1955

Pathogenesis of acute anterior poliomyelitis : a reveiw

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THE PATHOGENESIS OF ACUTE ANTERIOR POLIOMYELITIS A REVIEW

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Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

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April 1, 1955

Omaha, Nebraska

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I. Introduction

A. General

Throughout the years one of the least understood and most controversial phases of the knowledge of acute anterior poliomyelitis has been the pathogenesis. Since the first careful description of the clinical entity by Underwood in 1789 (1), many papers have been published concerning this disease. However, until recently most of these works dealt with subjects other than the mechanism of the production of the disease. Prior to the last two decades all mention of pathogenesis was purely conjecture with only meager amounts of sound evidence as basis for these statements. In view of the recent severe epidemics of this disease which have appeared in our country causing so much public concern and the recent advances in our knowledge of this disease, a review of this subject is timely.

B. Historical

Though understanding of this disease has been acquired only recently, its appearance as a disease is part of the ancient story of man. Lacey (2) in

1949 states that the disease is known to have existed between 1580 and 1150 B.C. Ruhrah (3) in 1934 reviewed the ancient history of poliomyelitis very beautifully. His illustrated discussion concerned a skeleton which had been found in flake beds near Sisbury, England. He described bony changes in the skeleton which gave mute evidence of a ravage which could have been poliomyelitis. He then commented on a picture which then was present in Copenhagen. This picture was of Egyptian origin dated about 1500 B.C. which depicted a man with an atrophied leg similar to that often caused by poliomyelitis. Ruhrah also had a photograph of the mummy of Syptah of the 18th Dynasty of Pharaohs whose foot was deformed in a manner typical of polio-myelitis, and he described an account of an apidemic of paraplegia believed to be poliomyelitis which was written before the time of Christ by Hippocrates. Aretaeus the Cappbdocian in the third century, referred to by Ruhrah, men ioned cases of paralysis in children. Ruhrah also discussed fifteenth century skeletons found in Greenland. Of the twenty-five skeletons in the group, six showed evidence of pathology which was probably poliomye itis.

The same author continued his dissertation with

references to historical facts of more recent date. Among them was a report by Salzman, a German, of a case of paralysis of one leg with recovery, a picture by a Dutch artist of the sixteenth century of cripples undoubtedly deformed by poliomyelitis, and a comment concerning Sir Walter Scott who had poliomyelitis in 1773. About the same time, Andy described a case of poliomyelitis in his wr tings on orthopedics. Other descriptions of cases of poliomyelitis mentioned by Ruhrah included John Hunter's description in 1750, W. J. Little's cases with club feet in 1839 and Heine's classical description in 1840 which attached his name to the disease. Ruhrah also mentioned Taylor, who called the disease "infantile paralysis" in 1867.

These facts, although very interesting, have no connection with the subject of this thesis. However, they serve to show that acute anterior poliomyelitis is not a "new", or a "young" disease but that it has plagued mankind down through the centuries. As the chronology above points out, man was slow to recognize the condition as a specific disease and has been even slower to understand the mechanisms which cause this disease condition. Not all the facts are yet known but the way is beginning to appear clearer. Much of

the credit for the recent advances in our knowledge of this disease all phases should be given to the National Foundat on for Infantile Paralysis which has financed much of the basic research in the past fifteen years. Many of these research projects were concerned with the development of our knowledge of the pathogenesis of acute anterior poliomyelitis.

II. Mechanisms of the Disease

A physician must know all facets of a disease from its diagnosis to itstherapy. In order that one may know a disease he must first understand how it comes about. This is the pathogenesis or the mechanism of the disease. In poliomyelitis most of the experi-mental work concerning pathogenesis has been done onexperimental animals and the disease which is caused in these animals s called "experimental poliomyelitis", since it differs in some respects from the human disease. Throughout this discussion every effort will be made to keep these conditions separated in order to prevent confusion.

A. Etiology

The etiology or cause of a disease must first be

known if one is to understand the mechanism by which the disease is produced. It is generally accepted that the same agent causes poliomyelitis in all of the animals susceptible to poliomyelitis, including man.

The earliest reports concerning the etiology of this disease were of a negative rather than positive nature (4). Many of the early reports mentioned cocci or other organisms found in living and post-mortem material without commenting as to their signif-icance (4). Schultze in 1898 ( ) believed that the specific agent was identical with that of cerebrospinal meningitis, neurit s and encephalitis but later changed his mind and state that caution must be used in interpreting such reports. In 1909 Flexner and Lewis (4) while giving evidence that the specific agent is

a filterable virus, state that no bacteria were found in their material to account for the disease. Wickman in 1911 (4) stated:

> "The results of experimental investigation have shown that the bacteria found have absolutely nothing to do with Heine-Medin's disease, and that in those cases in which they arose not from faulty technique, such bacteria must be regarded as having had an accidental and not a causal relation to the malady".

