CHAPTER VI

FORMULATION OF DIAGNOSTIC CRITERIA FOR CLASSIFICATION OF CASES

It became apparent early in the examination of case records that a substantial amount of data would have to be reviewed before limits of variation in diagnostic procedures could be established and before generalizations concerning diagnoses could be adequately drawn. To accomplish these objectives it was necessary that the accumulating data be examined repeatedly without knowledge of the vaccination status of the patients. Every effort was made to establish diagnostic criteria by detailed objective analyses of the records, to formulate them clearly, and to apply them consistently in the classification of all cases before identification of cases according to their vaccination or control status was undertaken. Consequently, first attention and effort were concentrated on obtaining complete and reliable data.

The data from each report were reduced to punched cards from which listings and tabulations could be made for study. Since there was an interval of at least three months between the onset of a case and receipt of the last required report, the complete data were accumulated slowly. As significant amounts became available, however, the data were compiled and subjected to careful study. Once again, it is important to emphasize that this was not an evaluation of data from a single investigative unit, but from many laboratories, clinics, public health departments, and hospitals throughout the United States; and while the procedures employed by them were basically standardized, qualitative and quantitative variation was evident. Interpretation must, of necessity, accept these facts.

DEFINITION OF PARALYTIC STATUS AND SEVERITY

Although each of the physical therapists was experienced and had received the same orientation course, it became apparent that differences existed in the evaluation of muscular state, especially in the "normal" and "good" classifications. Nevertheless, the detailed examination provided orderly data subject to confirmation and could be expected to detect involvement which would escape less expert or less detailed observation. A sound and interpretable statement made by the designated medical specialist regarding the presence or absence of paralysis was of considerable importance. Such a statement was not uniformly obtained, however, despite the attention directed by VEC to its need in every reported case. Where disagreements in evaluation of muscular impairment existed between therapist and physician, the Center and its consultants assumed responsibility for final interpretation of the total available data.

In the placebo areas, the 10-20 day examination of musculature was done in all but 37 instances (9 percent), and in all but 11 instances (3 percent) the 50-70 day examination was done. In the observed areas, 81 (14 percent) first examinations and 20 (3 percent) second examinations were not done.

The physical therapist's examinations were recorded on two forms (FT-7 and FT-8, see Appendix) which listed muscles or muscle groups on the basis of their anatomical

mass, rather than functional importance. The examiner was to enter a standardized estimate of the degree of impairment for each unit, grading from normal through five increasing degrees of severity: "good," "fair," "poor," "trace," or "no power." Involvement of muscles innervated by cranial nerves, or of respiratory muscles, was recorded, usually without indicating a specific grade of severity except for the degree of difficulty in swallowing.

Special problems became evident: The neck and abdominal muscles are obviously affected by muscular spasm and pain; asthenia of illness makes interpretation of minor muscular weakness difficult. It was necessary, therefore, to formulate criteria defining the extent of muscle involvement required to qualify a case as "paralytic" or, conversely, to classify the case as "not paralytic." In determining these criteria, Doctors Bennett, Green, Hodes, Top, and Wright gave continuously of their time and expert judgment. They reviewed intensively the tabulated data of both early and late muscle examinations, from a large proportion of the cases, uninformed of, and hence uninfluenced by, other clinical details, laboratory findings, or vaccination status of the patients, before criteria for classification of paralysis were adopted.

MINIMAL CRITERIA FOR CLASSIFICATION OF A REPORTED CASE AS PARALYTIC

1. The following were excluded from consideration as evidence of paralysis:
   a. abdominal and neck muscles graded bilaterally, good or fair;
   b. other muscles graded bilaterally good;
   c. record of hoarse voice, without supporting evidence or comment;
   d. check mark indicating deviation of the palate, without supporting evidence or comment.
2. All ratings of good, even though unilateral, were eliminated from scoring.
3. The following were the minimum of recorded involvement accepted as significant evidence of paralysis:
   a. A grading of good at the time of either the first or second muscle examination was accepted as significant if it applied to asymmetrical, spotty involvement of one or more of eight muscles characteristically affected by poliomyelitis, i.e., deltoid, triceps, finger extensors, opponens pollicis, gluteus medius, quadriceps, gastrocnemius, anterior tibialis. The patient so affected would be considered paralytic but because of the "good" classification no score would be given to the muscular impairment. It would constitute Grade I spinal paralysis without score.
   b. A grade of fair for a single muscle or single muscle group which would however, receive the appropriate score; this degree of impairment falls into Grade II spinal paralysis.
   c. Definite indication of facial, laryngeal, or pharyngeal involvement alone, or of palatal involvement with supporting evidence was accepted as evidence of bulbar involvement.

Any of these involvements could have completely disappeared by the time of the second examination, or could have been first recognized at the time of the second examination. The specialist's interpretation and comments were of major value in the review of these cases.

GRADING OF SPINAL PARALYSIS BY SEVERITY

Further examination of the data resulted in the following classification of spinal paralytic involvement by grades based partly on what appeared to be natural groupings. Grade I may be termed "minimal paralytic without a score," and frequently such cases were questionable clinically. Grade II may be termed "minimal paralytic with a score." No score was assigned to bulbar impairment of any degree nor to involvement of the diaphragm or intercostal muscles. The grades of paralysis

Grade	Score	Example
I	0	Left quadricips and right deltoid graded as "good". None of remaining critical muscles affected. No acceptable impairment of other muscles.
II	1-19	Score 4....."Fair" left inner hamstrings, 4....."Fair" right hip adductors, 4....."Fair" right inward rotators. 12.....Total score
III	20-89	Score 18....."Poor" gastrocnemius bilateral, 2....."Fair" left serratus magnus, 4....."Fair" left gluteus maximus, 2....."Fair" left hip flexors, 2....."Fair" left gluteus medius. 28.....Total score
IV	90-199	Score 18....."Poor" erector spinae bilateral, 6....."Poor" anterior abdominals bilateral, 12....."Poor" lateral abdominals bilateral, 3....."Poor" right hip flexors, 12....."Poor" right quadriceps, 6....."Poor" right inner hamstrings, 3....."Poor" right outer hamstring, 3....."Poor" left toe extensors, 8....."Fair" gluteus maximus bilateral, 2....."Fair" left hip flexors, 4....."Fair" gluteus medius bilateral, 4....."Fair" right hip adductors, 8....."Fair" left quadriceps, 12....."Fair" gastrocnemius bilateral, 4....."Fair" tibialis anticus bilateral, 4....."Fair" tibialis posticus bilateral, 2....."Fair" right peroneals, 4....."Fair" toe flexors bilateral, 2....."Fair" right toe extensors. 117.....Total score
V	200 +	Score 268....."No Power" trunk and lower extremities bilateral (except "Trace" in bilateral toe flexors), 148....."No Power" upper extremities bilateral (except "Trace" in left scapula adductors and left finger flexors), 12....."Poor" anterior and lateral neck muscles bilateral. 428.....Total score

and the accompanying scores of muscular impairment are listed on page 88 together with examples of the different categories.

The exclusion from scoring of all good muscles, muscles innervated by cranial nerves, and respiratory muscles, resulted in a maximal score of 440. However, all tabulations were arranged so that any scoring system could be employed for analysis.

GRADES ASSIGNED TO SEVERITY OF BULBAR INVOLVMENT

Grade 1. Involvement of one area indicated by physical therapist, without comment - minimal or doubtful.

Grade 2. One area of involvement with supporting comment, or involvement of two areas commonly related - definite.

Grade 3. Involvement of Grade 2 together with distinct difficulty in swallowing, or other moderate bulbar involvement.

Grade 4. Grade 2 or 3 but in addition required tracheotomy, or at times required respirator.

Involvement of diaphragm and intercostals, with or without use of respirator, was considered independently. Cases with both spinal and bulbar involvement were thus classified into grades of spinal involvement with the severity of the accompanying bulbar involvement designated.

INTERPRETATION OF LABORATORY INVESTIGATION OF CASES

The defining criteria adopted for classification of patients according to paralytic status were integrated with the data from other clinical and laboratory reports in order to furnish a final VEC diagnosis. The study by virus laboratories of specimens from reported cases in the total study population was made in order to add specific etiological identification to the clinical diagnosis of poliomyelitis. It required careful attention and the combined efforts of the local health authorities, clinical services, and laboratory staffs to assure collection of materials at the appropriate times, proper recording and transfer of specimens to the designated laboratory, and adequate examinations by the laboratory. VEC notified the regional laboratory of the occurrence of each case within the region; it served as monitor on the collection of specimens and the reports of examinations.

Some of the laboratories had previous experience in the use of tissue cultures in roller or stationary tubes for the isolation of poliomyelitis virus, and certain of them had obtained a high proportion of positive results with stools collected from paralytic patients soon after admission to a nearby hospital. In the Field Trial, however, conditions were often quite different, although a real effort was made to get specimens early. The procedures for testing of stools and some estimate of their efficiency are given in Chapter VII.

Area	Reported Study Cases	No Test for Virus		No Serology		No Test for Virus and No Serology	
		Number	Percent	Number	Percent	Number	Percent
Placebo	428	46	11	45	11	17	4
Observed	584	95	16	75	13	39	7
Total	1,012	141	14	120	12	56	6

Source: Table 27.

Reports, including those received after the April 1955 announcement, disclosed that stool specimens from 871, or 86 percent, of the patients were tested satisfactorily for the presence of virus. Serological tests were done with serum from 892 patients. Neither stool nor blood examinations were available in 56 instances, 5.5 percent of the cases. The extent to which laboratory data were not available for cases reported during the study period is shown in the table on page 89.

VIRUS ISOLATION

The summary of total tests for virus is given in the table at the bottom of this page.

Approximately half of the 871 specimens tested were positive for poliomyelitis virus. An orphan or "other" virus was isolated from 12 percent of the cases. In 22 instances where poliomyelitis virus was recovered from members of the patient's family but not from the study patient, the case was considered virus-positive. Thus, a virus of some nature was recovered from 64 percent of the patients tested. If tests demonstrating other viruses are excluded, 59.5 percent of the remaining 765 specimens tested yielded poliomyelitis virus. It should be re-emphasized here that after October, 1954, at which time relatively few tests had been completed, nearly all negative specimens were retested at least once so that the majority of negative reports were confirmed.

