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THE EARLY DIAGNOSIS AND TREATMENT OF POLIOMYELITIS WITH POLIOMYELITIS ANTISTREPTOCOCCIC SERUM

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It is my purpose to review very briefly the more important results obtained in studies on the relation of the streptococcus to poliomyelitis, and to show how these studies have culminated in a simple diagnostic skin test[1] and in an effective treatment of poliomyelitis with poliomyelitis antistreptococcic serum.[2-5] The need for an effective antiserum which can be prepared in adequate amounts is very great. Convalescent serum cannot solve the problem because poliomyelitis would have to continue to exist in virulent form with its dire consequences to insure a supply. The streptococcus first isolated in 1916 from the nasopharynx, brain and spinal cord and demonstrated in the lesions[6-11] has since been consistently isolated from the nasopharynx, brain and spinal cord of persons who succumbed to poliomyelitis in each of fourteen epidemics which I have studied, and from the brain and spinal cord (virus) of 511 monkeys

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that succumbed to inoculations with 128 different strains of poliomyelitis virus.

The incidence of isolation of the streptococcus was highest in those cases in which animals died or were anesthetized when in the acute stage of the disease. Thus cultures in dextrose brain broth made in the usual way yielded the streptococcus in 180, or 80 per cent., of 224 instances in which monkeys that subsequently had paralysis, died, or were anesthetized within ten days following inoculation of filtered or emulsified virus. In another series in which the serial dilution method[12] was used, the streptococcus was isolated from the spinal cord of 162, or 89 per cent., of 181 monkeys that had poliomyelitis. About 33 per cent. of numerous filtrates of the virus yielded the streptococcus almost always in pure culture. A close parallelism was found between viability of the streptococcus and the virus on prolonged preservation in 50 per cent. glycerol. By a special staining method[13] small, light diplococci, sometimes in chains of two or three, were found in filtrates of active virus and in filtrates of old cultures of the streptococcus in autoclaved chick mash medium.

The streptococcus was consistently demonstrated by microscopic examination of the sediment of the spinal fluid and by cultures in dextrose brain broth in the early stages of the disease in human beings and monkeys.[3, 14] In monkeys it was proved absent in the spinal fluid before intracerebral or intranasal inoculation of virus and during the period of incubation, but was proved present concomitantly with the onset of symptoms and then disappeared as symptoms

progressed and advanced paralysis or death occurred.

The streptococci isolated from the brain and spinal cord in instances of the spontaneous disease among human beings and in instances of the experimental (virus) disease among monkeys were identical or similar culturally and morphologically, in virulence and in immunologic characteristics. They produced flaccid paralysis in guinea-pigs, rabbits and monkeys.[15] They had, on isolation, identical "neurotropic" distribution curves of cataphoretic velocity.[16] They were agglutinated crosswise by the serum of horses that had been hyperimmunized with these respective strains. During the acute stage of the disease the serums of persons and monkeys were shown to contain streptococcic antigen,[1] and during convalescence they contained specific antibodies alike for the virus and the streptococcus.[17-19] Intradermal injections of suitable suspensions of the heat-killed streptococcus proved to be a test of susceptibility to poliomyelitis.[20] Several subcutaneous vaccinations of reactors (susceptible persons) with heat-killed streptococci caused the reactivity of the skin to disappear (immunity) just as occurred in all cases in which persons were tested during and following attacks of poliomyelitis.

By the use of a medium consisting of infantile tissue in which acid is not produced by the growth of streptococci (autoclaved chick mash), a transmissible filtrable virus has been produced from streptococci.[8] These experiments fulfilled a most important requirement for proof of causal relationship of the streptococcus to polio-

myelitis. The details of the methods used in these etiologic studies, full references to published work and the reasons for certain discrepancies in results and viewpoint will be published shortly.

