TREATMENT OF PREPARALYTIC POLIOMYELITIS WITH GAMMA GLOBULIN

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By July of 1944 it was obvious that New York State was about to experience a major epidemic of poliomyelitis. Dr. John B. Alsever of the U. S. Public Health Service, temporarily assigned to the New York State Health Department in connection with the development of its plasma program, saw in the situation an excellent opportunity to study the possible therapeutic effect of the gamma globulin fraction of pooled plasma [1] in poliomyelitis. At that time collaborators of Enders [2] had already reported finding poliomyelitis antibodies in fraction II + III of human plasma in concentrations ten times as great as in whole plasma. Moreover, it was found that a number of other antibodies, similarly concentrated four to ten fold in fraction II + III, were associated with the gamma globulins, since they were further concentrated [2] fifteen to thirty fold over plasma in fraction II,[1] which contains 80 to 95 per cent gamma globulin in different commercial preparations.[3] It seemed reasonable to assume, therefore, that the concentration of poliomyelitis antibodies would be appreciably greater in fraction II alone, from which commercial gamma globulin is prepared. This assumption has been borne out by an extensive and painstaking series of titrations by S. D. Kramer.[4] These experiments, as yet unpublished, indicate that neutralizing antibodies against the Lansing strain of poliomyelitis virus are present in fraction II at an average concentration eighteen to twenty-five times as high as in the corresponding whole plasma.

The present work basically constituted a repetition of the convalescent serum studies, and from the reports of the three recorded studies of this sort in which establishment of a control series of cases was attempted [5] there seemed little reason to be hopeful. However, with the much larger dosage of antibody theoretically available in a given volume of gamma globulin it was conceivable that a favorable result might be obtained. The question clearly needed to be investigated and the situation for doing so looked very promising. Accordingly a plan to study the therapeutic effect of gamma globulin in poliomyelitis, with a request for allotment of sufficient material, was submitted to the Technical Advisory Committee of the American Red Cross, which at that time controlled the national gamma globulin supply.

This committee approved the study as outlined and agreed to release enough material to carry it to a significant conclusion. Its approval had but two provisos—that, contrary to the plan as submitted, only preparalytic cases be included in the study, and that we be advised throughout by a special committee consisting of Drs. Edwards A. Park, Charles A. Janeway and Ernest L. Stebbins.[6]

The two major foci in the epidemic were in the Elmira and Buffalo areas, and it was decided to confine the study to two hospitals in each of these regions. There are only two hospitals in Elmira, the Arnot-Ogden and St. Joseph's, and essentially all patients of any age with poliomyelitis were being cared for in them by the two licentiate pediatricians in the city. Of the several hospitals in Buffalo, the two chosen were Children's, because it was bearing the brunt of the epidemic for the city as a whole, and Meyer Memorial, because it was receiving a fair number of adult patients. The project was presented to the various staff physicians concerned at each hospital, and all expressed themselves as willing to cooperate to the fullest extent.

As has already been noted, the idea was conceived in July, and all the necessary groundwork had been laid early in August. Because of complexities of production, however, the pharmaceutical company which was assigned the order for the gamma globulin was unable to fill it immediately, so that the material was not received until August 20. Consequently the study was not launched until August 22 in Buffalo and August 23 in Elmira.

All the staff men concerned gave their assurance that it would be feasible to enroll every preparalytic case in the study strictly according to plan regardless of whether they happened to be private or service cases, and in actual practice there was only one exception. In Elmira a nurse who had been working in the poliomyelitis wards and had seen the injections developed the disease and should have been in the treated group, but she refused to have the treatment and so had to be interchanged with a 4 year old girl who came in five hours later. All other cases were enrolled alternately without exception as treated and controls in the order of their admission to each individual hospital. The field team checked on every poliomyelitis admission and reviewed the hospital charts regularly for the clinical condition at the time of admission. These records show that every case which was unquestionably preparalytic poliomyelitis according to the stipulated criteria was included in the study.

The criteria for preparalytic poliomyelitis were established by the special advisory committee and were twofold: (1) the cerebrospinal fluid of the patient was required to contain more than 10 cells per cubic millimeter and (2) there could be no definite weakness of any major muscle group and no evidence of facial, pharyngeal or respiratory involvement in a patient who otherwise presented a clinical syndrome indicative of poliomyelitis. Every one concerned, including the committee, felt that the stipulation of a minimal spinal fluid cell count of 11 was regrettably arbitrary, but it was agreed on as necessary to substantiate the diagnosis and

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This study would not have been possible without the cooperation of a host of collaborators, whose names are listed in the reprints.

