THE THERAPEUTIC USE OF POLIOMYELITIS IMMUNE GLOBULIN IN THE TREATMENT OF ACUTE POLIOMYELITIS

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INTRODUCTION

The threat of widespread, severe epidemics of infectious diseases has been minimized by modern immunization practices, and fear of many of the acute infectious processes has been so reduced by antibiotic drugs it is somewhat startling to consider what small progress has been made in the specific treatment of the acute phase of viral diseases such as poliomyelitis. The purpose of this paper shall be to review past efforts at treating this disease with specific antiserum or immune globulin, and then report a series of cases which were treated with immune globulin during the 1955 season in Milwaukee, Wisconsin.

EARLY SERUM THERAPY

The first real hope to establish scientifically based specific treatment came with the isolation of the virus by Landsteiner and Popper in 1908. [1] From two human cases of fatal paralytic poliomyelitis, Flexner and Lewis were able to transmit the disease to monkeys and carry it through five successive generations by inoculating infected cord or brain suspensions into the cortex or cord of these animals. [2] Such experiments

were reproduced by these workers and about six months later, they succeeded in demonstrating the virus neutralizing effect of antipoliomyelitis serum. [3] A very potent spinal cord filtrate which invariably produced paralysis within six to eight days was rendered completely inactive by overnight incubation with equal quantities of serum from a recently recovered monkey, a recovered child, and an immunized horse.

In viro studies on the action of antiserum were the next logical avenues of approach and were reported by the same investigators. Daily subdural injection of 3.0 cc of immune serum, beginning eighteen to twenty-four hours after intracerebral injection of a paralytic dose of an infected cord filtrate and continued for seven to ten days, successfully inhibited the usual action of the virus. A specific treatment for acute poliomyelitis seemed at hand. Would not early human infections respond as well?

An unequivocal answer was not easily determined. In 1911, Anderson and Frost demonstrated poliomyelitis antibodies in the serum of patients convalescent from what was apparently abortive poliomyelitis as well as in serum from normal persons having no known history of poliomyelitis. [4] Antiserum was first used in the treatment of human cases by utilization of the intrathecal route of administration.

Sophian [5] reported such therapy beneficial but the number of cases treated was small and the study not adequately controlled. Zingher used 15.0 cc human convalescent intrathecally once every twenty-four hours for three days. [6] He reported a beneficial effect in preparalytic cases, but admitted the possibility of spontaneous, rapid recovery in such cases.

At about this time proponants of a streptoccal etiologic relationship to poliomyelitis, who supposedly had isolated streptococci from brains of patients dying of this disease, reported good clinical response in poliomyelitis patients treated with antistreptococcal horse serum either by the intravenous or intrathecal route. [7] To those convinced of a unitarian, viral etiology this suggested the possibility that what had formerly been interpreted as a specific action of poliomyelitis immune serum was merely a non-specific clinical response not at all dependant upon elimination of the true etiologic factor. In well controlled experiments by Amoss and Eberson [8] in 1918 confidence in the specificity of antipoliomyelitis serum was restored by demonstrating its neutralizing and therapeutic effects in monkeys inoculated with small doses of virus. Under identical conditions, the antistreptococcol serum of Nuzum was worthless.

During the next fifteen years, although many

clinical trials were repeated, they too were rather poorly controlled and the efficacy of convalescent serum was never unequivocally demonstrated. Nevertheless, as Faber observed, [9] human immune serum came to have "a generally recognized specific therapeutic effect in poliomyelitis". Serum therapy was being even more widely used since availability had become greater by ascertaining a high poliomyelitis antibody titer in normal adult serum. [10] The usual method of therapy was a combined assault by intravenous and intrathecal injection of a dosage usually totalling less than 100 cc.

During the early nineteen thirties, in the first fairly well controlled clinical study, Kramer concluded he was unable to show statistical evidence of the therapeutic effectiveness of convalescent serum. [11] His findings were substantiated by equally sound work by Park [12] and Fischer [13] and the use of immune serum fell into disrepute.

