Critical Review

POLIOMYELITIS

JOHN A. TOOMEY, M.D.
CLEVELAND, OHIO

GENERAL INTRODUCTION

TO UNDERSTAND a disease about which little is known, it is sometimes necessary to theorize from a few facts and to postulate axioms which become tenable only if they agree with clinical experience. It might be believed that such thinking may result in shrewd guesses, especially if the axioms suggested prove plausible and possibly correct. Such conclusions may often be reached with a minimum amount of visible effort, a condition anathema to the rabid experimentalist who may report or applaud work which shows a maximum amount of experimental effort, but which reveals a minimum amount of thought.

There has been a vast amount of research in poliomyelitis. Most of the experiments have been done on *M. rhesus* monkeys, animals not susceptible to this disease. Much of the information obtained has at times been diametrically opposed to clinical experience and simple logic. This has not troubled some experimenters who at times discard the obvious as unreasonable and enhance the unreasonable because not obvious and because supported by authorities. The only way to test any theory about a human disease is to test it against clinical experience.

PECULIARITIES OF THE POLIOMYELITIS VIRUS

To begin with, it has been suggested that the virus of poliomyelitis has almost an obligate affinity for gray fibers of the nervous system.[1] This conception is not novel, since it has been known that poliomyelitis virus does not remain long in white fibered or medullated tissue; that it is easily absorbed by gray fibered nerves, olfactory, etc., or the gray fibered axis-cylinders of medullated nerves; and that it is found in gray fibered areas.

It has been stated that the virus does not readily multiply in the higher regions of the central nervous system; that the cerebral cortex is not a favorable site for development or even of preservation of the virus.[2] Levaditi[3] states that the central nervous system, particularly the gray matter of the cord, is the principal reservoir of the virus. The very term poliomyelitis is significant—*polio*, gray, and *myelitis*, an inflammation of the gray matter.

Virus could not be absorbed in the human being by way of the many artificial pathways used to produce the disease in the experimental animal. It probably could be absorbed only by peripheral and superficially placed gray end fibers of somatic or autonomic nerves. Its spread would be along the axis-cylinders toward the central nervous system, and it would usually cause damage only when it reached the nerve cell.

From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

Aided in part by the National Foundation for Infantile Paralysis.

Virus can be absorbed peripherally from only two places: (1) through the skin, or (2) through the gastrointestinal tract. The former has sharpened its ability to react to external stimuli. The integument has come to serve as a protective covering. It prevents noxious elements in the external environment from entering the host. No longer do we actually surround and, absorb food as do many animals of the lower orders. No longer does the skin act as an organ of absorption. Only to a minor degree does it even retain the properties of respiration, excretion, and secretion. Biologically, it has become equipped with a specialized defense mechanism with epidermis, hair, nails, etc.—the exoskeleton comparable to the protective coverings of the invertebrates.

It may be asked, "What has this to do with poliomyelitis?" The connection becomes obvious if it is conceded that virus has an obligate affinity for gray fibers. The somatic peripheral nerves are medullated; they possess a myelin sheath and travel thus encased and protected through mesodermic tissues until reaching the dermis, where they shed their coverings and ramify peripherally in the dermis as gray unmedullated end fibers. There they stop. They do not extend through the epidermis. It then becomes obvious why absorption of poliomyelitis virus does not easily take place through the epidermis and why subcutaneous injections are not always successful.[4] Nature has provided a nerveless protective coating, a horny covering or epidermis which prevents virus from spreading to the dermis where the gray fibers and peripheral nerves are found; thus, the spread of the virus through the skin under natural circumstances is prevented, and since gray nerve fibers and virus do not become approximated, the disease is not produced. The skin is a poor experimental portal of entry unless virus is injected intradermally, thereby theoretically contacting the naked gray fibers; experimentally the disease is easily produced when virus is injected here.[5] This confirms the experience and the experiments which tend to rule out biting insects as transmitters of the disease.

The gastrointestinal tract is also an external organ, actually and embryologically speaking, although at birth it is contained wholly within the body. Since it is inside the body, it is not exposed as is the skin and its need for protection is less. Since its functions have followed other lines, it has no need for a protective covering.

There is no external layer in the intestine, no epimucosa to prevent absorption, and it should occur any place along the intestinal tract but more easily and more commonly from the mid-gut and hind-gut. The host is protected against a noxious agent by immune, mechanical, or chemical methods or means. If there is absorption of poliomyelitis virus, and the patient remains well, the protection may be immunologic or chemical in character. If one should have the disease and recover, immunity must have developed. The virus may not be absorbed in some, but it may be irritating enough to cause contractions of the gut, causing the contents to be rushed forward by peristaltic waves, to be excreted before absorption can occur or before there can be approximation of agent and nerve. (This occurs when virus is injected into the gut of a normal rabbit or monkey.[6]) In others, there may be local absorption of material from the gut with mobilization or paralysis of the intestines, which, as every clinician knows, may occur in human poliomyelitis as evidenced by obstinate constipation. In still others, the virus may act as a noxious agent that may be neutralized by some chemical found in the contents

of the normal gut, by the dihydrocholesterols, for example, common detoxifiers, or by enzymes; or, finally, the virus may not be virulent per se and in certain instances may become so only when it is combined with the toxins produced in a stased gut. Thus, there are many reasons why poliomyelitis virus may or may not produce disease—lack of virulence, immunity of the patient, excretion of virus before absorption occurs, or its neutralization in the gastrointestinal tract chemically or immunologically.

Although in the human being, absorption of virus occurs naturally only in those places in the body where naked axis-cylinders or gray fibered nerves come in contact with the virus, a "take" or the successful production of the disease depends upon an unbroken connection between the peripheral absorbing axis-cylinders and the central nervous system.

There are innumerable portals which are employed for the introduction of "takes" in the experimental animal—the sciatic nerve,[7, 8, 9] the cerebrum, the peritoneum,[10] the spinal cord, the eye,[11] the tonsil,[12] the taste buds and the seventh nerve,[13] the vagus nerve,[14] etc. No matter what the avenues, the principle is the same: the virus must be injected some place where it comes in contact with naked gray fibers or axis-cylinders of medullated nerves. If this is accomplished, it matters little where the injection is made. Therefore, one should not be too astonished at the ingenuity of the human mind which thinks up innumerable portals of entry through which to introduce the virus if he but admits the axiom that virus is absorbed anywhere where it may come in contact with gray fibers of peripheral nerves.

If this is true, then it is equally true that the virus could be absorbed from any part of the body where disease and abnormal conditions have removed the normal protective covering and have made it possible for virus and gray fibers to meet. This is especially true where a break occurs in the skin or mucosa or where inflammation is present. Wherever skin or mucous membrane is destroyed, the frayed edges of peripheral nerves stand exposed. In the denuded area, new vessels form, and with them, new peripheral gray fibers. The stage is set for easy approximation of virus and axis-cylinders. It is small wonder then that a tooth extraction, a tonsil operation,[15, 16, 17] or a flap cut[18] in the skin of an experimental animal will provide fields where virus and nerve fibers can meet, as a result of which disease follows. One should remember, however, that although the virus may be adsorbed from a highly artificial portal of entry, the distance between the periphery and the central nervous system must not be too great; otherwise, the virus may be absorbed, excreted, or destroyed long before it reaches the cord. Thus, rapidity of absorption, the speed and ease of transmission, the virulence of the virus, the condition of the neurones, etc., are factors which modify the pathogenesis of the disease.

PLACES FROM WHICH VIRUS MAY BE ABSORBED

Since it is now considered that the blood stream and the lymphatics are not involved in the pathogenesis of the disease, and the intracerebral route is entirely unnatural, it can be concluded that the portal of entry must be somewhere along the gastrointestinal tract, the most obvious areas being either from the upper portion of the gastrointestinal tract, i.e., the stomadeum of the fore-gut, or from the midportion of the hind-gut.

The places where peripheral axis-cylinders are present, and along which absorption could easily occur, are located in the olfactory area, about the taste buds in the tongue (tonsillopharyngeal region), from vagal or sympathetic fiber plexus in the gastrointestinal tract, possibly from the bladder wall, and the respiratory tract.

BASIC CLINICAL AND PATHOLOGIC FACTS

Before proceding further, let us examine some basic clinical and pathologic facts. The paralyses which occur in the human being are segmental in type and, in the vast majority of cases, they involve the peripheral nerves which have their origin in the lumbar, cervical, and bulbar enlargements, in the order named. Pathologic changes to any great extent are ordinarily found in only three places—in the lumbar and cervical enlargements and, to a lesser degree, in the bulbar area. There are modifications of this general dictum; cranial nerve paralyses may appear without paralysis of the lumbar nerves. On the other hand, the so-called bulbar symptoms may appear clinically during life and yet no evidence of bulbar involvement will be found at death.[19] The cord between these localized areas, i.e., between the lumbar, cervical and bulbar areas, is often free from pathologic reactions, or, if involved, has nothing like that extensive involvement seen in the areas just mentioned. One should remember these areas in the human being, especially when considering experimental paralysis in the monkey (Figs. 1 and 2).

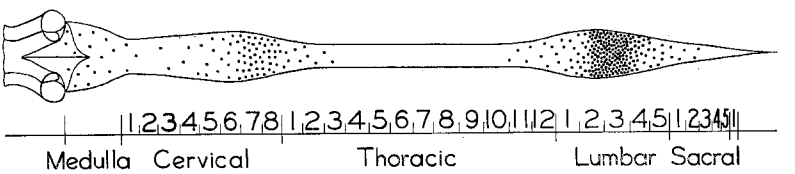

Fig. 1.—Schematic drawing to illustrate the location of pathology in the human being.

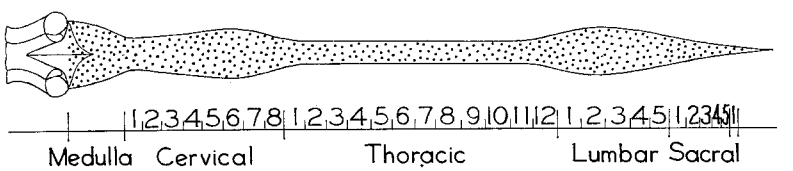

Fig. 2.—Schematic drawing to illustrate the location of pathology in the experimental animal (*M. rhesus*) after intracerebral, intranasal, intrasciatic, etc., injections.

