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EPIDEMIOLOGY OF POLIOMYELITIS AND ALLIED DISEASES—1963†**

A striking feature of paralytic poliomyelitis has been its ever changing epidemiology. In the past, changes seem to have come about in the course of natural evolution from an endemic to an epidemic pattern, first in one part of the world, and then in another. At present, the use of effective vaccines for prevention and for greatly reducing circulation of wild strains of the virus, have apparently had a real impact on the epidemiological behavior of the disease and we can perhaps anticipate further shifts, not only in connection with polioviruses, but with other members of the enterovirus family, some of which are capable of inducing poliomyelitis-like illnesses. These latter are assuming increased significance, for as the rates of true paralytic poliomyelitis decline, poliomyelitis-like illnesses assume greater relative importance.

In the following discussion, I shall review briefly our current knowledge of the epidemiology of poliomyelitis as a model for enteroviruses in general, with emphasis on newer knowledge which has accumulated as a result of investigations with oral vaccines, and on some of the factors of importance in planning current vaccination programs. For, although virtual control of paralytic poliomyelitis has been achieved in large geographical areas, in others (particularly tropical and sub-tropical ones) the disease is only now beginning to appear for the first time in epidemic form. In such countries, wise planning and effective execution of vaccination programs can forestall the evolution of poliomyelitis as the recurrent scourge that it has been over the past 75 years in parts of Europe, the United States, and elsewhere.

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HISTORICAL TRENDS

It is now well recognized that endemic poliomyelitis is world wide in distribution, and evolution of the disease as an epidemic one within the last century has followed a characteristic pattern. At first, a few small collections of cases are noted; then a higher than usual endemic rate for a few years is followed by severe epidemics with high attack rates. The age group attacked in endemic poliomyelitis and in early epidemics is the youngest—0-4 years, with 90 per cent of paralytic cases (particularly in urban areas) being under 5 years of age. Once this pattern of epidemicity begins, it is apparently irreversible unless preventive vaccination is carried out. As epidemics recur over a period of years and the average annual rate reaches 5 to 10 per 100,000 a shift in age incidence occurs, so that relatively fewer cases are in the youngest children, the peak often occurs in the 5-14 year group, and an increasing proportion of young adults is affected. This stage of development naturally poses an alarming situation since the disease is more severe and the mortality much higher with increasing age.

In reviewing the world history of poliomyelitis, it is clear that the above pattern of evolution of the disease has been experienced by many countries at different times:[1-5] the first were Norway and Sweden, beginning in the latter part of the 19th century; next, epidemics appeared in the northeastern part of the United States, near the turn of the century; in Australia and New Zealand in the first quarter of the 20th century; in the 1930's in Denmark, Austria, Hungary, Switzerland, Italy; not until the 1940's in Japan, Czechoslovakia, the Union of South Africa, the Netherlands, Great Britain and Germany; and in France, Belgium, and most of the U.S.S.R. after 1950. The years since 1950 have also seen the appearance of many first epidemics in tropical and sub-tropical countries: Jamaica and Costa Rica (1954); the Congo (1951); Nicaragua (1958); Singapore (1958-9); Puerto Rico (1960); and many others, including China (1952) and Argentina (1956).

Although the exact factors responsible for this pattern of behavior are still imperfectly understood in spite of more than 60 years of intensive investigation, a tremendous amount has been learned in the course of many studies in many parts of the world. During the past 10 years, with the availability of live, attenuated oral vaccine, a new chapter has been introduced and many earlier observations have been extended and confirmed. This has been possible because the oral vaccine provides a tool with which

to study experimental epidemiology in man, a unique opportunity in the annals of infectious disease research.

MODES OF SPREAD

The evidence clearly indicates that poliomyelitis is a highly contagious infection spread by human association. It is probably as infectious as measles, but unlike measles, the main source of infection is not the frank

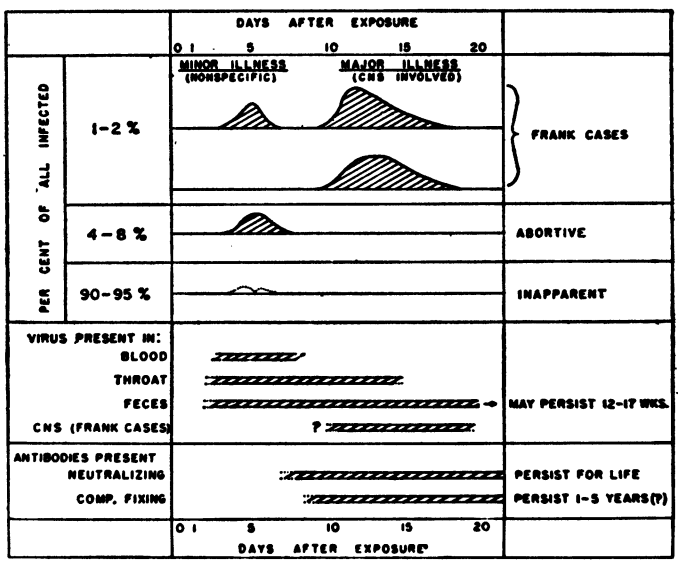

FIG. 1. Schematic diagram of the clinical and subclinical forms of poliomyelitis, correlated with the times at which virus is present in various sites, and the development of antibodies. (Redrawn from Paul, J. R.[1])

