The Etiology and pathogenesis of poliomyelitis

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THE ETIOLOGY AND PATHOGENESIS OF POLIOMYELOITIS

by

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INTRODUCTION

This subject was chosen for my senior thesis primarily because of my interest in the field of orthopedics.

A certain doctor, some years ago, made a statement to the effect that seventy five percent of orthopedic cases were concerned with deformities due to poliomyelitis. However, he continued, as soon as the etiology and pathogenesis of the disease is definitely known these cases will be practically unheard of, due to prophylactic measures and more efficient treatment of the disease which can then be instituted.

From this, my interest was aroused in the etiology and pathogenesis of poliomyelitis and therefore I chose it for the subject of my thesis.

Poliomyelitis is derived from two Greek words meaning gray marrow, and as we interpret it - an inflammation of the gray substance of the central nervous system.

It is an acute infectious disease, coming on suddenly, with symptoms of a general toxemia. Later there are manifestations of the results of damage to the ganglion cells of the central nervous system.

The disease often occurs sporadically, but has strong epidemic properties.
HISTORY

For some the disease of poliomyelitis is relatively new, while for others it has left visible traces in the records of the earliest human history and perhaps pre-history. Many of the following historical incidents are lacking in data to furnish grounds for reliable differential diagnosis, but they appear of sufficient interest to justify including them in this discussion.

The Archeological Museum of the University of Pennsylvania contains a skeleton, dating from about 3700 B.C., found in a village south of Cairo by Flinders Petrie, who noted that one leg was shorter than the other. This skeleton has been thoroughly studied and it is now believed that the shortening of the leg was caused by disease rather than by a pelvic fracture as was suspected at first. The disease was no doubt poliomyelitis, and offers us one of the earliest cases of the disease that is known.

The delineations on an Egyptian stele of the Eighteenth Dynasty shows that the artist has produced a man with a 'withered leg'. If the artist has drawn the man as he was in life, it is natural to think of poliomyelitis. Another picture of the Egyptian times, 1500 B.C., shows a priest, his wife and their son. The priest has a typical atrophied leg, shortened, with a club foot, and carrying a staff for support. Also, of that period, was found a mummy with a foot deformity similar to that of the priest. This was Syptah of the Eighteenth Dynasty of Pharoah. (29)
Hippocrates, in his writings, gives an account of paraplegia which was probably poliomyelitis. (35)

An archeological discovery in 1921 in South Greenland revealed twenty-five skeletons of which six, while living, had diseases involving physical deformities such as weakening of one arm or one leg, asymmetry, atrophy of skeletal structures, scoliosis, and various pelvic deformities. These changes are very probably due to an epidemic of poliomyelitis in which they were stricken during their childhood.

A plate of cripples drawn by a Dutch artist of the sixteenth century is evidence that poliomyelitis was prevalent in Holland at that time. (35)

Underwood was probably the earliest recognizer of the disease. He published a treatise in 1784 under the title of "Debility of the Lower Extremities." He describes the disease and presents several cases, terming it the 'Palsy'. (6) About this same time Sir Walter Scott must have suffered from poliomyelitis, as described in Lockholt's "Life of Scott". He states that one of Scott's legs was badly damaged, and gives an account of it.

In 1823 Shaw included in his volume on the "Nature and Treatment of the Distortion to Which the Bones of the Spine and Chest are Subject" a chapter entitled, "Enquiry into the Causes of the Partial Paralysis and Wasting of One of the Limbs during Infancy, Which Frequently Produce Distortion of the Spine". Badham, of England, about this same time, 1935, gave a very good clinical
description of four cases which occurred during that summer. They furnish the earliest group of cases known to occur within a small area and a brief time. This proved an incentive to Heine to study in more detail this strange form of paralysis in children.

In 1839, Wm. J. Little, of England, wrote a book on club foot deformity. He described many cases, but failed to grasp the significance of the disease. (35)

Heine is one of the outstanding names in medical literature in connection with poliomyelitis. He belonged to a family of skilled orthopedists, and he was interested in the field of corrective treatment of weakened muscles and skeletal deformities. Heine possessed keen clinical insight, and he was led to speculate on the etiology and to suggest the probable pathological basis which later microscopic studies were to substantiate. He published two monographs dealing with the disease, both of which showed that he possessed a greater insight into the disease than anyone up to that time. From his observation he concluded that the symptoms "point to an affection of the central nervous system, namely of the cord, of an irritative and congestive sort." However, Heine took into account only the deformity after it had happened. He hints that something may be done to prevent it, but doesn't give any details. (29)

In America, Charles F. Taylor, New York, orthopedic surgeon, was one of the first to consider poliomyelitis. He wrote a book on Infantile Paralysis in which he brought out that a lot
of actual deformity could be prevented under proper treatment, namely, that of protection of muscles, rest, and relaxation. (35)

Following Heine were Seeligmuller, Strumpell, Pierre Marie, Medin, Caverly, and Wickman, all of whom contributed to the knowledge of the disease. Seeligmuller had opportunity to observe seventy-five cases in various stages of the disease, and made detailed studies of the early symptoms and of the distribution of the paralyses. In 1887 Medin observed an outbreak of forty-four cases of infantile paralysis in Stockholm. The opportunity afforded to Medin to witness so large an outbreak made possible an important extension in the knowledge of the disease. The name given to the disease at this time was Heine-Medin disease. Caverly, in 1894, added a new and important type, the nonparalytic, to the list. He called attention also to the stiffness of the neck and back muscles as an early and significant symptom.

