Studies in Human Subjects on Active Immunization Against Poliomyelitis

II. A Practical Means for Inducing and Maintaining Antibody Formation

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Here is definitive evidence of the basis upon which a vaccine for poliomyelitis is being tested.

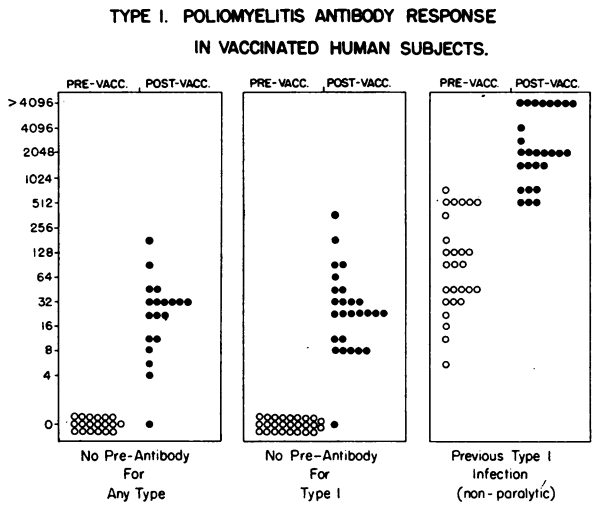
For almost two years we have been attempting to devise a practical means for immunizing man against paralytic poliomyelitis. As a guide for evaluating the approaches which have been employed, the assumption has been made that a method which will cause antibody to be present in the blood stream, in amounts comparable to that resulting from natural infection, might be expected to prevent the paralytic disease. A further assumption has been made that a method that will alter immunologic reactivity in a way that is similar to the alteration resulting from natural infection—that is to say, will cause the development of a state of heightened responsiveness to further inoculation (i.e., the "recall" reaction or the "booster" response) might be expected to provide long-term immunity. If these effects could be achieved with a noninfectious virus vaccine, further support would be provided for the hypothesis that it may be possible to simulate the immunizing effect of infection with chemically treated virus.[1]

The purpose of this report is to present the results of studies in human subjects, indicating the following: (1) By the proper use of a suitably prepared noninfectious vaccine, formation of antibody can be induced; and, in many instances, concentration of antibody in the serum can be raised to levels corresponding to those found in persons who have had a naturally acquired infection. (2) Primary immunization appears to sensitize the immunologic mechanism in a manner similar to that observed in persons who have had a natural infection.

Results

Primary Response to Vaccination in Persons with and without Prior Immunologic Experience with the Poliomyelitis Viruses—The data summarized in Figures 1, 2, and 3 contain a compilation of results of serologic studies in persons first inoculated in May, 1953. Some were inoculated with aqueous vaccines and others with adjuvant vaccines; still others with combinations of the two. Some received one inoculation, others received two, and still others received three. When two doses were administered they were given two weeks apart; the three doses were at intervals of one week. The antibody levels shown are those determined before and after three or six weeks following the first injection. In these charts no distinction

Figure 1



is made between those who received either one, two, or three injections; nor is any distinction made between those who received the aqueous or emulsified vaccines, or the combination of the two. These differences will be emphasized in another report on the relative efficiency and effectiveness of the different types of vaccines and different schedules of vaccination. As in so many other aspects of these continuing studies, large numbers of persons have been inoculated and numerous blood samples have been obtained; but not all have been tested. Rather, a sufficient number has been examined to indicate the trend and to answer an important question that would make possible the performance of another experiment. Even before the results are had from tests of all serum specimens the indication of the outcome is usually evident from an examination of suitably selected samples.

The principal purpose of the summaries in Figures 1, 2, and 3 is to illustrate the difference in immunologic responsiveness of individuals with and without prior immunologic experience with viruses of each of the three types. Another purpose is to illustrate the response of persons who before vaccination had no demonstrable antibody for any of the three virus types, compared with those who had no demonstrable antibody for only one or two types. In the left-hand frame of each chart (Figures 1, 2, and 3) is shown the levels of antibody induced in persons (mostly children) who had no detectable prevaccination antibody for any of the three virus types. In the middle frame is shown the levels of antibody induced for those types for which no antibody was detectable for the respective type in persons who had antibody for one or both of the other two types. In the right-hand frame is shown the distribution of antibody titers before and after vaccination for those types for

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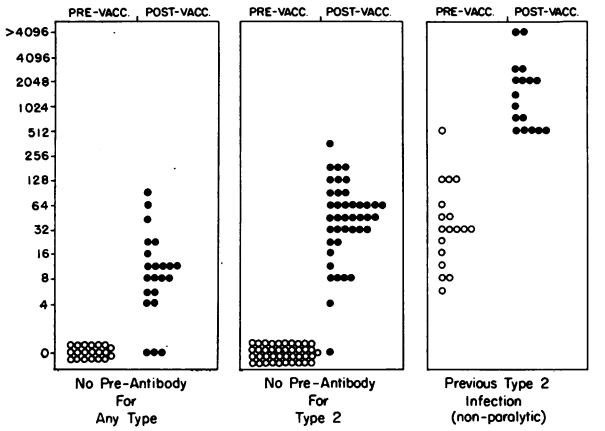
Figure 2

TYPE 2. POLIOMYELITIS ANTIBODY RESPONSE IN VACCINATED HUMAN SUBJECTS.



which prevaccination antibody was present.

