# THE PATHOGENESIS OF POLIOMYELITIS

HAROLD K. FABER, M.D.

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*By*

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# INTRODUCTION

FOR NEARLY a century, the pathogenesis of poliomyelitis has been a controversial subject and even today, with an imposing array of clinical, pathological and experimental observations at hand, differences of opinion persist among students of the disease, one group holding that the disease is primarily extraneural ("systemic," "general") and secondarily neural, and the other supporting the view that it is primarily neural with some secondary involvement of the extraneural tissues. The comparative popularity of these two conflicting views has alternated in surprising fashion, and at the moment the first is again in favor. It was first enunciated clearly in 1867 by C. F. Taylor[190] who remarked: "My own belief is that the disease is essentially peripheric and that the great nervous centers are only indirectly and secondarily implicated." The second was adumbrated by Charcot[25] in 1870.

The subsequent history, which need not be reviewed in detail here, was discussed with great care in 1941 by Goodpasture,[85] with particular attention to the pathological and experimental data that had been accumulated up to that time. His summation was as follows: "Experimental poliomyelitis in monkeys has thus equipped us with many new facts and novel points of view with which to reconsider the pathology and pathogenesis of the human disease. Not only has it demonstrated the general character of the etiological agent, but it has confirmed the impression of many that the disease is primarily an infection of the nervous system, and not a secondary or accidental involvement of it following a general extraneural infection; that the nerve cells themselves are the primary seats of injury and not merely secondarily damaged by inflammatory exudation and infiltration; that the infectious agent is located within

the neurones themselves spreading mainly by means of the infected processes of nerve cells rather than through the body humors."

Observations made or amplified since 1941 have not shaken these conclusions in so far as they concern the neural character of the process in the central nervous system; that is, the strict neurocytotropism and axonal transmission of the virus therein. However, certain pathological and experimental observations, mostly recent, have now led some students of the disease, notably Paul,[158] Jungeblut,[119] and Bodian,[11] to revive the old hypothesis, formulated with particular explicitness by Draper[32] in 1917, of primary extraneural infection with secondary extension through the blood stream into the central nervous system. Among these observations the most important are: the presence of lesions and sometimes also of demonstrable virus in certain "extraneural" tissues, notably cardiac muscle[119, 181] and lymph glands;[160, 187, 211] the occurrence of viremia, apparently with some regularity, in apes[11, 100] and human patients[17, 103] during the early stages of the infection; the demonstration of viral excretion and specific antibody formation, in apes and human subjects[129, 130] with asymptomatic infection after feeding; and the successful cultivation *in vitro* of poliomyelitis virus in various tissues free of nerve cells.[34, 205]

Bodian's[11] current concept of the pathogenesis of poliomyelitis embodies three successive steps: 1) an "alimentary" phase in which the virus becomes implanted in the "alimentary mucosa" (not otherwise defined in terms of the exact tissues involved); 2) a "vascular" phase, during which the virus enters the blood from the mucosa, and 3) a "neural phase" in which invasion of the CNS* from the

* The following abbreviations will be used in this article;
CNS: central nervous system.
LRE: lymphoid-reticuloendothelial apparatus.
CSF: cerebrospinal fluid.

blood stream occurs at a single site, possibly the area postrema in the medulla, and then spreads within the CNS entirely by neural pathways. In essence, Bodian's hypothesis regards poliomyelitic infection as strictly neurotropic within the CNS but not outside it.

The validity of this hypothesis and of other similar ones is, I believe, open to serious question in a number of respects, since it is partly based on certain inferences and assumptions that at present are either dubious or unproved. Among these the following may be mentioned: the inference that the results of tissue cultures are relevant to the problem of tissue-host affinities *in vivo;* the assumption that viral excretion in the alimentary tract (pharynx, intestine) is proof of viral multiplication in the mucosa; the inference that viremia *per se* constitutes evidence of infection of extraneural tissues; and the view that infection of the CNS is solely due to direct invasion from the blood-stream.

Something should be said about the controversy over the portal of entry. For several years up to the latter 1930's it was widely believed that the virus first gained access to the CNS by way of the olfactory nerve system, primarily infecting the olfactory nerve cells in the upper nasal mucosa and thence spreading by axonal propagation through the CNS. This thesis was elaborated in my review[37] of 1933, in which an attempt was made to explain the whole disease process on the basis of strict neurotropism and axonal spread of the virus. A few years later as a result of observations by Horanyi-Hechst,[95] Swan,[189] Sabin[169] and others showing that in the human disease the olfactory bulbs rarely if ever contain significant lesions, it became evident that this was not the normal pathway of entry. This did not, however, justify exclusion of entry by way of other peripheral nerves of the respiratory and alimentary surfaces. Observations that such entry can occur will be presently discussed, but, it is to be noted, do not exclude

other means by which the virus can reach the interior of the body.