Despite such rather definite refutation of serum therapy, renewed interest in the antibody approach to the problem was associated with the experimental demonstration of an invariable serum globulin rise secondary to immunization of rabbits [14] and the consequent hope that antibodies could be concentrated in that form.

GAMMA GLOBULIN

It was in the early nineteen forties that the plasma proteins were characterized in terms of electrophoretic mobility, sedimentation constants molecular weights and their relationship to osmotic pressure, diffusion constants, viscosity, and double refraction flow which reflects molecular shape. [15] In addition, on the basis of virus neutralization tests, the highly concentrated gamma globulin of electrophoretic fraction II was shown by various workers to have an antipoliomyelitis titer at least ten times that of pooled plasma. [16]

Commercial preparation of human immune serum globulin appeared and represented a sixteen percent solution of gamma globulin in which this fraction was concentrated twenty-five times over that of plasma. [17] Unfortunately, a careful clinical analysis of its therapeutic effectiveness in the treatment of preparalytic cases was discouraging.

Bahlke & Perkins [18], using comparable test and control groups injected intramuscularly (considered to be dangerous if given intravenously [19]) doses of gamma globulin ranging from 20 to 100 cc. In a series of one hundred and eleven cases with careful follow-up and detailed muscle evaluation, they concluded that no benefit was detectable. Since then the utility of gamma

globulin in poliomyelitis has been relegated to prophylaxis.

REASONS FOR RE-EVALUATION

Theoretically the use of antiserum or gamma globulin had been considered logical although little was known about the pathogenesis of the disease, the mode of virus distribution within the infected host, or the fate of such therapeutic substances when injected into patients.

Traditionally, the spread of virus had been considered to be axonal and the virus was thought to be transmitted in this way not only from the portal of entry to the central nervous system, but also from one area to another within the central nervous system as was shown experimentally by Bodian and Howe. [20] It should be pointed out, however, that the natural history of the disease in the experimentally inoculated animal may be quite different from that occurring in the naturally acquired human infection. Even though it was shown that the gastro-intestinal tract was the most likely portal of entry for the virus [21], the primary mode of transmission to the central nervous system was still considered to be via peripheral nerves. [22] Since that time, however, it has been definitely shown that the

most frequent method of virus dissemination from the portal of entry is a viremia.[23] It is interesting that as early as 1935 Faber observed that[24] "the protective effect (of antiserum) might conceivably occur even after infection is already present in the body by limiting its extension to areas not yet infected. Broadly speaking, this would appear to be the most effective in virus diseases in which, as in measles, after a period of local infection the virus invades the blood stream and becomes generalized; under these circumstances serum given before invasion of the blood stream could protect to some extent--".

Although this would seem to indicate that antiserum or gamma globulin would be effective in treating the viremia of poliomyelitis and prevent its progression, this is fallacious in practice because, as Horstmann has shown,[25] the viremia has already occurred and frequently no longer exists by the time central nervous system infection is manifest, i. e., by the time the disease can first be diagnosed. However, she has also shown that in some cases central nervous system lesions develop without a demonstrable preceeding viremia. It seems plausible that in such cases the spread may be via peripheral nerves and that even in cases exhibiting a viremia, this other mechanism of spread may be simultaneously occurring. Already in

1933 Faber suggested the early use of antiserum was theoretically sound because of the possibility of interrupting the progress of the disease by blocking viral passage from one neuron to the next. [26]

New horizons for study of such phenomena came into being with the advent of tissue culture methods for the study of the poliomyelitis virus. Very recently the study of the mechanisms of viral dissemination at the cellular level, known as micro-epidemiology, has been undertaken. [27] These workers have shown that in tissue cultures, viral spread from cell to cell may occur by one or both of two methods, (1) the virus may infect new cells after release from the parent (infected) cell by lysis or leakage into the surrounding milieu, or (2) the virus may pass from one cell directly to neighboring cells without existing in a free, extracellular phase. Both methods of spread were thought to be utilized by the herpes - B virus because rapid spread through the culture medium occurred even in the presence of immune serum. Significantly, however, several strains of poliomyelitis virus types I and II were incapable of spreading at an appreciable rate to new cells in the presence of immune serum. This would indicate that the chief mechanism of intercellular spread of poliomyelitis virus requires its passage

through a free, extracellular phase during which one would suspect it would be susceptible to a high antibody titer. However, the significant question is: Does immune globulin injected intramuscularly get to the proposed point of virus susceptibility, the interstitial fluid of the central nervous system?