Gamma globulin is the name used to achieve brevity in describing concentrated normal human serum gamma globulin (immune serum globulin) prepared by the method of Cohn, Oncley, Strong, Hughes and Armstrong[1] from blood collected by the American Red Cross.

1. Cohn, E. J.; Oncley, J. L.; Strong, L. E.; Hughes, W. L., Jr., and Armstrong, S. H., Jr.: The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation **23**: 417, 1944.

2. Enders, J. F.: The Concentration of Certain Antibodies in Globulin Fractions Derived from Human Blood Plasma, J. Clin. Investigation **23**: 510, 1944.

3. Williams, J. W.; Petermann, M. L.; Colovos, G. C.; Goodloe, M. B.; Oncley, J. L., and Armstrong, S. H., Jr.: Electrophoretic and Ultracentrifugal Studies of Solutions of Human Serum Albumin and Immune Serum Globulins, J. Clin. Investigation **23**: 433, 1944.

4. Dr. S. D. Kramer is associate director, Bureau of Laboratories, Division of Virology, Michigan State Department of Health.

5. Kramer, S. D.; Aycock, W. L.; Solomon, C. I., and Thenebe, C. L.: Convalescent Serum Therapy in Preparalytic Poliomyelitis, New England J. Med. **206**: 432, 1932. Park, W. H.: The Therapeutic Use of Convalescent Serum in Preparalytic Cases of Poliomyelitis, with a Comparison Between Treated and Untreated Cases, Tr. A. Am. Physicians **47**: 123, 1932. Fischer, A. E.: Human Convalescent Serum in the Treatment of Preparalytic Poliomyelitis: A Comparison of 447 Treated and 102 Control Patients in New York City in 1931, Am. J. Dis. Child. **48**: 481 (Sept.) 1934.

6. Dr. Edwards A. Park, chairman, is professor of pediatrics, Johns Hopkins University School of Medicine, and pediatrician-in-chief, Johns Hopkins Hospital. Dr. Charles A. Janeway is assistant professor of pediatrics, Harvard Medical School, visiting physician, Children's Hospital, Boston, and associate in medicine, Peter Bent Brigham Hospital. Dr. Ernest L. Stebbins is commissioner, New York City Department of Health.

prevent the otherwise inevitable subsequent criticism that probably some cases that were not poliomyelitis had been included. Actually the typical paralytic disease developed later in a number of cases excluded from the study because of cell counts under 11.

Each patient was seen on admission by one of the resident or attending physicians, and if there was no clinical evidence of paralysis the case was referred for a detailed muscle grading. This was done promptly by a specially assigned registered physical therapist on twenty-four hour call, who was required to commit herself immediately on the completion of her examination as to whether she thought there was any definite weakness of a major muscle group. If she found none, and if the total cell count of the cerebrospinal fluid which had been examined meanwhile was over 10, the case was considered suitable for inclusion in the study.

TABLE 1.—*Gamma Globulin Dosage Schedule and Estimated Equivalents in Whole Plasma* *

Buffalo and Elmira 1944

	Gamma Globulin	Whole Plasma
Under 1 year of age	20 cc.	360 - 500 cc.
1 year of age	30 cc.	540 - 750 cc.
2 years of age	40 cc.	720 - 1,000 cc.
3 years of age	50 cc.	900 - 1,250 cc.
4 years of age	60 cc.	1,080 - 1,500 cc.
5-7 years of age	70 cc.	1,260 - 1,750 cc.
8-11 years of age	80 cc.	1,440 - 2,000 cc.
12 years and over	100 cc.	1,800 - 2,500 cc.

* Based on titrations of antibodies against the Lansing stain of poliomyelitis by Dr. S D. Kramer.

Patients due to be treated received gamma globulin intramuscularly in accordance with the dosage schedule presented in table 1. It was felt that it was probably important to give the total dose as soon as possible. For that reason it was stipulated that each patient receive his full quota all at once, and that condition was met in every case. The dosage schedule was prescribed by the special advisory committee and was made as large as they thought could be tolerated by an intramuscular route. An age scale was employed rather than a presumably more accurate one based on body weight because of the practical difficulty of obtaining those weights by hospital staffs already harassed almost beyond endurance. It was suggested that the full dose be divided preferably into not more than four portions injected into the anterior thigh muscles and buttocks. In no case were more than four sites required and actually many of the patients were able to take the dose in two or three portions.