The indications are clear from these charts (Figures 1, 2, and 3) that persons with some antibody, acquired as a result of previous natural infection, respond much more strikingly than do those who have had no prior immunologic experience with the respective virus types. There is some indication in Figure 2 that the presence of antibody to one or more of the other types facilitates slightly the response to the type for which no antibody is present before vaccination. However, the difference between this effect, illustrated by comparing the first and second frame of each figure (in Figures 1, 2, and 3) and the effect illustrated in the third frame is very striking indeed.

Figure 3

TYPE 3. POLIOMYELITIS ANTIBODY RESPONSE IN VACCINATED HUMAN SUBJECTS.

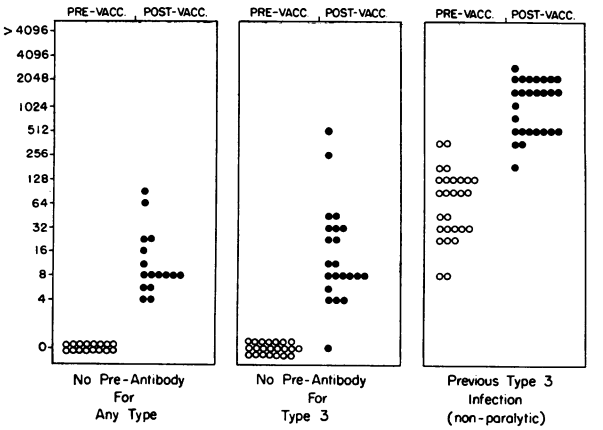


Table 1—Antibody Persistence Over Seven Months and Response to Booster Injection at that Time in Persons with No Prevaccination Antibody to Respective Types

Subject No.	Age	TYPE 1 Pre-Vacc.	TYPE 1 7 Mos.*	TYPE 1 12 Days Later	TYPE 2 Pre-Vacc.	TYPE 2 7 Mos.*	TYPE 2 12 Days Later	TYPE 3 Pre-Vacc.	TYPE 3 7 Mos.*	TYPE 3 12 Days Later
F-77	7	0	4	512	0	4	128	0	8	512
F-80	6	0	4	512+	0	0	256	0	4	512+
F-336	12	0	16	1,024	0	16	256	0	16	512
F-79	10	0	4	128	0	4	256	0	4	128
F-328	10	0	64	4,096+	0	4	256	0	4	256
F-332	3	0	8	256	0	128	1,024	0	0	512
F-4	6	0	64	1,024	0	4	1,024	0	4	512
F-47	10	0	16	1,024	0	4	256	0	8	1,024
F-2	9	0	32	512	0	8	128	0	4	256
F-45	9	0	32	4,096+	0	32	512	0	16	1,024
F-335	11	0	32	2,048	0	0	128	0	8	1,024
F-175	7	0	4	1,024	0	8	512			
F-176	9	0	4	64	0	16	256			
F-55	9	0	8	1,024+	0	8	1,024+			
F-56	5	0	4	1,024+	0	0	512			
F-76	9	0	16	512	0	4	128			
F-30	13	0	16	256	0	8	128			
F-31	4	0	8	512+	0	32	1,024			
F-52	7	0	16	1,024	0	4	512			
F-54	5	0	32	512	0	8	256			
F-53	12	0	32	2,048	0	64	128			
F-142	33	0	64	256				0	8	128
F-307	4	0	128	2,048				0	16	4,096+
F-308	4	0	32	512				0	0	32
F-330	3	0	128+	1,024+				0	8	2,048+
F-84	17	0	32	2,048				0	4	1,024
F-162	14				0	32	1,024	0	8	128
F-226	A †				0	32	512	0	16	32
F-337	8				0	16	128	0	16	2,048
F-74	15				0	32	1,024	0	8	64
F-85	12				0	32	256	0	16	1,024
F-104	13	0	32	1,024						
F-72	4	0	16	256						
F-318	A	0	64	256						
F-83	A				0	16	64			
F-1	18				0	16	1,024			
F-18	12				0	64	256			
W-48	A				0	8	256			
F-78	11							0	16	128
F-6	16							0	64	512
F-14	A							0	32	1,024+

* = Time of booster injection.
† A = Adult.

Degree of Persistence of Vaccine-Induced Antibody during an Observation Period of Seven Months and Response to a Booster Injection—When these data became available the question that arose immediately was whether or not those who had no demonstrable antibody prior to vaccination in May, 1953, would react upon reinoculation, with antibody formation, in the manner observed in those who had a natural infection prior to the injection given in May, 1953. Accordingly, on December 28, 1953, a group of 163 persons was reinoculated. In addition a new group of 26 was vaccinated for the first time.

