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SCIENCE

Pathogenesis of Poliomyelitis

Reappraisal in the Light of New Data

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The questions of special current interest in the pathogenesis of poliomyelitis are concerned with (i) the origin of virus in the alimentary tract, (ii) the source and significance of viremia, (iii) the mode of invasion of the central nervous system, and (iv) the factors which determine invasion and variations in the extent of involvement of the central nervous system. Concepts of the pathogenesis of poliomyelitis have varied and changed over the years with each new advance in our knowledge of the nature and behavior of the causative agent. Soon after the discovery of the virus, poliomyelitis was compared to meningococcic meningitis—the virus was pictured as propagating in the nasopharynx and occasionally invading the central nervous system across the hematoencephalic barrier. When experimental work indicated that polio as well as certain other neurotropic viruses had the capacity of spreading along insulated neural pathways, poliomyelitis was pictured as an infection in which the virus multiplied in the nose and spread to the central nervous system along the olfactory pathway. The experiments with the old MV strain of polio virus, which we now recognize as a strict neurotropic variant selected by repeated intracerebral passages in monkeys, and on which this concept was chiefly based, are as valid today as they ever were, but the inferences with respect to the natural disease became untenable when olfactory blockade in human beings failed to prevent poliomyelitis (*1*) and when the olfactory pathways were not found to be involved in the human disease (*2, 3*). In 1944, after a study of the localization of virus in human beings and in cynomolgus monkeys infected by the oral route with recently isolated virus, I proposed the following course of events as a working hypothesis of the pathogenesis of poliomyelitis: the virus entered by way of the mouth, localized, and multiplied in various levels of the alimentary tract with incidental invasion of the lymph nodes, blood, and viscera and with occasional invasion of the central nervous system along neural pathways connected with the peripheral sites of viral multiplication (*4*).

When it was subsequently found that virus was readily detected in the blood of monkeys, chimpanzees, and human beings in the early stages of infection (*5*) and that amounts of antibody, which were incapable of protecting monkeys from paralytic infection via the olfactory neural pathways, were protective in monkeys that received virus by the oral or intramuscular routes (*6*), Bodian interpreted the available data as indicating that the virus in the blood passed into the central nervous system across certain limited (presumably modified) vascular zones, but because of the character of the distribution of lesions in the central nervous system, he still found it necessary to assume that from the point of penetration further spread within the central nervous system occurred along specific neural pathways. When Bodian found virus in pieces of intestine containing Peyer's patches but not in adjacent pieces of ileum, he proposed that polio virus multiplies initially only in the tonsils and Peyer's patches. From these lymphatic collections, the virus was pictured as moving outward onto the surface of the alimentary tract and inward into the blood, which distributed it to other susceptible "target organs" such as lymphatic structures, "brown fat," and the central nervous system (*7*).

This interpretation of the existing data has come to be regarded as the theoretical basis for explaining the ability of relatively small amounts of antibody, either passively introduced or actively induced by killed virus vaccine, to prevent invasion of the central nervous system and the resulting paralysis. If this view is correct, the effect of the presence of antibody prior to infection should be all or none with regard to involvement of the central nervous system—that is to say that, if invasion is not prevented, there should be no modifying effect on the extent of involvement leading to nonparalytic or milder paralytic forms of the disease. The observations of Francis and his associates (*8*), however, suggested that the incidence of nonparalytic infections of the central nervous system due to polio virus was not strikingly affected during the 1954 field trials of the Salk vaccine, and there were also indications that in general the paralytic disease was milder when it was not prevented in vaccinated individuals. Hammon and his associates (*9*) had previously also suggested a modifying effect of antibody when paralysis was not prevented during the field trial of gamma globulin.

Faber (*10*) brought forth evidence of early invasion of the regional nerve ganglia after feeding polio virus to cynomolgus monkeys, and he has maintained that polio viruses multiply only in nerve cells in monkeys and human beings. According to this view, the ingested virus is absorbed by the nerve endings of the buccopharyngeal and lower alimentary mucosa, multiplies in the neurons of the regional ganglia, and from there moves centrifugally back into the mouth and throat and sometimes also centripetally into the central nervous system. Viremia, according to Faber, is the result of the continued absorption of this excreted virus into the lymphatics of the alimentary tract with an ultimate overflow into the blood. Having demonstrated that direct inoculation of thousands of infective doses of virus into the vertebral artery produced specific lesions in the spinal cord, Faber assumes that virus which is absorbed into the blood from the alimen-

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tary tract in sufficient concentration to reach the arterial circulation can invade the spinal cord directly. The central nervous system would thus sometimes be invaded by neural pathways and sometimes directly across the blood vessels.

Alimentary Tract

During the past 4 years I have been engaged in extensive quantitative studies dealing with variation among polio viruses and with comparative studies of their behavior in monkeys, chimpanzees, and human volunteers (*11–15*). The various aspects of these studies have thus far required the use of approximately 7500 monkeys, 134 chimpanzees, and 118 adult human volunteers. Although these studies were primarily designed to provide basic information relative to the possibility of using attenuated live viruses for immunization against poliomyelitis, much of the new knowledge thus acquired of necessity has a direct bearing on our understanding of the pathogenesis of poliomyelitis.

