# FACTORS INFLUENCING THE OCCURRENCE OF ILLNESS DURING NATURALLY ACQUIRED POLIOMYELITIS VIRUS INFECTIONS[1]

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. . . For want of knowing any other cause, epidemics were attributed, by the ancients, to the atmosphere, without any evidence; just as political and social events were believed to be occasioned by the stars. Now as people are not only exposed to the atmosphere, as soldiers in battle are to bullets, but are actually immersed in it, as fishes are in the sea, it became necessary to explain why certain persons were attacked and others not attacked, and the word predisposition was used as affording an explanation. The alleged predisposition, however, was nothing visible or evident: like the elephant, which supports the world, according to Hindoo mythology, it was merely invented to remove a difficulty.

<div align="right">John Snow (1853)</div>

Paralytic poliomyelitis has always been a relatively rare disease in spite of the fact that poliovirus infections are common in the United States and in most other countries. More than 99 per cent of these infections cause no paralysis.

This paper presents an analysis of factors that influence the course of a primary poliovirus infection in an unvaccinated individual. The central question is: What determines whether an infected person is like the 99 per cent who experience no real harm or is one of the unfortunate few who suffer paralytic illness?

The discussion is focused first on the virus, second on the status of the individual, and third on the circumstances under which infection occurs. No attempt is made to present a comprehensive documentation of all important information on the problem. Relatively little space is devoted to some of the well-established and generally accepted concepts; greater emphasis is placed on those aspects that, in my opinion, are of

more significance than is indicated by the little attention accorded them in most discussions of the subject.

Arguments will be made for the contention that the virulence of the virus causing the infection is usually of less importance than some, as yet undefined, characteristics of the infected person. It will also be suggested that environmental conditions related to the conditions under which virus spreads may be of substantial importance.

## VIRULENCE OF THE INFECTING VIRUS

There is imposing epidemiological evidence to support the contention that poliomyelitis virus strains as they occur in naturally infected human populations may be of relatively high virulence for man on one occasion and of much lower virulence at other times. One of the largest epidemics of paralytic poliomyelitis in this country was that of 1916 in New York City. More than 9,000 persons were paralyzed; this included nearly 2 per cent of all infants 1 and 2 years old (Lavinder, Freeman, and Frost, 1918). Scrutiny of the age-specific attack rates shows that, during the years preceding this epidemic, poliomyelitis virus was also prevalent; in fact, an estimated 30 per cent of all susceptible children were annually infected with virus antigenically related to that which subsequently caused the epidemic of 1916 (Sample and Evans, 1955). Yet paralytic disease was so infrequent before 1916 that poliomyelitis was not regarded as of sufficient importance to make it a reportable disease. There can be little doubt that the virus prevalent in New York City in 1916 was of high virulence and that an unusually high proportion of those infected were paralyzed that year (Sample and Evans, 1955).

Examination of the reported incidence of poliomyelitis for the entire United States shows changes from year to year that must be attributed in part to shifts in virulence and/or infectivity of the virus. As shown in table 1, 1916 and 1952 were years of high death rates. During the 5-year period from 1948 to 1952 the annual polio-

## TABLE 1*

*Number of poliomyelitis deaths reported per 100,000 population in 1916 and during two 5-year periods*

| Year | Deaths Reported per 100,000 Population | Year | Deaths Reported per 100,000 Population |
|------|------|------|------|
| 1916 | 9.4 | 1948 | 1.3 |
| 1938 | 0.4 | 1949 | 1.8 |
| 1939 | 0.6 | 1950 | 1.3 |
| 1940 | 0.8 | 1951 | 1.0 |
| 1941 | 0.6 | 1952 | 2.0 |
| 1942 | 0.4 | | |

\* Data from Howe and Wilson (1959).

## TABLE 2*

*Maximal age-specific attack rates for paralytic poliomyelitis in some severe outbreaks*

| Place | Date | Age in Years | Population | Paralytic Cases† | Attack Rate in Per Cent |
|-------|------|------|------|------|------|
| New York City.. | 1916 | 1 | 112,200 | 2,062 | 1.8 |
| Huskerville, Nebraska..... | 1952 | 1–10 | 347 | 16 | 4.6 |
| Car Nicobar‡... | 1947 | 1–35 | 8,722 | 566 | 6.5 |
| Chesterfield In-let, Canada... | 1949 | All | 275 | 57 | 21.0 |
| Maguse River, Canada....... | 1953 | All | 18 | 10 | 55.0 |

\* Data are from Lavinder *et al.*, 1918; Bancroft, Engelhard, and Evans, 1957; Moses, 1948; Peart, 1949; Johnsen and Wood, 1954.