Figure 4

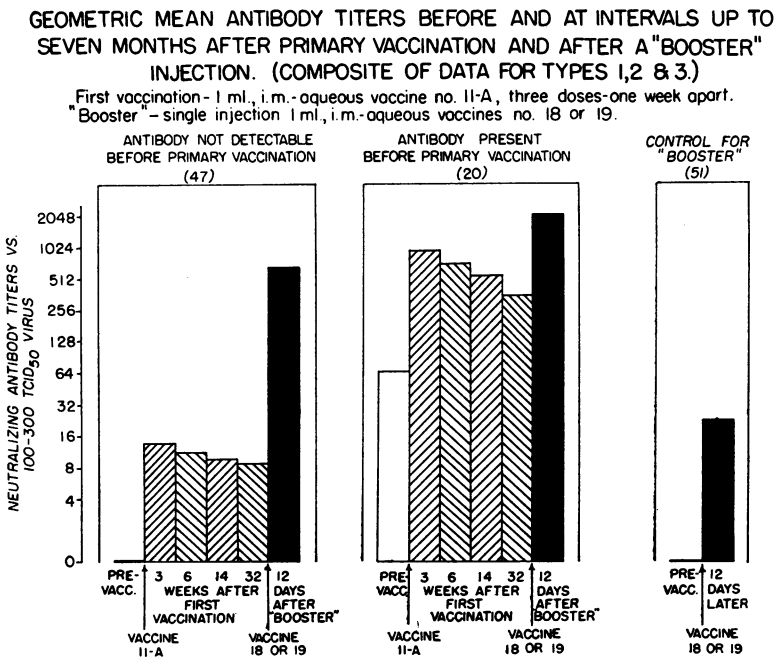


Figure 5

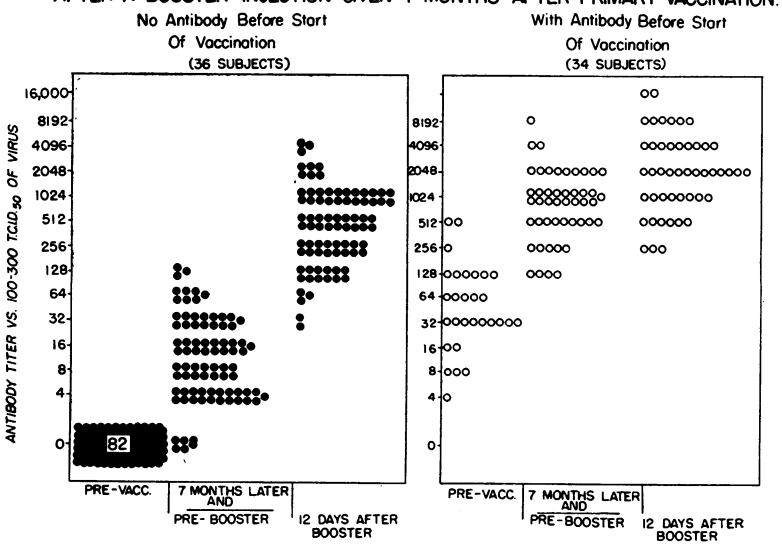


Table 2—Antibody Persistence Over Seven Months and Response to Booster Injection at that Time in Persons with Prevaccination Antibody for the Indicated Types

Subject No.	Age	TYPE 1 Pre-Vacc.	TYPE 1 7 Mos.*	TYPE 1 12 Days Later	TYPE 2 Pre-Vacc.	TYPE 2 7 Mos.*	TYPE 2 12 Days Later	TYPE 3 Pre-Vacc.	TYPE 3 7 Mos.*	TYPE 3 12 Days Later
F-306	A	4	128	256	128	2,048	2,048	45	2,048	2,048
F-59	A	+	1,024	1,024	+	512	512	+	256	256
F-78	11	+	512	512	+	1,024	1,024			
F-6	16	90	512	2,048	128	1,024	1,024			
F-14	A	11	1,024	2,048	22	1,024	4,096			
F-83	A	+	128	512				+	1,024	1,024
W-48	A	+	2,048	4,096				+	2,048	4,096
F-104	13				8	128	512	8	1,024	1,024
F-103	15				45	1,024	1,024	128	2,048	2,048
F-72	4				32	128	512	128	256	256
F-318	A				90	512	512	32	1,024	1,024
F-162	14	+	512	4,096						
F-85	12	+	1,024	2,048						
F-74	15	700	2,048	16,000+						
F-1	18	32	1,024	2,048						
F-18	12	128	8,192	8,192						
F-21	A	358	1,024	4,096						
F-337	8	512	2,048	8,192+						
F-142	A				+	2,048	8,192			
F-84	17				32	512	16,000+			
F-307	4				+	1,024	8,192+			
F-308	5				+	256	2,048			
F-330	3				+	512+	2,048+			
F-175	7							+	1,024	4,096
F-176	9							+	512	2,048
F-55	9							32	1,024	8,192
F-56	5							32	256	4,096
F-76	9							90	1,024	2,048
F-30	13							45	2,048	2,048
F-31	4							512	1,024	4,096
F-52	7							90	256	1,024
F-54	5							90	512	1,024
F-53	12							128	4,096	8,192+

* = Time of booster injection.
\+ = Presence of antibody at 1:4 dilution (not titrated).

The latter group was to serve as a control since the preparation of vaccine used was different from that employed in May and it was necessary to compare the effect of a single injection in persons treated previously with that which occurred in those who had no prior treatment.

In this particular study, opportunity was had to observe not only response to reinoculation seven months after the primary immunization, but to observe as well the degree of persistence of antibody over the seven-month interval. The degree of persistence of antibody and the booster response will be illustrated in Tables 1 and 2, and in the accompanying Figures 4 and 5.