Sensory Nerve Ganglia

First and foremost in this respect is the accumulated evidence that the capacity to damage neurons and the capacity to multiply in certain extraneural tissues, especially in the alimentary tract, represent distinct and independent properties of polio viruses. Thus it has been proved that variants which are incapable of producing either paralysis or lesions after direct inoculation of millions of infective doses into the gray matter of the lumbar cord of chimpanzees can nevertheless multiply extensively in their alimentary tracts (*14*).

Using the titer of a virus in monkey kidney tissue culture as a standard of reference, it has been established that different strains of experimentally segregated, as well as naturally occurring polio viruses, exhibit a very wide spectrum of neurotropic activity as measured by the number of tissue culture doses required to produce paralysis by intracerebral or spinal inoculation in monkeys. The spectrum ranges from the most highly neurotropic strains which are paralytogenic on intracerebral inoculation of 1 to 10 TCD_{50}, to those which in doses of 10^6 or more fail to produce paralysis in intracerebrally inoculated animals but are still paralytogenic by the spinal route in relatively small doses, to the lowest in the neurotropic series which require 1 million or more infective doses to produce a localized, nonprogressive paralysis in an occasional monkey when the doses are inoculated directly into the gray matter of the spinal cord.

Among the primates, there is now definite evidence that the neurons of the anthropoid chimpanzee are more resistant than those of the monkeys. Attenuated strains which are still paralytogenic in moderate doses by spinal inoculation in monkeys have invariably failed to produce paralysis in chimpanzees inoculated intraspinally with 10^6 to 10^7 infective doses; a total of 53 chimpanzees have now been tested in this manner with various strains of each of the three types of polio virus. Direct spinal inoculation of virulent strains obtained from the central nervous systems of human cases readily produced paralysis in chimpanzees, and Howe, Bodian, and Morgan (*16*) showed that even feeding of virulent strains can produce paralysis in at least 20 percent of the chimpanzees. The usually lower incidence of paralysis in nonimmune human beings even during severe epidemics is a strong indication that the neurons of the human species are at least as resistant as those of the chimpanzee.

It is of special significance in understanding the pathogenesis of poliomyelitis in different hosts that, with regard to the susceptibility of the alimentary tract, the primates were found to occupy a position which is the reverse of that obtaining for the neurons. Here actual quantitative tests with the same culture of attenuated virus (*15*) have shown that human beings are the most susceptible and monkeys the least susceptible, with chimpanzees in the middle (Table 1).

Alimentary Tract

I should now like to consider some of the data which have a bearing on the multiplication of polio viruses in the alimentary tract of monkeys, chimpanzees, and human beings. To begin with, a high degree of neurotropism does not by itself suffice to establish infection when virus is given by mouth. Melnick (*17*) obtained no evidence of infection in 21 cynomolgus monkeys that were repeatedly fed a monkey-pathogenic strain of Lansing virus. Neither clinical signs nor antibody—the most sensitive indicator of inapparent infection—appeared in any of 23 cynomolgus monkeys to which we had fed special variants of either the Lansing or MEF_1 strains that had high intracerebral activity in monkeys (*18*). From a Y-SK strain which was highly paralytogenic in cynomolgus monkeys by the oral route, it was possible, by a special mode of passage in mice, to obtain a variant that retained its full intracerebral virulence for monkeys but lost almost all its capacity to infect by the oral route (*13, 18*).

Not only must the virus possess the proper genetic constitution to permit it to multiply somewhere in the alimentary tract, but the tissues of the alimentary tract with which it comes in contact must in turn possess the necessary characteristics to support its growth. Thus, a simultaneous test in 40 cynomolgus and 20 rhesus monkeys indicated that an oral dose of the paralytogenic Y-SK strain that produced 97-percent infection and 62-percent "nonolfactory" paralysis in the cynomolgus monkeys produced only 40-percent infection in the rhesus monkeys and no nonolfactory paralysis (three of the rhesus became paralyzed but all had lesions in the olfactory pathways) (*18*). This test showed that the alimentary tract of rhesus monkeys is even less susceptible than that of cynomolgus monkeys, and although the virus is equally neurotropic for both, the alimentary infection in the rhesus monkeys was not associated with invasion of the central nervous system.

Evidence was also obtained that in the cynomolgus monkey the upper alimentary tract is more susceptible than the lower. In a simultaneous test using the paralytogenic Y-SK strain, the incidence of total infection was 100 percent and the incidence of nonolfactory invasion of the central nervous system was 75 percent among a group of 28 monkeys that received the virus by mouth without trauma, while among 17 monkeys that received the same dose by stomach tube, the incidence of total infection was only 41 percent and the incidence of nonolfactory invasion of the central nervous system was only 23 percent (*18*).