The distribution of types of poliomyelitis virus found in the 433 isolations is shown here:

	Number	Percent
Type I	241	55.7
Type II	55	12.7
Type III	137	31.6

Source: Table 29.

Relation Of Virus Recovery To Serological Response

The recovery of virus in relation to serological results is seen in Table 27.

The frequency of recovery of poliomyelitis virus in cases according to major serological groups is summarized in the excerpt shown on page 92. It shows that virus recovery was: (1) most common in cases with "positive serological" response; (2) somewhat less common in those with "probably positive" or "suggestive" response (primarily those with antibody to but one type of virus); and (3) decidedly less frequent in cases with "indeterminate" response (those with antibody to multiple types). Serological classifications are discussed later in this chapter.

These results strongly suggest that virus is less readily recovered from persons with greater previous experience with poliomyelitis virus, as indicated by the broader and indeterminate antibody content, and conversely, that it is much more easily re-

	Reported Study Cases	Cases Tested for Virus					Stool Not Collected or Not Tested
		Total	Poliomyelitis Virus Isolated	No Virus Isolated	Other Virus Isolated	Virus Isolated from Family Member	
Number	1,012	871	433	310	106	22	141
Percent	-	100	50	36	12	3	-

Source: Table 27.

Table 27

VIRUS ISOLATION BY DIAGNOSTIC CATEGORY AND SEROLOGY FOR STUDY CASES PLACEBO AND OBSERVED AREAS

Virus Isolation by Diagnostic Category	Serology - All Areas							Serology - Placebo Areas							Serology - Observed Areas						
	Total	Pos.	Prob. & Sugg.	Neg.	Ind.	Incon.	Not Done	Total	Pos.	Prob. & Sugg.	Neg.	Ind.	Incon.	Not Done	Total	Pos.	Prob. & Sugg.	Neg.	Ind.	Incon.	Not Done
Study Cases - Total	1,012	230	277	75	299	11	120	428	85	120	40	133	5	45	584	145	157	35	166	8	75
Positive	433	156	140	2	89	10	36	177	58	63	1	39	4	12	256	98	77	1	50	6	24
Negative	310	51	77	43	125	-	14	111	14	30	22	41	-	4	199	37	47	21	84	-	10
Other	106	3	26	18	48	-	11	83	3	19	11	39	-	11	23	-	7	7	9	-	-
Not Done	3	-	-	-	-	-	3	1	-	-	-	-	-	1	2	-	-	-	-	-	2
Not Collected	138	14	30	10	31	-	53	45	8	6	4	11	-	16	93	6	24	6	20	-	37
Detected in Family	22	6	4	2	6	1	3	11	2	2	2	3	1	1	11	4	2	-	3	-	2
Paralytic-spinal Poliomyelitis - Total	433	110	134	2	127	6	45	182	44	59	1	59	3	16	251	75	75	1	68	3	29
Positive	226	84	77	1	42	5	17	100	33	37	-	22	2	6	126	51	40	1	20	3	11
Negative	106	25	33	-	45	-	3	32	6	11	-	15	-	-	74	19	22	-	30	-	3
Other	37	1	11	1	20	-	4	30	1	8	1	16	-	4	7	-	3	-	4	-	-
Not Done	1	-	-	-	-	-	1	1	-	-	-	-	-	1	-	-	-	-	-	-	-
Not Collected	54	8	10	-	17	-	19	16	3	2	-	6	-	5	38	5	8	-	11	-	14
Detected in Family	9	1	3	-	3	1	1	3	1	1	-	-	1	-	6	-	2	-	3	-	1
Bulbar & Bulbo-spinal Poliomyelitis - Total	233	76	70	2	64	3	18	81	25	28	1	22	-	5	152	51	42	1	42	3	13
Positive	142	54	41	-	34	3	10	48	15	17	-	13	-	3	94	39	24	-	21	3	7
Negative	47	13	12	-	22	-	-	14	4	6	-	4	-	-	33	9	6	-	18	-	-
Other	7	1	4	-	2	-	-	4	1	1	-	2	-	-	3	-	3	-	-	-	-
Not Done	1	-	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	1
Not Collected	30	5	12	1	5	-	7	11	4	3	-	2	-	2	19	1	9	1	3	-	5
Detected in Family	6	3	1	1	1	-	-	4	1	1	1	1	-	-	2	2	-	-	-	-	-
Nonparalytic Poliomyelitis - Total	176	34	57	3	61	2	19	88	16	27	3	27	2	13	88	18	30	-	34	-	6
Positive	58	18	22	1	11	2	4	27	10	9	1	4	2	1	31	8	13	-	7	-	3
Negative	69	12	23	2	30	-	2	28	4	11	2	9	-	2	41	8	12	-	21	-	-
Other	28	1	7	-	13	-	7	26	1	7	-	11	-	7	2	-	-	-	2	-	-
Not Done	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Collected	18	1	5	-	6	-	6	6	1	-	-	2	-	3	12	-	5	-	4	-	3
Detected in Family	3	2	-	-	1	-	-	1	-	-	-	1	-	-	2	2	-	-	-	-	-
Fatal Poliomyelitis - Total	16	-	-	-	2	-	14	4	-	-	-	-	-	4	12	-	-	-	2	-	10
Positive	7	-	-	-	2	-	5	2	-	-	-	-	-	2	5	-	-	-	2	-	3
Negative	1	-	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	1
Other	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Done	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Collected	6	-	-	-	-	-	6	1	-	-	-	-	-	1	5	-	-	-	-	-	5
Detected in Family	2	-	-	-	-	-	2	1	-	-	-	-	-	1	1	-	-	-	-	-	1
Doubtful Poliomyelitis - Total	66	1	14	5	31	-	15	24	-	4	4	13	-	3	42	1	10	1	18	-	12
Positive	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative	37	1	8	3	20	-	5	11	-	1	2	7	-	1	26	1	7	1	13	-	4
Other	11	-	3	1	7	-	-	7	-	2	1	4	-	-	4	-	1	-	3	-	-
Not Done	1	-	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	1
Not Collected	16	-	3	1	3	-	9	5	-	1	1	1	-	2	11	-	2	-	2	-	7
Detected in Family	1	-	-	-	1	-	-	1	-	-	-	1	-	-	-	-	-	-	-	-	-
Not Poliomyelitis - Total	76*	-	1	61	8	-	6*	41	-	1	29	8	-	3	35*	-	-	32	-	-	3*
Positive	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative	42	-	-	36	4	-	2	21	-	-	16	4	-	1	21	-	-	20	-	-	1
Other	21	-	1	16	4	-	-	14	-	1	9	4	-	-	7	-	-	7	-	-	-
Not Done	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Collected	12*	-	-	8	-	-	4*	5	-	-	3	-	-	2	7*	-	-	5	-	-	2*
Detected in Family	1	-	-	1	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-
Other Specific Disease - Total	12	-	1	2	6	-	3	8	-	1	2	4	-	1	4	-	-	-	2	-	2
Positive	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative	8	-	1	2	4	-	1	5	-	1	2	2	-	-	3	-	-	-	2	-	1
Other	2	-	-	-	2	-	-	2	-	-	-	2	-	-	-	-	-	-	-	-	-
Not Done	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Collected	2	-	-	-	-	-	2	1	-	-	-	-	-	1	1	-	-	-	-	-	1
Detected in Family	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

* Includes 2 fatal "not poliomyelitis" cases.

covered from those with antibody primarily deriving from the current experience. The frequency of recovery was also much higher in paralytic cases than in those designated nonparalytic.

Relation of Virus Recovery to Date of Stool Collection

Table 28 shows the relation of virus recovery to the length of time between reported

POLIOMYELITIS VIRUS ISOLATION BY DIAGNOSTIC CLASS AND SEROLOGICAL STATUS OF PATIENT PLACEBO AND OBSERVED AREAS COMBINED

Diagnostic Class	Serologically Positive			Serologically Probable or Suggestive			Serologically Indeterminate		
	Tested for Virus *	Virus-positive		Tested for Virus *	Virus-positive		Tested for Virus *	Virus-positive	
		Number	Percent		Number	Percent		Number	Percent
Paralytic Poliomyelitis	176	138	78.4	163	118	72.4	145**	78**	53.8
Nonparalytic Poliomyelitis	30	18	60.0	45	22	48.9	41	11	26.8

* Includes only virus-positive and virus-negative cases.
** Includes 2 fatal cases.
Source: Table 27.

onset and collection of the stool specimen. The numbers include the "early" cases, those occurring before the actual study period began.

Excluding cases from whom orphan virus was recovered, it can be seen that recovery of poliomyelitis virus from stools of paralytic cases was less frequent in the first five days than in the remainder of the first three weeks when 73 percent of the specimens was positive. It is quite striking that the greatest percentage of positives was obtained in the 10-20 day period after onset. In the fourth week the number of specimens is smaller and the percentage positive begins to decline, but even in the 21-30 day period 61 percent of the tests was positive. In the subsequent period of 31-45 days after onset, 9 of 19, 47 percent, were positive. Of the specimens collected 46 days or later, only 18 percent was positive. No positives were obtained in tests made with specimens collected later than 60 days after onset of a paralytic case.

Approximately 47 percent of the specimens tested from nonparalytic cases, again excluding those yielding an orphan virus, was positive in the first two weeks after onset. The number of specimens thereafter was small, but positive results were obtained as late as the seventh week.

While the frequency of recovery of poliomyelitis virus from paralytic cases was greater than from nonparalytic patients there is little indication that persistence of virus excretion was strikingly different in the two groups. In fact, virus was recovered from half the paralytic and nonparalytic patients (13 of 27) during the period of 5-6 weeks (31-45 days) after onset.