Fifty years elapsed from the time of the first positive microscopical examination of a case of poliomyelitis by Cornil, in 1863, until Wickman began his examination in 1905. During this period, however, a fairly complete picture of the pathological anatomy of the disease had been built up, and theories were advanced as to the point of entrance of the causal agent and the route by which it was spread through the body. The modern conception of the pathological anatomy begins with the work of Wickman, who gives a comprehensive picture of the histopathology of the disease. He also studied the problems of the portal of entry of
the infection and of the pathogenesis. One important point raised by Wickman which had not previously been considered was why this disease, with strictly localized pathological lesions, should develop first clinically as a systemic disease. (29)

Following the publication of Wickman's monograph on poliomyelitis in 1907, three phases in the evolution of the modern conception of poliomyelitis attained a climax: the classic conception of a spinal infantile paralysis had expanded to include widely varying clinical manifestations; the pathological investigations had culminated in the first critical analysis of the pathogenesis; the epidemicity of the disease had been established, and the theory of its transmission by contact widely accepted. This monograph also marked the beginning of a new period, the present period of experimental research, with which work the remainder of this paper will largely deal.
ETIOLOGY

The question of the etiology of poliomyelitis has always been very perplexing, and it has presented a problem upon which a great amount of research work has been done. At the present time a filterable virus is accepted as the causal agent by the majority, but there are still many who do not agree with this.

At the time the disease was beginning to assume its importance in the field of medicine, there were various theories offered as to the cause of the disease. Traumatism, over exertion, exposure to the cold, nervous shock, acute febrile diseases, were all mentioned as exciting causes. Heine, Colmer, and Kennedy all thought that teething might be a predisposing factor.

Professor Landouzy, in 1880, first suggested that myelopathies were infectious, and in the same year Seeligmuller made a comparison between poliomyelitis and infectious diseases, saying that infantile paralysis was not infrequently preceded by febrile manifestations after the manner of acute infectious diseases.

The first to formulate a definite hypothesis was Strumpell in 1884. He affirmed the infectious nature of a "group of diseases, which, both in their course and in certain of their symptoms, show a similarity with each other that cannot fail to be recognized: acute multiple neuritis, acute poliomyelitis, and a still relatively little known form of encephalitis.
in children. All these diseases begin rather suddenly with an often considerable degree of fever. The patients are mentally dull, have headache, show gastric disturbances, sometimes a slight enlargement of the spleen, often, too, joint rheumatism and a slight albuminuria. According to the present views, these are all symptoms which point, undoubtedly, to an infection of the body with an organized toxin. The idea seems to us worthy of consideration of grouping the above named affections as an etiological entity, and to look upon them as variously localized manifestations of the same, or at least of very closely related specific agents." (29)

No mention is made of microorganisms in the early pathological studies. There is mention of studying the tissues in hopes of finding microorganisms, but these were without success. Cultures of cords, spinal fluid, blood, and brain, all showed negative results in early experimentations.

In 1908, Wollstein obtained spinal fluid from life, from twenty cases. Cultures, both anaerobic and aerobic, were made and were sterile in fifteen cases. Growth was observed in five, in one a white staphyloccoccus was identified, in one a short Gram-positive bacillus, and in three a large Gram-positive coccus in pairs and tetrads. Wollenstein looked upon the coccus as contamination, but later researchers re-discovered a very similar organism but have been unable to prove it to be the etiological agent of poliomyelitis. (38)
The causal agent has never been seen with certainty, and yet we know much about its nature and behavior. This is entirely owing to the fact that the infection can be transmitted to the monkey, in which animal it produces a disease which is very identical to that in the human. This has proved a most powerful weapon in investigation. The production of experimental poliomyelitis in monkeys, and the evidence that the specific agent belongs to the group of ultramicroscopic viruses, brought about a great change in the character of the bacteriological experimental work. Many of the investigators of this time had, however, already discarded any belief in a bacterial origin of the disease.

Romer, who carried on studies relative to the etiological agent over a period of years both before and after successful transmission of the disease to monkeys, made cultures from the pharynx and tonsils but found only the ordinary organism; cultures from the spinal fluid, blood, brain, and cord, were sterile. He concluded that he was able to state with confidence that it was impossible that a microbe which could be stained and cultivated easily could be the active agent in the causation of epidemic infantile paralysis.

It was in 1909 that Landsteiner and Popper, in Vienna, first succeeded in infecting a monkey by intraperitoneal inoculation of material from the spinal cord of a fatal case. They mention the fact that smears and cultures from the spinal fluid and central nervous system, and cultures from the spinal cord
emulsion on agar, blood agar, serum agar, blood and serum agar gave negative results.

Landsteiner and Popper, in making their transmission to monkeys, used two animals. The first animal died after eight days, after inoculation, and two days of illness. The histology of the cord and brain showed a typical high grade poliomyelitis, agreeing with human findings. The second monkey showed complete flaccid paralysis seventeen days after inoculation, of the posterior extremities. He was killed two days later, and showed similar although not as definite changes as the first. At this time they made the suggestion that the disease may be due to a filterable virus. Their results were confirmed by Knoepfelmacher in 1909.

Soon after the first transmission of the disease to monkeys, transmission in series was made by Flexner and Noguchi in 1909, Leiner and Von Wiesner in 1909, Lanssteiner and Levaditi in 1909, Romer in 1909, and Landsteiner and Prasek in 1909. From these groups of experiments it was concluded that the infecting agent of epidemic poliomyelitis belongs to the class of minute and filterable viruses that have not thus far been demonstrated with certainty under a microscope. They also showed that the monkey was a suitable experimental animal in which both the clinical picture and the pathological findings of the human disease could be reproduced. (29)

Amoss has said, "There is no experimental disease which
so clearly reflects in its clinical aspects the human analogue as does experimental poliomyelitis". It might be well at this time to give a brief account of the symptoms most frequently observed in experimental poliomyelitis in the monkey.