Rosenow (5) has written a long series of articles expounding the etiologic theory of a peculiar, pleo-

morphic, green-pigment-producing streptococcus which on anaerobic culture becomes very small and is filterable, appearing identical with the globoid bodies of Flexner and Noguchi (4). Greeley in 1917 (6) isolated from nerve centers in poliomyelitis a pleomorphic bacillus of the d stemper group which was a filter-passer, could live in milk and form spores. Many other investigators have completely disproved the streptococcic etiology of poliomyelitis (7).

Landsteiner and Popper (8) were first to transmit poliomyelitis to monkeys and suggested that the etiology was a virus. Soon others proved the infectious nature of the disease by serial transmission (8). Flexner and Lewis in 1909 (4) passed the infective agent through a Berkefeld filter (grade not stated) and concluded:

> "the infective agent of epidemic poliomyelitis belongs to the class of the minute and filterable viruses that have not thus far been demonstrated with certainty under the microscope".

Since these initial findings by Flexner enough infor-mation has been accumulated to fill a large book. Recently the virus has been classified as follows: Order - Virales (Breed, Murray and Hitchens), Suborder - Zoophagineae, Family - Erronaceae, Genus - Legio, Species - debilitans, and three subspecies Brunhilde,

Lansing and Leon (9). Since this classification over one-hundred different strains have been typed (10).

In the thirt s Toomey (11) advanced the theory that poliomyelitis infection depended upon the presence of enteric toxin as well as virus. This concept has not been supported by any other author.

Kramer in 1912 reported that dilute HCN injected into cerebrospinal fluid caused a degeneration of the anterior horn cells very similar to poliomyelitis if not actually identical (12). In the last few years Scobey has ressurrected this theory, laying the etiology of poliomyeli is to cyanide toxins present in drinking water; however, there has been no acceptance of this theory (13).

Other unusual ideas which have appeared recently concerning the et ology of poliomyelitis include the suggestion by McCormick that avitaminosis B1 is the etiologic factor this disease (14).

SUMMARY: At present the virus theory of the etiology of poliomyelitis s the one generally accepted.

B. Mode of Transmission

In most cases of poliomyelitis infection the infective agent enters the human host by way of the

oro-naso-pharyngeal route. The problem to be discussed here is the manner in which the virus passes from one human host to the next. Almost every conceivable avenue of transmission has been investigated, usually with negative results. Most of the positive and reproducible results have been in substances which might easily pass through the oropharynx, such as food and drink.

Many investigators have isolated the poliomyelitis virus from the gastrointestinal tract starting with Kling, et al, in 1912 (15). This discovery soon led others to study sewage or virus with positive results (19, 20). During an epidemic of poliomyelitis as many as 6 per cent of a city's population are excreting poliomyelitis virus through their feces into the sewage (19). Thus Sabin in 19 and Russell in 1952 have emphatically stated that faulty hygiene is responsible for the transmission of poliomyelitis via the feces-hand-mouth route (21, 22). Little in 1954 reported an epidemic of poliomyelitis in Edmonton which did not conform to the pattern expected from the spread by contact infection but was uniform as is a water-borne infection (23). He named as a possible reservoir a small town upstream which had an inadequate sewage system.

Some investigators have felt that sewage alone is not responsible for poliomyelitis infection and have incriminated milk, insec s, moles and fruit as vectors in the transmission of poliomyelitis. Most of the work has been regarding insects, including cockroaches, horseflies, mosquitoes, houseflies and many others, some of which have been found to contain the virus (24-27).

The other major mode of infection which has been considered is the droplet or contact spread of the virus. Faber (28) has been one of the champions of the droplet spread of infection in poliomyelitis. Others have been more strict stating that immediate contact with infected pharyngeal material must be made to allow transmiss on, ruling out air-borne transmission altogether (29-31), while several reports have definitely contradicted this manner of trans-mission (21, 22).

SUMMARY: Most reports suggest that the mode of trans-mission of the po iomye itis virus is generally in a cycle starting with virus-containing feces being excreted from the patient then going directly to the next host via the feces-hand-mouth route or indirectly via the sewage, thence into food or drink. The

position of other vectors, such as insects or animals, in this cycle, if present at all, is still in debate.

