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Current Status of Poliovirus Infections

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HISTORICAL PERSPECTIVE

Sporadic cases of paralytic poliomyelitis have occurred for at least as long as human history has been recorded. From ancient times into the late 1800s, polioviruses were widely distributed in most of the world's populations, surviving in an endemic fashion by continuously infecting susceptible infants newly born into the community (24). Because most poliovirus infections were subclinical, only rare sporadic cases of poliovirus-caused paralysis were noted. A syndrome retrospectively identifiable as paralytic poliomyelitis began to be mentioned in the medical literature in the mid-1700s—almost always in infants or young children—but it was not fully recognized and described as a clinical entity until the latter part of that century and the first half of the next. In the mid-1800s, outbreaks of paralytic polio began to be seen. For the next century, in urban, industrialized parts of Europe and North America, there followed epidemics that grew more severe, more frequent, and more widespread. Cases of what had been called infantile paralysis also began to be observed in adolescents and even in young adults. Large epidemics spread across the United States and Europe in the first half of the 20th century. In the United States in the summer of 1916, over 27,000 persons were reported to have been paralyzed, with 6,000 deaths. In New York City alone, more than 9,000 cases and more than 2,000 deaths were recorded.

Zamula's description of the times (40) indicates that "the 1916 epidemic caused widespread panic. Thousands fled the city to nearby mountain resorts. Movie theaters were closed, meetings were cancelled, and public gatherings were shunned. Children were warned not to drink from water fountains; amusement parks and bathing beaches were off limits. In some towns, visitors from the New York City area were turned away by armed citizens who feared the spread of contagion." Increased public awareness and fear, together with the ongoing developments that had taken place in medical science, led to intensified study of the disease and its control by vaccination, as described below.

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CLINICAL PRESENTATIONS

When a person susceptible to infection is exposed to poliovirus, one of the following responses may occur: (i) inapparent infection without symptoms, (ii) mild (minor) illness (abortive poliomyelitis), (iii) aseptic meningitis (nonparalytic poliomyelitis), and (iv) paralytic poliomyelitis (3, 24). As the infection progresses, one response may merge with a more severe form: a minor illness may be followed by a few symptom-free days and then by a major, severe illness. This biphasic course is more commonly seen in children than in adults. Only about 1% of poliovirus infections result in a paralytic illness.

Asymptomatic Infection

By far the most common form of infection is asymptomatic or is marked by no more than minor malaise. The subclinical course is taken by more than 90% of poliovirus infections.

Minor Illness (Abortive Poliomyelitis)

The most common form of disease caused by poliovirus is characterized by fever, malaise, drowsiness, headache, nausea, vomiting, constipation, and sore throat in various combinations. This manifestation has been estimated to occur in 4 to 8% of infections. Even during an epidemic, the diagnosis of abortive poliomyelitis cannot be made with assurance on clinical grounds, unless virus is isolated or antibody development is measured. Many other viruses may cause the same signs and symptoms and may circulate during the same seasons as poliovirus.

Aseptic Meningitis and/or Transient Mild Paresis (Nonparalytic Poliomyelitis)

In addition to the symptoms and signs of abortive poliomyelitis, the patient has stiffness and pain in the back and neck.

TABLE 1. Cell culture neutralization test with paired sera of normal patient infected with type 1 poliovirus

Virus[a]	Day after onset when serum was collected	Cellular degeneration (cytopathic effect) for each of three cultures[b] at final serum dilution of:					50% serum titer	
		1:2	1:10	1:50	1:250	1:1,250	Logarithm	Antilog
Type 1	1	+++	+++	+++	+++	+++	0.7	5
	20	000	000	000	00+	+++	2.5	320
Type 2	1	000	+++	+++	+++	+++	0.7	5
	20	000	000	0++	+++	+++	1.5	32
Type 3	1	+++	+++	+++	+++	+++	0	0
	20	+++	+++	+++	+++	+++	0	0
None	1	000						
	20	000						

[a] One hundred 50% tissue culture infectious doses of each virus were used in the test. Three cultures were inoculated with each virus-serum mixture.
[b] A plus sign indicates cytopathic change in culture because of virus growth. A zero indicates no growth of virus.

Occasionally, there is mild muscle weakness or transient paralysis. The disease lasts 2 to 10 days, and recovery is almost always complete. About 1 or 2% of infections take this course during epidemics. In a small percentage of cases, meningitis advances to paralysis. It should be noted that a number of other viruses, particularly other members of the enterovirus family, also produce this syndrome.