Immediately after intracerebral inoculation with a potent untreated virus, the monkey shows no symptoms save the effects of the anesthetic and the operation, and these usually disappear in less than an hour. Five to eight days after inoculation the prodromal period occurs. The animal becomes either passive or restless, cries and ruffling of the fur, these signs being especially conspicuous when the animal is stimulated. Tremors, varying from a fine generalized tremor to coarse intention tremors, are an almost invariable accompaniment. Finally flaccid paralysis appears, the date of its onset in relation to prodromal symptoms depending upon the strain of virus used. With the virus of moderate potency, originally obtained from Aycock, and used in most of our experiments, we have observed a consistent and well defined prodromal period occurring from twenty-four to forty-eight hours, and in rare instances from four to five days before the onset of paralysis. With the more potent virus obtained recently from Rhoads, prodromal symptoms have as a rule been observed only on the day immediately preceding paralysis. With the moderately potent Aycock virus, the extension of paralysis from its first appearance to the stage of total paraplegia requires from twenty-four to forty-eight hours,
while with the Rhoads strain less than twenty-four hours suffice for the change from earliest prodromal symptoms to an almost skeletal palsy. (29)

There have been many attempts to produce the disease of poliomyelitis in other animals than the monkey, but these have met with little success. Maurice Brodie has done considerable work in this field and has used guinea pigs, rabbits, rats, and mice. These animals as a whole do not develop the symptoms or the lesions characteristic of poliomyelitis. Although some of the animals become sick and die after injection of the virus, it is doubtful if the virus has been the cause of this. Probably it is due to trauma during the injection or to some foreign organism introduced at the same time. From all of his experiments it appears that the mouse should be the best in attempting to produce poliomyelitis, for the virus survives in its brain for a longer time than in that of the guinea pig, rabbit, or rat. Serial passages of the virus of poliomyelitis, for forty-five generations in the mouse, and sixteen in the rat, failed to adapt the virus to either host. Likewise, the use of very young mice or guinea pigs proved ineffective. (4)

In 1913 Flexner and Noguchi described minute formed structures which they referred to as 'globoid bodies', cultivated by special methods from nervous tissue of human or experimental origin or from filtrates. All sources of contamination had been ruled out. The bodies stained more intensely with Grams stain in older cultures than in initial ones. After several weeks they
became enlarged, though still filterable through Berkefeld filters. Not all of the cultures produced infection on inoculation into monkeys. Others proved to be pathogenic to eighteen and twenty generations. The authors expressed the view that an etiological relationship existed between the cultivated microorganism in the human and the experimental forms of poliomyelitis.

Further work was done with the globoid bodies by Flexner, Noguchi, and Amoss, in 1915, and by Amoss in 1917. The results were very similar as before. In 1918 Taen attempted to repeat the work of Flexner and Lewis and although he was able to cultivate the organism and pass it on to a few generations, he did not have the success that they had had. He brings out two points which he considers evidence against the supposition that the globoid bodies are the causative agents of poliomyelitis. "First, the globoid bodies have not yet been proved to be able to produce immunity against poliomyelitis, and second, the serum of monkeys immunized with the globoid bodies has failed to show neutralizing power against poliomyelitis virus." Subsequent statements by Amoss and Flexner would suggest that they, too, no longer believed the globoid bodies to be the causal factor. There have been several investigators of late that have cultivated the globoid bodies, and they present strong evidence in favor of the globoid bodies as the etiological agents, so that there still remains some question.

The globoid bodies of Flexner and Noguchi are approximately 0.25 μm in size.
Flexner and Lewis in their early experiments, while giving evidence that the specific agent is a filterable virus, state that no bacteria were discovered "either in film preparations or in culture that could account for the disease."

The nature of viruses has been investigated to some extent, but comparatively little is known concerning them. It is known that they are ultramicroscopic, infectious agents, capable of passing through the finest filters, and therefore their actions can only be tested on animals, such as the monkeys in poliomyelitis. It is not known definitely whether filterable viruses are living or are unorganized non-living agents. It is not possible to cultivate them in the absence of living cells. They have been shown to possess attributes of living things, that is, their power to multiply, and their power to adapt themselves to alterations in environment without loss of identity. Some have been definitely identified as microorganisms, such as the filterable virus causing psittacosis. Recently Levaditi, Haber, and Hornus have advance evidence in support of living nature of viruses. Gonacrine, a dye, which is bactericidal in nature, has a photodynamic action on viruses. This dye has no inactivating action on tetanus antitoxin and trypsin, whereas it inactivates viruses like herpes, rabies, vaccinia, and bacteriophage. However, for some reason, the supposed virus of poliomyelitis was not affected. (14)

Elford, Galoway, and Pandrwas have made investigations
on the size of the virus. Findings in this work by analysis of broth suspensions of spinal cord enlargements of poliomyelitic monkeys by means of fractional ultrafiltration indicated the size of the virus to be 8 - 12 mu. (15)

Rosenow, assisted by Towne and Wheeler, has done a great amount of work on the etiology of poliomyelitis. It is his belief that the disease is caused by a peculiar form of streptococcus, and he has good proof to back his views. He first isolated this streptococcus from the throats, tonsils, and tissular abscesses, and from the central nervous system of humans suffering from the disease or having died from it. Injections of cultures of this organism produced paralysis in animals when injected intravenously or intracerebrally, and lesions of the gray matter of the nervous system have been demonstrated. While the streptococcus has been isolated in pure cultures from the nervous systems, other tissues have been sterile. The organism is remarkably polymorphous, and appears to grow large or small according to the medium, even after passage through the Berkefeld filter.