The data contained in Table 1 indicate the titers of antibody seven months after vaccination in persons who had no demonstrable antibody before vaccination either for all three virus types or who had no demonstrable antibody for one or two types. It is clearly evident from these data that, in a majority of instances, antibody was still detectable seven months after vaccination; and,

that 12 days after a single booster dose, consisting of 1 ml. of aqueous vaccine No. 18 or No. 19, titer of antibody increased substantially. These vaccines had been prepared by treatment with 1:4,000 formalin at 36° C.[2] Before presenting the control data for persons inoculated for the first time with vaccine No. 18 or No. 19, attention is drawn to Table 2 which contains information on subjects who had antibody, for the respective types, from a previous natural infection. The purpose of this table is to show the high degree of persistence of antibody, resulting from the initial course of vaccination, in persons previously infected naturally and in whom the primary vaccination was, in effect, a booster treatment.

A summary of these data, in which information is included only for those who received the aqueous material intramuscularly in 1 ml. doses, is shown in Figure 4. Here may be seen the geometric mean antibody titer in those who had no detectable antibody before vaccination and in whom, three weeks after vaccination, antibody level was at its maximum; a gradual decline was evident when calculations were made of the geometric mean of antibody titers at 6, 14, and 32 weeks after vaccination. One can also see the sharp rise in antibody level that occurred within 12 days after the booster injection. In the middle frame of Figure 4 is shown the geometric mean antibody level before vaccination for those types for which antibody was present as a result of a previous natural infection and how antibody rose sharply within three weeks after start of immunization, and then declined gradually, only to be reinforced at the time of the booster injection. It is clear from these data that, following the "booster," in those who had no detectable antibody before vaccination, the geometric mean antibody level was considerably higher than in normal or unvaccinated persons who had experienced a previous natural infection at some indeterminate time in the past.

The two-step relationship showing the primary and the booster response is illustrated more clearly in Figure 5. In this composite chart is shown the distribution of antibody titers before the start of vaccination, and the levels at the seven-month period; this chart contains the data for subjects included in Tables 1 and 2, and a few additional ones. Here one can see quite clearly that the levels of antibody remaining seven months after primary immunization, with vaccines and dosage schedules employed in this experiment, involving persons with no immunologic evidence of natural exposure, is somewhat lower than in those who had had a prior nonparalytic infection. Nevertheless, when the second stage was effected, which represented the booster response, both groups appeared to be comparable. The difference between the two groups, evident at the time of the primary immunization stage, was obliterated following the booster inoculation.

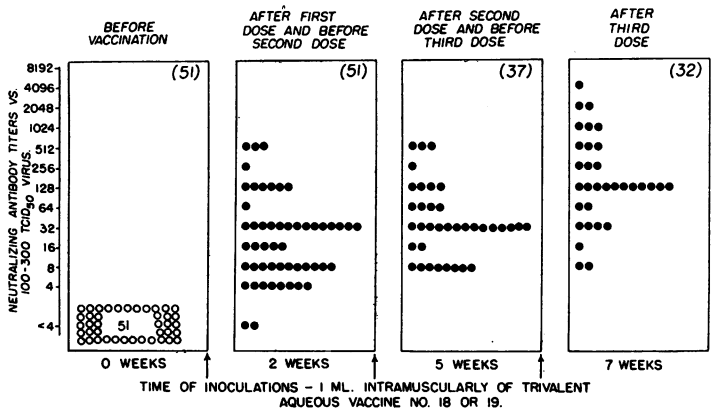
From the data shown in Table 2 and Figures 4 and 5, it appears that the level of antibody remaining seven months after vaccination, in persons who had had a previous natural exposure, was still well beyond that observed prior to inoculation. Furthermore, another injection at the seven-month point induced a limited rise in the majority.

Course of Antibody Development after Primary Immunization with Three Doses of Aqueous Vaccine—Other observations of interest are illustrated in Figures 6 and 7 which show the course of antibody development following three inoculations given with an interval of two weeks between the first and second, and three weeks between the second and third inoculation. The primary immunizing effect is that observed in persons who had no demonstrable antibody before vaccination (Figure 6) and the

Figure 6

COMPOSITE CHART FOR TYPES 1,2 & 3 POLIOMYELITIS ANTIBODY SHOWING RESPONSE TO VACCINATION IN 27 PERSONS WHO BEFORE VACCINATION HAD NO DETECTABLE ANTIBODY FOR THE RESPECTIVE TYPES.

Ten Had No Antibody To Any Of The Three Types And Seventeen Had Antibody To One Or Two Types.



secondary or booster effect is illustrated in those who at the time of vaccination possess antibody from a previous natural exposure (Figure 7). It is clear, in the latter group, that the major effect occurs as a result of the first injection.

To return to the group in which primary immunization was effected (Figure 6) it is evident that even the first injection induced a measurable response in the majority of persons and this response was of the magnitude illustrated at 12 days after inoculation. In other experiments in progress, in which

Figure 7

COMPOSITE CHART FOR TYPES 1,2 & 3 POLIOMYELITIS ANTIBODY SHOWING RESPONSE TO VACCINATION IN 17 PERSONS WHO BEFORE VACCINATION HAD ANTIBODY TO ONE OR MORE TYPES FROM NATURALLY ACQUIRED INFECTION.