The greater sensitivity of the chimpanzee alimentary tract has been demon-

Table 1. Inverse position of primates with regard to susceptibility of nervous system and alimentary tract.

CELLS	MOST SUSCEPTIBLE ⟶			MOST RESISTANT
NEURONS	MONKEY (Lower motor),	MONKEY (Brainstem),	CHIMPANZEE (Lower motor),	MAN
ALIMENTARY TRACT	MAN,	CHIMPANZEE,	CYNOMOLGUS,	RHESUS

strated (*16*) with the Lansing strain that was inactive in cynomolgus monkeys and with two attenuated type I strains that had a very limited activity in these monkeys (*14*). The fact that human volunteers were shown to be infected by mouth with doses of attenuated strains that were inactive in chimpanzees would appear to be the result of the greater sensitivity of the lower alimentary tract of human beings (*15*). Thus, in human volunteers virus multiplication in the oropharynx occurred regularly when the amount of virus swallowed in a teaspoonful of milk or cherry syrup was 10^6 TCD_{50} or more and only occasionally when the dose was 10^5 TCD_{50} or less. Infection limited to the lower alimentary tract has now been observed in 33 volunteers who swallowed the smaller doses of virus. The amount of virus recovered per gram of stool was about the same in those who had no demonstrable virus in the throat at any time as in those whose throats regularly yielded considerable quantities of virus. There was no evidence of viral multiplication in the buccal mucosa, gums, or anterior portion of the tongue, regardless of the dose fed to human volunteers (*15*).

A similar study (in association with Gerald Berg) on a group of 29 patients with naturally occurring paralytic or nonparalytic poliomyelitis, from all of whom polio virus was recovered within 2 to 8 days after the onset of symptoms, yielded no evidence of viral multiplication in the buccal mucosa, gums, anterior portion of the tongue, or nasal mucosa. In view of the results obtained with the smaller doses of the attenuated viruses, it was surprising to find that virus could be recovered from the throat of 75 percent of the patients. Such a high incidence might be expected to occur either as a result of swallowing 1 million or more infective doses or as a result of secondary localization from the blood following infection with "viremic" strains.

Quantitative studies on the amount of virus present on the surface of the oropharynx in human volunteers and patients showed great variation from mere traces to as much as 10^5 to 10^6 TCD_{50} per swab, depending mostly on the stage of infection and the strain of virus. The peak throat titers found among 18 patients early after the onset of symptoms were not higher than those observed in volunteers who received large doses of the attenuated strains. After the deposit of about 10^5 infective doses on the human throat by direct swabbing, there was first a latent period of about 24 hours during which no virus could be recovered; this was followed by a period of 7 to 10 days (rarely 14 to 21 days) during which the amounts of virus recovered reached peak levels and then gradually declined.

It has been assumed by some that the earlier disappearance of virus from the throat than from the stools is due to the appearance of antibody. In the majority of the volunteers, there was indeed a high correlation between these two events, but no such correlation was found among the patients. Nine patients had antibody titers of 1:64 to 1:384 at a time when as many as 10^3 to $10^{4.5}$ TCD_{50} were recovered per throat swab. The antibody titers of the six patients from whose throats no virus was recovered were about the same as those among the 18 patients from whose throats virus was recovered. It is not improbable that the main reason for the earlier disappearance of virus from the throat is that the available area for virus propagation is but a small fraction of that available in the many feet of intestines. It may also be worth noting here that with large doses of some of the naturally occurring attenuated strains, a certain proportion of the volunteers who had virus in their throats experienced a soreness of the throat, as a rule, about 75 hours after ingestion of the virus; this rarely lasted for more than 24 hours despite the fact that peak titers of virus continued to be recovered from the throat for many days thereafter.

Lymphatic Structures

The question whether the virus multiplies only in the lymphatic structures of the alimentary tract or in its surface epithelium can be analyzed only indirectly. Virus multiplication was as extensive in the throats of the human volunteers without tonsils or adenoids as in those who still had these structures. Although it, therefore, cannot be said (as Bodian, *7*, and Verlinde *et al.*, *19*, have stated) that the tonsils are the primary sites of infection, this does not eliminate the small lymphoid follicles in the mucosa as possible sites for viral multiplication.

Neither Bodian (*7*) nor Verlinde *et al.* (*19*) tested the washed pharyngeal wall in their experiments. Quantitative tests on the distribution of virus in the alimentary tract, lymph nodes, viscera, and nervous system were made in my laboratory (in association with Carlo Moscovici) on chimpanzees that died of intercurrent bacterial infections at different times after they had been fed attenuated type I polio viruses (Table 2). The amount of virus per gram of washed pharyngeal wall in chimpanzee A ($10^{5.2}$ TCD_{50}) was about 100 times more than Bodian found in the tonsils of two of his chimpanzees and 10,000 times more than that found in a third chimpanzee that he sacrificed during the "previremic" period after it had been fed virulent strains of virus.