† In some cases, as in New York 1916, a small proportion of nonparalytic cases may be included in the available data.

‡ Age-specific population data are not known. Attack rate is calculated from total population.

myelitis death rates were on the average more than double those of the corresponding years one decade earlier. The causes of these differences are not firmly established, but it seems probable that prevailing virus strains differ significantly in virulence and/or infectivity from year to year. There is no reason up to the present to ascribe periods of high poliomyelitis incidence to the appearance of new antigenic strains of virus. The age distribution of the 1916 epidemic demonstrates that the virus prevalent in 1916 was effectively controlled by immunity induced by poliovirus infection in earlier years.

It is of interest to inquire how virulent poliomyelitis virus can be. That is, in its most virulent form and under optimal conditions for disease production what proportion of infected persons suffer paralytic illness? The data in table 2 are from some of the most severe outbreaks on record.

In these epidemics it is probable that close to 100 per cent of the susceptible population was infected. It is obvious that the most virulent virus strains infecting under optimal conditions do not cause paralytic illness in all infected persons. In populations of moderate size, paralytic attack rates of more than 20 per cent are unusual but do occur. In larger populations a paralytic attack rate of 5 per cent is exceptional.

The significance of virulence of viral strains as a factor in the apparently low rate of paralytic poliomyelitis in countries with primitive sanitary standards is not clear.

Hammon and his associates (1955) as a result of their extensive studies of enteric viruses in the Philippines were led to speculate on the possibility that relatively nonpathogenic strains are more prevalent in countries where a high propor-

tion of the population is immune. "If passage through immunes has led to selection of such strains, we might then speculate further that 'epidemic strains' such as the type 1 strain of 1952 might have been imported, perhaps from the United States, where many opportunities occur for passage of strains from susceptible to susceptible in series." Gear (1955) has expressed similar ideas.

Others have attributed the apparently low incidence of clinical poliomyelitis in such countries either to under reporting or to the fact that initial poliovirus infection occurs in infants while they are protected from paralytic disease by maternally conferred passive protection (Howe and Wilson, 1959). The latter concept has usually been supported by data showing a high incidence of primary infection during the first 2 or 3 years of life. There are relatively few data showing a high infection rate during the first 4 to 6 months of life when maternal antibodies can be expected to protect (Sabin, 1951).

*Characteristics of Virulent Strains of Poliovirus*

It can be presumed that naturally occurring populations of poliovirus in an infected individual are not genetically pure. It can be argued further that disease of the nervous system occurs only in those persons in whom viral mutations to neuro-

virulence occur early in the course of the infection in the alimentary canal. The limitation of this concept, as a useful explanation of this problem, is indicated by the following facts: 1. Virus derived from the central nervous system has not been shown to be of greater virulence, for monkeys, than that obtained from feces. 2. Most infections resulting from feeding cynomolgus monkeys or chimpanzees infected brain tissue fail to cause paralysis. 3. A variety of individual conditions unlikely to alter mutation increases the likelihood that an infected person will experience paralytic disease. 4. Certain environmental conditions increase the incidence of paralytic illness.

In recent years there has been a growing interest in defining viral characteristics or markers that may be correlated with virulence of poliovirus. According to Burney (1959), the markers checked on virus strains under trial as a live-virus vaccine in 1959 included neurovirulence for monkeys, capacity to grow when the amount of bicarbonate in the medium is reduced (d marker), growth in a stable line of monkey cells (MS), and growth at 40 C (t).

It is well known that poliovirus strains, freshly isolated from human hosts, differ in their capacity to produce disease in monkeys. Unfortunately, the evidence fails to show a good correlation between monkey virulence of freshly isolated poliovirus strains and their apparent virulence for man. Although poliovirus strains of low virulence for monkeys have been isolated from persons with inapparent infection (Ramos-Alvarez and Sabin, 1954), there is no consistent difference in monkey virulence between strains from severe epidemics and those from symptomless carriers in communities with few if any clinical cases.