SEROLOGICAL TESTS

There was not sufficient previous information regarding the procedures employed to provide in advance a diagnostic evaluation of the serological results. A critique for interpreting laboratory investigations of reported cases had, therefore, to be developed with

Table 28

RESULTS OF TESTS FOR VIRUS IN STOOL BY NUMBER OF DAYS BETWEEN ONSET AND COLLECTION OF SPECIMEN AND BY DIAGNOSTIC CLASS
PLACEBO AND OBSERVED AREAS COMBINED

Number of Days between Onset and Collection of Stool by Diagnostic Class	Results of Tests for Virus										Positive Poliomyelitis Virus by Type							
	Stools Tested Total		Orphan Virus Cases		Excluding Orphan Virus Cases						Total		Type I		Type II		Type III	
					Total		Polio Virus		No Virus									
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Reported Cases - Total**	922	100	108	12	814	100	448	55	366	45	448	100	248	55	56	12	144	32
0-5 Days	295	32	52	18	243	30	120	49	123	51	120	27	73	61	13	11	34	28
6-10 Days	324	35	33	10	291	36	171	59	120	41	171	38	96	56	20	12	55	32
11-15 Days	153	17	11	7	142	17	92	65	50	35	92	21	47	51	15	16	30	33
16-20 Days	56	6	3	5	53	7	34	64	19	36	34	8	18	53	4	12	12	35
21-30 Days	31	3	5	16	26	3	12	46	14	54	12	3	7	58	-	-	5	42
31-45 Days	29	3	1	3	28	3	13	46	15	54	13	3	6	46	4	31	3	23
46 Days or More	30	3	2	7	28	3	3	11	25	89	3	1	-	-	-	-	3	100
Unknown Date	4	*	1	25	3	*	3	100	-	-	3	1	1	33	-	-	2	67
Paralytic Poliomyelitis - Total	612	100	44	7	568	100	388	68	180	32	388	100	214	55	45	12	129	33
0-5 Days	165	27	18	11	147	26	95	65	52	35	95	24	57	60	10	11	28	29
6-10 Days	231	38	14	6	217	38	153	71	64	29	153	39	85	56	17	11	51	33
11-15 Days	109	18	5	5	104	18	81	78	23	22	81	21	42	52	12	15	27	33
16-20 Days	44	7	1	2	43	8	33	77	10	23	33	9	18	55	4	12	11	33
21-30 Days	23	4	5	22	18	3	11	61	7	39	11	3	7	64	-	-	4	36
31-45 Days	19	3	-	-	19	3	9	47	10	53	9	2	4	44	2	22	3	33
46 Days or More	18	3	1	6	17	3	3	18	14	82	3	1	-	-	-	-	3	100
Unknown Date	3	*	-	-	3	1	3	100	-	-	3	1	1	33	-	-	2	67
Nonparalytic Poliomyelitis - Total	167	100	29	17	138	100	60	43	78	57	60	100	34	57	11	18	15	25
0-5 Days	66	40	13	20	53	38	25	47	28	53	25	42	16	64	3	12	6	24
6-10 Days	53	32	12	23	41	30	18	44	23	56	18	30	11	61	3	17	4	22
11-15 Days	24	14	2	8	22	16	11	50	11	50	11	18	5	45	3	27	3	27
16-20 Days	3	2	-	-	3	2	1	33	2	67	1	2	-	-	-	-	1	100
21-30 Days	4	2	-	-	4	3	1	25	3	75	1	2	-	-	-	-	1	100
31-45 Days	8	5	-	-	8	6	4	50	4	50	4	7	2	50	2	50	-	-
46 Days or More	8	5	1	12	7	5	-	-	7	100	-	-	-	-	-	-	-	-
Unknown Date	1	1	1	100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Not Poliomyelitis - Total	143	100	35	24	108	100	-	-	108	100	-	-	-	-	-	-	-	-
0-5 Days	64	45	21	33	43	40	-	-	43	100	-	-	-	-	-	-	-	-
6-10 Days	40	28	7	18	33	31	-	-	33	100	-	-	-	-	-	-	-	-
11-15 Days	20	14	4	20	16	15	-	-	16	100	-	-	-	-	-	-	-	-
16-20 Days	9	6	2	22	7	6	-	-	7	100	-	-	-	-	-	-	-	-
21-30 Days	4	3	-	-	4	4	-	-	4	100	-	-	-	-	-	-	-	-
31-45 Days	2	1	1	50	1	1	-	-	1	100	-	-	-	-	-	-	-	-
46 Days or More	4	3	-	-	4	4	-	-	4	100	-	-	-	-	-	-	-	-
Unknown Date	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

* Less than 1 percent.

** Includes cases which had onset during the vaccination clinic period; excludes 181 cases with no specimen collected or with specimen collected but not tested.

data compiled from the study itself. The standard serological test was devised to measure the antibody titers to the three types of poliomyelitis virus in the blood of the patient as early as feasible after onset, and to compare them with the titers in a specimen obtained about four weeks after onset, an advanced stage in serological convalescence. A primary expectancy was that a sufficient and specific increase in titer could be demonstrated against one type of virus to identify the causative agent in the individual case and

conversely that negative serological evidence could aid in the recognition of cases not related to infection with poliomyelitis virus. The probability was limited, however, by the fact that the elapsed time between reported onset of illness and the taking of the first blood specimen varied from case to case, and the intervals between reported onset, beginning infection and the attendant antibody response were also inconstant. The procedure finally agreed upon was the same as that employed for standard control sera. The serological tests on patients were consequently done mostly with paired 2-fold dilutions of sera in four tubes of tissue culture per dilution, or by screening with 4-fold dilutions in single tubes and retesting with 2-fold dilutions in four tubes to establish endpoints. Analysis has shown that this test gave reproducible results within a laboratory, usually within a ± 2-fold range. The numerical values of titers obtained in different laboratories, however, were not directly interchangeable.

Number of Tests

Serological tests, some incomplete, were made with poliomyelitis viruses and serum from 892, or 88 percent, of the 1,012 patients (Table 27). Efforts to develop reliable serological criteria for poliomyelitis turned to virus-positive cases which were clinically paralytic, as the most reliable basis for reaching diagnostic interpretations of the serological results.

	Number	Percent
Virus Positive Poliomyelitis Cases - Total	433	100.0
Serologically Tested	397	91.7
Paired Sera	370	85.5
Acute and Convalescent	315	72.7
Both Convalescent	55	12.7
Single Acute Serum	10	2.3
Single Convalescent Serum	17	3.9
Not Serologically Tested	36	8.3

Source: Table 29.

Of the 433 cases, both paralytic and nonparalytic, from whom poliomyelitis virus was recovered, serological tests were done with material from 397 as shown in the excerpt from Table 29.

A single specimen was considered convalescent if obtained 11 days or more after indicated onset, but when paired sera were available the first specimen was not considered convalescent unless taken 15 or more days after onset.

Significance of Rises in Antibody

Study of the serological reports as they accumulated pointed to laboratory difficulties or irregularities which required classification and correction. As the number of reports increased, it was possible to group results so as to seek interpretive generalizations. Earlier investigations had demonstrated that antibody to the infecting virus might be present in the blood of a high percentage of patients by the time a first serum specimen could ordinarily be obtained. The extent of that occurrence might be increased by delays inherent in the extended Field Trial.

Evaluation of the accuracy of the serological test itself indicated that its average variation in a given laboratory was within a ± 2-fold range. Inspection of the changes in titer between the first and second serum samples from cases of paralytic poliomyelitis from whom a specifically typed poliomyelitis virus was recovered, demonstrated that many of these cases exhibited a 4-fold or greater rise in titer to the type of virus isolated from them even though antibody had already made its appearance at the time of the first, usually acute stage, specimen of blood. A 4-fold or greater rise in titer, especially when it agreed in type with the identified virus, was finally accepted as diagnostically significant. The information upon which this conclusion was based is contained in the following ma-

Table 29

HOMOLOGOUS AND HETEROLOGOUS ANTIBODY CONTENT OF SERA BY FOURFOLD RISES TO HOMOLOGOUS TYPE VIRUS-POSITIVE POLIOMYELITIS STUDY CASES BY TYPE OF VIRUS ISOLATED PLACEBO AND OBSERVED AREAS COMBINED

Antibody Content of Sera in Poliomyelitis Virus Positive Cases	Poliomyelitis All 3 Types		Paralytic Poliomyelitis								Nonparalytic Poliomyelitis							
			All 3 Types		Type I		Type II		Type III		All 3 Types		Type I		Type II		Type III	
	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*	Total Cases	4x-H Rise*
Cases - Total	433	156	375	138	207	76	45	15	123	47	58	18	34	10	10	3	14	5
Paired Sera - Acute and Convalescent - Total	315	142	272	125	151	71	32	13	89	41	43	17	28	10	4	2	11	5
No Antibody in Acute Sera, Homologous Only in Convalescent	11	11	11	11	6	6	2	2	3	3	-	-	-	-	-	-	-	-
Homologous Only in Both Sera	150	76	132	68	68	36	21	8	43	24	18	8	14	5	2	1	2	2
Homologous + 1 Other in Both Sera	37	20	31	16	19	11	3	-	9	5	6	4	4	3	1	1	1	-
Homologous + 2 Others in Both Sera	64	20	52	17	32	13	1	-	19	4	12	3	7	1	-	-	5	2
Other Patterns of Antibody Present	43	15	39	13	20	5	5	3	14	5	4	2	1	1	1	-	2	1
No Antibody Present	1	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-
Inconsistents**	9	-	7	-	6	-	-	-	1	-	2	-	2	-	-	-	-	-
Paired Sera - Both Convalescent - Total	55	14	50	13	25	5	6	2	19	6	5	1	2	-	3	1	-	-
No Antibody in First Sera, Homologous Only in Second	1	1	1	1	-	-	-	-	1	1	-	-	-	-	-	-	-	-
Homologous Only in Both Sera	33	10	31	10	15	4	4	2	12	4	2	-	-	-	2	-	-	-
Homologous + 1 Other in Both Sera	9	2	8	1	7	1	1	-	-	-	1	1	-	-	1	1	-	-
Homologous + 2 Others in Both Sera	10	1	8	1	2	-	-	-	6	1	2	-	2	-	-	-	-	-
Other Patterns of Antibody Present	1	-	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
No Antibody Present	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inconsistents**	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-
Single Sera - Acute - Total	10	-	9	-	8	-	-	-	1	-	1	-	1	-	-	-	-	-
Homologous Only in Serum	6	-	5	-	5	-	-	-	-	-	1	-	1	-	-	-	-	-
Homologous + 1 Other in Serum	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Homologous + 2 Others in Serum	4	-	4	-	3	-	-	-	1	-	-	-	-	-	-	-	-	-
No Antibody Present	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inconsistents**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Single Sera - Convalescent - Total	17	-	12	-	7	-	1	-	4	-	5	-	-	-	3	-	2	-
Homologous Only in Serum	11	-	7	-	3	-	-	-	4	-	4	-	-	-	3	-	1	-
Homologous + 1 Other in Serum	3	-	3	-	2	-	1	-	-	-	-	-	-	-	-	-	-	-
Homologous + 2 Others in Serum	1	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-
No Antibody Present	2	-	1	-	1	-	-	-	-	-	1	-	-	-	-	-	1	-
Inconsistents**	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serology Not Done - Total	36	-	32	-	16	-	6	-	10	-	4	-	3	-	-	-	1	-

* Cases showing a 4-fold or greater rise in the level of the homologous antibody content of sera.

