Vaccination Against Paralytic Poliomyelitis

Performance and Prospects

For the Staff of the Virus Research Laboratory by Jonas E. Salk, M.D., F.A.P.H.A.

The studies upon which this report is based represent the joint efforts of many. That the product of their labors is greater than the sum of the individual contributions is the measure of the extra devotion for which there is no compensation save the satisfaction of doing what each enjoys most and can do best.—JONAS E. SALK

> *Here is evidence on which is based a newly recommended schedule of two-dose primary immunization against poliomyelitis.*

✤ In preparing a paper for presentation this morning (April 12, 1955) without prior knowledge of the details of Dr. Francis' report, it seemed best to orient the subject rather generally and let the evidence speak for itself.

General Observations

To comprehend more easily the various questions concerned in relation to the whole, I would like to repeat the hypotheses that have guided our studies. Apart from the immediate question of the possibility of preventing paralytic poliomyelitis by immunologic means, there is the further issue, in the broader realms of the field of immunology, con-

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cerning the relative advantages of immunization with so-called living-virus vaccines as compared with killed-virus vaccines. We have approached these questions from the viewpoint that, in accordance with well established immunologic principles, it should be possible, using a killed-virus preparation, to reproduce the immunizing effect of the infectious process.

During the course of our work it has become quite clear that commonly accepted opinions that are not founded on quantitative observations can not be supported for long. Having conducted a number of exploratory experiments, it became evident that destruction of virus infectivity with retention of antigenicity and the reaction involved in the immunologic response were both governed by certain definable and unalterable laws. While in some respects the existence of such rigid laws imposed restrictions and limitations, they also helped define the degrees of freedom within which certain effects could be reproduced consistently.

I shall dwell lightly upon these considerations merely to emphasize that it is not gambling in which we have been engaged, but rather in pursuits in a field of science. It would hardly be fitting, or proper, to set in motion an activity so involved in itself, and involving so many people, if all that were to be gained was that on a given occasion the preparation of vaccine in a certain way and used in accordance with a certain schedule did or did not perform in the "hoped for" manner. Each succeeding experience is of value if it adds to our understanding, and if it provides the basis for reducing the number of variables to within the necessary range required for greatest effectiveness.

This is not the occasion upon which to bring forth the wealth of evidence that has clarified our understanding of the dynamics of the various processes involved (1) in the preparation of virus for vaccine, (2) in destruction of virus

infectivity with retention of antigenicity, and (3) in the immunologic reaction that follows the injection of a vaccine. For completeness, however, I merely want to mention some of the primary considerations that are necessary for achieving a particular level of performance of a vaccine designed to prevent paralytic poliomyelitis.

We have discussed in considerable detail elsewhere the principles involved in destruction of virus infectivity with formaldehyde; suffice it to say that this reaction appears to proceed as does a first-order chemical process (Figure 1). This makes possible the prediction, rather precisely, of the time required to render each preparation free of living virus. In still other experiments the rate of decline of antigenicity has been studied similarly and it has been established that the chemical treatment required for the preparation of vaccine does not reduce, in measurable degree, the antibody producing power of the virus unless overtreatment is extended for a period equal to more than five times that required to reduce infectivity beyond the point at which it is no longer measurable. With a margin of safety of this magnitude, both for destruction of infectivity and retention of antigenicity, it might be said that this aspect of the problem demands little, if any, further attention. Moreover, the vaccine prepared in this way is of such stability that no special precautions are required for its maintenance.

Perhaps the most interesting aspect of these investigations has been in the area of the antigenic behavior of the poliomyelitis viruses. Much has been learned that can be considered new knowledge, since in these various inquiries many of the properties and potentialities of the poliomyelitis viruses have been revealed and defined. For example, it has been shown that the quantity of virus, after conversion into the noninfectious form, required to in-

Figure 1

Composite of Data on Rates of Destruction of Infectivity of Types 1, 2, and 3 Virus for 13 Lots of Vaccine Prepared by One Manufacturer and 20 Lots Prepared by Another

Points Indicate Mean of Virus Titers at Intervals After Addition of Formalin to Warmed Fluids
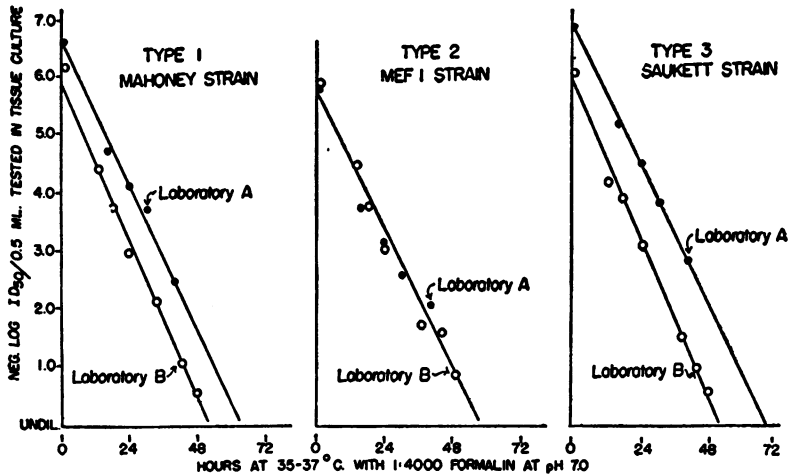
duce an immune response in man is far less than might have been anticipated on the basis of comparisons with most other microbial antigens. Another point of interest is the observation that it is far easier to induce an immunologic response in man than it is in the monkey; the monkey, in turn, is more reactive in this respect than is the mouse. Thus, any preconception that may have existed that the quantity of antigen necessary to induce antibody formation in the mouse or in the monkey would have to be multiplied proportionately for the weight of a child seems not to apply; in fact, the relationship that does exist seems to be an inverse one.

You may see from this, therefore, that the recognition of the existence of these two immunologic facts both simplified and complicated the further pursuit of the problem before us. Simplification was provided by the recognition that the poliomyelitis virus was a much better antigen than had been believed and the

complication introduced was in the recognition that valid answers, as applied to man, could not be had through the conduct of immunologic investigations in experimental animals. Quantitative immunologic studies had to be conducted first in man himself, after which tests in laboratory animals could be correlated and used for predicting probable antigenic performance in man.

In addition to the observation just cited, that it is easier to elicit antibody formation in man than in experimental animals, was the further demonstration that antibody persists for much longer periods of time in human subjects than in either the monkey or the mouse. Observations on the rate of decline of antibody induced by injection of killed vaccine into mice and monkeys would indeed make the prospects for a durable effect in man seem very dim; whereas, similar studies in human subjects present a much more hopeful prospect, indeed.

Other findings of interest are related to the length of the interval between primary and secondary stimulation, necessary to induce what is colloquially referred to as the "booster" effect. The length of the interval that must elapse for the hyperreactive mechanism to develop fully, after primary stimulation, is quite different in the mouse, in the monkey, and in man. Although intermediate degrees of hyperreactivity can be elicited by a second inoculation that is given earlier, the full effect in the monkey can be induced if the primary and secondary stimulations are separated by an interval of four weeks. The interval required to produce similar effects in the mouse is much shorter, and in man the interval required is very much longer. Thus, if one were to assume that the intervals required for completing the full immunologic response to a noninfectious vaccine is the same in man as in the experimental animals just cited, then the effects induced in man would have been incomplete and may have led to conclusions different from those to be drawn from our studies. As will be seen in a moment, the period required for the development of the hyperreactive state in man following primary antigenic stimulation seems to be a number of months rather than a period measured in weeks. The significance of these findings for utilizing the full potential of a vaccine has been amply confirmed, at least in so far as antibody measurement is concerned. These considerations have a very important bearing upon the question of persistence of vaccine effect, as well as upon the question of the most efficient utilization of a killed-virus vaccine.

