Paralytic Consequences of Poliomyelitis Infection in Different Parts of the World and in Different Population Groups* †

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IT is a great privilege and honor to deliver this lecture in memory of Dr. Don W. Gudakunst. His important contributions in the broad field of public health are particularly appreciated by the residents of the State of Michigan. Those of us who labored in the field of poliomyelitis before the advent of the National Foundation for Infantile Paralysis and who were privileged to know and work with Don Gudakunst, its first medical director, are especially aware of his contributions in furthering the progress of poliomyelitis research.

I have selected the particular subject for my lecture because the goal of poliomyelitis research is not the elimination of poliomyelitis infection but of the paralysis which is the important consequence of that infection. One of the axioms regarding poliomyelitis, well established by both epidemiologic and laboratory investigations, is that the clinical manifestations of infection with the poliomyelitis viruses are varied: (1) *inapparent,* i.e., silent or asymptomatic, (2) *abortive,* i.e., minor illness without evidence of involvement of the central nervous system, (3) *nonparalytic,* i.e., minor illness with pleocytosis but without paralysis, and (4) *paralytic,* which is both the most important and least common. It is also perhaps axiomatic that poliomyelitis infection occurs wherever human beings are present and persists wherever they live in large enough communities to maintain the chain of infection.

The question to be analyzed in this lecture is whether or not the paralytic consequences of poliomyelitis infection vary in different parts of the world and among different population groups living side by side. Consideration will be given also to a number of factors, which may conceivably influence the incidence of paralysis resulting from poliomyelitis infection, and an attempt will be made to evaluate their role in different population groups.

According to available information, it would appear that poliomyelitis infection is of importance as a cause of paralysis in such countries as the United States, Sweden, and Australia, among others, and that it is negligible among the indigenous populations of the Philippines, China, most of Africa, etc. It is assumed by some, however, that this difference is apparent rather than real. There are those who believe that the total amount of paralytic poliomyelitis

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is probably much the same in different parts of the world and in different population groups, and that it only seems different because:

a. it is not recognized and reported;
b. it occurs almost entirely in early childhood and is not as severe;
c. it occurrs continually at a more or less constant rate rather than in epidemic outbursts.

Paul has made important inquiries along these lines which illustrate the unreliability of official reports from certain countries. In 1943 he analyzed the admissions for "paralysis" in the children's hospitals of Cairo, Egypt, for the period of 1933 to 1942,[1] and in 1950 for the years 1948 and 1949.[2] The number of new admissions per year varied from 22 to 96 during 1933–1939, and from 110 to 201 during 1940–1942; the number was 260 and 211, respectively, for the years 1948 and 1949. From a personal inspection of some of the clinic records and patients, Paul estimated that approximately 80 per cent of the paralytic cases were due to poliomyelitis; and yet the reports to the Egyptian Ministry of Health listed only 2 to 11 cases per year, most of them fatal. However, beyond the fact that poliomyelitis occurs in Cairo much more frequently than would have been suspected without this inquiry, one cannot use these data for quantitative estimates of the incidence of poliomyelitic paralysis in all of Egypt, much less in other countries in which a large portion of the population lives under primitive sanitary conditions. Cairo is a metropolis with a striking admixture of European and African civilizations and ways of life, and it would have been of some interest to know the social and economic groups from which the children with poliomyelitic paralysis were derived. A similar survey in Palestine for the years 1915–1934 indicated that the average attack rate was 20 times higher among the Jews than among the Moslems.[3]

Paul[4] also drew attention to the fact that the mortality statistics for poliomyelitis in Japan between 1923 and 1943, the only statistics available prior to 1948, were not appreciably different from those in the United States, and suggested that the total incidence of paralytic poliomyelitis among the Japanese might also *not* be different from that in the United States. The reporting of poliomyelitis morbidity in Japan began in 1948. Yet during that year a total of only 980 cases of poliomyelitis and polioencephalitis were reported, a morbidity rate of 1.2 per 100,000, of which 775 were fatal. In 1949 the number of reported cases was 3,140 (3.8 per 100,000), of which 1,024 were fatal.[5] During the same period, the morbidity rate for the entire United States was roughly 26 per 100,000. It is clear that either the deaths reported from poliomyelitis in Japan are largely misdiagnosed or that only a very small proportion of the surviving paralytic cases are reported. The experience of the large pediatric clinics in Japan[4] and my own experience in Tokyo and Okayama in 1946, when a special effort was made to report and hospitalize all patients with acute infection of the nervous system, suggest that the former is more probable and that the total amount of paralytic poliomyelitis among the Japanese is relatively small.

Hillman,[6] Hernando and Alomia,[7] and Doull, Hudson, and Hahn[8] have all reported on the rarity of paralytic poliomyelitis among the natives in the Philippines, before World War II, where poliomyelitis was considered to be a disease of white people. During World War II, when the incidence of poliomyelitis among American troops in the Philippines was exceptionally high (88 and 43 per 100,000, respectively, in 1944 and 1945), repeated investigations of the native population in the affected areas revealed either no cases or rare instances of paralytic poliomyelitis among Filipino children.[9]

The uncommon occurrence of paralytic poliomyelitis among the natives of China has been reported by Zia,[10] Yen and Hsu,[11] and Scott,[12] drawing on large population centers with hospitals staffed by western-trained physicians. Personal communications from Dr. A. A. Weech of Cincinnati and Dr. George Van Gorder of Boston, who had spent a number of years at the Peiping Union Medical College as pediatrician and orthopedic surgeon, respectively, are in keeping with these observations. In 1946, while investigating an outbreak of poliomyelitis among American Marines in Tientsin, China, I was also informed by physicians in Tientsin, Peiping, and Shanghai that paralytic poliomyelitis was a most uncommon disease among Chinese children.[13]. Gear[14] has reported that in South Africa the incidence of paralytic poliomyelitis is ten times greater in Europeans than in Africans, and that while the ratio is 1 to 4 in urban areas, it is 1 to 300 in the native territories.