The blood-central nervous system barrier has received some attention in the past. It was shown that insult to the central nervous system, such as trauma or injection of starch solution, caused increased susceptability to intravenous crude virus cord suspension and it was postulated that such insult may cause increased capillary permeability. [28] This would suggest that under stress such as poliomyelitis infection the antibodies, too, may more easily cross the barrier.

Kempf [29] attempted to measure the penetration of antiserum into the central nervous system. Rabbit hemolysin serum against sheep red cells was injected intravenously into experimentally infected monkeys just after onset of paralysis. At nine to thirty-eight hours the monkeys were sacrificed and the hemolysin titer in C. N. S. tissue extracts, serum, and spinal fluid were determined. The titer in the cerebrospinal fluid was less than six percent of the serum titer. He suggested at that time that there was "little possible value in

the use of antiserum in preventing the spread of poliomyelitis if such occurs other than by the blood stream". Shortly thereafter he reinforced his opinion by carrying out a similar experiment but injecting the antiserum intracisternally rather then intravenously. Six to twelve hours later the titer was high in the blood, much lower in the cerebrospinal fluid, and practically nonexistent in the tissue of the C. N. S.. [30] This all seemed to indicate that antibody could not be forced into or even retained in the C. N.S. side of the blood brain barrier. However, it should be pointed out that he was using a nonspecific antibody and foreign protein. Had homologous serum containing antipoliomyelitis antibodies been used, it is not inconceivable the results would have been different, possibly on the basis of an antigen-antibody fixation mechanism.

Relative to this suggestion, it is interesting to point out that although normally, according to electrophoretic patterns, the spinal fluid gamma globulin is in a ratio to serum gamma globulin in the neighborhood of 1:300. In neurosyphilis an increase in cerebrospinal fluid gamma globulin concentration occurs, but this rise is not reflected in the serum. [31] From this one can assume that either the antibody can be elaborated by the central nervous system or it is drawn from extra-

neural sources.

On the basis of experiments carried out during the past ten years by various investigators, the latter possibility seems most probable. Although unconfirmed to date, White and Daugherty [32] have supposedly demonstrated that lymphocytes contain a high concentration of gamma globulin identical with that of serum. It is their contention that as one of the normal functions of lymphocytes this gamma globulin is released by dissolution of the cells, a process that is accelerated by a stimulus or stress which augments pituitary-adrenal cortical secretion. This is indeed an intriguing hypothesis since we know that in poliomyelitis a lymphocytosis occurs in the cerebrospinal fluid as well as in the areas of brain and cord which contain typical poliomyelitis lesions.

Studies to determine what actually happens to injected gamma globulin have also been carried out. Gamma globulin labeled with radioactive iodine was intravenously injected into humans by Myant. [33] A very rapid reduction in concentration occurred, presumably on the basis of simple dilution, but the reduction was of such magnitude as to indicate that the dilution was in a volume of that greater than plasma. This was followed by a gradual reduction in concentration considered secondary to metabolism of the protein.

The author suggests that "there is a freely exchangeable reservoir of plasma protein in lymph or interstitial fluid which may contain 300 gm. of protein".

This is clarified by Forker, Chaikoff, and Reinhart [34] who injected rats and dogs intravenously with labeled serum proteins derived from dogs. The thoracic duct was cannulated and simultaneous determinations were made of lymph and blood proteins. It was shown that in the dog one-half the total plasma protein traverses the thoracic duct each day. The rapid decrease in concentration of gamma globulin in the blood of humans as mentioned above was reproduced in rats and dogs and these authors also suggested that this was secondary to a reversible equilibrium between plasma protein molecules and similar molecules in an extravascular store. Such a dynamic equilibrium was confirmed by Gitlin and Janeway [35] who demonstrated that the extravascular deficit of gamma globulin in agammaglobulinemia is quickly rectified by intravenous administration of the protein. They have also shown that in rabbits the converse is true, i. e., the extravascular store can move quickly to re-establish a reduced plasma level. [36]