Although almost all of these immunologic facts were appreciated before the initiation of the field test in the spring of 1954, not only from the accumulated experience in the broad field of immunology but as related specifically to the poliomyelitis virus, it was not possible to put this knowledge into practice because there was barely sufficient time before the onset of the seasonal upsurge to begin the studies then initiated. We might say, therefore, that the study conducted in the field in the spring and summer of 1954 was a test of the question as to whether or not primary vaccination alone could prevent paralytic poliomyelitis and not a test of the question of the effectiveness of full immunization which could be achieved only if the course of inoculations could have been extended over a number of months at least. Needless to say, if primary vaccination did induce an effect, then there is implicit an answer to the further question that concerns the degree of persistence that might be anticipated if advantage is taken of the secondary, as well as the primary, vaccine response.

I would like, now, to turn attention to questions of vaccine performance, before arriving at the point in the discussion that will deal with the prospects for prevention of paralytic poliomyelitis by vaccination.

Comparisons Between Vaccine Lots

Method of Study—Having reached the present state of knowledge of the requirements for preparation of a vaccine, it seemed desirable before proceeding further to study the performance of one particular vaccine. against which all others could be compared. We proceeded, therefore, with the preparation of what we refer to as Reference Vaccine A to serve as a standard against which the vaccines used in the field tests were to be compared; this would be used, also, to help define the relative antigenic potency of vaccines that may be studied, or used, in the future. Figure 2 shows the kind of antibody response elicited by 1 ml of Reference Vaccine A, given intramuscularly, on each of three occasions separated by

Figure 2

Geometric Mean Titers After Each of Three Doses of Reference Vaccine "A"

1 ml., I.M., in 20 Subjects with No Preantibody to Any Type
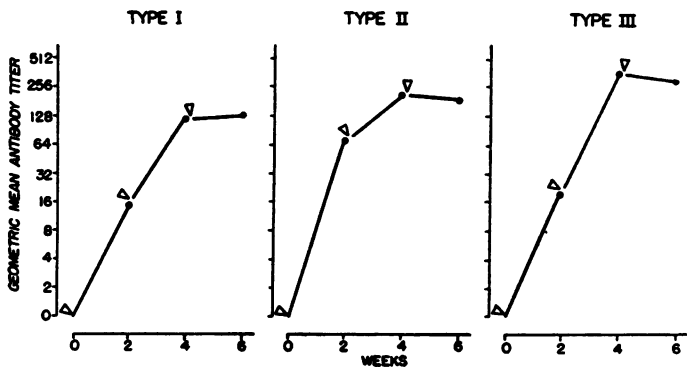
intervals of two weeks. The subjects involved in this study were children in the early grades of school who, prior to inoculation, possessed no demonstrable serum antibody to either of the three virus types. It is clear from this chart that a sharp response occurred after the first dose, a further rise after the second, but little, if any, change occurred after the third when given at this point in time after the two preceding inoculations.

You will recall the similar experience reported a year ago, and shown again in Figure 3, where three doses at zero, two, and five weeks failed to induce more than a primary effect. However, in another study, the booster effect was induced upon reinoculation at an interval of seven months after primary vaccination. The latter effect is shown in Figure 4. It is apparent that the spacing of inoculations, to which reference has already been made, plays an important

Figure 3

Primary Vaccination Effect

Influence Upon Antibody Level of Each of Three Doses Spaced at
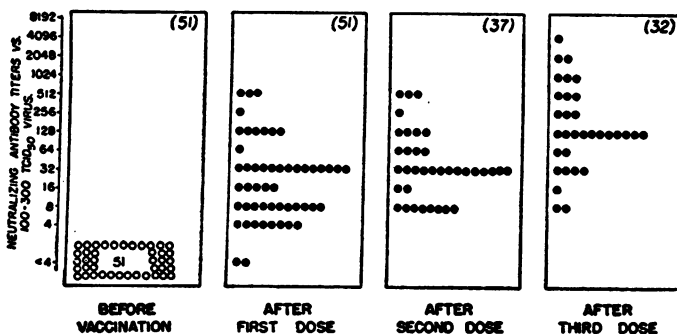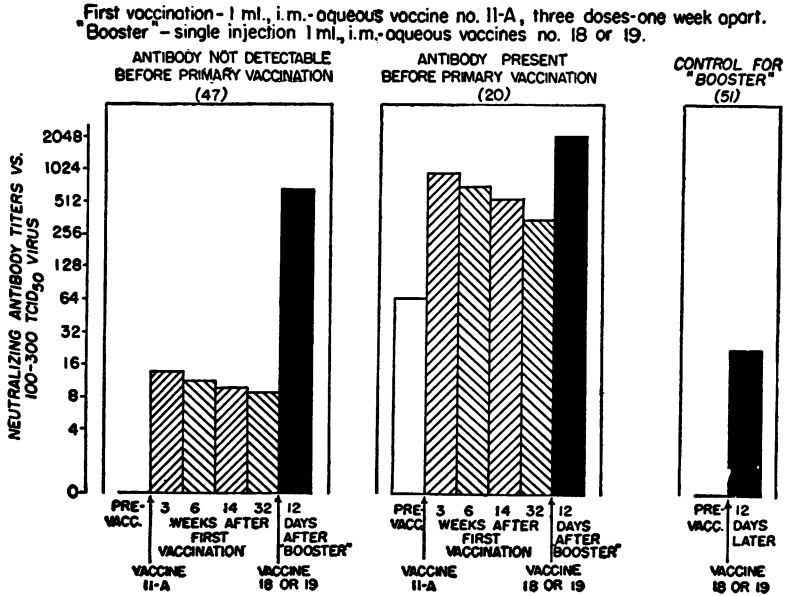Intervals of Two and Five Weeks After First Dose

Figure 4

Geometric Mean Antibody Titers Before and at Intervals Up to Seven Months After Primary Vaccination and After a "Booster" Injection (Composite of Data for Types 1, 2 and 3)


role in antibody response to vaccine; but, before we discuss this question in more detail, I should like first to shed further light on certain questions concerning the vaccine itself.

Figure 5 illustrates the importance of vaccine potency, or of vaccine dose, for inducing the primary effect. The degree of difference in antibody response elicited by three different concentrations

Figure 5

Geometric Mean Titers After Each of Three Doses of Different Quantities of Reference Vaccine "A" and of Lot 309
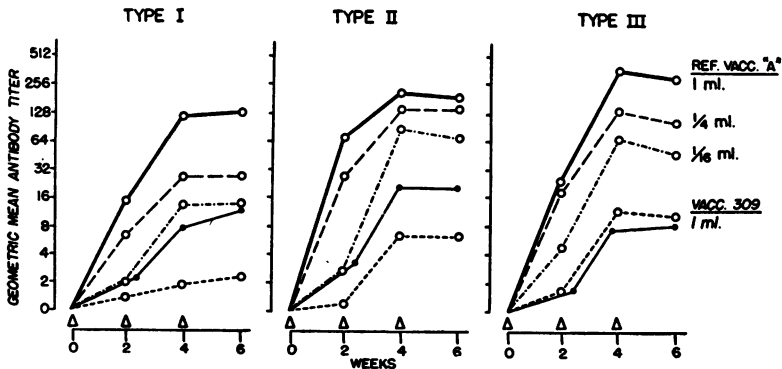
of Reference Vaccine A—namely, 1 ml, 1/4 ml, and 1/16 ml—are shown, along with a comparison of the response to 1 ml of one particular batch (Lot 309) of vaccine used in the field test in 1954. It is clear from these data that Vaccine Lot 309, as used, induced an effect less than that elicited by each of the three different quantities of the Reference Vaccine. The two lines describing the performance of Vaccine Lot 309 indicate the effect induced by this vaccine on two separate occasions; the first was approximately three months after the vaccine was prepared and the second approximately nine months after preparation. The continuous light line indicates the degree of response at three months and the dotted line the degree of response at nine months. It is evident that a greater gap exists between the three- and nine-month performance in the Type I antibody response; somewhat less in the Type II, with little, if any, in