C. Susceptibility of the Host

At present the general belief is that poliomyelitis infection is as common as measles. However, only 1 per cent of those infected have the paralytic disease (9). Even before this fact was known, many investigators were noticing that many factors other than infection alone were present in the production of the paralytic disease. Most of these factors tend to lower resistance to infection but a few increase the host's resistance. The factors which have been most often reported include hormones, pregnancy, physical activity, tonsillectomy and injections.

One of the earliest reports of a factor increasing the severity of poliomyelitis was that of Hochhause, who in 1909 noticed that vaccination increased the severity of the disease in one of his patients (33). DeToysion in 1921 made the first report of relationship of injections to poliomyelitis (34). Much more recently there have been many controversial reports in the literature concerning the effect of therapeutic hypodermic injections of various types in

increasing the incidence and severity of paralytic poliomyelitis. McCloskey started this controversy in 1950 (35) when he reported 340 cases which had had injections prior to the onset of the poliomyelitis. Several other series have been reported since which tend to support the theory that recent injections increase the incidence of poliomyelitis (36). Many reporters have correlated injection and paralysis of the muscles at the site of the injection (34, 36, 38). Greenberg, et al, states that this hazard is small in children under six months of age (34). The above findings caused much concern among physicians interested in public health, since it raised an obstacle to the indiscriminate routine immunization against communicable diseases. In practice it has been found that immunizations can be carried out during the time of the year, ie. the winter and spring months, when poliomyelitis is not prevalent, and other injections held to a minimum during the poliomyelitis season.

In 1929 Aycock and Luther (39) reported thirty-six cases giving history of having had tonsillectomy within the previous year. Little notice was made of the relationship of tonsillectomy to poliomyelitis during the succeeding decade until Krill and Toomey

reported five cases of tonsillectomized children who experienced bulbar poliomyelitis within two weeks after their operation (40). Since then there have been many reports citing the increased incidence of bulbar poliomyelitis following tonsillectomy (41-45). Others have contradicted these statements (46). Weinstein, et al, (47) recently stated that the absence of tonsils and adenoids increases the susceptability to the development of bulbar and bulbospinal poliomyelitis even in instances in which tonsillectomy has been carried out many years prior to contact with the virus.

In the past many investigators reported poliomyelitis occurring during pregnancy as a medical curiosity which might complicate the delivery (48). More recently many investigators are reporting that pregnancy predisposes the individual to poliomyelitis (37, 49-52). It has also been reported that age, gravidity and stage of the pregnancy are not factors in the susceptibility to poliomyelitis (53). Several authors have laid the increased susceptibility to poliomyelitis during pregnancy to the alteration of hormones during pregnancy (54), especially the increased adrenocortical activity during the first trimester (55) overriding the protective effect of the increased

estrogen-progesterone levels (56).

The effect of hormones on susceptibility to poliomyelitis has been more completely studied in recent years. The relationship of the hormone to poliomyelitis during pregnancy has been mentioned above. Some authors have gone one step further and have attempted to correlate an increased incidence of onset of poliomyelitis during menstruation and the week preceeding (52, 57). Aycock has stated that individual susceptibility to poliomyelitis is related to familial endocrine differences (58). Aycock and others (56, 59) later reported a protective effect of estrogen and progesterone, while Curley found that estrogens protected only castrates (61). ACTH, on the other hand, gives no protection (61) and in some cases increases susceptibility (62). Bodian and Shwartzman (63-67) have found that cortisone causes certain laboratory animals, including the Syrian Hamster, to be very susceptibile to experimental poliomyelitis.

Other factors decreasing the resistence to poliomyelitis include the effect of physical activity decreasing the individual's resistence which has been mentioned as early as 1913 by Wickman (33) and others since (21, 51, 68-70). Russell (69) states that

the activity is most dangerous during the preparalytic stage, while Horstmann (70) says that the activity is most dangerous after the onset of the major illness. Related factors which tend to put stress on the individual and thereby lower his resistance include infection (51,71), acute appendicitis with emergency appendectomy (72), chilling and exposure (73), and trauma (21,42,51,58,73,74).

Physical stress of any kind produced by injection, surgery, pregnancy and physical activity appears to lower the individual's resistance to poliomyelitis.