Using the organism in its large form, paralysis has been consistently produced in animals known to be insusceptible to inoculation with material from epidemic poliomyelitis. After paralysis was produced in a series of three rabbits, the strain caused characteristic paralysis and lesions of poliomyelitis in monkeys. It appears that the small filterable organism which has been generally accepted as the cause of poliomyelitis may be the form which
this streptococcus tends to take under anaerobic conditions in the central nervous system and in suitable culture mediums, while the larger and more typical streptococcus forms, which investigators have considered contaminations, may be the identical organism grown larger under suitable conditions. (34)

While he produced the main symptoms of the disease of poliomyelitis and encephalitis in animals by injection with streptococcus obtained from humans and monkeys ill with the disease, the lesions induced were usually atypical both in type and in distribution. However, recently, he has succeeded in producing with considerable regularity the symptoms and lesions of poliomyelitis and encephalitis in animals following intracerebral and other injections of the respective streptococcus thus grown, and of filtrates of old cultures. He has used mice, guinea pigs, rabbits, and monkeys.

Rosenow has also shown experimental production of a virus from the streptococcus isolated in cases of poliomyelitis. The streptococcus from which the virus was derived was usually demonstrated in smears and cultures of the spinal fluid during the early stages of the disease, and especially during symptom free but febrile period. Each of four strains has been passed consecutively through its 'streptococcus to virus' stage and 'virus to streptococcus' phase three times. (32)

Rosenow has developed a method of staining microorganisms and their capsular substance, and has shown its application
to the streptococcus and to filtrates of the viruses and spinal
fluids in poliomyelitis and encephalitis. The finding of other-
wise non-stainable organisms, resembling the streptococcus in fil-
trates of the viruses and in spinal fluid in poliomyelitis and en-
cephalitis, which sometime yields streptococcus in suitable cul-
tures, adds materially to the correctness of the theory that the
streptococcus is etiologic of these diseases and suggests the
nature of the indicated relationship between the virus and the
streptococcus. (33)

Frederick Eberson, in a series of experiments, has iso-
lated an organism, cultivated it, and successfully transmitted the
disease to monkeys by inoculation with the organism. Seven strains
of virus were studied from Berkefeld filtrates prepared from the
nervous tissues of monkeys inoculated with poliomyelitis. The
use of brain tissue suggested itself as a suitable culture medium
for a virus that is known to exhibit a marked affinity for the
nervous system. A reduced oxygen tension developed in the culture
medium was found satisfactory. Positive cultures were obtained
from poliomyelitis virus filtrates, and the transfers from the
original cultures have yielded successful growth in series. At
the present time these organisms are in the fourteenth subplant,
and the original cultures are still viable after growing in the
incubator for more than eighteen weeks.

The organism grows in an atmosphere of reduced oxygen
tension developed in the medium, stains best with Wright stain,
and in later subplants and older cultures it appears to be faintly or moderately Gram positive. Under a magnification of 1500 to 2000 diameters it is a minute ovoid body ranging in size from the lowest limit of visibility to 0.05-0.1 or 0.2 μ, and occurring in irregular clusters, in pairs, singly, very rarely in short chains, and in densely packed masses. The bodies are especially numerous in the particles of brain tissue found in the medium, for which they exhibit a marked preference. A sheath-like envelope appears to surround the organism, favoring the formation of zoogloal masses. Filtration experiments with the cultures during certain stages of growth suggest that ultramicroscopic forms are capable of developing into visible bodies in the culture medium.

Inoculation in monkeys of organisms obtained from cultures of poliomyelitis tissues caused clinical symptoms and pathological effects characteristic of experimental poliomyelitis. The cultures used were in the sixth to the thirteenth subplants, the infectivity remained unimpaired. Parallel experiments, in which heated cultures were used for inoculation into monkeys, resulted negatively. Materials derived from culture tubes that contained no demonstrable organisms were also without effect.

Attempts to recultivate the typical organism from monkeys experimentally infected with the cultures and developing poliomyelitis, were successful.

The cycle of the disease has been demonstrated in monkeys inoculated with cultures. The organism has been developed from an
invisible to a visible state and the typical disease induced in
the experimental animal, in the brain and spinal cord of which the
organism again returns to the invisible filterable stage. Eberson
is now studying a possible life cycle and other biological con-
siderations of this microbic agent. (12, 13)

Toomey has concluded, from a number of investigations
which he has made, that "poliomyelitis is accelerated when polio-
myelitis virus is combined with paratyphoid colon bacillus fil-
trate and injected subserosally or directly into the gastrointes-
tinal tract."

The paratyphoid colon bacillus filtrate was not toxic
for the animals as proved by controls, nor did the virus alone
produce the disease so characteristically and so quickly as the
virus combined with the paratyphoid colon bacillus filtrate. (45)

Toomey also gave massive injections of the paratyphoid
colon bacillus filtrate and vaccine subcutaneously to baby monkeys,
and thus rendered the monkeys less immune, so that when polio-
myelitis virus was later introduced by way of the gastrointestinal
tract, the production of the disease was accelerated. (45)

Experiments with monkeys showed that the agglutinin
titer for the colon group is depressed during the acute stages of
the disease. Enteric organisms may play a part, and many of the
clinical observations of typhoid are similar to poliomyelitis and
vice versus. Osler's observation that a state of poliomyelitis
occurred in typhoid fever with the symptoms of acute ascending palsy are pertinent to this point. From these facts one could surmise that a dual condition of immunity may exist against the disease. One may be immune to either the colon group or the virus, and not contract the disease.

Besides the theories regarding the Gram positive coccus discovered by Wollenstein, the virus, the globoid bodies, the streptococcus, Eberson's organism, and the combination of virus and enteric organisms, as the etiological agents of poliomyelitis, there are other factors which must be considered, although they admittedly play a minor role.