Figure 6

Relative Antigenic Stability for Monkeys of Vaccine Stored in Refrigerator for Approximately Three to Eight Months
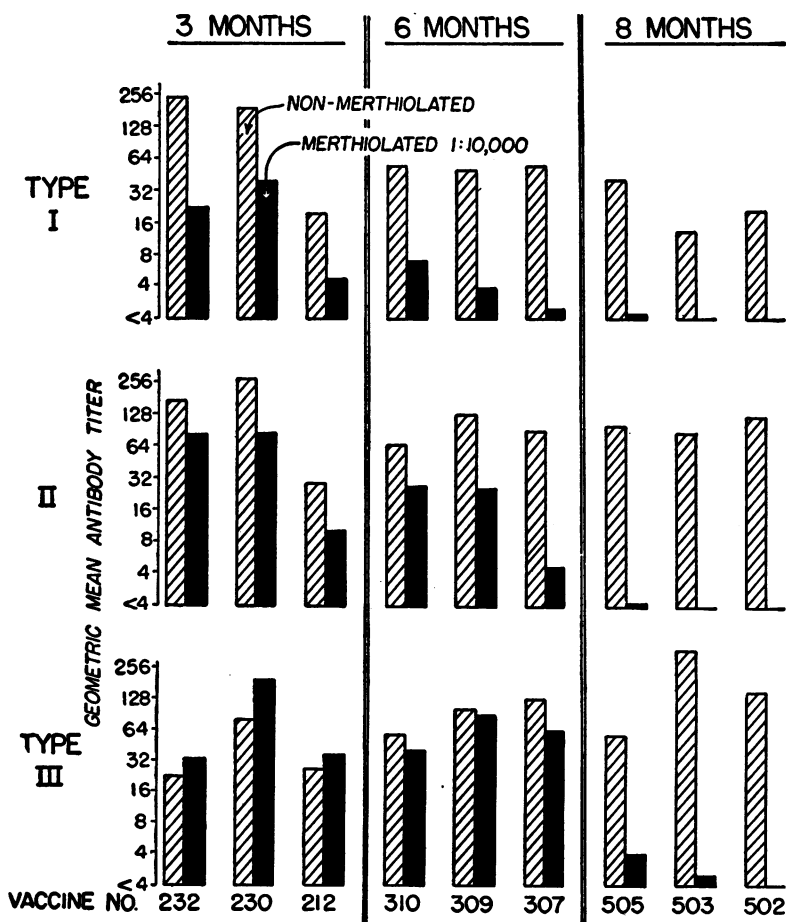
Type III. Without going into much more of an explanation at this point, I should like to say that these differences were due to the destructive effect upon the antigen of the merthiolate that was added to the finished vaccine to serve as a preservative to prevent the development of bacterial or mold contamination in the course of storage after manufacture or in the course of the use of a multiple dose vial. Even though the problem created by the relative instability of the vaccine in contact with this preservative has now been solved, I should like, before indicating to you the solution, to show how the merthiolate effect may have influenced the performance of the vaccine used in the field tests of 1954.

The Vaccines Used in the 1954 Field Tests—Figure 6 contains a summary of results of tests in monkeys of the antigenic activity of two samples of each of nine lots of vaccine stored for different periods of time with and without a 1:10,000 dilution of merthiolate. This chart indicates the geometric mean titer of antibody in the serum of groups of six to eight monkeys inoculated in a routine manner, i.e., three 1 ml doses given a week apart, with blood drawn

one week after the last dose. Although variation among lots with respect to each of the three components, and between lots, is evident, it is the purpose of this chart to draw attention to the difference in antigenic activity between the merthiolated and the nonmerthiolated sample of the same batch. It should be clearly evident that much greater differences exist between merthiolated and nonmerthiolated samples in proportion to the length of storage. It is clear also that the effect begins to be evident earliest in the Type I component, next for the Type II, and last for the Type III. There appears to be no demonstrable difference between merthiolated and nonmerthiolated samples with respect to the Type III component after storage for the shortest interval. As you may well imagine, the effect of merthiolate is markedly accelerated at elevated temperatures, effecting almost complete destruction of antigenicity within a few days of exposure at 37° C; under certain circumstances, rapid deterioration has been observed to occur even at refrigerator temperatures.

Now let us see how the vaccine used in the field performed when tested in man within a relatively short time after

Figure 7

Type I Antibody Response After Two Doses of Vaccine in Human Subjects with No Preantibody to Any Type
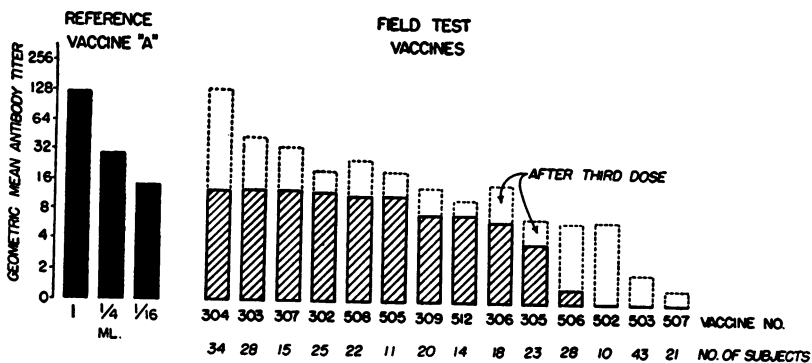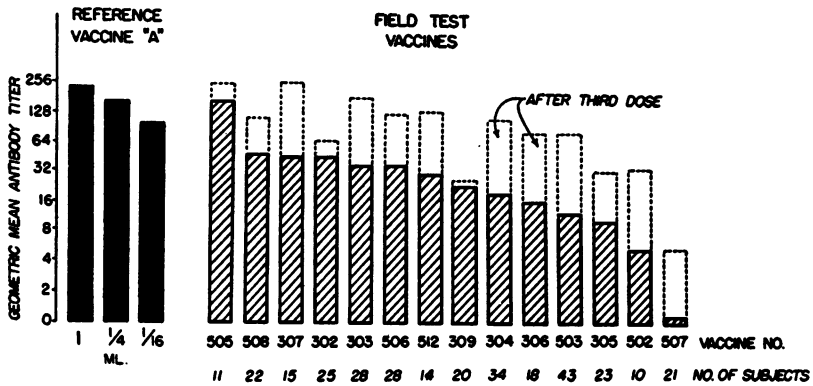
Figure 8

Type II Antibody Response After Two Doses of Vaccine in Human Subjects with
No Preantibody to Any Type

preparation, before use in the field tests. The data presented in Figures 7, 8, and 9 were obtained from studies in children in Pittsburgh who were inoculated at the end of March or in early April and May, 1954, with each of almost all of the lots of vaccines used in the field test. The few vaccines that were not tested were omitted because they were not available at this early period when these tests were initiated. I shall present these data to you by illustrating the performance of the three components of the vaccine separately.