Patients that fell into the control group were followed exactly as the treated ones, but they received no injections. The original plan was to give the controls normal serum or isotonic solution of sodium chloride. The special advisory committee decided against this plan and in favor of no injections because it felt that a better control would be obtained by the latter method and it questioned the importance of the psychologic aspects of control injections. The clinicians in charge of the cases were sure that omission of control injections would not lead to any selection of cases; accordingly uninjected controls were used.

One week after admission, again one week after that, and finally five to seven months from onset the muscle gradings were repeated on all patients, always by the same physical therapist who had made the initial grading. Three physical therapists were employed in all, one at Children's Hospital where the great majority of the data were obtained, another at Meyer Memorial Hospital and the third at the two Elmira hospitals. All three of these technicians are highly skilled, all follow essentially the same method of muscle examination and all used the same form to record their results. This form, which is the one currently used for muscle grading by the Medical Rehabilitation Division of the New York State Health Department, lists fifty-three individual muscles or functionally related groups. All fifty-three were checked each time except in a few patients who were too sensitive to grade on the second or third gradings. The condition of each muscle or group was evaluated as normal, good, fair, poor, trace of power or totally paralyzed.

It would have been ideal if the physical therapists could have been kept in complete ignorance as to which patients were treated and which were controls, but this possibility was lost when it was decided not to use a control injection. An earnest effort was made at the very outset, however, to inculcate them deeply with the idea that the value of the agent under investigaiton was entirely unknown, that there was no more reason to anticipate a favorable effect than a negative one, and that it was positively essential, if the efforts of every one were not to be wasted, that unbiased data be obtained. They were cautioned, moreover, not to attempt to refresh their memories if they should forget from one examination to the next which patients were treated. They kept the grading forms with them until the study was completed, so that it was not necessary for them to refer to the hospital charts to make their entries, and they had no access to our special case cards with a detailed record of treatment. As a result of all this—and this is particularly true in the case of the one technician who had 89 of the patients—the physical therapists were not aware for the most part which patients received treatment and which did not.

TABLE 2.—*Criteria of Comparability*

Buffalo 1944

Criterion	Number of Patients	
	Treated	Controls
Total	49	48
Month of onset:		
August	25	24
September	20	21
October	4	3
Male	34	30
Under 5 years of age	4	7
5-9 years of age	18	18
10-14 years of age	18	16
15 years and over	9	7
Interval from onset to hospital admission:		
1 day or less	13	12
2-4 days	17	17
5-7 days	13	13
8 days and over	6	6
Cerebrospinal fluid total cell count:		
10- 49	19	17
50- 99	11	10
100-199	13	14
200 and over	6	7
Received hot packs	47	43

The study was begun, as already stated, on August 22 in Buffalo and on the 23d in Elmira. It was not continued for a comparable interval in all four hospitals, however. By September 13 the admission rate had fallen so low at Meyer Memorial Hospital that the returns were not sufficient to justify the expenditures involved, so that no patients were enrolled in the study in that hospital after that date. By September 25 the same situation had developed in Elmira, and further

expansion of the study was discontinued. At Children's Hospital the admission rate stayed up appreciably longer, and termination was not indicated until October 19.

During these respective periods a total of 112 patients were enrolled, 90 at the Children's Hospital, 8 at Meyer Memorial and 14 in Elmira. In this total there was apparently only one mistaken diagnosis, in a control child at Children's Hospital who was subsequently found to have tuberculous meningitis and who has been excluded from the data.

On the basis of our knowledge of the actual working conditions of the experiment in the two Buffalo hospitals we feel justified in considering the patients from both as a single group, and the results have been so tabulated. Because of the violation of strict alternation of cases in the Elmira group, and also because the physical therapist there seemed to interpret the gradings or functionally related groups. For the calculation of the index, some additional combinations were made based on two factors: (1) spinal nerve innervation of muscle groups and (2) advice from the physical therapists as to the fineness with which they could distinguish between the functioning of various muscle groups. Thus all the flexors of the hand were combined in one group, all the small muscles of the hand in another, and so on to a total of thirty-five separate items. The various degrees of muscular involvement as noted by the physical therapists were given progressive numerical values, with normal = 0, good = 1, fair = 2, poor = 3, trace of power = 4 and total paralysis = 5. Where muscles were grouped, the total value for the group was divided by the number of muscles making up the group and the figure obtained was added with all the other separate values to produce a single numerical value for the body