Vogt, Dulbecco, and Wenner (1957) discovered one of the earliest and most useful markers *in vitro* related to virulence of mutant poliovirus strains. They found that a poliovirus strain of low virulence (LSc) failed to produce plaques or that plaques were small and were delayed in their appearance in tissue cultures under certain conditions entirely satisfactory for plaque production by the virulent parent strain of virus, Mahoney, from which LSc was derived. The crucial factor was the concentration of sodium bicarbonate in the agar overlay. Marked differences were evident if the concentration of bicarbonate was approximately one-fourth of the usual amount but were completely lost if the bicarbonate was increased.

This characteristic, the "d" marker, has been studied with many poliovirus strains. It is of great value in following the genetic stability of attenuated poliovirus strains used as oral vaccines. Tests of naturally occurring virus in human feces indicated that those strains associated with paralytic illness usually exhibit the d+ character. Strains from silent infections occurring in communities in which there is little disease may be either d+ or d (Hsiung and Melnick, 1958). There is no evidence that epidemiologically mild strains are generally different from naturally occurring virulent strains with respect to the d character.

Kanda and Melnick (1959) showed that MS cells, a stable strain of monkey kidney cells, can be used to distinguish between virulent strains of poliovirus and attenuated substrains that have lost virulence during selection and propagation in the laboratory. Like the d marker, the MS character has not been shown to provide a consistent difference between naturally occurring strains from paralytic cases and those obtained from symptomless carriers in communities free of clinical poliomyelitis.

Lwoff (1959) has studied the effect of temperature on the rate and extent of multiplication of poliovirus strains. In general, strains able to multiply rapidly and to produce high yields of virus at 40 C were virulent when injected into the brains of monkeys. Strains not able to multiply rapidly and extensively at this temperature were of low virulence.

To my knowledge this "t" marker has not been tested with the virus strains essentially as they occur in nature and selected on the basis of epidemiological histories indicating low virulence in man.

Sabin (1955), using an entirely different approach, provided what appears to be an excellent explanation for the inability of some laboratory strains of low virulence to cause paralytic infection. He showed that the LSc strain and some other strains derived by selection for low virulence during prolonged passage in the laboratory did not spread through the body of infected animals in the usual fashion. Chimpanzees inoculated intramuscularly did not develop viremia and did not excrete virus in their feces. Virus unable to spread cannot reach the central nervous system and, therefore, is harmless.

We have been interested to see whether markers of the sort described in the preceding paragraphs would differentiate between poliovirus strains isolated during a severe epidemic and

strains obtained when there was little or no illness in a community. Our studies and those of others have given essentially negative results. In this work we used strains of type 1 poliovirus from the Chesterfield Inlet epidemic, which was shown in table 2 as one of the world's most severe outbreaks.

For our studies we used virus in extracts of feces collected several weeks after the epidemic from patients with paralytic illness and their close contacts. The feces were sent to us by Dr. F. P. Nagler of the Canadian Laboratory of Hygiene. These virus strains were compared with type 1 poliovirus in extracts of fecal specimens supplied to us by Drs. John Fox and Henry Gelfand, who collected them from healthy subjects in their family studies in several communities in Louisiana. The feces were collected during a year when there was very little clinical poliomyelitis in the community.

The virus strains from Chesterfield Inlet showed no consistent difference from the Louisiana strains in plaque-forming ability on monkey kidney cells in the presence of medium with various concentrations of bicarbonate. Control tests with the Mahoney and LSc strains gave the results expected from the report of Vogt, Dulbecco, and Wenner (1957).

In view of Sabin's observations on the failure of attenuated strains to spread readily through the bodies of infected animals, we looked into the possibility that our Louisiana strains might behave similarly. For these studies we took advantage of the fact that poliovirus will localize in skin wounds of infected cynomolgus monkeys.

One square centimeter of skin was excised from each of 5 sites (figure 1). Three days later poliovirus was injected into the 3 lesions on one thigh, and the animal was placed in a restraining device to prevent him from transferring virus with his fingers from one skin site to another. Subsequently virus was assayed at appropriate intervals by collecting small amounts of the watery exudate that appeared under the scabs (figure 2).

As expected from Sabin's work, the avirulent LSc strain failed to spread from inoculated lesions to uninoculated lesions (figure 2). Tests were then made on virus from the Chesterfield Inlet epidemic. As expected, it multiplied readily and spread promptly to distant lesions.