PORTALS OF ENTRY OF POLIOMYELITIS VIRUS

There are two schools of thought regarding the portal of entry. Some believe that (1) the disease enters by way of the nose and others claim that (2) it ordinarily enters by way of the mid-gut or along isolated cranial nerves. The former dictum has been held nearly universally; the latter, until recently, had few remaining advocates save the writer in America[20] and Kling[21] and Lepine[22] in Europe.

A. The Olfactory Portal of Entry:

What evidence is there to support the contention that the olfactory area is the portal of entry? First, let us examine the anatomy of this area.

The olfactory nerves have from twenty to thirty unmyelinated gray fiber olfactory filaments in the region of the cribriform plate. But here

also is the nervus terminalis (cranial nerve XIII) "peripherally hypertrophied in man as compared to the known development in other mammals" (Brookover[23]). The olfactory area contains approximately 1,500 cells of the latter nerve, which with their processes make a vast interlacing network of unmedullated tissue whose fibers *end in the ganglion terminale on the olfactory bulb.* Significant indeed is the assertion made by Brookover that the "grouping of cells and fibers" is "such as might be found in the myenteric or submucous intestinal sympathetic." Most significant is the similarity of the peripheral nervus terminalis to an enteric plexus. The gray end fibers of both the first and thirteenth nerves could take up the virus and absorption could and does take place from here in the experimental animal. One wonders why stress is placed on the olfactory fibers and why the other types of fibers which so closely resemble these found in the mid-gut are ignored and forgotten. But, aside from this, Flexner[24] has stated that the "small olfactory filaments" of the nasal area "are advantageously placed to act as the means of transportation of the virus." The unbroken connection of the olfactory nerve to the central nervous system has been stressed. Flexner and Lewis[25] and others have shown experimentally that absorption may take place from the nasal area, since they reproduced the disease by packing the nasal passages of monkeys with gauze that had been soaked in poliomyelitis virus. All of these conclusions have been confirmed many times, but they merely prove that it is easy to produce poliomyelitis in the experimental animal in this way; such facts do not constitute even prima facie evidence that virus enters the human being by way of this portal. The natural disease never acts like an upper respiratory infection in the experimental animal for no animal gets the disease from another, no matter how intimately exposed.

It is believed that because virus is detected in the nasal washings the nose must be the portal of entry. If such logic is accurate, then the gut must also be a portal of entry because virus is easily detected in the feces.[26-34] It may be said that in the latter case the virus has been swallowed. This, however, does not explain why it is easier to isolate the virus from the gastrointestinal tract than from the nose.[35]

When virus is injected intravenously, it may be found excreted onto the nasal mucosa. It is asserted that it might then be absorbed from this area along olfactory fibers to the central nervous system causing the disease to be produced.[36] Although it is just as logical to suppose that the virus injected intravenously could, like any noxious material, be excreted anywhere along the upper or lower part of the gastrointestinal tract than excreted onto the nasal mucosa only, the dictum can easily be disproved. When the first and thirteenth nerves have been disconnected from the brain and the animals all given virus intravenously, they still get the disease,[37-39] proving that an intact olfactory area is not necessary for the production of the disease when the virus is introduced in this manner.

One would expect to find some pathology in the human olfactory bulb if the disease started here. Smith,[40] however, was the first to stress the fact that there was no evidence of bulb involvement in human autopsy material. This observation was ignored for a while, chiefly because pathology was so easily demonstrated in this area after the virus was introduced intranasally in the experimental animal. Some years later, Sabin[41] examined twenty-five olfactory bulbs from thirteen cases of human poliomyelitis and confirmed Smith's results when he found that

these patients did not reveal the pathologic changes which have been observed in the olfactory bulbs of monkeys succumbing after nasal instillation of poliomyelitis virus. Swan's[42] results as regards the olfactory area were somewhat similar. Sabin and Ward[43] suggested that the results of their "present study [1941] did not support the concept that the olfactory pathway is the portal of entry or exit of the virus." They now feel that the alimentary tract is not only "the probable area of invasion, but also the chief site from which the virus is eliminated."

When the experimental animal is given virulent virus either intranasally or intracerebrally, or even intrasciatically, quadriplegia usually results and usually death. Poliomyelitis is thus produced, but even though this is poliomyelitis, *it is not the kind of poliomyelitis that is seen in the human being.* If the objective is to produce the disease as it appears clinically, then such portals of entry can be excluded.

It is illogical to infer that because the disease is easily produced in an animal by way of the olfactory route this is the probable portal of entry. The ease with which poliomyelitis is produced experimentally in an animal that is naturally immune is no proof that the portal of entry used must be the natural portal of entry in man.

Since the thalamus is the center for effective tone, the area involved in emotions, and the place where effective experiences are intensified,[44] and since a great deal of pathology is found here in the human being and in the experimental animal, and since the olfactory thalamic relay is found in the mesial thalamus, and the formatio reticularis is intimately connected with centers in the hypothalamus and midbrain, and since this in turn is adjacent to or in the direct pathway of the olfactory tracts and there is a direct connection between cord and thalamus via the spinothalamic tract, etc., it has been suggested that most of the early symptoms of the disease—vomiting, drowsiness, restlessness, irritability, fever, generalized hyperesthesia, diarrhea, constipation, anorexia, retention of urine, etc.—probably represent a reaction to irritation as the virus passes by way of the olfactory bulb to the respective centers governing these actions. It is reasonable to assume that if the disease starts in the olfactory area, the areas mentioned previously are involved as the virus passes through the brain stem, and, as a result, the symptoms of the disease should appear here first.

If in the average patient this severe reaction were present in the bulb, there should be more persistent clinical evidence of involvement. Can one imagine that if the severe pathologic lesions seen in human beings at autopsy were present in the early stages of the disease, they would not cause more marked early symptoms? Can one imagine such lesions clearing as quickly as they would have to do in the average patient who recovers? If there is so much or even any pathology present in the bulbar areas in the average case, why do not the symptoms persist? One may say that such a pathologic reaction would appear only in those patients who died. Then the opposite would likewise be true, i.e., that they would not appear in those that live. Curiously enough, it is found at autopsy that they do not even appear in all those who die with bulbar symptoms.

Another objection to the concept that virus passes from the olfactory area to bulb, etc., rises from the fact that serial sections of these very areas in the experimental animal, taken the first few days after the virus is given intranasally or intracerebrally, show nothing more than a possible, slight capillary dilatation even though virus can be recovered from

the areas sectioned. The reactions described in the human being occur relatively late, often long after the early symptoms are forgotten. Nothing that resembles the later pathologic picture is present until symptoms begin to show about the fourth day after injection, at a time when the virus has reached the lumbar area. How can it be explained why the virus, although present, would cause so little damage or clinical reactions on its way through the bulb?

Once virus approximates gray fibers in the nasal area, the hypothetical spread toward the central nervous system can best be appreciated by examining Fig. 3. The virus goes along the olfactory pathways, skips over the synapses to get on a new track, and after passing medulla, pons, and cervical areas of the cord, finally reaches the lumbar enlargement. Specifically, it is thought to pass through the hypothalamus, thalamus, midbrain, and medulla, and then to travel down the spinothalamic tract by single neurones to the posterior column, finally reaching the anterior horn cell area in the lumbar area of the cord.[44] A connection to the dorsal root ganglion by way of Lissauer's tract is thought to bring inflammation to this point. Thus, involvement of either the posterior portion of the cord or dorsal root ganglia might lead to disturbance of pain and temperature sense.

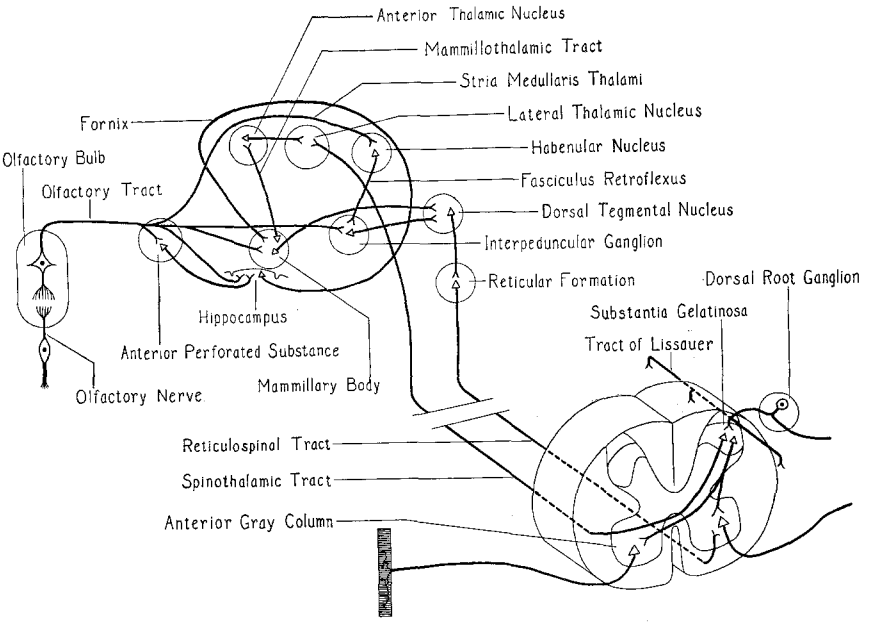

Fig. 3.—Schematic drawing showing possible spread from the olfactory nerve.

If this is the method of spread, then the spinothalamic tract should be involved in every case of poliomyelitis. Immediately it can be asked: "Why don't patients with poliomyelitis have more definite symptoms of spinothalamic involvement?"

The spinothalamic tract carries pain and temperature sense fibers in the lateral column, and touch and pressure in the ventral branch. If the lateral pathway is involved, why not the ventral also? Must we assume an area of anatomic susceptibility and specificity limited only to the lateral branch? It is known that the ventral fibers are not in-

volved in this disease, since touch and pressure are normal. As both fiber tracts run together in the spinal lemniscus and both connect with the thalamus, an almost anatomic predilection for the lateral tract would have to be presupposed to explain the absence of involvement of the ventral fibers, an illogical supposition.

The pain that poliomyelitis patients feel can best be explained by assuming that there is irritation of the somatic nerves prior to the time that the irritant has reached the cord. On clinical examination, it is found that the pain present is not in the skin but occurs in response to deep pressure and is usually limited to those muscles and tendons of muscles that later may become paralyzed. Stimulating the skin by stroking it lightly only occasionally elicits pain. In other words, although the muscle tendons may be painfully hyperesthetic on manipulation, the skin areas that have their nerve supply from the same segment are not hyperesthetic. There is nothing wrong with the *appreciation* of pain in the skin on the part of the average patient. It may well be that pain is caused by the virus as it irritates the sensory neurone of the somatic nerve on its way to the cord, as a result of which occur contraction of the vessels in the muscles and a decrease in the oxygen supply, with anoxemia and pain.