** Antibody content of sera inconsistent with type of virus isolated.

terial, using the cases of the clinically paralytic poliomyelitis from whom poliomyelitis virus was recovered as a standard of reference.

Table 29 presents the patterns of antibody content to homologous and heterologous viruses observed in the sera of all the study cases from whom poliomyelitis virus was recovered. The frequency of 4-fold or greater increases in antibody to homologous virus is also presented.

It is seen from columns 1 and 2 that in tests with 315 pairs of acute and convalescent sera, 142, or 45 percent, demonstrated a 4-fold or greater rise in convalescent antibody titer to the virus recovered from the patient. Increase in antibody titer of that extent was noted in 46 percent, (125/272) of the paralytic, and 40 percent, (17/43) of the nonparalytic cases in this group. Among the paralytic cases the percentages were 47, 41, and 46 for Types I, II, and III, respectively.

There were, in addition, 55 tests with pairs of sera, both of which were considered convalescent, 50 of them from paralytic patients. In 13 of 50 such pairs from paralytic patients, or 26 percent, a 4-fold or greater

FREQUENCY OF SIGNIFICANT SEROLOGICAL RESPONSE AND OF HOMOLOGOUS ANTIBODY ONLY IN PAIRED SERA OF VIRUS-POSITIVE PARALYTIC CASES PLACEBO AND OBSERVED AREAS COMBINED

Homologous Antibody 4X-H Rises*	Total Paired Sera		Paired Acute and Convalescent Sera		Paired Convalescent Sera	
	Number	Percent	Number	Percent	Number	Percent
Paralytic Poliomyelitis Cases - Total	322	100	272	100	50	100
With 4X-H Rise	138	43	125	46	13	26
Without 4X-H Rise	184	57	147	54	37	74
Homologous Antibody Only Present - Total	175	54	143	53	32	64
With 4X-H Rise	90	28	79	29	11	22
Without 4X-H Rise	85	26	64	24	21	42
4X-H Rise - Total	138	100	125	100	13	100
Homologous Antibody Only Present - Total	90	65	79	63	11	85
Homologous Antibody Only Present - Total	175	100	143	100	32	100
4X-H Rise	90	51	79	55	11	34

Source: Table 29.

* 4X-H = Cases showing a 4-fold or greater rise in the level of homologous antibody content of sera, with or without heterologous antibody present.

rise in homologous antibody was noted. In the total series of 322 paralytic cases with virus isolated and pairs of sera tested there were, thus, 138, or 43 percent, with serological tests which were accepted as positive.

In this series of 322 paralytic cases with paired sera, 175, or 54 percent, possessed antibody to only that specific type of virus which was isolated from the stool, and 90, or 51 percent, of the latter group had, in addition, 4-fold or greater rises in type-specific antibody with convalescence. Hence 90 of the 138 serologically positive results, 65 percent, had occurred in cases with homologous antibody only. There remained 85 cases, or 26 percent of the total, without adequate serological rise in the second specimen of serum, who nevertheless possessed only homotypic antibody; they had apparently reached the full level of antibody response by the time the first blood specimen was obtained. (See table, page 96.)

Interpretation of Homologous Antibody Only

Thus, while less than half of the patients in the best substantiated diagnostic group, paralytic with virus recovery, exhibited a significant rise in antibody to the homologous virus, there were strong indications that the presence of antibody in a patient's sera to only the specific type of virus recovered from the stool was of confirmatory value even though significant increases in titer were not observed. The presence of only homologous antibody indicated further that it was derived from the current episode and that those persons had possessed no antibody to any type of poliomyelitis virus prior to the current illness. This effect was most marked with Type II cases, suggesting that virus of that type more frequently attacks persons without previous experience.

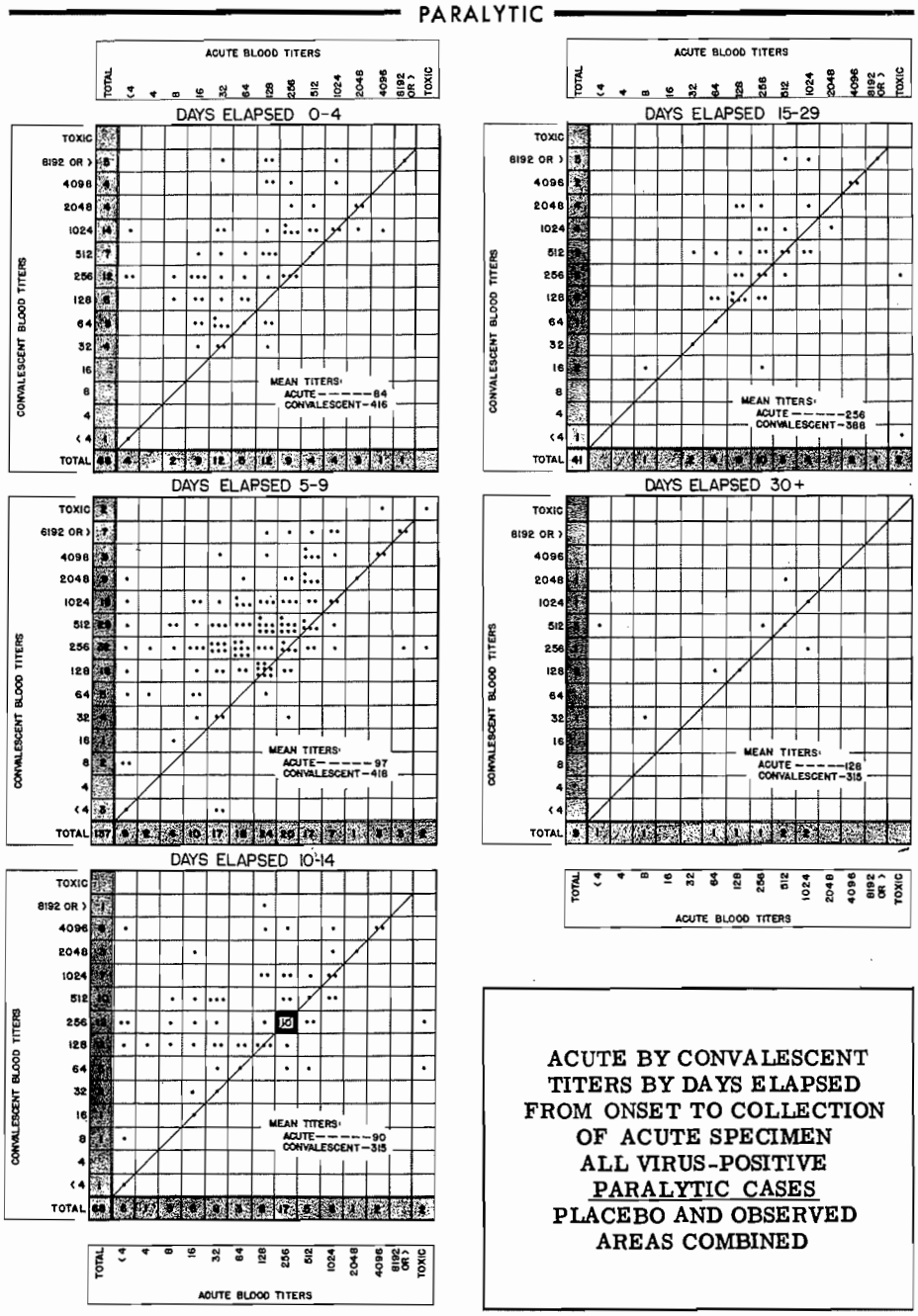
Of 12 single convalescent specimens from paralytic cases with virus isolated, 7, or 58 percent, had homologous antibody only (Table 29). The antibody here encountered must also have arisen from the present infection since it correlates specifically with the isolated type of virus and thus is of confirmatory diagnostic value. If these tests are added to those with paired convalescent sera, 39 of 62, or 63 percent of the tests involving late sera alone, revealed only homologous antibody.

The serological tests for all virus-positive poliomyelitis cases, including the nonparalytic with virus isolated, are grouped in the excerpt from Table 29 (page 100) showing that 42 percent of the paired sera exhibited a 4-fold or greater rise in titer to the homologous virus; 63 percent (98/156) of the specific 4-fold rises occurred in persons with homologous antibody only. When the first serum was obtained within 15 days of onset, 142 of 315 pairs, 45 percent, showed a 4-fold rise. In addition to the total 42 percent with specific increases in titer, 97, or 26 percent, of the tests with paired sera demonstrated only homologous antibody but with no rise or only a 2-fold rise in titer. Thus in 68 percent of the cases from whom poliomyelitis virus was recovered, the serological tests with paired sera confirmed infection with the reported type of virus either by demonstrating a significant rise in antibody to the virus isolated, or by the presence of antibody to only that type of virus, or by both.

The serological data from the study indicate that 21 percent of the study population tested before vaccination had no demonstrable antibody to any of the three types, but 54 percent of the paralytic cases, and 53 percent of all the poliomyelitis patients with paired sera and virus recovery occurred in persons without antibody to any of the three types prior to infection. There is obviously a selective concentration of clinical poliomyelitis in persons without previous experience with virus of any type. As mentioned earlier, this is most pronounced with Type II virus. It is noted, moreover, that about 50 percent of cases with antibody in the acute sera to one heterologous type also exhibited significant rise to the homologous type of virus.