For our present purposes the most interesting studies were those with the "Iberia" strain of



*Figure 1.* One square centimeter of skin was removed from the locations shown, three sites on the left thigh, one on the right thigh, and one on the head. Three days later poliovirus was injected into the base of the three lesions on the left thigh. Subsequent tests were made for local increase of virus and for spread of virus to the lesions on the right thigh and the head.

virus. This was one of the Louisiana strains. Although this virus was avirulent epidemiologically, it was fully as active as other strains in multiplying and spreading in the body, as shown in figure 2. Viremia occurred in all four animals and lasted several days. The "Iberia" strain was in no way like the LSc strain in this regard. Of the four animals infected, one developed typical paralytic illness.

In summary, one may state that naturally occurring strains of poliovirus may be of high or low virulence for men; the few pertinent studies have failed to reveal viral characteristics that account for these differences or that are consistently correlated with high or low epidemiologic virulence.
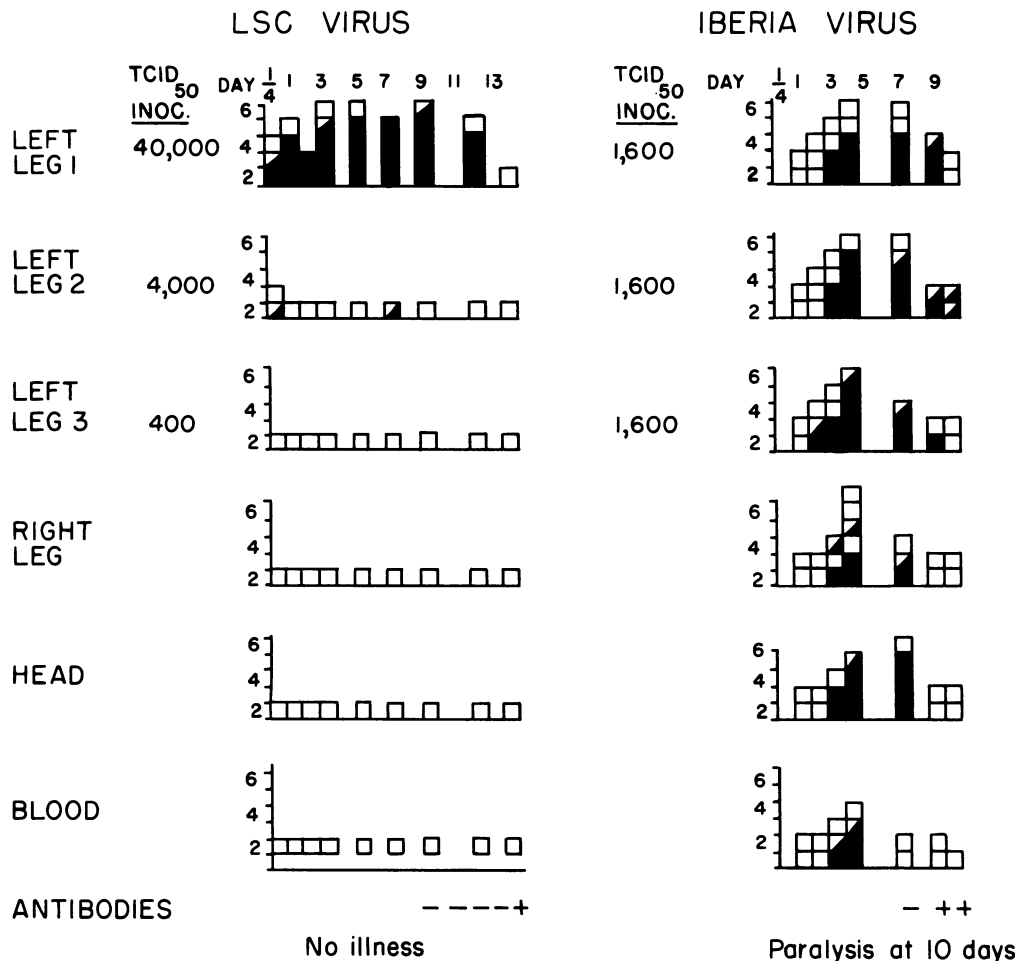
*Figure 2.* Concentration of virus in healing skin wounds and in blood of two cynomolgus monkeys, one inoculated with LSc strain of poliovirus and one with the Iberia strain. Virus was inoculated into three lesions on the left leg in the amounts shown. Note that the Iberia virus was recovered in relatively high concentration from all five lesions and from the blood. The LSc virus multiplied locally only in the lesion given the largest inoculum. It did not spread even to the other lesions on the same leg. Virus was assayed in monkey-kidney tissue cultures by the tube dilution method.