Paralytic Poliomyelitis

The major illness constitutes the manifestations listed above for aseptic meningitis plus persisting weakness of one or more muscle groups, either skeletal or cranial. It accounts for about 1% of poliovirus infections. The onset of paralysis may follow the minor illness after a symptom-free interlude or may occur without an antecedent phase of illness. The predominating sign is flaccid paralysis resulting from lower motor neuron damage. Incoordination secondary to brain stem invasion may also occur, and there may be painful spasms of nonparalyzed muscles. The amount of damage varies widely. Usually, muscle involvement is maximal within a few days after the paralytic phase begins. Maximal recovery usually occurs within 6 months, with residual paralysis lasting much longer, often for life.

DIAGNOSIS

Cerebrospinal Fluid Changes

The cerebrospinal fluid contains increased numbers of leukocytes—usually 10 to 200/μl, seldom more than 500/μl. Early in the disease, the ratio of polymorphonuclear cells to lymphocytes is high, but within a few days the ratio is reversed (3). The total cell count slowly subsides to normal levels. The protein content in the cerebrospinal fluid is elevated; the average is about 40 to 50 mg/dl, but higher levels may occur and persist for weeks. The glucose content is normal.

Recovery of Virus

For cultivating the virus, cultures of human or monkey cells should be used (19). In contrast to the situation with other enteroviruses, poliovirus has rarely been isolated from the cerebrospinal fluid. The virus may be recovered from throat swabs taken soon after the onset of illness; it is usually recovered from rectal swabs or feces for 1 or 2 months after onset but in falling concentrations. The virus has been recovered from about 80% of patients during the first 2 weeks of illness but in only 25% during the third 2-week period. No infected immunocompetent persons have been known to be permanent carriers, but immunosuppressed persons excrete virus for longer periods than do normal persons.

In fatal cases, virus tests should include the cervical and lumbar enlargements of the spinal cord, the medulla, and the colon contents. The spinal cord and parts of the brain should be examined histologically. If paralysis lasted 4 to 5 days, it may be difficult to recover the virus from the cord. Specimens should be kept frozen during transit to the laboratory and treated with antibiotics before inoculation of cell cultures. Cytopathic effects usually appear in 3 to 6 days. An isolated virus is identified and typed by neutralization with specific antiserum.

Serology

Paired serum specimens are required to show a rise in antibody titer (19) (Table 1). Neutralizing antibodies appear early and are usually already detectable at the time of hospitalization. If the first specimen is taken sufficiently early, a rise in titer can be demonstrated during the course of the disease. Only the first infection with a poliovirus produces strictly type-specific complement fixation responses. Subsequent infections with heterotypic polioviruses recall or induce antibodies, mostly against the heat-stable complement fixation group antigen shared by all three poliovirus types.

Table 2 summarizes the various combinations of laboratory results that may be obtained. The last column indicates the interpretation in terms of the presence and nature of a poliovirus infection (14).

Rapid methods, particularly those based on PCR, have been used for direct detection of poliovirus and other enteroviruses in clinical specimens (29). These tests hold great promise and are being introduced for use in routine diagnostic laboratories. It should be possible for a clinical or environmental (sewage) specimen (20) to be rapidly subjected to enzymatic amplification (with specific primers) and for the product of the reaction to be probed with a nonisotopically labelled probe specific for

TABLE 2. Interpretation of laboratory data in poliovirus infection

Interpretation of infection	Cell culture	Complement-fixing antibody	Neutralizing antibody	Antibody of IgM class
None	−	−	−	−
Early	+	−	−	−
Current	+	+	+	+
Recent	−	+	+	+
Old	−	−	+	−

poliovirus. The result of the analysis should be available within hours.

PATHOGENESIS AND PATHOLOGY

As the virus travels from the portal of entry (the mouth), implantation and multiplication take place in the oropharynx and the small intestine. The incubation period (defined as the time from exposure to onset of disease) is usually between 7 and 14 days but may range from 2 to 35 days. By 3 to 5 days after exposure, virus can be recovered from blood, throat, and feces. At this time, symptoms of the minor illness may appear, or the infection may remain asymptomatic. Viremia is present for a few days before the onset of central nervous system signs in those who develop either nonparalytic polio (aseptic meningitis) or the paralytic disease. Antibodies develop early and extinguish the viremia, usually before paralysis appears. However, infectious virus bound to antibody may be detected for a few additional days (18).