The spinothalamic tract also carries temperature sense fibers. Are there temperature changes which would confirm the impression of spinothalamic involvement? In my clinical experience, the appreciation of temperature has always been normal, although the skin of the leg or arm that is paralyzed may be colder than that of the nonparalyzed member. This, however, is an objective finding and may be easily explained on the basis of vasomotor phenomena secondary to a nerve irritation, such as is seen in many other types of paralyses. Although the skins of the patients whom I have examined were often colder than normal, all of those who were old enough to cooperate could easily tell the difference between heat and cold, even though they felt that the paralyzed areas were cold, an unlikely finding if the lateral spinothalamic tract were consistently involved.

The fact that no plausible reason is given as to why the disease is localized in the lumbar area also casts some doubt on the theory of virus spread from the olfactory area in the human being.

It could be said that ataxia might be the result of irritation of Clarke's column as the virus passes from posterior to anterior horn cells from the spinothalamic tract. Were this the pathogenesis, the virus must always pass from the posterior to the anterior column, and one wonders why ataxia is not more common. Certainly, Clarke's column must always be in the way. But none of our patients ever had acro- or proximoataxia. They always appreciated their position in space. Only an occasional patient had asynergy of movements, somewhat athetoid in type, and sometimes one might even have fibrillary twitchings. The most important point, however, is that these twitchings and tremors, although the rule in the experimental paralyses, were the exception in human beings. This difference may suggest that the pathogenesis of the disease in man and in monkey is different because of the different portals of entry involved.

Why are nerves from the cervical enlargement involved after lumbar paralysis has appeared? Or, still more curious, why is the bulb solely involved at times? Must we deduce that in patients with only bulbar involvement or only seventh nerve palsy, the lumbar motor areas are not

especially sensitive and that the involved motor cells are? Can one explain how the cervical area becomes involved after the virus has already passed through it to reach the lumbar area without doing any damage on its way through the cervical enlargement?

In the majority of human beings and monkeys, paralysis first develops in muscles which receive nerve supply from the lumbar enlargement and only secondarily in those whose nerve supply comes from the cervical area. This is a clinical fact. Those who believe in the olfactory portal of entry have never explained why the virus, in its travels down the spinothalamic tract in the cord, skips the cervical enlargement and, in most instances, involves first the lumbar enlargement and paralyzes *first* the muscles of the legs. Because (1) after intranasal instillation, the virus passes through the brain stem and spinal cord from above downward and because (2) the virus is found present in all levels of the cord just before paralysis appears, it cannot be concluded that this is the route the virus takes in the human being. This is only the route taken after intranasal instillation in the experimental animal, the route taken by a virus which will travel along any axis-cylinder. Must we accept the doctrine of especially sensitive cells? Even this fails us when it is seen that if the virus is injected directly into the lumbar enlargement, there is a delay before the disease is produced.[45]

Must the virus pass all the way through the central nervous system to get to the lumbar area and then trek back to the cervical and pontine areas to involve them later? Or does damage done stay latent everywhere and only reveal itself sooner in the lumbar area? The latter is a possibility; but if it were true, we would expect subsequent or simultaneous involvement of all these areas in every case, which, of course, does not happen clinically.

Recently, Bodian and Howe[46] have stated that the problems involving the portal of entry in poliomyelitis could be approached by methods of experimental neurology and experimental neuropathology, especially since there is no clear-cut evidence of the mode of entrance and dissemination in the central nervous system in man. They believe that their experimental studies have shown that there is a sufficiently close correspondence between the distribution of lesions in the nervous system and the distribution of virus to permit, by histologic examination, a reasonably accurate analysis of the paths of dissemination of the virus. In some of their experiments, the portal of entry employed was the olfactory nerve and, in others, the peripheral nerves. They noted a predominance of lesions in the midbrain as a characteristic phenomenon. When the virus was introduced intranasally, the pathology was present *all the way down* to the lumbar area. The most important thing to remember is that practically all of the motor cells in the anterior horns were involved from the bulb down to the lumbar area (see Fig. 2). They felt that when the virus was injected intrasciatically, intraperitoneally, etc., it entered the spinal cord before it entered the brain; in other words, the virus went up the spinal cord and in its passage destroyed all the motor cells on the way to the bulb, a reversal of the previous process. It is obvious that a definite pathologic picture is produced by the methods used and that the experimenters could tell from the findings at autopsy at which end of the central nervous system the virus had been introduced. But are these facts relevant? Would such findings be the same as those that would be obtained if the virus entered the human being by way of the gastrointestinal tract? Another important point is that the patho-

logic picture seen in the experimental animal where the virus starts from the cerebrum, nose, and peripheral nerves *does not have that distribution* seen in the human. In the latter instance, the pathology is spotty as noted previously. The thoracic area is usually exempt. The pathologic studies, although demonstrating neuronal spread, give no idea as to the method of the propagation of the virus in man. In fact, they demonstrate clearly how the virus could not spread. Nor can conclusions drawn from these experiments be applicable to man, since the localization of pathologic reactions in the experimental animal is totally different (Fig. 3). The thoracic area usually uninvolved in man is the area supplied by thoracic I to lumbar I and from sacral I down. In the experimental animal, the entire spinal cord is involved.

It is stated[46] that the total pathologic picture, including system selectivity, is determined by the differential susceptibility of certain centers based on metabolic or chemical peculiarities, accessibility of virus, and portals of entry. One could agree that the spotty distribution of the pathologic reactions in the human being depends for its existence on the portal of entry; and if the portal is through the gastrointestinal tract, a "take" would depend upon accessibility of gray fibers to virus. But, if one assumes that a virus has an obligate affinity for gray fibers of the sympathetic and parasympathetic nervous systems, the situation becomes clear. One need but know that the virus can be absorbed by gray fibers and can spread from the gut along the sympathetic and parasympathetic nerves to the lumbar, cervical, and bulbar enlargements.

In brief, there is no clinical or even pathologic evidence which demonstrates that the portal of entry in the human being is along the olfactory fibers to the brain.

B. The Gastrointestinal Portal of Entry:

Since 1922, I have taught that on anatomic evidence alone no other logical explanation of the pathogenesis of the disease in man could be made than to consider the portal of entry as being by way of the gastrointestinal tract. For nearly that length of time in the Department of Contagious Diseases, City Hospital, the stools of patients ill with poliomyelitis have been disposed of as are typhoid stools.

In most cases of human poliomyelitis the lower extremities are first affected. Because of this, Wickman and even Harbitz and Scheel first thought that the disease must have its entry through and spread from the gastrointestinal tract. Sicard[47] suggested that the spread to the cord might be by way of the sympathetic nervous system.

Most of those who object to the gastrointestinal tract as the portal of entry mention the studies of Clark, Roberts, and Preston,[48] although the facts presented by them did not rule out this area as a possible entrance of the disease. These workers put virus into the intestines of monkeys that are not naturally susceptible to poliomyelitis, and the disease did not develop. When one realizes that poliomyelitis virus acts like an enzymic catalyst with almost an obligate affinity for gray fibers and that the natural disease can be produced only after the axis-cylinders of the gray fibers have contacted and absorbed the virus, it is easy to understand why these authors did not produce the disease. The axis-cylinders were never contacted; the virus had been swept through the irritated intestinal tract by a succession of peristaltic rushes. However, when the gut becomes atonic and peristalsis is prevented by mechanically dilating the intestines, the virus is brought in contact

with the gray fibers and the experimental disease is easily produced—and it is like that paralysis seen in man.[49]

If the virus involves the autonomic nervous system from the gastrointestinal tract, it might be stated that patients have a peripheral neuritis of the sympathetic and parasympathetic systems, a condition of the autonomic nervous system analogous to peripheral neuritis of the somatic nervous system.

To understand the natural position of gray fibers in the nervous system, some facts must be reviewed. The simplest kind of nervous system consists of afferent and efferent neurones with their axis-cylinders connected with each other by an intercalated, integrated, or connector neurone nerve fiber. In the simple spinal arc of the human being, the fibers that make up the somatic nerves are protected until they reach the periphery, where they lose their myelin sheath and ramify as naked gray fibers in the dermis. In this reflex arc, there is a long sensory nerve component connecting the skin with the posterior horn in the cord; the motor component arises in a cell in the anterior horn and sends its long axis-cylinders from the cord to the periphery. It is important to remember that the connector neurone *lies protected* in the cord between the anterior and posterior horns (Fig. 4).

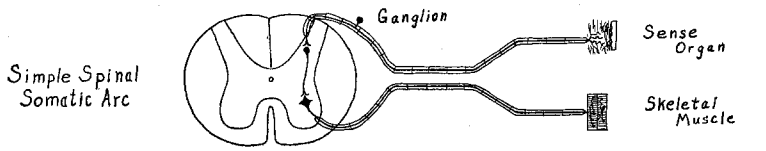

Fig. 4.—Spinal arc components.

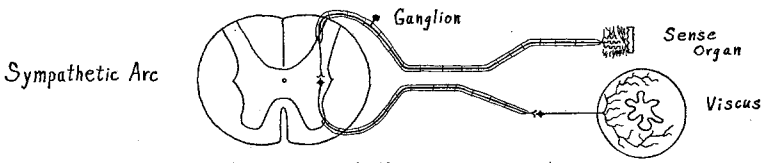

Fig. 5.—Sympathetic arc components.

In the sympathetic nervous system, the axis-cylinder of the sensory neurone (should there be one, and there is for the vascular network) travels from the periphery to the intermediolateral cell column area in the cord where its end connects with the connector neurone, the fibers of which arise in the cord and emerge as medullated nerves, as white rami communicantes. In most instances, except as indicated later, the axis-cylinder travels protected to the sympathetic ganglia, a long distance outside the spinal cord. Thus, at a distance from the cord, arising in the sympathetic ganglia, is the lower motor neurone of the sympathetic nervous system, the analogue of the spinal motor nerve, which in this case is an unmedullated type of nerve which supplies the viscera. It should be stressed that the lower motor neurone of the sympathetic system is unmedullated and its cell of origin *is not in the cord,* but far distant in the sympathetic ganglia. The striking difference between the two nerve arcs, the simple spinal and the sympathetic, is that the connector neurone is found inside the cord in the one and although it arises in the cord in the other, it emerges *from the cord* and runs all the way to the sympathetic ganglion as a medullated connection, except in certain spots (Fig. 5).