A DIAGNOSTIC SKIN TEST FOR POLIOMYELITIS

Intradermal injection of approximately 0.05 cc. of a 10 per cent. solution, in physiologic saline solution, of the euglobulin fraction of the antistreptococcic serum prepared from horses was found to elicit an immediate (ten minutes) erythematous-edematous reaction in patients suffering from a disease caused by streptococci immunologically identical or closely related to the streptococci used in preparation of the reacting serum.[21, 22] An erythematous reaction 2 cm. or more in diameter or approximately 3 sq. cm. or more in area to the poliomyelitis antistreptococcus euglobulin, no reaction or a lesser reaction to other artistreptococcic euglobulins and no reaction to normal horse serum diluted 1:10 are considered diagnostic of "poliomyelitic" infection. These together with suggestive symptoms indicate that therapeutic injections of the serum should be given at once. This test is an application to streptococcic diseases of the Foshay antibody-antigen reaction first noted in cases of tularemia.[23] By using the euglobulin or bacterial antibody fraction of the antistreptococcic serum the test serves to determine whether a given patient is suffering from a streptococcic infection and, if so, what particular type and what antiserum or stock vaccine had best be used therapeutically.[21] A summary of the results obtained in cases of acute epidemic poliomyelitis, in

groups of well persons who served as controls, in cases of chronic poliomyelitis, amyotrophic lateral sclerosis, chronic encephalitis, chronic infectious arthritis or ulcerative colitis, with the euglobulin obtained from the serum of horses that had been immunized to streptococci isolated respectively in studies of epidemic poliomyelitis, encephalitis, arthritis, and ulcerative colitis and normal horse serum are summarized in table 1.

The incidence of reactions 3 sq. cm. or more and maximal average reaction to the poliomyelitis euglobulin was highest during the acute stage of epidemic poliomyelitis (92 and 81 per cent., 9.8 and 7.3 sq. cm.), next highest during convalescence (44 per cent. and 4.1 sq. cm.), lower among person who had been exposed to poliomyelitis two to four weeks before (19 per cent.) and among well children within the epidemic zone (27 per cent.), and lowest among adults (12 per cent.) and children (15 per cent.) who were remote from an epidemic of poliomyelitis. These results have been corroborated independently in as yet unpublished observations made during a major epidemic of poliomyelitis which occured in 1937.

The incidence and degree of reaction among persons afflicted with chronic poliomyelitis and amyotrophic lateral sclerosis were also much higher (80 and 63 per cent., 7.9 and 8.2 sq. cm.) following like injection of euglobulin obtained from the other antiserums—encephalitis (32 per cent. and 3 sq. cm.), chronic infectious arthritis (25 per cent. and 2.5 sq. cm.) and ulcerative colitis (21 per cent. and 3.0 sq. cm.). Moreover in each group of persons having en-

TABLE 1

Erythematous reaction following intradermal injection of the euglobulin fraction of the serum of horses that had been hyperimmunized to streptococci

Groups	Persons	Average reaction in sq. cm. to the euglobulin of the serum of horses immunized to streptococci from Epidemic poliomyelitis: Average reaction	Epidemic poliomyelitis: Percentage of instances in which the size of the reaction was 3 sq. cm. or more*	Encephalitis	Arthritis	Ulcerative colitis	Normal horse serum 1:10
Epidemic poliomyelitis—							
Acute (1-9 days)	26	9.8	92	2.8	2.4	3.0	0.4
Convalescent (10-39 days)	39	4.1	44	..	5.9	1.6	0.5
Abortive (1-9 days)	16	7.3	81	..	3.9	..	0.8
Well persons; 2 to 4 weeks after exposure to poliomyelitis	52	1.0	19	..	1.3	1.8	0.5
Adults remote from epidemic poliomyelitis	51	1.3	12	..	5.3	..	0.7
Rural school children—							
Within zone of mild epidemic of poliomyelitis	60	1.6	27	..	..	..	..
Remote from poliomyelitis	53	1.3	15	..	..	..	..
Chronic poliomyelitis	30	7.9	80	2.2	2.5	3.6	0.3
Amyotrophic lateral sclerosis	19	8.2	63	3.9	1.4	..	0.2
Chronic encephalitis	92	3.0	32	6.0	3.0	3.0	0
Chronic infectious arthritis	43	2.5	25	2.5	7.9	2.9	0.9
Ulcerative colitis	13	3.0	21	5.0	5.0	10.0	1.0