case (paralytic or nonparalytic), but rather the mild or completely inapparent infection. The relative epidemiological importance of clinically apparent and inapparent cases is indicated by the estimated ratio of cases to infections[1] (Fig. 1). Thus in epidemics it has been estimated that only 1-2 per cent of infections are manifested by clinical signs diagnostic of poliomyelitis. Another 4 to 8 per cent have nonspecific "minor illnesses," and the majority, 90-95 per cent of infections, are completely inapparent. The ratio of infections to cases varies not only in relation to the virulence of the strain, but according to the age of exposed susceptibles: in young children there are probably closer to 1,000 infections for each paralytic case, while in adults this may be only 75 to 1. In any event, no matter which

form the infection takes, the presence of virus in blood, throat, and feces is similar, as is the duration of fecal excretion. The development and persistence of antibodies, both neutralizing and complement fixing, is also identical regardless of whether the infection is a severe paralytic one, or produces no symptoms or signs whatever.

As with so many contact infections, the exact manner in which polioviruses are transmitted from one person to another is imperfectly understood. Close association, however, such as exists in the family setting, is important in giving rise to contact infections.[6] The oropharynx has been established as the portal of entry and infection is readily induced with vaccine strains by either ingestion or swabbing of the throat. The main portal of exit is the intestinal tract, and large quantities of virus can be found in the feces often for many weeks and occasionally for many months. Excretion from the throat is more difficult to demonstrate: the quantities present there both in natural and in vaccine induced infections are smaller, and isolation from saliva has been accomplished only very rarely. Whether virus travels from the pharynx of one person to the oropharynx of another, or whether the fecal-oropharyngeal circuit is the major one, has not yet been firmly established. Epidemiologic evidence indicates that a case is most infectious during the early phase of infection, sometime before onset of symptoms or in the first few days of the clinical disease. This coincides with the rather brief period in which virus can be demonstrated in the throat, a fact which has led some to conclude that the pharyngeal-oropharyngeal route is the more important, despite the prolonged period of excretion from the intestinal tract. However, although the evidence is not conclusive one way or another, there is perhaps more data to support the view that poliomyelitis is an enteric infection spread primarily by contaminated excreta. Thus a poor sanitary environment is conducive to its dissemination, a feature which does not have a parallel in infections spread by the respiratory route.[7] It is evident also that the period of infectiousness of poliomyelitis parallels closely the period of maximum fecal excretion of virus, when titers of 10^4 to 10^6 tissue culture infective doses (TCD_{50}) per gram of stool are usual. Gard has pointed out that the reduced capacity of the child over two years of age to infect his contacts coincides with the age at which toilet training normally occurs.[8] Furthermore, it has been shown that in an environment with heavy fecal contamination such as in an institution for retarded children and young adults, far more spread of attenuated vaccine virus occurs than among normal individuals in a more sanitary environment.[9,10] In addition, studies with oral vaccine have indi-

cated that spread from vaccinees to contacts occurs even though no demonstrable virus is present in the throat[11] and in some instances when throat infection has been completely bi-passed by feeding virus in capsules.[12] Significant multiplication of attenuated strains in the throat, in fact, seems to be related to vaccine dosage, and only when large amounts (10^6 to 10^7 TCD_{50}) are administered has virus been recovered regularly from throat swabs.[13, 14, 15] With virulent epidemic strains of much higher infectivity, however, smaller doses are doubtless required, and spread via pharyngeal secretions is, therefore, more probable under these circumstances. Taking all the evidence together, the fecal-oral route seems the more important one, although direct pharyngeal-oral pharyngeal spread may also play a role, particularly in epidemic situations.

Extrahuman sources of poliovirus spread. These have never been regarded as being of particular importance. Although many animal and arthropod hosts collected in nature have been tested over the years, only flies and cockroaches have yielded polioviruses.[1, 16] Flies have been trapped and examined during epidemic and endemic times, and it is clear that various species (particularly the fecal-feeding ones) can be heavily infected in nature with various enteroviruses and can contaminate food with poliovirus. Recent precise quantitative studies by Gudnadóttir[17] even indicate that virus can multiply to some extent in at least one species of fly, and thus mutation in the fly is conceivable. Despite these varied pieces of information, however, the role of flies in dissemination of polioviruses has not yet been clarified. It has been postulated that they may act as mechanical vectors particularly in highly endemic tropical areas with poor environmental sanitation. It is obvious however that flies are not essential to dissemination of polioviruses, since epidemics have occurred in arctic areas under climactic conditions which preclude the presence of these insects.

The extent to which flies may be contaminated in nature with various enteroviruses has been documented recently in connection with oral vaccine trials in Arizona[18, 19] and in Costa Rica.[20] Flies were examined in an effort to determine whether or not they pick up vaccine strains, and perhaps can then act as supplementary vaccine disseminators. Figure 2 shows the isolation of polioviruses from vaccinees and from flies in Costa Rica during the same pre- and post-vaccinal periods. The patterns are more or less parallel. The lower part of the chart indicates the variety of other enteroviruses which were picked up from flies. All of these were also isolated from children during the same period. Some of the poliovirus

strains from flies had genetic markers like the vaccine strains, while others were classified as probably "wild." The interpretation of the findings is difficult, however, and at this stage we are still unable to fit together the data in a satisfactory manner or to assess the importance of flies in the over-all epidemiological picture.