TABLE 3.—*Results of Muscle Gradings*

(Second, about one week after admission; third, one week later; fourth, five to seven months from onset)
Buffalo 1944

Index of Paralysis	Number of Patients						Per Cent					
	Second Grading		Third Grading		Fourth Grading		Second Grading		Third Grading		Fourth Grading	
	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls
0	30	27	25	26	34	34	62.5	61.4	53.2	55.3	73.9	73.9
1 - 9	11	14	14	14	7	6	22.9	31.8	29.8	29.8	15.2	13.0
10 - 59	5	2	7	5	5	5	10.4	4.5	14.9	10.6	10.9	10.9
60 - 119	1	1	..	2	..	1						
120 - 169	1	..	1	..	..	..	4.2	2.3	2.1	4.3	....	2.2
Grading not obtainable	1	4*	2	1*	3	2*						
Total	49	48	49	48	49	48	100.0	100.0	100.0	100.0	100.0	100.0

* Including 1 fatal case.

TABLE 4.—*Relation of Interval from Onset to Treatment* and Grading Results*

Buffalo 1944

Index of Paralysis (4th Grading)	Number of Patients				Per Cent			
	Treated		Controls		Treated		Controls	
	Less Than 4 Days from Onset	4 Days and Over from Onset	Less Than 4 Days from Onset	4 Days and Over from Onset	Less Than 4 Days from Onset	4 Days and Over from Onset	Less Than 4 Days from Onset	4 Days and Over from Onset
0	20	14	19	15	74.1	73.7	76.0	71.4
1 - 9	4	3	3	3	14.8	15.8	12.0	14.3
10 - 59	3	2	2	3	11.1	10.5	8.0	14.3
60 - 119	..	..	1	..	....	....	4.0	....
Not obtainable	1	2	..	2†				
Total	28	21	25	23	100.0	100.0	100.0	100.0

* Regarded as interval from onset to hospitalization in control cases. † Including 1 fatal case.

during the acute stage of the disease somewhat more rigidly than the other two workers, it was thought best to consider those 14 cases separately, and they will be presented briefly after the Buffalo data.

Table 2 was compiled to test the comparability of the treated and control groups of cases with regard to certain fundamental factors: month of onset, sex, age, interval from onset to hospitalization, spinal fluid cell count and hot pack therapy. Inspection of the figures discloses the fact that the two groups, with the aforementioned case of tuberculous meningitis omitted from the controls, are strikingly similar with respect to every criterion listed. It seems justifiable to conclude on this basis that the study was adequately controlled, and there is no reason to assume that the comparison of treated cases and controls is any less valid where the data on muscle gradings are concerned.

The results of the muscle gradings were expressed in terms of a numerical index. It will be recalled that the grading form itemized fifty-three separate muscles as a whole. According to this scheme the maximum index possible with each muscular item showing complete paralysis would be 350.

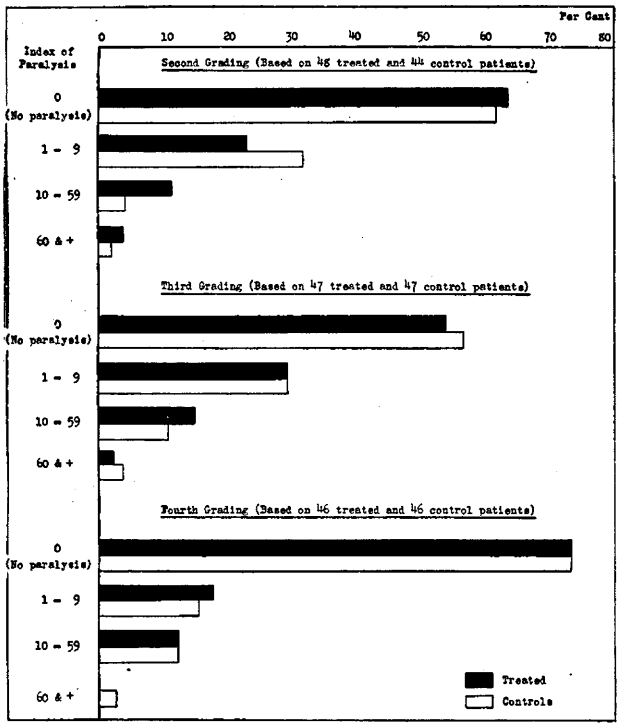
This method of course does not indicate the actual disability of the patient in functional terms, but it does express the disability in somatic terms; that is, in terms of the number of segments of spinal cord involved and the degree of that involvement. This claim seems sound, as muscles were grouped only when they were supplied by the same segments of cord. And for the purposes of this study it is the somatic involvement which is significant, since any significant effect of the agent under investigation would be expressed as the ultimate effect of the virus on the central nervous system.