Our data also show that the pharyngeal tissue with its smaller complement of lymphoid tissue in the mucosa contained 1000 times more virus than the ileum and jejunum with their large complement of Peyer's patches. It is furthermore noteworthy that the amount of virus found in the deep cervical and mesenteric lympth nodes showed the same approximate 1000-fold difference. This may be interpreted as indicating that the attenuated strains used in these tests did not multiply in the lymph nodes and that the virus was there as a result of lymphatic drainage from the sites of multiplication in other alimentary mucosal structures.

Another bit of evidence indicating that a strain of virus which cannot multiply in lymphoid tissue can nevertheless multiply in the alimentary tract was obtained in tests on human volunteers with our attenuated, type III Leon virus (*15*). A dose of $10^{4.4}$ TCD_{50} of this virus given by mouth produced an immunogenic alimentary infection of 4 to 6 weeks' duration in each of three volunteers, while $10^{6.4}$ TCD_{50} given intramuscularly to one and $10^{4.4}$ TCD_{50} given to another failed to produce antibody or other evidence of infection. To prove that these two men were susceptible to infection with this virus, they were both fed $10^{6.4}$ TCD_{50} of the same culture fluid 3 months later, and both developed an immunogenic alimentary infection. Since the intramuscularly injected virus must have reached the lymphatics, it is evident that this particular strain, although it is unable to multiply in the lymphatics, can multiply in the alimentary tract.

Still another factor that militates against the lymphoid tissue as the source of virus in the alimentary tract is the often long-continued elaboration of large amounts of virus in the lower alimentary tract long after antibody of considerable titer has developed. It has been demonstrated with many viruses that lymph nodes become noninfective when antibody appears. In our studies (*3*) on seven fatal human cases, no virus could be recovered from the cervical and mesenteric lymph nodes in patients who at necropsy had demonstrable virus in the pharyngeal mucosa or the intestinal wall, or both. In chimpanzee B, which died of intercurrent infection 4 days after the first appearance of a trace of antibody, the deep cervical lymph nodes had only 100 TCD_{50} per gram, while the washed pharyngeal wall had 5000 TCD_{50} per gram (Table 2).

In my opinion, all factors considered together point against both the sensory nerve ganglia and the submucosal lymphatic structures as the source of virus in the alimentary tract, and they favor the superficial epithelium of the alimentary mucosa as the site for primary virus multiplication. The absence of obvious lesions in this site does not militate against this conclusion since large amounts of virus can be released by cells which remain morphologically intact. In

my laboratory we have observed the release of millions of infective doses of dengue (*20*) and Japanese B encephalitis (*21*) viruses in tissue cultures of monkey kidney epithelial cells which remain morphologically intact and continue to metabolize.

Viremia

Viremia in poliomyelitis must also be considered from a quantitative as well as from a qualitative point of view. Bodian (*22*) has clearly shown that in monkeys some strains produce an extensive viremia with as many as 10^5 infective doses per milliliter of serum which does not disappear until antibodies are formed, while others give rise only to a negligible, barely detectable and transitory viremia which disappears long before antibody is formed. Both the extent and possibly also the sites of viral multiplication must obviously be different in these instances.

In our studies on chimpanzees (*14*) that were either fed or inoculated intramuscularly, and on human volunteers who were fed the laboratory-developed attenuated strains, we have never been able to detect viremia in repeated tests during the "preantibody" phase of the infection. These studies involved tests on a total of 40 chimpanzees and 72 human volunteers infected with strains of each of the three types of polio virus. Since these strains multiplied to very high levels in the alimentary tract of both chimpanzees and human beings, and since the chimpanzee study indicates that the deeper lymphatics are also invaded, it is clear that readily demonstrable viremia, to say nothing of high levels of viremia, must result from multiplication in sites other than the alimentary tract.

The small amount of virus found in the spleen of one chimpanzee (Table 2) in the absence of demonstrable viremia suggests that amounts of virus too small to be detected may spill over from the lymphatics and be taken out by the spleen. In some of the chimpanzees and human volunteers who received certain naturally occurring attenuated strains, traces of virus (about 1 infective dose or less per milliliter) could be detected for a brief period 3 to 5 days after ingestion of the virus and became undemonstrable long before antibody appeared. The studies of Wenner and Kamitsuka (*23*) on monkeys that were inoculated intramuscularly with a virulent strain of Brunhilde virus which yielded viremic levels as high as 10^5 to 10^7 infective doses per milliliter of blood showed the presence of large amounts of virus in all the lymph nodes tested, in the axillary fat, and in the adrenals, as well as in the inoculated muscle, even at a time when the blood no longer had demonstrable virus. Whatever the precise additional extraneural sites of multiplication may be, it is clear that significant levels of viremia occur only when a strain of polio virus can multiply in those tissues as well as in the alimentary tract or nervous system.

Table 2. Distribution and concentration of type I polio virus in tissues of chimpanzees dying of other causes at indicated time after oral administration of indicated dose and strain of attenuated virus. Titers represent the number of infective doses per gram as determined by tests in cynomolgus kidney tissue cultures.