*Dark columns* indicate presence of virus at the times indicated at the top of each graph; □ = test for virus was negative in all tissue cultures (usually 2, more if test was repeated); ■ = test for virus was positive in all tissue cultures (usually 2, more if the test was repeated); ◪ = test for virus was positive in at least one tissue culture and negative in at least one tissue culture. *Vertical axis* = negative log of dilution of exudate; 0.1 ml was used in each test.

In any case, one can assume that properties of the virus itself cannot account for the chief difference between those who suffer paralysis and those who have poliovirus infection without paralysis. This conclusion is evident from the fact that even the most virulent virus strain causes paralysis of only a small proportion of the persons it infects. Therefore, the characteristics of the infecting virus must be less important than some other factors in determining the occurrence of paralytic disease.

### STATUS OF THE INFECTED INDIVIDUAL

Let us next consider how the status of the infected individual may influence the infectious process. A number of conditions likely to involve

only isolated individuals rather than whole populations are considered to increase the likelihood of paralytic illness. Among these may be listed pregnancy, previous tonsillectomy, and injections during the month before infection. Age of the infected person, fatigue, and genetic constitution may also influence the course of some poliovirus infections.

In considering how factors of this sort may affect poliovirus infections, it is helpful to review briefly some of our ideas on the mechanisms that suppress the viral growth and spread in poliomyelitis. Antibody formed in the infected person undoubtedly plays an important role. In the usual infection, poliovirus first multiplies in the tissues of the pharynx and the intestinal wall. While this is occurring, viral antigen reaches antibody-forming tissues. In due course neutralizing antibody appears in the tissue fluid and blood stream. This antibody is presumably effective in preventing the spread of virus to the nervous system, if this has not previously occurred.

Obviously then, *early spread* of poliovirus to the central nervous system would make paralytic illness more likely. Likewise, *delay in the formation of antibody* might have the same effect. The significance of these factors has been well described in the case of several other viruses. Overman and Kilham (1953), for example, have documented well the crucial importance of the time and extent of antibody formation in determining the outcome of experimental mumps virus infections of the central nervous system of young hamsters. A shift from high susceptibility to resistance occurred with increasing age and was shown to correlate with an increased rate of antibody formation with aging. Precise data of this sort are not available for poliovirus infections. To my knowledge there are no comparable data on the rate of antibody formation as a factor in natural poliovirus infections of man. It is possible that the relatively high rates of paralytic disease associated with pregnancy, tonsillectomy, and injection of vaccines with certain poliovirus strains reflect conditions that favor invasion of the central nervous system by virus before antibody response is adequate to arrest viral spread. The same general concept can be extended to spread of virus within the central nervous system, with the qualification that substantially more antibody is required to be effective.

Although one can state with confidence that several specific conditions affecting the status of the individual may increase his chances of suffering paralytic disease, it remains true that these factors cannot be shown to apply in most cases of poliomyelitis. A relatively small proportion of the paralytic infections occur in pregnant women, or persons with a history of recent injections, for example. It seems that our ignorance of the host-controlled factors that influence the course of poliovirus infections is probably much greater than our understanding of this subject and that the personal conditions within the infected individual that are most important in determining the course of a poliovirus infection have eluded investigators up to the present time. Furthermore, there is evidence that circumstances outside the infected person are important.

## ENVIRONMENTAL CONDITIONS

We are here shifting to what might be called an ecological study of the virus and of the infections it causes. We are engaged in a search somewhat like that of the early naturalists who noted that mud and a warm sun generated insects in profusion. We are looking for the counterparts of mud and warmth that generate paralytic poliomyelitis. If we find them, it may be presumed that further research will permit us ultimately to trace the evidence back to a rational explanation of our findings.

It is well known that environmental conditions can increase the incidence of certain infectious diseases. This is brought about by either or both of two general mechanisms: by increasing the number of persons infected, as in waterborne typhoid; or by causing more of those who are infected to develop illness, as in the activation of latent psittacosis in parrots subjected to mistreatment. In poliomyelitis both kinds of environmental mechanisms are important.

### Season

The most obvious environmental influence on the incidence of poliomyelitis is season. This disease occurs predominantly in the summer and early autumn months. Turner and his associates (1950) showed many years ago that the spread of poliovirus in Baltimore was largely restricted to that time of year when paralytic cases occurred.