After initial multiplication in the tonsils, the lymph nodes of the neck, Peyer's patches, and the small intestine, the virus spreads by way of the bloodstream to other susceptible tissues, namely, other lymph nodes and the central nervous system. Poliovirus can also spread along axons of peripheral nerves to the central nervous system, and there it continues to progress along the fibers of the lower motor neurons to involve the spinal cord and/or parts of the brain. Tonsillectomy or other surgery in the oropharynx at times when polioviruses are prevalent increases the risk of central nervous system involvement (2, 36). This may result from virus in the pharynx gaining direct access to cut nerve fibers, or it may be a secondary consequence of the removal of immunologically active lymphoid tissue.

Poliovirus invades only certain types of nerve cells; in the process of its intracellular multiplication, it may damage or completely destroy these cells (32). The anterior horn cells of the spinal cord are most prominently involved, but in severe cases the intermediate gray ganglia and even the posterior horn and dorsal root ganglia are often affected. Lesions are found as far forward as the hypothalamus and thalamus. In the brain, the reticular formation, vestibular nuclei, cerebellar vermis, and deep cerebellar nuclei are most often affected. The cortex is virtually spared, with the exception of the motor cortex along the precentral gyrus.

Although flaccid paralysis is the hallmark of poliomyelitis, the virus does not normally multiply in muscle in vivo. The changes that occur in peripheral nerves and voluntary muscles are secondary to destruction of nerve cells within the central nervous system. Cells that are not killed but lose function temporarily may recover completely within 3 to 4 weeks after onset. Inflammation occurs secondary to the attack on nerve cells.

TREATMENT AND PROGRESS

Treatment involves reducing pain and muscle spasm, maintaining respiration and hydration, allaying fear, taking steps to minimize ensuing skeletal deformities, and anticipating and forestalling other indirect effects of the paralysis, some of which are transient and some of which are long-term (3). When the fever subsides, early mobilization and active exercise are begun. All pharyngeal and bowel discharges are considered infectious and should be disposed of quickly and safely.

Usually, recovery is complete in patients with nonparalytic polio and in those with mild muscle weakness. In cases of severe paralysis, recovery of muscle function starts soon after the acute phase and may continue for up to 2 years. However, 80% of the eventual recovery attained is achieved within 6 months. The extent of muscle recovery is inversely proportional to the extent of nerve cell damage. Some muscles seem to recover completely, whereas others never improve. The case fatality rate is about 4%, but in epidemics involving older age groups, it has reached 10%.

A late-onset post-polio syndrome consisting of muscle weakness, muscle pain, and unaccustomed fatigue has occurred with increasing frequency among former poliomyelitis patients (34). There are about 300,000 to 600,000 American survivors of the polio epidemics of the 1940s and 1950s who live with some degree of residual disability. In the 1990s, more than one-third of these patients are experiencing the new problems and symptoms of post-polio syndrome.

The age of the patient with post-polio syndrome is less important as a determinant of onset than the length of the interval following the time of acute illness. The incidence peaks at an interval of about 30 to 40 years following the time of acute poliomyelitis. It seems that the post-polio syndrome results from the neuromuscular disease process initiated at the time of the acute illness. The disease is not caused by a reactivation of the original poliovirus or by a reinfection with a current strain. It develops when the patient's remaining motor units in the central nervous system start to respond poorly to their overuse throughout many years (34) (Fig. 1).

EPIDEMIOLOGY

Human beings are the only known reservoir of poliovirus infection. At times when a poliovirus is widely prevalent in an area, houseflies become contaminated and may passively distribute virus to food (38). The significance of flies in transmitting the viruses is not fully understood; in areas of poor sanitation, they may play a more significant role. Polioviruses are often present in urban sewage (12), which may then serve as a source of direct or indirect transmission through flies or through contaminated water used for drinking, bathing, or irrigation. However, close human contact is the primary avenue of spread. From individuals who are infected, whether or not they develop clinical illness, the oropharynx and intestine can yield virus, which is generally shed for as long as a month or two in stools but for a much shorter period in oropharyngeal secretions. The usual source of transmission is infectious feces spread by contaminated fingers. Viruses are most readily spread within the family. Poliomyelitis occurs year round in the tropics and during summer and fall in temperate zones. Winter outbreaks occur but are rare (25).

