Serum therapy in the prevention and treatment of poliomyelitis

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SERUM THERAPY IN THE PREVENTION AND TREATMENT OF POLIOMYELITIS
After the period of the rapid growth of knowledge of poliomyelitis, following the 1907-1908 epidemics and those of the succeeding ten years, the experimental investigations, which were directly responsible for the accessions, gradually grew less. The reason for the falling off, which occurred almost simultaneously in the United States and in Europe, was that the studies which for ten years had been so fruitful ceased to yield rewarding results. The beginning of the experimental period dates from Landsteiner's discovery in 1909 that poliomyelitis can be communicated to monkeys by the inoculation of human nervous tissue and the determination by Flexner and Lewis soon after that indefinite animal to animal passage can be secured. It happened that as the experimental investigations declined, the epidemic outbreaks also grew less. This coincidence may have affected somewhat the zeal with which those investigations were pursued, because with the return of epidemic waves of the disease in America and Europe in 1927, an inclination toward renewed study has become apparent. The return of the severer out-breaks, although localized in 1927 in Roumania, Germany, and in Massachusetts and California, has created anew a feeling of anxiety as to whether a more general and serious prevalence may be
impending. This is clearly the feeling in certain localities in the United States, in consequence of which work has been resumed especially at the Rockefeller Institute on Immunity and Specific Therapy, the results of which follow in this paper.

No other experimental animal has shown itself susceptible to inoculation with the virus, or has developed specific anti-bodies on repeated injection of virus-containing nervous tissues but the monkey.

The method of use in favor is the combined intrameningeal and intravenous injection of human convalescent serum. No decision as to the best methods in humans has been reached.

Rosenow's and Nuzum's antiserum prepared by injecting streptococci will no neutralize the virus of poliomyelitis in monkeys.

Flexner and Amoss showed that large intra-venous doses of the virus are ineffective in monkeys when the meningeal choroid plexus apparatus is intact. They also showed that as long as this intactness continues, immune serum does not pass from the blood into the cerebro-spinal fluid.

Now in cases of poliomyelitis in man, even in the mild, recognizable cases, the meningeal choroid plexus is not intact, a fact shown by the increase in the cellular or
protein content or both of this fluid. When an intra-cerebral inoculation of the virus is made in monkeys, not only is a lesion produced in the brain at the site of the injection, but the virus-carrying salt solution floods the meninges and itself produces mild chemical effects which alter the intactness.

On the basis of the tests which have been made briefly outlined, it is proposed that human convalescent serum should be employed at times of stress and anxiety, when poliomyelitis is epidemic, for producing passive immunization. The doses of convalescent serum which is suggested are 10 cc. for children and 20 cc. for adults, injected subcutaneously and repeated after a period of four to six weeks, if the danger still continues.

If 15 cc. of convalescent serum is injected into the blood of a monkey twenty four hours before a suitable dose of filtered virus is injected intra-cerebrally, infection does not take place.

The fact has been recognized that the disease is one of low incidence and therefore the efficacy of the protective injections will not easily be determined. It is believed that they may be used to diminish anxiety on the part of others, but are not of course to take the place of the usual precautions exercised to avoid exposure to the disease.
In the passive immunization tests in monkeys, several days - called the incubation period of the disease - elapse between the incubation and the appearance of the first symptoms. This period permits the immune anti-bodies to become well distributed throughout the nervous system. In pre-paralytic or early paralytic poliomyelitis in man, the first effects of the virus have taken place, and the next events may follow very quickly. There is, therefore, not the same period of days or even hours provided for the immune bodies in the blood, to reach inconcentration all parts of the nervous system. This being the case it would seem advisable, theoretically at least, that one intra-spinal injection of the convalescent serum should be given at the earliest practical moment. This will insure flooding of the nervous tissues with anti-bodies through intermediation of the cerebro-spinal fluid, after which the maintenance of the anti-body contact may be left to the increased permeability of the meningeal choroid plexus barrier to the contents of the circulating blood.