Factors of lesser importance in decreasing the resistance to poliomyelitis which have been reported include age (30,75), enteric toxins (11,76), increased metabolic rate (13), vitamin B1 deficiency (14), genetic factors (77), idioblaptic allergies (a condition in which the pulse accelerates following the ingestion of food allergens) (78), and seasonal factors (51). Both youth and old age have been reported as periods in life when resistance to poliomyelitis is decreased (30,75). It has been reported that the blood groups have no effect on susceptibility (25) and that infection with Coxsackie virus tends to

increase resistance (79).

SUMMARY: Many factors have been reported as increasing the susceptibility of the individual to poliomyelitis. The most important of these are: injections, pregnancy, tonsillectomy, certain hormones and stress of any kind.

D. Route of Entry

In any discussion of the pathogenesis of a disease the route of entry of the infecting agent is of great importance. Early in this century two opposing theories of route of entry of poliomyelitis virus were offered. These were the nasopharyngeal-olfactory and the gastrointestinal routes (15,80-83). Many other routes have been proposed but the greatest controversy has been concerning the two routes mentioned above.

Interest in routes of entry of poliomyelitis virus waned until the thirties when Faber, Flexner and Fairbrother revived the olfactory route theory along with the axonal transmission of the virus theory (84-86). More recently Faber has continued to support these theories in experimental poliomyelitis (28,42, 87,88); however, Kumm states that the above theories hold in experimental poliomyelitis in monkeys but not

in the human disease (10). At one time the olfactory route received widespread acceptance and as has been previously mentioned this aroused much interest and speculation as to the influence of tonsillectomy in predisposing the patient to poliomyelitis (28,36,41, 43,44,89-92). The mechanism by which this was accomplished was believed to be that the trauma of the surgery exposed the nerves and allowed them to be more easily infected (43,44,90,91).

In those same years prior to the second world war many authors, notably Harmon (76,93) and Toomey (94), consistently produced evidence which tended to prove that the olfactory route theory was false (95,96). In succeeding years much more evidence has come forward to disprove the olfactory theory (46,92, 97-101).

The opposing theory, that of the gastrointestinal portal of entry, has gained increasing acceptance over the years with only a few dissenting opinions (84,102,103) until at present it is the one generally accepted. This theory was first mentioned about 1910, was reemphasized by Burrows in 1931 (104) and championed by Toomey (11,18,105) and others (93). More recent work has substantiated the gastrointes-

tinal tract as the portal of entry of poliomyelitis virus in most cases (9,10,17,25,26,30,92,99-101,106-116).

Other lesser important routes of entry which have been reported or considered are: intracerebral (11), wounds (108), direct inoculation of nerves (67,117-120), intrathecal (85,121), intracutaneous (96,122), intravenous (95,123,124), dental pulp (125,126), intraperitoneal (65,66) and intracardiac (63).

SUMMARY: The two important theories of the route of entry in poliomyelitis in the past have been the olfactory route and the gastrointestinal route with the latter receiving general acceptance at this time.

E. Site of Virus Multiplication

Infective agents are very often restrictive in their growth requirements. Viruses are especially so since they will grow only intracellularly. Early in the century when poliomyelitis became a popular subject for medical papers, it was believed by some, including Wickman, Peabody and Draper (101), that poliomyelitis was a systemic disease (104). In the thirties, Faber, Flexner and Fairbrother (28,84-86) proposed the theory that the poliomyelitis virus was

strictly neurotropic and unable to grow outside of nerve cells. They also suggested the olfactory route of entry theory (mentioned above) and the axonal transmission theory (see below) to explain how the virus could gain entry into the human host and yet stay within the nervous tissue. Faber and his associates (42,88,102,109,118,119,127,128) have continued to support these theories, while Bodian (129-131) and Horstmann (70) have given recent evidence which shows that the poliomyelitis virus is not strictly neurotropic. In the past many reporters, including Flexner, who reported finding poliomyelitis virus in a mesenteric lymph node (81), have reported isolation of poliomyelitis virus from extraneural tissue, including lungs, liver, spleen, kidneys, lymph nodes (100), intestinal mucosa (101,116), "brown fat" (fatty tissue resembling lipid storing endocrine tissue) (67), muscle (65,132,133), and blood stream (10,92, 107,134). In recent years most of the reports have been emphatic about the initial alimentary phase of poliomyelitis virus multiplication, ie in the wall of the intestine (21,66,101,112-114,135-140).

SUMMARY: At present the concept that poliomyelitis virus is a strict neurotropic organism is questioned,

and the accepted concept is that poliomyelitis is a systemic disease rather than a strictly neurologic disease, with an initial phase of multiplication in the wall of the intestine.