Figure 7 shows the degree of antigenic activity of the Type I component of each of these lots of vaccine in relation to the Reference Vaccine to which I have already referred. These data are expressed in terms of the geometric mean titer of antibody in groups of subjects of the size indicated at the bottom of each column. In all instances, prior to vaccination, no antibody was demonstrable

Figure 9

Type III Antibody Response After Two Doses of Vaccine in Human Subjects with
No Preantibody to Any Type
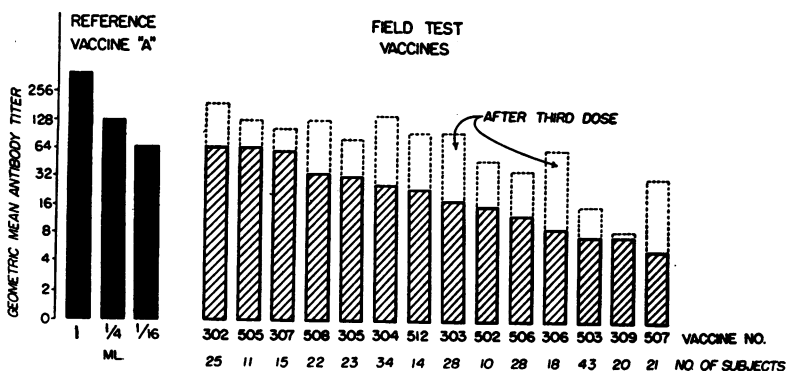
for any type. Many other individuals were included in these tests but are excluded from these analyses because, prior to vaccination, they possessed antibody for one or more virus types. This was done because it has been found that an antigenic relationship exists between members of the three virus types. For example, in spite of the absence of demonstrable Type I antibody in a person who has had a prior Type II infection, his reactivity to the Type I component of the vaccine is much greater than is that of the person who has no antibody to any of the three types. Therefore, analyses of the immunologic reactivity to different vaccines are best made by comparing the behavior of different vaccines in persons who have no demonstrable antibody to any of the three virus types.

The solid black bars at the left of the chart indicate the geometric mean levels of antibody induced by two doses of Reference Vaccine A when used in three different concentrations. The shaded columns indicate the degree of antigenic response elicited by two doses of the different field test vaccines employed. This comparison is made after the second dose of vaccine because in two instances (502 and 507) the third dose given consisted of a lot different from that used for the first two doses. I should like to draw your attention, first, to the strikingly lower activity of Vaccine Lots 502, 503, 507. You will see in a moment that the difference in performance of the Reference Vaccine and the field test vaccines is largely attributable to the effect of the merthiolate and, perhaps, to a somewhat lesser extent to a relatively lower potency in terms of virus content of the starting material (see Figures 12–14). Apart from any other considerations, there is the obvious fact that the field test vaccines differed in potency from one another and one could expect corresponding effects when tested in the field.

Figures 8 and 9 illustrate the performance of the Types II and III compo-

Figure 10

Antibody Response in Human Subjects with No Antibody for Any Type Prior to Vaccination

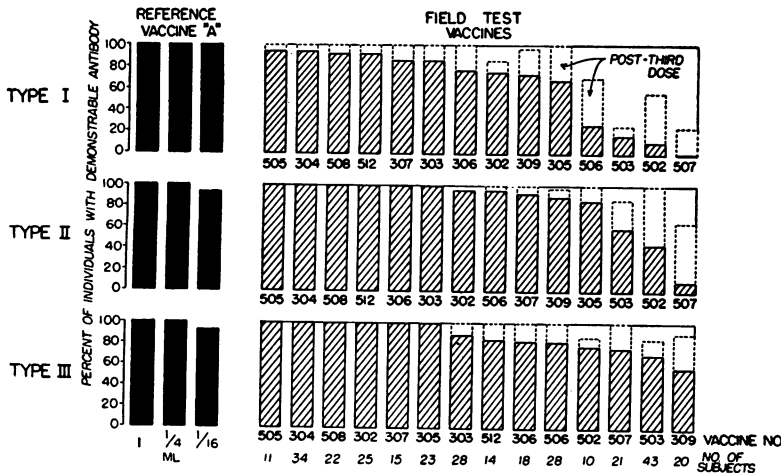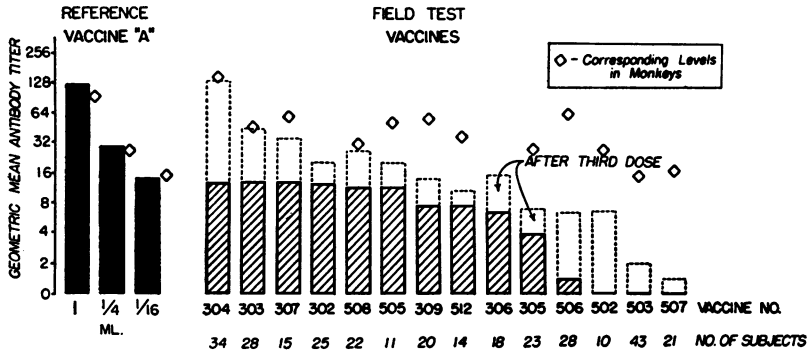Per cent with Demonstrable Antibody After Two Doses Given Two Weeks Apart

Figure 11

Type I Antibody Response After Two Doses of Vaccine in Human Subjects with No Preantibody to Any Type

nents of the field test vaccines in relation to the corresponding components of Reference Vaccine A. The data are self-explanatory.

I have attempted to summarize somewhat differently in Figure 10 the data included in the three preceding figures. The data in Figure 10 are in terms of the percentage of individuals with demonstrable antibody after two doses of vaccine given two weeks apart. Demonstrable antibody is considered to be a titer level of 1:4 when measured against 100 $TCID_{50}$ of virus. The increase in proportion of individuals with demonstrable antibody after the third dose is indicated by the dotted extension of the shaded columns. The degree to which the different dilutions of Reference Vaccine A elicited formation of measurable antibody is shown by the black columns. This chart is particularly meaningful if there is any validity to the hypothesis that the presence of demonstrable antibody in the serum is sufficient to prevent the development of paralytic poliomyelitis. If this be so, then it is clear, indeed, that Vaccine Lots 507, 502, 503, and 506 would fall far short of satisfactory performance, at least for Type I paralytic poliomyelitis. Although it is

clear that there is more to be desired with respect to the Type I components of the other lots of vaccine, as compared with Reference Vaccine A, their performance, nevertheless, is distinctly better than that of the four lots just mentioned. The points of interest are: that it does seem possible to prepare rather consistently vaccines that in a high proportion of instances do elicit antibody formation in man, and that the reasons are understood for the relatively poorer performance of the vaccines shown on the right hand side of the chart.