Exposure plays a large part in any infectious disease. It may be stated with a very considerable degree of certainty that certain "diseases of childhood" have come to be designated as such, first, because opportunity for infection is likely to come relatively early in life, and second, because with advancing age an increasing increment of the population is immune to the disease as a result of this earlier exposure. However, the diminution in the frequency with which certain of these diseases occur with increase in age in seeded population cannot be wholly accounted for by increase in serologic immunity with age. The variation in the occurrence of "infectious diseases" in non-immune persons at different ages would appear to be due, in part to a difference in the frequency with which persons of different ages are exposed to this virus, and in part to a difference in the frequency with which
persons of different ages are infected under the same apparent
degree of exposure. The differences in the risk of infection at
different ages would appear to be due to quantitative or qualita-
tive differences in personal, social, or household habits of per-
sons at different ages, which habits constitute sanitary habits in
the present connection. However, there is nothing in this which
would detract from the view that whether disease is to be the re-
sult of infection in a non-immune individual is determined by
autarceologic factors. In fact, Aycock states, from a series of
studies on "Exposure as a Factor in the Age Distribution of Measles,
Diphtheria and Poliomyelitis", that variation in these diseases
with age, can be accounted for wholly by exposure, infection, and
immunity. It implies that autarcesis, although varying with cli-
mate and possibly with season, does not vary with age. (2)

It is known that poliomyelitis is primarily a disease
of the very young. Children are most susceptible in their second
year. From there the incidence falls rapidly until it is almost
zero at twenty years of age. However, recently this disease has
attacked adults more than formerly. The type of person in the 1916
epidemic was a large, well grown child, plump and with certain
characteristics of face and jaws, broad brow and round face. The
arrangement of the maxillae showed a slight prognathism, the
features being rather sharp and pointed and the teeth crowded,
and there were many small pigmented moles over the neck and face.
All of this indicates a special susceptibility of certain
individuals.

In a study of six hundred and twenty two cases in 1935 it was shown that the disease was only two thirds as common among the Negroes as the Whites, but among the Indians it was four times as frequent. White males showed one third higher than white females, and this was slightly lower in Negroes and only half as high as in females among Indians. The highest incidence is among well nourished persons with high, narrow palates, widened interpupillary spaces and other measurements suggesting a 'thymic' constitution and a deficiency of the pituitary gland, gonads, and adrenal cortex, as well as the great absorbing surfaces for nasal infection. In children the correlation of the physical make up and the incidence is difficult to measure. (6, 3, 2)

Levine, Neal and Park detected no evidence of relation between physical characteristics and susceptibility to infantile paralysis in measurements made on fifty two cases of the disease and fifty two controls selected according to age and race. Wilder also agrees that susceptibility does not accompany any particular physical type. (49)
PATHOGENESIS

Cornil, in 1863, was the first to publish a report of a microscopical examination of poliomyelitis. The patient, who died of cancer at the age of 49 years, had had infantile paralysis at the age of 2 years. He found considerable atrophy of the anterolateral bundles of the cord, especially in the dorsal and lumbar regions, with amyloid bodies in the anterior horns, most numerous in the vicinity of the blood vessels. He failed, however, to recognize the significance of the absence of ganglion cells, although he described and illustrated this important fact. Charcot, nearly a decade later, comments on the fact that both he and Cornil had completely overlooked the motor cell lesions.

Prevost, Vulpian, Parrot, and Jeffrey also made reports on microscopical examinations of cases of poliomyelitis shortly after Cornil. They noted the changes in the nervous tissues, but failed to draw any conclusions to correlate the paralysis with the pathology occurring in the cord. Charcot was the first to present a hypothesis. He concluded that there was a correlation between the site of the alterations in the cord and the distribution of the paralyses, and inferred that irritation of the ganglion cells transmitted by way of the nerves resulted in trophic lesions of the muscles.

Much investigation was done in the next few years concerning the pathological process of poliomyelitis, and the investigators were divided into two opposing groups. Many believed that
the process was primarily parenchymatous, while others considered
the interstitial inflammation primary. During this period, too,
the possibility of a vascular origin of the disease was considered.
They suggested that the localization of the myelitis in the anterior
horns was influenced by the excessive vascularity of this part of
the cord.

Rissler, in 1888, had opportunity to study a number of
cases in the acute form, and gave accounts of some very interest-
ing findings. Wickman says that Rissler was the "first to give a
comprehensive description of the pathological anatomical process-
es of the acute stage". He was the first to describe softening of
the spleen and enlargement of the solitary follicles and Peyer's
patches of the intestine and of the mesenteric lymph nodes. In
the cord he described what he called a "form of ganglion cell
death, in which other cellular elements, most probably white blood
cells, play a prominent part". He became convinced that Charcot's
hypothesis of a primary degeneration of ganglion cells offered the
best explanation of the picture.

Wickman did a great deal to further the understanding of
the pathological picture. He raised the question really for the
first time, of the point of entrance, the method of infection, and
the spread of the virus. He later published a complete discussion
of the disease. In his earliest work, Wickman stated his convic-
tion "that the specific pathological changes could best be explain-
ed as a lymphatic infection". Later he felt that the experimental
work on monkeys had confirmed his hypothesis and that "the virus spreads from the site of inoculation especially by way of the nerves". With regard to the portal of entry in human beings, he expressed his "belief that human infection takes place by way of the alimentary canal". (29)

With the production of experimental poliomyelitis in monkeys came new opportunities for the study of the pathological changes of poliomyelitis in the acute stage, and of the distribution and spread of the virus within the organism. With subsequent studies on the portal of entry, and route of infection, together with numerous studies of autopsy material, the pathological picture is quite complete at this time.