The third type of arc is found in the parasympathetic system. Here the sensory neurone runs all the way to the nucleus of origin and the vagus nerve emerges well myelinated. This nerve is actually nothing more than a bundle of connector neurones arising in the central nervous system, the axis-cylinders of which run all the way to the internal organs they supply. The lower motor neurone of this system is but a mesh of plexuses in the walls of the various organs. The connecting neurone here is longer than that of the sympathetic system. In fact, it is almost as long as the lower motor neurone of the simple somatic spinal arc. It should be noted that the peripheral portion of this system, the lower motor neurones of the parasympathetic system, consists mostly of plexuses in the walls of the organs, and these nerves are unmedullated (Fig. 6).

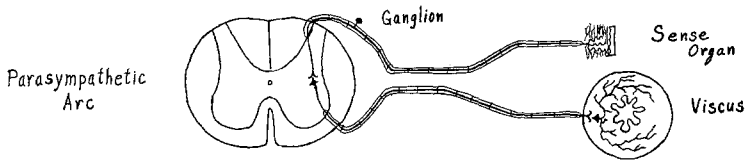

Fig. 6.—Parasympathetic arc components.

If virus would attack only unmedullated nerve fibers and if the portal of entry is the gastrointestinal tract, then it would involve the peripheral fibers of both sympathetic and parasympathetic systems.

If one remembers that the virus of poliomyelitis may have an affinity for gray fibers, he is at once struck with the anatomic fact that the disease usually attacks the nerves which come from those areas lacking white rami communicantes or medullated connections of myelinated fibers, areas located only in the cervical and lumbar enlargements, in those segments from which come the nerves that supply the muscles of the arms and legs. In other words, the somatic nerves to the body musculature possess no direct white nerve fiber connections with the sympathetic nervous system in the areas from the second lumbar down and none upward from the first thoracic segment. Here there are only gray fiber connections and it is in these segments of the cord that involvement occurs. There are medullated connector fibers of the parasympathetic coming from S. II to S. IV. Experimentally the disease can spread by way of the sympathetic nerve supply from the gut to the cord.[49] The spotty spread of the disease can be understood easily if one presages a spread of the virus from the gastrointestinal tract to the lumbar area in the cord by way of the sympathetic gray fibers and somatic nerves of those segments lacking white rami communicantes. With a greater susceptibility or a more virulent virus the spread would be up along the sympathetic collateral chain to the other segments that lack white rami communicantes, i.e., the cervical area (Fig. 7).

That this is not unlikely anatomically is seen from the fact that there is direct unbroken connection from the wall of the intestine to the intermediolateral cell column area in the cord along the sensory sympathetic blood vessel fibers.[50]

Recently, Sabin and Ward have reported their results on human autopsy material.[43] They tested the superior cervical and abdominal

sympathetic ganglia for the presence of poliomyelitis virus in seven patients (five bulbar, two spinobulbar) in whom the virus had been demonstrated elsewhere in the body. They demonstrated that the virus was present in the abdominal sympathetic ganglia of one patient, a patient who died of bulbar poliomyelitis. No virus was demonstrated in any of the others. We have isolated the virus from the sympathetic ganglia of two patients who had spinobulbar involvement. The epidemic last year (1940) was severe in that the virus was potent enough to bridge the synaptic gap of the vagus and produce more than the usual number of cases of bulbar palsy. The presence of virus in the vagus has been demonstrated, for the first time, by us in the nerves of a patient dying with bulbar palsy.[51]

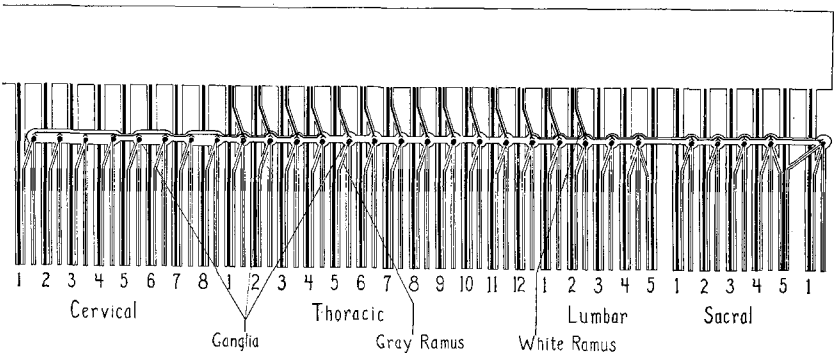

Fig. 7.—Schematic drawing to illustrate position of undefended spaces above T. I and below L. II.

Physiologically, the early reflex changes in this disease could be best explained by assuming an early involvement of the sympathetic nervous system.[52] They are similar to the early reflex changes in typhoid fever.[53] The loss of the abdominal reflex response, followed by hyperactive knee jerks with or without weakness of the quadriceps muscle and succeeded by the loss of the knee jerk reflexes, has its counterpart in physiologic experiments. If sympathetic stimulation increases tone, how would it be affected by thoracolumbar disconnection? The muscles of sympathectomized animals are soon fatigued. Such muscles tire easily when activated, although they may be wholly under voluntary control and still have a simple somatic spinal arc intact. It is reasonable to suggest that the stability of the reflex arc and its ability to withstand fatigue depend, to some extent at least, upon the presence of an integrated sympathetic nervous system. After virus hits the somatic nerve, it irritates it; and when any nerve is continually irritated, it becomes hyperactive and the observer finds hyperactive reflexes. Often, it is impossible to demonstrate these changes because the spread occurs so rapidly. As the virus passes centripetally it reaches the sensory spinal ganglion and produces that curious segmental type of pain that precedes somatic nerve involvement from the same segment. The other type of pain elicited when deep pressure is applied to muscle does not seem to be of central origin. Its presence could easily be explained on the basis of peripheral vasomotor spasm, with decreased blood flow to the muscles and pain on activation.

The virus spread might be compared to the progress of a river flood. The virus spreads along axis-cylinders and spills over in unprotected areas, the greatest damage being done at any break in the defense, in this case, the areas lacking white fibers. Once the virus breaks through, its force is dissipated as it spreads. This may explain the tendency to become spent, and why it does not spread to the lower segments of the cord; or it might be stated that an extensive paralysis of those muscles which have their innervation from the second sacral segment and below will not be seen because the preganglionic medullated fibers arise here. Usually, even the most severely paralyzed patient should be able to move the big toes, and the levator ani, coccygeus, and other perineal muscles should not be affected in the ordinary case. The fingers could likewise be flexed even though the arm muscles should be involved. This is exactly what is seen in the average clinical case. Only when the disease is massive would it involve those segments which have connector fibers (white nerve fibers), the thoracic and abdominal somatic nerves.

This manner of spread would explain the involvement of the lumbar and cervical enlargements, but not bulbar paralysis. The anatomic distinction, but at the same time the connection, is obvious. Virus is absorbed by any gray fibers, whether sympathetic, parasympathetic, sensory, or motor. The unmedullated, gray, and postganglionated fibers of the parasympathetic vagus nerves are located only in the wall of the gut. The vagus nerve itself is chiefly a set of medullated preganglionic connector nerve fibers. Since we have seen that medullated nerves are not too easy to affect, it is understood why all persons with poliomyelitis do not get spreads along both vagi and die because of bulbar palsies. In most instances, the virus is not potent enough to bridge the synaptic gap, but occasionally with a toxic virus it should and does. As the virus reaches the bulb, it would eventually affect the cells of origin. The isolated palsies of the seventh nerve and the bulbar types of involvements are easily understood if one can picture a spread along the chordae tympani, glossopharyngeal fibers, or along local branches of the vagus nerves.

In most instances the initial involvement is in the vagus nerve alone, and it is often incorrectly stated that patients die of bulbar poliomyelitis. A close study of these individuals with so-called bulbar palsies reveals that true bulbar symptoms come on only late in the course of the infection. Occasionally, patients will have an involvement of the vagus nerve nuclei with possible local extension or involvement of some other isolated cranial nerves; or there may be an isolated involvement of the seventh nerve. Long before the clinical evidence of vagal nuclei involvement develops, these patients have a vagus neuritis with dysarthria and dysphagia. They will also have many of the vague symptoms ascribed as being due to involvement of the bulb.

Years ago, Harbitz and Scheel found no evidence of bulbar involvement in cases where symptoms of bulbar poliomyelitis had been noted before necropsy.[19] This becomes clear if it is realized that these patients have a vagus neuritis first and often coincident involvement of the cervical area and are either drowned in their own secretions because they can't cough or expectorate or they are suffocated long before the virus has been able to reach the nerve nuclei in the medulla, and this despite the fact that they have what are termed classical signs of bulbar poliomyelitis.

It matters little to the patient whether he has a peripheral vagal involvement and drowns or suffocates, or has a vagal nuclei involvement and drowns or suffocates. However, the patient with the latter condition rarely lives, while one with the former may survive. This result only confirms the impression of a primary neuritis followed later by nerve nuclei involvement.

There is an orderly progression of signs found in these patients—a curious feeling of tightness in the chest, perhops associated with cardiac irregularities, followed by thickness of speech and a slight inability to swallow, especially heavy foods. Later fluids cannot be swallowed. As the virus extends up the vagus nerve, the pharyngeal reflexes become lost, mucus and secretions collect in the throat, and the patient cannot cough or expectorate. These individuals often die at this stage, the secretions entering the bronchi and drowning them; or virus may extend to and involve the cervical area, and the patient suffocates because the respiratory muscles are involved. If the virus extends up farther, it finally reaches the vagal nuclei and a typical response appears. There are a marked tachycardia and a decrease of the respiratory rate, with deepening and sometimes irregularity. The patient evinces all the signs of vagus escapement. When this condition exists, the patient has an involvement of the dorsal vagal nuclei and the probabilities are that he will die. In these instances pathology will always be found in the bulb.

Were the virus to have a central effect on the bulb from the beginning of the disease, vagus escapement should be commonly found when the illness starts, but since it is found only toward the end of a typical vagus involvement, it is safe to conclude that the condition could not have been present at the onset. It is also logical to believe that practically all deaths due to so-called bulbar involvement are the end result of a disease which started out as a vagus neuritis and that often patients may die of the effects of their vagus neuritis long before they have developed involvement of the vagal nuclei.