Tissues assayed for virus	Chimpanzee A L Sc-$10^{7.4}$ 27 days	Chimpanzee B "P 1553"-$10^{6.7}$ 18 days	Chimpanzee C "80-4"-$10^{7.5}$ 15 days
Alimentary tract			
Pharynx, washed tissue	160,000	5000	
Jejunum, washed tissue	32	0*	0
Jejunum, contents	160	0*	0
Ileum, washed tissue	100	0*	0
Ileum, contents	16,000	0	0
Transverse colon, washed tissue	0	0	0
Transverse colon, contents	16,000	1600	1600
Lymph nodes			
Deep cervical	500,000	100	
Mesenteric	160	0*	
Axillary	1,600†	32†	
Inguinal	0	0	
Viscera			
Lungs	500‡	0	0
Spleen	500	0	
Liver, kidneys, adrenals§	0	0	0
Axillary "brown fat"	0	0	
Periperal nerve ganglia			
Sup. cervical sympathetic	500	32	
Thoracic spinal and sympathetic	25	0	
Grasserian	32	0	
Coeliac		0	
Central nervous system			
Spinal cord	0	0	0
Medulla	0	0	
Viremia, tested at 3, 5, 7, 10, 14, and 21 days	0	1 per ml 5th day only	0
Antibody at time of death	0	1:4	1:20
Virus in feces during life	32 to 1000	+	1600 to 50,000

* Although no polio virus was recovered, small amounts of an enteric cytopathogenic agent with a long incubation period in tissue culture were present.
† The presence of virus in the axillary lymph nodes may be accounted for by absorption from cracks in the skin of the hands, which are constantly contaminated with feces.
‡ Terminal aspiration of virus from the pharynx into the lungs cannot be excluded as a possibility in this chimpanzee, which died of a bronchopneumonia. Blood obtained post-mortem by cardiac puncture through the chest wall and possibly also the lungs contained about one infective dose per milliliter.
§ The liver, kidneys, and adrenals were tested separately.

Mode of Invasion of Central Nervous System

And what do the available data permit us to say about invasion of the central nervous system? Faber (*10*) has shown that the regional nerve ganglia can be invaded early after ingestion of virus, and Verlinde *et al.* (*19*) have recently shown the presence of virus in the regional ganglia of the alimenary tract of orally infected cynomolgus monkeys at a time when no virus was found in the central nervous system. The data shown in Table 2 indicate that even a strain of virus that produces no detectable viremia and neither paralysis nor lesions on direct intraspinal inoculation in chimpanzees (eight chimpanzees were so tested with the strain fed to chimpanzee A) can nevertheless be found in minimal amounts in a pool of the thoracic spinal and sympathetic ganglia, as well as in the Gasserian and superior cervical sympathetic ganglia of a chimpanzee with virus multiplication in the throat and gut. Partial serial sections of the unassayed halves of the superior cervical sympathetic and Gasserian ganglia revealed neither neuronal lesions nor collections of lymphatic cells. In chimpanzee B, following ingestion of a naturally occurring attenuated strain, we also found a trace of virus in the superior cervical sympathetic ganglia, but not in the Gasserian, coeliac, or thoracic spinal and sympathetic ganglia. Bodian (*7*) tested only the Gasserian and coeliac ganglia of three chimpanzees with negative results.

Since the oropharynx is the site of greatest multiplication in the chimpan-

zee and since the Gasserian ganglia send only few or no fibers to this region, these negative results are not significant. The invasion of specific peripheral ganglia prior to the invasion of the central nervous system itself is best explained by neural spread from a site of viral multiplication, and polio viruses which undeniably exhibit the property of moving along insulated neural tracts and across synaptic junctions of neurons within the central nervous system can be expected to exhibit the same property in the neurons outside the central nervous system.

There appears to be no valid reason for assuming, as Verlinde *et al.* (*19*) have done, that virus in the blood would localize only in those peripheral nerve ganglia which are connected with sites of viral multiplication and not in other nerve ganglia or in the central nervous system. The assumption (*24, 25*) that there may be reflex vascular changes which might account for the highly localized penetration of virus into the central nervous system is not supported by the demonstration of Verlinde *et al.* (*19*) that in orally infected monkeys the virus can be in the blood stream and peripheral ganglia for several days before it is found in the central nervous system, and that when diphtheria toxoid is injected intramuscularly in one leg of such monkeys, virus is first found only in the corresponding sciatic nerve and not in the central nervous system. Bodian's experiment (*25*) on the failure of nerve freezing to prevent localization of paralysis in legs subjected to traumatic intramuscular injections when a highly viremic strain of virus is injected into the heart does not preclude the possibility of virus localization in the injured nerves with subsequent centripetal progression into the central nervous system. The early experiments of Bodian and Howe (*26*) with the almost strictly neurotropic MV strain of polio virus in which freezing effectively interrupted passage of virus along the sciatic nerve also showed that the nerve fibers central to the frozen area were still capable of conducting virus into the central nervous system.