Cecil states that the virus is widely distributed in the body. It is found present in the lymph nodes, tonsils, pharyngeal mucosa, spleen, bone marrow, and mesenteric lymph nodes and in the posterior ganglia of the spinal roots. The virus has never been detected in the spinal fluid of man. (1)

The characteristic pathological lesions are hyperplasia of lymph nodes, of the spleen, and of the interstitial lymphatic nodes. Often there is interstitial small cell infiltration of the portal spaces of the liver, with general cloudy swelling of all the parenchymatous organs. (6)

In the central nervous system the lesion is much more specific. The meninges of the cord and the medulla undergo a mononuclear infiltration around the blood vessels which enter the
fissures of the cord. The cellular invasion about the vessels within the lymphatics is heavy and often nodular. The distinctive degenerative lesions of the disease are found most commonly in the ganglion cells of the lower motor neurons in the lumbar and cervical enlargements of the spinal cord. The anterior horn cells are the most frequently attacked. There may be extensive necrosis of the substance of the cord, with frequent hemorrhages about the affected areas in the cord. Much interstitial cellular infiltration occurs about the vessels. (9)

Microscopically, the earliest change that can be seen is a perivascular infiltration of small round cells along the blood vessels of the leptomeninges. The virus, in experimental disease, is suspended in the spinal fluid and thus conveyed along the perivascular lymphatics and spaces causing the round cell reaction. The process spreads from the parietal meninges and enters the interior of the cord by the anterior fissure along the branches of the anterior spinal artery. Cellular infiltration, hemorrhages, edema, changes in the ganglion cells, are probably due to virus, mechanical, and toxic forces. (3)

Following the changes in the anterior horn cells there occurs a degeneration of the lower motor neurons down to the muscle, which becomes atrophied and replaced in time by adipose and fibrous tissue. The affected part of the cord is smaller, affected limbs are shorter, and the bones are of diminished size.

There are a number of classifications for this disease
depending on its paralytic manifestations and its severity. At this time the accepted classification includes four types. These are the spinal form, the bulbar form, the cerebral form, and the abortive form. (3)

Of these forms the spinal is much the commonest with chief incidence in the lumbar rather than the cervical enlargement of the cord, so that the lower limbs suffer more than the upper. The lesions involve the lower motor neurons, giving rise to flaccid paralysis. The paralysis may persist on recovery.

In the bulbar type the symptoms point to lesions of the medulla, pons, and the mid brain, such as facial palsy, strabismus and paralysis of respiration.

The cerebral type was first described by Strumpell in 1885. The patient develops a hemiplegia or monoplegia of the upper motor neuron type without atrophy or the reaction of degeneration in the muscles affected, and a spastic paralysis. The fatality in this form is greater. However, if recovery takes place, there are commonly no after effects. The cerebrum does not appear to be susceptible to the virus of poliomyelitis.

Cases are designated abortive when attention is centered on the paralysis as the chief symptom; but in poliomyelitis we are dealing with an infection that presents a great variety of symptoms. Atypical is probably a more suitable term than abortive. Pathological studies show that not only may there be lesions of the nervous system but also that the viscera and the entire lymphatic
system may be involved and that we may find palpable enlarged lymph nodes. (10)

Of one hundred cases in Philadelphia Childrens Hospital, fifty-two were nonparalytic; forty-three were of the spinal and bulbar type, and five were of the cerebral type. Of this number there were seven deaths, six of which were of the spinal and bulbar type and one death from the cerebral type. (37)

Waddell states from a study of one hundred and eleven cases in the University of Virginia Hospital, "We cannot consider poliomyelitis solely in terms of its neurological manifestations, as is the current medical tendency. A systemic disease with neurological manifestations. To think otherwise precludes the possibility of diagnosis of early abortive cases and nonparalytic cases, and interferes very materially with a proper conception of its probable incidence. The low death rate and the infrequent occurrence of muscle paralysis and weakness suggests the hope that poliomyelitis may fast be becoming a less malignant disease. (48)

The fact that the experimental disease could be produced by the nasopharyngeal and tracheal routes suggested, as first pointed out by Flexner and Lewis, that the nasopharyngeal mucosa was the path of entry and also the path of elimination of the virus. This view, that the upper respiratory mucous membrane would, under usual conditions, be the most frequent atrium of infection in the human disease and the site from which it could readily pass by way of the filaments of the olfactory nerve to the olfactory lobes of the brain
and thence to the medulla and the cord, has been held consistently by Flexner and his associates and is widely accepted at the present time.

Many authors, however, have felt that there was evidence to show that the virus may also gain access to the body by way of the digestive tract. Bulow-Hansen, and Harbitz were the first to suggest this possibility, and Wickman concluded that the GI tract was the more probable route of infection in man.

Other routes of infection have also been suggested to satisfy the occasional of a puzzling form of the disease.

The probable route of infection, if we suppose the portal of entrance to be the nasal mucosa, would be for the exciter to have access to the ciliated area of the nasal mucosa which covers about 250 mm, and offers direct access without trauma, to the nerve fibers. From here the exciter reaches the cells of the olfactory nerve, the axis cylinders of which rise without synapses, into the olfactory bulbs. The end of the trail is found in the crescents of the spinal cord, via the hypothalamus, thalamus, midbrain, spinothalamic tract, first to the posterior cornua and by the connecting fibers, to the spinal ganglia and the cells of the anterior cornue. The interval between infection and the first signs of a parenchymal injury, the so-called preparalytic stage, lasts 7 to 10 days. The parenchymal process proper begins in the motor regions of the spinal marrow; the appearance of paralyses corresponds to the ensuing disintegration of the ganglial cells. (21)
If the virus of poliomyelitis enters the body through the nasopharynx or the gastrointestinal tract, it may conceivably invade the central nervous system by way of the blood stream, the lymphatics, or by the fibers of the peripheral nerves.

Burrows made an extensive study of post mortems in the 1916 epidemic in Baltimore, and has described a pathological picture of a general lymphoid hyperplasia with the constant appearance of inflammation of Peyer's patches. He takes the extreme view and believes that poliomyelitis should be classed with the diseases of the lymphatic system. Gross enlargement of the lymph nodes was not always marked, but was always present to some degree, and according to Burrows was one of the necessary diagnostic signs in mild and abortive cases. (3)

Flexner's theory of the transmission of the virus has received more widespread support than any other theory. He believes the virus reaches the cord by passage along the lymphatics and vascular system, thus reaching the nervous elements, and because of perivascular reaction the anterior horn cells die of ischemia.