Mode of Entry.

Present opinion is that the virus enters and leaves the body by way of the upper respiratory mucous membrane, and especially in the secretions of the noso-pharynx. The virus has been detected in the secretions and the substance of this membrane, both in man and monkey. Moreover, the monkey, a relatively resistant species, can be infected by merely instilling a virus of sufficient potency into the
The precise path which the virus takes to gain access to the brain and spinal cord from the nasal membrane can be deduced with tolerable certainty. The virus appears not to pass first to the blood, through which it is carried to the nervous system. Much larger quantities of virus injected directly into the blood do not suffice to infect monkeys. On the other hand, there are cogent reasons for believing that the virus ascends along the olfactory nerve filaments which unite the mucous membrane of the nose to the olfactory lobe of the brain. Probably the descent is also by way of these filaments, in the reverse direction. Since there are reasons for believing that the virus reaches not only the brain but also the cerebro-spinal fluid in the ascent, it is likely that the movement upward and downward takes place in the lymph channels of the nerves, rather than in the axis cylinders themselves. Once the brain is reached in this movement, the spread of virus may spread by contiguity of nervous tissues; but as the early clinical manifestations are oftener paralysis of the extremities than of the bulb, it is inferred that the cerebro-spinal fluid receives the virus early.

However this may be, and whether the virus ascending along the olfactory nerves, works its way along the brain to the more vulnerable spinal cord, or is carried there by
the cerebro-spinal fluid, it is quite certain that before it can strike injuriously it must overcome certain obstacles to its penetration. One of these obstacles, discovered by Amoss and Taylor, resides in the nasal membrane itself; the other, determined by Amoss and Flexnor, is bound up with the anatomical integrity of the choroid plexus and meninges. If one of the obstructive mechanisms fails, the other may still operate effectively; but if both fail, the result is probably infection and paralysis. Between these two there appear to be partial failures of the protective mechanisms, which may be taken to account for that wide, if not yet accurately defined, set of clinical manifestations yielding immunity from subclinical and the several clinically abortive forms of poliomyelitis now described.

Since poliomyelitis is an infectious virus disease, from which recovery in whole or in part commonly occurs, it is not surprising to discover, in view of the general knowledge of the class of virus disease, that recovery results from specific immunization in which a rapid production of immune bodies takes place. These immune bodies have been detected in the blood as early as the sixth day of acute illness; and after recovery from the paralytic disease they have been found to persist in the blood in some degree of concentration as long as twenty years. Moreover, they are detectable in the blood of persons with mild and abortive attacks of poliomyelitis and even in so-called normal persons who have
been suspected of sub-clinical immunization. This last class corresponds of course to other recognized forms of sub-clinical infection, e.g. diphtheria, leading not to actual illness, but to active immunity.

With this knowledge of the clinical pathology of epidemic poliomyelitis before us, we may inquire whether the employment already made immune bodies is capable of influencing and moderating the experimental or the natural form of the disease. It is apparent that the first step is to determine the effect of the immune bodies as represented by convalescent serum on monkeys. Thus far it has not been found possible to produce immune serum in any animal other than the monkey. Since the virus of poliomyelitis is distince from streptococci it seems futile to employ an anti-streptococcic serum for specific therapeutic purposes.

The process as employed by Flexnor, Amoss, and Lewis to determine the specific protective powers assessed by the convalescent serum was, first, to mix virus and serum outside the body and inject the mixture into the brain of monkeys. This mode of inoculation is the severest test of infectivity which can be employed. When suitable combinations of serum and virus are used, no paralysis results. When insufficiently neutralized virus is used the usual incubation period of the experimental disease is prolonged, but ultimately paralysis develops. The next procedure is a far more severe test of
the potency of the convalescent serum. The virus is injected into the brain of the monkey, followed by serum injected by lumbar puncture into the cerebrospinal fluid. When the virus is introduced into the brain, it is deposited into injured brain tissue, under conditions favourable for its production and multiplication. A part always passes to the cerebrospinal fluid and is carried everywhere in the cerebrospinal axis, including of course the vulnerable spinal cord. In this experiment it was hoped that the serum placed in the cerebrospinal fluid would penetrate the nervous tissues, meet and destroy or neutralize the virus. This result has been actually achieved.