The mechanism that serves to restrict the spread of poliovirus in winter or to facilitate its

spread in summer is unknown. There are, however, plenty of winter outbreaks to show that man is susceptible to poliovirus infection and to neurological involvement during any season of the year.

### Children in the Household

A second environmental factor worthy of careful attention is the presence of young children in the household. Several reports (Rindge, 1957; Poos and Nathanson, 1956; Siegel, Greenberg, and Bodian, 1957) indicate that paralytic poliomyelitis occurs with a higher incidence among adults living in households in which young children are present than among other adults. Siegel and his associates, for example, studied the distribution of paralytic poliomyelitis cases in New York City. They stated that the presence or absence of children in the household is "the most significant factor influencing the rates of paralytic poliomyelitis in adults." Among pregnant women the attack rate was twice as great in those with children as in those not having children.

### Proximate Fecal Pollution of Water Supplies

A third environmental factor worthy of careful evaluation came to my attention during a study of an interesting epidemic in Nebraska in 1952 (Bancroft, Engelhard, and Evans, 1957). The poliomyelitis cases occurred in one part of a community called Huskerville but spared the remainder of this community.

Dr. Paul Bancroft, a local pediatrician with a special interest in bacteriology, carried out detailed epidemiological studies. He later enlisted the help of Dr. Warren Engelhard of the University of Nebraska to carry out serological tests, and they subsequently invited me to participate in the analysis of the data and the completion of certain laboratory tests.

Huskerville was a former military hospital where married World War II veterans attending the University of Nebraska lived with their families. It was an unusually homogeneous community. Barracks-like buildings, clustered in four rows on the open prairie, had been subdivided into apartments suitable for one family. An abrupt, severe outbreak of poliomyelitis occurred among residents of two and one-half rows of buildings. This section of the village will be called Area A, and the balance of the community will be called Area B.

In Area A there were 347 children. A clinical diagnosis of poliomyelitis was made in 11.5 per cent of these children; 4.6 per cent of them suffered paralysis lasting at least two years. In Area B there were 256 children. Among them there were no cases of paralytic poliomyelitis during the epidemic; one case developed three weeks later.

There were no geographical or social barriers between Area A and Area B. Nor were there any biological or other environmental factors correlated with the distribution of cases. The spread of measles and chickenpox showed no similar restriction to parts of the community.

The important questions in this case were as follows: Why were there no cases of paralytic poliomyelitis in Area B? Was the virus somehow restricted to Area A? Or did infection reach children in all parts of the village but cause serious illness only in Area A? Answers to these questions were obtained in terms of the most probable situation. Available evidence was remarkably good but not adequate to be completely certain in answering them.

Serum specimens available were collected approximately 18 months after the epidemic. In spite of this delay it was possible to deduce valuable information from tests for antibody. Serological tests established that the epidemic was caused by poliovirus of type 1. It further appeared that about 85 per cent of children of preschool age had been infected in Area A and about 65 per cent in Area B. There was an obvious disparity between the high infection rate in Area B and the absence of paralytic cases in that part of the community. From the serological evidence one might have expected a substantial number of paralytic poliomyelitis cases in Area B. The lack of such cases suggests that poliovirus infection was more dangerous in Area A than in Area B.

The probability that chance alone could account for the distribution of poliomyelitis cases with paralysis among those infected was less than 1 in 100. If we include cases that did not show residual damage after two years (and most bona-fide paralytic cases recover completely), the probability that chance alone caused the difference between Area A and Area B is reduced to 1 in 100,000.

A careful epidemiologic study revealed one environmental condition that might reasonably

be related to the distribution of paralytic cases. This was fecal pollution of the water supply close to the apartments where paralytic poliomyelitis occurred. Toilets with defective plumbing were present in 12 apartments in Area A and in one apartment in Area B. Aspiration of toilet contents into the water line was favored by several episodes of negative pressure in the weeks preceding the epidemic. Chlorination during and prior to the epidemic was insufficient to kill fecal bacteria.

The most probable source of infection in Area A appears to have been polluted water obtained close to the point at which fecal pollution occurred. In Area B infection was also prevalent, but we do not know how the virus spread.