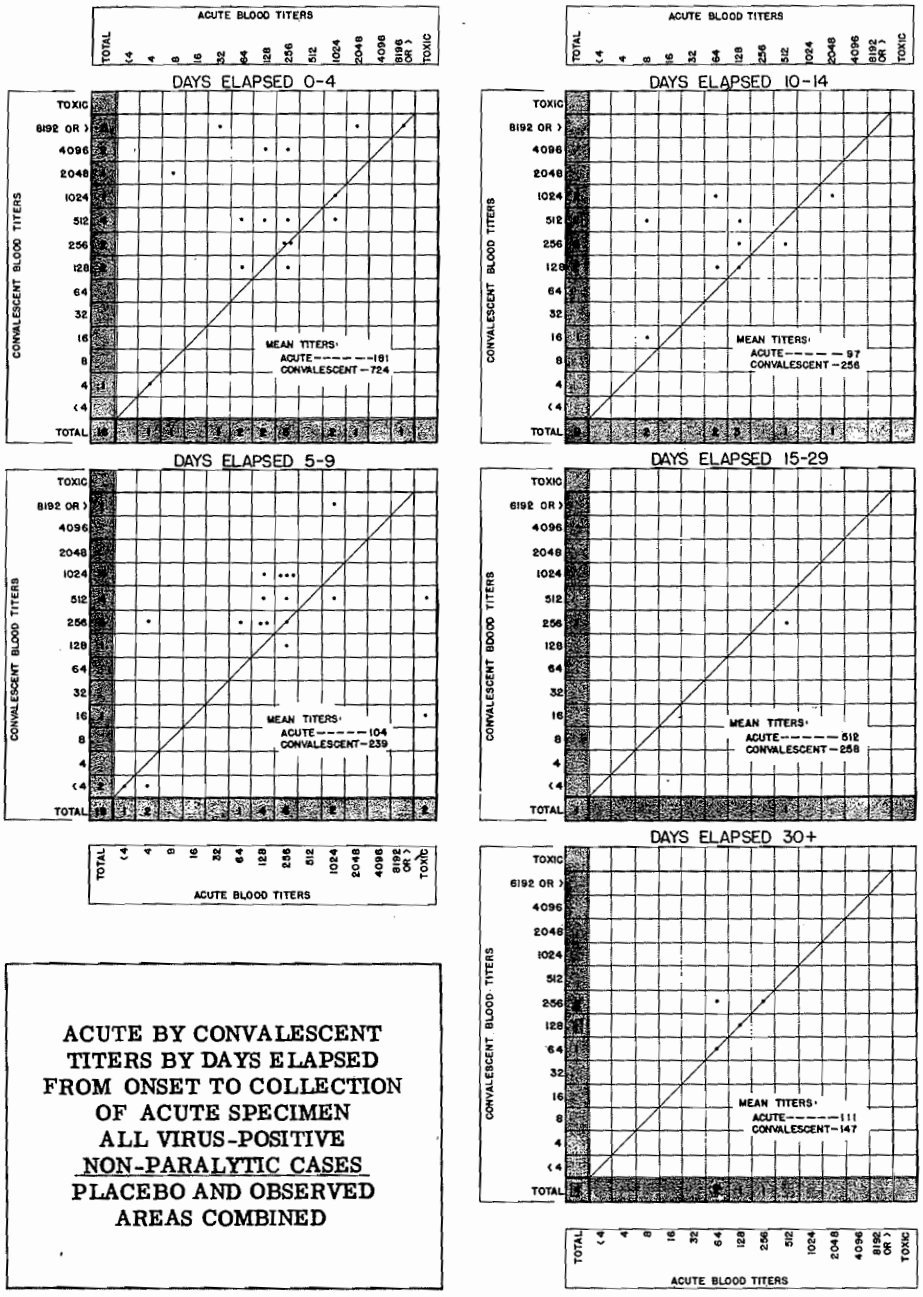
To summarize, on the basis of these observations, a 4-fold rise in titer to only the type of poliomyelitis virus recovered from the patient was classified as a definite posi-

Figure 4



ACUTE BY CONVALESCENT TITERS BY DAYS ELAPSED FROM ONSET TO COLLECTION OF ACUTE SPECIMEN ALL VIRUS-POSITIVE PARALYTIC CASES PLACEBO AND OBSERVED AREAS COMBINED

Figure 4 Continued



ACUTE BY CONVALESCENT TITERS BY DAYS ELAPSED FROM ONSET TO COLLECTION OF ACUTE SPECIMEN ALL VIRUS-POSITIVE NON-PARALYTIC CASES PLACEBO AND OBSERVED AREAS COMBINED

FREQUENCY OF SIGNIFICANT SEROLOGICAL RESPONSE AND OF HOMOLOGOUS ANTIBODY ONLY IN PAIRED SERA OF ALL VIRUS-POSITIVE POLIOMYELITIS CASES PLACEBO AND OBSERVED AREAS COMBINED

Homologous Antibody 4X-H Rises*	Total Paired Sera		Paired Acute and Convalescent Sera		Paired Convalescent Sera	
	Number	Percent	Number	Percent	Number	Percent
Poliomyelitis Cases - Total	370	100	315	100	55	100
With 4X-H Rise	156	42	142	45	14	25
Without 4X-H Rise	214	58	173	55	41	75
Homologous Antibody Only Present - Total	195	53	161	51	34	62
With 4X-H Rise	98	26	87	28	11	20
Without 4X-H Rise	97	26	74	23	23	42
4X-H Rise - Total	156	100	142	100	14	100
Homologous Antibody Only Present - Total	98	63	87	61	11	79
Homologous Antibody Only Present - Total	195	100	161	100	34	100
4X-H Rise	98	50	87	54	11	32

Source: Table 29.
* 4X-H = Cases showing a 4-fold or greater rise in the level of homologous antibody content of sera, with or without heterologous antibody present.

tive; a substantial level of antibody to only the homologous virus in the first and second specimens without an increase in titer, or in a late serum alone, was considered probably positive.

Relation of Titers to Time of Collection of Blood

Detailed information on patients from whom virus was recovered is presented in Figure 4. It concerns the relation of type-specific antibody levels, to the day after onset on which the first serum was collected, and to the changes observed in the second specimen. It is noted that the geometric mean titers of the first sera in paralytic cases were essentially the same when the first specimen was obtained 0-4, 5-9, or 10-14 days after reported onset; the median titers are the same also. After this time the original mean titer is considerably higher, 256 for specimens collected 15-29 days after onset and 128 for those 30 or more days after onset. Regardless of the time the first specimen was collected, the convalescent titers among paralytic cases are much the same, with a mean of 300-400. The numbers in the nonparalytic groups are smaller, but the same pattern of behavior obtains and there is

no indication that the antibody response of nonparalytic patients differs significantly from that of the paralytic. No marked difference was observed between types although the mean homologous convalescent titer in Type III cases tends to be somewhat higher than in Type I and Type II cases (Table 30).

is seen with initial titers up to a level of 64. In other words, the majority of poliomyelitis patients with original antibody levels of 64 or less show a significant type-specific increase in titer. This result provided valuable information in the evaluation of serological data in the absence of virus recovery.

Table 30

GEOMETRIC MEANS OF ACUTE AND CONVALESCENT TITERS FOR VIRUS-POSITIVE PARALYTIC CASES * PLACEBO AND OBSERVED AREAS COMBINED

Days from Onset to Collection of First Specimen	Number of Cases by Type of Virus Isolated			Geometric Means of Titers					
				Type I		Type II		Type III	
	Type I	Type II	Type III	Acute	Convalescent	Acute	Convalescent	Acute	Convalescent
0-4	39	5	22	66	295	111	776	136	638
5-9	72	18	47	84	408	81	391	138	410
10-14	39	9	20	108	290	81	203	74	416
15-29	23	4	14	199	298	813	512	312	538

* The numbers of nonparalytic cases and of specimens after 30 days for paralytic cases are too small to permit comparable grouping.

The frequency of positive serological response of 4-fold or greater in paralytic cases decreased as the interval between onset and collection of the first specimen of blood increased. The accompanying summary excludes the few instances with toxic first sera and those with original titers greater than 1024. When the first specimen of serum was obtained before the tenth day after reported onset, 62 percent of the tests in the series demonstrated a 4-fold or greater rise to the homologous virus. Thereafter the percentage of positives declined.

When the data are condensed, as in Table 31, without relating time to the height of the original titer, approximately the same frequency of 4-fold rises to the homologous virus

It is noteworthy that the percentage of serological positives for persons with low original titers is considerably greater in observed areas than in placebo areas.

Days from Onset to Collection of First Specimen	Paired Sera Tested	Serologically Positive	
		Number	Percent
0-4	61	38	62
5-9	128	81	63
10-14	63	27	43
15-29	35	10	29
30+	9	3	33

Source: Figure 4.

Table 31

ALL REPORTED STUDY CASES WITH VIRUS ISOLATION AND 4-FOLD OR GREATER RISE TO THE HOMOLOGOUS VIRUS TYPE, BY TITER LEVEL OF FIRST SERUM PLACEBO AND OBSERVED AREAS

Level of 1st Serum	Total			Placebo Areas			Observed Areas		
	Virus-Positive	4 x Rise - Homol. Only		Virus-Positive	4 x Rise - Homol. Only		Virus-Positive	4 x Rise - Homol. Only	
		No.	%		No.	%		No.	%
Total Study Cases*	448	164	36.6	180	60	33.3	268	104	38.8
Titers of 16 or Less	76	45	59.2	28	11	39.3	48	34	70.8
Titers of 32 or Less	122	74	60.7	47	21	44.7	75	53	70.7
Titers of 64 or Less	168	97	57.7	66	28	42.4	102	69	67.6
Titers of 128 or More	228	67	29.4	98	32	32.7	130	35	26.9
Titers of 1st Serum Unknown	52	-	-	16	-	-	36	-	-

* Seven cases with a toxic first serum are included (3 in placebo and 4 in observed areas). For these cases, titer change was measured from the level where a nontoxic reading could be taken. Cases with onset during the period of the vaccination clinics are included.

Relationship Between Homologous and Heterologous Antibody

The fact that a large proportion of patients had demonstrable antibody to a single specific type of virus even in convalescence suggested examination of the data for information of relationships between antibody titers to homologous and heterologous types of virus. Considering, again, paralytic cases from whom virus was recovered and with paired sera, 93 percent, that is, all but 23 of the 322 patients, had demonstrable antibody against the homologous virus in the first specimen of serum. As seen in the accompanying table, however, 84 percent of Type II and 67 percent

Virus-Positive Paralytic Cases		No Antibody to Respective Types Present in 1st Serum						No Antibody to Respective Types Present in 2nd Serum					
Poliomyelitis Virus Type	Total	Type I		Type II		Type III		Type I		Type II		Type III	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Type I	176	15	8.5	122	69.3	112	63.6	5	2.8	118	67.0	114	64.8
Type II	38	32	84.2	3	7.9	31	81.6	34	89.5	-	-	34	89.5
Type III	108	72	66.7	70	64.8	5	4.6	74	68.5	68	63.0	1	0.9
Percent Without Homologous Antibody		7.1%						1.9%					

Source: Table 32.