The disease occurs in all age groups, but children are usually more susceptible than adults because of the acquired immunity of the adult population. In isolated populations (Arctic Eskimos), poliomyelitis has attacked all ages equally. In developing areas, where conditions favor the wide dissemination of virus, poliomyelitis continues to be a disease of infancy. In developed countries before the onset of vaccination, the age distribution shifted so that most patients were over age 5 years and 25% were over age 15 years (22). With rising levels of hygiene and sanitation, a similar trend has occurred in developing countries.

Under conditions of poor hygiene and sanitation in warm areas, where almost all children become immune early in life, polioviruses maintain themselves by continuously infecting a small part of the population. In temperate zones with high levels of hygiene, epidemics have been followed by periods of little spread of virus, until sufficient numbers of susceptible children have grown up to provide a pool for transmission in

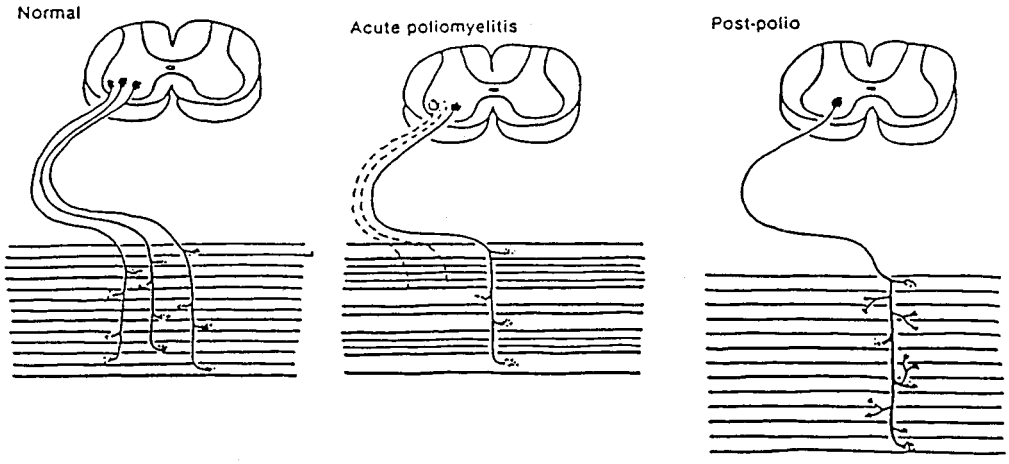

FIG. 1. Schematic representation of motor units to a muscle. "Normal" represents the 100 to 1,000 motor neurons of a muscle and the 5 to 1,500 muscle fibers each axon innervates. "Acute poliomyelitis" depicts viral destruction of some of the anterior horn cells with atrophy of denervated muscle fibers. Post-polio represents axon sprouting by recovered nerve cells with reinnervation of the orphaned muscle fibers and subsequent hypertrophy. Reprinted from reference 34 with permission.

the area. Warm weather favors the spread of virus by increasing human contacts, the susceptibility of the host, or the dissemination of virus by extrahuman sources. The prevalence of infection is highest among household contacts. When the first case is recognized in a family, all susceptible individuals in the family are already infected, the result of rapid dissemination of virus (22).

CONTROL THROUGH VACCINATION

While the above studies were going on, virologists were also concerned with vaccines. Koprowski in 1950 had fed his rodent-adapted type 2 poliovirus to a small group in California, and within the next decade he and Cox and their associates (5, 10) had fed millions more throughout the world with the three types of viruses. Others (13, 30), including Sabin in the United States (30), had also developed attenuated strains, and Chumakov and his associates in the USSR (7) had fed these to millions more. The results were so striking that a number of countries immediately adapted the above strains as the polio vaccines of choice. However, in Berlin, the father of a child vaccinated with Cox strain developed paralysis and died (14). From his brain tissue, our laboratory isolated poliovirus with the properties of the Cox strain, and the strain was withdrawn. Our laboratory (17) also tested in monkeys by the intracerebral and intraspinal routes the Sabin, Koprowski, and Cox strains. Our results, plus the similar ones obtained at the National Institutes of Health (21), favored the Sabin strains, which were then licensed for use in the United States.

