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Poliomyelitis

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P O L I O M Y E L I T I S

SENIOR THESIS

Submitted by

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The time is late summer, the last of dog days, and the night hot as "blazes." The weary doctor has just fallen asleep in the stirring breeze of a small fan which will drone throughout the night. His face is relaxed in benign repose. The telephone jangles shrillingly and his features suddenly convulse in a protest of outraged conscience. He is at the phone before it can ring again.

"Hello, this is Dr. Sm--."

"Hello, is this the doctor?"

"Yes, what---------?"

"Johnnie just vomited; he has been sick at his stomach all evening--------Yes he is feverish and his bowels haven't moved yet today. He just took sick this morning all of a sudden. His headaches just above his eyes real badly. When he vomited, I tried to help him sit up in bed to use the basin but he said his back hurt and began crying; and doctor, when I went to help him he swore at me! Can you come right over?"

The man who carries the worries of his small world on his shoulders responded to the plea of helplessness and what he expected to be just another "stomachache" proved to be some stranger out of Osler attempting to catch him off guard.

The child was apparently sicker than his temperature would seem to indicate. The doctor pondered long, and "out of the blue" recalling a ten minute talk by one of "them all-fired smart city specialists" he clinched the diagnosis with his spinal needle, had serum brought from the city by airplane and was the cynosure of all eyes and the center of conversation at the "County Medical" the following week-----a regular devil for brains.

Were the above picture universal as far as diagnosis and treatment of poliomyelitis were concerned, we would probably sit back in our chairs with a smug feeling that medicine had certainly progressed and be thankful that we were living in such an age. However, radio instruction is not always available, and poliomyelitis has become universal in incidence. Because of its devestating effect on the morale of man by the severe residual

paralysis of the untreated, its discussion is always interesting and at times instructive. Mere plugging along in behalf of its clarification is justified by the end sought. Self-preservation spurs us on in our endeavors to conquer this enemy.

In addition to the motive of self-preservation, the poliomyelitis problem is intriguing because of its complex epidemiology. Unlike measles, in which exposure is usually followed by the clinical disease and subsequent immunity, the usual course of poliomyelitis is repeated exposure producing the subclinical infection ~~followed by subclinical~~ followed by subclinical immunity.(15) Rarely (an average of two per thousand in an epidemic) an individual developes the clinical disease on initial exposure.(20) Why is there such an apparent reversal of disease and immunity in this entity and what alterations in the individual economy determine that in some the clinical infection shall follow exposure? Surely poliomyelitis presents a problem of scientific interest.

HISTORY: Poliomyelitis has been known for at least two hundred years, but only since the beginning of the twentieth century, has it assumed world wide proportions.(15) With our scientific approach to perfection in many fields this disease interposes a complex obstacle to progress in the field of medicine. Much work is being done in an attempt to understand the malady. Much work remains to be done especially as regards etiology and treatment.

Cases of poliomyelitis have existed in Great Britain for two hundred years.(15) The first recognizable description of the symptoms was written by Michael Underwood (1784) in a treatise on diseases of children. The affection was called "Debility of the Lower Extremities, of unknown etiology except in cases of teething and foul bowels."

Thirteen years previously, Walter Scott, then an infant, developed teething fever, with a paralysis of his right leg. Badham, in 1835, described a localized outbreak of flaccid paralysis, which we now call poliomyelitis.(31) In this, he separated from spastic paralysis and palsies a group of flaccid paralysis. He described the clinical picture well and observed that in this group a febrile period preceded the onset of paralysis. In 1840, a German, Jacob Heine, wrote a monograph on infantile paralysis, in which, he associated the symptoms with the lesions of the cord.(15) His was the first good clinical description of the disease- and he also noted a spastic type of the disease.(31)

Colmer, 1843, described an outbreak similar to that reported by Badham . ~~1873 in~~ Charcot (1873) believed chief pathology to be a primary degeneration of the ant-horn cells of the cord. (31) In 1880, Oscar Medin, a swedish physician, discussed an outbreak at Stockholm and concluded that poliomyelitis was an infectious disease.(15) Subsequently the condition was called the Heine-Medin disease. His pathological, epidemiological and clinical studies of the acute stage are classical. In 1907, Wickman described cases of a feverish disorder without paralysis in close proximity to cases of Heine-Medin disease. These were considered abortive cases.(15)

1884 Strumpel published a report on the encephalitic, neurotic and poliomyelitic types with features similar to those in Heine's cases and suggested the infectious nature of the disease. His report concerning the similarity of acute encephalitis to spastic paralysis in children and to poliomyelitis was the first description of the cerebral form. 1897, Caverly first recognized the non paralytic form in the study of 130 cases of poliomyelitis in Vermont - 6 of which had the clinical symptoms of the preparalytic stage, but did not become paralyzed.

The infectious nature of the disease was not accepted until Wickman, in 1905, adduced evidence of the communicability based on a study of 1200 cases in the great Swedish epidemic.(31)

In 1909 Landsteiner and Popper in Vienna first produced poliomyelitis in monkeys by the intraperitoneal injection of infectious material from human cases. Similar results were obtained a few months later by Strauss, also by Flexner and Lewis. In a few months the latter, together with Levaditi of Paris, succeeded in passing the disease throught a series of monkeys, thus proving that the disease is caused by living microorganisms and not by filterable toxins.(29) (13) (28_3)

The organism producing the disease was apparently discovered in 1810 simultaneously at the Rockefeller Institute in New York and at the Pasteur Institute in Paris. The former discovered that the microbe of poliomyelitis escapes from the body in the secretions of the nose and throat; also that there was a substance in the blood of an individual who had had the disease, which, when inneculated into monkeys is capable of preventing the development of the disease. They also showed that the serum was capable of preventing the onset of paralysis in monkeys when the microbe is introduced first follow-

ed in 24-48 hours by the injection of serum from recovered human beings or monkeys. This observation is the experimental foundation for the convalescent serum treatment of the disease first applied in man by Professor Netter of Paris in 1911.(28$_4$) In 1910, Flexner reported an attempt to produce an immune horse serum against the disease. Banzhof and Park assisted him in further experiments with horse serum. In 1918 A. Petit took up the work using sheep and horse serum and subsequently reported successin 25 frankly paralytic cases. Netter, of Paris, reported 22 cases successfully treated with horse serum. (26) Rosenau isolated a strain of streptococci which he believed to be the causative organism in poliomyelitis and produced an anti-streptococcus serum which has not been used extensively enough to judge its value. (32)(10)(29)(31) General opinion is that the streptococcus is a secondary invader and not the etiological organism. W. L. Aycock of the Massachusetts poliomyelitis commission with his co-workers has done much work in the elucidation and solution of the problems in poliomyelitis. As stated previously, the disease is world wide in distribution though the worst epidemics have occurred on the North American continent and the most discussed endemic was New York State in 1916.

At present the most energy in combatting the disease is being concentrated on the diagnosis of the infection in the preparalytic stage as treatment with convalescent serum is most efficacious at that time.(19) Aycock and Kramer are doing considerable work on a neutralization test, the purpose of which is to ascertain the presence of immune bodies to poliomyelitis in the serum of those known not to have had the clinical disease, thus proving their concepts on epidemiology and providing a possible source of immune serum should the stores of convalescent serum prove insufficient in an epidemic.(4,5) The use of monkeys is necessary in this test and their cost may prohibit extensive use of the test.

With this brief introduction to poliomyelitis an attempt will now be made to discuss the disease as a clinical entity with special reference to epidemiology and treatment with convalescent serum.

The terms "Infantile Paralysis" and "Poliomyelitis" are used interchangeable by most authors and shall be so used in this paper.

DEFINITION:

Poliomyelitis is an acute generalized infectious disease caused by a filterable virus characterized clinically by a primary phase of systemic infection with fever, vomiting, diarrhea, pharyngeal catarrh and general malaise; a secondary phase of meningeal invasion with headache, rigidity of the neck, resistance to anterior flexion of the spine, pain in the back and limbs, and apathy; and a paralytic stage in which motor disability varies from slight paresis to complete paralysis with death, with a tendency for paralysis to be reversible within indefinite limits; characterized anatomically by generalized toxemia, indicated by cloudy swelling of parenchymatous organs and lymphatic tissue with acute swelling most marked in the mesenteric glands and Peyer's patches, involvement of the leptomeninges and posterior root ganglia, subsequently localizing in the central nervous system most evident in the gray matter of anterior horns; the laboratory findings early are those of an acute infection, a neutrophilic leucocytosis of 15--25,000 and later by spinal fluid findings which are characteristic. Because of the infrequent incidence of paralysis, the latter might be considered a sequel even though it is the most emphasized feature of the disease. It affects all ages but mainly children.(31)(10)(13)(35)(28_3)34)

ETIOLOGY:

The exciting cause of the disease is generally considered to belong to the group of filterable viruses.(13)(31) There are two schools of belief as regards a specific organism. One of these was sponsered by Flexner of the Rockefeller Institute. He and Noguchi in 1913 reported the cultivation on a specially devised media of a minute globoid body 0.15--0.3 microns in diameter cultered from the nervous tissues of human beings and monkeys with acute poliomyelitis.(10)(31)(29)(28_4) The organism passes through a Berkefield filter, is a strict anerobe, grows best on ascitic fluid in deep tubes with a bit of sterile kidney or brain tissue at the bottom overlaid with paraffin oil and is arranged in pairs, small groups or chains. It is highly resistive to freezing and is not injured by 0.5% phenol. Flexner and Amoss have found it to remain virulent after exposure for six years to 50% glycerol. It is destroyed by exposure to a temperature of 45-50 degrees Centigrade for half an hour; by 2% hydrogen peroxide; by menthol, and by corrosive sublimate.(29)

Cultures of the organism injected into monkeys reproduce an experimental picture typical (31) of the disease in the 1st, 4th, 18th and 20th generations(31) although not all cultures are sufficiently pathogenic to cause infection, and the organism can again be recovered in culture from infected animals.(29) Thus, since the organism can be isolated from human cases, it can be cultivated in pure culture, injections into a laboratory animal produce the typical disease and it can be isolated again from the experimental animal and cultures. Koch's postulates seemed to be satisfied.

The organism in culture withstands preservation and glycerinization as does the virus in the nervous tissues and Flexner, Noguchi and Amoss have found that it maintains its pathogenicity in culture for more than a year.(29) It has been demonstrated in film preparations and sections from the tissues of infected monkeys and humans, by Flexner and Noguchi in the incubated brain tissue of infected monkeys in which it has apparently multiplied, and in the blood of a monkey by Amoss. Because of technical difficulties of demonstration and cultivation the relation of this organism to the disease has not been generally confirmed.(29) Flexner believed that he had found the actual organism of poliomyelitis. However, subsequently he was not able to find the glaboid bodies in highly infectious filtrates and Amoss could not detect any immunological relationship between these bodies and the disease remains unsolved. It is possible that these bodies absorb and keep viable the true virus.(31)

The other school as regards etiology headed by E. C. Rosenow, Mathers, Nuzum and Herzog claims to have regularly cultivated a strain of streptococcus from the cords and brains of fatal cases which they consider to be the etiological organism.(29)(10)(32)(31) This streptococcus is pleomorphic and in one of its stages resembles the globoid bodies of Flexner and Noguchi and passes through the Berkefield bilter. Serologically it will not provoke the production of anti-bodies in animals immunized against it, nor does it regularly produce the typical clinical symptoms and pathological changes in the monkey. The strains of streptococci from human and monkey poliomyelitis tissue have not been proved to belong to the same group. The general consensas of opinion is that these streptococci are secondary invaders. (31) This relationship has been shown as follows: infective doses of streptococci free filtrate of virus were injected into 2 monkeys at the same time. The first monkey was killed as soon as definite paralysis appeared.

Though the true virus was present in the nervous tissue proved by subsequent innoculations into other animals, no streptococci were present. The second monkey was allowed to die of respiratory paralysis. This animal corresponds to a fatal human case. Streptococci were easily cultured from this animal and must be considered agonal invaders. Thus though 3 rabbits successively producing paralysis and then the same organisms isolated from the rabbit and injected into a monkey producing the typical clinical picture of poliomyelitis; he has not excluded the presence of the virus in his cultures. Again the streptococci may absorb and keep the virus viable. Monkeys recovered from infection with the streptococci derived from cases of poliomyelitis are not protected from infection with filtered virus and the blood does not neutalize the filtered virus in vitro. Again in thousands of cases of poliomyelitis no instances of metastatic infection and inflammation characteristic of the streptococci have occurred.(31)

Now that the organisms suggested in specific etiology are excluded from consideration the belief that poliomyelitis is caused by a filterable virus holds sway once more. Thus, a few facts on viruses in general are indicated.(31) Frequently young cells seem essential for virus activity. In the higher forms of life virus activity is best exhibited, not in old undernourished, sickly individuals, but in young healthy ones. Injury, whether traumatic or inflammatory, seems to play a role in the infectiousness of many viruses by furnishing young cells or growth producing factors usually found in the vicinity of such areas of dead tissues. Poliomyelitis virus exhibites an affinity for cells of certain tissues and apparently can neither multiply nor produce the typical signs of the disease unless it comes into close relation with these cells. The general effect of viruses on cells is to cause an increase in the size and rate of division of cells producing a ballooning degeneration, following which the cells die and go to pieces. This description is called by Amoss "reticulating colliquation." The picture in virus disease depends on which of these two processes, ballooning degeneration or reticulating colliquation, predominates.(31)

Rivers reports that in each succeeding passage of poliomyelitis virus in monkeys the mortality mounts until nearly all the animals die of respiratory paralysis and less and less virus is needed to produce the disease. The virus, on repeated passage and storage in the interin in glycerol at 4°c, retains its violence, but after several years its activity decreases on further passages and amounts needed to produce the disease become greater. After still further passage the virulence appear to be renewed and the virus regains its infecticusness. Roughly this corresponds to the epidemicity of the virus of poliomyelitis.(31)(29)

The virus of poliomyelitis has been demonstrated in the nasal and buccal secretions and in the intestinal content, not only of paralytic, but of abortive or non-paralytic cases and healthy carriers.(16)(14)(2)(15)(30)(28_4)(6)(16) The disease is spread by contact direct or indirect and is most contagious early during the phase of pharyngeal catarrh. The portal of entry is the nasopharynx and the subsequent extension probably occurs by the lymphatics thru the cribiform plate to the nervous tissues,(29) along the fibers of the olfactory nerves to the brain, into the general circulation to the nervous tissue, or upon ingestion, the gastro-intestinal tract may serve as the portal of entry. (10)(29)(16)(18)(28_4) This route must be considered because of the frequency with which the lumbar enlargement is hit first. The manner in which the infection passes from the intestine to the cord will be considered later. Predisposing factors in the production of the disease will be thoroughly reviewed in the discussion of epidemiology.