By means of these experimental observations was found a basis for specific serum therapy of poliomyelitis in man. It has now become the rule to inject the serum before obvious paralysis occurs. This pre-paralytic stage of poliomyelitis can be detecte by means of accurate laboratory methods.

It has been learned that the virus of poliomyelitis passes from the nasal mucosa to the nervous system. It is well known that complex chemicals, including protein, do not pass from the blood to the cerebrospinal fluid as long as the meninges and choroid plexus are anatomically intact. These structures constitute a real barrier between the blood and the substance of the brain and cord. But the barrier is very sensitively adjusted, and can quite readily be impaired by artificial means. The injection of so innocent a fluid as
Ringer's Solution, and the even more innocent fluid from another monkey of the same species, into the sub-arachnoid space, suffices to open the barrier. When the serum is injected by lumbar puncture, a marked aseptic meningitis is produced and the gates are thrown wide open to the constituents of the blood.

The effects of this impairment can be shown by placing on the nasal mucosa a virus in itself incapable of producing poliomyelitis, or injecting into the blood a quantity of virus impotent in the normal monkey. In both instances, infection and paralysis may follow.

However, this anatomical and physiological impairment of the meninges and choroid plexus may be rendered ineffective if convalescent serum is introduced into the spinal fluid. By this means the action of the virus in the nares and the blood may be effectively blocked.

Now, in all cases of symptomatic poliomyelitis now matter how mild, changes are probably to be found in the cerebro-spinal fluid. These changes are signs of inflammation, and inflammation indicates a broken barrier. Under these circumstances convalescent serum injected into the blood may pass into the cerebro-spinal fluid and act to prevent and stop an impending virus infection.

Convalescent serum introduced into the blood of monkeys will prevent an intracerebral injection of poliomyelitis virus from producing paralysis. It is hardly necessary to
point out the significant application of this observation. If in time of danger of epidemic poliomyelitis, adequate supplies of human convalescent serum were available, they could doubtless be employed for purposes of passive immunization.

The specific treatment is carried out by injecting the serum into the subarachnoid space and into the blood. A question arising at this time is; do the effects of the serum so injected pass off quickly or are they endured for a time. It has been found that when 2 cc. of convalescent serum are injected by lumbar puncture, monkeys are protected against the intra-cerabral inoculation of the virus for at least four days. The opinion is therefore, that while the first spinal injection is essential, the second may not be so, and that the continued presence of immune serum in the nervous tissue may be sufficiently provided for by the convalescent serum which has been injected into the blood.

Therapy with Human Serum.

Serum from persons who have recovered from an attack of poliomyelitis possesses some power to neutralize the virus in vitro. Serum from persons who have been in contact with cases of frank poliomyelitis possesses this power in equal or greater degree than serum from those who have actually been ill. Serum from normal adults never in contact with known cases of the disease seems to possess neutralizing power at least equal to that of persons known to have been
in contact with the disease. Moreover, normal adult serum appears to be more potent in its action against the virus in these in vitro tests than is the serum of convalescents. Serum from normal infants between six months and two years of age seems almost devoid of neutralizing powers.

