "new" and puzzling diseases suddenly appear on the scene for in the 1970s we were surprised by legionella pneumonia, and in the 1980s by acquired immunodeficiency syndrome (AIDS). Approximately a hundred years ago, however, it was paralytic poliomyelitis that was the mystery. This disease turned up in epidemic form in several European countries and in the United States, to the complete bafflement of the medical profession. No one knew what caused it, how it spread, or why there should suddenly be epidemics when for the previous 100 years it has been a curiosity seen largely as rare sporadic cases in the youngest age group. The story of how the various pieces of the puzzle were put together to provide an understanding of the etiology, epidemiology, and pathogenesis of poliomyelitis—basic information for development of preventive measures—is a long and tortuous one, covering the first half of the twentieth century. It has much to teach us about the way scientific research moves—sometimes forward, sometimes back—and how the powerful personalities of investigators sometimes accelerate and sometimes retard scientific progress [1].

HISTORICAL BACKGROUND

To go back a bit in history, it seems probable that polioviruses have been around about as long as man. The first recorded evidence of their capacity to induce paralytic disease is a beautiful Egyptian stele of the eighteenth dynasty (1580–1350 B.C.) now in the Carlsberg Glyptotek in Copenhagen. It shows a young priest with a withered and

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shortened right leg, the foot held in the equinus position, deformities interpreted as most probably due to paralytic poliomyelitis. There is evidence that the disease also occurred in Greco-Roman times, but the first medical description did not come until the eighteenth century. In 1789, Michael Underwood, a London pediatrician, included in the second edition of his book, *Treatise on Diseases of Children,* an unmistakable description of paralytic poliomyelitis under the heading "Debility of the Lower Extremities." He described the limitation of its occurrence to infants and young children, the onset with fever, and the sudden appearance of weakness of the extremities. The clinical description was enlarged in subsequent editions; the disease was mentioned as being not uncommon but there is no mention of epidemic occurrence.

Underwood and those who subsequently described cases in the early nineteenth century were greatly puzzled about the cause of the paralysis and the nature and site of the lesion. Heine, a German orthopedist, published a monograph in 1840 focusing primarily on the long-term paralytic consequences, which he correctly concluded were due to involvement of the spinal cord [2].

Although much was learned in the second half of the nineteenth century about the clinical and pathologic aspects of the disease through the observations of Medin and Wickman in Sweden, and Charcot and his colleagues in France, it was the sudden appearance of epidemics that aroused even greater interest and concern around the turn of the century. The first outbreaks occurred in Scandinavia, but in 1894 the largest one so far recorded—132 cases—appeared in Rutland County, Vermont. In his report Caverly noted a shift in the age incidence of cases, with adolescents and young adults being affected as well as young children [3]. This same change in the behavior of the epidemic disease was documented by Ivar Wickman who studied the 1905 epidemic (>1,000 cases) in Sweden. Wickman, in analyzing the outbreak, stressed the contagious nature of the infection (until then an unsettled point) and also recognized the occurrence of mild, nonparalytic cases [4]. One of the puzzling epidemiologic features had been the usual lack of a history of contact between paralytic cases. Wickman's meticulous investigations led him to conclude that the mild cases were as contagious as the paralytic ones and were responsible for wide dissemination of the agent. This was a tremendously important discovery made, remarkably, before the discovery of the etiologic agent.

The outbreaks described by Caverly and by Wickman pointed up two important features in the changing epidemiology of poliomyelitis which became increasingly prominent over the years. First, epidemics emerged only in economically advanced countries of the world while in the underdeveloped areas the disease remained endemic; and, second, ever-larger outbreaks occurred (9,000 cases in New York City in 1916), and older age groups were increasingly involved as well as children under five. The likely explanation of these patterns is thought to be related to ways of life—to an improved sanitary environment in industrialized countries which protected young children from early exposure to the virus, allowing a build-up in the number of susceptibles among whom epidemics could get under way. In contrast, in the underdeveloped, largely tropical countries of the world where the sanitary environment remains poor, infection and immunity develop in the first few years of life. Thus there are not enough susceptibles for an epidemic to occur, and cases remain confined to the youngest age group.