PATHOLOGY and PATHOGENESIS:

The clinical features and anatomical lesions in the human illness and the experimental disease in monkeys are identical for all practical purposes. For the pathological changes during the course and at the termination we must rely upon post mortem

examination in monkeys and humans for elucidation.(17)(10) If, as is generally condeded, the lesions in monkeys and in humans are identical, the ideal way of determining pathological changes would be to examine monkeys with the disease killed at varying intervals from the onset to the termination by death. The animals cost about $15 each, so it is obvious that such experimentation is expensive. Fairbrother and Hurst of the Lister institute experimented in the above manner.(17) Monkeys killed two days after intracerebral innoculation showed a meningitis at site of entry, which was rather localized. Those killed on the third or fourth day showed early lesions in the form of cellular foci and perivascular infiltration in the cortex adjacent to the site of entry. On the fifth day, before paresis developed, there were cellular foci and areas of perivascular infiltration occurring in the absence of overlying meningeal irritation. Nerve cell degeneration took place in the anterior horn even in the absence of local interstitial changes. This might favor the idea of spread along the axial cylinders of nerves suggested by Hurst. Cellular foci occurred at random over the anterior and posterior horns. Meningeal infiltration took place only when the infiltrated vessel reached the surface and was not due to a primary meningitis. The intervertebral ganglia were also the site of early changes. On the eighth day the disease was fully developed. Lesions of the cortex and basal ganglia were not much altered from the early picture. Lesions of the brain stem and cord had increased in severity and clinically produced paralysis and prostration. Nerve cell destruction was greatest in the lumbar and cervical enlargements. (17) Possibly this fact is based on better blood supply here than in intervening cord. This destruction was very rapid and present even in the absence of perivascular infiltration. However, we must remenber that the virus was injected initially into the nervous tissue. In the preparalytic stage when tremor was present, the nerve cell lesions were alone present. Twenty-four hours later the majority of cells might be necrotic masses of debris. When this happened the cells could be placed in two groups, those obviously necrotic and those in which change seems definitely reversible. In the former as degeneration proceeds neuronophagia begins and the neutrophils and glial cells remove the dead cells. In the medulla and pons the nerve cell damage is never so severe as in the cord. In the mid-brain the perivascular infiltration is intense though nerve cell damage was rarely severe. They concluded from this study that poliomyelitis was an

inflammatory disease of the entire central nervous system with a predilection for the anterior horns, that the nerve cells were affected primarily by the virus and not degenerated as a result of interstitial inflammation.(17)

Hurst in 1929 showed that the cord changes were well advanced before infiltration of the leptomeninges took place. He concluded that the mode of spread was along the nerve fibers.(13) This view is supported by Goodpasture working with the virus of herpes simplex and Flexner and Lewis working with the virus of poliomyelitis.(7)

Frances Peabody writing for Oxford medicine gives the following post mortem description of human cases.(29) There is injection and edema of the meninges with slight increase in cerebro-spinal fluid. On section the brain and cord are moist and edematous and the gray matter bulges beyond the level of white matter. Minute hemorrhages are visible. The earliest changes he believes are hyperemia and an acute interstitial meningitis with accumulation of small mononuclears in the perivascular lymph spaces of the blood vessels of the leptomeninges. The perivascular infiltration is most marked in the anterior fissure from which it spreads along the vessels as they enter the cord from the meninges forming a sheath surrounding the blood vessels in such a way as to suggest in places that it might exert pressure and interfere with the blood supply.(29) These primary lesions, perivascular infiltration, hemorrhage and edema are dependent on vascular changes and the fact that the pathological process is most marked in the cervical and lumbar regions of the cord and in the anterior portion of the cord corresponds to the more abundant blood supply in these regions. If we accept the fact that poliomyelitis is a systemic disease the idea that the vascular changes are primary is plausible. The experimental disease does not parallel the human disease as the virus in the former is innoculated directly into the nervous tissue and the sequence of events must as a result differ.(17) If the hemorrhage and edema are absorbed soon enough the nerve cells of the region whose function may have been interferred with by pressure will recover and to this is probably due the rapid disappearance of paralysis in certain cases in the early days of convalescence. If the process does not regress degeneration of the nerve cells takes place. Where the virus had involved nerve cells specifically, at the time of death degeneration had been completed, the debris having been carried away by the neuronophages and replaced by granulation tissue.(29) The lesions in the cord are always more severe than in the

brain. Boyd believes that direct damage to nerve cells and effects due to vascular changes are independent; either one or both may be present or absent.(7) As long as paralysis constituted the chief feature the lesions in other organs were not considered of importance but as we came to recognize the disease earlier when there is systemic dissemination these systemic lesions are assuming more importance. In all of eleven cases dying during the acute stage, Flexner, Peabody and Draper report that there was a more or less extensive involvement of the lymphoid tissue throughout the body and parenchymatous organs. The former appears to react to the virus generally but is most marked in the mesenteric lymph glands and Peyer's patches which show acute swelling. Cloudy swelling occurs in the parenchymatous organs.(29) The virus has been recovered from the cord, brain, prevertebral and retro-peritoneal sympathetic ganglia, the gasserian ganglia, the nasal mucosa, tonsils, lymph glands, spleen and bone marrow.(31)(13)(29)

Draper divides the histo-pathology into three groups: perivascular infiltration, parenchymatous degeneration and interstitial extravasation of red cells monocytes and polymorphs.(10) He belives that local anemia, pressure from edema and toxin from the virus all combine so that the anterior horn cells are both poisoned and strangled to death. It does not seem logical that we can take any one of the above factors and say that it alone is the cause of the pathology in poliomyelitis. The experimental disease shows that before the virus reaches the cord the choroid plexus shows injury.(14)(31)(10) Here again if we accept the fact that at the beginning the disease is systemic the above relationship loses the importance which it might assume if we believed that the virus followed the nerves to the brain, entered the circulation there, penetrated the choroid plexus and spread to the cord via the cerebro-spinal fluid before cord damage took place.

Rivers description of the pathology contains some points pertinent to the elucidation of the clinical course of the disease.(31) Microscopically cross section of either of the cord enlargements showsbulging of the gray matter and varies from a diffuse pink to an obvious hemorrhagic myelitis. The lesions are most often present in the enlargements of the cord and diminish in succeeding sections. In human cases the medulla is usually distinctly congested though there are no gross lesions visible. Microscopically the virus

provokes a round cell infiltration. There is always more or less response in the meninges especially around the vessels of the pia. The reaction may be mild and localized to certain levels or intense and disseminated. The meningeal reaction is the first lesion according to this author and is the organic basis for the back and neck signs. The next lesion in order of development is in the posterior root ganglion. There is a focal round cell infiltration with mid-interstitial hyperplasia and various degrees of nerve cell destruction which progresses in the same manner as in the motor cells of the cord. This is the first nerve tissue involved and is the first to recover. There is usually no residual disturbance of sensation though the changes do account for the hyperesthesia. Lesions occur in the gasserian, ciliary and sympathetic ganglia which correspond to the root ganglia.

In the substance of the cord both the white and gray substance are affected. In the white substance there is perivascular infiltration about the capillaries, slight edema and at times hemorrhage. The gray matter suffers most and the posterior horns are nearly as often involved in the acute process as the anterior horn. There are focal, perivascular and diffuse infiltrations of round cells and edema especially around the blood vessels and nerve cells. The vessels may be further damaged and hemorrhage small or extensive may result. The vessels outside the nervous system are not affected to this extent. It would seem, therefore, that injurous effects are due to multiplication of the virus. The nerve cells are susceptible to the virus directly or indirectly. The sequence of nerve cell changes is perineuritic edema, granulation of the protaplasm with loss of the finer markings and less deep staining of the nucleus. The neuronophages become arranged peripherally about the cell, the peripheral cytoplasm dissolves leaving a granular debris and the neuronophages enter the dead cell. After solution is complete scar tissue fills the space. Permanent damage results in paralysis. However, the cells damaged to the extent of loss of function may recover as shown by return to normal in a short time of completely paralyzed muscles. This suggests edema as the cause of loss of function. Edema here is not a question of osmotic pressure alone.

The medulla shows lesions in the majority of cases though they may be slight. Lesions are present most often in the cord though the distribution in both is irregular. In the latter,

lesions are most frequently present in the enlargements while in the brain a frequent site is beneath the floor of the fourth ventricle. The basal ganglia and subcortical regions of the cerebrum are at times involved and lesions may be present in the cerebellum.

All lymph glands and lymphatic tissue of the spleen show hyperplasia. The virus has been found in the mesenteric nodes. In the liver at times there have been focal infiltrations with small areas of necrosis.(31)

Distribution of the virus on intravenous injection of large quantities into monkeys subsequently killed at varying intervals is illuminating as to the general systemic nature of the disease and the probable course of the infectious process in man.(31)(10) The virus is withdrawn from the blood first by the spleen and bone marrow, next by the posterior root ganglia, and finally by the tissue of the central nervous system. Another supposed result of this experiment is that before the virus reaches the cord the choroid plexus shows injury. Here again, the evaluation of this finding is difficult for it is known that the cord is well supplied with blood from the spinal arteries and if the disease is systemic it should reach the cord as soon by this route as by way of the cerebrospinal fluid from the choroid plexus. The above finding may be coincidental. In explaining the frequency with which the lumbar enlargement is involved, Dr. J. Jay. Keegan and C. M. Hector(16) suggest that ingestion of the virus occurs after implantation in the naso-pharynx, and passes indirectly by way of the bowels up the nerves to the cord. Hector reports an observation by a Dr. Shore that a sharp purge may be followed by a large offensive evacuation and a rapid amelioration of the condition.(16) However, he does not state that the virus was isolated in the above case so we have no way of knowing that the patient would have developed the disease without the purge. Dr. Keegan bases his belief on some work with filterable viruses by Goodpasture drawing an analogy to interpret the picture in poliomyelitis.(7) This route must be considered for we know well that tetanus toxin passes up the peripheral nerves to the cord and produces the clinical picture as a result of cord involvement. However, tetanus toxin is a soluble product and it may be presumptive to even suggest a possible analogy.

In the production of the experimental disease the intra-cerebral route requires the

least amount of virus.(31) The intra-spinal, sciatic, nasal, peritoneal, subcutaneous and venous routes are employed requiring greater amounts of the virus to produce the disease in the order named.(31) Enormous doses are needed by the intra-venous route if the central nervous system is intact and even then infection is inconstant. To me this seems the most plausible explanation of the low incidence of poliomyelitis (2 per 1000)(10) even in epidemics and explains how individuals in whom there are some antibodies may by the multiplication of virus have their immunity overcome with production of the clinical disease. If normal horse serum, ringers solution, monkey or human serum or isotonic N_aCl are injected intraspinally 15-18 hours before the virus is injected intravenously infection occurs almost constantly.(31)(17) This also occurs in production of the disease by nasal applications of the virus for a short period.(31) Thus, we see that a possible choroid plexus injury or sterile meningitis may be hypothesized in lowering the threshold of the cerebrospinal system to the virus.(14)

If gastro-intestinal motility is cut down in monkeys by morphia and the acidity is neutralized by $NaHCO_3$ infection is accomplished by oral administration of the virus in 2 out of 5. Half grown monkeys could not be so infected and remain susceptible to intracerebral innoculations. This route is important in view of the apparent milk borne epidemics of the disease.(31)(18)

When large volumes of active filtrate are injected into the circulation the blood is infective for at least 72 hours but is probably not infective after 10 days, when paralysis appears.(31) When smaller doses or large doses of less active virus are employed the blood fails or irregularly conveys infection to the nervous system. Therefore a mechanism capable of excluding virus from the nervous system is inferred as indicated above. In humans in the acute stage the virus has never been found in the blood or spinal fluid.

Goodpasture working with the virus of Herpes Zoster has been able to produce lesions in the motor nucleus of the fifth cranial nerve in the pontine region by injection of the virus into the masseter muscle.(7) Flexner and Lewis have infected monkeys by the intranasal route and followed the virus to the olfactory lobes.(31) The first symptoms of the clinical disease were due here to root ganglia involvement. The most logical route

from the portal entry is by way of the cerebrospinal fluid but Flexner and Lewis have not been able to follow the virus in this system by innoculation tests. Flexner and Amossafter injection of large doses of the virus intravenously found the virus present in the spinal fluid in increasing amounts from 72-96 hours and it was still present with onset of paralysis in 19 days. Even with such injection the virus passed inconstantly to the cord and brain. The root ganglia can remove the virus directly from the blood and indirectly from the spinal fluid. Aseptic meningitis facilitates and insures passage fo virus from the blood to the nervous tissues with subsequent paralysis. The virus in transit from the blood through the spinal fluid is capable of being neutralized by spinal injection of immune serum. The virus possesses an affinity for nervous tissues, but for no specific element of these tissues. This is shown by observations that nerve cells do not alone or in advance of other structures attract the virus.

All intraneural means of infection are successful and the virus passes along the nerves to the intersties of the nervous system probably utilizing lymphatic communications. (13)(31)(7) Except for the root ganglia none of the nervous organs can remove virus from the blood prior to damage to vessels and choroid plexus.(31) In monkeys these lesions permit differentiation from lesions caused by intra-neural modes of infection. The latter modes are effective in proportion to the degree in which virus is brought into intimate contact with nervous tissues.

Generally the upper-respiratory mucosa is the most often contaminated and most readily favors conveyance of virus to the brain. Distribution of the virus is effected largely by the spinal fluid a fact established by prevention of infection by intraspinal injection of immune serum after virus is injected into the blood stream under conditions insuring infection.(31)(14)

SYMPTOMATOLOGY:

By definition it was stated that poliomyelitis is an acute generalized infectious disease which produces a somewhat characteristic series of general symptoms and may become localized in the nervous tissues. Localization, which in over half the cases, leads to hyperesthesias, asymmetry of reflexes and depending on severity varying degrees of motor debility from transient and reversible paresis to permanent paralysis of muscle groups.(31)

Peabody states that paralysis occurs only when the meningeal choroid plexus vascular mechanism is injured so that the virus escapes into the cerebro-spinal fluid and reaches the brain and cord.(29) For convenience Fleming divides the clinical course into three phases, that of general infection, meningeal invasion and paralysis.(13)(34)(31)(10) These stages are most marked in epidemics. The first two taken together constitute the preparalytic stage of most writers on this subject.(19)(35) The incubation period varies from three to ten days. The phase of general infection lasts from a few hours to three or four days and may be entirely overlooked. There is fever varying from 100-103 degrees, general malaise, vomiting, diarrhea and catarrh of the upper respiratory tract. The cerebro-spinal fluid is normal. The phase of meningeal invasion may occur synchronously with the first stage or there may be an interval of 3-4 hours to 8 days between the onset of the two in which there is a feeling of well being. The intensity here varies from so slight as to pass unnoticed to the simultation of an acute meningitis. Its duration is usually short. The fever carries over from the first phase; there is headache which is frontal in location and persistent; pain in the back and limbs due to posterior root involvement, muscle tenderness which may persist for weeks;(34) rigidity of the spine with resistance to passive anterior flexion the so-called "spine sign"; twitchings, head retraction producing characteristic protective opisthotonus; drowsiness when left alone; irritability when disturbed; retention of urine for 12-24 hours not requiring catheterization, hyperesthesia noted on handling the sick child and infrequently coma.(31)(29) The cerebro-spinal pressure is increased moderately to 150-200 mm. water pressure.(19) There is an increase in cells in the fluid from 30--2000 with almost 100% polumorphs the first 24 hours which subsequently becomes practically 100% lymphocytes.(10)(13)(19) Globulin is increased and continues to increase even when the cell count is decreasing. It reaches the highest point in 2-3 weeks. The chlorides and glucose remain normal. There is a leucocytosis of from 15,000--25,000 according to Draper with a 10-15% polymorphonuclears.