Perhaps the best model among other neurotropic viruses for what may happen in poliomyelitis is to be found not among the arthropod-borne encephalitis viruses which can enter the central nervous system at numerous sites, apparently by multiplication across the blood vessels, but rather among the pantropic viruses of the pseudorabies-B virus-herpes group which have been shown to multiply in various viscera and then spread into the central nervous system along neural pathways via the regional ganglia. The intranuclear inclusions produced by the herpes group of viruses and the fact that rabbits infected with pseudorabies virus regularly bite the skin areas corresponding to the sensory ganglia that are first involved provide excellent indicators of the pathways pursued by these viruses into the central nervous system (*27*). In rabbits that were inoculated intravenously in the ear with B virus, specific lesions were found in the stomach and intestines, the liver, spleen, and adrenals, and the earliest neuronal lesions were found in the thoracic spinal ganglia and spinal cord but not in the other spinal ganglia or in the cervical and lumbar enlargements of the cord, brainstem, or brain (*28*).

With these and other neurotropic viruses, it has been shown that extensive multiplication in the nonnervous tissue must occur before the virus can invade the nerve endings except after traumatic inoculations of very large quantities. In muscle fibers, and perhaps also in other cells; the nerve endings are in very intimate association with the cell walls and may not be affected until the virus has multiplied to a certain level within these cells. Antibody or other factors which may modify or prevent viral multiplication may be expected also to influence invasion of peripheral nerve endings.

In poliomyelitis one must, therefore, keep in mind that the neural pathways for invasion of the central nervous system may be expected to vary in different species and different individuals, depending on the extraneural sites sustaining the most extensive multiplication of the virus. According to this view, polio virus in human beings might be expected to invade neural pathways not only from some portion of the alimentary tract in which primary multiplication may be most extensive but also and perhaps even more readily from those other extraneural tissues that are secondarily infected by virus from the blood. By preventing secondary localization in parenteral extraneural tissues, as well as by influencing the extent and level of viral multiplication in the alimentary tract, circulating antibody could greatly affect both the incidence and extent of involvement of the central nervous system. Thus the observation that relatively small amounts of antibody can prevent paralysis would not necessarily indicate that virus invades the nervous system across blood vessels. The potential capillary damage produced by direct intraarterial injection of a virus suspension as was done by Faber and Dong (*29*) cannot be taken as evidence that the same would occur under natural conditions.

Factors Involved in Invasion of Central Nervous System

Among the factors which determine whether or not the central nervous system shall be invaded, the most important in naturally occurring infection is probably concerned with the neurotropism of the virus. Our studies on 49 strains of polio virus derived from healthy children under epidemiologically quiescent conditions indicated great variation in neurotropism as measured by quantitative methods in monkeys. Thus far, I have obtained only highly neurotropic strains from the central nervous system of fatal human cases. The spread of polio virus from one neuron to another or from a group of neurons in one site of the central nervous system to another more remote group is influenced by the extent of viral multiplication. The lower the neurotropism of a strain, the lower the level of multiplication and the larger is the dose required to initiate a spreading and clinically recognizable infection. The behavior of low neurotropic strains in relation to the most highly susceptible lower motor neurons of the monkey may be comparable to the behavior of high neurotropic strains in relation to the more resistant neurons of the chimpanzee and presumably also of man. It may be expected, therefore, that in human beings low and moderately neurotropic strains would fail to get beyond the first group of neurons that may be invaded, and the extent of spread of the most highly neurotropic strains may be expected to be influenced by the amount of virus that invades the peripheral ganglia and the central nervous system.

There is more than suggestive evidence that previous infection with certain heterotypic strains of polio virus may influence the incidence of paralysis. Experiments in my laboratory have shown that in cynomolgus monkeys, which were previously either infected inapparently with the type II, Y-SK strain per os (*30*) or immunized with Y-SK formalinized vaccine (*31*), the incidence of paralysis following ingestion of the highly virulent type I Mahoney strain was only one-half to one-third of that occurring in large numbers of simultaneously infected controls; since the remaining monkeys developed antibody without paralysis, it is evident that the heterotypic immunity did not prevent infection but only reduced the incidence of paralysis. Horstmann (*32*) reached a similar conclusion regarding the effect of heterotypic immunity in human beings from an epidemiologic analysis of the incidence of paralytic and nonparalytic infections in different age groups.

While the generally greater severity of the paralytic disease in human adults may be related in part at least to fatiguing work or exercise, it is also possible that the neurons themselves are different and that, as in mice (*33*), spreading infections in the central nervous system are more readily produced by small doses of virus in adults than in the very young. The fact that the influence of exhausting ex-

ercise and work in increasing the incidence as well as the severity of paralysis is observed usually within about 24 hours and especially in individuals with signs and symptoms suggestive of early involvement of the central nervous system (*34*) indicates that this provoking factor acts not by aiding invasion of the virus into the central nervous system but rather by inducing more extensive involvement of the neurons corresponding to the exercised muscles. One patient put it very succinctly to me: "The muscles I used are the muscles I lost."