F. Virus Migration Within the Host

The controversial subjects mentioned above, that is, the route of entry of the virus and the site of virus multiplication within the host, were merely preludes to the greatest controversy of all, the question of the manner in which the virus reached the central nervous system where it leaves its irreparable mark. Early authors felt that there was a viremic phase (101,141,142) or lymphatic spread (81,82,104, 145).

In the thirties, as was mentioned above, the axonal theory of migration of poliomyelitis virus was proposed (28,84-86). This theory stated that poliomyelitis virus was a strictly neurotropic virus and entered the infected animal via the olfactory nerves which are in very close approximation with the epithelial structures of the nose and passed on into the central nervous system through the axons of the olfactory nerves. Other nerves were capable of transmitting

the virus in a like manner, according to the theory, except they were less likely to come in contact with the virus. Many investigators, notably Faber and Toomey, have supported this theory (11,18,28,42,44, 83-89, 91,94,98,102,105,108,109,112,117-121,123,127, 128,138,139,144-148). However, the dissenting opinions have been gradually gaining in strength through the years (95,96,99,113,129,135,149).

The viremic phase of poliomyelitis has been mentioned many times in the literature (101,141,142, 149), but no one had been able to demonstrate it until Ward and his associates in 1946 demonstrated a viremia in a nine-year-old girl (155). Since then many authors have been able to detect a viremia in both human and experimental poliomyelitis (10,51,63, 65-67,92,101,107,109-111,114,134-137,140,148,150-154). Recently Bodian (107,136,152) and Horstmann (92,101, 110,134,150) have shown that the viremic stage occurs during the preparalytic stage prior to the formation of antibodies which seem to clear the blood of the virus. This viremic stage occurs in all cases of poliomyelitis infection whether abortive or paralytic. Apparently there is a blood-brain barrier according to Bodian (151) which is subject to the factors discussed

above (See above pp. 10-14). These factors come into play in approximately one of one-hundred infections and break down this barrier allowing a paralytic case to occur.

Since the viremic phase of poliomyelitis has been uncovered, the other extraneural phases of poliomyelitis have become understandable, the myocarditis of poliomyelitis (156-158) is no longer inexplicable and the reports of lymphatic involvement now fit into the disease picture instead of complicating it (67,81,82,104,112,113,123,135,136,140,142-144,149) as does Shwartzman's "brown fat" (67). Lesions in the Skeletal musculature (132,148) and bloody organs (135,136) likewise are part of the systemic phase of the disease. The paralytic form of the disease ensues only if the central nervous system is invaded (139,159).

In the past most authors stated that the virus was not transmitted <u>in utero</u>, that it could not pass the placental barrier (50,52,53). However, more recently Abramson, Greenberg and Magee (160) have suggested <u>in utero</u> transmission and Schaffer, Fox and Li have reported a case in which poliomyelitis virus was recovered from an aborted fetus and placenta (161).

SUMMARY: A viremic stage of poliomyelitis has been definitely proved to exist overshadowing the axonal theory of transmission to the central nervous system and explaining the extraneural lesions often found in poliomyelitis. There are reports which suggest that the poliomyelitis virus may be able to pass the placental barrier allowing *in utero* transmission.

G. Excretion of the Virus

Since Kling, *et al*, in 1912 reported isolating poliomyelitis virus from the human intestinal tract (15) there have been many subsequent reports which demonstrate general acceptance and collaboration of the fact that poliomyelitis virus is excreted into the lumen of the gastrointestinal tract (9,17-21,25, 76,100,103,105,107,111,119,128,162). Toomey in 1935 reported urinary excretion of poliomyelitis virus (11). The actual manner of virus excretion from these sites is not clearly understood. When the olfactory route of entry was in vogue authors insisted that the virus in the feces was swallowed (117,162). Later the virus was believed to be excreted from nerve endings in the wall of the gastrointestinal tract (102,113,128). The recent findings of Bodian (129-

131) and Horstmann (70) coupled with the reports of finding poliomyelitis virus in the wall of the intestinal tract (101,118) suggest multiplication and excretion from a site within the wall of the intestine. Howe and Bodian (113) have suggested lymphatic tissue as the vehicle for the virus when it is within the intestinal wall.

SUMMARY: There is general agreement that poliomyelitis virus is excreted in fecal material from an unknown site in the wall of the intestine.