INCUBATION PERIOD

In relation to spread of virus the length of the incubation period is of considerable interest. On the basis of observations on illnesses developing

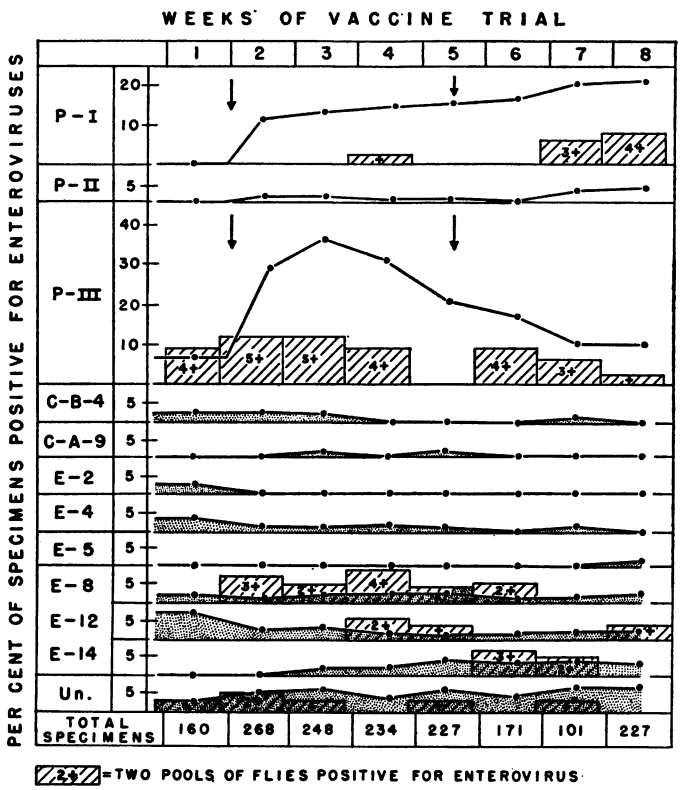

FIG. 2. Enterovirus excretion rates in vaccinees and contacts; concurrent enterovirus isolations from pools of flies. The vertical arrows indicate the times at which the first and second doses of trivalent vaccine were given to the index children. The signs (+, 2+ etc.) in the blocks with diagonal hatching indicate the numbers of pools of flies from which enteroviruses were isolated coincidentally with isolations from rectal swabs. The non-poliovirus enterovirus rates are distinguished by stippling. Column to the left indicates agents isolated; P, poliovirus; CA & CB, Coxsackie A & B viruses; E, ECHO; Un, untypable. (From Paul, J. R., *et al.*[20])

in contacts of known cases, and to some extent on the experimental disease in monkeys, the usual estimate of the incubation period is given as 7 to 14 days with extremes of 5 and 35 days. In general, these intervals refer to the time between exposure and the appearance of the CNS or second phase of the disease, i.e. the so-called "major illness." The interval between exposure and the first phase ("minor illness") has on the other hand long

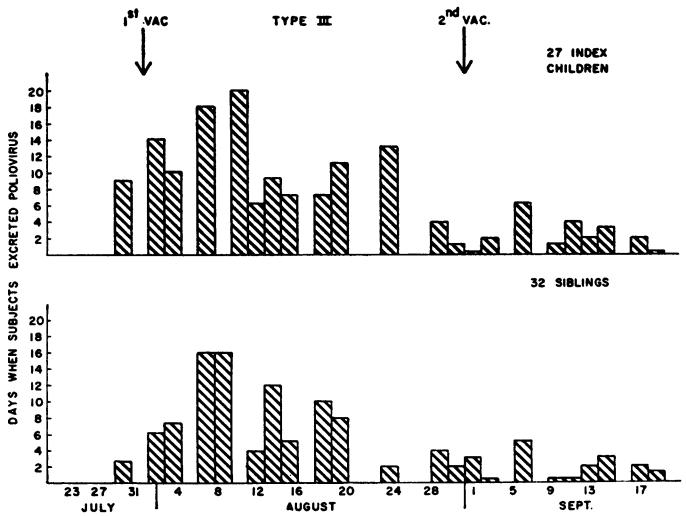

FIG. 3. A comparison of the days on which 27 index children excreted type III poliovirus with the days on which 32 siblings contacts excreted this same virus. The siblings' infections follow quite closely those of the index children. (From Paul, J. R.: The spread of attenuated polioviruses among household contacts. In *Poliomyelitis. Papers and Discussions Presented at the Fifth International Poliomyelitis Conference, Copenhagen, Denmark, July 26-28, 1960.* Philadelphia, J. B. Lippincott Co., 1961.)

been recognized as being much shorter.[21] Just *how* short the period can be for the establishment of infection was not appreciated until it was possible to study the question in persons infected with oral vaccine strains.[13,14] It soon became apparent that within 24 to 48 hours after vaccination, multiplication occurs, and virus excretion in throat and stools can be observed. This pattern is now well established, and it would appear that the true incubation period of the infection is usually 1-3 days, rarely 4-5 days or more. However, the interval between initiation of infection and appearance of CNS signs may be as long as several weeks, which accounts for the great variation in the incubation period of the *disease*.[21]

In line with an exceedingly short incubation period is the evidence of the remarkable speed with which infection can spread from one individual to

another. This has been demonstrated in a number of investigations including a recent one by Paul, *et al.*,[20] in which it was found that when the first post-vaccinal specimens were collected 4 days after one child in each family had ingested trivalent vaccine (Lederle-Cox), both the vaccinees and their non-vaccinated siblings were excreting polioviruses. As shown in Figure 3, within 5 days of vaccination of the index child, 63 per cent of susceptible sibling contacts were excreting type III poliovirus, the most infectious of the three types contained in the vaccine; the subsequent patterns of excretion by vaccinees and contacts were similar.