*Percentages are given to the nearest whole number.

cephalitis, chronic arthritis or ulcerative colitis maximal reaction occurred with the euglobulin obtained from the respective homologous antiserums. In other words, each of these antiserums when injected intradermally had diagnostic value. The antiserum with which the results summarized in the table were obtained, was prepared with streptococci isolated in studies of the epidemic in Los Angeles in 1934. The cases of acute poliomyelitis occurred in four widely separated outbreaks. Four different batches of antiserums were used and the results were comparable. However, not all patients tested reacted equally to the different antiserums. Young children with typical attacks usually had the greatest reaction following injection of the antiserum prepared with streptococci obtained from typical acute anterior poliomyelitis (Heine-Medin disease), and older children or young adults with atypical or bulbar symptoms had the greatest reaction following injection of the antiserum prepared with streptococci obtained in cases of atypical poliomyelitis in the Los Angeles epidemic of 1934.

Therapeutic injection, once or twice daily, of the 10 per cent. solution of the euglobulin to which the cutaneous reaction is positive, or a mixture of the euglobulin and pseudo-globulin in like concentration in 5 cc. amounts for children five years or less of age, and of an additional 1 cc. at each injection for each additional year of age up to twenty years for one or two days in the "prepoliomyelitis" stage and for two to four days in the "preparalytic" stage usually caused the results of the skin test to become

negative and resulted in recovery without paralysis. Like injection for four to six days of the reacting euglobulin in cases of paralysis usually caused the results of the skin test to become negative and seemingly had therapeutic value in checking paralysis, especially in the early stages. In mild cases in which the patients had not received the poliomyelitis antistreptococcic serum or had been given one large injection of convalescent serum, the results of the skin test became negative first in from ten to fourteen days, while in severe cases, especially those in which the patients continued to be peevish, to have slight fever, and to have little or no return of muscular function, the results of the skin test often remained positive for two to four weeks.

THE PROTECTION OF MONKEYS AGAINST EXPERIMENTAL POLIOMYELITIS

Many of the monkeys that had atypical attacks of poliomyelitis following injection of the freshly isolated streptococci and that were immunized with the living streptococci became immune to intracerebral inoculation of virus.[3] In a new series of experiments in which great precautions were taken in the isolation and in the preservation of the specificity of the streptococcus from which the vaccine was prepared and in inoculating highly virulent virus intranasally instead of intracerebrally, it was possible to obtain a high degree of protection by methods applicable to human beings.[7] Moreover, by using this method of inoculation in which the usual route of infection in human beings, as now understood, was closely simulated, it was possible

uniformly to neutralize the virus with the poliomyelitis antistreptococcic serum.[3, 7] In our studies we injected the different batches of fresh streptococcic antiserum used in the treatment of this disease into human beings throughout many years, intravenously or intramuscularly into monkeys after intracerebral inoculation of virus, with many failures but with success in a significant number of experiments.[3] Altogether only thirty-six, or 40 per cent. of ninety-one monkeys that received the serum intravenously or intramuscularly before and after onset of symptoms following intracerebral inoculation of highly virulent virus died from poliomyelitis. In contrast, twenty-one, or 78 per cent., of twenty-seven monkeys treated in like manner with normal horse serum died of poliomyelitis.