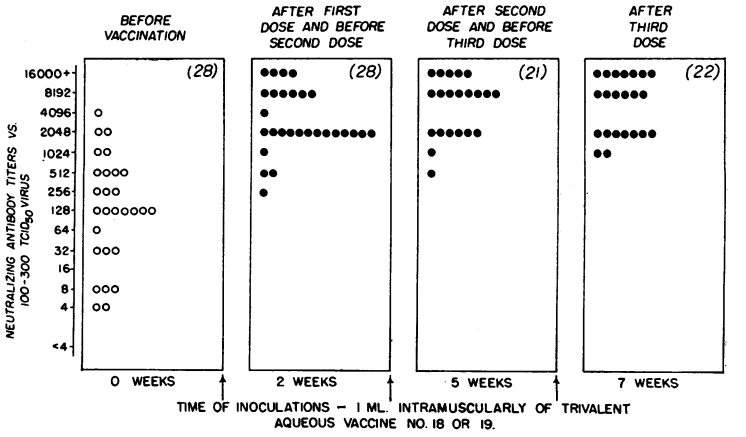
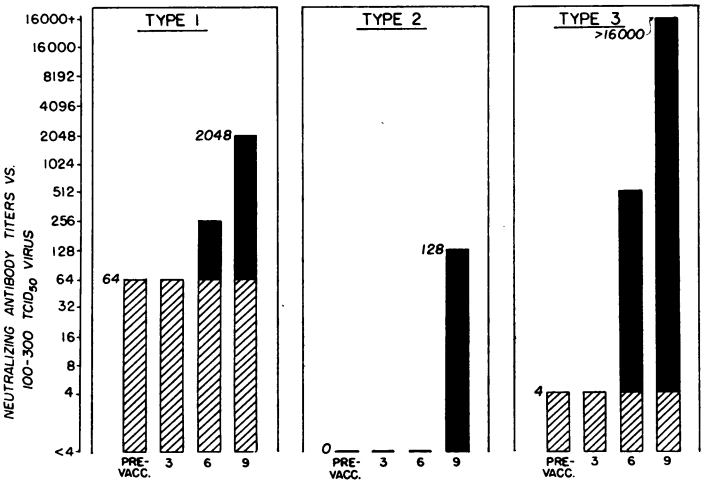


Figure 8

TIME OF APPEARANCE OF ANTIBODY AFTER A SINGLE INJECTION OF AQUEOUS POLIOMYELITIS VACCINE.



blood samples have been drawn at intervals of three days (Figure 8), it appears that antibody begins to become apparent between the third and sixth day, if there had been a prior immunologic experience with virus of the homologous type, or between the sixth and ninth day if there is no evidence of previous contact (i.e., Type 2 in Figure 8). Nevertheless, when three injections were given at 0, 2, and 5 weeks, the levels of antibody measured two weeks

Figure 9

DISTRIBUTION OF TYPES 1,2 & 3 ANTIBODY TITERS BEFORE AND AFTER VACCINATION WITH AQUEOUS, TRIVALENT POLIOMYELITIS VACCINES NOS. 18 AND 19 IN PERSONS WITH

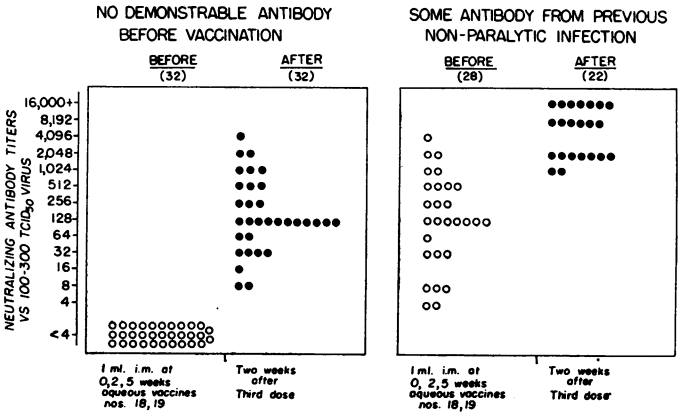
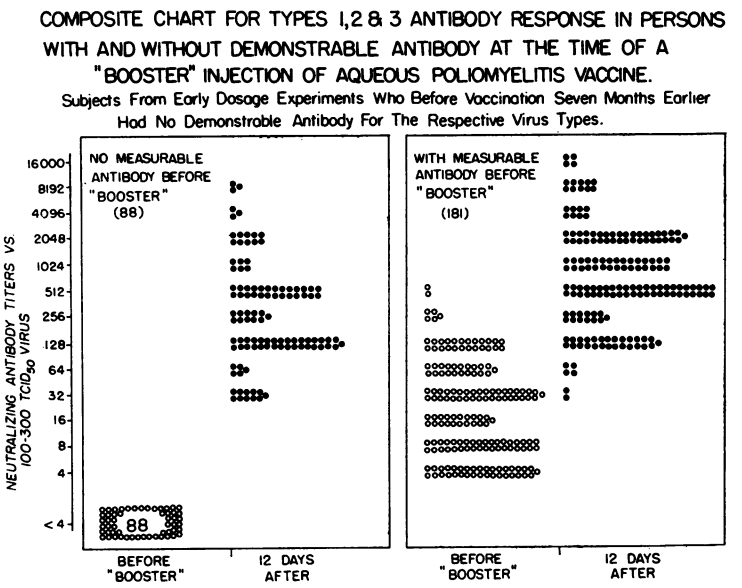
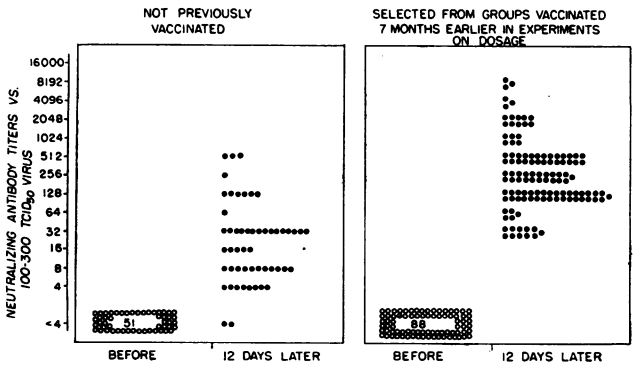