Table 3 shows the grading results expressed as the numerical index of paralysis, with the treated and control groups broken down according to this index on the second, third and fourth examinations. The results on the first examination are omitted, since all cases had a zero grading at that time by virtue of the basic con-

ditions of the study. Viewed even in terms of individual cases the results are clearcut, but to simplify presentation the indexes were grouped as noted in the table. It is readily apparent from the table that treated and control cases are of essentially equal distribution in each paralysis-index group.

The patient with the highest index in the study (169 on the second examination and 163 on the third) happened to be in the treated group. This child was inaccessible for the six months follow-up because he had moved out of the state, but it was learned at that time through relatives that he still had definite involvement of all four extremities.

Of the other cases classified as "grading not obtainable," all except the fatal case had to be omitted on the second examination because of hyperesthesia of extreme degree. The muscles of 1 of these patients were still too sensitive for grading at the time of the third examination. The other patient missed on the third examination was an air force cadet who was considered well enough for discharge to the infirmary at his base before the grading was due, and the military authorities declined permission for the physical therapist to follow him at the base. On the second grading he had only minimal involvement of the left shoulder with an index of paralysis of 3, and at the time of his discharge from the hospital he was regarded clinically as having no residuum.



Results of muscle gradings, Buffalo 1944.

With the obvious exception of the fatal case, all those missed on the fourth grading had moved to some point too far from Buffalo to be reached by the physical therapist.

Certain clinical details regarding the 1 patient who died warrant special mention. This child appeared critically ill to the resident at Children's Hospital when she first saw him in the admitting room, and she had a presentiment that he might be a bulbar case. Since she and two other house officers were unable to detect any signs of facial, pharyngeal or respiratory involvement, however, he was admitted to the study in the proper order as a control case. Within one and one-half hours of his transfer to the ward he developed definite respiratory embarrassment. The next day there was a rapid progression of symptoms, and the day after that, forty-eight hours after admission, he died.

TABLE 5.—*Criteria of Comparability*

Elmira 1944

Criterion	Number of Patients	
	Treated	Controls
Total	7	7
Month of onset:		
August	4	3
September	3	4
Male	2	5
Under 5 years of age	2	2
5-9 years of age	..	1
10-14 years of age	3	3
15 years and over	2	1
Interval from onset to hospital admission:		
1 day or less	4	4
2-4 days	2	2
5-7 days	1	1
8 days and over	..	..
Cerebrospinal fluid total cell count:		
10 - 49	1	2
50 - 99	1	4
100 - 199	2	1
200 and over	3	..
Had hot packs	7	6

The negative quality of the results in table 3 is emphasized by the percentage distribution also presented there, and it is rendered even more striking by the chart, in which these percentage values are shown in graphic form.

Despite this negative outcome for the group as a whole, consideration was given to the possibility that the therapeutic agent might be of some benefit in early cases. To test this possibility table 4 was prepared, with the patients divided according to whether they were treated within four days of onset or later. Here again the equality of numbers in treated and control groups is striking at each index level, and it is obvious that patients who were treated early in the course of their disease were no better off than those treated late.

With 97 cases from Buffalo as a background, the Elmira cases merit some consideration even though they numbered only 14. The comparability data on them are presented in table 5. It will be noted that even with such small numbers the treated and control groups are apparently quite comparable with respect to the factors considered, with the possible exception of somewhat higher spinal fluid cell counts in the treated group.

TABLE 6.—*Results on Fourth Muscle Grading*

Elmira 1944

Index of Paralysis	Treated	Controls
0	1	4
1 - 9	2	2
10 - 29	3	0
Unknown	1*	1†
Total	7	7

* Not available for fourth grading but essentially normal at third grading.
† Not available for fourth grading but information by correspondence claimed complete recovery.