From the available evidence we were led to suggest an hypothesis to explain the peculiar distribution of poliomyelitis in Huskerville. In our hypothesis we proposed two related concepts: First, that *the mechanism of spread of virus* may have been the crucial difference between Area A and Area B; second, that the specific dangerous mechanism that occurred in Area A may have been ingestion of poliovirus in polluted *water obtained close to the point of pollution*. We have used the phrase proximate pollution in referring to this particular kind of viral spread.

The concept that mode of spread might be crucial in determining whether man develops paralytic illness or latent immunizing infection is not new. Lepine (1955) and Wilson (1955) suggested that inhalation of infected pharyngeal secretions might be more dangerous than infection from ingestion of "excretal material." Wilson pointed out the difficulty of accounting for predominant occurrence of the disease in summer if significant infection is chiefly by the respiratory route.

In attempting to assess the hypothesis that proximate fecal pollution of water can increase the paralytic attack rate of poliovirus, it is of interest to consider how this might alter the course of the infection. At least three possibilities can be mentioned. First, transfer of unusually large amounts of virus might cause the virus to multiply and spread more rapidly than usual in the infected person, before an immune response developed. Second, ingestion of unusually large amounts of virus with water might cause primary infection of tissues at an unusual location in the alimentary canal, a location from which inva-

sion of virus was favored. A third possibility is that there was transfer of other fecal viruses or microbes with potentiating effects on the invasion of poliovirus. It is conceivable that any one of these 3 factors might make a poliovirus infection more hazardous. There is only a limited amount of information of use in evaluating them.

Sabin and Winsser (1953) summarized data indicating that the amount of virus fed to orally infected monkeys had a substantial effect on the nature of the proportion developing neurological disease. Rhodes and van Rooyen (1958) suggest that exposure to a large amount of virus increases the likelihood of infection but add, "There is no evidence that the actual variety of illness developing is directly dependent on the amount of virus entering the body."

Dalldorf and Wiegand (1958) have presented experimental evidence that some Coxsackie viruses of group A may act synergistically with poliovirus to increase the likelihood of paralytic illness. Epidemiological evidence of an association of group A Coxsackie viruses with poliovirus in paralytic cases has been reported repeatedly (Melnick et al., 1951) and has been noted specifically not to occur on other occasions (Curnen and Melnick, 1951). If a second infectious agent is indeed an important factor in making "proximate" pollution a dangerous mode of spread of poliovirus, it may be presumed that more distant pollution is less dangerous because the agent is lost by dilution or by instability in cold water. Both Coxsackie viruses and poliovirus survive many days in cold water.

Re-examination of reported poliomyelitis outbreaks reveals many in which proximate fecal pollution of water can be presumed to have occurred. However, in nearly all cases, it is impossible to assess the significance of this factor, for suitable data are not available. Furthermore, it is impossible to rule out the occurrence of proximate pollution in situations in which it is not suspected. Plumbing cross connections and other sanitary defects are undesirably common in water distribution systems of our cities. Such cross connections might be a factor in the well-known clustering of paralytic cases in some epidemics, some outbreaks in hospitals and other institutions (Sims-Roberts and Thomson, 1953; Ingalls and Aycock, 1951), or for single or multiple cases in private homes. The many studies of multiple cases in single families have failed to

give a clear picture of the factors involved (Siegel and Greenberg, 1954; Littell and Smith, 1955; Pierce, 1958; Strom, 1959).

One wonders whether a common denominator exists between proximate fecal pollution of water and the importance of young children in the household in relation to paralytic poliomyelitis in adults. All parents are fully aware that fecal contamination from young children is still proximate, frequent, and ample.

### Epidemics in Virgin Populations

It is well known that infectious diseases may cause unusually severe epidemics in previously unexposed populations. The paralysis of 55 per cent of the Eskimos in the Maguse River outbreak and 21 per cent of those in the Chesterfield Inlet epidemic are good examples of this phenomenon. The explanation is, however, not clear.

It has been suggested that epidemics in isolated virgin populations are severe because prior selection for resistance has not occurred. A genetic susceptibility might be established in this manner. This explanation for the severity of epidemics in virgin populations is open to serious question.

In the devastating measles epidemic among Fiji Island natives in 1875, 40,000 died. This was one-fourth of the total population. If this high fatality rate were due to a genetically determined susceptibility, it might be expected that measles would continue to be exceptionally severe over a period of several generations during which selection for resistance to measles would occur. Contrary to this prediction, measles has not shown unusual severity among Fijians since that date.[2] Others have pointed out (Pickles, 1939) that the concept of genetically determined high susceptibility of Fijians in 1875 is contradicted by the low fatality rate among those who, as members of the police force, lived under conditions quite different from other natives of the island and received some care during their illness. It seems desirable to keep an open mind on the explanation of the severity of viral epidemics in virgin populations.