THE DISCOVERY OF THE VIRUS: EXPERIMENTS IN MONKEYS

In Vienna in 1908 Landsteiner and Popper isolated poliovirus by inoculating spinal cord material from fatal cases intraperitoneally into monkeys [5]. The animals developed typical paralytic poliomyelitis and the characteristic lesions of the anterior horn cells of the cord that had been seen in humans were demonstrated. This breakthrough caused an immediate reaction and burst of activity at the Rockefeller Institute in New York. Epidemic poliomyelitis had already become a problem in New York City and elsewhere in the United States, and the staff at the Rockefeller, the leading medical research institution in the country, was ready to deal with the challenge of this devastating disease. Dr. Simon Flexner, the Director, was a towering figure who championed scientific medicine and had already made important contributions to several infectious diseases. He immediately took on poliomyelitis with vigor and enthusiasm. His first paper on the subject, in 1909, dealt with his finding that the disease could be transmitted to monkeys serially by intracerebral inoculation [6]. This observation laid the groundwork for the extensive investigations by Flexner and his colleagues over the next 25 years. Unfortunately, by concentrating on serial intracerebral passage of the MV strain of virus, a highly neurotropic form of the agent evolved. Using this strain to infect monkeys by the intranasal route led to the erroneous conclusion that, in humans, virus entered by way of the nasal passages and travelled directly to the central nervous system via the olfactory pathway. A method of prevention was even devised on this basis: zinc sulfate was swabbed on the nasal mucosa of many children, resulting in the loss of the sense of smell in some but not in prevention of poliomyelitis.

Flexner succeeded in convincing his colleagues that poliovirus was strictly neurotropic; i.e., unable to multiply except in nervous tissue. This view became the accepted dogma and remained so for more than 20 years. Such a turn of events was particularly unfortunate because as early as 1912 Swedish investigators, Kling and his associates, had reported isolation of the virus from throat and fecal specimens of both paralytic and nonparalytic cases [7]. Flexner ignored these findings, with the result that progress in understanding the epidemiology and pathogenesis of poliomyelitis was delayed until the 1930s and 1940s.

CLINICAL VIROLOGY OF POLIOVIRUS INFECTIONS

The approach that led Dr. Flexner astray was concentration on laboratory experiments in monkeys, to the complete exclusion of studies involving patients. The tide did not begin to turn until 1931 when James Trask and John Paul at Yale, faced with a large epidemic that filled the New Haven Hospital with acute cases, decided to undertake investigations on the clinical virology of poliomyelitis. They formed The Yale Poliomyelitis Study Unit, somehow managed to acquire $1,500, purchased a few monkeys, and began work. Their objective was to see if they could isolate the virus from patients who had the minor illness or abortive form of the disease rather than those with paralysis. Two of 11 throat washings from such patients seen during the 1931 epidemic yielded virus when inoculated into monkeys [8]. This was the first definite recovery of the agent from living patients since the report of Kling et al. in 1912. It began a new phase of poliomyelitis research. A few years later the Yale group demonstrated the presence of the virus in the feces of a case of mild nonparalytic

disease for up to 24 days after onset. These findings were soon confirmed by others, and, not surprisingly, virus was also recovered from sewage [9]. The gathering laboratory evidence that poliomyelitis is primarily an enteric infection and that mild or inapparent infections are just as infectious as paralytic cases proved at last the correctness of Wickman's 1905 interpretation based on his epidemiologic observations.

By the early 1940s the thesis that poliovirus is strictly neurotropic and travels via the olfactory pathway to the central nervous system was no longer tenable. Sabin and Ward had conclusively demonstrated that in fatal human cases no involvement of the olfactory bulbs was present, but virus was recovered from the alimentary tract, primarily from the pharyngeal wall and the ileum, as well as from the nervous system [10].

PATHOGENESIS

Recognition that primary infection with poliovirus takes place in the alimentary tract stimulated renewed interest in the pathogenesis of the disease. It was generally agreed that the oropharynx is the portal of entry, and the major site of primary virus multiplication is in the ileum. But how does the virus travel to the central nervous system? Invasion via the blood seemed a likely possibility, but attempts over the years to demonstrate viremia in monkeys and in the course of the human disease had yielded largely negative results. The reason became apparent when it was shown that, by the time the patient is hospitalized with paralysis, antibodies are already present in the serum and it is too late to detect circulating virus. By examining the blood of orally infected monkeys and chimpanzees early in the incubation period, it was finally shown in 1952 that viremia occurs regularly [11]. This same pattern was then found in human infections by testing the blood of contacts of paralytic cases who were still in the incubation period, or were experiencing the minor illness or even inapparent infection, and had not yet developed antibodies [12,13]. These findings were very exciting at the time, for they indicated that a likely route of invasion of the central nervous system is through the bloodstream. There is also evidence, however, from the experimental disease and human infections, that under certain circumstances the pathway travelled by the virus is via autonomic nerve fiber endings in the alimentary tract to motor neurons of the brain and spinal cord [14].