In addition to the above experimental data, another source of renewed interest in immune globulin therapy in acute poliomyelitis has been associated with attempts

to treat other viral diseases in this mammer. In measles treated after the appearance of Koplik's spots but prior to the rash [37], and in mumps treated during the first twenty-four hours of parotitis but prior to any sign of orchitis [38] there seemed to be some benefit. In measles the disease was thought to be quite definitely modified, and in the latter affliction, the incidence of orchitis was significantly reduced. It is probable that in both these infections the gamma globulin was administered prior to the viremia, whereas in poliomyelitis, as was pointed out earlier, it is impossible to treat cases that early because the diagnosis has not yet been made.

Gunderson [39], however, has presented a series in which he has thirty-nine controls and twenty-two cases of herpes zoster ophthalmicus treated with 250-450 cc convalescent blood. He is convinced that among those treated a significantly greater percentage retained useful vision. This is of interest because if such benefit was achieved it would have to be a result of inhibition of progression of the disease process on a local level within the specific tissue involved, of course would correlate with the type of action one would hope to obtain by using gamma globulin in poliomyelitis after the disease process is under way.

With this in mind, and also on the basis of recent experimental work related to the micro-epidemiology of the poliomyelitis virus and the fate of injected gamma globulin, it would seem appropriate to attempt to re-evaluate the effect of gamma globulin in the treatment of acute poliomyelitis.

SELECTION OF CASES

At the South View Isolation Hospital in Milwaukee, Wisconsin five hundred and seventy-two cases of acute poliomyelitis were treated during the 1955 season. Of this number 27.0% had signs of bulbar and/or encephalitic involvement, only 25.5% were nonparalytic, and 7.8% terminated fatally.

The cases included in this study represent all poliomyelitis cases admitted to the hospital between July 19 and August 24, 1955 with the exception of fourteen cases excluded for various reasons: Eleven had received gamma globulin prior to admission, one had been inoculated with the Salk vaccine, and two received gamma globulin later than twenty-four hours after admission. Two hundred and twenty-six remained; ninety-six were treated with gamma globulin and the other one hundred and thirty were used as controls.

Unfortunately test cases and control cases were not alternate admissions. Test cases were chosen

arbitrarily by the writer, but at times choice of cases was probably somewhat accidental, depending ~~as~~ at various times on admission load, adequacy of professional help in terms of numbers, or availability of gamma globulin. In any event, in all cases it was attempted to make the decision of whether or not to include a case in the test group independent of the condition of the patient or the presenting signs or symptoms.

MATERIAL AND METHODS

Within twenty-four hours of hospital admission test cases were treated by intramuscular injection of "Poliomyelitis Immune Globulin (Human)" having a poliomyelitis virus neutralizing capacity equal to or greater than an immune globulin standard prepared and provided by the National Institutes of Health.[40] Potency of the globulin had been determined by its ability to neutralize virus suspension having a titer of P. D. (paralytic dose)50. If the globulin being tested had an antibody titer equal to or greater than that of the standard, the virus was rendered avirulent, and when injected intracerebrally into four to five week old mice caused no disease.

Dosage of such immune globulin was calculated on the basis of 0.3 cc per pound body weight with mini-

mum and maximum dosage limits of 5.0 cc and 40.0 cc respectively. The total amount was simultaneously injected, usually into two areas of the gluteal muscles.

COMPARABILITY OF TEST AND CONTROL GROUPS

The comparability of the two groups was established on the basis of criteria such as residence of the patient, time of onset of symptoms, and spinal fluid findings. Patients cared for at our hospital were residents of either the city of Milwaukee or of one of the surrounding suburbs or communities. This resident-nonresident ratio for each group is shown in table 1. Although in

TABLE 1. CRITERIA OF COMPARABILITY: RESIDENCE AND SEX

	Test Group		Control group	
	number	percent	number	percent
Residents	51	52.0	84	64.5
Nonresidents	45	48.0	46	35.5
Total	96	100.00	130	100.0
Male	51	52.0	77	59.0
Female	45	48.0	53	41.0
Total	96	100.0	130	100.0

the control group there was a definite preponderance of residents, among the test cases this difference was very much less marked. The only possible significance of this is that, during the summer, it became our opinion that

cases presenting at our hospital but coming from certain suburbs, particularly West Allis, were in general more frequently severely ill than those from Milwaukee proper. There is no statistical evidence to support this impression.