The isolated seventh nerve palsies can easily be explained on the same basis. Such paralyses are not uncommon and since these patients rarely die, little pathologic material is available. However, there occasionally may be a concomitant vagal and seventh nerve involvement at times with sixth nerve involvement and paralysis of accommodation as well.

Ordinarily, somatic motor paralyses are thought of in connection with poliomyelitis. We forget the autonomic nervous system. What would happen if the lower motor neurones of both sympathetic and parasympathetic nervous systems became involved? There are local or general paralyses of the gut; gas pockets form as a result and intractable constipation may occur long before any somatic spinal paralysis pain appears, a condition often diagnosed as intestinal flu. In the occasional case, the local stimulus increases peristalsis and causes diarrhea. How can one explain the intestinal involvement which appears before somatic paralyses on the basis of central nerve involvement?

If the lower motor neurone of the sympathetic is involved, the thoracolumbar outflow may be disturbed. Since these nerves supply the sweat glands, experimental evidence may be secured of their involvement experimentally. When pilocarpine is injected into a patient who has one-sided paralyses, there is sweating of the skin over both the paralyzed and nonparalyzed sides.[54] When the specific thoracolumbar stimulant

adrenaline is given later, the sweating ceases on the normal side and still continues over the paralyzed area, demonstrating that the sympathetic fibers are out of order. A similar condition sometimes exists in these patients clinically in that sweating autonomically appears even without the aid of stimulants, and the sweating may be long, profuse, and intractable.

The urinary bladder is often found to be paralyzed and involved before any symptoms of somatic paralysis have appeared anywhere. The urinary paralysis could not be central or cord in origin, since in most instances there is no paralysis of the muscles innervated from the same segment.[55] This paralysis of the bladder usually disappears within from seven to ten days, irrespective of the massiveness of the somatic lesion remaining. Such ready recovery would be impossible were the origin of the lesion in the cord.

The superficial abdominal reflexes are modified. This is not due to an upper motor neurone lesion.[52] The reflex condition occurs even before somatic paralysis comes on. They are also found modified in another gastrointestinal disease, typhoid fever.[53] Like typhoid fever, these reflexes return when the poliomyelitis patient is better.

Is there any evidence that the virus can spread along sympathetic nerve fibers? Monkeys with the spinal cord removed from T. X to L. III, inclusive, leaving the sympathetic as the only connection between the upper and lower parts of the cord, still get the disease, the arms becoming paralyzed if the sciatic nerve is injected, demonstrating that virus can probably spread over the sympathetic nerve fibers. Other animals in which the cords had been similarly excised got the disease when the virus was injected intracerebrally. The virus was found not only in the cord central to the cut, but also in areas caudad, in places where the circulation had not been disturbed, and where the area was still viable.[56]

Other points may be mentioned. When the innervation of the gastrointestinal tract is disturbed, a paralysis occurs much sooner after the intracerebral injection of virus.[57] The disease given experimentally by way of the gastrointestinal tract progresses as quickly in the animal as it does in the human being and is recognizable within twenty-four hours in the spinosomatic nerves when the peripheral nerves are studied between Nicol's prisms. Involvement of the somatic nerves occurs about three to four days after intracerebral injection.[7] After gastrointestinal injection, they are found to be involved within twenty-four hours.[58, 59]

Most of the information about this disease has been deduced by observing animals injected either intracerebrally or intranasally. We have conditioned our minds in terms of these portals of entry. Obviously, specific conclusions regarding pathogenesis, drawn from the results of experiments in which the intracerebral portal was used, can be discarded. The conclusions about pathogenesis made following intranasal injections are questionable. Certainly the explanation of the possible anatomic spread by this portal does not stand critical examination.

The *M. rhesus* monkey is not susceptible to poliomyelitis. It has normal resistance in the gastrointestinal area. However, if this tract were put out of commission or made abnormal, so that the virus could be absorbed and approximate the gray fibers, the disease might be produced naturally. This can be done by making the monkeys rachitic, after which the disease is easily produced by way of the gastrointestinal tract.[60] If

rachitic animals are to be made more susceptible, all that is necessary is to inject them with enteric organisms or toxins. One would deduce that the most vulnerable species of animals to be used would be one that would grow most actively after birth, one presenting an enormous percentage of growth during the first few weeks of life; and it is this very type of animal, the Eastern cotton rat, that has lately been discovered as a proper medium for the production of this disease.[61]

The fact that the glands of the mesentery are enlarged does not imply a general infection, but merely indicates that the area of the intestines which they drain is involved, as would be expected in a stased gut, a local reaction like in typhoid fever.

There are a lymphocytic reaction and a response in the glandular elements that are typically of a typhocoli nature. A distinct leucopenia and a relative lymphocytosis would be the expected result from an infection caused by such a close generic relative of the typhoid organism as the colon or the paratyphoid bacillus. Such a blood picture in poliomyelitis has been described by Müller,[62] Taylor,[63] and Gay and Lucas,[64] although the figures of the latter have not been completely accepted by Peabody, Draper, and Dochez.[65] The most complete and accurate observations on the blood count in experimental poliomyelitis have been made by Harmon, Shaughnessy, and Gordon.[66] They reported that in the stage of prostration there is always a marked drop in the white blood cell count to a point far below the normal for a given animal, a leucopenia with both lymphocytes and polymorphonuclear neutrophilic leucocytes participating. They could not confirm the opinion that a change in lymphocytes with a leucopenia was a characteristic experience in the stage prior to the appearance of paralysis. In most of their experimental animals, there was a preparalytic increase in neutrophilic leucocytes coincident with a rise in body temperature and a corresponding drop in circulating lymphocytes, a drop frequently of sufficient magnitude to mask the leucocytosis when only the total number of white blood cells was observed. An initial transient leucocytosis was noted by these authors within a few days after the injection of the virus. These findings were confirmed in duplicate studies.[67] During the latter stages of the disease, the lymphocytes seem to be withdrawn from circulation. This would fit in well with the advent of local intestinal stasis and the accumulation of intestinal toxins.

Osler's observations that a state of poliomyelitis occurred in typhoid fever with the symptoms of acute ascending paralysis are pertinent to our thesis.[68] Recently, when enteric toxic filtrates were added to old acclimated monkey virus strain, the disease was produced in the cotton rat.[69-72]

Other things suggest the gastrointestinal tract to be the area previously involved in this disease. When morbidity curves of infantile paralysis are considered in relation to the season, it is found that they may be practically superimposed on dysentery curves.[73] Aycock and Eaton[74] have described a spring and summer peak of poliomyelitis morbidity and have noted that the curves occur about the same time as do those for the spring and fall epidemics of typhoid fever. Like typhoid fever, infantile paralysis disappears with the onset of cold weather.

The disease occurs during the typhoid fever season and Kling[75] has claimed to have demonstrated the presence of virus in water. Virus has been found in urban sewage[76-78] (Kling quoted by Paul and Trask[76]),

and infected water might be swallowed in swimming. In this connection, Caverly's[79] and Murphy's[80] observations are interesting. A history of swimming and swallowed water is frequently given to us. As Paul and Trask state, the virus has never been isolated from "running water," but their experiments demonstrate that it can be isolated from "running sewage." In incorporated places in Louisiana with water supply and no sewage disposal, the disease incidence was greater than in those places with good water supply and proper sewage disposal.[81]

The disease has been produced experimentally by way of the gastrointestinal tract. When peristalsis was prevented in the *M. mulatta* monkey by mechanically dilating the intestine and the virus brought in contact with gray nerve fibers by injecting a suspension directly into the gut, the disease was produced.[49] When the virus was introduced into the intestinal wall and contact made with subserosal nerve fibers, the disease was easily produced.[49, 81a, 81b] When monkeys were made rachitic and the virus merely introduced by stomach tube, the disease developed. The important point is that the clinical disease produced was similar to that which appeared in man, i.e., monoplegia, paraplegia, etc., were found. In the few animals examined by us, the pathologic picture was likewise similar to that which appears in man in that the lesions of the experimental disease were limited to the lumbar and cervical enlargements and in one instance to the medullary area.

Trask and Paul[82] were able to infect the green African monkey after feeding food artificially contaminated with virus. The disease has been noticed in nature in a chimpanzee,[82a] and has been produced by way of the gastrointestinal tract in the chimpanzee by Howe and Bodian.[82b]

Sabin and Ward[82c] caused the production of poliomyelitis in *Cynomolgus* monkeys by feeding them contaminated bananas as well as 2 to 4 c.c. of a heavy suspension of virus. Burnet and Jackson[82d] also described similar reactions in *Cynomolgus* monkeys following oral injections. They felt that the spread to the central nervous system was by way of the autonomic nervous system.

THE ROLE OF MEDULLATION AS A BAR TO SPREAD OF THE VIRUS

Myelin seems to be a bar to the spread of the virus. Since the virus does not seem to spread well along medullated nerves, it is plausible to suppose that it may be stopped by the factor which constitutes the only marked difference between gray and white nerve fibers, namely, the myelin.

Conversely, one could deduce that if the myelin is unhealthy the spread of the virus may not be stopped. Theoretically, one might state that the myelin of a normal nerve fiber functions as a colloidal chemical and adsorbs or repels the virus of poliomyelitis. Were this true, a factor in natural protection against the disease would also depend to some extent upon the state of the myelin in the nerves and natural inherent immunity would be partially a question of colloidal balance, with protection in the average case depending on the presence of a sufficient amount of something, perhaps phospholipids, in the myelin, as well as antibodies, etc.

Goodpasture[83] inoculated an encephalitogenic strain of herpes virus into the area supplied by the fifth sensory division. He found that there might be no nervous lesions until a point is reached immediately centrad to the planes where the sheath of Schwann disappears, where the myelin sheath is not sufficiently developed to prevent the escape of virus into the susceptible neuroglial tissue. When the masseter muscle was injected

with the virus it was taken up by the motor branch which has a substantial myelin sheath and the first intracerebral lesions were in the motor ganglion cells of the fifth nerve nucleus, even though the medullated fibers pass through a wide zone of susceptible tissue without evidence of neuroglial involvement. Such a virus spreads like water through a tunnel.

Virus adsorbed or repelled by healthy myelin in normal persons could be in a state of colloidal equilibrium and give little or no symptoms of its presence after injection via the gastrointestinal tract. Certainly, it is difficult to give a monkey the disease by this route if the animal has previously been fed adequate amounts of vitamin D,[84] which produces good myelin. When the myelin is insufficient, the nerves may not be protected.