I should like to add several additional examples of the varying incidence of poliomyelitis in different regions and populations, using data which lend themselves more readily to quantitative comparison. The morbidity rates for three of the largest cities of the world, New York, London, and Berlin (Table 1), indicate that all three have had many years of low incidence but have varied in the number of epidemics which they experienced. If one adopts an attack rate of 20 per 100,000 as the arbitrary minimum level for an epidemic in these cities, New York had four epidemics up until 1947 (counting 1916 as the first epidemic year), while both Berlin and London have had only one—their first in 1947. The mean annual attack rate during the interepidemic years between 1928 and 1947 was remarkably similar for New York and Berlin—3.83 and 3.88 per 100,000, respectively—while that for London was only about half, or 1.96 per 100,000. If one includes the epidemic years, the mean annual rates for the periods shown in Table 1 are 8.86, 7.5, and 3.12 per 100,000 for New York, Berlin, and London, respectively. Thus over a period of 20 years, the incidence of poliomyelitis was almost three times greater in New York than in London.

TABLE 1

Annual Attack Rates of Poliomyelitis in New York, London, and Berlin 1928–1947

Year	Cases Reported per 100,000		
	New York	*London*	*Berlin*
1928	8.7	—	1.8
1929	1.1	—	2.0
1930	1.1	—	1.1
1931	*59.1**	—	1.0
1932	2.0	1.9	4.8
1933	11.5	1.8	5.0
1934	1.0	1.5	1.9
1935	*28.5*	2.0	1.8
1936	0.8	2.2	2.4
1937	3.5	3.4	10.8
1938	0.8	2.7	3.4
1939	3.0	2.1	8.3
1940	1.0	0.6	1.4
1941	5.5	2.5	10.9
1942	1.0	1.6	6.2
1943	5.0	1.5	4.0
1944	*24.6*	0.9	2.2
1945	7.1	2.9	2.0
1946	9.2	1.9	2.8
1947	2.8	*20.6*	*76.2*
Mean annual rate for all indicated years	8.86	3.12	7.5
Mean annual rate for inter-epidemic years	3.83	1.96	3.88

* The italicized figures indicate epidemic years.

The data presented in this table were calculated from reports supplied by Dr. S. Frant, New York City Health Department, for New York; Dr. W. H. Bradley of the Ministry of Health for London; and Dr. F. Pfabel of the Landesgesundheitsamt for Berlin.

The data shown graphically in Figure 1 indicate the varying poliomyelitis rates over periods of many years in Sweden as compared with the United States; in New York City as compared with Washington, D. C.; and in three states of relatively high incidence as compared with three states of low incidence. It does not seem likely that gross failures in reporting or recognition are

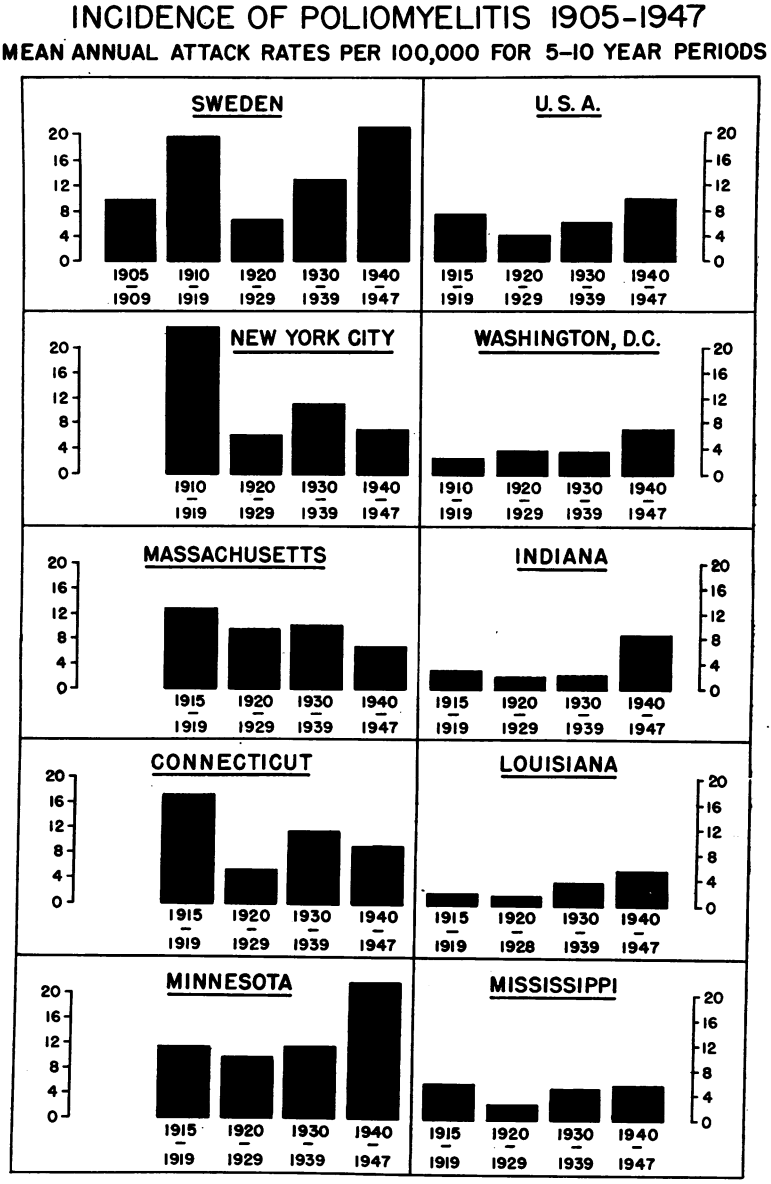

FIGURE 1—Reproduced from Sabin [35]

responsible for the marked differences observed in these particular areas.