So that I may clear up the merthiolate question at this time, I would like to show a comparison between data obtained in monkeys, on the antigenic activity of the nonmerthiolated samples that corresponded to the merthiolated samples that were tested in man. To illustrate this point I have taken for Figure 11 a chart that you have just seen (Figure 7) and superimposed a series of points indicating the geometric mean titers of antibody induced by three 1 ml doses of nonmerthiolated vaccines given to monkeys at intervals of one week. It is interesting to observe that the geometric mean level of antibody after two doses of Reference Vaccine A,

Figure 12

Relative Antigenic Potency for Monkeys of Field Test Vaccines in Comparison with Reference Vaccine "A"

TYPE I COMPONENT
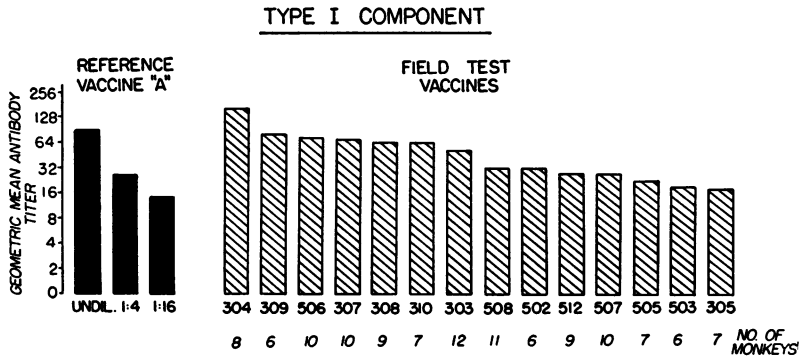
given two weeks apart, in man corresponds to the level observed in monkeys given three doses within the same interval of time; this is true even though the monkeys weighed 1/10 to 1/20 less than the human subjects. The comparability between the relative response to the three doses of the Reference Vaccine, both in man and in monkeys, is striking. You will recall the statement made earlier that man was more responsive than was the monkey, but you will note from Figure 11 that the monkey was more responsive than was man. This apparent paradox can be explained by the fact that the monkeys were given nonmerthiolated vaccine and man was given the merthiolated preparation.

The original potency tests in monkeys of vaccine used in man was done with

Figure 13

Relative Antigenic Potency for Monkeys of Field Test Vaccines in Comparison with Reference Vaccine "A"

TYPE II COMPONENT
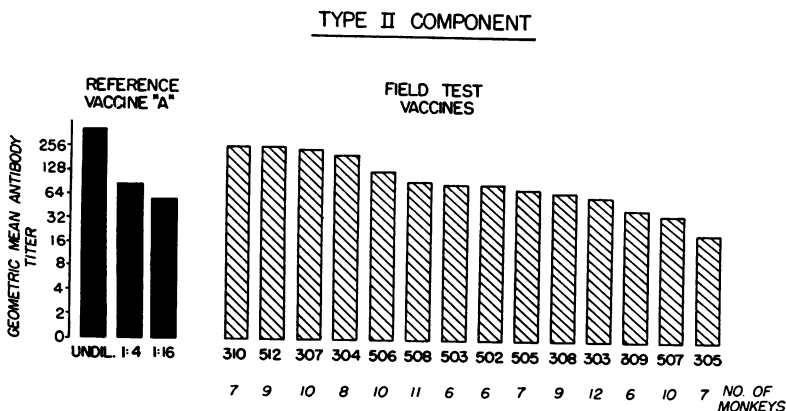
merthiolated vaccines, and data on the nonmerthiolated preparations are drawn from studies on the stability of the merthiolated and nonmerthiolated preparations. Data on antigenic potency for monkeys of samples of the field test vaccines to which merthiolate was not added in relation to Reference Vaccine A are shown in Figures 12–14.

In the earliest tests the difference between the merthiolated and nonmerthiolated samples was not perceptible and, as was shown in a previous figure (Figure 6) the effect began to emerge with increasing time of storage. However, we did become aware of the low antigenic potency of the Type I component of Vaccine Lots 502, 503, and 507 some time before the third dose was given in the field test. The suggestion was then made that a third dose of more potent vaccine be used and this was done in some, but not all areas which were started with lots 502 and 507; no change was introduced, however, where lot 503 was used since this lot had been put up for the placebo test.

The final chart dealing with the merthiolate question is Figure 15 in which is illustrated the performance in man of a 1954 vaccine, lot 506, with and without merthiolate, tested when approximately two-months-old. The difference in antibody response elicited by each is clearly evident. In comparison, there is shown the performance of a 1955 vaccine to which a 1:10,000 dilution of merthiolate had been added but which, in addition, contained a quantity of versene sufficient to prevent the merthiolate from having a destructive effect upon the antigen; the antiseptic or preservative qualities of the merthiolate are still retained in such mixtures.

It should be clear from the findings just summarized that complete antigenicity of the formalinized vaccine, as we have described its preparation, can be retained for long periods of time at refrigerated temperatures (and for a number of weeks at 37° C) without demonstrable loss of antigenic activity. This has been true of the vaccine, per se, without an added preservative. However, it now appears that it is possible to retain the stability of the antigen while still retaining the advantages of the preservative by the addition of versene.

The solution of the merthiolate prob-

Figure 14

Relative Antigenic Potency for Monkeys of Field Test Vaccines in Comparison with Reference Vaccine "A"

Figure 15

Type I Response to

1955 VACCINE (LOT A-1)	1954 VACCINE (LOT 506)
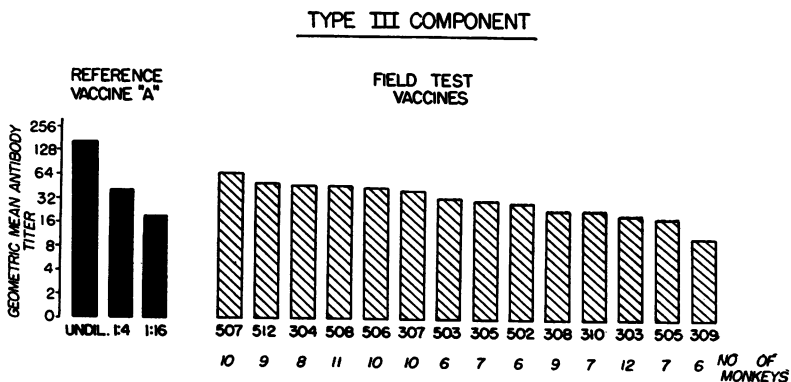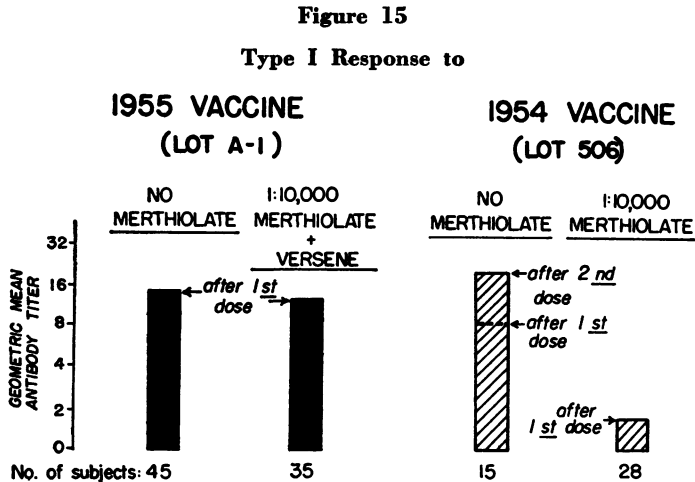
lem by the addition of versene is the result of the efforts of the research staff at Eli Lilly and Company. Other laboratories, similarly engaged in vaccine production, are solving the preservative problem in a variety of ways, either by not using it at all, as is the case at the Connaught Research Laboratories in Canada and in certain European laboratories or by the use of other chemicals that can be shown to exercise the necessary antimicrobial effect without impairing antigenic activity. The requirement for a satisfactory preservative is that it not affect adversely the stability of the antigen, not only under normal conditions of storage, but under the more severe conditions of elevated temperatures.