Fairbrother and Hurst renew the concept first given by Lenier and Wiesner that direct toxic action on the cells antidates the generalized infiltration and perivascular cuffing found at autopsy. Research on the blood and spinal fluid indicates that these fluids are of importance in transporting the virus from the portal of entry to the central nervous system. (26)
J. A. Toomey has published a report on the 'Mechanism of Poliomyelitis in the Human', in which he gives an interesting explanation of the disease process. He states that the olfactory nerves, consisting of unmyelinated gray fibers with their twenty or thirty olfactory filaments, are not the only unmedullated fibers in this region of the cribiform plate. It is precisely here that the nervus terminalis is peripherally hypertrophied in man. The olfactory area contains approximately fifteen hundred cells of the terminal portion of this nerve situated under the mucosa cells, which, with their processes, make a vast interlacing network of unmedullated tissue and whose fibers end in the ganglion terminale on the olfactory bulb. (46)

It is conceived that the portal of entry of the virus in the human could be any place where the virus could easily and normally come in contact with either the gray nerve fibers or the axis cylinders of the medullated nerves. The disease may be produced experimentally in a number of ways such as, when the virus is injected directly into the sciatic trunk after irritating the nerve with the needle so that the axones are exposed to the virus, when intracerebral injections are made, by intraperitonial injections, by intraocular injections, and by intraspinal, intracisternal injections, and intranasal instillations. There have also been some isolated success and many failures when the gastrointestinal tract has been used. Unmedullated nerve fibers do ramify in the corium so that subcutaneous injections may bring about the infection consis-
tently. One could almost postulate that the virus has nearly an obligatory affinity for gray nerve fibers.

An area of absorption where there are gray fibers present an unbroken connection to the central nervous system so that virus can reach the central nervous system before it is absorbed by the host. The rate of absorption, ease of transmission, virulence, resistance of the host would all be factors in the production of the disease either impeding or accelerating the disease process.

If it is true that the virus has nearly an obligate affinity for gray fibers, there are only three places in the body that would qualify as natural portals of entry. These are the nasal mucosa, the gastrointestinal tract and the respiratory tract (lungs). Of these the gray fibers in the gastrointestinal tract and the respiratory tract are not as accessible as in the nasal mucosa. Little experimental work has been done on the lungs as a portal of entry. In the gastrointestinal tract the virus often never approximates the gray fibers but the emulsion usually is swept on through. However, subserosal injections produce the disease.

Toomey has produced the disease in monkeys by the gastrointestinal tract route. He used subserosal injections and met with very good success.

Clark and his associates failed to produce poliomyelitis by the oral administration of large quantities of virus or by-the
injection of 10 cc. of virus into a loop of the small intestine. Infective quantities of virus were demonstrated in the feces of these monkeys. The fecal concentrate from two monkeys that had been injected with 10 cc. of active brain broth suspension in a loop of the small intestine was injected into two other monkeys, intracerebrally, both of which developed the disease. Attempts to demonstrate the virus in the feces of these animals suffering from the disease proved futile. (7)

Lennette and Hudson sectioned the olfactory tracts of five monkeys, and five months later each was given 2.5 cc. of ten percent virus intranasally on each of three days. None of the monkeys developed any sign of infection, whereas all of nine control animals with unsectioned tracts died of the disease. Later these same five monkeys with sectioned olfactory tracts, and five control animals were given 10 cc. of ten percent virus on three consecutive days intravenously. None of the monkeys with the sectioned olfactory tracts died, but four out of the five controls died. In this way they showed that the virus causes infection when the olfactory tracts are accessible, and that poliomyelitis results when the virus is given intravenously by the excretion of the virus from the blood stream into the nasal mucosa, and there enters the ending of olfactory nerves and migrates to the central nervous system. (25)

Flexner, in an article dealing with the respiratory route versus the gastrointestinal route of infection in poliomyelitis, shows that Kling and Levaditi in Europe carried out experiments in
1929-1933 which led them to the conclusion that the gastrointestinal tract affords a ready entrance to the virus of the disease into the body. They believed that the substitution of Macacus cynomolgus for Macacus rhesus as the animal of choice for the tests supports this point of view. Toomey arrived at similar conclusions by the use of drastic measures which insure that the virus makes contact with the unmyelinated nerve fiber embedded in the intestinal wall, too severe and too artificial to be regarded as simulating a natural mode of infection. The tests of Kling and Levaditi were repeated but in a far more comprehensive manner, and like Clark and his associates, who early repeated them, failed to confirm them.

From this Flexner reaffirms the previous conclusion, and this is confirmed independently by investigators in Europe and America, namely, that the only established portal of entry into the central nervous system of man is the nasal membrane, and especially the olfactory nervous areas in that membrane." (16)

The number of times that the virus of poliomyelitis has been isolated from the nasopharynx of individuals either ill or in contact with this disease is small. Perhaps this is because of inadequate methods. Nasopharyngeal washings were obtained from patients in various stages of suspected or diagnosed cases of poliomyelitis in the Los Angeles epidemic of 1934. A few determinations were also made on contacts. The results may be summarized by the brief statement that the "virus of poliomyelitis was isolated from the nasopharynx of a single individual with an illness which con-
formed in its symptomatology to a case of suspected abortive poliomyelitis. "It can not yet be decided, however, whether the difficulty is due to absence of virus or to unsatisfactory technique. The facilities for this investigation were excellent, but the epidemic was mild. A search for the poliomyelitis virus in the living still needs to be made during a more severe epidemic by means of an experimental method, the sensitivity of which can be determined." (31)

Toomey believes that the explanation of the mechanism of the production of the disease in the human lies in the fact that the disease is spread through the sympathetic nervous system. By experiments he has shown that the virus follows the sympathetic system where other routes have been cut. Clinically the early reflex changes in this disease could best be explained as an early involvement of the sympathetic system.