White fibered or medullated nerve tissue contains about 5 per cent of cholesterol. Gray fibered tissue, which has an affinity for poliomyelitis virus, contains only 0.7 per cent.[85] Could cholesterol act like a colloid and adsorb or in some way inactivate the virus in vitro?

In a few experiments, inconclusive it is true, it would seem that cholesterol, ergosterol, and crystalline vitamin D inactivate suspensions of purified poliomyelitis acclimated monkey virus, although ergosterol, like cholesterol, did not inactivate unpurified poliomyelitis.[86, 87]

In the adrenals, the postganglionic unmedullated fibers are limited to the organ, while practically all of the preganglionic fibers are well medullated up to the capsule of this "abdominal brain." Normal vitamin-D-fed monkeys resist the disease even when the gland is injected, the preganglionic medullated fibers presumably preventing a spread of the virus. However, when the myelin of these medullated nerves was rendered deficient by withholding vitamin D to where the phosphorus content was from 1.2 to 1.5 mg. per 100 ml. of blood, the disease was easily produced when the virus was injected into the organ. Deficient medullation, if such it is, therefore permits a spread of poliomyelitis virus.[88]

When monkeys are made rachitic and their peripheral nerves are ground with virus, the virus is absorbed since the supernate is not infective; on the other hand, when nonrachitic nerves from vitamin-D-fed animals are ground with virus, the virus is not absorbed and the supernate is infective.[88] It may be suggested, therefore, that the spread of poliomyelitis virus to the central nervous system might be stopped by the myelin contained in the sheath which covers the gray fibers.

IS THE VIRUS THE SOLE CAUSE OF THE EXPERIMENTAL OR HUMAN DISEASE OR MERELY THE EXCITING CAUSE?

After intrasciatic, intranasal, or intracerebral introduction of a virulent poliomyelitis virus in monkeys, the disease comes on within four to seven days. When the virus was injected directly into the lumbar cord itself, the animals did not become paralyzed at once, two and one-half days elapsing before this condition was noted. Why should there be such a delay? It is strange indeed that the virus can be absorbed and be present in doses lethal for monkeys in the tissue of the cord, medulla, and even brain long before the production of somatic paralysis in this animal. It argues for the fact that the acclimated monkey virus, although easily absorbed by gray fibers and transmitted to the brain and cord along axonic pathways, does not, in its passage, immediately produce pathologic changes of sufficient intensity to result

in clinical evidence of disease. The virus does not cause demonstrable destruction along its axonal pathway.

Although the virus initiates the disease, there are some clinical and experimental findings which make one wonder whether the virus alone, as it is carried in the laboratories, is the sole cause of infantile paralysis. Other diseases, such as swine influenza[89] and oroya fever,[90] are produced by a combination of factors. Perhaps poliomyelitis also is such an infection.

An accelerated production of the disease may result in the experimental animal when stool or sewage containing the virus is used to start a strain. Once a virus is acclimated, however, its behavior becomes somewhat fixed. This leads one to ask whether there is something lost on acclimation.

More attention was paid to stools, and it was found that those obtained from patients ill with poliomyelitis during the acute stage of poliomyelitis were much more toxic to guinea pigs than those obtained from the same patients during convalescence.[91] Obviously, something had been produced in the stools during the course of the disease that was more toxic to guinea pigs, something that was not present in normal human stools; and yet it was equally obvious that this something was not the virus of poliomyelitis,[91] although it had been neutralized by convalescent poliomyelitis serum.

Stools collected from young normal monkeys were emulsified and injected subcutaneously into guinea pigs; there were but slight local reactions. The stools obtained from the same monkeys after they had had an attack of experimental poliomyelitis were much more toxic to guinea pigs, in some of which the abdominal areas sloughed and some of which died.[92]

It occurred to me that a secondary factor must be present in some patients before the clinical condition of infantile paralysis could be produced. The colon bacillus was considered in this light. The agglutinin titers contained in the blood sera of poliomyelitis patients, taken at the height of the disease and later during convalescence, were compared. It was found that there was a marked difference, since the agglutinin titers of the sera taken at the height of the disease were much less for the enteric group of organisms than they were for those taken during convalescence.[93]

It was not possible to say at first whether the agglutination titer values were lowered with disease and returned to normal with recovery, or whether the titers were lowered before the disease occurred and increased with recovery.

This information had to be supplied experimentally. The young *Macacus mulatta* monkey is very susceptible to poliomyelitis when the virus is injected intracerebrally and has little or no agglutinins in its blood serum against the colon bacillus. As the animal gets older, its serum agglutinin titer for colon organisms becomes higher. Young monkeys were injected intracerebrally with potent poliomyelitis virus. When they contracted the disease the agglutinin titers of their blood sera were found decreased, and immediately before their death the agglutinin titer values were practically nil. From the results found in the human and from those obtained experimentally in monkeys, it may be inferred that the agglutinin titer for the colon group is depressed during the acute stage of poliomyelitis.

The idea that the enteric organisms have some part to play in the production of this disease was further bolstered by the fact that the monkeys which had been actively immunized with enteric organism vaccine had a definite, although incomplete, nonspecific protection, since a longer time interval elapsed before the protected animals contracted the disease.[94]

When enteric organism filtrates are injected into monkeys intracerebrally, there is no effect; virus injected the same way causes the disease to appear within seven days; the injection of virus and enteric organism filtrate into the motor area of the brain causes immediate paralysis of the heterolateral side.[95] Add to this the fact that we have acclimated the Flexner M. V., Philadelphia, and the Toomey strains to the cotton rat by the use of enteric organism filtrate as menstruum, and one must admit that there might be some connection between virus and resident enteric organism filtrates.

Toxins produced in the intestines might be absorbed by and travel over the sympathetic and parasympathetic nerves as far as their cells of origin, conditioning them as it were. Later, in the experimental animal, when the virus would enter the gastrointestinal tract, it might spread directly from the intestines, over the conditioned autonomic nerves to the spinal cord or bulbar areas.

It has occurred to us that the difference in virus strains might be due to the added character supplied by a secondary factor; in this case, the type of organism and its toxin found in the gastrointestinal tract, leaving the pure virus when purified and experimentally acclimated always the same.

THE PATHOLOGY OF POLIOMYELITIS

There has been a great deal of dispute about the pathology of the disease (see discussion[7]). For a long while, it was believed by Flexner and Amoss[96, 97] that the specific causative factor entered the system through the upper respiratory mucous membranes to the olfactory lobes of the brain, from which, by means of the cerebrospinal fluid, it was distributed throughout the substance of the nervous organs. These authors also state that the virus might reach the brain by any nerve channel and with great difficulty from the blood. This theory was supplemented by the one of neuronal spread, first definitely demonstrated by Fairbrother and Hurst.[7, 8, 98] In itself, this was not a new theory, but it was the first definite demonstration of this theory.

For a long while, it was believed that the interstitial reaction and edema occurred first and cell destruction later. The march of events may occur so rapidly in man that the processes will overlap and distinctions are not clear. This probably is the reason why an earlier school thought that edema, etc., caused the death of cells. Schreiber's opinion (quoted by Hurst), expressed in 1911, that there is a direct action on the nerve cell has been borne out by later experience. In any event, the toxic material injures or destroys motor cells, an action which immediately is followed by leucocytosis and neuronophagia. After this the vascular phenomenon may occur: dilatation of pre-existing capillaries; rupture of some local foci of red cells; edema; and finally perivascular infiltration with round cells. Any cell of the cord may be destroyed, including the neuroglial.

SECOND ATTACKS OF THE DISEASE

It has been demonstrated that animals receiving injections of virus either by way of the gastrointestinal tract or intracerebrally may contract the disease again when subsequently given injections of homologous or heterologous virus intracerebrally.[99] Flexner has also called attention to the fact that monkeys might again get the disease.[100, 101] Although later experiments confirmed previous experiences[102,104] in the experimental animal, it is nevertheless believed that once immunity is established in the human being, it is fairly permanent.

TABLE I

POSSIBLE METHOD OF VIRUS SPREAD IN INFANTILE PARALYSIS

PHASE	POSITION OF VIRUS	SYMPTOMS
I	At first the virus is free in the gastrointestinal tract.	There are none; or possibly some with diarrhea and pain.
II	The virus becomes fixed in the unmedullated postganglionic fibers of the thoracolumbar outflow and parasympathetic nervous system and spreads along the sympathetic nerve fibers to the ganglia.	The abdominal reflexes are absent or modified. There may be constipation, indefinite pain in the belly, and pain over the back.
III	The virus spreads from the sympathetic nervous system and reaches the somatic segmental nerve.	In addition to the symptoms described in phase II, there is hyperactivity of the reflexes with tiring on repeated stimulation.
IV	The virus, spreading backward over the somatic segmental nerve, reaches the spinal ganglia.	In addition to the symptoms described in phases II and III, there is segmental pain in the muscles and tendons supplied by nerves of the segments involved.
V	Simultaneously, the virus is absorbed and excreted; enough may accumulate at one time in the urinary bladder to involve the detrusor and sphincter.	A peripheral type of urinary bladder paralysis with overflow dribbling may now appear when the virus factors present are absorbed by the terminal gray nerve fibers of the bladder and its neck, whether of the sympathetic or parasympathetic nervous system.
VI	The virus reaches the cord and involves the anterior horn cell.	In addition to the symptoms described previously, the reflex reactions now become diminished or lost. Muscle paresis or paralysis begins to appear.
VII	The virus travels up the sympathetic nerve chain to involve the cervical area.	Here the train of events is the same as outlined in phases III and VI.
VIII	The virus may be virulent enough to be absorbed directly by the vagus nerve (i.e., the connector fibers in the gastrointestinal tract).	A condition simulating bulbar palsy appears. There is dysphagia, dysarthria, etc.
IX	The virus may be absorbed directly over the chorda tympani, from the pharynx, etc., directly to the nucleus of origin of the cranial nerve in the bulb.	The results are the same as in phase VIII.
X	In the rare instance, the virus may travel along the gray nerve fibers of the autonomic nervous system to the bulb, the internal capsular and the cortical areas.	The symptoms here would depend upon the localization of the virus, with bulbar palsy, hemiplegic and encephalitic reactions.