The remarkable family survey in 84 cities and towns in 19 states, which was carried out by the U. S. Public Health Service and reported by Collins,[15] clearly showed that the incidence of clinically recognizable poliomyelitis was four times as high among whites as among Negroes in the Northeast; while in the South and intermediate states, the incidence was equally low among the whites and Negroes (Figure 2). Turner, *et al.*,[16] have recently reported that in Baltimore the incidence of poliomyelitis has been consistently higher in whites than in

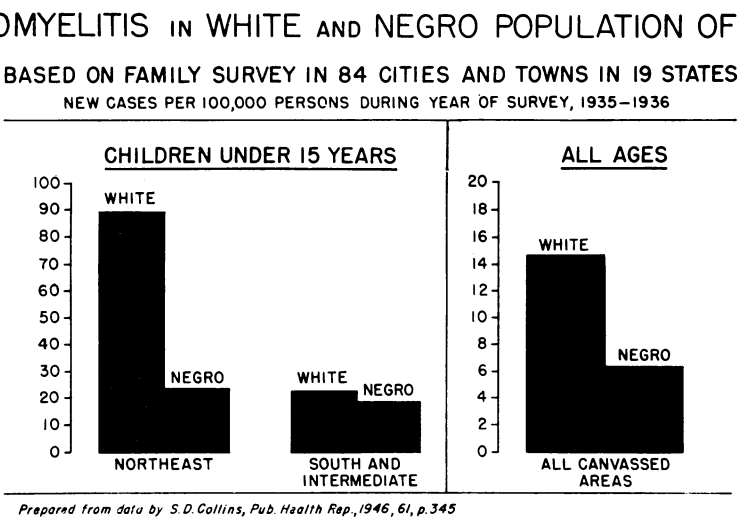

FIGURE 2—Reproduced from Sabin [35]

Negroes, the difference being most marked (threefold to fivefold) during years of increased incidence. Enright's [17] study on the incidence of poliomyelitis over a 10 year period among different population groups in Hawaii was made with special care, because he personally saw most of the cases, checked on the reporting doctors and also on the cases which appeared in the Crippled Children's Service. All this checking turned up only two cases which had not been reported. The results, summarized in Table 2, indicate clearly that

TABLE 2

Poliomyelitis in Different Races in Hawaii, 1938–1947

Population	about 525,000
Total No. of Cases During Decade	291

Race, Total Population	*Per cent of Total Population* 100	*Mean Annual Rate Per 100,000* 5.5 (Range, 0.6–15)
Caucasian	33	10.2
Part Hawaiian	15	9.0
Japanese	33	3.9
Chinese	6	2.7
Filipino	10	1.6
Hawaiian	2	1.3

Based on data reported by Dr. James R. Enright at First International Poliomyelitis Conference.

over a decade the incidence of clinically recognized poliomyelitis was markedly different for different population groups living together in the same neighborhoods and attending the same schools without segregation. Enright pointed out that the incidence of tuberculosis was just the reverse, being highest where poliomyelitis was lowest, and lowest where poliomyelitis was highest.

Thus far, I have called attention to countries and population groups exhibiting tendencies to a negligible or low incidence of paralytic poliomyelitis. The high incidence of poliomyelitis antibody among such groups, as well as the high incidence of paralytic poliomyelitis among American or British adults stationed in these countries, has indicated not only that poliomyelitis infection can be widespread where poliomyelitic paralysis is not, but also that the viruses do not lack virulence in the countries with a low incidence of poliomyelitis in the native population.

I should now like to call attention to population groups, in the Arctic as well as in the tropics, in which poliomyelitis infection was associated with extraordinarily high paralytic attack

TABLE 3

Some Examples of Exceptionally High Poliomyelitis Paralytic Attack Rates in Relatively Isolated, Inbred Populations

Region	*Year*	*Size of Population*	*Attack Rate Per 100,000* *
Chesterfield Inlet—Arctic Eskimos [18]	1949	275	21,000
Nicobar Island, India [19]	1948	10,000	8,000
Sukkertoppen, Greenland [20]	1914	700	5,300 dead many more paralyzed
Sukkertoppen, Greenland [20]	1932	700	2,400
Kangamiut, Greenland [20]	1932	300	4,300
Holsteinborg, Greenland [20]	1932	400	4,000
St. Helena [21]	1945	4,000	1,920
Guam [22]	1899	8,660	808 dead many more paralyzed

* The rate per 100,000 is given to permit easy comparison with rates of 20 to 100 obtaining in usual epidemics in U.S.A., etc.

rates—rates which would be catastrophic if they occurred in countries which now regard themselves as being afflicted with poliomyelitis. The available data on the outbreaks listed in Table 3 leave little doubt regarding their poliomyelitic nature. It seems to me especially important, however, not only that they occurred in unusually isolated populations but also that, because of this very isolation, they were highly inbred. The broad age distribution in these epidemics is evidence that the immunological type of the invading virus was either entirely new to these populations or had not been in their midst for many years. However, the paralytic attack rates are so high that they can hardly be attributed entirely to lack of immunity or to the virulence of the virus. To my knowledge, the highest paralytic attack rate which might perhaps be expected under such conditions is that which occurred in the 1 to 4 year age group in the 1916 epidemic in New York City, namely 1,469 per 100,000.[23] The outbreak among the Eskimos at Chesterfield Inlet was at least 14 times more severe.