Table 6 shows the results in 12 of the 14 cases on the fourth muscle gradings. The second and third gradings were not tabulated because of the physical therapist's tendency to make numerous qualifying notations

on her records. This made it difficult to evaluate her findings and reduce them to a numerical index. For the fourth grading, however, when the muscles were no longer hypersensitive, the records are concise and could be coded in accordance with our scheme. From this coding, as presented in the table, it is clear that the 7 treated patients were not benefited by the treatment.

In summary it can be conclusively stated that, in a series of 111 patients with preparalytic poliomyelitis observed for approximately six months after onset, no benefit is detectable when 56 of them who had received large doses of gamma globulin intramuscularly in the preparalytic stage are compared with 55 alternate, untreated controls.

As a corollary to the foregoing conclusion, these data compiled with gamma globulin offer further indication that serum in any form is, for all practical purposes, ineffective in the therapy of poliomyelitis. This is evident from the comparison of dosages in terms of poliomyelitis antibodies in gamma globulin and whole plasma presented in table 1. These values are for normal adult plasma collected without reference to an antecedent history of poliomyelitis, but there is no definite evidence that the concentration of neutralizing antibodies against poliomyelitis virus is any higher in convalescent serum than it is in normal pooled adult plasma.[7]

A STUDY OF THE ORIGIN OF AN EPIDEMIC OF POLIOMYELITIS

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Few reports have been published concerning the sources of the initial cases of poliomyelitis in a large and widespread epidemic, although many investigators have demonstrated the radial spread of the disease from established epidemic areas. Wickman[1] focused attention on a parish school as the possible common source of some of the early cases in the Swedish epidemic of 1905, but he offered no suggestion as to how the infection entered the school prior to the first clinical case. In 1911 Kling and Levaditi[2] reported that an immune carrier was probably responsible for the introduction of the disease into two small islands off the coast of Sweden. However, in view of present day knowledge, this circumstance is probably not significant since at that time the incubation period of poliomyelitis was erroneously thought to be from two to three days.[3] The 1916 epidemic in New York City and environs presented additional evidence to support the thesis that the disease spreads by person to person contact, but again there was no clue as to the source of the early cases. In several communities, however, an important observation was made, namely that in a previously uninfected area the first recognized case may have had no contact with a clinical case of poliomyelitis from the epidemic areas. Furthermore, in several instances the epidemic was ushered into a new community by several simultaneous, widely separated cases having no possible direct contact with one another.[4] The obvious conclusion was that during an epidemic period the reservoir for the spread of the virus was not confined to the paralytic cases. Today this a well accepted fact.

In recent years increasing emphasis has been placed on the importance of abortive forms and healthy carriers of the virus in the spread of the disease from person to person and community to community.[5] Although since the studies of Wickman the existence of such foci of spread has been repeatedly discussed, no observations have been made concerning the role played by such circumstances in the outbreak of a fresh epidemic. In spite of a large body of data supporting the thesis that very mild or abortive forms may be the source of the paralytic cases of the disease, discussions of the origin of epidemics have emphasized the environmental and sanitary factors. Lumsden,[6] in his report of the 1941 outbreak in Mississippi, stressed specific environmental factors as a background for the outbreak of the disease rather than person to person contact. Similarly, Casey[7] hypothesized that the first patient and many sporadic cases in the Walker County, Alabama, epidemic of 1941 were exposed to stagnant waters, polluted from an epidemic area. Ward and Sabin,[8] during a cold winter, isolated the virus from the intestinal contents of 2 patients with poliomyelitis and from a healthy sibling of each. One of the healthy carriers was found to be harboring the virus as long as six months later. Although drawing no conclusions, they inferred that during the interepidemic period patients and healthy carriers may be the reservoirs for virus which may in some way become disseminated.

At the present time the known facts are insufficient to permit conclusions to be drawn regarding the relative importance of environmental and human reservoirs in the initiation of a fresh early summer epidemic. This study was undertaken, therefore, to determine the role which human reservoirs, in the guise of healthy carriers or unrecognized illnesses caused by the virus, may have played in the origin of the first paralytic cases of poliomyelitis in the 1944 epidemic in the Buffalo area. Thus, two pertinent questions presented themselves:

1. Why did 3 almost simultaneous cases suddenly appear in a rural township in which no previous cases had been known for fifteen years?[9]

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