The onset of the paralytic stage is sudden and the paralysis is maximal at the onset.(13) It appears from within 24 hours to 5 to 9 days of the onset of the disease. Fleming reports over one third of 108 cases which he observed showed paralysis in one

day. In epidemics the average interval is three days. According to Peabody the acute or paralytic stage terminates when pain and hyperesthesia decrease and there is beginning restoration of muscle function.(29) The former usually lasts 2 to 4 weeks after onset of paralysis. With the onset of paralysis general symptoms and especially those due to central nervous system involvement may become accentuated. From a review of 600 cases Aycock and Luther state that cerebral, cerebellar, brainstem and spinal paralysis occur and may vary from the involvement of a smaller area of the cord producing paresis of a few muscles to lesions so wide spread as to cause complete paralysis of the whole motor system with death from a respiratory failure. The sphincters are rarely permanently affected.(29)

Stephen speaks of seven clinical types: the spinal, the bulbar, Landry's type, cerebral or encephalitic form, cerebellar type, meningitic and abortive types.(34) In addition, Wickman speaks of a polioneuritic type; Kramer suggests a dromedary form.

The spinal type is most prevalent and represents a lower motor neuron involvement which varies from paresis to paralysis which is flaccid.(34) In the latter event there is a loss of deep reflexes and wasting of muscles. There is a tendency of the arms and legs to be involved due to the frequency with which the cervical and lumbar segments are affected.(17) The proximal muscles are more often and more completely affected than the distal groups and recovery is apt to be more rapid and complete in the latter. The extensors are more often involved than the flexors. In the lower limbs this is shown by the great frequency with which the anterior tibial group is hit.(29) Stephen reports 63 out of 75 cases suffering from residual paralysis of the lower limbs.(34) He states that respiration remains almost normal if either diaphragm or intercostals alone are knocked out. This does not seem logical for if the paralysis of the diaphragm is flaccid as is true in a lower motor neuron type of involvement it would interfere with expiration. If the paralysis were spastic then the diaphragm would serve as a point of fixation allowing the elastic recoil of the thorax to aid in the process.

The terminal stage here shows no toxic clouding of the sensorium as a rule and death is due to inability to breathe. Fatal cases are often striking-----a child who has been drowsy or apathetic suddenly becomes alert and wide awake watching anxiously everything

about him and in respiratory embarrasment he bends every effort ot sustain respiration. This psychic stimulation is an evil omen.(10)

The jump or stepping type may progress in an ascending or descending manner an average period of ten days between jumps affecting the muscles of the legs, abdomen, arm, neck, diaphragm and intercostals.(34) Some authors doubt that this type is true poliomyelitis and believe that cases of Landry's paralysis detected during epidemics are coincidental.

The bulbar and pontive types involve the medulla and any muscles supplied by 3rd to the 12th cranial nerves. The nucleus of the facial nerve is most often involved. Cases of this type show a greater mortality than any other group because of the paralysis of vital functions. The prodromal period here may be very brief or absent and paralysis may appear simultaneously with other symptoms. Occasionally the first suggestion that the child is ill is a nasal voice, dysphagia, regurgitation through nose or combination of these.(34)(35)(33)

The cerebral or encephalitic form involves the frontal, the motor, or occipital regions, is either unilateral or bilateral and is characterized by general symptoms of invasion: convulsions, choreiform movements, drowsiness, strabismus and papillitis.

The cerebellar type shows a more intense menigeal involvement than the spinal form. In the latter the meninges are only moderately congested. The cerebro-spinal fluid shows a high cell count simulating meningitis but is characteristic otherwise and all the symptoms of meningeal irritation are present.(25) In the Dromendory form(34) which constitues 10-15% of cases, patients are ill for one or two days, get well, apparently, then symptoms reappear and paralysis occurs in 1--3 days.

The abortive type shows fever, headache, pains in the limbs, general weakness but no paralysis. Sore throat or diarrhea may be present. This type is noted in the presence of an epidemic, otherwise it is usually missed.(20) A few signs of meningeal irritation to an indefinite degree may be present. Draper believes that 70-80% of all cases present merely the aspect of an acute generalized infection without signs of central nervous system injury.(13)(10)(19) This relationship of systemic phase to phase of central nervous system invasion renders diagnosis difficult and complicates correct interpretation of epidemiological phenomena and constitutes one of the interesting problems of this malady. In the future we must lean to select certain cases from that heterogenous group dubbed "the flu" and because of one or two suspicious symptoms or findings label them as early poliomyelitis. Mere reservation in our minds of this possibility will aid us in picking up many cases now missed. We must purge our thinking of its paralytic mindedness before we can progress far in the early diagnosis of this disease.

Peabody's description of the symptomatology in the child is interesting because it gives the doctor something enabling him to set this illness in this individual apart from the case he has called the flu.(29) After an incubation period of a week symptoms of general infection appear lasting from 1-3 days. This phase may be absent or coincident with meningeal invasion. Usually the symptoms of the early stage are of such a degree that the patient is seen by a doctor. There is fever, sweating, nausea and vomiting, constipation or diarrhea and an infection of the upper respiratory tract or bronchitis. Later there may be drowsiness, apathy, a tendency to sleep, a mild stupor out of proportion to the fever, nervous irritability, complaining, a desire to be left alone, a reluctance to be touched or moved due to hyperesthesia demonstrated by pain on passive motion and the spine sign. In older patients there may be spontaneous pain in the neck, back or legs, paresis or twitching of the muscles with increase or decrease of the tendon reflexes. In the child, there is a peculiar expression of the eyes of mingled apprehension and resentfulness quite unlike the alert bright shining eyes of other fevers. The child may shrug his shoulders when touched or spoken to, with an accompanying whine of resentment. He is restless, breathes rapidly and seems to be

busily and actively resisting some uncomprehensible disturbance to his usual comfort. There is a universal overstimulation; a pressor state of the nervous system, so marked that an impulsive ataxic tremor is present on every motion.(29)

DIAGNOSIS:

The ideal to strive for in the diagnosis of poliomyelitis is to recognize all cases in the preparalytic stage when treatment is known to be productive of favorable results.(19) The difficulties in diagnosing poliomyelitis in the preparalytic stage have not been due to absence of diagnostic signs and symptoms but due chiefly to the lack of opportunity to observe that stage of the disease, to the fact that we have been "paralytic minded" and to the low incidence of the disease even in severe epidemics which gives the physician slight opportunity to become acquainted with the illness.(19) In all cases of early general systemic infection poliomyelitis must be included in our differential diagnosis. We must diagnose the disease early to prevent the "humiliating infirmities of age being inflicted on infancy" and youthful adolescence.(19) Few diseases give rise to such great alarm and hysteria in a community as does poliomyelitis and the community turns to the doctor for advice. Early diagnosis followed at once by treatment with convalescent serum will prevent permanent paralysis in the majority of cases. Such results will prove us worthy of our "hire."

The New York State Department of Health outlines the following symptoms of the disease which it believes valuable in diagnosis before paralysis appears.(28_4) They are: Fever, averaging 102 degrees; headache which may be severe, general, may be nuchal, or replaced by severe back pain; rigidity of the neck; distinct resistance to anterior flexion; tremor on attempted movement; apathy varying from mild indifference to drowsiness, vomiting once or twice on the first day, but never severe or persistent; retention of urine for 12-24 hours not requiring catheterization; constipation and sweating usually seen as beading around the lips and neck, but never profuse. The preparalytic stage presents a distinct clinical entity with symptoms of a mild meningitis; headache, tremor and stiff neck constituting an outstanding triad. With the above clinical picture diagnosis should be confirmed by examination of the spinal fluid. Since the major epidemics in this country have occurred in New York State the above compilation of symptoms is valuable. At present there is no practical way of identifying individuals infected with poliomyelitis.

unless the virus invades the central nervous system. Thus the phase of general infection would of itself be suggestive only but in recognized epidemics or in the absence of other epidemics of diseases characterized by a similar phase its presence would require that poliomyelitis be ruled out. When the infection reaches the central nervous system symptoms of a more definite character are manifest which have been mentioned above.

Several epidemiological features are of value in leading one to suspect the disease. These are seasonal variation, geographical distribution, and the age incidence. Poliomyelitis is a disease of warm weather occurring with great regularity in the early summer and late fall though epidemics have occurred in the winter and sporadic cases occur throughout the whole year. The peak of most epidemics is reached in the last 2 weeks of August. The disease is decidedly more prevalent in temperate climates where the seasonal variations are extreme and attacks the younger members of the population with greater frequency than the older groups.(28_6)(30)(13)(15)(2)(14)(16)(10)(6) These three facts have been observed independently on both sides of the equator in the temperate zones in the United States and Australia respectively. Young children in whom it is difficult to say a limb is paralyzed or not being moved because of pain makes diagnosis even in the paralytic stage hard unless spinal fluid examination is done.(13) This is indicated in all cases showing meningeal symptoms.

The spinal fluid findings are present only after invasion of the central nervous system. Because of the short duration of the meningeal stage the margin of safety before paralysis is narrow and the diagnosis should be made at the first evidence of this phase. The spinal fluid findings are:(19) moderately increased pressure(150-200 mm. water) fluid is clear in direct light but a faint ground glass appearance is noted when examined by transmitted light against a dark background; the globulin is increased when tested by Pandy's reagent, the reducing substance is normal or slightly increased and the chlorides are normal. The cells are always increased in this stage varying from 30-2000 per cu. mm. the average being 100-400; polymorphonuclears predominating the first 24 hours and the lymphocytes becoming practically 100% later in the disease. A smear fails to show the presence of organisms. After the most acute symptoms are over a fibrin coagulum has been noted by E. H. M. Stephen in the presence of 90 mgm. of protein per 100 cc.(34)

The differential diagnosis of the disease is important because the incidence even in time of epidemics is low. Other conditions which might be confused with poliomyelitis are all forms of meningitis due to pyogenic organisms; tuberculous, mumps and luetic meningitis; all forms of encephalitis; loss of voluntary movement due to rheumatism; the tender limbs in scurvy; head symptoms due to dentition or otitis media and the meningismus of pneumonia.(19)(13)(34)(28_2)

Meningitis due to pyogenic organisms ~~are~~ is excluded by stained smears or the test for reducing substance which is diminished. As a rule the pressure is greater, the fluid more turbid, the cell count higher with practically 100% polymorphonuclears, the globulin increased to a greater degree and the chlorides diminished. In the forms other than the meningococcic there will usually be a history of some preceding infection.

In tuberculous meningitis the history of chronicity and exposure are usually obtained and in the spinal fluid the cells early are 100% lymphocytes becoming 50% polymorphonuclear late, the tubercle bacillus is present and the glucose and chlorides are diminished. In mumps meningitis a history of exposure and of recent or associated swelling of the parotid gland may be noted. In luetic meningitis the wasserman reaction or a family history of lues and possibly congenital stigmata establish this form of meningitis.

Encephalitis due to poison is a febrile and characteristic history can be obtained as of lead poisoning. The post-infectious forms of encephalitis are suspected when a recent history of vacinia, chickenpox, measles or other acute infectious diseases can be obtained. In all of these the drowsy or stuporous condition of the patient is the most valuable differential point. Though poliomyelitis patients may appear drowsy when left alone, on stimulation they are unusually alert as evidenced by the hyper-irritability and are well oriented. In the absence of apparent associated infections or in presence of epidemic encephalitis it is hard to differentiate from an encephalitis due to the poliomyelitis virus and here subsequent developments alone can determine the nature of the disease. The behavioristic and mental changes frequently following other forms of encephalitis are not observed in polio-encephalitis.

The tenderness of the limbs in scurvy may be confused with the muscle tenderness which occurs in poliomyelitis and may last for several weeks or more. Here the history of dietetic errors and the presence of subcutaneous hemorrhages should indicate the diagnosis. History and presence of definite localized inflammation rule out the possibility of poliomyelitis being mistaken for rheumatism.

To summarize, any disease in a young child or an adolescent occurring especially in late summer or early fall in a temperate climate showing symptoms of systemic infection and meningeal invasion should be suspected as poliomyelitis to be excluded only by a negative spinal fluid and failure of condition to progress to paralysis.

TREATMENT:

Upon positive diagnosis of poliomyelitis by lumbar puncture convalescent serum therapy is indicated immediately because clinically it is the only form of treatment which can be relied upon consistently when given early enough and experimentally its injection into animals previously innoculated with virus has in a majority of cases prevented develcpement of the disease.(28$_2$)(19)(14)(37) Flexner and Amoss have shown that lumbar puncture subsequent to injection of large doses of virus by vein in monkeys, results in slight hemorrhages into the subarachnoid space, which determines invasion of the central nervous system and a typical attack of poliomyelitis which did not otherwise occur.(31) Therefore lumbar puncture without treatment would most certainly insure central nervous system involvement, especially in a preparalytic case with meningeal symptoms. It would be instructive to know if in the attacks following lumbar puncture the paralysis was confined chiefly to the lumbar enlargement. This would indicate ~~a systemic distribution of the virus which on trauma to the leptomeninges would indicate~~ a systemic distribution of the virus which on trauma to the leptomeninges would permit invasion of the nervous tissue. Such a finding would also negate the necessity of having choroid plexus injury before nervous tissue involvement, a view held by numerous writers. However since the virus produces an inflammatory reaction there is no reason why it cannot enter the nervous tissue by way of the spinal fluid from the choroid plexus, the latter being injured by inflammation as well as by way of the circulation of the cord. The latter is the more extensive and probably accounts for the greater incidence of the

spinal type. Because there are no experimental or clinical findings to discount the work of Amoss and Flexner it is good practice to have serum available to inject by means of the same needle used in lumbar puncture without removal upon positive diagnosis at the bedside, of poliomyelitis.(19) With our present limited supplies of serum this procedure would be practically impassible except in epidemics. However with the demonstrations of immune bodies in a large proportion of normal adults, in sporadic cases where serum is not available, transfusion of the patient after typing or injection of adult blood in the buttocks in indicated.(12)(4)(5) Such treatment is not 100% efficacious but in the absence of convalescent serum we are doing something which has an even chance of preventing development of paralysis. Since specific treatment depends upon spinal puncture we must educate the general public to permit its judicious use. Serum therapy especially as concerns convalescent serum will be extensively reviewed at the end of this paper.