Comparison of Field Trial Vaccines with Recently Prepared Material—While still on the subject of vaccine performance I should like to show a comparison between vaccines used in the 1954 tests and a number of lots of vaccine prepared for test, and possibly for use, in 1955. These data (Figure 16) could have been presented in any of a number of ways, but I have selected to present to you an analysis based upon the percentage of individuals who developed

clearly demonstrable antibody within 14 days after the first injection of vaccine. In all cases the individuals involved had no demonstrable antibody to any of the three types prior to vaccination, and all received 1 ml intramuscularly. These data show that the 1955 vaccines induced levels of antibody of 1:4 or greater in approximately 90 per cent or more of groups of the size indicated by the numbers at the bottom of the respective columns. By comparison, vaccines used in the 1954 field tests exhibited a somewhat lower efficiency of conversion from negative to positive after the first dose, and the three lots to which attention has already been drawn were virtually nonreactive.

The geometric mean levels of antibody induced as a result of the first dose of vaccine were between 1:8 and 1:16 for the 1955 preparations and slightly under 1:8 for the 1954 preparations, except, of course, in the case of Vaccine Lots 502, 503, and 507. This summary of the performance of the first seven lots of 1955 vaccine available for test in man provides some indication of the degree of consistency and uniformity with which vaccine of satisfactory potency, at least in terms of antibody measure-

Figure 16

Percentage of Children with Antibody Response (Type 1) on the Fourteenth Day After First Dose of Vaccine

No Prior Demonstrable Antibody to Any Type
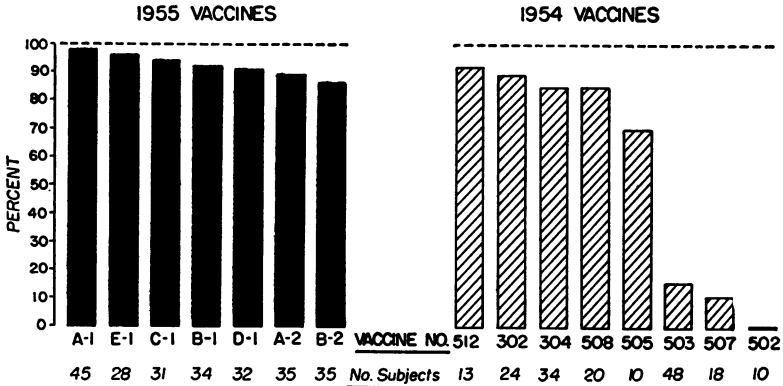
ments, can be prepared. It reveals, also, the effect of improvements that have resulted from the experience gained since a year ago. Six of the seven 1955 preparations contained no merthiolate and one contained merthiolate and versene.

The other point that I wish to make, in presenting these data in this way, is to show the speed with which antibody formation is evident even after the first dose of vaccine. This is a question to which an answer is desired, and from other studies from which data are not being presented now we have found that following primary vaccination measurable antibody appears in some individuals sometime between the sixth and ninth day.

Comparison of First Dose Response Administered by Different Routes—I have just touched upon one aspect of vaccine performance that impinges upon that area dealing with the prospects for the control of the paralytic disease. If it is possible to create a measurable amount of antibody by the 14th day after first vaccination, it is conceivable that there would result a corresponding reduction in the probability of contracting paralytic poliomyelitis, if exposure occurs subsequent to the time when antibody is present in the serum in such concentration. Therefore, the use of vaccine for the first time during the poliomyelitis season, or even in epidemic areas, could be expected to have a beneficial effect so long as one keeps in mind the limitations imposed by the time required to induce the immunologic effect in relation to the time of exposure to infection.

Immediately the question that comes to the fore is the possible danger of inducing paralysis, especially involving the injected limb, if vaccine is administered at a time when any inoculation might induce the "provoking effect." Since Bodian has shown that the "provoking effect" can be induced in monkeys with a variety of substances injected intramuscularly, and since he has suggested that the effect might be somewhat less if injections are made by other routes, we made a study of the antibody response to vaccine given by three different routes. The data in Figure 17 show the levels of Type I anti-

Figure 17

Type I Antibody Response in Children to First Dose Given by Different Routes of Reference Vaccine "A"
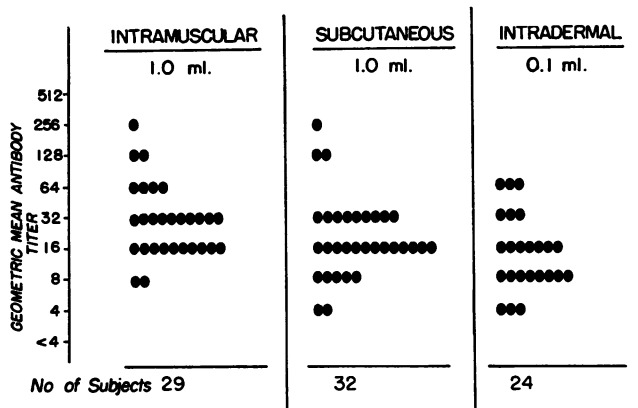
body present on the 14th day after the first dose of vaccine which was given by three different routes. It was to be expected that the response to the intradermally injected vaccine would be somewhat less than to the vaccine given intramuscularly and subcutaneously, because the quantity administered was only 1/10 as much. However, when comparisons were made between corresponding amounts of antigen given intradermally and intramuscularly, it was found that the response to the first dose of vaccine was such that 0.1 ml intradermally produced an effect equivalent to that elicited by 0.25 ml given intramuscularly. It is of interest that the difference between intramuscular and subcutaneous routes is not very great, although the trend here observed is in favor of the intramuscular route. It was on the basis of observations of this kind, which have in other studies been more striking, that the intramuscular route was preferred over the subcutaneous route. In this study it was noted that the vaccine tended to leak from the puncture site when given subcutaneously, but when given intramuscularly

this was not observed. It would seem from these data, therefore, that if there are any strong opinions against the administration of vaccine intramuscularly during the poliomyelitis season, there is some choice in the use of vaccine via other routes.

Observations on Persistence of Vaccine Effects—I should like to turn now to another aspect of vaccine performance that touches upon prospects for the control of the disease; this can be illustrated best by the data summarized in Figure 18. I have selected examples of two groups of individuals, each of which was given a different vaccine in the spring of 1954. Following the injection of Vaccine Lot 303 there occurred a rise in geometric mean level of antibody to all three types when three doses were given at zero, two, and five weeks. The levels after the second and third dose are shown, as well as the level prior to the booster injection which was given 10 months later. I would like to call your attention to the rather gradual decline in the geometric mean level of antibody after primary vaccination and the very sharp rise in antibody titer

following the booster dose. You will note that this was true for each of the three types in the group given Vaccine Lot 303 for the primary vaccination; the booster injection consisted of 1 ml of one of the 1955 vaccines.

In contrast children first inoculated with Vaccine Lot 507 and then again reinoculated 10 months later with a potent vaccine exhibited a booster response to the Type III component of the vaccine, a lesser response to Type II, and not a booster response but rather a primary response to the Type I component. That the response to the Type I component was primary is indicated by the comparability of the reaction observed in these children with that of another group given one dose of the vaccine for the first time; the latter group received the same lot employed for the booster. It should be clear from this that the level of antibody induced by the booster dose given 10 months after the primary vaccination was influenced by the intensity of the primary sensitization. The complete absence of

Type I antigenic activity in Vaccine Lot 507 is reflected not only in the absence of an antibody response, but in the absence of the hyperreaction to a later dose of potent vaccine. Similarly, the lesser response to Type II in children vaccinated with 507 as compared with 303 was due to the poorer antigenic quality of the Type II component of Vaccine Lot 507. This reflects itself not only in fewer individuals exhibiting a booster effect, but in those who do, the degree of response is a lesser one.