It is curious that when proper doses of poliomyelitis virus are injected subserosally the disease that develops in monkeys is more like that seen in humans, since only a monoplegia may result, in marked contrast to the fulminating quadriplegia seen in experimental animals after intracerebral or intranasal instillation of the virus. For anatomical reasons it is not illogical to assume that the spread is by the sympathetic system. The spotty spread of the disease by a virus that travels up or down the cord and involves first the lumbar and then the cervical segments could be explained if one presupposed a spread of the virus
from the gastrointestinal tract by way of the sympathetic gray fibers to the sympathetic ganglionated chain, then down to the lumbar area where no white rami are present and to the somatic nerve. In more marked involvements the spread would be up along the sympathetic collateral chain to the only other place that lacks white rami communicantes, the cervical cord. Only when the disease is massive would it involve segments which have connector white fibers, thoracic and abdominal; and an involvement of the preganglionic vagal fibers with the upward spread of the virus would produce a simulation of the clinical conditions of bulbar palsy. (46)

Toomey continued his experiments of this nature with an attempt to experimentally produce bulbar poliomyelitis. He had previously noticed that forty-five out of four hundred and forty cases of poliomyelitis admitted to the Cleveland City Hospital showed that the initial involvement in every case was vagal in character, that is, they were accompanied by vomiting, dysphagia, dysarthria, aphonia, and other symptoms indicating spread to other cranial nerves. The fact that the vagus is the motor nerve to the small intestine made it logical to suppose that absorption of the virus could take place not only along the thoracolumbar outflow, but in some cases along the vagus nerve as well, and that the spread of the virus in cases manifesting bulbar symptoms was along the vagal nerves directly to the nucleus ambiguous on both sides and from there to other locations. The object then was to produce the disease in monkeys by way of the vagus nerve, note the symptoms and
signs, and to determine if the picture was like that found in the human being. Eight animals were used, 0.2 cc. of a one percent virus solution was injected into the right vagus nerve of each. All but three of the animals developed the disease and died from it.

The animals acted similar to humans in that they showed evidence of dysphagia, dysarthria, and paralysis of the muscles of the arms that is commonly seen in bulbar paralysis.

The histological results were similar to those found in the bulbar poliomyelitis in humans. (44)

It is illogical to expect typical central development in every case, since the virus can pass down as well as up the gray fibers. These experiments lend further belief that the disease arises from the gastrointestinal tract.

Occasionally the seventh nerve nucleus becomes involved and there are a few cases in which the only demonstrable lesion is a lesion of the lower motor neuron of the seventh nerve. Cases such as these show low mortality, and the anatomic involvement is limited and well marked. Obviously the same mechanism that produces spinal and vagal types of the disease cannot effect solitary involvement of the nucleus of the seventh nerve. It has been stated that the virus has merely an obligate affinity for naked gray fibers or axis cylinders of medullated fibers. Each of the papillae or taste buds situated in the tongue has unmedullated fibers inside its cuplike excrescence. It may be that the virus
could be absorbed by the end fibers of the chorda tympani nerve, and pass by way of this nerve to the medullary area to involve the nucleus of the seventh nerve. Possibly, also, the ninth nerve could be involved in this way.

Although the virus of poliomyelitis may be absorbed by any gray nerve fiber, the production of the clinical entity, poliomyelitis, depends on the size of the absorbing nerve fiber and its nearness to the central nervous system. Although the skin contains gray fibers, it would take thousands of maximal paralyzing doses of the virus to produce the effect that a single dose of the same amount would produce after intracerebral injection into a monkey. The length of the chorda tympani, the small size of the nerve, the fact that it is medullated, and its devious course, tend to retard the virus from spreading to the medullary area. It is obvious that there are fewer cases in which the seventh nerve is involved than cases in which the spinal nerves are involved. (40)
SUMMARY

In this thesis I have attempted to clarify to some extent the puzzling nature of the etiology and pathogenesis of poliomyelitis by reviewing the outstanding articles and books concerned with this subject. The reader no doubt, after having read the preceding pages, has reached the conclusion in his own mind that nothing definite can be stated concerning this subject. However, the great amount of work done on this subject has brought forth only a few outstanding theories, and these have been proven by repeated investigation and experimentation.

The most generally accepted theories regarding the disease are:

1. The disease is a true disease of the central nervous system.

2. The disease is due to a filterable virus.

3. The portal of entry is the nasal mucosa.

4. The virus has an almost obligate affinity for gray nervous tissue, and is transmitted by the unmedullated gray nerve fibers, or by the gray axis cylinders of medullated nerves.

5. There are four definite forms of poliomyelitis, the spinal type, the bulbar type, the cerebral type, and the abortive form. The pathological picture of each of these forms is quite complete.

While the above are the generally accepted conceptions
of the disease, the following theories have many supporters who offer experimental evidence in proof of their beliefs:

1. That poliomyelitis is a systemic disease.

2. That the disease may be due to:
   (a) Wollenstein's large Gram positive coccus.
   (b) The globoid bodies of Flexner and Noguchi.
   (c) The form of streptococcus described by Rosenow.
   (d) The organism isolated by Eberson.
   (e) The virus combined with enteric organisms as described by Toomey.

3. The portal of entry may be:
   (a) The gastrointestinal tract.
   (b) The respiratory tract (lungs)

4. The virus may be transmitted by:
   (a) The blood stream.
   (b) Lymphatics.
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