The complexities of the pathogenesis of poliovirus infections are still not completely understood. The significance of demonstration of the regular occurrence of viremia lay in the implication that if antibodies could be induced by vaccines, viremia would not occur, invasion of the central nervous system would be blocked, and paralytic poliomyelitis could be prevented. Thus the discovery of viremia provided a surge of optimism about the potential of vaccines for control of the disease.

ANTIGENIC TYPES OF POLIOVIRUS AND SEROEPIDEMIOLOGY

Investigations in the 1930s and 1940s also focused on immunologic responses to infection and to serologic surveys of normal persons. At first these were hampered by the necessity to use monkeys in neutralization tests, a cumbersome, expensive, and not entirely reliable technique. Another difficulty which led to confusing results was that in earlier work it had been assumed that there was only one strain of poliovirus, although in the early 1930s, Burnet and Macnamara had demonstrated that there were at least two distinct virus types [15]. This observation was of extreme importance, for if

a vaccine were ever to be developed it would have to protect against all strains to be generally useful. In recognition of this fundamental point, a large collaborative typing program was set up in 1948 by the National Foundation for Infantile Paralysis. The results, reported in 1951, indicated that the 100 isolates tested fell into only three distinct antigenic types [16].

Another large step forward had been made by Dr. Charles Armstrong who, at the National Institutes of Health, succeeded in adapting the Lansing strain of virus (later identified as Type II) first to cotton rats and then to mice [17]. As a result, quantitative neutralization tests on large numbers of sera could be readily performed. The mouse-adapted strain was used extensively in the 1940s in serologic surveys in the United States, and during World War II in Africa, the Far East, and elsewhere. The results of such surveys provided important insights into the epidemiology of poliovirus infections. In a study conducted in Egypt, Paul et al. demonstrated that Type II poliovirus infections were highly endemic: 80 percent of children living in Egyptian villages had acquired Type II antibodies by two years of age, and close to 100 percent by the age of four years [18]. These findings explained the dearth of cases in Egyptian adults, and pointed to the large reservoir of circulating virus which served as a source of infection for susceptible immigrants: e.g., American soldiers, who had high attack rates of poliomyelitis when stationed in Egypt during World War II, far higher than comparable troops stationed in the United States.

Perhaps the most telling use of serologic epidemiology was the survey carried out by Paul et al. in 1950 in an Arctic Eskimo village [19]. The findings indicated that a single subclinical infection with poliovirus resulted in immunity which could persist for more than 40 years. Such remote Arctic areas with small population groups could not sustain continued circulation of the virus; it therefore disappeared when the supply of susceptibles was exhausted. The Type II antibody patterns revealed that some 20 years earlier this type had made its way through the population, infecting virtually all persons alive at that time; however, no one born since had Type II antibodies. Later, similar reconstruction of Type I and Type III activity indicated that only those over 35 were seropositive for Type I and over 45 for Type III. The implications of these findings were of immense importance, for they suggested that if an attenuated live poliovirus vaccine could be developed, it might induce lasting immunity comparable to that achieved by natural infection, but without the risk of paralysis.

GROWTH OF POLIOVIRUS IN TISSUE CULTURE AND DEVELOPMENT OF VACCINES

The great German pathologist Virchow is quoted as saying of scientific research "Die Methode ist Alles." The long road leading to an understanding of poliomyelitis and eventually to its control has many examples of the truth of this dictum but none more dramatic than the demonstration that poliovirus could be grown in cultures of human cells derived from non-nervous tissue [20]. This discovery by Enders, Weller, and Robbins, reported in *Science* in January of 1949, had a far-reaching impact not only on poliovirus research, but on the whole field of virology, and in addition on cell biology, genetics, and immunology.