Table 32

ANTIBODY LEVELS OF PAIRED SERA OF PARALYTIC CASES PLACEBO AND OBSERVED AREAS

Antibody Levels	Cases with Type I Virus Isolated												Cases with Type I Serology* and No Virus Isolated											
	Acute and Convalescent Sera						Both Convalescent Sera						Acute and Convalescent Sera						Both Convalescent Sera					
	Type I		Type II		Type III		Type I		Type II		Type III		Type I		Type II		Type III		Type I		Type II		Type III	
	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.	Acute	Conv.
<4	14	4	102	98	94	96	1	1	20	20	18	18	-	-	14	14	11	11	1	-	3	4	4	4
4	-	-	12	13	7	4	-	-	-	2	-	1	-	-	2	2	-	1	-	-	-	1	1	2
8	6	2	9	18	5	3	1	-	1	-	-	-	2	-	-	1	1	1	-	-	2	2	-	1
16	20	-	10	2	3	3	-	1	1	1	1	-	1	-	2	1	-	-	1	-	2	-	1	-
32	23	6	4	4	4	6	2	1	2	1	-	-	5	-	-	-	1	-	1	1	-	-	1	-
64	12	14	3	4	4	2	3	1	-	-	1	1	4	3	-	-	1	1	1	1	-	-	-	-
128	27	23	3	2	3	2	5	6	-	-	2	2	2	3	-	1	1	1	-	1	-	-	-	-
256	16	34	3	3	5	6	7	4	-	-	1	1	3	8	1	1	1	1	1	2	-	-	-	-
512	13	24	3	4	9	10	3	5	1	1	1	2	3	2	1	-	1	1	1	1	-	-	-	-
1024	4	7	-	-	3	5	-	1	-	-	1	-	-	-	-	-	2	2	-	-	-	-	-	-
>1024	7	7	-	-	3	2	1	-	-	-	-	-	-	2	-	-	1	1	-	-	-	-	-	-
2048	3	8	-	-	4	6	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
4096	5	10	-	1	2	2	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8192	-	1	-	-	4	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16384 or >	1	11	2	2	1	1	1	3	-	-	-	-	-	1	-	-	-	-	1	1	-	-	-	-
Geometric Mean	74	362	4	4	7	7	169	329	4	4	4	4	74	315	4	4	11	10	95	282	4	4	4	4
Number of Sera >16	111	145	18	20	42	45	23	23	3	2	6	6	17	20	2	2	8	7	5	7	-	-	1	-
Total Paired Sera	151						25						20						7					
	Cases with Type II Virus Isolated												Cases with Type II Serology* and No Virus Isolated											
<4	27	29	3	-	26	28	5	5	-	-	5	6	16	17	2	-	15	15	-	-	-	-	-	-
4	2	1	-	-	3	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-	-	-	-
8	2	1	2	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-
16	1	-	1	1	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-
32	-	-	3	1	2	-	-	-	1	-	-	-	-	-	4	1	-	-	-	-	-	-	-	-
64	-	1	6	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-
128	-	-	3	2	-	-	-	-	-	-	-	-	-	-	-	2	-	1	-	-	-	-	-	-
256	-	-	10	11	-	2	-	-	-	2	-	-	-	-	3	6	-	-	-	-	-	-	-	-
512	-	-	1	5	-	1	-	-	2	3	1	-	-	-	3	-	-	-	-	-	-	-	-	-
1024	-	-	-	6	-	-	-	-	2	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-
>1024	-	-	2	3	1	-	-	-	1	1	-	-	-	-	-	2	-	-	-	-	-	-	-	-
2048	-	-	1	1	-	-	-	-	-	-	-	-	-	-	2	1	-	-	-	-	-	-	-	-
4096	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8192	-	-	-	-	-	-	1	1	-	-	-	-	-	-	1	2	-	-	-	-	-	-	-	-
16384 or>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Geometric Mean	4	4	79	362	4	4	5	5	455	455	4	4	4	4	134	355	4	4	-	-	-	-	-	-
Number of Sera >16	-	1	26	30	3	4	1	1	6	6	1	-	-	-	14	18	1	1	-	-	-	-	-	-
Total Paired Sera	32						6						17											
	Cases with Type III Virus Isolated												Cases with Type III Serology* and No Virus Isolated											
<4	59	61	56	54	4	1	13	13	14	14	1	-	21	22	20	21	4	-	4	4	3	4	-	-
4	4	1	7	3	3	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-
8	3	1	6	8	2	-	2	2	1	-	1	-	1	-	-	1	1	-	-	-	-	-	-	-
16	2	2	5	6	5	1	-	-	1	1	-	1	-	-	1	1	4	2	-	-	-	-	-	-
32	1	2	2	3	11	3	-	-	-	1	-	1	-	-	-	1	1	2	-	-	-	-	1	-
64	-	1	3	5	8	6	-	-	1	-	2	-	1	1	2	-	5	2	-	-	-	-	-	1
128	2	4	2	2	15	9	2	2	-	2	5	4	2	1	-	-	3	3	-	-	-	-	1	-
256	5	3	2	3	20	18	1	2	1	-	4	1	-	1	-	-	3	3	-	-	1	-	-	-
512	4	5	1	-	12	17	1	-	-	-	2	4	-	-	-	-	2	4	-	-	-	-	2	3
1024	5	3	-	-	2	13	-	-	-	-	1	2	-	-	-	-	-	3	-	-	-	-	-	-
>1024	3	1	-	1	2	3	-	-	-	-	1	1	-	-	1	1	-	1	-	-	-	-	-	-
2048	-	4	2	2	1	7	-	-	-	-	1	4	-	-	-	-	1	3	-	-	-	-	-	-
4096	1	-	1	-	1	9	-	-	1	1	1	1	-	-	-	-	1	-	-	-	-	-	-	-
8192	-	1	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16384 or >	-	-	-	-	3	2	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-
Geometric Mean	5	6	4	5	119	461	4	4	4	4	185	443	4	4	4	4	48	357	4	4	4	4	181	305
Number of Sera >16	21	24	15	18	75	87	4	4	3	4	17	18	3	3	3	2	16	23	-	-	1	-	4	4
Total Paired Sera	89						19						25						4					

*Includes cases with "positive" and "probably positive" serology.

of Type III cases were without Type I antibody; a proportionate lack of heterologous antibody is observed in all other comparisons. Generally, the percentage of negative heterologous titers is somewhat higher with the pairs of convalescent sera than with the acute and convalescent pairs. There is little difference between the distribution of heterologous titers in the first and second sera. There is, however, a distinct reduction in the number remaining negative to the homologous virus, as would be expected, although six of the convalescent sera were reported to contain no antibody to the type of virus recovered from the stool. The distribution with respect to the presence of homologous and heterologous antibody in the first and second sera of paralytic virus-positive cases is summarized by virus type in Table 32.

Analysis of antibody level to the homologous and heterologous types, in paralytic cases, is presented in Table 32. The geometric mean titer to the homologous virus in acute stage serum is much higher than to either heterologous type and rises impressively in the convalescent serum, 4.9-fold for Type I, 4.6-fold for Type II, and 3.9-fold for Type III. Even when paired convalescent sera are considered, increases of 1.9- and 2.4-fold for Types I and III, respectively, are seen. The shift in individual titers, too, is almost uniformly upward. Mean titers for heterologous types are extremely low with no significant change between first and second specimens. The results give little indication that infection with one type of virus is effective to any significant degree in stimulating production of antibody to the heterologous types, since the majority of cases remain negative to the heterologous. In contrast to the pronounced shift in the distribution of homologous titers between acute and convalescent sera, no distinct alteration is seen in the distribution of first and second heterologous antibody titers. The variation in the latter was mostly within a $\pm$ 2-fold range with few showing a rise beyond that limit. It is evident, therefore, that if increases in heterologous titer occurred during the illness, they must have largely taken place before the time of the first blood specimens.

Excluding as serologically negative the 6 instances in which the homologous antibody titer in the second blood is zero, 2 of which are certainly technical errors, there are but 7 of the other 316 paralytic cases with virus recovered whose second titer to the homologous virus is less than 32, and only 3 in which it is less than 16. In 2 of the latter, only homologous antibody was detected, and it rose from zero to 8; the other had a mixed

Table 33

OCCURRENCE OF HOMOLOGOUS AND HETEROLOGOUS ANTIBODY IN FIRST OF PAIRED SERA FROM VIRUS-POSITIVE PARALYTIC CASES

Poliomyelitis Virus Type	Number With Positive Virus	Serological Patterns						
		Homologous Only*		Homologous and Heterologous				Single Heterologous Type
		No.	%	I & II	I & III	II & III	I, II, & III	
Type I	176	97	55	13	20	2	35	9 (8-III, 1-II)
Type II	38	27	71	4	5	1	1	-
Type III	108	63	58	6	8	-	30	1 (II)
Total	322	187	58	23	33	3	66	10

* Includes those children who had no antibody in first sera but who had homologous only in second.

response. These data are also presented for both paralytic and nonparalytic cases in Figure 5. They show the marked shift in levels of homologous antibody, and the infrequency of major changes in heterologous titers is clearly seen. No significant difference in the character of the serological response of nonparalytic and paralytic patients was observed.

Examination of the first sera alone revealed that the majority of patients possessed antibody to the homologous virus only, and that when heterologous antibodies were present, they were more commonly found against two types than against any single type. There is the suggestion that Type III antibody occurred more frequently as a single heterologous antibody than did the other types.

Serological Interpretation

These analyses clearly demonstrated the sharp differences between homologous and heterologous antibody in prevalence, quantitative levels and patterns of change during illness. The observations led to the conclusion that in the absence of antibody to another type of virus, antibody in a titer of 16 or greater to the virus recovered from the stool of the patient was diagnostically significant - even if no significant rise in titer was noted in the convalescent specimen of serum or if homologous antibody alone was present when only convalescent serum was obtained. A result of this nature was, therefore, designated as probably positive.