The data, which I have assembled here, by no means all that are available, are intended to show that, with due regard for differences in recognition and reporting, the paralytic consequences of poliomyelitis infection are not the same in different parts of the world or even in different population groups living in the same part of the world. I should now like to consider a number of factors which under different circumstances may each play an important role in determining the extent to which poliomyelitis infection shall be paralytic or shall manifest itself as a minor illness or in no illness at all. Among these factors I should like to pay special attention to the role of (a) the genetic constitution of the host, (b) the virulence of different strains of virus belonging to the same immunological type, (c) infection under the influence of maternal immunity, and (d) the size of the infecting dose of virus.

GENETIC CONSTITUTION OF THE HOST

The role of the genetic constitution of the host on the outcome of viral infections in plants is well established and has led to many practical benefits. Webster's [24] classical experiments with specially bred strains of mice and the viruses of St. Louis encephalitis and louping ill have clearly demonstrated the genetic basis of susceptibility and resistance to certain viruses affecting the nervous system. His studies, furthermore, established that something in the nervous tissue itself regulated the level of viral multiplication, and that in the genetically susceptible mice the virus multiplied to a level that was 1,000 to 10,000 times higher than in the resistant

mice. Webster's studies on the mechanism of inheritance of the resistance factor were partly complicated by the fact that a varying proportion of the resistant mice developed encephalitis and died.

As a result of a fortunate accidental discovery of a strain of mice which is 100 per cent resistant to the intracerebral injection of the 17-D mutant strain of yellow fever virus, I have recently been able to confirm Webster's observations that a multiplication-regulating factor constitutes at least one important genetic basis of susceptibility and resistance; and to work out the mechanism of inheritance of this factor. The experimental data, which I obtained in various types of cross-breeding experiments, were in complete accord with the theoretical data for the hypothesis that inheritance of the viral multiplication-regulating factor was dependent on a single gene—susceptibility being inherited as a recessive characteristic and resistance as a dominant.

It was furthermore established that this multiplication-regulating factor which affected the multiplication of the 17-D strain of yellow fever virus also influenced the multiplication of the French neurotropic yellow fever virus, the mouse-adapted Hawaii dengue virus, and the viruses of Japanese B and St. Louis encephalitis and of West Nile fever, but was completely without effect on viruses of Western equine encephalitis, rabies, herpes, Rift Valley fever, lymphocytic choriomeningitis, Theiler's mouse encephalomyelitis (TO strain) and the Lansing and Y-SK strains of poliomyelitis virus. It was also found in studies with the French neurotropic yellow fever and the Japanese B encephalitis viruses that some of the resistant mice developed paralysis and encephalitis despite the lower level of viral multiplication, and that this special susceptibility of the nerve cells to irreversible damage at lower levels of viral multiplication, also, was genetically determined.[25]

In human poliomyelitis, Taylor [26] suggested as early as 1898 that there existed a tendency to paralysis in certain families. Stephens [27] in 1908 and Aycock [28] in a series of reports between 1934 and 1942 brought forth additional observations in support of this view. In 1948 Czickeli [29] reported the occurrence of 16 cases of poliomyelitis *during different years* among 23 members of the families of four married brothers in Austria. I have also been impressed in my own experience with the not infrequent occurrence of paralytic poliomyelitis in multiple members of certain families, especially the instances in which the events are separated by years or generations. The very interesting study reported by Addair and Snyder [30] on the family relationships of every case of crippling, paralytic poliomyelitis which occurred in McDowell County, West Virginia, over a period of 50 years led to the conclusion that the most reasonable explanation for the observed incidence was that susceptibility to paralytic poliomyelitis was determined by an autosomal, recessive gene. This conclusion appears particularly plausible to me in the light of my own experiments on the inheritance of susceptibility to other neurotropic viruses in mice.

It also seems to me that the most plausible explanation for the exceptionally high paralytic attack rates in the relatively isolated, highly inbred populations (listed in Table 3) is that they represent instances of primary infection in populations of special genetic susceptibility. The consequences of poliomyelitis infection among these populations should therefore not be regarded as something that might be expected in any population spared from contact with poliomyelitis virus. There are many other instances of relatively isolated populations both in the Arctic [31] and in the tropics of Africa,[14] in whom there

is evidence of widespread dissemination of poliomyelitis virus with only rare instances of paralytic poliomyelitis.

ROLE OF VIRULENCE OF DIFFERENT STRAINS OF VIRUS

There are certain epidemiologic and laboratory observations which suggest that different strains of poliomyelitis virus vary in virulence. The capacity to produce a higher incidence of the paralytic disease or of a higher case fatality rate may be taken as an indication of greater virulence in human beings. In monkeys the virulence of a given strain of virus can be measured by the incidence of nonparalytic infections, by the severity of paralysis, by the capacity of small numbers of intracerebral infective doses to produce paralysis after inoculation by extraneural routes, and by the level of viral multiplication in the central nervous system. Since the host also plays a role in determining the outcome of infection, it is self-evident that it is not a simple matter to correlate events in individual patients with the behavior of strains of virus recovered from them in monkeys.