Here general treatment alone will be considered. This resolves itself into several aspects preventative, curative and palliative.(13)(6)(28_4)4 Preventative treatment is concerned with the isolation of infected individuals and detection of carriers. However attempts to limit spread offer little hope of success. In spite of strenuous efforts of the New York State Department of Health to discover and isolate cases quarantine contacts and to restrict travel from infected districts, the epidemic of 1918 followed the ordinary course ending when the season for poliomyelitis drew to a close. It seems unwarranted in view of its usual occult method of spreading and the low incidence even in epidemics(2 per 1000 to)impose irksome restrictions on any except the patient himself and even here the infrequency of multiple cases in the same family and of cases traceable to contact would cast doubt upon the value of such quarantine. The latter in fact might lead to concealment of cases and delay the time when a physician would be called, thus, resulting disastrously in many cases.(28_4)

We know that the virus enters by way of the naso-pharynx and given off in the secretion of the naso-pharynx. It becomes implanted on the surfaces and upon injury to the naso-pharyngeal mucosa it gets into the blood stream lymphatics or nerve sheaths. (30) Normal intact mucosa in this location prevents entrance and may even have a virucidal effect.(29)(16) The virus may be ingested and following constipation or excessive purging which causes the gastro-intestinal mucosa to become permeable it gets into the blood stream, lymphatics or passes along the nerve sheaths, The virus disappears in recovered cases in from 10--14 days after the acute attack. The virus has been found to be present in the nasal washings of a girl 6 days before the onset of an attack of definite poliomyelitis. Thus, communicability is possible from 6 days before to 10 days after acute stage. Immune bodies appear in the blood of human cases in 5 days. The virus has a greater chance to persist in the naso-pharynx of healthy contacts than in a recovered case because of greater concentration of antibodies in the latter. In prevention we must preserve the integrity of the naso-pharyngeal and gastro-intestinal mucosa. In case of the former, this cannot be done by strong gargles or antiseptics or mouth washes. Two per cent peroxide and menthol are virucidal and are not strong enough to traumatize the tissues.(29) Constipation must be combatted not by drastic catharsis but by increasing the fluid intake, by enemas, or by inert oils. Although contact cases are few it is well to protect attendants from fomites by burning all secretions from the naso-pharynx and sterilizing dishes, cooking utensils and bed clothing.(13)(31) Rivers believes that intimate contacts should be quarantined for 3 weeks, that traveling should be limited to necessity and that rinsing the pharynx with isotonic sodium chloride mechanically removes the bulk virus in corners.

When a motor cell is destroyed the resulting paralysis of the part of the muscle supplied becomes permanent. Curative treatment therefore, must be instituted before paralysis occurs.(31) Convalescent serum if given early in the preparalytic stage will prevent permanent paralysis.(13)(19)(6) Since most of the damage occurs to the central nervous system, intra-thecal injection should be the chief route of therapeutic approach. (14) Anti-poliomyelitis horse serum has been used more in Europe than in America with fair results and may be tried.(26) Rosenow claims similar success for his acute-streptococcus serum though its use has not been extensive enough for comparison with conval-

escent serum. The dosage and prodedure will be considered later. Because perineuronal edema plays a role in the production of paralysis relief from it until the natural defenses can become mobilized should produce beneficial effects. It has been shown that dehydration following intravenous hypertonic sodium chloride. Aycock and Amoss after such dehydration attempted to saturate the host with immune bodies so that when the edema returned an influx of immune bodies would take place. This was not proved experimentally, but they treated a child with the ascending type of paralysis which is usually fatal with resulting complete recovery.(31) Palliative treatment is concerned with those steps which give the paralyzed muscles the best possible chance for recovery, in-so-far as that occurs.(13) Paralysis in poliomyelitis is maximal at first and unless death ensues more or less recovery always takes place. This recovery takes place as a result of the relief from pressure, the restoration of circulation and the neutralization of toxins, which occurs on the regression of the inflammatory process and allows incompletely destroyed nerve cells to regain some degree of function.(13)(10) Therefore, any treatment which will aid in the recovery of the nerve cells will also aid in the recovery of the paralyzed muscle. Here, repeated lumbar puncture for several days to relieve pressure is of value. The patient should be flat in bed, avoiding all movement and at complete mental as well as physical rest. Pain should be relieved by sedation as it interferes with rest. After the temperature has been normal for a week and the pain gone the extent of paralysis may be ascertained and the affected parts maintained in relaxation for a prolonged period resorting to orthopedic measures when indicated.(13)

The Drinker Respirator should be used in those cases of respiratory muscle paralysis as long as there is any hope of recovery.(6)(19) The restoration of the infantile paralysis victim and the prevention of deformities after the active stage of the disease may best be accomplished by rest, carefully directed axercise and mechanical relaxation of the affected muscles under the supervision of a competent physician.(28_4) Muscle classification according to the amount of resistance they can overcome offers a method of determining progress of treatment and is valuable in prognosis. The classification used by the New York State Department of Health is grouped as follows; 1. Normal muscle-compare with other side if the latter is unaffected, 2. muscle capable of overcoming gravity and outside force - good, 3. muscle capable of overcoming gravity alone-

fair, 4. muscle capable of overcoming friction of joint and table - poor, 5. muscle incapable of producing movement but showing contraction - trace, 6. muscle showing no tightening of tendon or muscle belly - totally paralyzed. Illustrating, if the knee can be extended while the patient lies on his side, the quadriceps belongs to class 4. In every case where the operator resists with his hands, the action of a set of muscles, he should be careful to graduate his resistance from weak to strong to weak. The resistance should be just short of that needed to stop the movement. Resistance should be initiated when any given movement can be performed freely to its fullest extent in its absence. All movements should be carried through the full arc of motion and assistance given at the end when the patient cannot complete the arc actively.(28_4)

The training of muscles should be begun as soon as the patients limbs can be moved freely without pain.(28_4)(13)(34) In some cases as soon as this may be in three weeks and again it is possible to accomplish a great deal for cases that have been neglected for years. Fleming maintains that electrical treatment and massage should not be employed until all hope of recovery from paralyses is gone and then only to improve circulation and nutrition of the affected part.(13) This attitude, though extreme, seems to sound a warning against ill-directed exercise and premature manipulations which are harmful.(28_4) Weight bearing is very deteterious to weakened muscles and allowing patients on their feet too soon may cause severe crippling. The patient must be observed from the onset to prevent toe drop, sagging shoulders or other positions which stretch weakened muscles. Hence splints, sandbags and cradles to bear the weight of the bedclothes are some of the measures useful for this purpose. Actual training of muscles falls best on the parents who must first be trained by the physician.(28_4) The latter prescribes the exercises, however changing them from time to time as the muscles gain strength.

The patient should never be left to do his exercises alone for the response of muscle and nerve is dependent on the strength of the stimulus and the volition of the patient is materially aided by the outside stinulus of a word of command. When the muscle does not respond at all the physician should perform the movement passively while urging the patient to make the greatest possible effort.

The patients mental attitude may present the first obstacle in muscle training.

The director of exercises should exude confidence and make the patient feel that though he has not up until the present made any progress, he is going to in the future, thus approaching the problem from the psychic as well as the physical point of view.(28_4) The affected muscles should be uncovered during exercise so they can be closely observed. A hard, smooth horizontal surface is necessary for proper performance of the exercises, as it eliminates as much as possible the resistance from friction which could not be done on a soft yielding bed or couch. The surface should be wide enough to allow hip abduction, when patient is lying on his back and hip flexion when lying on the side.(28_4) Sometimes movements can be foulitated by taking advantage of the buoyancy of warm water though the actual training can be best supervised on a table. Water can be used for patients who have learned the proper exercises and the ones to be avoided(28_4) The whole attention of the patient is required to prevent underestimation of his ability to use his muscles and those other than trainer and patient should be excluded from the room. For kiddies the exercises may be turned into an interesting game. The exercises proper are graded from those which the weakest muscles are able to do to those requiring normal strength and must be fitted to the patient by testing out each affected muscle group separately. All exercises must be done without fatigue and when a muscle outgrows a given exercise the next one in order of strength should be substituted.(28_4) The patient should be allowed to go through all his exercises once a day for six days a week. The one day off prevents his going stale. Each exercise may be performed 10-12 times in succession pausing between so that the last one is done as strongly as the first. When contractures of joints exist they should be done away with before exercises are initiated. In all exercises and positions stretching of weakened muscles must be avoided.(13)(28_4) It is common knowledge that many of the muscles that at first appear to be paralyzed recovery spontaneously if the patient could be kept alive long enough for recovery to take place especially as concerns such vital groups as the intercostals. This has been substantiated by the use of the Drinber Respirator in different sections of the country,(6) and is commensurate with the pathological picture in-so-far as the latter is reversible. Summarizing the treatment consists essentially of convalescent serum therapy in the pre-paralytic stage, complete rest in bed with mechanical relaxation in proper position of affected parts during the acute stage, proper diet and elinination throughout and rehib-

ilitation of involved muscle groups after subsidence of the acute stage. This does not include special measures indicated in bulbar paralysis which must be governed by the individual muscles affected.

PROGNOSIS:

Because of the fickleness of poliomyelitis as evidenced by its variegated clinical picture definite prognosis of course and termination can not be given. However, there are various factors which have been observed to exert prognostic influence favorable or otherwise. The first of these depends on the recognition that the severity of the systemic phase has no relation to the central nervous system invasion.(10) The second is concerned with the recognition of the preparalytic stage and immediate treatment with serum for Gonce reports that even with such favorable treatment paralysis occurs in a majority of the cases but of lesser extent and severity than the untreated.(14) The Harvard Infantile Paralysis Commission reports that the grade of paralysis is 63.6% for the untreated and 19% for the treated.(19) Aycock and Luther show a lower mortality rate, a lower average total paralysis and a lower paralysis of the severer grades in the treated cases.(19)(14) Hence, if a case is not diagnosed until the onset of paralysis serum therapy mught be of aid in the spreading type preventing further paralysis byt otherwise of little value.(37) If the time elapsing between a positive diagnostic puncture and serum therapy is prolonged the chances of central nervous system involvement are enhanced. (37)(14) In the San Francisco epidemic of 1930 it was an impression that when central nervous system invasion occurred in the adult it was more severe, more widespread and more likely to end fatally than in children.(23) In other epidemics it has been noted that the presence of relatively greater incidence(Silverman) of bulbar cases corresponded with an increase in the mortality rate.(33)

Draper believes the cell count of the spinal fluid to be of prognostic value in the first 12-18 hours after meningeal invasion.(10) He believes counts under 100 rarely develope paralysis. Counts between 200-500 usually develope paralysis and between 100-1000 fatality usually resulted with few exceptions. Patients with counts up to 300 occasionally escaped paralysis. The approach of paralysis is heralded by loss of tendon reflexes or twitching of muscles. If there is no progression of the paralysis 6-12 hours after the onset there will as a rule be no further weakness.(10) As far as the ultimate stage of recovery of the patient, who has passed the acute stage, is concerned, we must

depend on efficient after care so as to provide the best possible chance for muscle and nerve cell recovery.(13) It has been found that complete restoration of power varies in different epidemics, those observed by Draper varying from 16-44%.(10) Thus, we may say as a rule that though paralysis is maximal at the onset its extent at this time is no accurate measure of its endurance. Mortality varies from 7-25% averaging 14%. Death usually occurs on the 4 or 5th day and rarely after the 8th. The prognosis is better in the encephalitic form and in those with early coma.(31)

EPIDEMIOLOGIS:

The essential nature of infantile paralysis has been determined within the twenty year period during which the disease, escaping from its endemic home in Norway and Sweden, has made its epidemic progress over the world. (13) (28_4) Only the tropics, and even they not wholly, have escaped its raveges. It is probably just because infantile paralysis had never before prevailed in a world wide epidemic that we are witnessing the periodical outbreaks which are so tragic in their consequences.(28_4) On the whole, the outbreaks have been larger and more servere in North America then elsewhere, and for reasons which will be considered later on, that are bound up with the nature of the disease. (19)(28_4) In 1911 there was an increase in cases in the United States, England, Scandanavia, Denmark, these being the only countries with records.(15) In 1916 there was a heavy outbreak in New York. Europe was not affected at this time. The United States was a site of another epidemic in 1920, and again Europe escaped. Since 1925 there has been an increase incidence all over the world. Thus, in 1925 New Zealand and Norway experienced epidemics, 1926 England, 1927 United States and Roumania, 1928 Scotland and Canada, 1929 Scandanavia, Holland and Italy. The increased incidence has occurred in waves over different countries in different years, (15) In the past two decades the disease has become established in this country and if the total number of cases has not shown an alarming increase, the distribution has certainly become wider.(19) The larger outbreaks have been in the northern areas of the country but cases have been reported from every state in the Union. The total number of cases of the disease from the Registration Area of the United States for the past two decades is as follows: -(19)

1910	-	1303	1915	-	1796	1920	-	2350	1925	-	5651
1911	-	309	1916	-	28316	1921	-	6292	1926	-	2662
1912	-	2648	1917	-	4197	1922	-	2265	1927	-	9487
1913	-	2048	1918	-	2568	1923	-	3344	1928	-	5101
1914	-	1555	1919	-	1945	1924	-	5256	1929	-	2830

1930 - 6556 (incomplete)

Poliomyelitis occupies a relatively minor numerical position in the infectious diseases of childhood, yet hardly any disease is a terrorizing to the public, presents such a problem to the doctor and the health officer, or has been so perplexing to the epidemiologist.(6) A child who has not even remotely been associated with any source of infection developes a headache, fever, and vomiting, and often before it is realized that the condition is more than a trivial upset, permanent paralysis has taken place. These characteristics account for the public alarm in time of epidemics. For the doctor, the long drawn out case of these patients is a problem and two many men do not encounter this condition.often enough to be either familar with or to maintain adequate facilities for the diagnosis and treatment.(6)(19) The health officer has to admit that he has little to offer that will insure protextion against the disease. The epidemiologist encounters unparalleled difficulties in the study of the disease for it is only in exceptional cases that relationship can be established with other cases.(6) There are no practical tests of suspected abortive cases and healthy carriers capable of widespread use and the general epidemiology presents many seeming inconsistencies.(20)(15)

The virus of poliomyelitis lurks in the upper respiratory tract and is given off into the air by the acts of respiration.(15) If a person inhales air contaminated with the virus several things may happen. The virus may not succeed in implanting itself on the respiratory passages and die out due to immunity of the host from previous contact, or it may multiply in the respiratory tract and produce a reaction by the host with no clinical manifestations which checks the activity of the virus and results in subclinical immunity. If the reaction of host to invader is more severe clinical manifestations appear with the development of either an abortive or full blown case of the disease. If the latter takes place the incubation period varies from 2-10 days with an average of 3-4 days and paralysis usually appears on the 3rd day after the onset. Again the virus and host may assume the status of symbrosis with the development of a healthy carrier. This constitutes

the theory of infection advanced by Halliday.(15)

If we grant that the virus is given off in the respiratory secretions, it is necessary to consider certain factors at work in bringing about an epidemic of an endemic air borne disease. The first of these is the refractory period during which epidemics rarely develope. This is probably related to meteorological conditions and is a constant factor. Secondly we must consider the varying phases in the equilibruim between activity of the virus and immunity of the general population. Comparing with measles as the activity of the infective agent increases, the "herd" reacts by producing clinical measles and also subclinical infections. In other words, there occurs a visible epidemic of subclinical infections as a result of this herd reaction, immunity is raised, the influence of the virus is delimited and the epidemic declines. The infective agent cannot again provcke an epidemic until the herd immunity has fallen below a certain level. The fall is brought about by new children being born among the population and the wearing away of the subclinical immunity. It has been deduced from statistical data that subclinical immunity to measles is only temporary, lasting on an average of 18 months.(15)(14)(6)(3)(2)(21)

At least 95% of the adults of large cities have had measles, but only a small proportion(under 0.5%) have had classical poliomyelitis with paralysis. The herd immunity to the latter must be higher than to measles.(15) As sporadic cases continually occur and as these are scattered all over any city, the inference is that there exists an extensive and constant resivoir of infection. If this is so the majority of the population must have come into frequent contact with the virus andundergone subclinical immunization which lasts longer than that to measles. A proportion of the population may also have acquired actually an abortive attack.(15)(20)(28_2)

During every year even in the absence of an outbreak the months of June to October provide more cases of poliomyelitis than from November to May. Thus a refractory period is superimposed on the phases of saw saw equilibrium between the activities of the virus and herd.(15) In this disease the number of clinical cases is relatively small compared to the number of subclinical infections in contrast to measles in which nearly everyone at some time of life suffers from the clinical disease. A graph of poliomyelitis over a period of years cannot represent the predominating phenomea, subclinical reaction on the

part of the herd and the epidemics appear irregular only because they are largely invisible.(15)

It would seem that in the winter months when people are more crowded together there would be more carriers and more cases, but it seems as though the winter months for some unknown reason constitutes a period refractory to the development of an epidemic. (15) Thus the life history may be controlled by seasonal changes.(19)(6)(3)(15)(16)(31) Dr. Keegan maintains that because the gastro-intestinal tract serves frequently as a portal of entry the disease is more prevalent in summer and early fall because of the greater incidence of gastro-intestinal diseases in those months. Aycock considers the temperature change in summer to be in some way related to lowered body resistance and greater resultant susceptibility to the virus.(6)

Populations in concentrated communities which maintain a constant resvoir of infection are spoken of as salted.(15) This complicates the problem of epidemiology. In isolated communities or diffusely scattered populations the problem is simpler. Here we have a virgin soil and on introduction of a virus and a resultant outbreak all age groups are affected because, due to lack of constant exposure there is no widespread subclinical immunity and the disease spreads like wild fire.(15) A contrast as regards age distribution of air borne diseases is found among concentrated populations which are in frequent communication with other populations. Here is a constant resvoir of infection and interplay between virus and all of the population. The majority of persons thus come into contact with the virus at an early age and owing to frequent exposures, either build up subclinical immunity or take the disease in early childhood. Thus in an outbreak in Glascow in 1928 - three-fourths of the cases were under 5 years of age, and in the New York epidemic of 1916 over two-thirds of the cases were under 4 years. In Winnipeg in the 1928 outbreak only one-third and in Manitoba the same year only one-fourth of the cases were under 5 years.(15) It seems therefore that the age incidence in an epidemic of an air borne virus infection is an index of the extent to which a virus resvoir previously existed in the population affected. The more constant and extensive the resvoir, the younger the predominating age group affected.

