THE FIGHT AGAINST POLIOMYELITIS

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POLIOMYELITIS is an ancient disease known probably to the Pharaohs, for records of the deformity produced by muscular paralysis have been found on carvings from ancient Egypt. Yet its clinical manifestations were only separated with certainty from other neurological disorders by Heine in 1843 and the first epidemic ever to be described was that noted by Médin in 1887 in Stockholm. Wickman described the first country-wide outbreak in Sweden in 1905 and there has been little to add since to his admirable account. Yet these earlier records were concerned with poliomyelitis as a disease of infants, which justified its earlier name of infantile paralysis. In Great Britain sporadic cases and small outbreaks were reported from 1897 onwards, and the incidence rose in 1938 to a level of four per 100,000 of the population. The first large epidemic, however, occurred in 1947 quite unexpectedly. In this year over 7,000 cases were notified and still larger outbreaks were experienced in 1949 and 1950. Since then waning and waxing prevalence in Britain has compelled the conclusion that this country had begun to follow the earlier experiences of Scandinavia, the U.S.A. and Australia. These countries experienced epidemics of poliomyelitis even before 1920, and though the worst year in American and Danish history was probably 1952, the strange lack of protection afforded by epidemicity contrasted with the apparent low level of the disease in the period before outbreaks set in.

A second feature of the epidemic experiences in western countries was the changed age-incidence. Whereas the earlier experience of the disease in all these countries was dominated by the occurrence of 60 to 80 per cent of cases in children under five years of age, that of the large epidemics of the U.S.A. before 1945 and our own epidemics since then was that two-thirds of the cases occurred above this age. It was largely the occurrence of the disease in older children and adults that led to the abandonment of the name “infantile paralysis” and the substitution of the word “poliomyelitis.” No explanation for the shift in age-incidence was found, however, before the extensive investigations of the serological status of the populations in many areas of the world had been accomplished, and these were made largely by Paul and his associates at Yale (Melnick et al. 1955). Indeed the puzzle was accentuated by the war-time epidemics on the islands of Malta and Mauritius in which the infants of the civilian population were exclusively affected, whereas the temporary military population in these islands including British troops and R.A.F. were attacked even though of adult age. Thus of the 426 Maltese affected only 29 were over five, but there were 57 cases in British servicemen. Even more recently outbreaks in certain South American states and in Africa have continued to exhibit infantile paralysis.
with sparing of the attack on adults. It must be appreciated, however, that the adult section of our own population when once attacked exhibited a high mortality rate, so that the infant exhibits both a higher degree of susceptibility to infection and a greater resistance to neurological attack than does the adult. The strange phenomenon of a low level of endemic disease, yet a high attack-rate in temporary adult immigrants, was well shown by the comparative attack-rates in U.S. Forces in the different theatres of war (Paul, 1949). The only possible explanation of this contrast was that polioviruses are most prevalent where disease among the resident population is clinically inappreciable.

Virological explanations of the epidemiology

So long as the virologist was limited to studying polioviruses in the laboratory by inoculating rhesus monkeys and chimpanzees, it was impossible either to examine large numbers of virus strains or to investigate the level of antibodies in the blood of many patients or of healthy persons. The first step in improved ability to handle the virus in the laboratory came from the transmission of Type II poliovirus—the Lansing virus from Michigan—to the cotton rat and the mouse. Although this virus opened the way to large-scale serological study, the more important epidemic strains were known to be unrelated to it, and thus only a partial picture was obtained of the behaviour of the virus in nature. Nevertheless, these earlier serological tests using the Lansing virus adapted to mice showed that in countries such as Egypt where poliomyelitis outbreaks are exceptional, antibodies to Type II virus are rapidly acquired in infancy and persist throughout life, suggesting a high level of endemic infection. In the U.S.A., however, antibodies in young children develop at a slower rate, so that many children of school age have no antibodies. There were instances of sera without antibodies in American children and adults at all ages. Again, it was shown that antibodies were present in a higher proportion of children from an overcrowded, unhygienic area in the U.S.A. than in children from a better social and economic area. These findings hinted at the fact that epidemics of poliomyelitis were correlated in places with a slow acquisition of antibodies in the earlier years of life.

The brilliant achievement of Enders and his colleagues at Boston in adapting tissue cultures to the growth of polioviruses in the test-tube had a catalytic effect on the acquisition of knowledge (Enders et al. 1949). It had already been shown by a monumental study of many virus strains by Salk and others using monkeys that there were three major types of polioviruses distinguished on an antigenic basis. Now that in vitro methods were available for the recovery of virus strains from epidemics it was possible to confirm this on a larger scale. It was soon obvious that most of the large epidemics of poliomyelitis in modern times were predominantly due to Type I viruses. A lesser number yielded Type III viruses, and Type II infections were the least common. At the same time, antibodies against Types I and III, the important epidemic types, were studied in many different countries using neutralization tests in tissue cultures. In some American white populations as many as 40 to 50 per cent of children reached the age of 15 without developing antibodies to Types I or III viruses and similar figures were obtained in other countries such as Sweden (Melén
et al. 1958). Yet in areas where poliomyelitis was hardly ever recorded, antibodies to all three types of poliovirus rose rapidly in early infancy and were almost universal by the age of two. Thus the results with Types I and III viruses confirmed the earlier studies with Type II viruses in mice.