In both groups table 1 also demonstrates the usual, slightly greater percentage of male patients. This compares favorably with the male rate of 55% of all poliomyelitis cases during the entire 1955 season at South View Hospital.

As shown by table 2, the age distribution was similar for the two groups except for a rather definite increased frequency in the 15-19 and 20-29 age groups of the control series. This cannot be explained, but, in spite of the known greater severity of the disease in young adults, on the basis of the relatively small numbers involved, this was probably not significant.

TABLE 2. CRITERIA OF COMPARABILITY: AGE DISTRIBUTION

	Test Group		Control Group	
Age in years	number	percent	number	percent
less than 5	32	33.4	35	27.0
5-9	30	31.1	35	27.0
10-14	16	16.8	19	14.6
15-19	3	3.1	9	6.9
20-29	10	10.4	24	18.4
30-39	5	5.2	6	4.6
40 or more	0	0.0	2	1.5
Total	96	100.0	130	100.0

Of great importance in a study such as this was the time of onset of symptoms in relation to the time of admission, since this directly reflected the time of administration of the gamma globulin in terms of the progress that the disease had already made. The number

TABLE 3. CRITERIA OF COMPARABILITY: TIME OF ONSET

	Test Group		Control Group	
Onset of Symptoms; Days Prior to admission	number	percent	number	percent
0-1	34	35.4	43	33.0
2-3	26	27.2	38	29.3
4-5	19	19.8	16	12.3
6-7	6	6.3	19	14.6
8 or more	11	11.3	14	10.8
Total	96	100.0	130	100.0

of days elapsing after onset of symptoms and prior to hospital admission was partially responsible for variation in presenting symptoms and signs, variation in condition of the patient on admission, and probable treatability of the disease in terms of whether immune globulin would be administered during or after the viremia or at a time of minimal or widespread C N S seeding of virus.

In many cases it was naturally difficult to determine the exact time of onset of symptoms both because of poor observation or memory on the part of the patient and because of difficulty in differentiating between a so-called prodromal symptomatology and other febrile episodes of children particularly. This problem was of course encountered equally in both groups and no significance seemed inherent in such error insofar as establishment of comparable groups. In respect to the time of onset, as judged by the examiner and listed in table 3, there was good correlation between the two groups.

Symptomatology in most cases was fairly typical throughout the epidemic. Table 4 illustrates the frequency of the most common complaints and the similarity of the groups is obvious.

TABLE 4. CRITERIA OF COMPARABILITY: SYMPTOMS

	Test Group (96 cases)		Control Group (130 cases)	
Symptoms	number	Percent	number	Percent
Fever (subjective)	56	58.4	74	47.0
Muscle Weakness (inc. bulbar symptoms	46	48.0	57	43.9
Neck Pain	29	30.2	57	43.9
Headache	33	34.4	43	33.0
Vomiting	35	36.5	35	27.0
Nausea and/or Anorexia	32	33.3	31	23.8
Muscle pain (extremities)	23	24.0	26	20.0
Back pain	10	10.4	35	27.0
Sore Throat	19	19.8	21	16.1
Abdominal Pain and/or Diarrhea	10	10.4	22	16.9

Less frequent symptoms were lethargy, irritability, malaise, urinary symptoms, paresthesias, tremor or twitch, chilliness, other symptoms suggestive of an upper respiratory infection, dizziness, epistaxis, and in one case convulsions. Although many patients or their parents were aware of fever, it was rarely as distressing as other symptoms experienced simultaneously. The temperature

TABLE 5. CRITERIA OF COMPARABILITY: TEMPERATURE ON ADMISSION

	Test Group		Control Group	
Temp. (Degrees F.)	Number	Percent	Number	Percent
Less than 100	18	18.8	25	19.2
100-102	48	50.0	61	46.9
102-104	26	27.0	40	30.8
104 or more	4	4.2	4	3.1
Total	96	100.0	130	100.0

level on admission is shown in table 5.