The low incidence of clinical poliomyelitis even in time of epidemics shows a high rate of immunity to the disease in the general population and the distribution of this immunity is correlated with the incidence of the disease not only in the different ages but with concentration of population.(20) The mechanism by which this general immunization takes place is being sought. Since Wickman's suggestion of the probable occurrance of abortive forms of the disease the impression has developed that much if not all of this immunity is accomplished through abortive attacks. Aycock and Kramer after intensive studies in Massachusetts and Vermont over a period of years were not convinced that large numbers of such mild cases occurred concurrently with an outbreak of the frank disease.(6)(20)(2) In October, 1930 five frank cases of poliomyelitis occurred in Bedford, Mass. (population 1700) This gave Aycock and Kramer an opportunity to ascertain the incidence of abortive forms.(20) Residence was established and histories of illnesses from two weeks previous to the appearance of the first case to six weeks after onset were obtained. Such illnesses numbered fifty of which thirty-three were in persons under fifteen years of age. The neutralization test of Aycock was used to determine if the abortive cases were actually poliomyelitis, and was done on half of 28 children in the same town, who had no illnesses and another in an adjacent town where there had been no poliomyelitis, were tested. The result of the immunity tests in the three groups proved identical. A high rate of immunity in those who had passed through mild illnesses failed to materialize. The blood for these tests was taken five months after the illness so that immunity would have had time to develope. These men concluded that widespread immunization of a population does not take place entirely at the time of an outbreak, but rather in a uniform manner throughout the year or in inter-epidemic periods, varying of course with variations in the presence of the virus in a community. (20)(6)

Early students of poliomyelitis had little upon which to construct a conception of its epidemiology except by observations in attempting to trace the infection from one case to the next occurring in the vicinity. One of the earliest theories was that the disease is transmitted by contact.(6) This theory originated in the suspicion that mild illnesses comudent with frank cases suspedted as abortive cases aided in the

Dissemination of the disease. These were not found in numbers sufficient to account for the spread of the disease. Then the supposed transmission of the virus through healthy carriers was invoked. Failure to find the evidence usually sought to establish contagiousness and the observation of so many cases in which such circumstances could be ruled out, led to bizarre and mysterious theories as to mode of spread of the virus.(6)(15)

Modern spidemiology does not deal alone with attempts to trace each case to its source of infection, although this is its ultimate object. It included analysis of the more general circumstances under which the disease occurs or with which its occurrence varies, and consists as much in the multiplication of probabilities as in actual demonstration of fact.(6) The accumulation of data since the increased occurrence of the disease in the past 25 years and the experimental transmission of the disease to monkeys have enabled studies to be made which are essential to an understanding of its epidemiology. The mistake has often been made in assuming that the whole of the epidemiology is to be seen in the epidemic itself and it is largely from more indirect studies with the limited available laboratory tests that it is possible to formulate anything like a complete idea of the epidemiology of poliomyelitis.(6)

A point of first importance is the actual extent of the spread of the virus. Frost first suggested, from the more rapid decrease in the incidence of poliomyelitis with increase in age in urban than in rural populations, that in older persons there is a widespread immunity from previous exposure to the virus.'15)(6)(2)(10) Exposure, in spite of fewer clinical cases, as extensive as in such common contact diseases as measles and diphtheria. That the extensive immunity suggested by age distribution of the disease actually exists has been demonstrated by Aycock and Kramer on a small but signigicant number of individuals at different age groups in urban and rural populations by means of a neutralization tests.(6)(5) This test consists of mixing the serum to be taken with a fatal dose of virus, incubating for 2 hours at 37° followed by 24 hours on ice and subsequent injection intra-cerebrally into monkeys.(29)(5) If the monkey fails to develope poliomyelitis the serum contained immune bodies and vice versa with gradations between as regards concentration of immune bodies, paralysis and paresis.

When the findings of the virus, in the upper respiratory secretions of patients suffering from the disease, in animals experimentally infected and in healthy persons, and the ease with which animals can be given the disease by placing a drop of the virus in the nasol mucosa, are added to the correspondence between both the extent and rapidity of exposure to the virus of poliomyeltis with that of measles and diphtheria, when it is considered that exposure to the virus is as world wide as only contact infections are known to be, it is apparent that the early students of the disease were right.(6) The difference between the epidemiology of poliomyelitis and other contact diseases are due to differences in frequency with which initial exposure to the virus results in immunization or the clinical disease.

Some of the features of poliomyelitis which have seemed not to fulfill the criteria for contact transmission which have been held as arguments against transmission in this manner are the infrequence of contact cases, the infrequency of multiple cases in families or in institutions, the infrequency of transmission to nurses and attendants of cases and more generally the tendency to rural preponderance and the seasonal prevalence of the disease.(6)(2)

When these features are viewed in the light of widespread immunization with low disease incidence the failure to correspond to the criteria of contact diseases can be explained. In immunization without disease it would be expected that traceable contact between cases of poliomyelitis would be relatively rare and that the majority of cases would arise from contact with mild cases or healthy carriers. Kramer reports a presumptive calculated carrier rate of 1% would be sufficient to explain a 90% immunization by the time adult life is reached.(6)(21) The infrequency of multiple cases in families and institutions and the rarity of the disease in nurses and attendants of cases can be explained in the same way, for nurses as a rule being adults must be assumed to be immune from previous exposure and only a small proportion would be expected to contract the disease on initial exposure, the rest being immunized without showing clinical signs. Thus the occurrence of two cases of poliomyelitis among 200-300 nurses attending 1,189 cases in Massachusetts in 1927 is about the frequency of obvious contagion expected.(6)

An exception to an obscure rule as is the dissemination of the poliomyelitis virus in its usual manner may serve to emphasize the rule. Thus the exceptional outbreaks of poliomyelitis apparently distributed through milk have shown those departures in age, space and time distribution of cases which would be expected when the orderly contact dissemination of the virus is changed to simultaneous and selective exposure of a relatively large number of individuals.(28_2)(18) A specific example is reported by Aycock, Godfrey, and Knapp.(18) From 12-14-25 to 12-25-25 there developed in Cortland, N. Y. a city of 15,000 population, eight cases of poliomyelitis in patients found to have consumed milk from the same dealer with one possible exception. This dealer sold less than 4% of the cities total supply. The cases were widely enough distributed to make it improbable for the milk supply to be a mere coincidence of geographical distribution. Added to these facts was an actual paralytic case on the dairy farm from which most of the milk came. This patient was milking cows and handling milk for four days while in the acute stage and as the time elapsing between this date and the dates of the onset of the subsequent cases was consistent with the generally accepted maximum and minimum incubation periods, the chain of circumstances is as complete as is found in the majority of milk borne outbreaks of other diseases. The characteristics of the epidemic concede also. There was a sudden of cases which developed all at once apparently from the same contaminated single milking with no new ones subsequently. The cases attacked all age groups.

The idea of rural preponderance of cases of poliomyelitis has gained emphasis more from the striking occurrence of the disease in remote localities removed from other cases than from adequate statistical analysis.(15)(6) With the exception of 1916 there actually has been such preponderance in the rual portion of the registration area. On the assumption of a constant exposure rate greater in urban than in rural populations due to concentration of population the number of immunes in an urban population would exceed those in a rural population, But due to the more rapid accumulation of immunes in the former the number of initial exposures in a given period would decrease more rapidly in the urban group so that in time with an exposure rate in the rual population of only one half the urban rate, the number of initial exposures would actually exceed those in the urban. Thus if immunization of a population

has already reached a more advanced stage before initial exposure results in the disease, the slower transmission of the virus in a rural population would result in a greater number of cases than in the urban group.

Aycock has shown that the worst epidemics which we have could occur without any increase in the rate of spread of the virus over that, which in order to maintain the degree of immunity shown to exist, must be occurring on the average all the time.(6) He also shows that if initial exposures take place at an even rate the year around they are sufficient in number in any given month to account for the largest number of cases of poliomyelitis occurring in any month even in the worst epidemics (around 2 cases per thousand). Thus the frequency with which initial exposure results in disease may be determined by the season at which such exposure takes place due to some seasonal variation in the quality of the virus or in the resistance of the host.(15)(6)

That season may be an important factor in determining the frequency with which initial exposure to the virus causes immunity or disease is suggested by a correlation of statistics of the disease in cool and warm climates with changes in season in the two climates.(6)(16)(34)(29) The occurrence of the disease in Iceland in 1924 suggests that the cooler the climate the higher the incidence though previously norther Europe and the United States were supposed to constitute the belt of greatest incidence. The southern hemisphere has an incidence agreeing with corresponding latitudes in the Northern hemisphere. Thus in New Zealand the incidence is comparable to Norther United States. In the United States the diminishing incidence as the Southern latitudes are approached is decidedly noticeable though the immunity in the south is as great according to neutralization tests which showed 90% of adults immune. Thus the exposure to virus must be as great, but due to smaller fluctuations of climate the effect seems to be a lower incidence of cases on initial exposure. Thus though the incidence seems to vary with the degree of fluctuation of temperature from winter to summer no change in virulence of the virus can be hypothesized which would explain both the seasonal and climatic variation.(6)

However climatic and seasonal changes changes in the physicology of the host may take place in such a way that by altering the resistance they could cause the variations in frequency with which exposure would cause disease or immunization without disese.(6) Such an example is apparent in theclimatic difference and seasonal fluctua-

tion shown to exist in the iodin content of the thyroid and the resistance to certain poisons. Failure of the patient to adjust normally might result in deficiency or imbalance greater in summer than in winter, greater in cooler than in warmer climates.

Draper first pointed out indications of imbalance in the physiocogy of persons attacked by poliomyelitis.(10) This would suggest that some such failure of the body to meet the stress of seasonal adjustment may be the factor which determines whether initial exposure produces disease or immunization. He believes that susceptibility of the host and virulence of the organism is the chief factor. Race is no factor, males are attacked more often than females in the ratio of 5 or 6 to 4. Halliday believes this greater incidence of central nervous system greater in males than in females is a characteristic of all infectious diseases of the central nervous system.(15) Draper also describes a type of individual more susceptible than the average. Such a person, if a child, is very often large, plump, with broad face, unusual dentition (50-60% cases) showing wide separation between invisors, also suggested by association of disease with teething since first recognized. If an adult or adolescent type the patient may be more delicately made, usually brunette with only delicate dark skin and high coloring of cheeks and lips. There usually is a definitely, finely chisled prognothism and a tendency to crowding of the teeth. Draper also believes that parental abnormalities play a part in susceptibility, such as acromegalic and Froelich types. Others are dark hair, fat faces and bodies, narrow shoulders, broad hips, knock knees, marked maxillary prognothism, widely separated upper incisors, large broad hands and great physical strength. The above observations were made by diagnosticians of the New York State Department of Health in Long Island during epidemics.(10) Numerous instances of 2-5 cases in families with such parental types occurred suggesting a true family susceptibility. Environment and social status have little bearing on the incidence.

The age of incidence depends on the extent of the resvoir of infection. Thus in the New York epidemic of 1916 the following cases were over ten years of age - between 10-15 years 94, 15-20 years 32, 20-30 years 40, 30-40 years 25, 40-50 years 7, a total of 198 cases in 5, 486. Below ten years the age of greatest susceptibility was the second year.(10)

The basis for the belief that immunity to poliomyelitis is the result of exposure to the causal agent rests on the findings that: immunity follows an attack; immunity developes in experimental animals upon injection of the virus; the presence of immune bodies in the blood stream parallels immunity to poliomyelitis as indicated by neutralization tests; and the ratio which immunity developes with reference to age and density of population is indicative of its development through contact.(5)

By parallel tests with the Shick and neutralization tests the parallelism of results strongly indicates a similar mechanism in development of widespread immunization in diphtheria and poliomyelitis.(5)(21) By neutralization tests Aycock and Kramer have proved that the virus is neutralized by larger proportions of serum from the older age groups than from the younger groups both from rural and urban districts and that urban serums neutralized the virus with greater frequency than rural serums.(5) Thus the neutralization can be considered a test of immunity.

Because of the extent of immunity to poliomyelitis, exceede the demonstrated distribution of virus, and because it increases in extent with age, the idea of widespread subclinical immunity has been challenged by some, it being held that adult immunity arises spontaneously and is not of antigemic origin, a maturation immunity.(3) Discussions of other possible explanations have appeared in editorials under titles of Panimmunity and Phylogenetic - Immunologic Recapitulation. Because of the far reaching significance of such conclusions, possible errors in logic must not be overlooked.