The unusually high incidence of paralysis among certain isolated, and of necessity also highly inbred, population groups may reflect the influence of genetic constitution in addition to their virgin immunologic status and the virulence of the particular strain of virus (*35*). Experimental inoculations of very large doses of cortisone have led both to more extensive multiplication in certain extraneural tissues of hamsters and to more extensive neuronal involvement in the central nervous system of hamsters and monkeys (*36, 37*), but whether or not the large amounts of adrenocortical hormones required for such an effect are liberated under natural conditions of "stress" is open to question. Since the number of circulating eosinophiles provides a measure of the extent and duration of excessive adrenocortical secretion, G. R. Nugent and I in 1952 investigated 83 patients by means of daily eosinophile counts during the febrile and postfebrile periods; no difference was found between those who had developed paralysis (37 patients) and those who had not (27 patients), and the pattern in both groups was not significantly different from that observed in 19 patients with other febrile illnesses.

Synthesis

The diagram in Fig. 1 illustrates a reconstruction of the pathogenesis of naturally occurring poliomyelitis based on my interpretation of currently available data. According to this view, the ingested virus first attaches itself to the superficial epithelium of the mucosa of the oropharynx (only occasionally when the amount is less than 1 million infective doses) and of the lower alimentary tract and multiplies there, extending from one group of cells to another until developing resistance halts further propagation. Virus liberated in the oropharynx ordinarily is not found in detectable amounts in the mouth and probably does not contribute much to the virus present in the stool except when it infects the lower alimentary mucosa. The last statement is based on the fact that no virus has been recovered from the stools of immune volunteers who swallowed 1 to 10 million infective doses when no multiplication occurred.

The virus in the feces is derived chiefly from the cells of the lower alimentary mucosa. From the superficial mucosal cells, the virus is absorbed into the regional lymph nodes. With certain attenuated strains, the amount of virus in the regional lymph nodes is proportional to the extent of multiplication in the mucosa, and there is no evidence of multiplication in them. Other strains may multiply in the lymph nodes. When the amount in the lymph nodes exceeds that which the cells can absorb, there is an overflow into the blood.

Virus reaching the blood is quickly removed by the cells of the reticulo-endothelial system and certain other tissues. No significant viremia occurs unless the virus so distributed by the blood can multiply in a variety of extraneural tissues—this is a property possessed to a varying degree by some strains of polio virus and not by others. Virus in the blood can also localize in the alimentary mucosa, and it is conceivable that the high incidence of virus in the oropharynx of clinically diagnosed cases of poliomyelitis may in large part be due to this mechanism rather than to the initial ingestion of as much as 1 million or more infective doses of virus.

From the various sites of multiplication in the alimentary tract and other extraneural tissues, the virus is then visualized as invading the corresponding sympathetic or sensory peripheral ganglia, and if the dose is large enough and the strain of virus is sufficiently neurotropic, enough multiplication occurs in this first group of neurons to permit invasion of the corresponding area of the central nervous system. Here it is important to keep in mind that invasion of the terminal nerve endings can also be influenced by the extent of viral multiplication in the nonneural cells with which they are in contact and that this process of neural invasion may occur more readily from some tissues than from others. Further progression within the central nervous system would also be along neural pathways and would also be influenced by the dose and the neurotropism of the virus. According to this interpretation of the observed phenomena, antibody would exert its main effect on the sites of extraneural multiplication. While even large amounts of antibody may not be able entirely to prevent infection of the superficial cells of the lower alimentary mucosa, particularly when the infecting dose is large, any level of antibody could interfere with the amount of virus absorbed by the peripheral nerve endings in the alimentary mucosa, and by preventing secondary localization of virus in other tissues as well as in the alimentary tract, it has the capacity of preventing or greatly reducing the extent of invasion of various peripheral nerve ganglia. According to this view, antibody would have the function not only of completely preventing invasion of the central nervous system but also of reducing the amount of virus that might invade and thereby increase the proportion of nonparalytic and mild infections of the central nervous system.