The picture thus revealed strongly suggests that the three polioviruses are ubiquitous and a cause of widespread infantile infection, probably in the first six months of life, largely unaccompanied by disease in countries and areas with a low standard of hygiene. In western countries the improvement in hygiene since the early part of the twentieth century has gradually led to a decline in infection in infancy and a postponement of first infection to a later age-group. Thus in these countries increasing numbers of children and adults acquire infection at an age when the central nervous system is less resistant to attack than in infancy and neurological disease is thus more likely. The process becomes a vicious circle as children are born to mothers themselves without antibodies, so that even infection in the first six months of life is more likely to be accompanied by disease.

Perhaps as a corollary to these findings, the purely epidemiological inverse correlation of the infantile mortality rate and the incidence of poliomyelitis charted by Payne of the World Health Organization may be quoted (Paul, 1958). Nature meant us to exchange our polioviruses with each other while crawling around the floor, and the well-meant efforts of our hygienists have, in fact, helped to create the problem of epidemic disease. We thus derive our infection with poliovirus from infected persons and particularly from infants and children who are excreting virus while remaining symptom-free. Although the possibility of extra-human infection also exists, as by the intermediary of meat-eating flies, it is hardly likely that such a reservoir is important except when sanitation is primitive. It is far more likely that the reservoir of infection is the human herd, through which a relatively narrow ribbon of virus spreads, particularly when seasonal conditions favour faecal-oral transmission. The possibility of transmission by airborne droplets also exists and may in fact be the more important under certain conditions.

**The mechanism of infection by poliovirus**

While knowledge has been advancing on the epidemiological front, much has also been learned about the pathogenesis of infection in man. By whatever route virus actually reaches the victim, the portal of entry is believed to be the alimentary tract and particularly the pharyngeal and small intestinal mucosa. Multiplication of virus occurs in the mucosa, and virus passes to the regional lymph-nodes but not usually to other organs. It also passes down the lumen of the alimentary tract, probably infecting other areas of mucosa, and eventually is excreted in large amounts in the faeces. In most cases these events are clinically silent, but in a small percentage they are accompanied by minor illness with symptoms such as a slight pyrexia, headache or a sore throat. In a still smaller proportion of instances, virus does pass beyond the lymph-nodes to other organs. One route is probably along peripheral nerves and another is via the blood. Viræmia has proved extremely difficult to demonstrate, because it occurs in the first few days of infection at a time when virus is also present in the pharynx, and before any symptoms are present. Though there is still
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doubt concerning the exact way in which virus passes from the alimentary tract to the central nervous system (C.N.S.), there is now no doubt at all that the composition of the blood can influence the process. The introduction of antibodies parenterally in the form of gamma globulin or their stimulation by immunization with inactive virus vaccine both afford significant protection against neuroparalytic disease in animals and in man, and these favour the view that the blood-stream is an essential pathway in invasion of the nervous system.

What follows after the arrival of virus in the C.N.S. is, however, influenced by several factors concerned with both the virus and the host. First the strains of polioviruses differ in their ability to multiply and to cause lesions in the C.N.S. even after direct injection into the monkey brain or cord. Some viruses found in nature are relatively attenuated in terms of monkey neuro-virulence and others are highly virulent, spread widely within the C.N.S. and produce destructive lesions and necrosis of motor neurones. Therefore by analogy the biological properties of the infecting strain are of great importance to man. Secondly the host himself plays a significant part. Trauma, exercise, pregnancy and other metabolic changes can all predispose to an enhancement of neuroparalytic disease, and the first two may determine the site and extent of virus multiplication within the C.N.S.

The consequence of infection of the nervous system with the production of lesions is the familiar clinical pattern of paralytic poliomyelitis involving the brain stem, spinal cord or both organs. In some more fortunate persons invasion is arrested at the stage of meningeal involvement, but even in these some neurones undoubtedly suffer. The frequency with which paralysis occurs is dependent very much on the particular hosts concerned, and paralytic disease may only occur once in every 100 to 1,000 instances of infection in the average European community. In rare instances, however, as for example among the Eskimos, the paralytic attack-rate has been as high as 20 per cent of the population at risk. In more normal circumstances age is a determining factor in the host-virus relationship, and the heightened susceptibility to infection of the child or infant is accompanied by a lesser risk of death from actual paralysis than in the adult. There is no better example than poliomyelitis for demonstrating the subtle effect of those poorly-understood host factors which determine the outcome of what we naively term infection by a particular virus species.