THE TREATMENT OF POLIOMYELITIS OF HUMAN BEINGS WITH POLIOMYELITIC ANTISTREPTOCOCCIC SERUM

Results of the treatment of epidemic poliomyelitis with the streptococcic antiserum prepared from the horse or its euglobulin fraction, have been reported from time to time. A summary of all cases in which this treatment has been used thus far, in large part according to the condition of the patient at the time of the first injection of serum and in regard to the outcome as regards death and residual paralysis, is given in table 2.

The patients who were treated represented those observed in many different epidemics in widely separated localities, including one epidemic in the tropics. All patients receiving serum, no matter whether dying at the time of

the first injection and regardless of the amount injected, were included. The results when compared with control cases in which serum was not used were consistently favorable in every epidemic studied. The mortality and incidence of residual paralysis, the two most important factors in this disease, were always lower in cases in which the serum was administered, and if the

TABLE 2

Results of treatment of acute poliomyelitis with poliomyelitis antistreptococcic serum

Condition of patient at the time of first injection of serum	Total number of cases	Deaths		Cases in which follow-up data were available		
		Number	Per cent*	Number	Severe residual paralysis Number	Per cent*
No paralysis	387	10	3	351	7	2
Slight paralysis	231	16	7	196	3	2
Moderate paralysis	257	20	8	225	10	4
Severe paralysis	661	118	18	521	124	24
Total number of cases, irrespective of condition of patient at the time serum was first administered	2445	202	8	1566	180	11
Cases in which serum was not administered.	2377	493	21	429	154	36

*Percentages are given to the nearest whole number.

serum was given in the early stages of the disease, they were much lower, often tenfold lower, than they were in the cases in which serum was not administered. Only those cases in which there was no reasonable doubt of the correctness of the diagnosis were included. The favorable results according to the early administration of the serum treatment are well shown in table 2. The earlier the serum treatment was begun, the

more favorable were the results. Thus the mortality (3 per cent.) and incidence of severe residual paralysis (2 per cent.) were lowest in the group of cases in which the serum treatment was begun in the preparalytic stage. They were about the same (7 and 2 per cent. respectively) in the group of cases in which slight paralysis was present, somewhat higher (8 and 4 per cent. respectively) in the group of cases in which there was moderate paralysis, and then rose abruptly to 18 and 24 per cent. respectively in the group of cases in which severe paralysis was present at the time of the first injection of serum. It is a deplorable fact that the group of patients who had severe paralysis at the time of the first serum treatment was proportionately so large (661 of a total of 1436 cases in which the condition at the time of the first serum injection was recorded). At that, the mortality in the 2445 cases in which serum was administered was only 8 per cent. and the incidence of severe residual paralysis was 11 per cent. in the 1566 cases in which this fact was ascertained, in contrast to a mortality of 21 per cent. in 2377 cases in which serum was not employed in the same epidemics, and in contrast to the incidence of severe residual paralysis in 36 per cent. of 429 cases in which follow-up data were obtained in the control group.

This statistical evidence for the curative action of the serum is in accord with the good effects noted at the bedside. Restless nervous children often fell asleep soon after the first injection of serum. Headache, and pain in the involved extremity or part were often lessened or relieved.

The temperature curve usually often dropped rapidly to normal after an initial rise. Progressing paralysis was often seemingly arrested. Restoration of muscle function was also seemingly more rapid than it was in cases in which serum was not administered. Favorable effects were noted in all of the epidemics studied. Results comparable to these have been obtained, in an as yet unpublished work, during a major epidemic of poliomyelitis in 1937 and have been reported in widely separated epidemics by Rowan,[24] Sugg,[25] Clarke and Dow[26], and Moody and Hesselberg.[27]

SUMMARY

Studies made by special methods indicate causal relationship of the streptococcus to epidemic poliomyelitis. Poliomyelitis antistreptococcic serum affords a simple method for the early diagnosis of poliomyelitis. The results from the use of this serum in the treatment of poliomyelitis in a period of twenty-two years have been uniformly encouraging.

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