An editorial entitled Panimmunity appeared in the J. A. M. A. in Vol. 96:775.(11) Its gist was that the demonstration of virucidal properties in normal adult serum against poliomyelitis reviewed the question as to whether adult immunities are due to previously unrecognized specific infection. Arguments against such explanation were based on a study of diphtheria immunity amony Eskima children in which the same per cent of immunity to diphtheria toxin existed as in children in crowded environment even though diphtheria was practically unknown.(11)(3) Aycock reputes such testimony in this group of Eskimos as clinical diphtheria had been observed in this particular group several years previously and as only a single examination of 200 healthy people had been done which would be inconclusive. He also figured that a single carrier would have been sufficient to account for the existing immunity and that such a possibility could not be ruled out on a single

examination.(3)

Friedberger, Bock and Furstenheim of Berlin suggest the presence in young children of antibodies against such noninfectious agents as sheep and rabbit red cells, antigins that presumably never came into contact with their internal tissues.(11) They report that the umbilical blood of a new born contains no such antibodies, at the end of 1 year 20% yield 60% and by the tenth year 90%. These hemolysms and agglutinins remain at a ralatively high titer through adolescence,,early adulthood and then decrease giving quantitative curves simulating those for spontaneous immunization of the adult population to scarlet fever and diphtheria. These authors argue from parallelism that anitbodies in growing children form and increase as a result of general maturation and that the observed mass immunizations to polio are not necessarily due to previous subclinical infection. Certain factors which must be considered are that mutton and rabbit are common articles of diet in Europe and that food proteins are only partially denatored by cooking so that gastro-intestinal absorption of such proteins which has been demonstrated by Americans to take place gives us something in contact with the internal tissues to serve as an antigin with the production of antibodies.(8) Such food proteins are secreted by the mothers milk as may be the antibodies, thus accounting for the appearance of antibodies to proteins of rabbit and mutton before the child is old enough to ingest such articles of diet. To prove that these antibodies are due to maturation immunity Friedberger must prove that the formation of antibodies is specifically stimulated by the gastro-intestinal absorption of habitual foods. In fact such absorption has been advanced to explain the fact that we do not suffer from explosive protein toxicity, when due to injury of the gastro-intestinal mucosa there is a sudden shower of habitual proteins.(8)

That gastro-intestinal absorption of undigested proteins does occur has been demonstrated by A. F. Coca.(8) He worked with a collodion sac, an air bladder from a fish and the parliment diffusion shell. He showed that all egg proteins of egg white are dialyzable through all three membranes used. The average hourly rate was one part in twelve thousand. This is equivalent to one milligraim of egg protein absorbed into circulation by the end of fifteen minutes after swallowing a raw egg, assuming no increase in absorption surface and an identical peameobility. He believes that this absorption may conceivably maintain the human body in a constant state of immunization against habitual proteins.

The process he calls automatic raw herring has apparently proved such absorption to take place by means of sera from patients sensitized to the above injected intradermally into other patients with subsequent passive sensitization and reaction following ingestion of either the raw egg white or herring.

Another interesting theory is that called phylogenetic - Immunologic recapitulation. (9) It states that the current theories of allergy and immunity are based on the assumption that normal human proteins are unchanged in specifity from the time the ovum is fertilized until death. It argues for a dynamic protein specificity pictured as a normal panimmunity; and for the consideration of observed allergies as arrested maturations, atypical differentiations or embryonic protein reversion. As illustrations of the above views, the antibodies as a quantilative diagnosis of age groups and the failure of the Chinese and Japanese to react to Dick toxin are advanced.(9)

In the virus diseases the only antibody or immune reaction, the existence of which appears to be generally accepted or for which practical tests are available is the virucidal antibody, which is shown by the neutralization tests,(6)(5) passive immunization and the curative effect of immune serum. That the virucidal antibody is an indication of exposure to virus is shown by the facts that; It is not found in an animal known not to have been exposed; It can be produced experimentally only by virus; and in Diphtheria the test corresponds with the test for the antibacterial antibody.(3) In poliomyelitis because of the expense of laboratory animal only limited tests have been used. These tests are valuable in-so-far as they correspond with the more complete data relating to immunity in some of the bacterial diseases. Again some one aspect of immunization may be shown in one disease and not in another. Thus the quantitative carrier rate in diphtheria can be obtained by a comparatively simple technic. Here the extent of distribution of the organism can be proved sufficient to account for the observed adult immunizaty. No such evidence can be proved for poliomyelitis though the occasional findings of virus in nasal secretions of healthy persons mught be indicative of a carrier rate equal to that in diphtheria and thus explains the immunization of 90% of the urban population by the time they have reached adult age.(20)(21)

If adult immunity is attributed to exposure to virus such immunity must either represent permanent immunity from the initial exposure or more or less temporary

immunity reinforced by subsequent exposure often enough to maintain the accumulated immunity observed with increase in age.(3) That such reexposure may be an important factor is emphasized by the suggestion of some loss of adult immunity in later life corresponding with a period od diminishing chance of exposure, shown by Chapin in a diminishing attack rate among non-immune persons.

From the consideration of a number of diseases, each one of which represents particularly well one or another element involved in adult immunity, one is led to believe that what has been called panimmunity is evidence of paninfection.(3) In those panimmunizing infectious agents which are transmitted by person to person contact it would appear that the host-parasite relationship represents a type of parasitism so well adopted to ordinary and irreducible human contact that there is little hope of bacteriologic control of such diseases in checking the spread of respective etiological organisms.

A brief review of several epidemics with their obvious implications will serve to illustrate some of the factors pointed out in the previous discussion of the epidemiology of Poliomyelitis. The first to be considered is a clinical analysis by Silverman of Acute Poliomyelitis in Syracuse, New York occurring in five successive outbreaks from 1922-1929. (33) As a basis for comparison in the 1916 epidemic there were 229 cases with 64 deaths in a population of 160,000. In the former outbreaks the incidence of cases up to the age of nine years constituted 78-79% of the total number of cases in the years 1922, 1924 and 1928; 64% in 1926; and 70% in 1929. The incidence of the disease in males predominated in all the epidemics. Only two colored children were affected which is half the expected indicence based on percentage population. With the exception of 1922 when the majority of cases started in September, the most marked incidence was in August. Deaths were also the maximum in August, except in 1922 when the peak occurred in October. In a general way foci spread from one part of the city to an adjoining part and often a relationship seemed to exist among cases in any given locality even though actual exposure to cases by contact was rarely proved. The incidence of types of the disease is as follows:-

Spinal - 63% in 1922 and 24, 41% in 1926, 58% in 1928, 41% in 1929.

Bulbar and Bulbo-Spinal - 22% in 1922, 8% in 1924, 21% in 1926, 12.5% in 1925, 29% in 1929.

Mortality - 20% in 1922, 7% in 1924, 17% in 1926, 8% in 1928, 18% in 1929.

There is a marked parallelism between the incidence of bulbar and bulbo-spinal cases with paralysis and the mortality rate. There were relatively more deaths in the higher than the lower age groups. The above report covers 200 cases in a population of 200,000. Thus while the 1916 epidemic showed the expected incidence for moderately severe epidemic the subsequent outbreaks showed only half the expected incidence necessary for a severe epidemic.(2 per 1000) This corresponds however, with the number of colored children affected which was half the expected incidence. Because these outbreaks occurred in a large city where there was a constant resvoir of infection the majority of cases occurred in children up to 9 years of age which is in agreement with concepts previously expounted. The greater incidence of spinal types over others is characteristic and the increased mortality corresponding to the increased incidence of bulbar and bulbospinal cases is expected because of known severity of the latter types.

C. M. Hector noted that the epidemic in the Wellington District of New Zealand began in late spring and ran through the warmest period of the year, declining with the advent of cool weather.(16) He also noted that the warmer parts of the country suffered more than the cool which is at variance with the findings of Aycock though the occurrence of the epidemic in the warm season is in accord with the views of the latter. Many cases were noted where a series of abortive cases in families led up to a paralytic case, showing increase of virulence where circumstance favored or individual alteration in susceptibility to an organism whose virulence was constant in-so-far as such a group was concerned. 89% of the cases were in individuals under sixteen years of age. There was no general relation of cases to population density and the mode of spread was considered to be chiefly by direct contact.

The report of Thelander, Limfer and Shaw of poliomyelitis in California in 1930 is interesting because of the greater proportion of adult cases than in eastern epidemics.(23) On the San Francisco epidemic of 1930 there were 268 cases, 72 of which or 26.8% occurred in persons over 16 years of age. There were 1836 cases in the whole of California for 1930. 21.47% of this number occurred in patients over 15 years of age. The adult incidence in rural sections of 19.37% was exceeded by the adult incidence of 23.57% in the larger cities.

This report represents a study of 60 adult cases whose ages varied from 16-47 years, though the majority occurred in the younger adults. Males represented 55% and females 45% of the cases. A large number of socially and financially prominent people were affected. The early symptoms as described by the patients were invariably ascribed to recent indiscretions in eating and drinking or to continued vocational strain. The incidence and severity in this epidemic are in contrast to the view that the disease is especially limited to children. Apparently Hallidays' theory of constant resvoir of infection with widespread subclinical immunity among adults does not apply here at first on superficial scrutiny. The cases occurred to some extent in those whose chances for immunization through repeated exposure had been reduced to a minimum. It was suggested that poliomyelitis had not been widespread on the Pacific coast for a number of years to an extent comparable with that on the Eastern seaboard and that acquired immunity was less than in the East where most of the studies have been made. The disease itself was more severe in course sequelal and mortality rate which was 27% of the adult cases or 70% of the total for the whole epidemic considering all age groups. It was noted that adults withstood exposure to the disease more successfully than children. They waged a more vigorous defense against the disease when it was once acquired but when central nervous system involvement occurred it was likely to be more severe, more widespread and more likely to result fatally. Because there had been no constant resvoir of infection on the pacific coast for a number of years the region could be considered as relatively virgin soil. Thus those in the cities would be as susceptible as those in the rural sections. When an epidemic occurred we would expect it to be more severe in the cities for here the virus could pass through a large number of individuals in a relatively short time stepping up the virulence sufficiently so that more adults contracted the infection. We would expect this incidence in adults to be greater in the urban than the rural sections and that the course of the disease would be more severe. These facts are recorded concerning this epidemic.

A sharp increase in the incidence of poliomyelitis was noted in New York City during the week ending July 25th.(28) While only 35 cases had been reported in the city during the first half of the year, 195 cases were reported during the single week of July, 19th, 1925. Of these 155 were in Brooklyn, where the 1916 outbreak had its beginning.

The rapidity of the increase suggested the possibility of an unusually high prevalence extension to other places but the late beginning signified a shorter and much less extensive outbreak than occurred in 1916, when the significant increase began early in June both in New York City and upstate. In the latter outbreak there were 9,000 cases in the city and 4,000 in the rest of the state before it ended in October. The recent epidemic on the basis of reported cases began three weeks later than in 1916 though due to failure to report cases with onsets a month previous to those first reported in the latter the actual difference intime of onset was 2 months. The first upstate focus to develope in 1931 was in Hudson which occurred in the same city in the 1916 epidemic. However the first case in 1931 was in the third week of July as compared with the first week in June in 1916. The following table indicates the progress of the 1931 epdicemic.

Cases Reported.

	New York City			Upstate.		
	1916	1930	1931	1916	1930	1931
First 6 mo.	331	15	34	60	29	31
July	3, 443	4	620	611	41	47
Aug, 1-8	1, 410	6	659	313	20	81
Aug. 9-15	1, 089	2	512	232	46	88
Aug. 16-22	831	4	422	440	67	133
Aug. 23-29	635	4	432	415	25	180
Aug. 30-Sept. 5	412	0	347	381	47	206
Sept. 6 - 12	319	1	254	361	59	175
Total	8, 470	36	3,280	2, 913	334	941

The marked increase in cases in New York City occurred especially in the Borough of Brooklyn which simulated the 1916 epidemics. In the latter confirmatory evidence of a greater incidence than was indicated by reports came in the increase in calls for assistance in diagnosis and the appearance of several recently paralyzed infants at the Baby Health Station serving the affected area in Brooklyn. In the 1931 epidemic a convass failed to discover any unreported cases.

A preliminary report was available for the upstate epidemic but not for New York City. Up to December 1st, 1, 968 cases had been reported upstate. Of these only 31 oc-

rred in the first half of the year. The peak of the epidemic was reached in the week ending September 5th when 206 cases were reported. For the week ending December 5th there were only 14 cases reported, the epidemic being nearly at at end. Prior to September 1st - 81% of the cases were concentrated in the counties in the vicinity of New York City and in the counties along the Hudson river and vicinity. About the latter part of September cases began to be reported from a more extended and widely scattered area. At this time there was a tendency for the incidence to be relatively higher outside the area of greatest previous prevalence. Of 1789 cases on which this report is based, 778 or 43.5% were urban and 1, 011 or 56.5% were rural. By rural is meant all incorporated places under 2500 and all unincorporated territory. The upstate population as of 7-1-31 was 63% urban and 37% rural. The urban case rate per 100,000 was 21.5% as of 11-1-31 is less than one-half the rural rate of 48.5%.

In this outbreak more than two-thirds or 67.2% of the cases were in children under 10 years, 33.7% under 5 years and 33.5% in the 5-9 year group than females and the latter more cases under 5 years than males. 92.3% of the cases were under 20 years and only 33 or 1.9% were under 1 year. Relatively more of the urban cases were in the lower age groups as compared with the rural cases. Of the 778 urban cases 289 or 37.1% were under 5 years and of the 1,011 rural cases 313 or 31% were in the above group. The percentages for the 5-9 year group were about equal for both rural and urban, those over 10 years the incidence was 5% greater in the rural sections. Thus in the latter 355 cases or 35.1% were over 10 years while in the urban cases 232 or 29.9% were over 10 years.

Of the 1789 cases studied 1,053 or 59% were in males and 736 or 41% were in females. The ratio for all ages was 1.43 ♂ to 1 ♀. Under 5 years ♂ 1.32 and ♀ 1; 5-9 years ♂ 1.61 and ♀ 1; ; 10-14 years ♂ 1.73 and ♀ 1; 15-19 years ♂ 1.28 and ♀ 1; 20 years or over ♂ 0.87 and ♀ 1. The sex distribution for rural and urban cases was approximately the same.

Based on data available for 1,275 cases in 1,197 families. 95% of the families had only one case each and the remaining 5% had multiple cases. 2 cases occurred in each of 53 families which is 4.4%; 3 cases in each of 8 families, or 0.7%; and 4 cases in 3 families, or 0.2%.

In the 1931 epidemic the death rate was 8 per 100 against 21 per 100 for 1916. The age groups are as follows -

All ages 8 per 100 10-14 years 9.5 per 100

Under 5 years 5.3 per 100 15-19 years 11.1 per 100

5-9 years 6.8 per 100 20 years or over 18.2 per 100

Summarizing, in this epidemic,we have a typical illustration of points espostulated under the earlier discussion of epidemiology. The epidemic began in mid-summer, reached its peak late in August and early September and decreased with the advent of cold weather. It began in a location where presumably there was a constant resvoir of infection though there has been no real epidemic in New York City since 1916. With the large numbers of new births and the wearing away of subclinical immunity to some extent due to dimminished exposure is compared to that in time of epidemics it is plausible to expect an epidemic which should be in and around New York City and then spread to the neighboring counties as did this epidemic. The greater total incidence in the upstate epdiemic of cases in the younger age groups corresponds with the idea of a constant resvoir of infection with earlier exposure andimmunity. Most of the cases occurred in rural areas and the incidence as shown by case rate per 100,000 was over twice as great as in the urban centers. This is to be expected if we remember that due to greater exposure the urban incidence is less.than in rural sections. In addition, we would expect a greater incidence in the rural sections of cases of the higher age groups. These facts are borne out be records. As has been the case since epidemics were first studied, contact spreads in this disease can only rarely be recognized in a small proportion of cases and here it could only be suspected in about 5% of the cases.