Both live (16, 31) and killed (33) vaccines are now readily available, but most countries have relied almost entirely on live, oral poliovaccine (OPV), the vaccine recommended by the World Health Organization. In 1977, only 5% of all children in the world had received the required three doses of OPV in the first years of life, but in 1995, this percentage had increased to 80%. By 1995, OPV was preventing at least 400,000 cases of paralytic poliomyelitis each year.

Injectable vaccine (Salk) (33) is prepared by formalin inactivation of virus grown in monkey kidney cell cultures. It is known as IPV. At least four inoculations over a period of 1 to 2 years are recommended in the primary series. Periodic booster immunizations are necessary to maintain immunity. IPV induces humoral antibodies, but upon exposure, virus is still able to multiply in the gut and be transmitted to another susceptible person. Currently, commercial preparations of IPV have increased potency and are known as enhanced IPV or eIPV.

OPV (16, 31) contains live attenuated virus grown in primary monkey or human diploid cell cultures. OPV multiplies and infects and thus immunizes. In the process, infectious progeny of the vaccine virus are disseminated in the community. Although the viruses, particularly types 2 and 3, mutate in the course of their multiplication in vaccinated children, only extremely rare cases, about 1 per 500,000 susceptible children, of paralytic poliomyelitis have occurred in recipients of OPV or their close contacts. Booster vaccinations are important to establish permanent immunity. The vaccine induces not only immunoglobulin M (IgM) and IgG antibodies in the blood but also secretory IgA antibodies in the intestine, which then becomes resistant to reinfection (23).

All living creatures undergo some degree of mutation, and live polioviruses are no exception. As mentioned above, the mutations that occur during replication of OPV have produced, in very rare instances, viral progeny with neurovirulence sufficiently increased to cause paralysis in vaccine recipients and their susceptible contacts. From the study of poliovirus, we have learned a great deal about viral genetics. Poliovirus replication is accompanied by an error frequency of about $10^{-3.5}$ per nucleotide incorporated into the nascent poliovirus RNA genome, which consists of about 7,400 nucleotides. This error rate suggests that most newly synthesized poliovirus RNA molecules differ in at least one nucleotide from the sequence of the parental template RNA. Thus, every batch of poliovirus is a population of viral genomic sequences that compete for dominance in the mixed population of sequences. Any change in growth conditions will alter the relative replicative efficiency of the competing viral sequences. This concept of a dynamic viral population explains the rapid changes of viral phenotype that can occur during manufacture or after application to a vaccinated person. A sensitive measure of reversions from uracil to cytosine at nucleotide 472 of type 3 OPV can be used to predict the result of the expensive and somewhat variable monkey neurovirulence test, the test being used by most manufacturers today (28).

Other poliovirus types have similar reversions (27). Thus, for type 1, a G-to-A reversion occurs at nucleotide 480. Batches of type 1 in which the level of A-480 was 2.7% of revertants have

passed the monkey neurovirulence test. Thus, the in vitro genetic test which detects A-480 is even more sensitive than the monkey test for neurovirulence (28).

Trivalent OPV is generally used in the United States, where primary immunization begins at 2 months of age, simultaneously with the first diphtheria-tetanus-pertussis inoculation. The second and third doses should be given at 2-month intervals thereafter, and a fourth dose should be given at 18 months of age. The multiple doses are recommended to maximize immunity for all three serotypes. A trivalent vaccine booster is recommended for all children entering elementary school. No further boosters are presently recommended.

Circulating antibody in serum is not the only source of protection against poliovirus infection. Local or cellular immunity is manifested by protection against intestinal reinfection after recovery from a natural infection or after immunization with OPV. Local or secretory IgA is generally recognized as having an important role in defense against enterovirus infection. The development of serum and secretory antibody responses to OPV and to intramuscular inoculation of IPV has been investigated. The IPV was not very effective in inducing secretory antibody in the respiratory or intestinal tracts. It had been hoped that the newer eIPV would stimulate a more effective secretory antibody response. In a study (23) on the development of antibody responses to the whole virus and to the subunit virion proteins in humans, infants immunized with eIPV or with OPV were studied for serum and secretory antibody responses to the poliovirus itself and to polypeptides VP1, VP2, and VP3. Both vaccines induce neutralizing IgG and IgG detectable by enzyme immunoassay to the whole virus and to VP1 and VP3 and similarly detected secretory IgA to VP1 and VP2 in the nasopharyngeal secretions without any anti-VP3 response. However, with regard to the neutralizing-antibody response in nasopharyngeal secretions, OPV was markedly more effective than was eIPV: 70% of the infants developed this response after OPV, compared with only 27% of those who had received eIPV.