Data of this type would seem to make it unnecessary to invoke the earlier concept of poliomyelitis as being, possibly, a "place infection." According to this latter view, the time relationships in family outbreaks in which paralytic disease and minor illnesses occurred in various members all within a matter of a few days, suggested a common source of infection for the entire group. The newer observations on spread in both institutional settings[9] and natural environments[11,20] point rather to an infection which is introduced by one person but spreads at once to infect susceptible contacts within a few days.

FACTORS AFFECTING DISSEMINATION

Immune status. In general, the circulation of wild polioviruses in a community is dependent upon the availability of enough susceptible hosts in which to multiply. Neither susceptibility nor resistance to infection are simple or absolute, however, as investigations with oral polio-virus vaccines have emphasized.[9,18,20] This is illustrated in Figure 4 which compares the duration of vaccine virus excretion by antibody negative—i.e. susceptible children, and those who have naturally acquired antibodies and immunity—resistant children.[20] It is apparent that far more virus was excreted for far longer periods by susceptible than by resistant children. As has been noted by others, among the resistant children there was a roughly inverse relationship between height of antibody and virus excretion.[11,44]

Oral vaccine trials have also brought out the complexities of the immune mechanisms in poliomyelitis: it has become apparent that humoral immunity is by no means the whole story, and that there exists a so-called "local resistance" or tissue immunity which seems to be induced by actual multiplication of virus in the intestinal tract.[9,18] The nature of this intestinal resistance is not clearly understood. It may be associated with some cellular alteration, or possibly a local concentration of antibody in

extracellular fluids. In any event, its presence is of equal if not greater importance than serum antibodies in providing a barrier to reinfection.

The inactivated vaccine, since its introduction in 1955, has greatly reduced the incidence of paralytic poliomyelitis in countries in which its use has been extensive. This has been accomplished by inducing serologic immunity in vaccinees, which prevents CNS invasion. However the extent

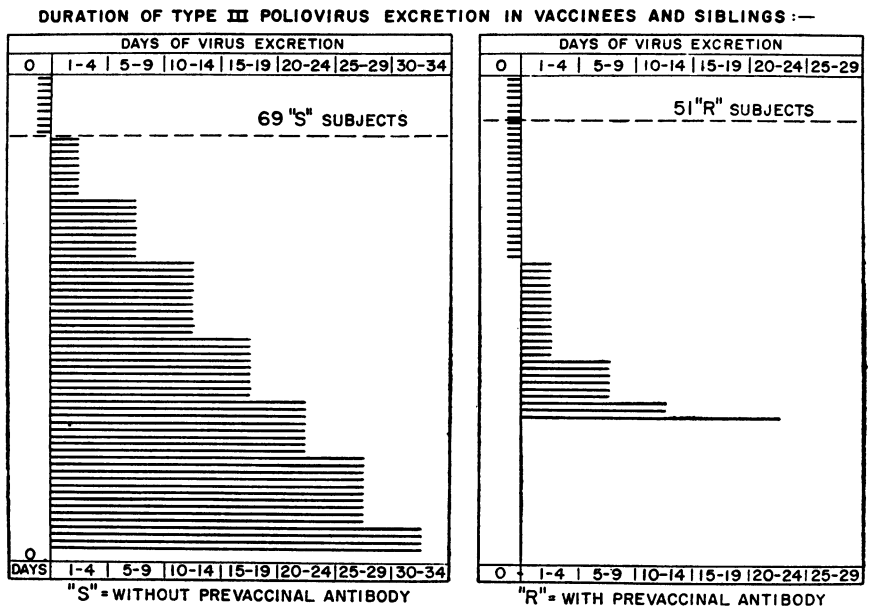

FIG. 4. Duration of type III poliovirus excretion in vaccinees and siblings infected by contact. Each line represents one child. The left panel illustrates the situation found in 69 susceptible (S) subjects, and the right panel the situation in 51 resistant (R) children. (From Paul, J. R., *et al.*[20])

to which the inactivated vaccine has suppressed the circulation of wild polioviruses and the incidence of inapparent intestinal infection is not well documented. That it has had some effect in this connection seems definite,[22] but there is also evidence that wild viruses have continued to spread and have even caused epidemics in certain well-vaccinated communities.[23] This is not surprising, for although the vaccine induces antibody formation, it does not provide a significant barrier to intestinal infection with either wild or vaccine strains. In contrast, inapparent infection, either natural or oral vaccine induced, does result in a marked degree of resistance to intestinal multiplication of virus, although in neither case

is this resistance absolute.[9,11,24] Reinfection thus can and does occur to some extent under natural circumstances of exposure, and it can be induced readily with oral vaccine strains if a large enough dose is administered. However, when reinfection occurs, virus excretion is limited both in amount and duration, and reinfected persons are ineffectual virus disseminators.