Figure 10



after the third injection appear to be comparable in distribution to that observed in persons who in the past had a naturally acquired nonparalytic infection (Figure 9). It is clear that three doses of vaccine within a five-week period (Figure 6) had not induced the levels of antibody that can be achieved by utilization of the longer interval before administering the booster dose, as was possible in persons in whom an interval of seven months had elapsed since primary immunization (Figures 4 and 5), or in persons who had a prior natural infection at some indeterminate time in the past (Figure 7). The data

Figure 11



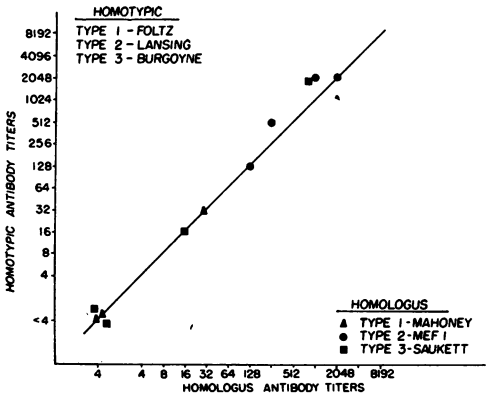
in Figure 9 suggest, therefore, that multiple inoculations at short intervals (Figure 6) are not as efficient as primary immunization followed by a booster dose at a somewhat longer interval than from two to five weeks. Evidence that bears on this suggestion is presented in Figures 10 and 11.

Immunologic Hyper-Reactivity in Vaccinated Persons—It is to be recalled that in the studies begun in May, 1953, numerous variables were studied simultaneously. Serologic studies have been completed thus far in a portion of more than 400 subjects involved. In the experiments begun in May, 1953, studies were made of the influence upon antibody response not only of vaccines treated with different concentrations of formalin and prepared from different virus pools, but of different numbers of inoculations and different sizes of inocula. For example, in some subjects one injection was given; in some, two; and in still others, three. Some inocula contained a total of 0.3 ml. of tissue culture fluid representing 0.1 ml. of each type; in many individuals a single injection of such material was all that was administered. It is understandable, therefore, that in the course of these exploratory experiments many individuals, particularly those given only one dose, would have responded poorly or not at all. This is reflected in Figure 10, showing that seven months after inoculation there were 88 instances in which antibody to Types 1, 2, or 3 was not detectable; in 181 instances Types 1, 2, or 3 antibody was measurable; this represents all data available for analysis in 269 instances in which there was no detectable antibody before vaccination in May, 1953. When the response to reinoculation at the seven-month interval is examined, it is clear that both groups responded sharply. The mean level achieved in those who had some demonstrable antibody at the time of inoculation was approximately four-fold higher than in the group that had no detectable antibody before the reinoculation. This is not surprising for two reasons: (1) the higher prevaccination levels in the group with antibody before the booster, and (2) this group might conceivably represent the better antibody producers in this population group.

However, the most significant feature about the observations made in this study is shown in Figure 11 which compares the behavior of two groups of individuals who had no detectable antibody at the time of inoculation; one group was composed of persons who had not previously been inoculated and the other contained persons who had been inoculated seven months earlier. The mean response in the two is strikingly different indeed. The range of antibody levels after vaccination in those who had not previously been inoculated was from < 4 to 512, with a mean in the region of 16; this was the response to a single inoculation in persons who did not possess any detectable antibody. Whereas in the 88 instances in which antibody was not present, but where vaccination, of borderline stimulation, had been employed seven months earlier, the response ranged from 32 to 8,192, with a mean value in the region of 1:256. Thus, it would appear that there is a sharp difference between what might be referred to as an "immunologically experienced negative" as compared with an "immunologically inexperienced negative." Accordingly, it would seem that inoculation even with poor antigens or with a minimal course of vaccination did have some effect even though not demonstrable in terms of detectable antibody seven months after the primary immunization procedure. However, the imperceptible effect was clearly brought out by the reinoculation. This has very important practical implications and suggests that it should be possible to maintain measurable levels of antibody

Figure 12

COMPARABILITY OF ANTIBODY TITERS FOR TWO DIFFERENT STRAINS OF THE SAME TYPE IN SAMPLES OF HUMAN SERA



for long periods of time, and to reinforce, or further enhance, these levels.