Moreover, on the basis of the information gained, it was at first proposed that a result be considered suggestive when antibody to the homologous virus was present in titer of 32 or greater, without a 4-fold rise, even though heterologous antibody was present at low levels. Further review, however, led to the realization that results of this order were of much the same significance as the preceding category; consequently, they also were commonly interpreted as probably positive. The occurrence of a 2-fold rise in antibody to the isolated virus appears less significant than an unchanged high homologous level; therefore, it was considered only suggestively positive and not diagnostically meaningful.

Although the mean titers to heterologous virus were uniformly low, dominated by the high frequency of negatives, a minority of sera, 31 percent, did possess heterologous antibody, and 20 percent had titers of more than 16 to one or another heterologous virus.

Infections with Type II virus were apparently more limited by the presence of heterologous antibody than were infections of Types I and III; heterologous antibody to Type II virus was encountered less frequently than to Type I or Type III. Nevertheless, a scattering of high heterologous titers was noted with each type, least commonly with Type II and somewhat more with Type III than with Type I. If infection with a given type of virus influences the development of heterologous antibody at all, it may be suggested from these data that Type II virus infection has a mild

HETEROLOGOUS ANTIBODY TITERS OF MORE THAN 16
IN SECOND SERUM OF VIRUS-POSITIVE PARALYTIC CASES

Poliomyelitis Virus Type	Total Number	Cases With Heterologous Antibody					
		Type I		Type II		Type III	
		Number	Percent	Number	Percent	Number	Percent
Type I	176	-	-	22	13	51	29
Type II	38	2	5	-	-	4	11
Type III	108	28	26	22	20	-	-

Source: Table 32

Figure 5

ACUTE AND CONVALESCENT SEROLOGY OF ALL PARALYTIC

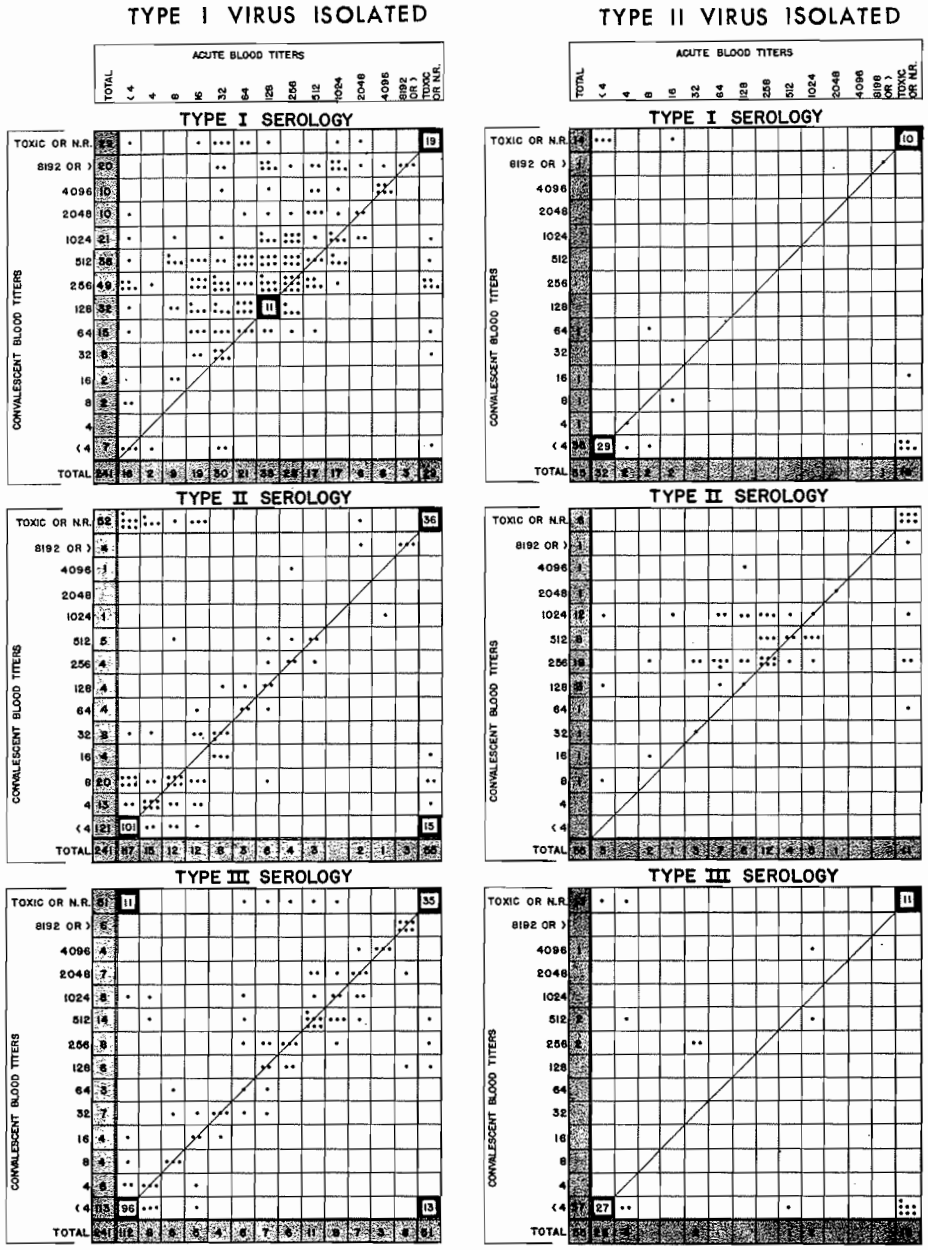
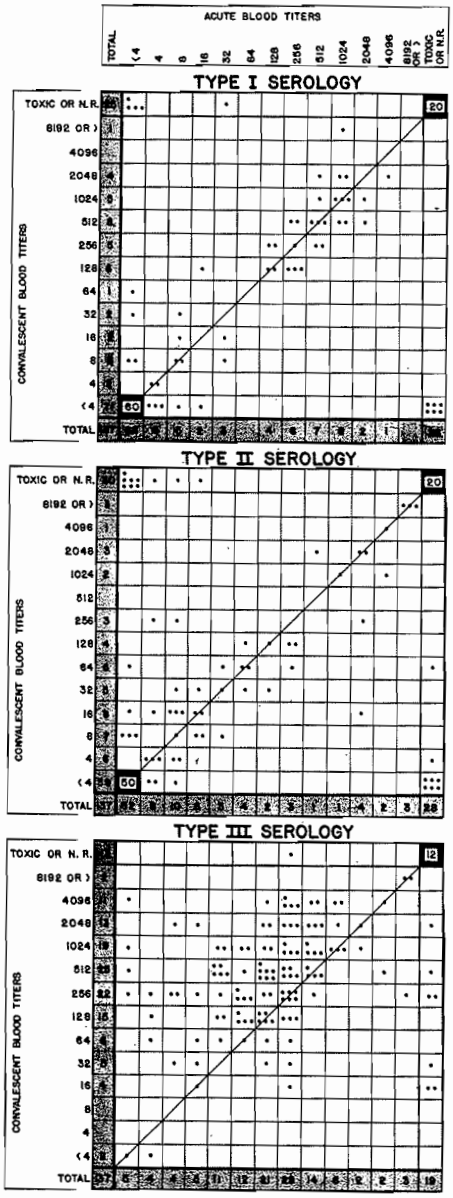


Figure 5 Continued

AND NONPARALYTIC CASES

TYPE III VIRUS ISOLATED



heterologous effect, more noticeable on Type III antibody than on Type I; that Type I virus influences the Type III antibody more than it does the Type II; and that Type III infection affects Types I and II antibody to about the same degree.

Changes in Heterologous Titers

There was little change in the distribution of heterologous titers between first and second sera. In only 14 instances out of 644 tests did heterologous titers of less than 16 in the first blood become greater than 16 in the second. On the other hand, mild declines in heterologous titers occurred in 25 percent or more of those sera in which antibody to both heterologous types was present. This relative stability of heterologous titers adds to the significance of changes observed in the homologous titers.

There were, however, among the 322 paralytic cases from whom a specific virus was recovered and whose paired sera were tested, 41 instances in which a 4-fold or greater antibody rise to a heterologous type of virus was reported. In 7 of them the rise and the final titers attained against the heterologous virus were of such a degree as to indicate that they were double infections, since pronounced rises to the identified virus also took place. (See listing which follows.)

Poliomyelitis Virus Type	1st Blood			2nd Blood		
	Type I	Type II	Type III	Type I	Type II	Type III
Type I	0	0	4	1024*	0	1024
Type I	4	4	64	256	4	1024
Type I	0	0	0	256	0	1024
Type II	16	16	4	8	1024	512
Type III	1024	8	4	2048	256	256
Type III	0	0	150	43	0	525
Type III	512	4	32	1024	256	1024

* Toxic at low levels.

In one, a similar heterologous increase occurred in the presence of substantial but unchanged titers to the homologous virus.

In 12 additional instances increases were from 0 to 4, 8, or 16 against heterologous types although the homologous titers and responses were quite clear-cut. Six of the cases were Type I according to dominant serology and virus isolation, and 6 were Type III; in all but one the low titered heterologous rise was to Type II. The homologous titers completely overshadowed the heterologous increases, and interpretation was not difficult. If changes such as these do, in fact, represent heterologous responses rather than technical variations, they are in sharp contrast to the much more pronounced rise usually seen to an infecting virus.

In another group of 10 cases, antibody tests with the homologous type of virus gave, with one exception, acceptable positives; but rises, usually just 4-fold to both heterologous types, were also observed. Heterologous antibody was usually present in the first specimen. Certain of the results could be satisfactorily correlated with the virus isolated because the heterologous titers were low, but the majority were not readily interpretable without making undue assumptions, since they commonly presented at least one high heterologous level in addition to exhibiting an homologous rise. In most of these instances, the nature of the results indicated variations in the technical procedures of testing. This entire group was classified as indeterminate.

An additional group of 8 patients had homologous and heterologous antibody in the first serum, 6 of them with antibody to all three types. Approximate 4-fold rises were reported to the homologous and to one of the heterologous viruses, but the level of the various titers was such as to make the serological result uninterpretable diagnostically.