H. Causation of Pathology

Contrary to past beliefs there are several pathologic tissue changes resulting from poliomyelitis infection. The best known findings are those of the central nervous system. Archambault (141) in 1917 believed that the central nervous system lesions were due to local toxemia and vascular disturbances. Lovette suggested that the anterior horn cells die of ischemia resulting from perivascular reaction (142). Kniesely in 1945 discovered the blood of poliomyelitis patients often sludged, and Boines in 1952 suggested that this "sludged blood" thrombosed the tiny vessels of the central nervous system causing the characteristic

pathology (163). Bodian (129) stated, "the virus is first detectable in the central nervous system where the lesions are demonstrable histologically, ie, on the day preceeding paralysis. Einarson has explained the pathology of the central anterior horn cell degeneration on the basis that these cells are proximal to the venous end of capillaries and therefore get less oxygen and other essential nutrients, particularly vitamin E (164). Elliott (165) noticed that the lesions in the cord seemed to radiate from a dorsomedial point ventrolaterally. He suggests that this may be due to proximity to the source which may be the ventral arteries or the dorsal root fibers. However, he believes that this pattern of spread is related to the connections between the neurons and follows a certain path related to the portal of entry. Most authors have not been so specific and have merely assumed that once the virus invaded the anterior horn cell it destroyed it in the course of virus multiplication. Brown (166) reported that 85 per cent have evidence of hypothalamic damage.

In 1950 McCloskey (35) and others (36) reported many cases in which the muscles paralyzed were the muscles in the region of previous injections. Several

other authors have confirmed this view (34,36,167) and Dean (38) has reproduced this experimentally. Contradictory findings have been reported (124,168). Trueta and Hodes have found by experiment that application of casts, exercise, and injection of irritants cause an increase in the vascularity of the spinal cord in the segment which supplies the affected area (33). This they believe decreases the anterior horn cells' resistance to infection.

Many authors have attempted to correlate tonsillectomy with bulbar type poliomyelitis, suggesting that the exposed nerve endings were more easily invaded by the virus which was already present in the nasopharynx (39-47,91). Now the mechanism suggested by Horstmann (111) and Trueta (33) of peripheral trauma causing central reaction seems more likely. Other forms of trauma have been reported in relation to poliomyelitis infection with similar results (47, 74). Physical activity has been reported by Horstmann (70) and Russell (69) as affecting the severity of the paralysis only, while Trueta (33) reported the localizing effects of exercise on the paralysis.

Several authors have reported finding pathological changes in skeletal muscle in poliomyelitis (36,67,148,

169). Carey reported the following changes in the myoneural junction during poliomyelitis coincident with and shortly after paralysis (133): (1) disappearance of many end plates resulting in denervation at the myoneural junction, (2) ephemeral appearance of masses of inclusion bodies some of which are cross-striated within and near the degenerating motor end plates, (3) differential rates of motor nerve degeneration, (4) degeneration beginning in the motor end plates and proceeding in a centripetal direction in the axis cylinders of many motor nerves. Whether this is due to peripheral infection or merely degeneration was not made clear.

There have been reports of finding poliomyelitis virus in cerebrospinal fluid (81,120). Leukocytes and a decrease in protein are the usual findings in poliomyelitic spinal fluid (169). Field and Woolam have attempted to show that the passage of the virus through the spinal fluid to reach the anterior horn cell is important for the formation of pathology, but their work is only suggestive (171).

Various ganglia, including the peripheral sensory ganglia of trigeminal and spinal accessory nerves (130), gasserian (87,109), petrosal nodose

(87,109), superior cervical sympathetic (87,109) and celiac (87,109), have been reported as containing poliomyelitic lesions. Pollock was unable to find clinical evidence of lesions within the sympathetic nervous system during poliomyelitis (172).

In 1942 Saphir and Wile (173) reported six cases of myocarditis occurring in poliomyelitis. Since then many cases of acute focal myocarditis have been reported as occurring during poliomyelitis (62,114,156,158, 173-175). Jungeblut (175) reported isolation of poliomyelitis virus from the myocardium in three of five fatal cases of poliomyelitis. Peale (158) and Teloh (176) were unable to correlate age, sex or duration of symptoms with the myocarditis.

SUMMARY: Most of the typical pathological findings are limited to the anterior horn cells of the spinal cord. However, other parts of the nervous system, such as the brain and certain ganglia, also may be involved. Non-nervous tissue, such as skeletal muscle and the myocardium, may also contain lesions. The pathological reaction is apparently due to the presence of the virus, although vascular changes have been blamed in some instances.