That is not to say, however, that observations on large numbers of strains derived from many patients with different clinical varieties of illness due to poliomyelitis infection cannot yield useful information on variations in virulence among different strains of virus. Studies carried out in Cincinnati on individual strains of virus recovered from 24 patients who in 1947 exhibited "summer grippe," nonparalytic or paralytic poliomyelitis provided suggestive evidence for a correlation between the severity of the clinical condition in patients and the virulence of the strains in monkeys and indicated that strains of high and low virulence were in circulation at the same time.[32] Thus, the four strains recovered from patients with summer grippe produced predominantly nonparalytic infections in monkeys; 7 of the 10 strains recovered from paralytic patients after intracerebral passage in monkeys yielded high titers, i.e., 10^{-3} or more; while 8 of the 10 strains recovered from nonparalytic patients yielded low titers. Seventeen of these strains, of both high and low virulence for monkeys, were typed in the program sponsored by the Typing Committee of the National Foundation for Infantile Paralysis and all were found to belong to the same immunological type (Type 1—Brunhilde-like).

Examination of the poliomyelitis morbidity statistics for a variety of communities reveals annual variations in incidence which cannot possibly be explained away on the basis of irregularities in reporting and recognition of cases. The data for New York, London, and Berlin, shown in Table 1, have already been discussed, and it is clear that in these cities, as in many other communities, clinically recognizable poliomyelitis is a disease of relatively low incidence except during the epidemic years, which occur at unpredictable and sometimes long intervals. In New York City, for example, the attack rates during the five epidemic years have been 6 to 46 times higher than the mean annual rate for the 17 nonepidemic years between 1928 and 1947 (Table 4). The attack rate of 20.6 per 100,000 in the first London epidemic of 1947 was about ten times higher than the mean annual

TABLE 4

Comparison of Poliomyelitis Morbidity and Case Fatality Rates During Interepidemic and Epidemic Years in New York City

Years	*Number of Cases per 100,000*	*Case Fatality * Per cent*
Mean annual rate for interepidemic years, 1928–1947	3.8	—
1916	176.3	27.1
1931	59.1	12.2
1935	28.5	4.4
1944	24.6	5.4
1949	30.3	7.3

* The case fatality rates are quoted from Greenberg, Siegel, and Magee.[33]

rate of 1.96 for the period of 1932 to 1946. The attack rate of 76.2 per 100,000 in the first Berlin epidemic of 1947 was 20 times higher than the mean annual rate for the period of 1928 to 1946.

In 1928 Aycock [34] pointed out that the accumulation of nonimmunes cannot be a major factor in the production of epidemics, because the age incidence was not found to vary materially from year to year, even during epidemics which occurred after a number of years of comparative freedom from the disease. Twenty years later, I [35] showed that Aycock's observation was still valid, despite the fact that age selection patterns had changed over the years in certain communities. The conclusion seems inescapable that poliomyelitis epidemics are the result of the invasion of a community by strains of unusual virulence, and that the reason the age incidence generally does not vary materially from year to year is that strains of the same immunological variety but of lower virulence are widely disseminated during interepidemic years.

Although the poliomyletis experience of any but the most isolated communities can supply data to illustrate this point, the epidemic in Malta and Gozo in 1942 and 1943 is especially informative.[36] During the 20 years between 1921 and 1941, the mean annual poliomyelitis rate was roughly 1 per 100,000. In the 1942–1943 epidemic the paralytic attack rate was 158 per 100,000, but 93 per cent of all the cases were in children under 5 years of age. While the older Maltese children and adults were thus predominantly immune, the United Kingdom troops, aged 20 to 40 years, who lived in their midst had an attack rate of 250 per 100,000. The virulence of the strain may further be attested by the fact that despite great vigilance for nonparalytic cases, among the troops, 55 of the 57 cases were paralytic, with a case fatality rate of 19.3 per cent.

A high case fatality rate may in itself also be an index of the special virulence of certain epidemic strains, without relationship to the involvement of older age groups. The data for New York City in Table 4 show that the case fatality rate was highest for the 1916 epidemic when the attack rate was highest and 79 per cent of the cases were under 5 years of age, practically all the reported cases being paralytic. Beginning with the 1931 epidemic, approximately 40 per cent of all reported cases during the epidemic years have been nonparalytic. However, even if one multiplies the case fatality rates of the later epidemics by two to correct for this, it is still evident that the milder epidemics in New York City have also had lower case fatality rates. A striking example of variation in virulence reflected more in the case fatality rate than in the paralytic rate is available in two carefully studied outbreaks in Cincinnati and vicinity in 1911 and 1947 (Table 5). It may be seen that despite the fact that 83 per cent of all paralytic cases in 1911 occurred in children under 5 years, among whom lower case fatality rates usually obtain, the case fatality

TABLE 5

Case Fatality Rates During Two Carefully Studied Outbreaks of Poliomyelitis in Cincinnati and Vicinity

Year	*Number of Paralytic Cases Per 100,000*	*Case Fatality among Paralytic Cases Per cent*	*Paralytic Cases under 5 Years of Age Per cent*	*Nonparalytic Cases Reported Per 100,000*
1911 *	25.4	30 7	83	0
1947 †	11.4	2.2	40	10

* The 1911 data are calculated from the report by W. H. Frost.37

† The 1947 data are based on a personal study aided by Dr. J. H. Peyton.

rate was 30.7 per cent as compared with 2.2 per cent of the paralytic cases in 1947, even though 60 per cent of the paralytic cases were over 5 and 13 per cent over 15 years of age.