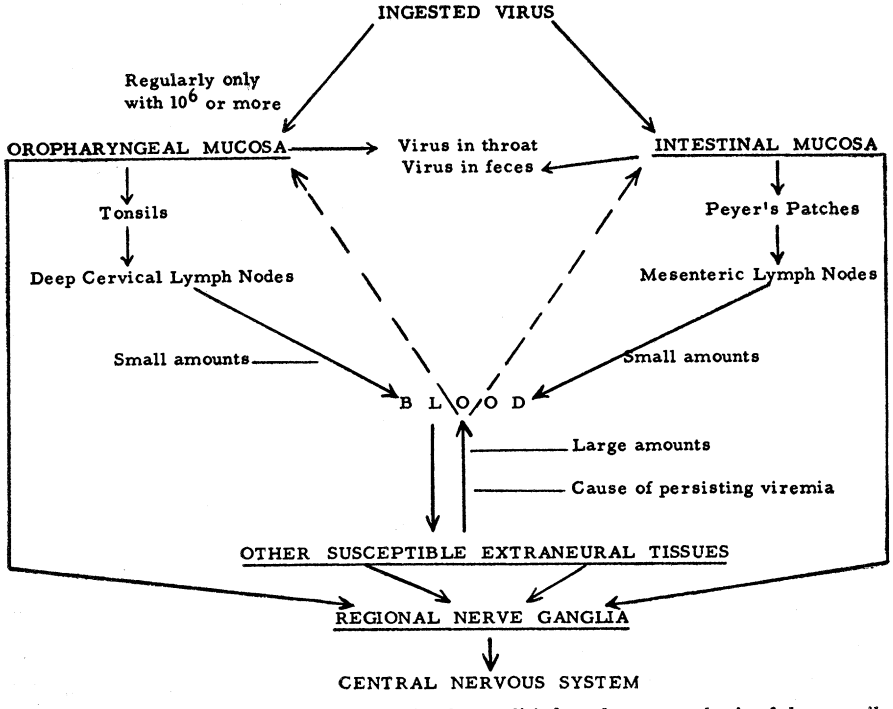

Fig. 1. Schema of possible pathogenesis of poliomyelitis based on a synthesis of data available in 1956.

This interpretation of the course of events is more in keeping with the observations made during the field tests of gamma globulin and formalinized vaccine than is the hypothesis that the central nervous system is invaded directly across the blood vessels.

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Genetic Effects of Atomic Radiation

The coming of the atomic age has brought both hopes and fears. The hopes center largely around two aspects: the future availability of vast resources of energy, and the benefits to be gained in biology, medicine, agriculture, and other fields through application of the experimental techniques of atomic physics (isotopes, beams of high-energy particles, and so forth).

Gains in both of these areas can be of great benefit to mankind. Advances in medicine and agriculture are obviously desirable. The wide availability of power can also be of great benefit, if we use this power wisely. For not only should there be enough power to meet the more obvious and mechanical demands, there should be enough to affect society in much more far-reaching and advantageous ways, so as to reduce world tensions by raising the economic standards of areas with more limited resources.

On the other hand, the atomic age also brings fears. The major fear is that of an unspeakably devastating atomic war. Along with this is another fear, minor as compared with total destruction, but nevertheless with grave implications. When atomic bombs are tested, radioactive material is formed and released into the atmosphere, to be carried by the winds and eventually to settle down at distances which may be very great. Since it does finally settle down it has been aptly named "fallout."

There has been much concern, and a good deal of rather loose public debate, about this fallout and its possible dangers.

Are we harming ourselves; and are there genetic effects which will harm our children, and their descendants, through this radioactive dust that has been settling down on all of us? Are things going to be still worse when presently we have a lot of atomic power plants, more laboratories experimenting with atomic fission and fusion, and perhaps more and bigger weapons testing? Are there similar risks, due to other sources of radiation, but brought to our attention by these atomic risks?

What Complications Are Met in Reaching a Decision?

Now it is a plain fact, which will be explained in some detail later in this report, that radiations [Throughout this report, the word *radiation* is not used in its broadest sense, but refers primarily to gamma rays and/or x-rays and sometimes to other sorts of radiations.] penetrating the bodies of human beings are genetically undesirable. Even very small amounts of radiation unquestionably have the power to injure the hereditary materials. Ought we take steps at once to reduce, or at least to limit, the amount of radiation which people receive?

There are two major difficulties that make it very hard to decide what is

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This article is the major portion of the text of the summary report of the Committee on Genetic Effects of Atomic Radiation. It is one of six reports prepared for the Study of the Biological Effects of Atomic Radiation by the National Academy of Sciences. The other five summary reports will be published in subsequent issues of *Science*. The members of the committee are Warren Weaver, Rockefeller Foundation, *chairman*; George W. Beadle, California Institute of Technology; James F. Crow, University of Wisconsin; M. Demerec, Carnegie Institution of Washington; G. Failla, Columbia University; H. Bentley Glass, Johns Hopkins University; Alexander Hollaender, Oak Ridge National Laboratory; Berwind P. Kaufmann, Carnegie Institution of Washington; C. C. Little, Roscoe B. Jackson Memorial Laboratory; H. J. Muller, Indiana University; James V. Neel, University of Michigan; W. L. Russell, Oak Ridge National Laboratory; T. M. Sonneborn, Indiana University; A. H. Sturtevant, California Institute of Technology; Shields Warren, New England Deaconess Hospital; and Sewall Wright, University of Wisconsin. The following changes have been made in the text: The "Foreword," the section entitled "Radioactive material and radiations," and the section entitled "Some basic facts about genetics" have been omitted. References to these sections in the remainder of the text have also been omitted (omissions are marked by ellipsis). A few additions, including a definition of radiation taken from one of the omitted sections and references from one section to another by title instead of number, have been made (additions are marked by square brackets). In addition, all units of measurement have been spelled out. The full texts of the summary reports are available from the National Academy of Sciences, and the texts of the technical reports will be published in monograph form by the NAS.