During physical examination one or more signs of meningeal irritation, such as the Brudzinski or the Kernig signs, were present in over 90% of patients in both the test and control groups. Detailed muscle evaluation was not performed upon admission, but by gross clinical methods, the presence or absense of weakness was re-

TABLE 6. CRITERIA OF COMPARABILITY: MUSCLE WEAKNESS ON ADMISSION

	Test Group		Control Group	
Muscle Weakness	Number	percent	number	Percent
Absent	36	37.6	64	49.2
Present	60	62.4	66	50.8
Total	96	100.0	130	100.0

corded as well as an impression as to the degree and distribution of weakness if present. As table 6 indicates, the frequency of muscle weakness among those in the test group was 62.4% while 50.8% of control cases demonstrated weakness at that time. This initial variation seems great enough that it should be kept in mind when analyzing the end condition of these patients.

Cerebrospinal fluid obtained by lumbar puncture was used in most cases to verify the clinical diagnosis of poliomyelitis. A few cases without spinal fluid evaluation resulted because of either contamination of the fluid by traumatic tap, objection on the part of the patient or parent, or in one case, because the patient was in a state of severe respiratory distress at the time of admission. Despite failure to examine the spinal fluid, these cases were included because it was felt the clinical picture was definite enough to make a positive diagnosis of poliomyelitis. The range of spinal fluid findings is shown in table 7. The dif-

TABLE 7. CRITERIA OF COMPARABILITY: CEREBROSPINAL FLUID

	Test Group		Control Group	
WBC/mm^3	Number	Percent	Number	Percent
less than 10	2	2.1	3	2.3
10-50	15	15.6	27	20.8
50-100	26	27.0	28	21.5
100-300	31	32.3	46	35.4
more than 300	19	19.8	18	13.8
no fluid exam.	3	3.2	8	6.2
Total	96	100.0	130	100.0

ferential cell count is not included because the preponderance of polymorphonuclear or mononuclear cells was extremely variable among cases of both groups. This is in accord with the variability in the degree of progression of the disease before the patient was hospitalized.

Protein studies, likewise, were done but are not tabulated. Some were reported in Pandy units of trace, one plus, two plus, or three plus, whereas the greater number were reported in milligrams percent. The Pandy was usually a trace, one plus, or occasionally two plus. By the other method the range was 20-145 mg.% except for one finding of 216 mg. %. Most frequently the protein level was 45-90 mg. % and no variation between test and control groups was noted.

RESULTS

In order to determine the possible effectiveness of immune globulin in interrupting the progression of the disease, the cases were evaluated on the basis of duration of fever, the degree of muscle weakness that eventually developed, and the estimated progression that this degree of weakness represented in respect to the condition of the patient at the time of admission.

TABLE 8. PROGRESS OF THE DISEASE: DURATION OF FEVER

Days Duration of Fever	Test Group Number	Test Group Percent	Control Group Number	Control Group Percent
0 (no fever)	12	12.5	19	14.6
1	10	10.3	21	16.2
2	23	24.0	28	21.5
3	23	24.0	22	16.9
4	12	12.5	27	20.8
more than 4	16	16.7	13	10.0
Total	96	100.0	130	100.0

When the temperature returned to below 100° F. and stayed there, the patient was considered afebrile. Since the hospital during this period was extremely hot and humid, and many temperatures were measured rectally, and reading up to 100° F. was not considered abnormal. As illustrated in table 8, the duration of the fever in the test and control groups corresponded extremely well. After the third hospital day 70.8% of test cases and 69.2% of control cases were afebrile.