Preliminary Data from Studies on Different Strains of the Respective Immunologic Types—A very important question that remains to be answered is whether or not the different strains of each type of poliomyelitis virus are sufficiently similar so that any strain may serve as the prototype. This question arises because of differences among strains within each of the types of influenza virus, and in other groups of microbial agents that are immunologically complex. Data are available thus far in a comparison of two strains for each of the three types, i.e., the strains in the vaccine, which are called homologous, and one other strain for each type, which is called homotypic. The indication, from the limited data shown in Figure 12, is that the two arbitrarily selected viruses of each type are closely related immunologically. This chart is presented merely to indicate that thought has been given to the question that has been posed, and to show the first results available.

Clinical Observations in Vaccinated Subjects—In the course of the month after vaccination of approximately 4,000 children, with vaccine made in this laboratory, and of 3,000 children inoculated with vaccine prepared from fluids made at the Connaught Medical Research Laboratories, University of Toronto, and then processed in laboratories of producers of biological products, no untoward effects were observed either at the site of inoculation or systemically. There was but one instance of transient urticaria of a mild degree in one child who was reported, by the parent, to be allergic to penicillin. Prior to skin test and reinoculation, the child's pediatrician was consulted and he reported that he had given the child penicillin many times without any symptoms suggestive of penicillin allergy. The report from the parent was that the child had hives following an injection, thought to be penicillin, administered on a trip to Mexico City some four years earlier. It is possible that the episode four years earlier, as well as the one associated with the first inoculation of vaccine,

may have been coincidental. On the other hand, one must keep in mind that the vaccine can be an offender in penicillin-sensitive individuals since the culture fluid used for the preparation of vaccine contains a maximum of 500 units of penicillin/ml (the antibiotic activity is markedly reduced by the time the vaccine is finally processed). However, many children believed to be allergic to penicillin or to a number of other allergens have been vaccinated without any discernible difference in clinical reactivity as compared with nonallergic children. Observations made in the course of one month indicated that the rate of absenteeism in both inoculated and uninoculated children was similar; the reasons being essentially the same in both groups. This is illustrated in Table 3. Thus it would appear that the absence of untoward local or systemic effects, observed in the course of earlier studies, continues.[2-4]

Discussion

Perhaps it would be best to summarize and discuss the new findings presented here in the form of answers to practical questions that exist in the minds of many.

First, it may be said that a practicable procedure is available for inducing the formation of poliomyelitis antibody that appears to persist for an, as yet, undetermined period of time. Still to be established is the optimal interval between injections for the most effective primary immunization schedule, and the optimal interval for whatever reinoculations may be required for long-term immunization.

As part of the foregoing, there is the further problem of determining the minimal amount of virus necessary to produce the desired level of antibody for immunity. In this regard, it is pertinent to mention that the efficiency

Table 3—Absenteeism Among Groups of Vaccinated and Nonvaccinated Children in First Three Grades Beginning on the Day After Inoculation

	Vaccinated (2520) *		Nonvaccinated (1289) †	
	Number	Per cent	Number	Per cent
First Week				
1 day	228	9.0	130	10.1
2 days	70	2.8	35	2.7
3 or more days	84	3.3	38	2.9
Second Week				
1 day	175	6.9	122	9.5
2 days	43	1.7	24	1.9
3 or more days	66	2.7	36	2.7
Third Week				
1 day	70	2.8	32	2.5
2 days	5	0.2	6	0.5
Duration unknown ‡	104	4.1	45	3.4

* Vaccine prepared for field tests was used.

† Includes only group in which consent for vaccination was not given and does not include those absent on day of vaccination.

‡ Easter week-end.

(Table derived from analysis made by Mr. Morton Boisen and Dr. Robert Korns of Dr. Thomas Francis's staff of the Poliomyelitis Vaccine Evaluation Center, University of Michigan, Ann Arbor, Mich. Report in more detail to be made.)

of virus cultivation has increased beyond earlier expectations and that several liters of fluid of high virus titer can be obtained regularly from cultures of kidney tissue of a single monkey. The final limit of yield may, as yet, not have been reached.[5]

Further experience with inactivation of virus by formaldehyde and studies on the retention of antigenic activity upon "overexposure" during the virus-inactivation procedure indicates that a substantial margin of safety exists between the point at which it may be presumed that the last virus particle has been converted to the noninfectious form and the point at which antigenicity is significantly reduced.[5]

Because of the fact that virus for vaccine is propagated in cultures of monkey kidney tissue, some have wondered whether or not immunization with such vaccines may have some damaging effect upon the kidneys. Although, on a priori grounds, there is little reason to believe that this might occur, this question has been the subject of continued study, in a variety of ways, and there are no indications thus far of any harmful effect upon the kidney, either in experimental animals or in man.[5]

The question has also been raised as to the possibility of sensitization to the Rh factor, since vaccine is derived from cultures of monkey tissue. It is difficult to visualize how this might occur, particularly since it appears that the Rh antigen is not a soluble one but one associated with red cells or stroma. In the absence of particulate material, which is removed from the fluids by passage through bacteria-withholding filters, it would be difficult to see how the Rh antigen might be retained in the fluid used for immunization. Nevertheless, this question is under study by interested investigators and their reports will be made in due course.