SERUM THERAPY:

The basis that immunity to poliomyelitis is due to exposure to the causal agent rests on the following facts;

1. Active immunity of the disease, no matter how slight the intensity of the latter.
2. The development of immunity in an experimental animal by injection of graded doses of virus.
3. The presence in the blood stream of antibodies which parallels the immunity as indicated by neutralization tests.
4. The rate at which immunity developes with reference to age and density of population is indicative of its development through contact.

The above facts must be considered in any discussion of the value of serum therapy in poliomyelitis. The sera used are four in number; convalescent, anti-poliomyelitis Horse serum, normal adult serum and the anti-streptococcus serum advocated by Rosenow.

First, the use of anti-streptococcus serum will be considered. Since it is generally believed that the streptococcus is a secondary invader and not the etiological agent in poliomyelitis and since it has not been possible to produce typical poliomyelitis in experimental animals by innoculation this organism it is doubtful that this serum has any specifi value. Its use in treatment of the disease has hot been extensive enough and there have not been sufficient controls for comparison so that its seeming value arouses the suspicion that possibly a considerable number of cases would recover without such therapy if seen in the preparalytic stage and given proper rest and symptomatic treatment.(28_2) This latter fact applies likewise to horse serum and human serum and constitutes one of the baffling problems in the evaluation of serum therapy in general.

In 1910 Flexner reported an attempt to produce an immune horse serum against poliomyelitis.(26) He injected trypanized filtrates of cord and brain suspensions of children who had died of poliomyelitis, into a horse. These injections were carried over a period of 13 years. The serum was then obtained from the horse and it protected a monkey from an intra-cerebral innoculation of 0.5 cc. of 5% suspension of a potent virus. In 1918 August Petit continued this work using a horse serum and a sheep. His serum neutralized the virus in the proportion of 2 parts serum to 1 part virus. Banzhof subsequently with a known virulent virus produced a potent horse serum and concentrated it so that 1 part neutralized 100 parts of virus in vitro. The attempts to produce an antipoliomyelitis horse serum probably were based on the production of diphtheria antitoxin and according to the tenets of immunology it is a logical step in securing large enough reserves of protective substance which can be standardized and are readily available in time of epidemics. The effeiacy of this serum was tested by Neustaedter on 4 frankly paralytic cases in the United States and by Netter of Paris on 2 such cases. The latter used 500 cc. of serum sent to him by the Americans. He also used anti-poliomyelitis horse serum on a single case of Landry type in 1910. The serum was given 40 hours after onset of paralysis with complete success. Again in 1913 he gave serum to a case 50 hours

after onset of the paralysis with complete disappearance of the paraplegia and retention. Petit of Paris reports a high degree of success in 60 frankly paralytic cases. Horse serum can be concentrated which is an advantage in administration.

The intra-spinal injection of horse serum in man produces violent reactions such as temperature 104-105,° convulsions and even coma.(26) The muscular and venous routes are devoid of such unpleasant effects. To forestall an anaphytoctic reaction a preliminary dose of morphuce gr. $\frac{1}{4}$ and atropin gr. 1/100 should be given. Then in several minutes a few mimms of serum subcutaneously and if there is no reaction in 18-20 minutes it is sage to proceed. The dose of unconcentrated horse serum is 20-30 cc. q. day or on alternate days. In severe cases 20 cc. may be given twice a day the dose being continued until the temperature drops or until 10 doses have been given if necessary. The concentrated serum is given in 5 cc. doses. When given by muscle a Herxheimer reaction occurs after the third dose. This is abviated by venous therapy. The production of anti-poliomyelitis horse serum is fraught with many difficulties as is indicated by the fact that Dr. Park in 1928 found that the horse of Flexner had no neutralizing power after being carried along a couple of decades. At present such serum does not seem to be of widely accepted value probably because of the comparatively restricted use due to limited supplies and cost.

Convalescent serum therapy is based on the following evidence: One attack apparently confers a lasting immunity to the disease; the blood serum of persons who have suffered an attack of the disease and that of monkeys which have passed through an attack of the experimental disease neutralizes the virus; Amoss convalescent serum when tested experimentally exerts a protective action against the virus.(28_2) Thus in 1910 it was discovered at the Rockefeller institute that the serum of the blood of a recovered patient when mixed with the virus rendered the latter inactive and also that when the virus was first introduced into monkeys and the serum from recovered humans or monkeys was injected 24-48 hours later, the onset of paralysis was prevented. This is the experimental foundation for the use of convalescent serum which was first used on may by Netter of Paris in 1911.(28_2) It is now known not to be of value when paralysis has been present more than 24-48 hours. The earlier its administration after the onset of symptoms the better the results.

With convalescent serum it has not been possible to use a product of standard strength as is the case in other serum therapy.(1) Each lot of serum employed is only presumptively good. Thus we would not expect as great a concentration of antibodies in a patient himself treated with convalescent serum as from a patient who had suffered a frank attack of the disease.without such treatment.(1) This statement is based on the accepted results of passive and active immunity. The actual evidence that the above condition is possible is suggested by the findings of Shaughnessy, Harmon and Gordon.(12) They showed that only in four of seven persons, who had suffered from poliomyelitis from 6 mo. - 2 years before test, did the serum neutralize the virus. Aycock and Kramer, in 60 tests with 41 samples of which 24 were pooled lots from 3 or 4 persons, had 5 failures. (12) These were two of the individual samples and 1 pooled sample from 3 individuals. There was no statement as to whether any of the cases whose serum failed to neutralize the virus had been treated with convalescent serum at the time of their attack.

Another disadvantage is that patients have not been treated individually but with an arbitrarily uniform dose of serum. This is certain to produce imperfect results. (1) Since adequate controls have not been available and since it is not possible to predict the severity of a case during its early stages the results of this type of therapy have been criticized on the basis that by reason of early diagnosis, mild and non-paralytic cases are included in the compilation of data which would ordinarily be missed in the untreated group.(1)(19) However a number of investigations have failed to unearth any large number of mild cases and Kramer has noted that 65% of cases treated by himself and colleagues actually developed some form of paralysis, thus indicating that they were not treating non-paralytic forms of the disease. Even allowing for the inclusion of such cases the outcome of serum treated patients is on the average so much more favorable than untreated patients reported in the same outbreaks that the use of convalescent serum must be considered as effective. The Harvard Infantile Paralysis Commission reports the results of treatment of nearly 300 cases compared with a similar group of cases seen too late for treatment. Covering a period of four years (19) the following points were noted: The differences observed between treated and untreated groups in any single year are almost duplicated in other years; The lower average paralysis of the treated group; Only a small proportion of those treated fall into the severer forms of paralysis referred to as a

"trace" and "gone," this grade of paralysis for treated being 19 and for the untreated 63.6%; And a low case mortality rate has been the rule in the treated cases.(21)

Since the supply of convalescent serum is necessarily limited, it seems possible in the light of recent tests suggesting that normal serum from adults may contain as much or more of the neutralizing property than convalescent serum, that the development of the use of normal adult serum may greatly facilitate serum therapy.(4)(5)(12) Such a finding is to be expected when it is correlated with the idea that immunization without apparent infection constitutes the chief feature of poliomyelitis. Shaughnessy and his associates found that the serum of 13 out of 15 or 87% of normal persons with no history of the disease neutralized the virus, 11 in a dilution of 1-30 and 2 in 1-200.(12) 8 of 9 persons over 12 years gave positive neutralization tests and the 2 highest tilers were in normal adults. Aycock and Kramer found that in 46 urbans 32 or 70% neutralized the virus. Of 34 - 5 years or older, 27 or 86% neutralized the virus. The figures for rurals were much lower as we would expect from lower and less constant exposure rate. Thus of 29 rurals 6 or 20.7% succeeded and 23 or 79.3% failed to neutralize the virus. Aycock also tested 21 adults in Atlanta, Georgia with 18 or 86% positive results. Thus the virus is neutralized by larger proportions. This is the basis for the use of normal adult serum in the treatment of poliomyelitis. This finding also suggests the necessity of testing all samples of convalescent serum for potency before use. This would require a laboratory equipped with monkeys at $15 a piece and a standard virus. Such prodedure would exclude samples of no value thereby raising the average antibody content of pooled samples. It would also allow the testing of transfusion donors for possible stocks of serum and direct transfusion in severe cases. Normal adult serum was used in the treatment of polio by Zingher of the N. Y. S. D. Health in 1946.

Experimental data are needed as to the serum reaches its height and the tiler of the serum according to the length of time elapsing from the attack of the disease. Blood may safely be drawn after all symptoms of the acute stage have subsided notably fever and muscle tenderness. Specimens taken years after the disease neutralize the virus giving rise to the belief of permanent immunity following an attack. Donors for serum are obtained through after care-clinics, local health departments, physio-therapy departments, splint and surgical bootwear and by direct appeal through the newspapers.

A bleeding clinic in which a number of persons could be seen at the same time would facilitate collection especially in time of threatened epidemics.

Actual collection consists primarily in getting the blood from the patient using strict asepsis and antisepsis into a sterile collecting container.(1) It is then incubated at 37°c for an hour to promote clot retraction and then placed in an ice box over night or for several hours. Young centrifuges the blood after it is collected for a half hour instead of incubating.(35) After the sojoum in the ice-box the blood is centrifuged for from 10-15 minutes at 1500 revolutions per minute. The serum is then aspirated into a special outfit smaller than the collecting set-up, care being taken to prevent hemolyns and staining of the serum with diffused hemoglobin. The latter increases the initative effect of the serum on the leptomeniges. Young then places the serum in large tubes for inactivation, which is accomplished by placing it in a water bath at 56°c for a half hour.(35) Samples are then taken for a wasserman test and for sterility as recommended by the Hygienic Laboratory. If these are negative the remainder is put up in ampules of from 10-20 cc, sterilized and heometically sealed. The ampules if kept in the ice-box retain their potency for at least a year without preservative according to Young's experience. Aycock uses serum stored with and without preservative but is not able to state the effect of the latter on the antibody content.(1) Allan Lilley uses a complicated set up for collection and preparation of the serum for which he claims the advantages of absence of danger of clotting in the needle while withdrawing blood and the use of a needle of approximately only half that usually used.(22) However the apparatus is so complicated that it requires an expert to operate it, it is bulky and not readily transportable and does not give any greater proportion of finished product than the simple methods. F. G. Morgan uses the simple method of collecting and aspirating bottles but places 1½ cc. of a 10% solution of potassium oxalate in his collecting bottle. He lets the blood set over night, centrifuges it and then adds calcium chloride of 1.022 specific gravity the quantity used being determined by a special formula.(25) His apparatus is immersed in melted paraffin before use so that the blood will not clot in the collecting tubes. By this method he obtained 38.2% of total blood volume removed in the form of the finished bottled product. This is not more efficient than the first method described and the complicated determination by mathematical formula is a definite disadvantage.

As yet there are not sufficient data clinical or experimental to determine what constitutes an adequate dose of convalescent seeum or what is the best method of administration.(1)(14) Because of difficulties in obtaining serum the dosage has been regulated by supply and demand rather than with regard to its adequacy. This is illustrated by the suggestion of the New York State Department of Health of a total dosage of 45 cc.; 10-20 cc. to be given intraspinally, in the recent epidemic (1931).(28) Again its use is further restricted, it being required that an authorized representative pass on the diagnosis before serum administration. The serum is not standardized and what would constitute an adequate dosage of one lot might prove inadequate with another. The average total dosage varies between 30 and 100 cc.(28) As the serum must reach the spinal fluid to prevent paralysis and since in epidemics paralysis occurs on an average of the third day from onset, intra-thecal injection is indicated as the route of choice during the preparalytic stage.(14) Because the disease is systemic intravenous and intra-muscular injections of serum to compliment the spinal injection should be done at the same time. Because lumbar puncture before central nervous system involvement by its lowering of resistance of the choroid plexus facilitates spinal fluid invasion and subsequent nervous system invasion immediate diagnosis and treatment with the needle remaining in place in the interin is indicated.

The patient is placed in the usual position for lumbar or cysternal puncture, the point of election prepared with iodine and alcohol and the needle inserted. As much fluid as can be obtained is withdrawn and should be examined at the bedside. If more than 20 cc. is obtained 20 cc of warmed serum is instilled without pressure. Following intrathecal injection Aycock slowly injects 60 cc. of warmed serum into the veins of the elbow.(1) Then he repeats the intrathecal injection the next day and if the patient still has fever he repeats the intravenous injection. Although the New York State Department of Health suggests a total dosage of 45 cc. because of supply and demand it prefers 80-90 cc. for a case.(28) In the Winnipeg epidemic of 1928 and in the Ontario epidemic of 1929 human immune was used intra-muscularly in 25 cc. doses with good results. In the former 93% of cases so treated during the acute stage recovered without paralysis. In the latter 80.7% of the cases treated before the onset of paralysis made complete recoveries. All treated on the first day recovered and 87% of those on the second day. The percentage

of complete recoveries diminished on succeeding days and all treated after the 5th day were paralyzed. In the city Ottawa, 95% of the cases treated with serum before paralysis recovered completely.(28_2) The fatality rate in the above epidemics was very low either because of prompt treatment or low virulence of the virus. Young uses 10-30 cc. of serum intra-spinally twice a day in severe cases and once a day in the moderate types depending on the age and size of the patients. Cysteonal injections are given by him in bulbar cases and he believes intra-muscular injections are of value at times. He has seldom found it necessary to give serum more than two days in succession.(35) Gonce suggests a dosage of 10-30 cc. by spine and an equal amount by vein or muscle.(14) Helms uses 20-100 cc. and believes administration is justified even as late as 24 hours after the onset of paralysis.(17)

Reactions to convalescent serum are encountered not infrequently, though they are seldom alarming.(1) The most common reaction is an increase in the meningeals signs of stiffness in the neck and back, presence of Kernig's sign if absent before, an increase in the number of cells and a possible diminuation of transluscence of the spinal fluid so that it may even appear turbid. The amount of fluid may be increased. This reaction may last from 24-48 hours.

The next in frequency of incidence is the occurrence of a chill, a sharp rise in the temperature (105°) frequently accompanied by vomiting. This reaction comes on usually about 15-20 minutes after injection of the serum. Another reaction is the complaint of abdominal pain and pain referred to the legs after the spinal injection. Though this is occasionally severe it is of short duration and is probably due to too rapid injection of the serum. Aycock has not observed delayed reactions such as urticaria and arthritis.

The N. Y. S. D. H. collected more than 140,000 cc. of convalescent serum for use during the recent epidemic. Though reports are not available for the results of treatment the administration of such a large amount of serum is enlightening.(28_6) The following figures were compiled from a study of 1227 cases with onsets since 7-1-31. 830 cases or 65% received serum. 661 or 79.6% received the serum in the preparalytic stage and 60% of the cases were diagnosed in this stage. In 771 cases in which the method of administration was known 63% received serum by muscle, 56% by spine, 35% by vein and 5% subcutaneously, either solely by the method incidated or in combination with some other route. Thus we see

that even in time of an extensive epidemic when doctors are "poliomyelitis - minded" the clinical picture is not always district enough to allow of diagnosis in the preparalytic stage. Judging by the results of early use of serum in the Canadian epidemics we would expect about 70% of complete recoveries.