The 1949 *Science* paper dealt with the growth of the Lansing (Type II) strain of poliovirus in human embryonic cells. In a series of papers over the ensuing two to three years, the Harvard group described propagation of all three types of poliovirus in cell cultures from various embryonic and postnatal organs. They also demonstrated that

the virus damaged the cells and produced a characteristic "cytopathogenic effect" easily visible on microscopic examination; this effect served as a marker to indicate presence of the virus. Thus tissue culture could supplant monkey inoculation as a method of detecting poliovirus in specimens from patients and in serologic tests. This was an enormous step forward.

Of greatest importance, however, was the contribution that the growth of the virus in tissue culture made toward making possible the development of vaccines against poliomyelitis. In 1954 Enders, Weller, and Robbins received The Nobel Prize in Medicine in recognition of their signal accomplishment.

Early Attempts to Develop a Poliovirus Vaccine

Recovery of the etiologic agent of a disease immediately conjures up dreams of developing a vaccine to prevent the infection. This was as true in 1908 when Landsteiner reported the isolation of poliovirus as it is today, when the identification of HTLV3 as the probable cause of AIDS has burst on the horizon. In 1911 Flexner, who had been hard at work on poliovirus for a year and a half, was reported in *The New York Times* to have said that within six months a specific remedy would be announced, for the way to prevent the disease had already been discovered in his laboratory [1]. Such optimism was sadly misplaced, as subsequent events proved: it was to be 44 years before the first successful vaccine was launched by Salk and his colleagues in 1955. There had been a number of previous attempts to immunize experimental animals, however, beginning as early as 1910. Serial infection with small amounts of live virus or of virus partially inactivated by various physical and chemical methods was used. The test of successful immunization was resistance of the monkeys to intracerebral challenge with large amounts of virulent virus. Some success was achieved, but the results were often erratic.

In the early 1930s, Dr. Maurice Brodie, working with Dr. W.H. Park at the New York City Health Laboratory, devised an effective method of inactivating poliovirus by treatment with formalin. Using such material they succeeded in immunizing 20 monkeys. They then moved on to test the vaccine in 12 children who responded with rises in neutralizing antibody; a few months later they boldly set out to immunize 3,000 children. At about the same time, in Philadelphia, Dr. John Kolmer attempted to produce a live attenuated poliovirus vaccine by exposing suspensions of infected monkey spinal cord to sodium ricineolate, which he claimed would partially inactivate the virus. This preparation was distributed to the medical profession and was given to thousands of children.

The ultimate result of both the Brodie-Park and the Kolmer vaccine trials was disaster. At least 12 cases of paralytic poliomyelitis (six of them fatal) occurred among those given the Kolmer vaccine, and apparently some cases were also attributable to the Brodie-Park formalin-treated material. Considering the crudeness of the preparations, the non-quantitative methods used, and the failure to recognize that antigenically different types of poliovirus existed, all of these factors made the whole enterprise decidedly premature. The two major proponents, Brodie and Kolmer, were vigorously denounced at several national medical meetings by such powerful voices as those of Dr. Thomas Rivers of the Rockefeller Institute and Dr. James Leake of the U.S. Public Health Service. Kolmer turned to other subjects and managed to survive the storm, but, for Brodie, a promising career fell in ruins. He died several years later, allegedly by his own hand [1]. Ironically, he had been on the right track, for it was formalin

treatment that eventually was used in the inactivated virus vaccine of Salk. And Kolmer's idea of attenuating but not killing the virus proved a fruitful approach years later when Sabin succeeded in attenuating the three virus types and producing the oral vaccine.

One of the most unfortunate effects of the vaccine trials of the 1930s was that they left such a cloud over the whole subject that for 15 years no respectable investigator would even think of a vaccine. But, by the early 1950s, when so much had been learned about the pathogenesis and immune mechanisms of the infection, when the three antigenic types were known, and the advent of tissue culture-grown virus circumvented the necessity for using monkey central nervous system as a substrate for growing the virus, the climate had gradually changed: the development of a vaccine seemed feasible after all, and work started in several laboratories.