The author and his associates have conducted experiments and published a series of papers, most of them since 1940, on which much of the following review is based. Some of our observations are published here for the first time. Our work has been oriented largely to the mechanisms involved in the initial infection and the pathways followed by the virus during invasion and excretion. Some questions, of course, remain to be answered. Nevertheless, it is felt that the present state of our knowledge is such as to justify another attempt at analysis and synthesis. Herein the role of the peripheral nervous system, hitherto largely neglected or minimized, has been carefully taken into account as one of the major pathogenetic features of the disease. In general, my aim has been to formulate a unitarian concept of poliomyelitic infection and, with as little theorizing as possible, to correlate the established facts.

Our experimental work from 1940 to 1953, as well as the preparation of the present review, has been aided by grants from the National Foundation for Infantile Paralysis, Inc.

H. K. F.

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# PROPERTIES OF THE VIRUS

THE PATHOGENESIS of viral diseases in general and of poliomyelitis in particular must be considered, and can only be understood, in the light of certain general principles. These have recently been simply and cogently described by Delbrück. According to him, as reported by Adams,[30] the biological process involved in viral infections consists of three different phases or states of the virus, "the infective, vegetative, and provirus states. In the infective state the virus is extracellular, metabolically inert, resting between cycles of reproduction. It is extracellular virus which has been most extensively studied by physical, chemical and immunological techniques, and which is best known for its accessibility. It is, however, of less interest to biologists than the intracellular states in which virus demonstrates some of the properties of a living organism. In the vegetative state, the virus is intracellular, virus reproduction occurs, genetic changes of the virus take place, and the host cell metabolism is so disorganized that the pathology of the virus diseases is produced. In the provirus state, the virus coexists with its host cell in a symbiotic relationship in which the virus assumes the *de facto* role of a genetic unit of its host cell. The provirus protects its host cell against the attack of related viruses, profoundly affects the genetics of its host cell, and is the natural method of storage and preservation of viruses."

In poliomyelitis, the infective or extracellular state is represented by free virus in the pharyngeal secretions and stools, in the blood, and probably in the fixed macrophages of the LRE after removal of virus from the blood or lymph. The intracellular state is reflected in the chromatolytic and necrobiotic changes in the nerve cell which are a constant feature of the disease. While Howe and Bodian[108] have ex-

pressed the opinion that virus does not multiply in the axons, the fact that axoplasm is an integral part of the neuronal cytoplasm stands in favor of viral multiplication in the former, and, indeed, it is difficult to understand the centripetal and centrifugal migration of virus in the axons unless it actually does occur. There is no clear physiological evidence of two-way or alternating flow of the axonal contents but only of a very slow centrifugal movement, measured by Weiss and Hiscoe[204] at about 1 mm. a day, which is about one-fiftieth of the rate of centripetal migration of virus in peripheral nerve as measured by Bodian and Howe.[15]

Whether under ordinary conditions intracellular multiplication of poliomyelitis virus can occur in non-neural tissues *in vivo* is an interesting but actually unproved question. Many viruses are so highly specific that they can infect only one particular kind of cell in a single animal species and there are indications (brought out in other parts of the present communication) that poliomyelitis may fall in this category. Hyperplastic and necrotizing changes do, however, occur frequently, though not constantly, in the LRE,[160, 187] although virus itself is recoverable from it much less often.[211] The function of the LRE is largely defensive: the reticulum removes circulating pathogenic organisms from the blood and destroys them, while the plasma cells concurrently produce specific antibodies which are discharged into the blood stream as gamma globulin. It seems highly improbable, in view of their phagocytic and destructive properties that the virus could multiply even briefly within the cells of the LRE. The virucidal power of the reticulum must be considerable and its action rapid, since Lennette[138] has shown that when virus is injected intravenously in large amounts it can be recovered from the spleen for only a short time thereafter. The pathological

changes in the LRE may, in part, represent Selye's[184] alarm reaction, in which necrosis plays a conspicuous part.

The provirus (latent," Horsfall's "steady") state, which may persist for a long time in infected but surviving and essentially intact host cells, is thought to be responsible for the long enduring immunity characteristic of many viral infections, including poliomyelitis. Possibly the intranuclear inclusions that are occasionally found in neurocytes in poliomyelitis subjects may represent one aspect of this state.

The cycle of cell invasion and of multiplication and release of virus in and from cells has been described by Horsfall[97] as occurring in five successive steps:

1. Virus-cell union, assisted by a cofactor (tryptophane, etc.);
2. Cell surface alteration (RBC agglutination, etc.);
3. Viral penetration into cell;
4. Viral multiplication, in which the intracellular metabolism engages;
5. Release of viral particles from the cell.

It should be noted that Step 1 of the invasive process is dependent upon an extracellular factor or factors.

Step 5 is followed by repetition on a geometrically increasing scale of the same process (chain-reaction): larger and larger amounts of virus being released extracellularly into the environment to invade more and more cells. This would correspond in poliomyelitis with the processes of excretion, reinvasion and viremia. The invasion of the telodendra of axons from the mucosal surfaces is presumably governed by the same conditions and factors, as is also the release of virus from them on the surfaces of the alimentary tract.

While the taxonomy of poliomyelitis virus has not yet been officially decided, Rhodes[165] in a recent discussion has