Young reporting the outcome of 32 dases 19 of which received serum treatment divides them into 3 groups with respect to manner of treatment and percentage of complete recoveries.(35) Group one,in which no serum was given with 30% complete recoveries. Group two, in which serum was given irrespective of age and stage of the disease with 68% complete recoveries. Group three, in which serum was given in the preparalytic stage with 91.5% complete recoveries. This latter group compares favorably with the Canadian experience and shows the value of early use of serum. Young notes 126 cases reported by Ayer treated with serum with 8 deaths and 93 or 74% complete recoveries. Of 46 cases seen in the first 24 hours after onset 41 or 89% recovered with no paralysis.

Kramer gives a comparison of treated and untreated cases in Mass., 1927, 1928 and 1930, and in Maine 1930.(19) Convalescent serum was used in the preparalytic stage in the Massachusetts epidemics. The report includes the percentage of various grades of muscle damage.

Year		Cases	Deaths	Case Fatality Rate	No Muscle Exams.	Total	Good	Fair	Poor	Trace	Gone
1927	All cases	1189	166	13.9							
Mass.	Untreated	1083	165	15.2	482	66.6	18.7	13.0	17.7	7.5	6.7
	Treated	106	1	0.9	106	19.0	8.6	4.2	4.7	0.9	0.6
1928	All cases	431	62	14.4							
Mass.	Untreated	297	55	18.5	99	46.8	15.9	10.4	12.7	4.5	3.3
	Treated	116	7	6.0	107	12.9	4.7	2.7	3.4	1.2	0.8
1930	All cases	504	33	6.5							
Mass.	Untreated	392	29	7.4	184	65.6	16.0	12.9	18.2	10.8	7.7
		75	0	0	40	21.4	6.0	5.4	4.7	3.1	2.2
1930	All cases	166	28	16.9							
Maine	Untreated	117	27	23.1	49	80.6	18.2	16.5	20.2	13.2	12.5
	Treated	49	1	2.0	26	53.5	17.3	10.6	13.7	7.9	9.0

A few cases in the Maine epidemic were treated after the appearance of paralysis which accounts for the relatively higher residual paralysis in the treated group than in the Massachusetts epidemic. These figures also suggest that those locations where poliomyelitis has not been endemic usually show a more severe grade of the disease.than those

regions where there have been repeated epidemics. This is as we would expect according to the mode of immunization. Kramer states that although the results indicated in the above chart favor the continuation of convalescent serum therapy, he does not believe the series of cases to be large enough, nor well enough controlled to say that this form of therapy is definitely established. He advises caution in the evaluation of such results lest the medical profession surrender to a false sense of security in the belief that we can look forward to some fairly definite ideas on such therapy when the results of the 5,000 cases in the recent epidemic in New York State are available. There will always be conflicting reports from treatment in epidemics depending on the degree of immunity of the general population in the region affected, the time when serum is administered, the amount of serum administered and the care with which serum of no protective value is excluded from the pooled samples.

Case Reports

The following case records of poliomyelitis were obtained through the generosity of Doctors A. G. Young and A. E. Bennett from their office files. There are no cases of Poliomyelitis in the acute stage on record at the University Hospital.

Case I.

That of an adult in whom the possibility of contact infection must be considered. The patient is a white housewife, 35 years of age. The onset of illness was 10-15-30 with the symptoms of nausea, headache, dizziness and diplopia. There was fever on the second day and again on the third day reaching 103? There was a remission and the patient was not seen by a doctor until 10-21-30, a week after onset. At this time the patient was afebrile. There were no objective signs of central nervous system involvement but muscular tenderness. Lumbar puncture was done and the spinal fluid reported negative. The day after lumbar puncture pain was noted in the back and shoulders. This became worse and two days later weakness of the left arm appeared. The patient remained in bed and two weeks later on getting up found that her left leg was weak and dragged on walking. A physical and neurological examination on 1-11-31 was negative except for slight weakness of the left hand grip and lateral extensors of the elbow. It was noted that the baby in the family had had a febrile condition just prior to the onset of the mother's illness showing a good recovery without residual symptoms.

The subsequent course of the case after seen by the doctor on 10-21-30 was as follows. Patient ran a temperature for 2 days of more than 1°. She vomited twice and then developed pain and soreness in the arms, then the neck, legs and back. The left arm became weak, the grip was poor and she could only raise a teacup. 10-31-30 there was still muscle tenderness and pain. 11- 2 - 31 the left arm and leg were still weak. The pain and soreness of the muscles had ceased about three weeks after the lumbar puncture on 10-21-30.

1-11-31 Examination showed weakness of moderate amount of the lower extremities in flexing the thigh on the abdomen. The right thigh was one-half inch greater in circumference than the left. The ankle jerk was exaggerated. The diagnosis at this time was residual poliomyelitis.

5-19-31 Patient showed a tremor of left arm when tired. The legs became spastic on walking and she tires easily. The leg muscles are sore and there is a suggestion of atrophy of the left forearm and leg.

With a history of febrile condition in her baby and the appearance of the paralytic disease in the mother soon after contact infection probably accounts for the transmission here. We must also assume that the patient had not sufficient exposure to the virus to build up immunity expected in an adult. The fact that a person of this type contracting the disease lessens the attractiveness of the maturation theory of immunity.

This case probably represents the Dromedary Type of the disease and though the appearance of the symptoms after the remission corresponds with the procedure of the lumbar puncture which is thought by some to favor nervous system involvement. I believe that this represents the expected recrudesence of symptoms after the remission characteristic of the Dromedary Type.

Case II

White, male child, 22 months age. Walked at 11 mo. Talks normally for age. At 13 mo. in September '31 contracted pertussis and coughed all winter. In March or April, 1930 had measles and developed a running nose which persisted for a considerable time. Seen by doctor 8-10-31 and history obtained as follows:- For past 2 mo. patient very irritable and cutting a molar tooth. Sunday P.M. 8-10-30 he vomited. Same night he slept fitfully crying frequently. Has slight temperature. Monday it was noted that right eye did not close. Temperature in A.M. 100.° Tuesday - 8-12-30 temperature 103.° Was taken to Methodist Hospital. 8-13-30 spinal puncture done. Fluid showed 45 cells - lymphacytes. Examination showed a chronic mastoid right side with sclerosis and slight breakdown of intercellular septa. Mother stated child had had intermittent discharging ear since 6 weeks of age. This discharged when he had the measles. Physical showed foot drop left side and some respiratory embarrassment. Temperature was 103.° Was given anti-spreptococcus serum. Prognosis was not considered good. 8-16-30 entered paralytic stage. Noted "Patient has been in stupor since second day after arrival. Temperature 103-104.° All extremities have become paralyzed. There was a white count of 20,000 with the febrile period. There was a suggestion of balbar paralysis but this was not progressive. 8-29-30 still slight temperature, right arm and leg completely paralyzed. 10-24-30 patient brought to office apparently recovered. No blood could be taken for the immune serum because of the small size of the veins.

Since all four extremities were involved we may say that this probably represents an ascending type of the disease. Foot drop alone on one side was noted first. Then all four extremities were knocked out and patient showed respiratory embarrassment. Apparently the anti-spreptococci serum did not arrest the further development of the disease. If we are to believe the report of Amoss that this serum has no specific effect we must conclude that the course would not have progressed further without serum therapy or again by a slight stretch of the imagination we might decide that the antibodies which have been demonstrated in human cases by the 5th day had reached a concentration sufficient to halt the further progress. By the marked degree of recovery we might also conclude that the loss of function was perhaps due chiefly to the perineuronal edema and only partly to actual destruction of nerve cells. This case is associated with

teething as described 200 years ago when it was called a debility of the extremities associated with teething and foul bowels. However the only association is probably that of age of incidence and has nothing to do with teething. The presence of only lymphacytes in the spinal fluid suggests that lumbar puncture was probably done about 24-48 hours after the onset. The cell count of 45 falls below the figure set by Draper (100) below which paralysis does not usually occur.

Case III

White girl 6 years of age. 8-21-30 patient was restless, vomited and developed headache and fever. There was a slight sore throat. Temperature was 102^{8}-pulse 130, resp. 30. 8-22-30 developed an acute pain in R.L.Q. accompanied by tenderness. Temperature 101.° 8-23-30 temperature 100° and pain in R.L.Q. still present. 8-24-30 pain in right extremity diminishing in intensity and then appeared in the calf muscles. A week prior to onset of acute pain stiffness had been noted when stockings were put on. This was worse on the right side. At time of onset of acute pain the latter was so severe as to prohibit handling of the leg. When the pain diminished paralysis of the flexor of the thigh and foot drop was apparent. This was on 9-2-30. Mother also noted that toes doubled in when the right shoe was put on. 9-5-30 patient on office call found to be unable to dorsi-flex the foot on the leg right side. Exam 9-12-30 showed a lower motor neuron paralysis involving the right quadriceps, adductor brevis and tibi-peroneal muscles. There was also paresis of flexor of the right knee and also of the gluteal muscles. There was muscle tenderness of the entire right extremity. There was faccid steppage gait with the right leg. Patient was immobilized in a cast and put to bed for 6 weeks to be followed by massage and electricity.

This case represents the typical spinal type of poliomyelitis of moderate severity. We would expect the lesions to involve small focal areas in the region of the lumbar enlargement with a moderately intense pathological picture of interstitial, pervascular and parenchymatous changes. With the pronounced hyperesthesia appearing a week prior to onset of the acute illness the usual sequence of events is followed. The involvement of posterior root ganglia before the cord.

Case IV

White boy 3 years of age. Developed poliomyelitis early in September, 1930. The onset was acute with a meningitis reaction in the spinal fluid - 140 cells. The arms were paralyzed and there was some difficulty in swallowing for several days. At time of office call he had been up for a month.(seen 10-28-30) Examination at this time showed a slight defect, paralysis of the right arm and faulty head posture. The scapular muscles showed improvement but the deltoid is not at all active.

This case apparently represents bulbar and cervical enlargement involvement. The pronounced meningeal reaction indicates the meningitic type of Poliomyelitis. According to Draper's point of view of prognosis by cell count we would expect this case to show only mild paralysis. He believes that counts under 100 usually do not develope paralysis and that those from 200-400 usually do. This case falls in between these two points.

Case V

White girl age 11 years. 9-14-30 patient turned right ankle while wearing high heels. 9-16-30 while going up stairs at school fell and struck bridge of nose on a door with a resulting skin wound. She returned to class in an hour, went to lunch and came back to school limping on her right leg. 9-17-30 could not use the right leg properly. It would giveaway and was partially numb. She had a headache and vomited. She continued in school the rest of the week and the limp became worse. 9-20-30 patient received a massage by an osteopath over the involved limb and the face. 9-21-30 there was numbness of the face, poor articulation, dysphagia, and strangling and the leg was worse. Was taken to Methodist Hospital 9-23-30. Lumbar Puncture showed normal pressure, lymphosytes and twice normal amount of protein in the spinal fluid. Immediately after puncture collapse with cyanosis and slight respiratory embarrassment occurred necessitating a stimulate (caffern) 15cc. of immune serum was given by systemal puncture and 20cc. into the buttocks. Exam. at this time showed a bilateral facial palsy of the lower motor neuron type, partial paralysis of the right shoulder girdle, deltoid, partial paralysis of the vagus involving the pharynx and vocal cords, partial paralysis of right quadriceps

and calf muscles, a loss of the deep tendon reflexes, deep seated muscle tenderness in both legs, a febrile reaction of 100° and a white count of 15,900.

This is the bulbar type of poliomyelitis and is usually considered more severe than the other types with a greater mortality. Trauma may have produced a break in the continuity of the nasol - mucosa permitting the virus of polimyelitis to pass through it and along the olfactory nerves to the brain. The case is not purely bulbor as there is evidence of lumbar and cervical enlargement involvement in addition to the lesions of the bulb. Here apparently the acute stage lasted between 24 - 48 hours, as there was evidence of beginning paralysis the day after injury. The fact that the Osteopathic massage made the affected leg worse and resulted in facial paralysis provides proof that massage in the acute stage aggravates the paralysis.

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DISCUSSION

The question as to how the virus of poliomyelitis reaches the central nervous system from the portal of entry, the nasopharynx, is as yet debatable. Two possible routes of transmission have been indicated neither one of which probably explains the mechanism in all cases. Though the virus has never been found in the spinal fluid of human cases it has been found in the spinal fluid of monkeys for a period of from 24-48 hours after intravenous injection of virus, the latter preceded by an intra-thecal injection of isotonic sodium chloride 15-18 hours earlier. This was proved by the failure to produce the paralysis in monkeys if the above procedure was followed within 24-48 hours by spinal injection of convalescent serum. In the human cases we have only the spinal fluid findings to suggest the presence of the virus. Since the virus probably enters the cerebro-spinal fluid before the onset of paralysis any model of transmission must take that system into account in its discussion.

The first route to be considered is by way of the systemic circulation. The virus gets into the circulation from the mucosa of the nasopharynx and passes to the cord. The blood supply to the cord is greatest to the posterior root ganglia, anterior portions of the cord and the cervical and lumbar enlargements. The virus passing by way of theblood stream to the cord would be most concentrated at the above locations. Thus the meninges show an inflammatory reaction first, the root ganglia next and then the anterior horn cells. This corresponds to the clinical picture and also to the experimental disease in monkeys following large intravenous doses of virus. In some of the monkeys the injection failed to produce the paralysis. Though it has been proved that the virus multipplies in the blood stream because of the above facts and the additional one that the cord enlargements are most frequently involved in human cases it would seem that the circulatory distribution is a factor in the production of the cord lesions. It may be argued that those cases which fail to develope paralysis

do not contain the virus in the blood stream in sufficient concentration to produce the paralytic stage. Any paralysis or paresis occurring in this manner is probably due to edema. If the inflammatory reaction results in rupture of capillaries the virus has access to the nerve cells and true paralysis may result By this route the virus may also pass through the choroid plexus into the cerebro-spinal fluid to the nerve cells.

The other route of transmission is by way of the peripheral nerves to their respective nuclei in the central nervous system. Thus following intra-nasal implantation of the virus in monkeys the virus has been traced along the olfactory nerves to the bulb. It has not been traced through the spinal fluid though it is probably in this manner that the virus is disseminated to the cord. Upon ingestion it has been suggested that the virus passes up the nerves to the cord. Being motor nerves we would expect the lesion to appear in the anterior horn cells and to be localized unless the virus penetrated into the spinal fluid. Such transmission may account for the paralysis of single muscles or muscle groups noted in some cases. Since the tissues outside the nervous system do not show the characteristic perivascular infiltration it has been suggested that the virus multiplies only in that environment, that these tissues furnish something favorable to the growth of the virus.

More work needs to be done on the histo-pathology of poliomyelitis before any definite conclusions as to the mode of spread to nervous tissues can be postulated.

C O N C L U S I O N S

1. Poliomyelitis should be regarded primarily as an acute systemic infection subsequently involving the nervous system.

2. Poliomyelitis can be recognized in the pre-paralytic stage when serum therapy is most efficacious.

3. Convalescent serum has definite therapeutic value in the prevention of paralyses if administered under proper conditioms.

4. General adult immunity as evidenced by neutralization tests is due to exposure to the virus and not to maturation immunity.

5. In the course of time general immunity will be built up in the population of the United States so that epidemics will become less frequent. This course of events has taken place to a great extent in Europe.