I. Causation of Symptoms

According to Jungeblut (114) the initial or alimentary phase of poliomyelitis is asymptomatic. However, the visceral stage with lymphatic involvement, viremia and muscular lesions cause symptoms of systemic infection, such as fever, malaise, anorexia and general aches and pains. These symptoms are reversible if the infection does not progress. However, the last or neurologic phase results in neuronal destruction with more or less permanent symptoms of paralysis, weakness and muscular atrophy depending upon the relative number of neurons destroyed and the compensating power of the remaining motor units. Encephalitis may occur during poliomyelitis due to the Brunhilde virus with ataxia, intention tremor, nystagmus and dysphonia (177). Ganglia, such as the trigeminal and spinal accessory often contain evidence of neuronal damage, focal and perivascular infiltration which would account for the symptoms in areas supplied by these ganglia (130). The changes in the myoneural junction reported by Carey (133) and described above may account for part of the pain and muscle cramping so typical of this disease (148). Brown (166) has reported that 85 per cent of bulbar poliomyelitis cases

have microscopic evidence of hypothalamic damage which probably accounts for the more severe and general symptomatology which is present in this type of the disease. Cook and co-workers (178) have reported gastrointestinal ulceration, perforation, with and without hemorrhage during bulbar poliomyelitis.

SUMMARY: Early reversible symptoms in poliomyelitis are due to visceral stage of the infection; whereas the irreversible or paralytic symptoms are due to neuronal destruction which occurred during the neurologic stage of the infection.

J. Immune Mechanism

Immunity to poliomyelitis has been studied in both experimental animals and human. Aycock (59) has been able to produce "subclinical immunity" in mice by subcutaneous injection of poliomyelitis virus. Estrogen tended to protect the mice from active disease yet allowed development of immunity. Bodian (107) found that passive antibody in low levels would prevent paralysis and that fecal virus excretion can occur without viremia in the presence of high levels of serum antibody. Flexner (179) was able to isolate the antibodies from cerebrospinal fluid. Horstmann (92)

reported that antibodies appeared shortly before paralysis from a peripheral site of antibody production. Howe (103) reported that three of thirty-five orally infected monkeys without paralytic symptoms developed antibodies. Von Magnus (45) found that thirteen of seventeen orally infected monkeys developed antibody on the first day of paralysis.

It has been more difficult to study immunity in man; however, there have been several enlightening reports. Bodian (180) has reported two cases with second attacks of poliomyelitis with the Leon strain. In 1952 Bodian (135) stated that the vascular phase was responsible for antibody production, and in 1954 he reported that antibody appears shortly after the viremia (151). A year before (152) he found that the antibodies persisted for two to four weeks after the disappearance of the viremia. In 1917 Flexner (181) found immune particles in the blood of human poliomyelitis patients after several days. Koprowski (115) reported that the sera of fourteen mentally defective children who had been fed the TN strain of Type II rodent adapted poliomyelitis virus with parental consent three years previously showed persistence of high titre of neutralizing antibodies. Kumm (10) and Steigman (182) have reported that each of the types of

poliomyelitis produces type-specific antibodies. Rosenow (5) claims that he is able to show a relationship between poliomyelitis virus and his "neurotropic" streptococcus by antigenic reactions. McGoogan (48) has reported passive transmission of poliomylitis immunity from the mother to the infant.

SUMMARY: Antibodies to poliomyelitis virus appear shortly after the viremia and shortly before the onset of paralysis and persist for several weeks at high levels and for many years at low levels. The antibodies are apparently produced during the extraneural phase of the disease.

III. Importance of Current Findings with Special Emphasis on Viremia

The most important finding in poliomyelitis in recent years have been Bodian and Horstmann's findings of viremia during poliomyelitis infection. This work was initiated by Ward's isolation of poliomyelitis virus from the blood of a patient in 1946 (155). Bodian (51,63,107,130,131,135,136,151,152) and Horstmann (92,101,110,111,134,150,183) have proven that viremia occurs regularly during the course of poliomyelitis. However, it occurs prior to the onset of

paralysis and the appearance of antibodies. Consequently, other investigators who had previously attempted to isolate the virus from the blood of paralytic patients met with failure, since the antibodies which have already appeared by the onset of the paralysis have cleared the blood of the virus. The presence of viremia was considered early in poliomyelitis literature, but due to the difficulty in proving its presence it was given up and other ideas, such as the olfactory-axonal transmission theory of Flexner (see Migration of the Virus), were accepted. It has been very difficult to reconcile the isolation of poliomyelitis virus from extraneural sites with these theories. The presence of viremia in poliomyelitis simplifies the concept of the mechanism of the disease.