On the basis of these considerations it is clear that the maximum barriers to spread of wild polioviruses in any community can be achieved by inducing both humoral immunity and intestinal resistance in as large a segment of the susceptible population as possible. Oral attenuated poliovirus vaccine offers a means of accomplishing this, but it is necessary to vaccinate a high proportion of the susceptibles in any given area (at least 85 per cent) in order to achieve adequate community protection against invasion by wild polioviruses.[45]

Age. Oral vaccine studies have also yielded important information in terms of identifying precisely the most likely spreaders of polioviruses. It is not surprising that age has a profound effect, and that young children, particularly those under two, besides being the most susceptible to infection, turn out to be the most successful disseminators of polioviruses. Thus Gard,[8] using the Chat strain of type I vaccine, found that whereas only 4 per cent of orally vaccinated individuals above the age of two years infected susceptible contacts, more than 40 per cent of children aged six months to two years did so. Similar results have been reported by Fox, *et al.*[11] and others.

These observations bring into sharp focus the importance of adequate immunization of this youngest age group in any vaccination program. In any population, pre-school children constitute the bulk of susceptibles (except perhaps in remote arctic areas) and they are the major spreaders of virus, acting as the source of infection for susceptible older children and adults. They have also come into prominence once more as the chief sufferers of paralytic poliomyelitis, in the United States at least. In this country, school age children have been the ones most adequately immunized with inactivated vaccine, but efforts to reach young children have been less successful. Outbreaks of epidemic poliomyelitis in the past five years have, therefore, been concentrated in the 0-4 age group,[25] whereas before inactivated vaccine was introduced, the peak incidence occurred in the 5 to 14 year olds.

Interfering enteroviruses. The important role which other enterovirus infections have in interfering at times with poliovirus infections has been

demonstrated in oral vaccine studies in several countries. In tropical and sub-tropical areas such infections are common the year round, particularly in young children. Thus, in Mexico, Ramos-Alvarez, *et al.* have shown that "takes" with poliovirus vaccine strains can be reduced almost 50 per cent in the presence of high infection rates with other enteroviruses.[26] The complexities of the interference mechanisms are great; the evidence indicates that not only the nature of the agent causing the pre-existing infection, but the time in the course of such an infection, the amount of virus being

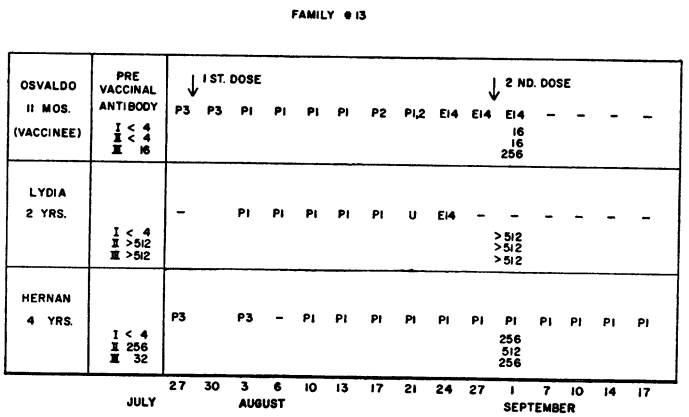

FIG. 5. Virus excretion by vaccinee and siblings in a family free of enterovirus infection at the time that trivalent vaccine was administered. P = poliovirus. E14 = ECHO 14 virus. U = untypable agent.

excreted, and the dose of poliovirus constituting the exposure, are all important determinants. Thus, if oral vaccine is given very early in the course of another enterovirus infection, it commonly obliterates the latter and a poliovirus infection is readily established. The same is true if exposure occurs at the end of another infection. However, if vaccine is fed in the middle of a vigorous infection in which large amounts of virus are being excreted, the attenuated poliovirus often fails to gain a foothold: no excretion and no antibody response occur. These patterns have been shown by Drozdov and Shirman[27] and Hale, *et al.*[48] in connection with interference between wild and vaccine strains of poliovirus; others, including ourselves, have made similar observations on interference by various enteroviruses.[20] Figure 5 depicts the course of events in a family in which one child only was fed trivalent vaccine (Lederle-Cox) twice. In the absence of other enterovirus infections, the vaccinee became infected with all three types and

rapid spread to susceptible siblings occurred. In another family, however, (Figure 6) in which ECHO 12 and an unidentified enterovirus were circulating, no infection and no spread of the vaccine strains was detected. In a third family (Figure 7) in spite of the presence of infection with ECHO 2, ECHO 12 and an unidentified agent, the highly infectious poliovirus