In reviewing the experience of the Army with poliomyelitis during World War II, I [9] was impressed with the variations in virulence of strains encountered in the few explosive outbreaks which occurred in the United States. The attack rates in these few explosive outbreaks among young adults varied from 57 per 100,000 to 2,500 per 100,000. In some of these outbreaks, there were nonparalytic cases as well as paralytic, while in others, despite a careful search by qualified consultants, all the cases were paralytic. The case fatality rate varied from zero among 17 cases, 8 of which were nonparalytic, representing an outbreak with an attack rate of 2,300 per 100,000, to 36 per cent among 11 cases, representing an outbreak with an attack rate of 800 per 100,000, all paralytic.

In the Philippines, shortly after the invasion in 1944, the case fatality rate was 62.5 per cent among 16 paralytic cases in Northern Leyte and 5.3 per cent among 19 paralytic cases in Central Leyte. It is noteworthy, however, that a careful investigation revealed no recent cases of poliomyelitis among the natives on Leyte. The last definite case of poliomyelitis reported from Leyte had been in 1938, and the civilian health records of the area were found to be remarkably complete because the Japanese authorities required a daily report on infectious diseases. The Filipino population numbered over 61,000 in the area in which poliomyelitis was occurring at a high rate among American adults. While no clinical poliomyelitis was discovered among them, the circumstances left little doubt that the natives were the reservoir of the virulent virus which was infecting the Americans. The suggestion that the tropical climate was, by itself, responsible for this high incidence [38] does not find support in the fact that these troops were free from poliomyelitis during the preceding years while they were stationed elsewhere in the Southwest Pacific beyond the range and influence of native villages. This brings us to a consideration of the problem why the virulent strains of poliomyelitis virus produced little or no recognizable paralysis, even among the Filipino children, while the American troops in this particular area and time were becoming paralyzed at a rate which was at least 20 times higher than that obtaining for the troops in the United States or in Europe.[9]

INFECTION UNDER THE INFLUENCE OF MATERNAL IMMUNITY

It is now well established that poliomyelitis antibodies follow the pattern of other antibodies in human beings with regard to their transmission across the placenta and their period of persistence during the first months of postnatal life.[16] While the time of disappearance of placentally transmitted antibody generally depends on the original concentration, the majority of infants are devoid of placentally transmitted antibody at 5 to 6 months of age. It has occurred to many people that exposure to poliomyelitis virus during that period of infancy when placentally transmitted antibody has dropped to low levels might result in modified or inapparent infection capable of engendering active immunity. Thus, it appeared possible that in countries and population groups with a high rate of poliomyelitis virus, the vast majority of the population might acquire their infection and immunity while still partially protected by their maternal antibody.[13]

It seemed to me that if the events postulated by this hypothesis actually occurred, the incidence of poliomyelitis antibody between the sixth and twelfth months of life should be very high in

TABLE 6

Appearance of Lansing Poliomyelitis Antibody in Early Childhood in the United States and the Far East

Region	Per cent Positive *				Number Tested			
	9 to 23 Months	2 + 3 Years	4 + 5 Years	18 to 50 Years	9–23 Months	2 + 3 Years	4 + 5 Years	18 to 50 Years
Cincinnati (Ohio), U.S.A.	2	20	40	100 †	43	40	40	30
Korea and Okinawa	13	70	97	100	23	36	31	30
Japan	23	50	64	90	47	55	67	40

* Positive = undiluted serum protected against at least 50 LD_{50} of Lansing virus.

† This applies only to 30 individuals of lower income group. In a group of 10 in the middle income group, only 50 per cent were positive.

parts of the world where the viruses were believed to be disseminated very extensively and rapidly, in contrast to the relatively low incidence observed in the United States under 2 years of age even among children from low income groups. Accordingly, early in 1947, together with Dr. Irving Young, I undertook to compare the incidence of Lansing antibodies in infancy and early childhood, beginning with nine months of age, among the children of the lower income groups in Cincinnati with that occurring in Korea, Okinawa, and Japan. The results of tests on 482 sera are summarized in Table 6. The data are grouped under 9 to 23 months, 2 and 3 years, and 4 and 5 years, because the total numbers of sera tested and the results obtained did not warrant their subdivision into smaller intervals. It is evident that, in general, the Lansing antibodies are reacquired more rapidly by the children in the Far East than by those from the lower income groups in Cincinnati.

Similar tests recently carried out by other workers indicate that poliomyelitis antibodies are acquired more extensively at an earlier age in certain other population groups. Thus, Hammon informed me that about 50 per cent were positive in Guam between 1 and 2 years of age (although the impression conveyed in the published accounts of this work [39] was that this high incidence developed before 1 year of age). Paul [2] recently found 50 to 75 per cent positive between 14 and 24 months of age in a village close to Cairo, Egypt, while less than 10 per cent were positive in the 7 to 12 month age group. It is evident from these data that neither among the lower income groups in the United States nor in the Far East or Egypt were Lansing antibodies (and presumably infection) acquired to any significant extent during the period of diminishing placentally transmitted antibody. The hypothesis of extensive immunization as a result of modified or subclinical infection among certain population groups during the first year of life therefore became untenable.