The Inactivated (Salk) Vaccine

Dr. Jonas Salk, at the University of Pittsburgh, first worked on poliovirus during the collaborative typing program of 1948. He was already a highly respected young investigator as a result of his work on influenza with Dr. Thomas Francis at The University of Michigan. During World War II, as a member of the Commission on Influenza of the Armed Forces Epidemiologic Board (headed by Dr. Francis), he had been intimately involved in the successful influenza immunization program. With his knowledge of influenza vaccine as a background, Salk was in a strong position to apply the lessons learned to the development of a similar type of vaccine against poliomyelitis. Accordingly, using tissue culture-grown virus, the optimum conditions for inactivation of the agent by formalin were determined and a killed poliovirus vaccine was prepared. It proved immunogenic in animals, and when inoculated into susceptible humans satisfactory levels of antibodies were induced after several spaced doses [21]. The ultimate test of the safety and efficacy of the vaccine came in 1954, with the famous Francis trial, a mammoth undertaking [22]. Its director, Dr. Thomas Francis, laid down stringent conditions for a scientifically sound program which involved two groups of controls, one placebo-inoculated, and the other "observed." In all, some 1,800,000 children from various parts of the country, all in grades one and three, participated. When analysis of the vast amount of serological and statistical data was completed the results were presented at a meeting in Ann Arbor, Michigan, on April 12, 1955, the anniversary of Franklin Roosevelt's death. The event, staged by the National Foundation for Infantile Paralysis, had many features of a Hollywood extravaganza—features that were far from pleasing to the scientific community. Nevertheless, the important point was that the vaccine had indeed proved successful, giving a protective rate of greater than 50 percent. Furthermore, there had been no evidence of any untoward effects in vaccinees. The announcement was greeted with great relief and enthusiasm by scientists, the public, and, not least, by the press. The vaccine was immediately licensed—that very afternoon.

Calamitous events that followed several weeks later put a decided pall on the program. Large stockpiles of the vaccine were released immediately after licensure, and within ten days cases of poliomyelitis began to appear in recipients. In all, there were 260 vaccine-associated cases, 94 among vaccinated children and 166 in family and other contacts. Almost 75 percent of the cases were paralytic; 11 patients died. Vaccination was halted until the nature of the problem could be identified. It turned out that the lots containing live virus could be traced to a few produced by one

manufacturer. No cases followed use of the vaccines of other producers, but it was nonetheless an extremely anxious period for, by the time the first cases appeared, some four million children had already been inoculated.

Once the problem with the offending vaccine lots had been identified and corrected, the immunization program went forward speedily. A minimum of three doses over a six-month period was recommended. The potency of the vaccine and therefore its effectiveness was increased and between the years 1955 and 1960, paralytic poliomyelitis in the United States fell from close to 20,000 cases per year to approximately 2,500.

Live Attenuated (Sabin) Vaccine

By 1952, several investigators had shown that the virulence of polioviruses could be modified by laboratory manipulation. By passage in cotton rats, Koprowski had already produced an attenuated Type II Lansing strain that induced antibodies in volunteers [23]. More important, Enders et al. found that serial passage in tissue culture resulted in attenuation of a virulent Type I strain [24]. Sabin was quick to capitalize on this observation and rapidly began an all-out attack on the problem. While Koprowski and Cox at Lederle Laboratories also went on to develop attenuated strains in tissue culture that were used in trials in various parts of the world, it was Sabin who dominated the field, and whose strains were eventually the ones that were licensed for use.

Sabin had been a highly productive investigator in the poliovirus field from the time he first met the disease on the wards of Bellevue Hospital in New York in 1931. His many contributions toward the elucidation of the nature of the infection and the pathogenesis of the disease constituted a rich background from which to pursue the difficult task of developing a safe and effective live-virus vaccine.

It was evident from experimental work and from the field studies that naturally occurring polioviruses differ greatly in their paralytogenic capacity. The goal was therefore to derive strains of the three virus types that had greatly reduced neurovirulence but nevertheless resulted in infection of the alimentary tract and development of serologic and local mucosal immunity. To identify the most avirulent preparations of the three virus types, Sabin used individual poliovirus particles from artificially manipulated or naturally occurring attenuated strains which were defined by their behavior on intraspinal inoculation of cynomolgus monkeys, the most sensitive test for the neurotropism of the virus [25]. Those with the lowest residual neurovirulence and the greatest stability on multiplication in the chimpanzee intestinal tract were selected for inclusion in the vaccine. The process required 2½ years and involved some 9,000 monkeys and 150 chimpanzees [25]. By 1956 the first tests in small numbers of volunteers who were given the virus orally had proved successful in that intestinal infection was rapidly induced and was followed by brisk immune responses. There was, however, considerable dismay when it was shown that the virus excreted by vaccinees was slightly more neurovirulent than that ingested. For Sabin this was something of a dilemma but, after discussing the problem with various colleagues, the decision was to go forward cautiously with trials in humans conducted by various investigators in the United States and abroad—first in institutions, then among families, and gradually in increasingly larger population groups [1]. The results established the immunogenicity of the vaccine, its safety, and its capacity to spread to susceptible contacts of recipients, thus increasing the immunization rate.