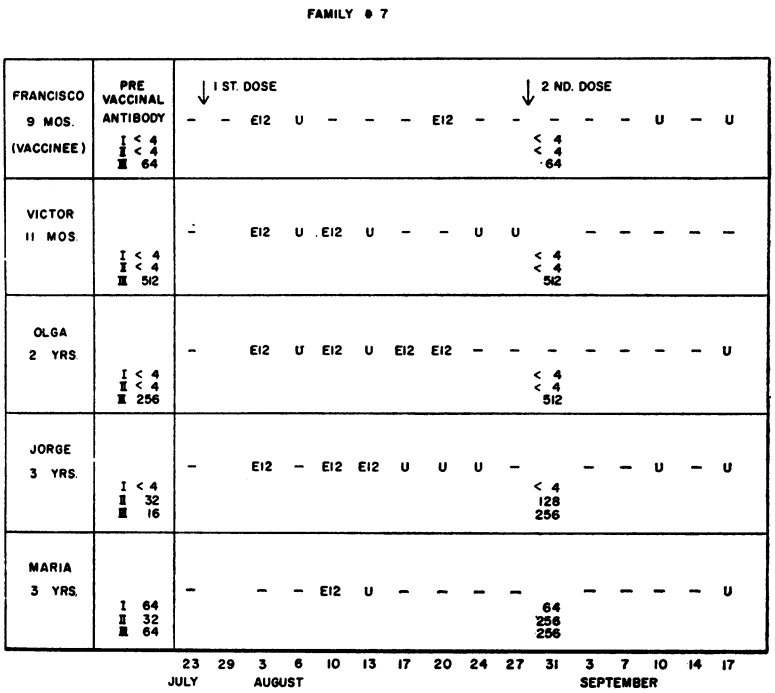

FIG. 6. Failure of vaccine strains to become established in a family already infected with ECHO 12 and an untypable (U) agent. (From Paul, J. R., *et al.*[30])

type III component of the vaccine was able to get through, infect the vaccinee, and spread to susceptible siblings. It is likely that similar dynamics of infection are involved in the case of natural exposure to wild polioviruses in the presence of infection with other members of the large and heterogeneous enterovirus family.

Environmental factors. The important impact of the sanitary environment on the dissemination of poliovirus infections was elucidated first in connection with serologic surveys.[1] Thus in populations living under conditions of poor sanitation and hygiene, poliovirus (as well as other enteroviruses) have been found to be widely disseminated, with infection and

antibody responses developing in the first few years of life in close to 100 per cent of children. This results in a highly immune population in which only the youngest children are susceptible to primary infection; in such a community epidemics are unknown, and paralytic cases are relatively few and limited to the infantile age group. In contrast, in populations with high standards of living, exposure, infection, and antibodies appear at increasingly

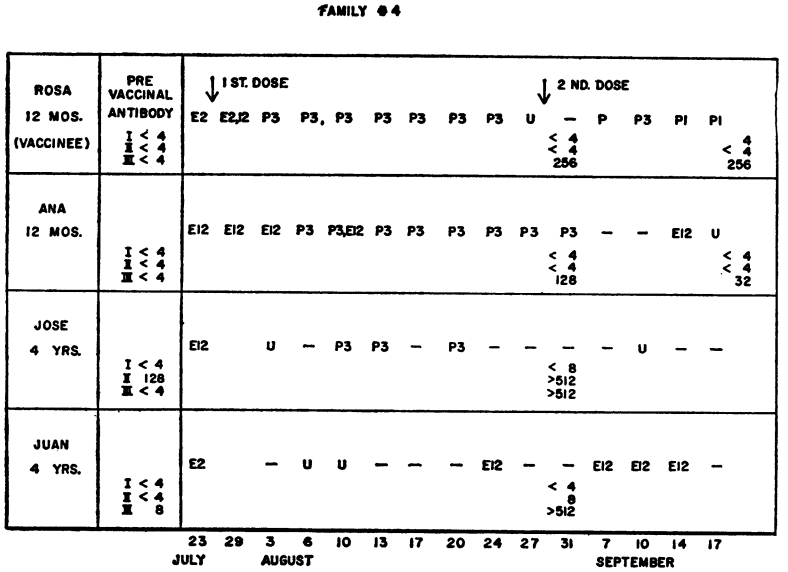

FIG. 7. Infection and spread of type III poliovirus vaccine in the presence of other enterovirus infection. E2 and E12 = ECHO 2 and 12. U = untypable agent. (From Paul, J. R., *et al.*[20])

older ages. This leaves a considerable segment of the population susceptible, so that when a virulent strain appears, an epidemic may result. The changing age incidence of paralytic poliomyelitis in economically advanced countries is well illustrated by the experience of Sweden, where 57 per cent of cases in the 1953 epidemic occurred in the age group over 20 years; in contrast, in the Swedish epidemic of 1911, the corresponding figure was 12 per cent.[3, 4, 29]

The close tie between social and sanitary conditions and the appearance of epidemics in a given population has also been reflected in an inverse relationship between infant mortality and epidemics. Payne[28] and Paul[20] have presented analyses of the history of poliomyelitis in various parts of

the world in which it has been shown that when the infant mortality falls to a level of 70-80/100,000, epidemics of poliomyelitis are likely to make their appearance. This is not a direct relationship but it would seem that infant mortality is a rough measure of hygienic standards, and the decrease in rate is a reflection of improved sanitation. With this improvement comes decreased circulation of enteric agents, including polioviruses, fewer immunizing infections in the early months of life, and consequently a build-up of susceptibles among whom an epidemic may start should a virulent strain of poliovirus begin spreading. With these facts in mind, a campaign of immunization against poliomyelitis becomes a particularly important feature of health department planning wherever and whenever improved environmental sanitation is causing a rapid fall in infant mortality and a build-up of susceptibles. In this situation, the problem of vaccination is relatively simple since adequate levels of immunity can be maintained in the community if only the youngest children are given oral vaccine—i.e. those under five, and particularly those under two years of age.