All second attacks of poliomyelitis reported in the literature have been analyzed. Many cases cannot be considered bona fide second attacks of poliomyelitis. It is probable that if the gastrointestinal tract is considered the portal of entry, this area would be sufficiently immunized after one attack so that subsequent attacks would hardly ever occur.[105]

THE EPIDEMIOLOGY OF POLIOMYELITIS

The epidemiology of the disease is interesting. It appears in our district between July 15 and November 1. These dates coincide with the time when perishable fruits and vegetables begin to ripen. In southern and midsouthern states, epidemics appear earlier than in the Lake border states. Occasionally cases may be seen just before or after the dates mentioned, but the majority of epidemics in our locality start in late summer and early fall, a time which corresponds to the same seasons in which it appears in the other half of the equator—in the south temperate zone, in Australia, New Zealand, and the Argentine Republic.

The histories of these patients have always been interesting. Many date their attacks to a dietary indiscretion such as eating unripe fruit or vegetables, such as apples, pears, peaches, plums, corn, and especially grapes. The handling of infected fruit or vegetables by infected people, the eating of infected fruits and vegetables by cattle, with subsequent infection of milk, and the spreading of the infection from fruit to fruit by flies—all of which occur at the season of greatest plenitude of fruits and vegetables—could serve to explain the spread of the disease and the incidence at this time of the year. If we add this to Kling's conception of water as a possible source of infection, all the factors of the epidemiology of the disease could be explained. One should not believe that the fruits, etc., cause the disease, but they may carry the infection. Thus, contaminated food and milk may provide the greatest source of infection.

POSSIBLE METHOD OF VIRUS SPREAD IN INFANTILE PARALYSIS

What is present objectively in patients ill with poliomyelitis? There is segmental paralysis of muscles, the nerve supply of which comes from the lumbar enlargement; to a lesser extent of the muscles that receive their nerve supply from the cervical enlargement; sometimes of the muscles supplied by the vagus and the seventh nerves; and if the exposure is massive, occasionally of the muscles supplied by the third and sixth nerves or intercostal and abdominal wall nerves. One might construct a chart of pathogenesis (Table I) as well as Fig. 8.

PROPHYLAXIS

Considering prophylaxis in a broad aspect and with the epidemiologic facts in mind and with the idea that the portal of entry is by way of the gastrointestinal tract, it is believed that (1) children should be taught to wash their hands before eating anything, not before every meal, but before eating anything; (2) no milk should be drunk which has not been pasteurized, especially milk obtained during the summer months; (3) no water should be taken unless obtained from an approved source; (4) no unripe fruits or vegetables should be eaten without first having them washed; (5) children should avoid dirty swimming holes and, if possible, should not swallow water while swimming; (6) the bowels should be kept open, especially during the summertime.

THEORY OF DISEASE CAUSATION

A dual condition of immunity may exist against this disease in man. This idea indicates several mechanisms and explanations.

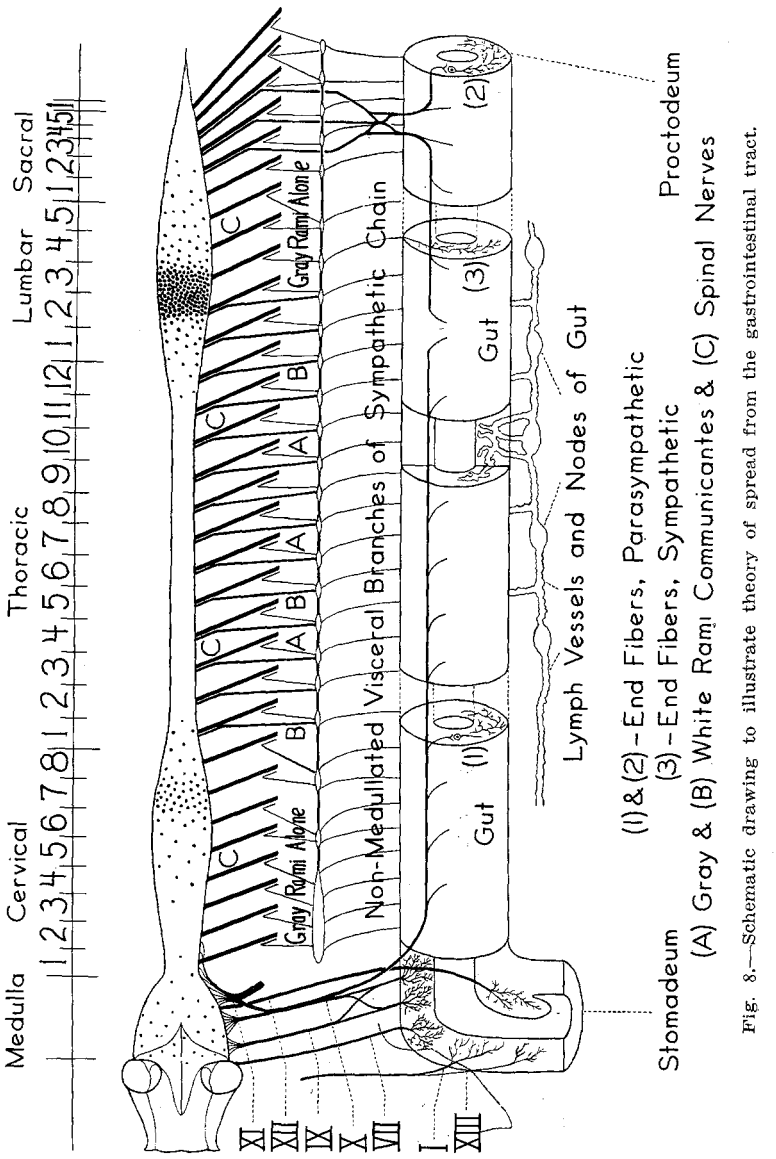

Fig. 8.—Schematic drawing to illustrate theory of spread from the gastrointestinal tract.

1. One person may have a marked degree of protection against the gastrointestinal group of organisms and their toxins. Even though the virus is taken into the gastrointestinal tract, such an individual might never get the disease.

2. Another person may be sensitive to the dysentery typhoid paratyphoid or to the colon bacillus factor, but immune to the virus and thus escape the disease.

3. One person may be exposed to an extremely virulent combination of factors, i.e., virus and enteric toxins as in sewage, which when swallowed would produce the disease at once.

4. One may ingest virus which may be nearer the purified state of a fixed laboratory strain. If there is no protection, it would first cause stasis and symptoms; later, it would combine with the enteric toxins of a stased gut and spread over the autonomic nervous system to produce the disease (two-humped; incorrectly termed dromedary).

5. Or the virus in its laboratory phase may enter the gut of an individual whose sympathetic system to the cells of origin has been previously conditioned to gastrointestinal toxins, and when the virus reaches the axis-cylinders, it immediately spreads to the cord.

CONCLUSIONS

I might conclude by stating that it is my belief that poliomyelitis is a peripheral neuritis of the autonomic nervous system, and that the virus enters by way of the gastrointestinal tract. It is a disease probably caused by nonliving entity in the nature of an enzymic catalyst with an almost obligate affinity for the axis-cylinders of gray nerve fibers; a disease, the causative factor of which is a combination of virus and intestinal toxins; a disease possibly checked by normal healthy medullated nerves, as well as by immunologic means; a disease, the happening of which might be termed an accident occurring during the course of mass exposure.

EPOCHAL EVENTS IN POLIOMYELITIS RESEARCH

If one should attempt to estimate the progress of poliomyelitis research, it could be concluded that the epochal events in the past forty years have been: (1) the isolation of the virus from the human being and its transference to monkeys; (2) the demonstration of virus-neutralizing antibodies in the blood sera of convalescent poliomyelitis patients; (3) the evaluation of the pathology of the disease and the acceptance of the conception that nerve cells are destroyed first and that other phenomena follow: (4) the demonstration that the virus spreads along neurones to the central nervous system; (5) the discovery that the virus can be acclimated to some smaller laboratory animals; (6) the fact that the virus can be easily isolated from the stools of patients who have had the disease.

We have conditioned our minds along certain lines for the past forty years. Most of the experiments described during this period have been made in animals given the disease by injecting virus intranasally, intrathecally, intrasciatically, or by some other artificial avenue of approach. If the virus enters the human being by way of the gastrointestinal tract, practically all, except the broader conclusions, especially those that have to do with pathogenesis and the explanation of symptoms, have to be discarded in toto.

It is important to ascertain if the smaller laboratory animals, such as eastern cotton rats, mice, etc., can be acclimated to poliomyelitis virus and used wholesale in experiments. We still need the monkey, however; or, we would still need an animal whose susceptibility can be demonstrated by way of the gastrointestinal tract nearly 100 per cent. When this is accomplished, we may really be able to evaluate convales-

cent serum, for instance, and the various factors pertaining to the gastrointestinal tract which protect certain individuals from contracting the disease.

All of the experiments done during the last thirty years, in which the olfactory, the intracerebral, and other areas were used as the portals of entry, will have to be repeated, using the gastrointestinal tract as the portal of entry.

REFERENCES

1. Toomey, J. A.: Ann. Int. Med. **8**: 856, 1935.
2. Fairbrother, R. W., and Hurst, E. W.: J. Path. & Bact. **33**: 17, 1930.
3. Levaditi, C.: Ectodermoses Neurotropes, Monographie de l'Institut Pasteur, Paris, 1922, Masson.
4. Amoss, H. L.: New York State J. Med. **22**: 256, 1922.
5. Brodie, M.: Report to the Banting Research Foundation.
6. Toomey, J. A., and von Oettingen, Wolfgang F.: Am. J. Dis. Child. **48**: 33, 1934.
7. Fairbrother, R. W., and Hurst, E. W.: J. Path. & Bact. **33**: 17, 1930.
8. Hurst, E. W.: J. Path. & Bact. **33**: 1133, 1930.
9. Toomey, J. A.: Proc. Soc. Exper. Biol. & Med. **31**: 502, 1934.
10. Landsteiner, K., and Popper, E.: Wien. klin. Wchnschr. **11**: 1830, 1908.
11. Levaditi, C., and Landsteiner, K.: Compt. rend. Acad. d. sc. **149**: 1014, 1909.
12. Sabin, A. B.: J. A. M. A. **3**: 605, 1938.
13. Toomey, J. A.: Am. J. Dis. Child. **51**: 58, 1936.
14. Toomey, J. A.: Proc. Soc. Exper. Biol. & Med. **32**: 628, 1935.
15. Aycock, W. Lloyd, and Luther, Elliot H.: New England J. Med. **300**: 164, 1929.
16. Silverman, A. C.: Am. J. Dis. Child. **41**: 829, 1931.