An important development beginning in 1956 was the collaboration between Sabin and investigators in the Soviet Union, where poliomyelitis epidemics were emerging as a serious problem [25]. Chumakov and Voroshilova, and Smorodintsev and their associates, using seed virus provided by Sabin, prepared large quantities of vaccine and proceeded to use it on an increasing scale. By 1959, when as a WHO consultant I had the opportunity to visit the USSR and review poliovirus vaccine programs under way in several of the republics, close to 15,000,000 children had already received the oral vaccine (OPV). It was clear that the trials had been carefully carried out, and the results were monitored meticulously in the laboratory and in the field. By mid-1960 approximately 100 million persons in the Soviet Union, Czechoslovakia, and East Germany had received the Sabin strains. The result was a dramatic drop in paralytic cases. Of great importance was the demonstration that the vaccine was safe, not only for the recipients, but for the large numbers of unvaccinated susceptibles who must have been exposed as contacts of vaccinees. The USSR experience was crucial in leading to eventual acceptance of the oral vaccine in the United States as a safe and effective product.

By the end of 1961 there had been increasingly large and successful trials of OPV in the United States, and rapid mass vaccine programs had been demonstrated to be effective in terminating epidemics in Japan, Israel, Chile, and elsewhere. Finally, after prolonged comparative testing of the candidate strains, the Sabin strains proved to be the most attenuated, and in 1961–62 they were approved for licensure in the United States.

Sabin's recommendation that in the beginning OPV should be administered community-wide was adopted enthusiastically throughout the country. So-called "Sabin Sundays" were organized in many cities by health departments and local medical societies. They were well publicized and proved highly successful in reaching the public. Between 1962 and 1964 some 100 million doses of the oral vaccine were given in the United States. OPV was also incorporated into the routine vaccination program for young children, and as its use increased there was a further striking decline in the attack rates of paralytic poliomyelitis—from 2,600 per hundred million in the period 1956 and 1960 when only IPV (inactivated poliovirus vaccine) was used, to four per hundred million after 1973 when OPV had largely supplanted IPV [25]. In 1984 only four cases of poliomyelitis were reported in the U.S. population of 230 million. The success of OPV has been remarkable considering that, until recently, immunization rates in the United States have been far from optimal: only 60 to 70 percent of children received the recommended three doses.

Two problems have been encountered in the use of OPV. One is the occurrence of possible vaccine-associated paralytic cases in vaccinees and their contacts. Since all poliovirus strains mutate during multiplication in the human intestinal tract, the vaccine has no doubt been causally related to some of the cases, but this is an extremely rare event. During the period 1972–1983 the Centers for Disease Control of the U.S. Public Health Service reported a rate of one case per 8.7 million doses distributed for vaccine recipients, and one per 5.1 million for contacts.

The second problem with OPV has been the less than optimal immune responses in children living in tropical areas where the sanitary environment is conducive to the continual circulation of many enteric viruses. That this difficulty can be surmounted by yearly mass vaccine administration to all children under four years has been amply demonstrated in several tropical countries including Cuba, Brazil, and the Dominican Republic [25].

THE NATIONAL FOUNDATION FOR INFANTILE PARALYSIS

The story of poliomyelitis is incomplete without mention of the unique role played by the National Foundation for Infantile Paralysis in supporting research on the disease in the United States, and in development of the two vaccines. The organization began as The President's Birthday Ball Commission, which was established in 1933 shortly after Franklin Roosevelt took office, and was replaced in 1938 by the National Foundation for Infantile Paralysis (NFIP) with Basil O'Connor, a former law partner of Franklin Roosevelt, as president. O'Connor was a highly successful, powerful, and dedicated man. He devoted himself unstintingly to the cause of poliomyelitis and, with his extraordinary administrative skills, built the Foundation into a national organization which raised some twenty-five million dollars annually. The funds were used for two principal purposes: to fund medical care for every patient with poliomyelitis, and to support research on various aspects of the disease, including its prevention.