Nature of the infecting strain. Marked differences in the virulence of naturally occurring strains of polioviruses have been noted. It is apparent that in most parts of the world, endemic strains of relatively low virulence circulate widely and often quite silently, particularly among young children. During this process, mutations are occurring continually, and occasionally epidemic strains of high virulence arise. Such strains are characterized not only by their invasiveness and affinity for the CNS, but also by their extraordinary capacity to spread with ease and rapidity to susceptible members of the population. Wild endemic strains, on the other hand, spread less well than do epidemic ones, and attenuated vaccine strains have an even more limited momentum: their dissemination often terminates while there are still susceptibles avaialble.[11] Although less data is available on non-polioenteroviruses, it is clear that their circulation is governed by more or less similar rules. In general the greater the disease producing potential of a strain, the greater is its spreading potential, whether it be a virulent poliovirus, or an ECHO 9 such as swept Europe and the United States in 1957 and 1958.

From the foregoing discussion it is apparent that many factors besides strain virulence are involved in precipitating first epidemics of poliomyelitis and in bringing about their recurrence. It is probable that at different times and different places environmental aspects, host resistance, and virulence of the virus are of greater or lesser relative importance. But

since epidemic strains are presumed to arise by a process of mutation, the greater the circulation of polioviruses the more likely is the emergence of a paralytogenic variant which also has the capacity to spread rapidly. The conditions in tropical and sub-tropical areas where continual high rates of infection prevail are optimum for this to occur. Once such a strain has evolved, it may precipitate an epidemic in its place of origin if enough susceptibles are available at the time; and it may also be the source of spread to other areas, if circumstances are right for its transport—i.e., if virus carriers with inapparent infections are available to introduce it elsewhere. A possible train of events such as this was proposed by Gear in 1948[30] to account for the sudden appearance of first epidemics in Africa in the 1940's. These all took place on the overland route from South Africa to the Middle Eastern theater of the war. Gear concluded that virulent strains had been introduced probably by allied troops ("susceptible immigrants") who had become infected in the Middle East where the strains had originated. Extensive troop movements resulted then in spread throughout Africa, and to Mauritius and Malta as well. The new strains were highly virulent and probably differed antigenically in some subtle way from the endemic ones which had been circulating previously in these areas. Conceivably, rapid passage in susceptible hosts further enhanced their virulence, and the result was a series of severe epidemics among the susceptible age groups in each country in turn.

It is reasonable to suppose that the great movements of military and civilian populations which accompanied and followed World War II probably did provide opportunity for introduction of new strains into various parts of the world. Voroshilova[31] has mentioned this as a likely contributing factor in the series of epidemics which began in the U.S.S.R. in the 1950's. Epidemic poliomyelitis has also appeared for the first time in many tropical countries in the past 10 years, including Latin America.[29] While changing socio-economic patterns, improved sanitation, and falling infant mortality rates are undoubtedly exerting their influences, the possibility that new strains have arisen and been disseminated widely as a result of increased travel also deserves reconsideration, as has recently been emphasized by Sabin.[5] In general, once epidemics start in a country, they continue; if unusually virulent strains are now widely prevalent in developing countries of the world, the need for immediate and extensive immunization programs in these areas is greater than ever. The situation may indeed be considered critical.

UNSOLVED PROBLEMS

Throughout the above discussion, emphasis has been on poliomyelitis, the most extensively studied of the enterovirus infections. This approach would seem to have some reason, since the available evidence indicates that the epidemiology of this entire family of agents is similar: the same factors are involved in terms of virus dissemination and the same patterns as far as susceptibility and immunity.[32-34] The unanswered questions which remain concerning the epidemiology of poliomyelitis and other diseases caused by enteroviruses are also similar. It is clear, for example, that in temperate climates these agents are far more prevalent in the summer season than in the winter. Why epidemics of enterovirus infection and disease have such a striking seasonal pattern remains unexplained. The agents are present the year round, and circulate silently to some extent in the coldest as well as the warmest season. Still, some as yet mysterious concatenation of circumstances (probably involving the virus, the host, and the environment) seems necessary to bring them out in the open, as it were.

Another major question involving the entire enterovirus family concerns the possible effects of mass oral vaccination on the ecology of these agents. If an entire population has been immunized and offers a relatively solid block of resistance to the spread of wild polioviruses, what effect, if any, will this have on the circulation and the disease producing potentials of other enteroviruses? This question is an open one at present. As has been pointed out by Dalldorf[35] it can perhaps be answered best by our colleagues in the U.S.S.R. who have carried out the most extensive oral vaccine programs, reaching close to a staggering 100,000,000 persons. Since the various Soviet Republics represent diverse populations and environmental features as exemplified by the Baltic republics on the one hand, and the Central Asian ones at the opposite extreme, it should be possible to obtain answers in relation to various epidemiological settings. Will reduced circulation of wild polioviruses occur and persist indefinitely? Will other enteroviruses be more prevalent, or less so, or unaffected by a reduction in circulating polioviruses? With these questions in mind, the Yale Poliomyelitis Study Unit has followed one small New England city of 30,000 population in which 90 per cent of the child population under 18 years, consisting of 10,000 individuals, was vaccinated in 1961 with the Sabin strains of oral vaccine. The method of surveillance used was isolation of virus from sewage, which we have found to be a more sensitive indicator of enterovirus circulation than rectal swab surveys. Specimens were collected at regular intervals from various areas of the city, and to our surprise it was found