[2] In a personal communication dated November, 10, 1952, Dr. G. Loison, of the South Pacific Commission, provided statistics on the occurrence of measles in Fiji 1875 to 1951. This information came from the "Annual Reports of the Medical Department" and was sent to Dr. Loison by the Inspector General of the South Pacific Health Service at Suava.

There is great need for careful, on-the-spot investigation of severe epidemics in previously unexposed populations. These should include an evaluation of the interrelated effects of the quality of care provided and the evidence concerning the route and circumstances of viral transmission. A microbiologist would also wonder whether the so-called normal flora of isolated populations might be different and might in some way influence the growth and spread of pathogens.

### VIRAL INFECTIONS *IN VITRO* AS MODELS FOR NATURAL INFECTIONS

In concluding this discussion I wish to shift away from a consideration of specific investigations of poliomyelitis and present a broader view of some of the main lines of virological research that bear on our problem.

Exciting new knowledge of viruses and their mechanisms of infecting cells appears almost daily. We have good reason to hope that we will soon possess a much-improved understanding of the physiological processes involved in viral infections of a cell either with or without destruction of the cell.

There is now great interest in virus infections that persist for months in healthy, thriving tissue cultures. A related field of fruitful research is the study of systems in which virus-infected cells produce substances which will confer on other cells protection against viral infection. In our laboratory, Chambers (1957), Lockart (1960), and Wilcox (1959) have studied two "carrier culture" systems in which most of the cells are protected by "auto-interference." The work of Isaacs and Lindeman (1957) and others with interferon and the studies of Ho and Enders (1959) represent major contributions in this field. We are probably only on the threshold of a comprehensive understanding of such systems.

The healthy, infected cultures have an obvious resemblance to the person who remains well throughout the course of an infection with poliovirus. However, one can predict with reasonable assurance that this broad area of research will fall short of providing a full understanding of the reasons why most persons infected with poliovirus have no illness and proportionately few are paralyzed.

It seems clear that there must ultimately be an explanation for such questions as the following:

Why does paralytic poliomyelitis occur more commonly in adults who share a home with children? Why can poliovirus cause a high rate of paralysis in one part of a community and spread without such effects in another part of the same community Why are the highest paralytic attack rates restricted to rather small and sharply defined population groups?

Solution of the problems posed by the virus as it manifests itself in nature will undoubtedly require that studies focused on the course of virus infections in cell populations *in vitro* be linked with further studies of epidemiology and attempts to define more precisely the successive events that occur during infection of experimental animals.

## CONCLUSIONS

From the evidence presented, the following conclusions appear justified:

1. Naturally occurring poliovirus strains differ in their paralytogenic capability for man. No viral characteristics or markers have as yet been shown to have general validity as indicators of the degree of virulence of these "wild" virus strains as they occur in naturally acquired infection.

2. Most naturally acquired human infections with even the most virulent strains of virus result in no paralytic illness. Therefore, factors other than the nature of the infecting strain of poliovirus must be crucial in determining the outcome of most infections.

3. A number of personal characteristics such as pregnancy, tonsillectomy, or recent injections increase the likelihood that poliovirus infection will lead to paralytic disease. Most cases of paralytic poliomyelitis occur in persons to whom the known factors of this sort do not apply. It may be presumed that the individual conditions that are of greatest significance in determining the course of a poliovirus infection are still not identified.

4. A number of environmental circumstances have an important influence on the occurrence of paralytic poliomyelitis. Of these, only the obvious effect of season appears to be generally acknowledged at this time. In addition, the presence of children in the family, the ingestion of fecally polluted water close to the place of pollution, and infection of isolated populations under undefined circumstances appear to merit serious attention.

5. Research on chronically infected and apparently healthy tissue cultures and on substances derived from virus-infected cells that confer protection on other cells can be expected to have significance in resolving some problems in the pathogenesis of poliovirus infections. Additional epidemiological studies and investigations of the sequence of events in experimental infections of animals are also needed if we are to understand what determines whether a person infected with poliovirus develops paralytic illness or suffers no significant harm.

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