These results may be thus interpreted: The normal infant of a few months of age has no immunity against poliomyelitis, but immunity to poliomyelitis gradually develops with age so that most adults are immune. Some persons are attacked by the disease before sufficient immunity has developed to afford protection. The immunity following the attack does not appear to be so great, judging by the neutralization test, as the immunity acquired by the "normal" person; this is true also of diphtheria. While such an hypothesis seems adequate to explain the known facts, it remains to be proved that there is a direct relation between immunity to poliomyelitis and the possession of serum with virus neutralizing properties. Aycock's work, as well as that of Rhoades and Stewart has proved that serum from artificially immunized monkeys possesses neutralizing properties. The recent work of Aycock and Kramer with serums from the Virgin Islands indicates that the virus is distributed as widely in areas where the disease is not known to be endemic as in the United States. This suggests that the factor, which determines whether the first reaction to the virus is to be immunity or infection is bound up in peculiarities of the individual
attacked. Perhaps the same variations within the individual as those which govern the seasonal incidence of the disease.

These results may prove of practical importance in that they suggest that the serum of normal adults, properly tested beforehand for neutralizing potency, may be used therapeutically with as much promise of relief as when convalescent serum is used. Extensive laboratory and clinical investigations must, of course, be made before it is certain that a serum that neutralizes in vitro will also be effective against the virus in vivo. Such a correlation seems to have been established for convalescent serum. That this same correlation may exist for normal serum from man is indicated by the results of Lingher, who got about the same results from either serum.
Serum Treatment in Poliomyelitis.

Experimentally, the neutralizing or protecting power of human immune serum has been conclusively proved. In 1910 Levaditi and Landsteiner, Flexner and Lewis, and others demonstrated that 1cc. of human or monkey convalescent serum rubbed up with 0.3cc. of cord suspension, a fatal dose of virus, would neutralize that virus in vitro, in that this combined intra-dural implantation in monkeys was not followed by the otherwise usual development of the disease. Also twenty four hours after the intra-dural injection of a fatal dose of virus, 10cc. of convalescent serum given intra-spinally likewise protected the monkey from paralysis. Injections of serum given later than twenty four hours were not so successful in aborting the process. These results were at once utilized as a basis for serum therapy in man.

The method is as follows:

Blood is collected from individuals who have recovered from the disease preferable within a four year period. However, donors with paralysis of 20 years standing were also used, with no apparent difference in results. The serum is carefully separated and inactivated; to it may be added as a preservative 0.2% tri-cresol. In Syracuse, this serum was obtained by paying for it. About 250ccs. of blood is usually taken from adults and about 1000ccs. of clear serum is obtained.
Administration of the serum is most usually intra-spinally but may be given by other routes. In brief, the dosage and mode of administration for the intra-spinal method is as follows: The patient is placed on his side with his knees drawn up. The back is prepared with Iodine and a lumbar puncture is done. The spinal fluid is examined at the bedside with a small portable microscope thus confirming the diagnosis. As much fluid as can be obtained is withdrawn. Withdrawal of fluid may be continued until definite nuchal pain is complained of. If more than 20ccs. of spinal fluid is obtained, 20ccs. of warm serum is introduced by means of a syringe through the lumbar puncture needle. Care should be used not to put the serum in under pressure. The amounts of serum given vary from 10 to 25ccs. according to the size and age of the individual. It is now believed that one mistake of the earlier cases was too small dosage; 10 cc. in an infant is not too large, and 25 cc. should be given to an adult. Successful results have also been obtained by giving the serum intravenously or intramuscularly. The dosage of the serum given by these methods is the same as by the intra-spinal method.

Reactions to the serum treatment are frequent but are seldom alarming. The most common reaction is an increase in the meningeal signs, increased stiffness in the neck and back and the presence of a Kernig sign. This is accompanied with an increased cell count of the spinal fluid, which
may become turbid. The cellular response does not necessarily parallel the clinical signs. The amount of fluid may be increased, or decreased at the second puncture.

The next most common reaction is a chill with a sharp rise in temperature, which may reach 105 °F and is frequently accompanied by vomiting. This comes on in twenty or thirty minutes and is like that during certain transfusions. Whether or not blood typing would reduce the frequency of this reaction is not known.