I want to re-emphasize once again that the exaggerated reaction that occurs at the time of the secondary dose 10 months later could not have been elicited if this dose had been given very much earlier. From an extensive study, too detailed to present here at this time, it is possible to say that for elicitation of the full effect the booster injection should be given seven months, or later, after the first dose of vaccine. While it takes a number of months for a state of hyperreactivity, corresponding to that shown here, to develop, it now appears

Figure 18

**Effect of Booster Dose Ten Months After Vaccination with Two Different
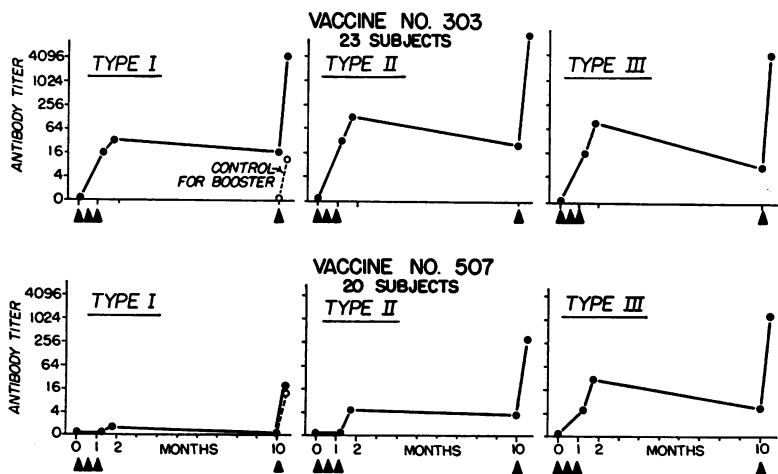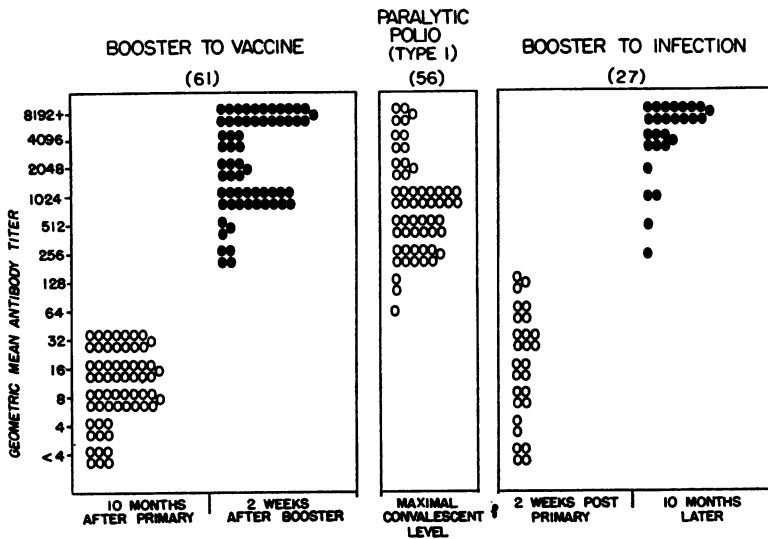Vaccine Lots Used in 1954 Field Tests**

Figure 19

Comparison of Antibody Response to Vaccination and to Infection

that the hyperreactive state lasts for a considerable period of time. The longest interval over which we have had the opportunity to test for the persistence of the hyperreactive state has been two and one-half years after primary vaccination. Only time will permit a determination of the full extent to which the hyperreactive state persists following primary stimulation.

From the data in Figure 18 it is clear that antibody induced in the course of primary immunization is not evanescent and, in fact, in most individuals it is still present at a level only slightly lower than that observed shortly after completion of the primary phase of immunization; when a single dose of vaccine is given after the lapse of a sufficient period of time, the antibody induced thereby reaches extraordinarily high levels. If the rate of antibody decline after the booster is equal to that observed in the primary period, or even if the decline is somewhat more rapid at first, until it descends to moderate levels

before the decline assumes a more gradual rate, it might be expected that antibody induced following such a course of vaccination would last for a considerable period of time.

## Antibody Response to Vaccination and Infection

As a matter of interest let us compare the levels of antibody observed in vaccinated individuals with those observed in persons who have experienced natural infection. To illustrate this point we have put together in Figure 19 the pre- and postvaccination antibody titers of a group of 61 individuals for whom we had such data from among those who had received their initial inoculations with Vaccine Lots 303, 305, 306, or 512. In the prebooster period the Type I antibody levels of all individuals were below 1:32; 14 days after the booster they all had levels beyond this range with a high proportion clustering at the level of 1:8,000+. For comparison,

there is charted the levels of antibody observed in a group of 56 persons with Type I paralytic poliomyelitis and from whom serial bleedings were obtained at approximately weekly intervals while they were hospitalized. The geometric mean level of antibody was 1:128 at the time of hospital admission and shortly after onset of paralysis; there was no serologic evidence of prior infection with any other virus type. The antibody measurement recorded in Figure 19 was the highest observed in the series for each individual; the geometric mean level of the highest titers was slightly less than 1:1,024. From other experiences, it is to be expected that these high titers will decline over a period of time and will stabilize at a mean level of approximately 1:128.

It is evident from these data that there occurred, as a result of an infection with paralytic consequences, levels of antibody that in general were higher than that induced by primary vaccination with a killed vaccine. However, it is equally clear that the level of antibody induced with a killed vaccine, when a booster dose was given at a suitable interval, was higher than that induced by the infectious process.

In the right-hand portion of Figure 19 are data from another group that is of interest. These data are from a study of 27 children who had been vaccinated either in the spring of 1953 or the spring of 1954 and, in the course of follow-up bleedings in the winter of 1953 or 1954, respectively, it was evident that these children had experienced a natural in-

Figure 20

Time of Appearance of Rise in Serum Antibody Titer in Human Subjects After Secondary Antigenic Stimulation
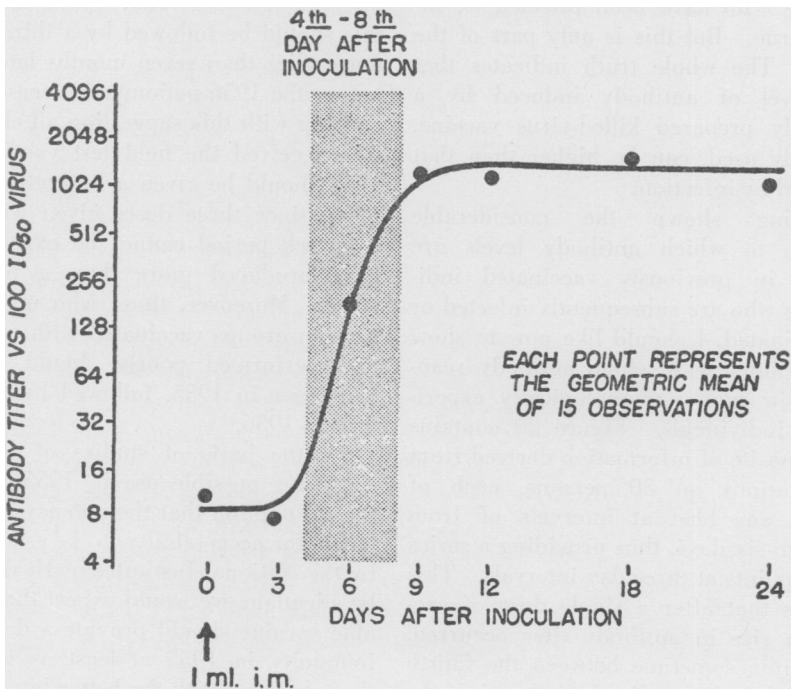
fection. This was indicated by the sharp difference in the level of antibody for one type only when the early and late postvaccination blood samples were compared. In this group of 27 there are two children who had a Type III infection, diagnosed serologically; 12 had Type I infections and 13 had Type II infections. It is clear that the level of antibody observed in these subjects was, in general, higher than that observed in paralyzed convalescents. It is as if infection in a previously vaccinated person elicits a booster-type antibody response corresponding to the infecting type.