Jungeblut (114) has given a very good resume of the mechanism of poliomyelitis incorporating the concept of viremia even before Bodian and Horstmann were able to prove its presence:

> "The first stage of infection is probably represented by entrance of the virus through the alimentary tract, its penetration through the intestinal mucosa and initial growth within the wall of the gut. At this level infection remains asymptomatic, being maintained at a silent portal of entry. The second stage, ushered in as the result of a breakdown of the local mechanism of defense in the lymphatic system, might lead to transient viremia with

rapid removal of virus from the blood stream by means of filtration and fixation in muscle tissues. Coincident with virus multiplication in skeletal and heart muscle, a number of diverse peripheral lesions may aid in thus advancing the process to the symptomatic stage of reparable dysfunction. The third or final stage of the infection would be allowed only under exceptional conditions which permit excessive growth of the virus. Subsequent passage across the myoneural synapses and eventual transport along peripheral nerves to the spinal cord with irreparable destruction of the ganglion cells in the anterior horn."

Now that the pathogenesis of poliomyelitis is better understood, other investigators in other fields of poliomyelitis research, notably in the field of immunity and prevention of infection, have been able to make remarkable strides in the production of a protective vaccine which may make poliomyelitis a disease seldom encountered.

The many reports of myocarditis in recent years (62,156,157,174-176) are important to those caring for patients who are acutely ill with poliomyelitis, since myocarditis has been blamed for many of the fatalities which occur with poliomyelitis. Enders' (132) proof that poliomyelitis virus will grow in extraneural tissue has been a great aid to those who are attempting to cultivate the virus in order to facilitate the production of vaccine.

SUMMARY: The concept of viremia, proven in recent years,

in the pathogenesis of poliomyelitis has made poliomyelitis an understandable disease rather than a little understood malady.

IV. Summary

1. A few poliomyelitis facts of historical interest are related.
2. At present the virus theory of the etiology of poliomyelitis is the one generally accepted.
3. Most reports suggest that the mod of transmission of the poliomyelitis virus is generally in a cycle starting with virus-containing-feces being excreted from the patient then going directly to the next host via the feces-hand-mouth route or indirectly via sewage, thence into food or drink. The position of other vectors, such as insects or animals, in this cycle, if present at all, is still in debate.
4. Many factors have been reported as increasing the susceptibility of the individual to poliomyelitis. The most important of these are: injections, pregnancy, tonsillectomy, certain hormones and stress of any kind.
5. The two important theories of the route of entry in poliomyelitis in the past have been the olfactory route and the gastrointestinal route with the latter

receiving general acceptance at this time.

6. At present the concept that poliomyelitis virus is a strict neurotropic organism is questioned, and the accepted concept is that poliomyelitis is a systemic disease rather than a strictly neurologic disease, with an initial phase of multiplication in the wall of the intestine.

7. A viremic stage of poliomyelitis has been definitely proved to exist, overshadowing the axonal theory of transmission to the central nervous system and explaining the extraneural lesions often found in poliomyelitis. There are reports which suggest that the poliomyelitis virus may be able to pass the placental barrier allowing in utero transmission.

8. There is general agreement that poliomyelitis virus is excreted in fecal material from an unknown site in the wall of the intestine.

9. Most of the typical pathological findings are limited to the anterior horn cells of the spinal cord. However, other parts of the nervous system, such as the brain and certain ganglia also may be involved. Non-nervous tissue, such as skeletal muscle and the myocardium, may also contain lesions. The pathological reaction is apparently due to the presence of

the virus, although vascular changes have been blamed in some instances.

10. Early reversible symptoms in poliomyelitis are due to visceral stage of the infection; whereas the irreversible or paralytic symptoms are due to neuronal destruction which occurred during the neurologic stage of the infection.

11. Antibodies to poliomyelitis virus appear shortly after the viremia and shortly before the onset of paralysis and persist for several weeks at high levels and for many years at low levels. The antibodies are apparently produced during the extraneural phase of the disease.

12. The concept of viremia, proven in recent years, in the pathogenesis of poliomyelitis has made poliomyelitis an understandable disease rather than a little understood malady.

V. Conclusions

1. Viremia is now a definite, proven part of the pathogenesis of poliomyelitis.

2. Poliomyelitis is now known to be a systemic disease rather than a disease limited to the central nervous system.

3. Poliomyelitis is an infectious disease with widespread distribution in the nonparalytic form; about 1 per cent of the infections occur in individuals with decreased resistance from one or more causes resulting in the paralytic form of the disease.

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