17a. Stillerman, M., and Fischer, A. E.: Am. J. Dis. Child. **56**: 778, 1938.
b. Fischer, A. E., Stillerman, M., and Marks, Herbert H.: Am. J. Dis. Child. **61**: 305, 1941.
c. Eley, R. C., and Flake, C. G.: J. PEDIAT. **13**: 63, 1938.
d. Top, F. H., and Vaughan, H. F.: Detroit Outbreak of 1939, American Public Health Association, 1940.

18. Paul, John R., and Trask, James D.: Cutaneous Infection in Experimental Poliomyelitis: Neurological Studies, Tr. Am. Pediat. Soc., April, 1937.
19. Harbitz, F., and Scheel, O.: Deutsche med. Wchnschr. **33**: 1992, 1907.
20. Faber, H. K.: Science **82**: 42, 1935.
21. Kling, Carl: The International Bulletin for Economics, Medical Research and Public Hygiene, Vol. 40, Infantile Paralysis, 1939-1940.
22. Lepine, Pierre: The International Bulletin for Economics, Medical Research and Public Hygiene, Vol. 40, Infantile Paralysis, 1939-1940.
23. Brookover, C.: J. Comp. Neurol. **28**: 349, 1917.
24. Flexner, S.: Science **36**: 685, 1912.
25. Flexner, S., and Lewis, P. A.: J. A. M. A. **54**: 1780, 1910.
26. Harmon, P. H.: J. A. M. A. **109**: 1061, 1937.
27. Kramer, S. D., Hoskwith, B., and Grossman, L. H.: J. Exper. Med. **69**: 49, 1939.
28. Trask, J. S., Vignec, A. J., and Paul, J. R.: J. A. M. A. **111**: 6, 1938.
29. Kling, C., Olin, G., Magnusson, J. H., and Gard, Sven: Bull. Acad. de méd., Paris **121**: 826, 1939.
30. Lepine, Pierre, Sedallian, P., and Sautter, V.: Bull. Acad. de méd., Paris **122**: 141, 1939.
31. Kramer, S. D., Gillim, A. G., and Molner, J. G.: Pub. Health Rep. **54**: 1914, 1939.
32. Trask, J. D., Paul, J. R., and Vignec, A. J.: J. Exper. Med. **71**: 751, 1940.
33. Howe, Howard A., and Bodian, David: J. Infect. Dis. **66**: 198, 1940.
34. Toomey, J. A.: Arch. Pediat. **56**: 693, 1939.
35. Kramer, S. D.: Personal communication.
36. Lennette, E. H., and Hudson, N. P.: Proc. Soc. Exper. Biol. & Med. **32**: 1444, 1935.
37. Toomey, J. A.: Am. J. Dis. Child. **57**: 338, 1939.
38. Rasmussen, A. F., Jr., and Clark, Paul F.: Proc. Soc. Exper. Biol. & Med. **45**: 232, 1940.
39. German, W. F., and Trask, J. D.: J. Exper. Med. **68**: 125, 1938.

40. Smith, L. W., and Landon, J. F.: Poliomyelitis, New York, 1934, The Macmillan Co.
41. Sabin, A. B.: Am. J. Dis. Child. **60**: 1313, 1940.
42. Swan, C.: Australia J. Exper. Med. **17**: 345, 1939.
43. Sabin, A. B., and Ward, Robert: J. Bact. **1**: 49, 1941.
44. Faber, H. K.: Medicine **12**: 83, 1933.
45. Toomey, J. A.: Proc. Soc. Exper. Biol. & Med. **32**: 1185, 1935.
46. Bodian, David, and Howe, Howard A.: Brain **63**: 135, 1940.
47. Rolleston, J. D.: Citation on Sicard, Brain **29**: 99, 1906, from Presse méd. **2**: 19, 1905.
48. Clark, P. F., Roberts, D. J., and Preston, W. S., Jr.: J. Prev. Med. **6**: 47, 1932.
49. Toomey, J. A.: Proc. Soc. Exper. Biol. & Med. **31**: 680, 1934.
50. Rasmussen, A. T.: The Principal Nervous Pathways, New York, 1932, Macmillan Co., p. 64.
51. Toomey, J. A., and Takacs, William S.: Poliomyelitis Virus Isolated From the Vagus Nerve. In preparation.
52. Toomey, J. A.: Am. J. Dis. Child. **46**: 730, 1933.
53. Toomey, J. A.: Am. J. Dis. Child. **48**: 1296, 1934.
54. Toomey, J. A.: Am. J. Dis. Child. **47**: 573, 1934.
55. Toomey, J. A.: Am. J. Dis. Child. **45**: 1211, 1933.
56. Toomey, J. A.: Proc. Soc. Exper. Biol. & Med. **31**: 702, 1934.
57. Toomey, J. A.: Am. J. Dis. Child. **52**: 559, 1936.
58. Toomey, J. A.: Am. J. Dis. Child. **52**: 1361, 1936.
59. Toomey, J. A.: Am. J. Dis. Child. **53**: 79, 1937.
60. Toomey, J. A.: Am. J. Dis. Child. **60**: 548, 1940.
61. Armstrong, Charles: Pub. Health Rep. **54**: 1719, 1939.
62. Müller, E.: München. med. Wchnschr. **56**: 2460, 1909.
63. Taylor, H. D.: J. Exper. Med. **29**: 97, 1919.
64. Gay, F. P., and Lucas, W. P.: Arch. Int. Med. **6**: 330, 1910.
65. Peabody, F. W., Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monograph of the Rockefeller Institute for Medical Research, No. 4, 1912, pp. 1-187.
66. Harmon, P. H., Shaughnessy, H. J., and Gordon, F. B.: J. Prev. Med. **5**: 115, 1931.
67. Toomey, J. A., and Ranta, K. E.: Blood Counts and Temperature Changes in Monkeys Experimentally Infected With Poliomyelitis. Unpublished.
68. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, ed. 10, New York, 1926, D. Appleton & Co., p. 25.
69. Toomey, J. A., and Takacs, W. S.: Proc. Soc. Exper. Biol. & Med. **45**: 364, 1940.
70. Toomey, J. A., and Takacs, W. S.: Proc. Soc. Exper. Biol. & Med. **46**: 22, 1941.
71. Toomey, J. A., and Takacs, W. S.: Proc. Soc. Exper. Biol. & Med. **46**: 319, 1941.
72. Toomey, J. A., and Takacs, W. S.: Proc. Soc. Exper. Biol. & Med. **47**: 123, 1941.
73. Toomey, J. A., and August, M. H.: Am. J. Dis. Child. **46**: 262, 1933.
74. Aycock, W. L., and Eaton, P.: Am. J. Hyg. **4**: 356, 1924.
75. Kling, C.: Svenska läk.-sällsk handl. **55**: 23, 1929.
76. Paul, J. R., and Trask, J. D.: J. A. M. A. **116**: 493, 1941.
77. Paul, J. R., Trask, J. D., and Gard, Sven: J. Exper. Med. **71**: 765, 1940.
78. Paul, J. R., Trask, J. D., and Culotta, C. S.: Science **90**: 258, 1939.
79. Caverly, C. S.: Yale M. J. **1**: 1, 1894.
80. Murphy, J. Harry: Personal communication; demonstration maps, A. M. A. Exhibit, 1940.
81. Casey, Albert, and Aymond, Branch J.: Pub. Health Rep. **55**: 1295, 1940.
    a. Toomey, John A.: Proc. Soc. Exper. Biol. & Med. **32**: 423, 1934.
    b. Toomey, John A.: Proc. Soc. Exper. Biol. & Med. **32**: 869, 1935.
82. Trask, J. D., and Paul, J. R.: J. Exper. Med. **73**: 453, 1941.
    a. Müller, W.: Monatschr. f. Kinderh. **63**: 134, 1935.
    b. Howe, Howard A., and Bodian, David: Proc. Soc. Exper. Biol. & Med. **43**: 718, 1940.
    c. Sabin, Albert B.: Personal communication.
    d. Burnet, F. M., and Jackson, A. V.: Australian J. Exper. Biol. & M. Sc. **18**: 361, 1940.
83. Goodpasture, E. W.: Am. J. Path. **1**: 547, 1925.
84. Toomey, J. A.: Am. J. Dis. Child. **53**: 1202, 1937.

85. Bodansky, Meyer: Introduction to Physiological Chemistry, ed. 2, New York, 1930, John Wiley & Sons, Inc., p. 496.
86. Toomey, J. A.: Am. J. Dis. Child. **54**: 1272, 1937.
87. Toomey, J. A.: Am. J. Dis. Child. **56**: 1274, 1938.
88. Toomey, J. A., and Takacs, W. S.: Poliomyelitis Virus and Deficiently Medullated Nerves, Proc. Soc. Am. Bacteriologists, 1939; Abstracted, J. Bact. **39**: 64, 1940.
89. Shope, R. E.: J. Exper. Med. **54**: 373, 1931.
90. Oroya Fever (current comment), J. A. M. A. **100**: 191, 1933.
91. Toomey, J. A.: J. Prev. Med. **6**: 379, 1932.
92. Toomey, J. A., and von Oettingen, W. F.: Proc. Soc. Exper. Biol. & Med. **30**: 1082, 1932-1933.
93. Toomey, J. A.: J. Infect. Dis. **54**: 74, 1934.
94. Toomey, J. A.: Non-specific Immunization of Monkeys Against Poliomyelitis Virus, Tr. Am. Pediat. Soc., 1935.
95. Toomey, J. A.: Proc. Soc. Exper. Biol. & Med. **31**: 1015, 1934.
96. Flexner, S., and Amoss, H.: J. Exper. Med. **20**: 249, 1914.
97. Amoss, H. L.: Filterable Viruses, Baltimore, 1928, Williams & Wilkins Co., p. 158.
98. Hurst, E. W.: J. Path. & Bact. **32**: 457, 1929.
99. Toomey, J. A.: Am. J. Dis. Child. **52**: 802, 1936.
100. Flexner, S.: Science **83**: 487, 1936.
101. Flexner, S.: J. Exper. Med. **65**: 497, 1936.
102. Toomey, J. A.: J. Immunol. **34**: 1, 1938.
103. Toomey, J. A.: Am. J. Dis. Child. **58**: 41, 1939.
104. Kessel, J. F., and Stimpert, F. D.: J. Immunol. **40**: 61, 1941.
105. Toomey, J. A.: Am. J. Dis. Child. **56**: 969, 1938.