The prevention of poliomyelitis

Efforts to limit the spread of poliomyelitis under epidemic conditions have largely failed. By the time the first case of paralysis has occurred in a family or community, familial and often extrafamilial contacts, themselves clinically unaffected, are nevertheless infected and actively excreting virus. Moreover, the paths of spread from case to case are only clearly discernible in a restricted population such as a village, and little use can be made of quarantine in urban populations. Closing schools is ineffectual once cases of paralysis have occurred, and the effect of closing swimming-baths is largely that of diminishing fatigue and its provocative action in terms of host paralysis. The banning of tonsillectomy is a wise measure, however, because the operation has been shown to be followed by an increased risk of bulbar poliomyelitis under epidemic conditions. In military communities the occurrence of poliomyelitis
is certainly an indication of the need for overhauling hygiene and for diminishing temporarily circumstances leading to muscular fatigue.

**Salk vaccine**

With this background of failure of normal hygiene measures it is hardly surprising that the prospect of immunization was eagerly awaited, but nothing could be done until a method of artificial cultivation of the virus was available which could provide a rich growth of virus readily separable from unwanted foreign protein. The method of tissue culture evolved by Enders and his colleagues (1949) provided just such a method, and Salk’s energy and the material resources given by the people of the U.S.A. to the National Foundation for Poliomyelitis enabled mass cultivation to be achieved. Salk’s second contribution was that of a practical method of inactivating the virus by incubating the virus-containing culture at 37°C with a critical concentration of formalin. Even then the prophets might well have been sceptical that the total virus antigenic mass in a 1 ml. dose of vaccine would be enough when injected intramuscularly to stimulate the formation of antibodies. It was soon found, however, that antibodies were produced by such a vaccine, and that although primary immunization in children or adults without prior antibodies was relatively inefficient, a tremendous booster response occurred, either after a suitably spaced third dose, or with one or two doses in those who had even small quantities of preformed antibodies. These immunological findings have been widely confirmed and Salk’s claims have, in general, been fully vindicated. Once it had been shown that artificial immunization with a vaccine containing all three types of polioviruses was feasible and led to the formation of antibodies in amounts comparable with those found during recovery from infection, field trials were indicated.

The famous trial in the U.S.A. organized by Dr. Thomas Francis of Ann Arbor, Michigan, gave results which exceeded even the forecast. Paralytic disease was reduced by 66 per cent or more in those children receiving three doses of vaccine at short intervals. The British experience of the effect of two doses of vaccine at three to four weeks interval using a British-made vaccine, prepared according to Salk’s technique though with a substitute Type I strain, gave very comparable results to the American trial. The ill-fated experience of the introduction of mass vaccination in the U.S.A. was traced to a failure of manufacture of certain batches of vaccine. Since the process was modified and stringent tests were made for the presence of residual live vaccine after formalization, no further event similar to the Cutter disaster has been experienced anywhere in the world. Resumption of mass immunization of children and adults in the U.S.A. and its introduction elsewhere have led to a remarkable change in the incidence of the paralytic disease.

However, two weaknesses have become apparent in the Salk vaccine which have been important in the drive towards the alternative of attenuated live virus vaccine. First, the concentration of virus antigen achieved in the ordinary Salk vaccine appears adequate for the stimulation of antibodies against Type II and III viruses but is inadequate in the case of Type I virus. This is shown by the fact that about 30 per cent of children receiving three doses of Salk vaccine at the recommended intervals are still deficient in Type I antibodies. It is not enough to give a fourth dose to such
children—what is needed is a better vaccine for the basic immunization by the first two doses. There are now available better vaccines with a more concentrated Type I component, but they are expensive or not yet in good supply.

The second defect of the Salk vaccine is that it fails to immunize against oral infection of the alimentary tract. In consequence it is as easy to produce alimentary tract infection of Salk-vaccinated subjects as it is to infect normal children. There is a little evidence that vaccination may reduce the duration of virus excretion, and in this way it may upset the transmission of virus in the community. But experience in Canada and the U.S.A. has shown that if an epidemic occurs primarily in unvaccinated subjects, the fire of infection may spread to involve also those who have been vaccinated. In the sharp outbreak in Quebec Province of Canada in 1959 there were instances of paralysis in children who had received three and four doses of Canadian-manufactured Salk vaccine. It is true that the attack-rate was much lower in the immunized than in the non-immunized, but the estimate made of the so-called vaccine-effectiveness was based to some extent on speculation about the exact numbers of children in the two categories at risk. Instead of the 90 per cent effectiveness estimated during these outbreaks, it is possible that the true effectiveness is only 70-80 per cent, which was in fact found during the controlled trials of 1955 and 1956 in the U.S.A. and in Britain. At any rate, apart from the degree of effectiveness of immunization with Salk vaccine, the experience in certain American epidemics and in Israel indicated a failure of mass vaccination given during the course of the epidemic to arrest its progress.