In a search for other factors which might influence the response of infants to poliomyelitis virus, it appeared desirable to obtain information on the antipoliomyelitic properties of mother's milk, particularly that which might be consumed after the placentally transmitted antibodies had disappeared from the blood. Breast feeding is common for as long as two years in the Far East and Africa, and among Eskimos it is said to be common for as long as three years. The age-specific attack rates for the unusual epidemic which occurred among Canadian Eskimos, shown in Table 7, emphasize the remarkable sparing of the youngest children. The 4 per cent attack rate among the zero to 4 year age group represents two cases in children over 3. Since, in my opinion,[40] the available evidence points to the mouth as the usual portal of entry of poliomyelitis virus, it became of

TABLE 7

Poliomyelitis in Eskimos—District of Chesterfield Inlet, Canadian Arctic February 14–March 7, 1949

Age Group Years	Population	Paralysis Per cent
0– 4	53	4
5– 9	56	23
10–19	59	32
20–29	30	20
30–39	33	21
40–49	19	26
50 and Over	25	20
All Ages	275	21

From data by Peart, A.F.W. *Canad. Pub. Health J.* 40:405, 1949.

considerable interest to know what human milk might do to the virus.

The results of simultaneous tests on the milk and serum of 40 Cincinnati mothers, summarized in Table 8, indicate that early as well as late milk contains a substance capable of neutralizing poliomyelitis virus.[41] However, unlike certain other antiviral factors which we have discovered in human milk, the antipoliomyelitic factor appears to be specific antibody synthesized in the breast and appears only in mothers with antibody in their serum and presumably, also, previous exposure to infection. However, experiments which I have carried out thus far with *Cynomolgus* monkeys infected with Y-SK virus by the oral route have failed to demonstrate that the drinking of antipoliomyelitic milk can prevent or modify the paralytic consequences of the infection. It is still possible that in human beings the consumption of very much larger amounts of milk and very much smaller amounts of virus may serve to diminish the incidence of infection during the period of breast feeding. However, the serological survey data shown in Table 6 indicate that approximately 80 per cent of the children were still without antibody by the end of the second year of life, when breast feeding usually ceases in Japan, Korea, and Okinawa. Accordingly, the lower incidence of paralytic poliomyelitis in the Far East and in certain other primitive communities cannot be attributed to subclinical immunization of infants under the influence of either placentally or milk-transmitted antibody.

ROLE OF SIZE OF INFECTING DOSE OF VIRUS

The possibility has long been entertained in epidemiologic thinking that the severity of an infection may depend on the size of the infecting dose. Accordingly, it has occasionally also been assumed that small doses of poliomyelitis virus might be more likely to give rise to clinically mild or inapparent infections, while larger doses might result in a higher incidence of the more severe paralytic infections. The difficulty with this hypothesis has been that no experimental confirmation of its occurrence could be obtained in animals infected by the intracerebral or intranasal routes. Experimental infection by these routes was pretty much an all-or-none phenomenon, i.e., a given dose of virus either produced paralysis, the severity of which was not dependent on the size of the dose, or no evidence of inapparently

TABLE 8

Antipoliomyelitic Activity of Undiluted Human Milk and Serum

Income Group	Days after Delivery	Milk: Number of Mothers Tested	Milk: Per cent Positive *	Serum: Number of Mothers Tested	Serum: Per cent Positive
Low	2 to 5	10	100	10	100 †
	38 to 340	20	75	20	100 †
Middle	2 to 5	10	40	10	50 †

* Positive = protected against at least 50 LD_{50} of Lansing virus.
† X^2 with Yates correction for small numbers = 12.9.

TABLE 9

Paralysis and Inapparent Infection in Two Groups of Cynomolgus Monkeys After Swallowing Same Amount of Y-SK Poliomyelitis Virus Twice Daily for 3 Days

Group 1—Milk given before and after virus
Group 2—No milk; half total dose of virus on "empty" stomach
(Same Lot of Virus Given to All Monkeys Simultaneously in One Experiment)

Group	Number of Monkeys	Paralysis Per cent	Polio Lesions but No Paralysis	Total Infection Based on Development of Antibody Per cent
Milk	26	54	0	96
"Empty" stomach	10	0	0	70

X2 with Yates correction for small numbers = 6.7; P = 0.01.

acquired immunity. The occurrence of nonparalytic infections in monkeys inoculated with certain freshly isolated strains has, as a rule, been found to be not dependent on the dose of virus.

I should like to present the results of a recent experiment with *Cynomolgus* monkeys infected by the oral route with the mouse-adapted Y-SK poliomyelitis virus which strongly suggests that the amount of "ultimately effective" virus can determine whether or not the consequences of the infection shall be predominantly paralytic or nonparalytic. The experiment, summarized in Table 9, was not planned as such but is the result of an accidental procedure by which the control monkeys received neither food nor water from 2 to 3 p. m. until about 10 a. m. the following morning and were given the first dose of virus on an empty stomach at 9 a. m. on each of the three days of virus administration. It should be pointed out that the method of infection was completely nontraumatic, in that the monkeys were merely allowed to swallow 2 ml. of 10 per cent virus suspension at 9 a. m. and 3 p. m. on each of three days. There was no swabbing or rubbing of the buccal or pharyngeal mucosa, as has been done by some other investigators.

The monkeys which received milk were allowed to drink 20 ml. of milk immediately before each dose of virus and also at noon, not only on the days of virus administration but also one day before and for three days thereafter. It may be seen that while 54 per cent of the monkeys which were drinking milk developed paralysis and 96 per cent developed antibodies for the virus, none of the 10 control monkeys, which received half the total dose of virus on an empty stomach, developed either paralysis or poliomyelitic lesions in the nervous system, and yet 70 per cent developed neutralizing antibodies.