CRITERIA FOR INTERPRETATION OF VIRAL AND SEROLOGICAL RESULTS

The correlations obtained by association of the serological results with the immunological type of poliomyelitis virus recovered from patients, especially the paralytics, provided a reasonable basis for interpreting them and integrating them with other data for diagnostic application.

The recovery of a typed poliomyelitis virus from the patient was accepted as confirmatory evidence of the diagnosis of poliomyelitis although there were a few inconsistencies between the type of virus reported and the serological evidence. It has been noted that in six instances no antibody to the reported type of virus was recorded in the convalescent serum; these could be considered errors in typing of virus; but repetition of the tests were reported with the same results.

Classification of Virus Tests

Tests intended for isolation of virus were classified as positive, negative, unsatisfactory, poliomyelitis virus of unidentified type, or virus other than poliomyelitis, test not done, unsatisfactory or no specimen. From 106 patients viruses were recovered which were not identifiable as poliomyelitis; they were called "orphan" viruses (ECHO) or Coxsackie viruses and are discussed in Chapter XIII, Orphan Virus. In 3 instances both poliomyelitis virus and another virus were isolated from the stool of a patient, and it is probable from the serological evidence that dual infections occurred in other cases from whom only an orphan virus was recovered. Recovery of virus from a member of the family of a clinical case was considered a positive if not inconsistent with the patient's serology.

The serological data relating to cases with virus isolation has been discussed. From them, categories of significance were developed. The presence of antibody in acute and convalescent sera to but a single type of poliomyelitis virus, corresponding to that recovered from the patient, has acquired high significance even though no rise in titer was noted. The specificity of that correlation between type of infecting virus and the presence of only homotypic antibody must be interpreted as cause and effect.

Interpretation of antibody to only one type of poliomyelitis virus was then considered

with respect to cases from whom poliomyelitis virus was not recovered. It is recognized that patients with illnesses other than poliomyelitis may exhibit previously acquired antibody to a type of poliomyelitis virus which is unrelated to the illness under observation. If, however, the current illness is poliomyelitis the serum of the patient would contain the pre-existing antibody of one type and would acquire, in addition, antibody to the type of virus involved in the present episode. If a single antibody was encountered in a virus-positive case, it was with rare exceptions homotypic, and in addition, 63 percent exhibited 4-fold or greater rises in homologous antibody. Further, the data in Table 29 show that only 12 percent of the total virus-positive cases with serological tests had antibody to the homologous type as well as to one heterologous type in the acute and convalescent sera; half of them showed significant rises to the homologous virus. More frequently, when heterologous antibody was present, it was for both heterologous types. The accumulated data indicate, therefore, that in children of the age group concerned, the presence of antibody to one type of poliomyelitis virus in a patient with an illness classified as paralytic poliomyelitis is likely to be specifically related to a current, active infection with virus of that type rather than a carry-over of pre-existing antibody. Despite this great preponderance of evidence, the presence of antibody in reasonable amounts to one type of poliomyelitis virus, in the absence of virus recovery or significant rise in titer, was conservatively assessed, diagnostically, as suggestive or possibly positive.

Interpretation of Serological Results

Criteria were then formulated and employed for interpretation of serological results in relation to virus isolation as follows:

A. With Poliomyelitis Virus Isolated:

1. Positive: 4-fold or greater rise in antibody to homologous type only.

2. Probably positive:

   a. Antibody present at level of 16 or more in first and second sera to only homologous type without rise; or in convalescent serum obtained 15 days after onset or later, if earlier specimen was not obtained.

   b. In both first and second sera, antibody level of 32 or more to homologous type and antibody present at low levels to heterologous type. (This combination was originally considered to be of "suggestive" importance; however, observations indicate that it is essentially equivalent to "2a" listed above. Ordinarily, homologous type levels were much higher than 32. Two cases in this category of less definite character, were, however, called "suggestive.")

3. Suggestive: 2-fold rise to homologous type only. (Only five cases were classified on this basis.)

4. Indeterminate:

   a. Only acute-stage serum available, obtained less than 10 days after onset.

   b. Multiple antibodies:

      (1) In paired sera with no distinctive change in titers, or irregular changes up or down.

      (2) In single convalescent serum.

   c. 4-fold rise in antibody to more than one type of virus.

5. Negative:

   a. No antibody to any type in first and second sera or in second serum alone.

   b. Low levels, 4 to 8, to one or more types; no rise.

6. Inconsistent: not in agreement with type of virus reported.

7. Serological evidence of other etiology reported by laboratory.

8. Unsatisfactory test: This indicates test in which toxicity of serum prevents proper reading, or a test in which gross irregularities occurred.

B. No Isolation of Poliomyelitis Virus or No Test For Virus

1. Positive: 4-fold or greater rise in antibody to one type of virus only.
2. Suggestive or possibly positive: The criteria called "Probably positive" under "A" above, when limited to one type only with or without 2-fold rise; also, high level to one type only, with or without 2-fold rise, and low levels to other types.
3. Classifications 4, 5, 7, and 8 as listed under "A."

C. Other Virus Reported: When other virus alone was reported, Criteria B were followed. When positive serologic tests for poliomyelitis were obtained under these conditions, they were given diagnostic priority. This entire series of cases required close consideration and decision.

D. Family Associates With Virus Isolated: In some laboratories studies of the family associates were conducted. When virus was isolated from a family member but not from the patient, Criteria A were employed in interpreting patient's serology.

Final Diagnostic Classification

Although the frequency with which virus was isolated tended to increase with increasing clinical severity of illness, the failure to recover virus from a significant number of characteristic paralytic cases indicates that lack of virus isolation is not sufficient to eliminate the patient from classification as poliomyelitis. Consequently, a combination of clinical findings, muscle evaluation, and laboratory data were utilized in arriving at the final classification, but it should be reemphasized that this was done without knowledge of the vaccination status of the patient.

The conditions acceptable for a diagnosis of paralytic poliomyelitis were outlined as follows:

Paralytic Poliomyelitis: A case with findings consistent with a clinical diagnosis of poliomyelitis, with evidence of muscular impairment classified as paralysis - spinal, bulbar, or bulbo-spinal - in accordance with the established criteria previously discussed, with virological and/or serological evidence of infection with poliomyelitis virus as defined, was accepted as paralytic poliomyelitis and placed in the appropriate paralytic class.

If a case, clinically paralytic, yielded a type-specific poliomyelitis virus but serological data were indeterminate, negative or not obtained, it was still considered paralytic poliomyelitis caused by virus of that type.

If a clinically paralytic case failed to yield poliomyelitis virus but had serological evidence clearly demonstrative of specific infection it was classified as paralytic poliomyelitis, serologically positive; if the serological evidence was uninformative but not contradictory to poliomyelitis virus infection the clinical interpretation and muscle evaluation were of necessity the sole basis for classification as paralytic poliomyelitis.

When other viruses were isolated, careful judgment was required in deciding whether the case should be considered poliomyelitis; serological evidence of poliomyelitis virus infection was considered significant and, if such a case was also classified as paralytic, a final diagnosis of paralytic poliomyelitis might still be assigned. The tendency was clearly to lean to a diagnosis of paralytic poliomyelitis if a reasonable probability existed.

The criteria for classifying illnesses, other than paralytic poliomyelitis, were then formulated.

Nonparalytic Poliomyelitis: Cases called by the physician "poliomyelitis," exhibiting

characteristic clinical features, with positive spinal fluid, with or without virus isolation or positive serology, but without significant evidence of muscular impairment on the physical therapist's and other reports.

It is recognized that this is a difficult group to define, shading gradually as it does into cases in the minimal paralytic class. These cases were repeatedly reviewed for consistency within the classification.

Doubtful Poliomyelitis: Cases which, after careful review of all data, leave considerable doubt as to whether they are poliomyelitis.

Fatal Cases: In each fatality great effort was made to obtain a detailed record of the patient's history and course of illness leading to death, to urge post-mortem examination, and to obtain a complete report. When possible, histological sections were obtained for review by consultants. In some instances the examination was conducted after embalming, and specimens for laboratory study were only then obtained. In others, the post-mortem was done without obtaining laboratory specimens; in others, no autopsy was done.

1. Diagnosis of poliomyelitis was based upon history of characteristic severe disease and histological evidence described by a well-qualified pathologist, whether virus had been isolated or not.

2. Fatal cases were considered to be not poliomyelitis when the history specifically indicated other disease, when major evidence from post-mortems examination demonstrated other disease, or if there was a lack of changes characteristic of poliomyelitis in the bulb or spinal cord. No poliomyelitis virus was recovered from cases in this group.

Not Poliomyelitis:

1. Those cases in which the clinical record and comments, laboratory data, or diagnosis established otherwise, indicated other disease.

2. Cases with lack of common symptoms or signs of poliomyelitis and in which examination of spinal fluid was negative or not done.

3. Cases in which orphan viruses, or Coxsackie virus only, were isolated without serological evidence of poliomyelitis; or cases with serological evidence of active infection with mumps or other virus.

4. Cases without virus recovery and with no antibody to poliomyelitis virus detected.

DISTRIBUTION OF CASES BY DIAGNOSTIC CLASS

The distribution into major diagnostic classes of the total cases accumulated during the study period is shown in the following table. Cases classified as paralytic consti-

SUMMARY OF STUDY CASES BY DIAGNOSTIC CLASS

Diagnostic Class	Total		Placebo Areas		Observed Areas	
	Number	Percent	Number	Percent	Number	Percent
Total	1,012	100.0	428	100.0	584	100.0
Paralytic Poliomyelitis	682	67.4	267	62.4	415	71.1
Nonparalytic Poliomyelitis	176	17.4	88	20.6	88	15.1
Doubtful Poliomyelitis	66	6.5	24	5.6	42	7.2
Not Poliomyelitis	88	8.7	49	11.4	39	6.7

tute two-thirds of the total which is well above the proportion of 50 to 60 percent generally reported. This weighted effect is undoubtedly caused by the acceptance of cases with minimal involvement as paralytic. The exclusion of 15 percent of the cases as "doubtful" or "not poliomyelitis" means that essentially 80 percent of those accepted as poliomyelitis were considered paralytic. This approaches conformity with the probability suggested by our clinical and orthopedic consultants that every patient with involvement of the nervous system by poliomyelitis virus has muscular impairment.