TABLE 1. VIRUS ISOLATIONS FROM SEWAGE BEFORE AND AFTER ORAL POLIOVIRUS VACCINE ADMINISTRATION, JAN.-DEC., 1961

	*Middletown**							*Portland**						
	No. samples tested	*Per cent Pos.*	*No. of strains isolated***					*No. samples tested*	*Per cent Pos.*	*No. of strains isolated***				
			P1	*P2*	*P3*	*ECHO*	*Cox. B*			*P1*	*P2*	*P3*	*ECHO*	*Cox. B*
Jan. 3-24 (pre-vaccinal)	17	62	0	0	0	1	9	5	80	0	0	4	0	0
Jan. 31-7 Mar. (after type 1)	23	100	23	0	0	1	0	6	100	6	0	1	0	0
Mar. 15-25 Apr. (after types 2+3)	22	100	5	21	21	0	0	6	100	2	5	5	0	0
May-June	36	92	2	22	29	2	1							
July-5 Sept.	40	85	3	6	5	12	14	10	100	0	4	1	5	4
Sept. 11-21 Nov.	43	93	0	0	0	15	26	10	100	0	0	0	10	2
Nov. 26-28 Dec.	20	80	2	0	4	7	7	5	60	0	0	2	1	

* In Middletown, 8,052 of the 35,300 persons living in the 4 areas sampled had received oral vaccine; in Portland, the "control" city across the river, 19 of 4,000 were vaccinated.

** P1, P2, P3 indicates poliovirus isolations of the three types. Cox. B refers to Coxsackie B viruses; types 2-5 were recovered.

that *before* vaccination was begun, in the middle of an extremely cold January, at least six different enteroviruses (including type III poliovirus) were circulating silently in this population.[86] Immediately following the introduction of type I oral vaccine, however, the sewage was flooded with this type of poliovirus for six weeks and all else was virtually obliterated (Table 1). At the end of this time, when types II and III were administered together to the 10,000 vaccinees, type I was rapidly replaced by these other types. The latter persisted for some three months when during July, other enteroviruses, which had apparently been blotted out for the previous five months, re-appeared and took over for the next three or four months. The non-polio-enteroviruses isolated were chiefly Coxsackie B3, B4 and B5 and ECHO 4, 7, and 8. By the end of November, eight months after vaccination, type III virus re-appeared in the sewage, and in December, type I did so. Since oral vaccine had not been used after the community program terminated in the previous March the presence of polioviruses in December may represent residual circulation among new susceptibles born or immigrating into the area, or possibly some circulation of wild strains newly introduced.

The virtual obliteration of the usual enteric viral flora following massive application of oral vaccine has also been observed by Sabin in Toluca, Mexico, where trivalent vaccine was given to a population heavily seeded with enteroviruses.[87] In this situation too, the polioviruses became dominant in the weeks following vaccine administration, but after three months they were replaced by other agents and poliovirus circulation almost ceased. These two experiences in two epidemiologically dissimilar environments support the earlier findings of Žáček, *et al.*[88] and Dömök, *et al.*[89] that the vaccine strains tend to disappear a few months after community-wide administration. In both Toluca and Middletown, it was apparent that the circumstances were suitable for spread of enteroviruses, for a variety of these circulated steadily after initial apparent suppression by the vaccine strains.

Knowledge of the ultimate effects of community-wide vaccination in terms of the behavior of agents which at present seem to have a limited potential for causing serious or paralytic disease will depend on extensive laboratory and field investigations carried out in different parts of the world. In the meantime, it is challenging to speculate on the outcome. Dalldorf,[85] while emphasizing the unpredictability of ecological changes generally, has considered the possibility that a decrease in poliovirus circulation may encourage viruses like the Coxsackie B's to become more

pathogenic. There is both experimental and field evidence of antagonism between these two groups of agents; in Denmark in particular, high poliomyelitis years have been low pleurodynia (Coxsackie B) years, and vice versa. Furthermore, both Coxsackie and certain ECHO viruses are known to be capable—on occasion—of producing paralytic disease.[40, 41] Thus it is possible that they may rush into the vacuum left by the departing polioviruses, and a new breed of enterovirus disease may conceivably appear.

Reasoning somewhat similarly, Voroshilova[31] has suggested that an evolutionary gradient of neurovirulence is apparent in the enterovirus family, with poliovirus type I representing the extreme in severity, followed by the other poliovirus types, the Coxsackie B and A7 viruses, down through various ECHO types to those of lowest pathogenicity. There has not yet been enough time to determine whether the marked reduction in poliovirus circulation following vaccination will accelerate the development of greater virulence in other members of the enterovirus family, or whether as Gard believes[22] no striking change will occur. In the U.S.S.R., there seems possibly to have been some increase in paralytic disease due to Coxsackie A7 virus, at least in the Karaganda area;[43] but elsewhere there has as yet been no striking upsurge in poliomyelitis-like disease due to other viruses. As Gard has pointed out, diseases and even epidemics associated with various ECHO and Coxsackie viruses seem to follow an epidemiologic pattern similar to that of poliomyelitis, but independent of it. Furthermore, since there are so many different types of enteroviruses, the disappearance of one member—viz. poliovirus—would hardly be expected to have a noticeable effect on the rest. Their very number is probably an indication of infinite capacity for mutation, and new types with new potentialities may well arise in the future as in the past.

Definitive answers to these questions we hope—and expect—will become apparent in the next decades. But in the meantime, perhaps we should be prepared for surprises, for our knowledge of Nature is very limited.

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