Faber and Dong [42] have reported that Lansing virus is rapidly destroyed at a pH which is found in an "empty" stomach. The most plausible explanation of the results of this experiment is that the milk neutralized the stomach acidity and more of the virus was available for infection. Other experiments have indicated that a drink of water immediately before the virus also increases the incidence of paralysis but is not as effective as milk. The possibility that small doses of virus taken by mouth can give rise to immunity with only a small risk of paralysis and that such simple physiologic factors as increased stomach acidity can serve to reduce the size of the infecting dose are of great epidemiologic importance and will be the subject of considerable additional experimentation. It is also clear that in population groups which live under conditions that are especially conducive to extensive dissemination of poliomyelitis virus, the continuous availability of small doses of virus may be an important

factor in the acquisition of immunity without paralysis.

OTHER FACTORS PREDISPOSING TO PARALYTIC CONSEQUENCES OF POLIOMYELITIS INFECTION

Such factors as tonsillectomy, severe exertion, pregnancy, and various inoculations may under certain conditions serve to convert any otherwise inapparent or nonparalytic infection into a paralytic disease. Some of these factors are also more common in some population groups than in others. The 1936 report by Lambert [43] of a severe epidemic of paralytic poliomyelitis among Samoan children inoculated with neoarsphenamine for yaws provides a good example not only of one way in which "civilization" may contribute to the increase of paralytic poliomyelitis, but perhaps also one of the earliest incidents suggesting the role of inoculations at a time when a virulent virus is widespread. The Samoans believed that the neoarsphenamine injections were responsible for the paralysis, while Lambert and his associates thought that it was pure accident, since the disease was typical of poliomyelitis. Since the paralysis, as a rule, affected first the inoculated extremity within seven to ten days after the injection, it is quite probable, in the light of more recent observations on the effect of other types of inoculations during epidemic periods, that the combined views of the Samoans and of Dr. Lambert were closest to the truth.

SYNTHESIS

The data that I have presented in my opinion justify the conclusion that the paralytic consequences of poliomyelitis infection are not the same in different parts of the world and in different population groups. Experimental observations on other neurotropic viruses, as well as epidemiological observations on human beings, suggest that genetic factors are of importance in determining whether poliomyelitis infection shall result in paralysis, minor illness, or inapparently acquired immunity. The extraordinarily high paralytic attack rates among certain highly inbred and isolated population groups in the Arctic, as well as in the tropics, may very well be a reflection of the genetic constitution of that particular population. An analysis of a variety of epidemiologic data leads to the conclusion that epidemics are caused by strains of virus of unusual virulence and that during the interepidemic years strains that are immunologically identical or related but of low virulence are also widely disseminated.

The incidence of paralytic poliomyelitis during interepidemic years is relatively low even in communities in which poliomyelitis is an important problem. The frequency with which epidemics strike a given community actually determines whether, over the years, the incidence of the paralytic consequences of poliomyelitis infection shall be high or low. Thus, the march of epidemics is in fact equivalent to the dissemination of strains of virus of high virulence among populations that are insufficiently immunized by strains of low virulence. The low incidence of paralytic poliomyelitis, even among the children of the Far East, Africa, and certain other primitive population groups, at a time when virulent virus is known to be in their midst, as indicated by the high attack rates among adult foreigners in their midst, cannot be attributed to subclinical immunization of infants under the influence of either placentally or milk-transmitted antibody, because serological surveys have revealed that 80 to 90 per cent are still without antibody at the end of the first or second year of life. Serological surveys furthermore have brought forth more than suggestive evidence that the incidence of paralytic poliomyelitis is

inversely proportional to the extensiveness of viral dissemination. In general, the poorer the population, its standard of living and sanitation, the more extensively is poliomyelitis virus disseminated among them and the lower is the incidence of paralytic poliomyelitis when virulent strains of virus come their way.

Experimental observations on infection of *Cynomolgus* monkeys by the oral route suggest that small doses of virus can give rise to immunity with only a small risk of paralysis, and that such simple physiologic factors as increased stomach acidity can serve to reduce the size of the infecting dose. Population groups which live under conditions that are especially conducive to the continuous dissemination and consumption of small doses of virus may thus be in the best position to acquire poliomyelitis immunity without paralysis.

In a recent newspaper I read an account of the first English translation of important letters by Sigmund Freud. In one of these letters Freud wrote: "Even lectures I have given up, in order not to be forced to tell something that I only hope to learn some day." I realize now how much his observation applies to the lecture I have just given and can only hope that this lecture will stimulate rather than inhibit the learning process.

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New Markle Scholar Nominations

Nominations for the fifth group of Scholars in Medical Science are now invited by the John and Mary R. Markle Foundation. The dean of each medical school may nominate one candidate—on or before December 1, 1951. The grants are intended for candidates who have completed the usual fellowship training in an area of science related to medicine and who hold full-time faculty appointments in a medical school for the academic year 1952–1953. A grant of $30,000—payable $6,000 annually for 5 years—is made to the school toward the support of each scholar and his research.

A total of 67 scholars in the United States and Canada are currently being aided through these research grants. In both 1950 and 1951, 20 were selected. The number for the coming year has not been determined. A booklet of complete information about the plan and suggestions for making nominations is available from the Foundation, 14 Wall St., New York 5.