In the 1950s, just prior to the beginning of vaccination campaigns in the United States, about 21,000 cases of paralytic poliomyelitis occurred annually. Currently, each year fewer than 10 cases occur; they are vaccine associated and are a result of back-mutations. No wild virus has been isolated in the United States since 1979, and the disease has almost vanished in all industrialized countries globally and in all of the western hemisphere through the special programs of the Pan American Health Organization, a division of the World Health Organization. However, there is a continuing global need for adequate vaccination schedules to limit the spread of wild viruses. This is particularly important when wild viruses are introduced from countries that have not brought polio under control.

In developing countries, particularly in tropical areas, the usual schedule should be accelerated. Not only should primary immunization begin very early—even at birth—but also, in particular, immunization should be completed early in infancy; in some tropical areas where neither OPV nor IPV was able to eliminate all cases, a combined schedule of OPV and IPV has been used successfully to eradicate the clinical disease in spite of the occurrence of wild viruses in the region (9, 11, 35). Denmark (37) has adopted this schedule. The United States is considering a combined schedule as of this writing.

Molecular characterization of poliovirus strains isolated from the stool samples of 70 patients with vaccine-associated cases of poliomyelitis showed that 50% of type 2 and 67% of type 3 strains had a recombinant genome (8). This was in contrast with the very low proportion of recombinants among strains serially isolated from healthy OPV vaccinees up to 2 months postvaccination. The majority of these strains, from both paralyzed and healthy vaccinees, carried mutations in nucleotide positions that play a role in poliovirus attenuation. It appears that recombination plays a role in the neuropathogenicity of vaccine-derived strains. In some vaccine-associated cases, both recombinant and nonrecombinant strains have been found, indicating that the stool isolates might not be always representative of the etiologic agent of the paralysis. All strains isolated from the spinal cords of patients with vaccine-associated cases had lost the attenuated phenotype of the original Sabin strains as tested in transgenic mice carrying the receptor gene and thus being susceptible to poliovirus infection (1, 26).

The global situation has recently been reviewed by the U.S. Centers for Disease Control and Prevention (6). "Since 1988, the global incidence of paralytic polio has decreased substantially, and polio apparently has been completely eliminated from the Western Hemisphere. The number of global polio cases reported in 1993 represents a 33% decrease compared with 1992 and with a 70% decrease compared with 1988. Furthermore, nearly three-quarters of all countries reported zero cases of polio in 1993, and polio-free zones are present or emerging in the Americas, northern, southern, and eastern Africa, the Arabian peninsula, Western and Central Europe, and the Western Pacific.

Despite this substantial progress over-all, paralytic polio remains highly endemic throughout the Indian subcontinent, and continues to occur in most countries of sub-Saharan Africa and Asia, including many republics of the former Soviet Union. In 1993, nearly two-thirds of all polio cases reported worldwide were from the Indian subcontinent, including 42% from India, 19% from Pakistan, and 2% from Bangladesh. Lower than optimal levels of routine vaccination coverage, pockets of unvaccinated children within otherwise highly vaccinated populations, crowding, poor sanitation, and suboptimal seroconversion to poliovirus types 1 and 3 following three routine doses of OPV in many tropical and subtropical regions probably contribute to ongoing wild poliovirus transmission in these areas.

In addition to remaining areas of endemic transmission, outbreaks of paralytic polio have recently occurred in several countries 2 or more years after the last previously reported case of polio, despite high levels of routine vaccination coverage. Genotypic comparisons between wild poliovirus strains in the global laboratory network have demonstrated that outbreaks in Oman, Jordan, Malaysia, and the Netherlands occurred as a result of importation of wild poliovirus from polio-endemic countries in the Indian subcontinent. Thus, until polio is eradicated globally, every polio-free country may be at risk for importation of wild poliovirus from remaining polio-endemic reservoirs.