As far as research was concerned, the Foundation's support was critical, for its came well before the time when the NIH was in a position to provide research grants on a large scale. In the development of the two vaccines, which made the subsequent control of poliomyelitis possible, the NFIP was a major force, supporting the work of both Sabin and Salk, and many other investigators in the field. As has been characteristic of the history of poliomyelitis, however, the road was far from smooth. There were spirited—sometimes bitter—disagreements on scientific matters with the Foundation leaders pitted against members of its scientific advisory groups [1]. Basil O'Connor and Dr. Thomas Rivers, president and scientific director of the NFIP, respectively, were both aggressive and outspoken men. They concluded in the late 1950s that the success of the Salk vaccine was such that there was no need to go forward with the live attenuated-virus vaccine. But Sabin, also an aggressive and outspoken man, was not to be deterred. He persevered undaunted, and numerous small oral vaccine trials using his strains were carried out successfully in the U.S. and elsewhere. Encouragement came in 1957 when the World Health Organization Expert Committee on Poliomyelitis recommended that field trials of increasing size be continued. By 1961 many millions of persons had received OPV. Sabin proposed that in order to break the chain of transmission of wild polioviruses, there should be rapid mass immunization programs in which OPV would be given to persons of all age groups regardless of the number of doses of IPV previously received. The National Foundation was vigorously opposed to this, as was the U.S. Public Health Service. On advice from a specially appointed committee, however, the American Medical Association approved the recommendation in June of 1961 [25]. At this time OPV had not yet been licensed. But the medical community and the American public were ready when the Sabin strains were finally approved for use in late 1961 and early 1962.

POLIOMYELITIS IN THE 1980s

Remarkable control of paralytic poliomyelitis has been achieved in countries which have used either IPV or OPV extensively. OPV has been administered more widely and accounts for the general striking reduction in the incidence of the disease in the industrialized world. In three countries, Sweden, Finland, and Holland, where only IPV has been used and close to 100 percent of the population has been immunized, virtual elimination of the indigenous infection has also been achieved. These results are indeed gratifying. Unfortunately a very different and disturbing picture in the developing countries has come to light as a result of recent "lameness surveys."

Because in third-world countries few cases of poliomyelitis are reported and epidemics do not occur, it has been assumed that the wide dissemination of the virus resulted in immunizing infections in the first years of life at a price of only rare paralytic cases. This assessment proved false when surveys of school children in a number of tropical countries revealed that the prevalence of residual paralysis characteristic of poliomyelitis was surprisingly high [26]. Estimates based on the findings suggested incidence rates comparable to those during the peak years in the United States before the introduction of vaccine in 1955.

Several approaches to the continuing poliomyelitis problem in the developing countries have been proposed in addition to the vigorous ongoing World Health Organization Programme on Immunization. One advocated by Sabin involves the country-wide administration of OPV to all children under four years of age each year, on two days, two months apart. This approach has been shown to be highly effective [25]: saturation of the childhood population with attenuated-vaccine virus displaces virulent polioviruses and, in addition, continued circulation of the attenuated strains increases immunization through contact infection if ingestion of the vaccine failed to induce a "take." Such programs present many administrative and logistic problems; they require cooperation at many levels of government and enthusiastic community participation. Another approach has been proposed by Salk. As a result of work at the Rijks Institut in Holland a killed-virus vaccine of greatly improved immunogenicity has been developed [27]. In tropical countries, two spaced injections of this preparation have proved effective in inducing satisfactory antibody responses in young children [28]. Incorporation of the vaccine into a routine DPT vaccination program would therefore be an appropriate means of increasing coverage; however, cost and the need to inject the vaccine are drawbacks in third-world areas.

The recent resurgence of interest in poliomyelitis prompted the convening in 1983 of an International Symposium on Poliomyelitis Control, sponsored by the Fogarty International Center of the National Institutes of Health, and other agencies [29]. The agenda covered aspects of the accomplishments of the past and the problems presented by the disease today. The prospects for better vaccines as a result of rapid advances in the molecular virology of the agent provide an optimistic note for the long term. But, as stressed by Robbins in summarizing the proceedings, the tools are currently available for the virtual elimination of the paralytic disease even though it is unlikely that polioviruses can be eradicated [30]. The decision as to how such improved control is to be accomplished and which of the two vaccines is to be used will differ in various countries, depending on many factors including local circumstances, cost, availability of personnel, and technical support systems. The challenge is to try to assure that every child in every country receives one or the other vaccine.

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