There is a similarity between the levels of antibody following a booster injection, and the postinfection levels in previously vaccinated individuals. The distribution of levels in each appear to be higher than that observed in recently paralyzed convalescents. It would seem from these data, therefore, that the assertion that the levels of antibody following the use of a killed-virus vaccine are lower than those observed in persons who have been infected is, indeed, true. But this is only part of the truth. The whole truth indicates that the level of antibody induced by a properly prepared killed-virus vaccine, properly used, can be higher than that induced by infection.

Having shown the considerable heights to which antibody levels are raised in previously vaccinated individuals who are subsequently infected or revaccinated, I should like now to show the rapidity with which antibody reappears in such immunologically experienced individuals. Figure 20 contains a composite of information derived from observations on 30 persons, each of whom was bled at intervals of from three to six days, thus providing a series of 15 points at three-day intervals. This reveals that after a single dose of vaccine a rise in antibody titer occurred, beginning sometime between the fourth and eighth days. By the latter time the maximum level appears to have been reached. Thus, we see as another expression of the hyperreactive mechanism the greater rapidity with which new antibody formation begins, as well as the augmentation of the amount of antibody that is induced.

Practical Considerations

On the basis of all the evidence that has been gathered thus far, it would seem that antibody in the circulating blood could intercept virus invasion of the central nervous system. The question about which evidence is awaited is in regard to the level of antibody necessary for such an effect. This question should be answered, in part, by the field evaluation of vaccine effectiveness.

If the assumption is made that the presence of demonstrable antibody in the serum will be sufficient to produce the desired effect, I would then propose that for the year 1955 vaccine be administered in two doses, separated by an interval of two to four weeks and that this should be followed by a third dose, not earlier than seven months later, but before the 1956 poliomyelitis season. In keeping with this suggestion all children who received the field test vaccines in 1954 should be given a booster dose in 1955, since three doses given within a five-week period cannot be expected to have produced more than a primary effect. Moreover, those who may have been in groups vaccinated with vaccines that performed poorly should receive two doses in 1955, followed by a third dose in 1956.

On the basis of studies of vaccines made for possible use in 1955 and on the assumption that the potency requirements for acceptability, to be established by the National Institutes of Health, will be adequate, we would expect that available vaccine should provide a degree of immunity in 1955 at least as good as that observed with the better lots of field

Figure 21

Concept of Influence of Previous Immunologic Experience in the Prevention of Paralysis
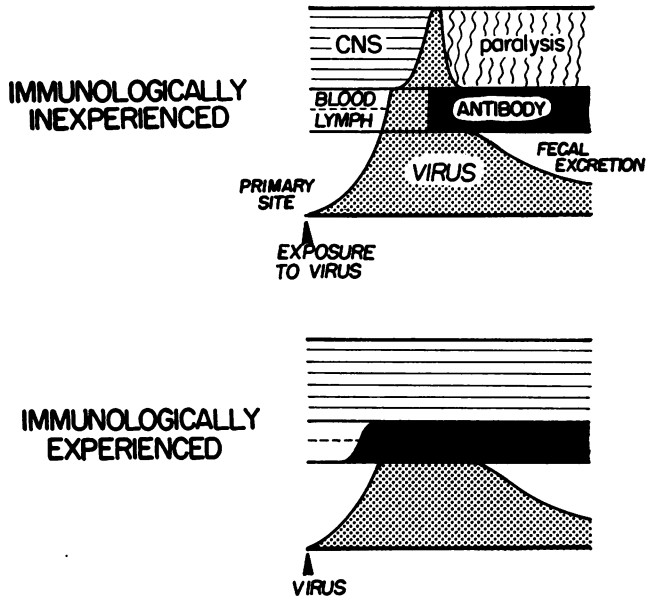
trial vaccine. The booster dose prior to the 1956 season can be expected to enhance immunity further and to be effective not only for 1956 but, very likely, for a period the full length of which is still to be determined.

Concept of the Mechanism of the Persistence of Immunity

The question that cannot be answered until sufficient time has elapsed is how long will immunity last. Will it last only so long as antibody is present in the blood stream or might immunity be more persistent than that? It would appear from the observations here reported that if vaccination induces a long-lasting alteration in the state of reactivity of the immunologic mechanism, then subsequent contact with the poliomyelitis viruses under natural circumstances should cause antibody formation to begin sufficiently rapidly and

might be expected thereby to increase the likelihood that long-lasting immunity will follow the proper use of a properly constituted vaccine.

The foregoing hypothesis is illustrated graphically in Figure 21. The concept here illustrated suggests that even though antibody may not be demonstrable in the serum at the time of virus invasion, that a prior immunologic experience would have so primed the immunologic mechanism that antibody in good concentration would appear in the serum within a short time after the initiation of multiplication of virus at the portal of entry. If such antibody development occurs prior to invasion of the blood stream and is present in sufficient concentration to prevent systemic invasion, then access of virus to the central nervous system would be intercepted.

I am not unmindful that the thesis that has just been proposed may not be acceptable to all. I do not propose it

because of any concern lest a killed vaccine fail to induce and maintain the formation of respectable levels of antibody in the circulating blood. I propose this hypothesis principally to indicate our thinking, and the direction of our further investigations. I realize full well the practical limitations involved in trying to maintain immunity artificially if reimmunization is required frequently. This will be true particularly in older children and in adults, and especially at times and under circumstances where the disease against which one seeks to maintain immunity by artificial means is not highly prevalent. It is desirable, therefore, that means be developed for inducing immunity routinely in early life and for this to be done in such a way as to make it unnecessary for repeated treatments beyond the very minimum.

It may well be that the answer we are seeking is implicit in the knowledge that we now possess—time alone will tell.

Physicians, Dentists, Nurses, and Sanitary Engineers in Mobilization

A picture of the current status and predictions of the future status of health manpower in case of total mobilization is drawn in a pamphlet recently issued by the Health Resources Advisory Committee. This 49-page report to the director of the Office of Defense Mobilization entitled "Mobilization and Health Manpower" points out that expanding educational facilities to train health personnel, our national population growth, and the rising level of demands for health services will cause a continuing shortage of health personnel for many years. The committee recommends improved utilization of health personnel by both governmental and nongovernmental agencies to meet the national civilian and military manpower needs. It stresses the importance of building up the regular corps of career officers in the military health services.

The committee concludes that if mobilization should be increased substantially, either special legislation must be extended with the draft reaching veterans with the shortest period of prior service, or an alternate must be devised. If many more physicians and dentists were to be withdrawn to the Armed Forces, the protection of civilian health could become a matter of serious concern, particularly in view of a threat of attack on the civilian population.