Although the objective of these studies is the creation of a barrier within the circulatory system, and even along nerve pathways, that might prevent virus from gaining access to the central nervous system, it would be equally acceptable if the immunizing procedure were so satisfactory as to prevent the establishment of infection. Whether or not infection is prevented is of academic importance if the paralyzing effect of virus invasion does not occur. Since procedures are now available for inducing and maintaining antibody formation, and since evidence has been presented indicating that a state of heightened immunologic reactivity is produced by vaccination, it would seem reasonable to determine whether or not the immunologic effects of vaccination result in protection against paralysis under natural conditions of exposure.

The principal question that can be answered only by studies under natural circumstances will be, "Does a procedure that induces antibody of a certain level have a corresponding effect in the prevention of the paralytic disease?" If the correlation is incomplete then the question to be answered will be, "What are the factors responsible for any lack of correlation between presence of antibody in the serum and clinical immunity?" The many factors to consider are: (1) whether or not there are but three immunologic types of poliomyelitis virus; (2) whether or not there are major immunologic differences among strains within each type; and (3) whether or not the level of antibody induced is sufficient to intercept virus before invasion of the central nervous system, not only via the blood stream but via nerve pathways, since the relative frequency of the two modes of pathogenesis is not yet known.

It is clear that only by studies made in the course of application of vaccination under natural circumstances can these questions be answered. The evidence is clear that it is possible to induce antibody formation with a non-

infectious vaccine and that the antibody so induced tends to persist at demonstrable levels for a period of time, the full length of which is still to be determined. An equally interesting finding is the observation of a sharp rise in antibody titer that occurs following a suitably spaced booster injection. The term "booster" is strictly applicable only to injections that are made after intervals that are sufficient to allow adequate development of the state of immunologic hypersensitivity which is a prerequisite for the booster effect. It would appear from the data here presented that the term "booster" cannot be applied to the last of a series of three injections given within a five-week interval; a clearly demonstrable booster effect was achieved when an interval of seven months had elapsed since primary immunization. Studies now under way are designed to determine the shortest interval within which the booster response can be elicited for the full immunization effect.

Thus, within time limitations for setting up the field tests on efficacy of vaccination, during the summer of 1954, the only test that can be made is to determine the influence of primary immunization. This will provide an extraordinary opportunity to obtain an answer to some very important theoretical as well as practical questions. It will be of interest to know whether or not the course of immunization being employed, without sufficient time for the full booster response, induces full or partial resistance; it will be of further interest to determine whether or not the natural exposure will provide the booster stimulus to reinforce any basic immunity that is provided by so-called primary immunization effect. If this be so, then it would suggest either that a sufficient level of antibody is present at the time of exposure or, if low or not demonstrable, that sensitization of the antibody mechanism by vaccination was adequate and that the interval between infection and the reappearance of antibody may be shorter than the incubation period for central nervous system invasion.

One might question the justification for the conduct of a study such as the one under way when it is known, from the immunologic evidence here presented, that a different schedule of immunization is capable of producing a more substantial effect. The answer to this question might well be, "What justification is there for not proceeding with test of a procedure that on theoretical immunologic grounds, and thorough laboratory studies in experimental animals, as well as observations in man, indicate that the presence of antibody in serum, even in low levels, may be capable of preventing paralysis—at least in some individuals." Since the final answer to the question of efficacy of any procedure can be had only by direct test, it would seem that only by proceeding in the manner currently under way can any progress whatever be made in gaining the ultimate objective—the prevention of paralysis in children.

No experiment, well conceived, ever fails. We must keep an open mind and, based upon whatever findings are made, plan for the next step beyond.

Summary

Results of serologic tests in human subjects indicate that: (1) By the proper use of a suitably prepared noninfectious vaccine, formation of antibody can be induced; and in many instances, concentration of antibody in the serum can be raised to levels corresponding to those found in persons who have had a naturally acquired infection. (2) Primary immunization appears to sensitize the immunologic mechanism in a manner similar to that observed in persons who have had a natural infection. It

would appear from the data here presented that the term "booster" cannot be applied to the last of a series of three injections given within a five-week interval; a clearly demonstrable booster effect was achieved when an interval of seven months had elapsed since primary immunization. Clinical-epidemiologic observations in the course of one month following the use of laboratory prepared vaccine in 4,000 and vaccine processed by producers of biologicals in 3,000 indicated no untoward effects, either local or systemic. The question of penicillin allergy has been mentioned.

The implications of these findings in relation to the tests on efficacy of vaccination in 1954 are discussed.

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National Health Council Directory

The 1954 Directory of Member Organizations was published by the National Health Council in June. It is made up of capsule descriptions of the broad objectives, immediate program, services, structure, and sources of financial support of 48 national organizations that are presently members of the council. Also shown are the names of the executives, addresses of the headquarters offices, and publications of the 48 members. The membership includes professional and voluntary health organizations, citizen agencies with an interest in health, federal health organizations as advisory members and two sustaining members.

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