Another reaction is abdominal pain and pain referred to the legs after the spinal injection. This is occasionally very severe. However, it is usually of short duration.

Delayed reactions such as urticaria and arthritis are rare if ever present with the human serum injection.

Untoward reactions are rare and those seen consisted of marked increase of meningeal signs and coma lasting for 24 or 48 hours.

The decision for a repeated administration of serum is often a delicate one and much depends upon the accuracy of observation. In general it is considered good therapy to give a second injection if the temperature observations at the eighteenth to the twentieth hour shows a fever of 101 °F or more. The spinal fluid is usually cloudy from the first serum and is no true index of activity. However, some observers advise the serum administration only as the cell
counts are two hundred or over. The determination by temperature is considered the safest determination. This decision should mainly rest with the consultant, who should again see the patient at this period. There is rarely the opportunity of a third dose as the patient is either paralyzed or recovered after a second. Again, the attending physician must watch his case. Temporization with "waiting till tomorrow" is often disastrous.

In 1916 thirty six early cases were treated with intraspinal serum; nineteen cases cleared without paralysis. Sometimes, due to lack of immediately available human convalescent serum, normal human, pneumococcic, and normal horse serum were given, and given mainly on an empirical basis, but surprizingly, often with equally favourable results. These non-specific results and the then reported high incidence of the abortive case made analysis difficult and observers at this time were somewhat guarded in their opinion, feeling that such recoveries might be coincidental, but since that time and mainly by experience here presented, they are now convinced as to the value of serum treatment and earnestly advise it as the proper procedure in the early period of this disease.

Of a series of twenty three cases given anti-pneumococcic serum alone and eight which were given an initial dose of
of pneumococcic serum and a subsequent dose of human convalescent serum. As far as can be determined from such a small number, there is no great difference in results as compared to the human immune serum. This fact is very disturbing, since it is non-specific therapy. Little explanation has been offered, except that the apparently beneficial results may be partially due to the phagocytic action of the additional aseptic meningitis produced by this introduction of a foreign serum.

However, it is strongly urged that the human convalescent serum on the experimental evidence be used. It should also be remembered that the introduction of pneumococcus serum or other non-specific horse serum is often attended later by severe reactions with urticaria, joint inflammation and acute kidney irritation. Many severe reactions have been noted in cases previously sensitized to diptheria toxin anti-toxin. Such serum sickness does not occur with human immune serum. For the greater part it has only been used when human immune serum was not available. Flexner and Amoss showed in the experimental animal, that the intra-spinal introduction of horse serum seemed to increase the susceptibility to the virus.

Serum in the Paralytic Stage.

The intra-spinal administration of serum to the paralized
cases is considered futile, but sometimes decision in the early paralytic stage is a difficult one. It is often demanded by the parents and attending physician. Paralysis well established, cannot be very much affected by serum, but in the very early hours of paralysis with the temperature remaining high, it has been the plan to examine the spinal fluid and if the cell count is above 200, serum is given, this on the premise that if, in the early meningeal stage it is of value, then it might also be still of value in neutralizing the virus still present and possibly active in the surrounding meninges.

In bulbar types puncture and intra-spinal serum are contraindicated. These patients are to be left severely alone and must be kept absolutely quiet. With such quiet they sometimes "slip-by" and the added disturbance by puncture and serum might well reverse the balance.

Intravenous serum is recommended by Amos, Draper and others but is difficult of attainment. It necessitates a large amount of serum which is not always available and, in the opinion of some, such treatment is not necessary.
Conclusions.

2. That convalescent serum must be given in the pre-paralytic stage in order to be of benefit.
3. That human convalescent serum is the best treatment for the prevention of poliomyelitis when the disease is endemic.
4. The initial dosage in infants should be 10cc. and for adults 20cc.
5. That no better method of administration has been found than the intraspinal route.
6. That in the future outbreaks of the disease may be successfully treated with human convalescent serum.
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