Routine vaccination alone is probably insufficient to eliminate wild poliovirus transmission in most countries, and supplementary vaccination activities are necessary in countries where polio remains endemic. National Immunization Day (NID) mass campaigns over a short period [days to weeks] have been successful, in which two doses of OPV are administered to all children in the target age group, regardless of prior vaccination history, with an interval of 4-6 weeks between doses. In 1993 and early 1994, NIDs were conducted for the first time in China, Vietnam, Philippines, Laos, Iran, and Pakistan, which together accounted for 31% of all polio cases reported globally; by the end of 1994, at least 63 (30%) of 209 countries were conducting NIDs as a polio-control strategy. As more countries adopt this strategy, further progress is expected toward global eradication of polio.

Despite substantial progress toward global eradication of

polio, several challenges remain, including (1) reversing the decline in global routine vaccination levels; (2) increasing vaccination levels in unvaccinated subpopulations; (3) preventing the reintroduction of wild poliovirus into polio-free areas by eliminating reservoirs in polio-endemic countries (particularly the Indian subcontinent); (4) increasing the awareness of donor agencies and governments in industrialized countries of the substantial financial and humanitarian benefits of global eradication of polio, thus engendering support from unaffected countries beyond that already provided by organizations such as Rotary International; (5) encouraging all countries that remain polio endemic to make polio eradication a priority activity, including the implementation of NIDs and the initiation of acute flaccid paralysis surveillance; and (6) providing support to vaccination program managers for training to develop managerial skills for implementing and maintaining effective vaccination and surveillance programs in all countries. The success of the polio eradication initiative will depend on finding solutions to these financial, managerial, political, and technical challenges." The CDC *Morbidity and Mortality Weekly Report* was subsequently able to write on 29 September 1994, "Based on recommendations of the national certification committees on polio eradication, and after review of surveillance and laboratory data, PAHO announced that wild virus transmission has been interrupted in the Americas.

The certification of the interruption of wild poliovirus transmission in the Americas is an important achievement in the global effort to eradicate poliovirus. In addition to successful vaccination strategies, other factors that contributed to the achievement include (i) the high level of political commitment of the member governments; (ii) substantial community participation; and (iii) strong collaboration among participating agencies and organizations through interagency coordinating committees.

Although poliovirus transmission has been interrupted in the Americas, transmission of wild poliovirus continues in other parts of the world and creates an ongoing risk for the importation of wild poliovirus into the Americas. If importations occur, polio outbreaks may develop, especially in localities with low vaccination coverage and poor sanitation. As a result, the Region of the Americas must maintain high levels of vaccination coverage.

Ongoing surveillance for acute flaccid paralysis cases and/or the presence of wild poliovirus must be maintained. International communication and collaboration will continue to be necessary for the rapid detection of importations of wild poliovirus and timely implementation of control efforts. Only the global eradication of polio will ensure that the Region of the Americas remains polio-free."

The results in one area are illustrative of what can be done (9). Following the introduction of trivalent OPV, the incidence of paralytic poliomyelitis in Israel declined dramatically. Yet, in 1988, an outbreak of 15 cases of type 1 polio occurred, most in fully vaccinated people aged 11 to 35 years. It appeared that the young adult population was not adequately immune against the epidemic virus. All persons up to age 40 years were offered a single dose of OPV. In addition, a new infant vaccination schedule was introduced, based on a combination of three doses of eIPV and three doses of OPV. Since the outbreak, no cases of paralytic poliomyelitis have occurred in Israel, as of this writing, even though the disease remains endemic in neighboring countries and wild polio isolates were detected in sewage in Gaza. Two studies were conducted to assess the immune status of the population. The immediate antibody response and long-term persistence of neutralizing antibodies were examined in adults vaccinated with OPV in 1988. Four years later, geometric mean titers were lower than the levels immediately following the booster, but all vaccinees had titers of at least 64 against the type 1 epidemic strain. In a second study, blood samples were drawn from 65 infants aged 16 to 20 months who had been vaccinated with the new combined (and enhanced) eIPV-OPV schedule. All had antibody titers of at least 64 against the epidemic strain, and geometric mean titers against all poliovirus types were considerably higher than those achieved in schedules based on OPV alone. These findings indicate that the mass vaccination campaigns in 1988 and the new combined vaccination schedule for infants have produced extremely high levels of immunity in the population. As a result, paralytic poliomyelitis has been eradicated as of 1988 from Israel, as it had been for Gaza and the West Bank, where combined IPV-OPV or eIPV-OPV schedules have been used since 1978 (11).