The final diagnosis, on the basis of clinical judgment alone and without the aid of detailed muscle evaluation by the physical therapist, was thought to be of some value in representing the progression of the disease from the time of the first evaluation. According to this

TABLE 9. PROGRESS OF THE DISEASE; FINAL CLINICAL DIAGNOSIS

	Test Group		Control Group	
Type of Disease	Number	Percent	Number	Percent
Nonparalytic	14	14.6	41	31.5
Paralytic	82	85.4	89	68.5
Total	96	100.0	130	100.0
Spinal	51	62.1	52	58.4
Spinal-Bulbar and/ or Encephalitic	31	37.9	37	41.6
Total	82	100.0	89	100.0

judgment, the paralytic rate was considerably higher among the test cases, 85.4% as compared to 68.5% for the controls. No significant difference existed in the frequency of cases having bulbar and/or encephalitic involvement in comparing the two groups.

TABLE 10. PROGRESS OF THE DISEASE; MUSCLE EVALUATION

	Test Group		Control Group	
Post-Acute degree of Paralysis	Number	Percent	Number	Percent
0	21	21.8	43	33.1
/	28	29.3	20	15.4
//	21	21.8	38	29.2
///	14	14.6	20	15.4
D	12	12.5	9	6.9
Total	96	100.0	130	100.0

In table 10, no paralysis is indicated by a zero. A one plus means slight weakness in one extremity or some other area, two plus represents severe weakness in one extremity or moderate weakness in more than one extremity, three plus indicates paralysis of greater or more widespread severity, and D indicates those who died of the disease. These categories are on the basis of the report of the physical therapist who examined

each patient after the acute phase which was usually between the sixth and tenth hospital day. It should be pointed out that the therapists study and the evaluation of his muscle charting were done without awareness of which were the treated cases.

In addition each chart was reviewed and a comparison was made between the examiners note, made when the patient was originally admitted to the hospital, and the muscle chart prepared by the physical therapist at the time mentioned above. Again this was done without differentiating between the treated and untreated cases. This estimate of progression, therefore, represents not the end result per se, but rather, the end result relative to the condition of the patient when treatment with immune globulin was instituted. Using such a method, if a patient was admitted without weakness, but eventually, developed severe paralysis or

TABLE 11. PROGRESS OF THE DISEASE; ESTIMATED PROGRESSION

	Test Group		Control Group	
Degree of Progression	Number	Percent	Number	Percent
0	53	55.2	83	63.9
/	9	9.4	17	13.1
//	10	10.4	9	6.9
///	2	2.1	8	6.1
Q	22	22.9	13	10.0
Total	96	100.0	130	100.0

terminated in death, the progression was considered

severe (+++); but if a patient died after entering the hospital in very poor condition, it was considered to represent moderate or possibly only mild progression (+ or ++). The categories used in table 11 were: no progression (0), questionable progression (Q), definite but mild progression (+), definite progression of moderate degree (++), and definite, severe progression (+++). Using these criteria there was definite progression in 21.9% of test cases and 26.1% of control cases.

INTERPRETATION OF RESULTS AND DISCUSSION

Unfortunately, the test group inadvertently contained a lower percentage of residents and a higher percentage of cases presenting to the hospital with weakness already present. Since the groups corresponded very closely so far as the time of onset, this higher paralytic rate among the test cases at the time of admission would seem to indicate that this happened to be a group with somewhat more severe disease. No other data in the criteria of comparability corroborates such a difference however.

It is interesting to note that of thirty-six test cases having no weakness on admission (table 6), fourteen, or 39.0%, remained nonparalytic, whereas on the other hand, of the sixty-four controls entering without weakness, forty-one, or 64.0%, remained nonparalytic.

These figures are on the basis of the final clinical diagnosis (table 9), but there is some discrepancy between the paralytic rates tabulated there and those based on the physical therapists evaluation (table 10). The former interpretations were made during the acute phase on about the third hospital day and because of the difficulty in determining muscle weakness during the acute phase, especially among children who are ill, uncooperative, and may have muscle pain or spasm, it was felt that the number of nonparalytic cases as determined by the therapist was a more accurate estimation. Using the data from tables 6 and 10 then, the discrepancy between the test and control groups is somewhat readjusted insofar as the rate of conversion of initially nonparalytic cases to paralytic cases is concerned. With these figures, 58.4% of the test cases admitted without weakness remained free of paralysis, and 68.2% of the nonparalytic control cases remained nonparalytic.