**Live attenuated poliovirus vaccines**

In the last three years increasing use has been made on a world-wide scale of a living oral vaccine, prepared from various strains of the three types of polioviruses previously subjected to laboratory manipulation designed to attenuate their neurovirulence for monkeys. Three sets of such vaccines, prepared by Koprowski, Cox and Sabin, have been used. This is not the place fully to discuss the relative properties of these candidate seed viruses, but it is clear that they are not all equally attenuated in terms of monkey neurovirulence or in certain other desirable properties (Report of the Expert Committee of W.H.O. on Poliomyelitis, 1960). What has been learnt is that when given by mouth, large doses of these tissue-culture viruses produce infection of the alimentary tract in children, lead to the development of neutralizing antibodies and cause excretion of virus in the stools for two or more weeks. Contagion of those in intimate contact with the vaccinated subjects has occurred, but there does not appear to be any widespread infection of the community. Vaccinated subjects who have been infected are immune to re-feeding within short periods of time. The viruses excreted by the vaccinees differ from the parent vaccine strains, and in a low percentage of instances they show a degree of reversion towards monkey virulence of a level found in natural wild viruses. In general, however, they are still 1,000 to 10,000 times less neurovirulent than ordinary viruses recovered from paralytic cases of poliomyelitis.

The vaccine prepared from Sabin's seed viruses has been most widely used, having been given by mass methods to many millions of children and adults in Russia, Czechoslovakia, Hungary and certain American communities. No harmful effects
have been reported either in vaccinated persons or their contacts. Similar good results have been obtained with Koprowski vaccine which has been used widely in Poland and the Congo. The Cox-Lederle vaccine has been used in South America, in the U.S.A. in Minnesota and Florida, and in Europe in West Berlin. The only possible adverse effects were noted in Florida and West Berlin, where the vaccine was used in the face of undue prevalence of poliomyelitis. Events in these areas indicate the extraordinary difficulty of disentangling the origin of cases of polio in immunized communities. In no case has it been possible to prove more than a possible association of the cases in time with the use of the live vaccine. Infection by epidemic strains could equally have been the explanation. Nevertheless, because the Cox viruses appear in comparative tests to be less well attenuated in monkey-virulence than the Sabin viruses, their use is likely to diminish.

Now although these massive experiences have shown the general safety of live vaccines, it cannot be said that there is equal proof of their effectiveness. The vaccine does not "take" in those who have previously been infected by natural means and thus no antibody rise occurs. The proportion of those who are immunized is claimed to be high as shown by antibody tests, particularly if multiple doses of trivalent vaccine or the three types separately are used. There have been instances where live vaccine has been given in the face of outbreaks of poliomyelitis. The most impressive results achieved were those reported from Singapore by Hale and co-workers (1959). The Sabin Type II vaccine used in the face of a Type I outbreak could be traced subsequently in the community. It did not give rise to cases of poliomyelitis. It appeared to cause a real fall in the incidence of poliomyelitis in those to whom it was given, after three, but not within two, weeks from its administration (Hale, personal communication). In some countries such as Czechoslovakia and certain Baltic states poliomyelitis has been at a very low level since mass immunization with Sabin vaccine. Much more time is needed, however, before it will be known whether the vaccine can stop an epidemic or can eliminate poliomyelitis from a community. The claims of the proponents of live vaccine verge on the extravagant, and it is hard to preserve a balanced point of view.

Conclusions

For the people of our country subject to normal risks of infection it appears that either inactivated or live vaccine would probably furnish a good basis for protection. It is clearly unwise to substitute live for inactivated vaccine without more careful ground-work. But for those, such as the military, whose risk of infection may be many times greater in tropical climates than at home, it appears to me that it is unwise to rely solely upon one form of immunization. A combination of three doses of inactivated vaccine at the usual intervals followed by feeding on at least two occasions with live attenuated vaccine would be worthy of exploration and may, I suppose, receive attention by those responsible for the Army's health.

In all this long history of research on poliomyelitis one is conscious of the word "risk." Risk from the disease if nothing is done, risk from an imperfectly-prepared vaccine if this is used. Our thoughts should turn from risk to safety. How remarkable has been the general freedom from reaction after the Salk vaccine! How amazing to
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hear of 70 millions given the Sabin vaccine in the U.S.S.R.! As with all new remedies, new prophylactics must be judged by practical experience before we crow over their effectiveness. The elimination of a disease not dependent upon an intermediate vector is a very hard feat to accomplish. Perhaps this will happen in the case of poliomyelitis, perhaps it will not.

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