An immunization schedule in which IPV is given prior to the first feeding of OPV would be expected to eliminate the risk of vaccine-associated paralytic poliomyelitis for OPV recipients and reduce the risk among contacts of OPV recipients and immunocompromised children. In the United States, two doses of eIPV given at 2 and 4 months of age are being considered for complete protection against subsequent doses of OPV. The gastrointestinal and mucosal immunity induced by a sequence of IPV-IPV-OPV-OPV given at 2, 4, 6, and 25 months of age has been suggested for use in the United States.

FUTURE DIRECTIONS

Poliomyelitis is one of the most thoroughly studied diseases (15). Before the development of vaccines, knowledge had advanced to such an extent that we understood the epidemiology and clinical forms of the disease. We had determined the high ratio of inapparent infections to paralytic disease, about 100:1. We realized that three types of poliovirus existed and that they were members of a large family of enteroviruses, of which more than 70 members are recognized. Subsequently, great strides were made in understanding the molecular biology of poliovirus, particularly through knowledge of its complete genome sequence and the detailed structure of the virion. With the development and use of vaccines, poliomyelitis has been brought under control and complete eradication of the disease is now the goal.

A key determinant of poliovirus infection is the cell receptor, upon which the restricted tropism of the virus depends (1, 26). Molecular clones of the poliovirus receptor have been isolated, and the encoded protein has been identified as a new member of the immunoglobulin family. Transgenic mice, in which the human gene encoding cellular receptors for poliovirus has been introduced into the mouse genome, have been developed. The new mice have proven to be susceptible to all three poliovirus types and are being investigated as models for testing OPV lots for neurovirulence, which currently requires the monkey test.

Studies with synthetic peptides that contain neutralizing epitope residues revealed that they are weak immunogens. Thus, when nonliving antigen is required, the use of IPV is indicated (33). However, OPV continues to be the vaccine of choice worldwide (16, 31).

The application of recombinant DNA technology may permit the development of a live poliovirus that cannot mutate to increased neurovirulence. A key technological advance was the construction of infectious cDNA clones that made possible the manipulation of nucleotide sequences to generate poliovirus mutants with specific and desirable alterations in the genome. Recombinant viruses have been constructed from parental vi-

ruses belonging to different poliovirus serotypes and between virulent and attenuated strains of the same serotype (4). Sequences in the viral genome that are responsible for an attenuated phenotype have been identified.

The type 1 vaccine virus, which is extremely stable genetically, has been used as a vector for type 2 and 3 nucleotide sequences encoding immunogenic regions of their VP1 proteins (4). The new "chimeric" strains have the desired biological characteristics of type 1 but the added immunogenic properties of type 2 or type 3, respectively. Such advances may lead to a more genetically stable type 3 vaccine. However, it will be difficult to field test such a new vaccine candidate, because it will be necessary to prove that the new vaccine produces fewer than one vaccine-associated case per million susceptible recipients. In the meantime, the widespread application of OPV has achieved eradication of the disease from the Western Hemisphere, and with each passing year, the number of cases in the entire world continues to fall. The global application of the present OPV is fast achieving an interruption of the circulation of wild poliovirus, closing the window during which any newly developed vaccine strains can be properly field tested. Worldwide eradication may be achieved through the use of the currently available and properly safety-tested vaccines (39).

This leads to a new question soon to be considered: should we simply stop vaccinating for a disease that no longer exists in the world? In the case of smallpox, the answer was clear. No harm was done to those vaccinated and to their healthy contacts. With OPV, 1 in about every 500,000 children receiving their first dose will develop paralysis. The virus recovered from such patients is virulent and has produced devastating paralysis in some healthy contacts. Another factor is the long period during which vaccinees are healthy carriers and remain contagious. It is essential that the contacts of vaccinated children be immunized together with or prior to immunization of the vaccinated child.

How can this be done with no risk? I believe that there is an important place here for the injectable vaccine, IPV. The virus is inactivated, so that healthy carriers cannot be produced. Such a vaccine will not lead to any contact cases or vaccine-associated cases. Moreover, the virus being excreted by those who have been OPV immunized will fade away. To lessen a potential risk involved in manufacture, the virulent strains in presently available IPV can be replaced by Sabin's attenuated strains of OPV. At least one manufacturer is already testing such an IPV. Following the eradication of polio by OPV, there should be a year or two during which only IPV is used. Since intestinal excretion of OPV progeny will have stopped, there will not be any poliovirus about and the world can say good-bye to an unwanted virus.

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