To state this in the opposite way, of those test cases admitted in a nonparalytic state, 41.6% developed paralysis while in the hospital, whereas among the controls, 31.8% converted from nonparalytic to paralytic. This would tend to indicate that gamma globulin failed to prevent progression, or more accurately, that gamma

globulin may have had a deleterious effect. To support such a hypothesis one may point out that the test group death rate was 12.5% as compared to 6.9% among the controls and an overall rate of 7.8% for the entire season.

It is important to point out, however, that of the twelve fatalities among test cases, eleven already showed paralysis when admitted; but of the nine fatalities among controls, four had come to the hospital free of any weakness. In terms of the nonparalytics this means that out of thirty-six test cases admitted as nonparalytics only one went on to die; of the sixty-four controls admitted as nonparalytics, four went on to die. Such argument suggests the beneficial effect of the gamma globulin. This theory could also be supported by pointing out again that in evaluating all cases, 21.9% of test cases showed definite progression as compared with 26.1% of control cases who showed definite progression.

The small differences between the two groups, in terms of death rates and degrees of progression, have been shown to be contradictory. It must be concluded that immune globulin therapy has not been shown to be beneficial, but at the same time, neither has it been shown to be deleterious.

By this time the difficulties of interpretation

have become obvious. They are the same today as they have been during the last fifty years when similar studies were attempted. Some of the most important of these are variability in the progression and severity of the disease from one epidemic to another and from one individual to the next, variability in the stage of the disease when the patient is first seen, and difficulty in determining the exact extent of muscle weakness, particularly when the disease is still in the acute phase.

SUMMARY

The therapeutic use of poliomyelitis immune serum and globulin has been briefly reviewed. More recent work concerning the microepidemiology of this disease and the fate of injected globulin have been discussed and suggested re-evaluation of immune globulin therapy. A controlled study on the therapeutic utility of poliomyelitis immune globulin in the acute phase of the disease has been reported. The results were inconclusive and did not indicate that such therapy rendered any definite or predictable benefit. Attention was called to the difficulties encountered in evaluating such a study.

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FOOTNOTES

1. Landsteiner, K. and Popper, E.
2. Flexner, S. and Lewis, P. A. (a)
3. Flexner, S. and Lewis, P. A. (b)
4. Anderson, J. F. and Frost, W. H.
5. Sophian, A.
6. Zingher, A.
7. a) Rosenow, E. C.; b) Nuzum, J. W.
8. Amoss, H. L. and Eberson, F.
9. Faber, H. K. (a)
10. a) Aycock, W. L. and Kramer, S. D. (a); b) Aycock, W. L. and Kramer, S. D. (b); c) Brodie, and d) Kramer, S. D.
11. Kramer, S. D., Aycock, W. L., and Soloman, C. I.
12. Park, W. H.
13. Fischer, A. E.
14. Boyd, W. and Bernard, H.
15. Cohn, E. J. and others
16. Enders, J. F.
17. Conference on Therapy
18. Bahlke, A. M. and Perkins, J. E.
19. Council on Pharmacy and Chemistry
20. Bodian, D. and Howe, H. A.
21. a) Sabin, A. B.; b) Sabin, A. B. and Ward, R.
22. Toomey, J. A.
23. Horstmann, D. M.
24. Faber, H. K. (b)
25. Horstmann, D. M.
26. Faber, H. K. (b)
27. Black, J. L. and Melnick, J. L.
28. Lennette, E. H. and Hudson, N. P.
29. Kempf, J. E., Nungester, W. J., and Soule, M. H.
30. Kempf, J. E., and Soule, M. H.
31. Kabat, E. A., Moore, D. H., and Landow, H.
32. White, A. and Daughtery, T. F.
33. Myant, N. B.
34. Forker, L. L., Chaikoff, I. L., and Reinhart, W. O.
35. Gitlin, D. and Janeway, C. A. (a)
36. Gitlin, D. and Janeway, C. A. (b)
37. Stokes, J., Maris, E. P., and Gellis, S. S.
38. Gellis, S. S., Mc Guiness, A. C., and Peters, M.
39. Gunderson, T.
40. Becker, B. A.

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