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Poliomyelitis Vaccine in the Fall of 1955

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This paper reflects Dr. Salk's conclusions growing out of the 1955 practical experience with poliomyelitis vaccine.

The results of the experiences with poliomyelitis vaccine in 1954, and again in 1955, take on much more meaning when they are viewed in the light of the underlying theory and the basic experimentation upon which the practices of each year were based.

It is understandable that, as a result of the episode of last spring,[1,2] a prominent doubt developed and still continues to exist concerning the fundamental safety of a killed-virus vaccine. This is true even in view of the earlier work[3,4] and of the field trial evidence,[5] and even though there has accumulated from the experience in three countries[6-8] evidence for the fundamental safety of properly prepared vaccine. In view of the doubt, then, "How does one ascertain vaccine safety?"

Determination of Safety

The principal objective is to eliminate, for all practical purposes, the presence of infectious virus from each single dose of each batch of vaccine released for use. This reduces the problem to each individual inoculated. This degree of safety cannot be ascertained merely on the basis of a test made on a sample of a "finished" batch—no matter how large the sample—unless, of course, the entire batch is tested and none remains to be used. Therefore, to provide the kind of assurance that is required for a vaccine that is made from an agent that possesses the potential hazard of *any* strain of poliomyelitis virus, more than the usual kind of care in processing and in testing is required[9] than had heretofore been applied to other less hazardous antigens.

This particular problem requires that tests be applied—not only on samples of the finished material, but on samples

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PRODUCTION SEQUENCE OF STRAIN POOLS (pool no.)	CUMULATIVE VOLUME OF STRAIN POOLS PRODUCED (1 pool = 400 liters)	CUMULATIVE VOLUME TESTED IN TISSUE CULTURE (1000 ml/lot)	RESULT OF TEST FOR LIVE VIRUS Example A	Example B
1	400,000 ml	1,000 ml	0	0
2	800,000	2,000	0	0
3	1,200,000	3,000	+	0
4	1,600,000	4,000	0	0
5	2,000,000	5,000	+	0
6	2,400,000	6,000	+	0
7	2,800,000	7,000	0	0
8	3,200,000	8,000	0	0
9	3,600,000	9,000	0	0
10	4,000,000	10,000	0	0
11	4,400,000	11,000	+	0
12	4,800,000	12,000	0	0
			Negative tests are less significant in proportion to the number of positives	Negative tests are of increasing significance as cumulative experience is extended

Figure 1—Significance of a Consistent Negative Record in Production and Testing of Monovalent Strain Pools (Assuming Sensitive Testing and Representative Sampling)

removed at several stages in the course of processing—to demonstrate the extent to which a calculated amount of overtreatment has been applied to each batch of vaccine, to create what is referred to as a "margin of safety." [9] This means a degree of treatment beyond that calculated to be necessary to care for the lingering virus that is expected to be the last to be acted upon.

It was recognized early in this work that a single negative test, of itself, was inadequate to establish safety with sufficient significance, but that a sequence of negative production lots is of increasing significance.[10] Therefore, any single negative test, in an erratic experience, is of diminishing significance in proportion to the frequency with which positives are interspersed when, theoretically, there should be negatives. This concept is illustrated in Examples A and B, in Figures 1 and 2, which show the influence upon the degree of confidence for safety that can be expected from a process that results

PRODUCTION SEQUENCE OF TRIVALENT VACCINE (lot no.)	CUMULATIVE VOLUME OF TRIVALENT VACCINE (1 lot = 1200 liters)	CUMULATIVE VOLUME TESTED IN TISSUE CULTURE (1500 ml/lot)	RESULT OF TEST FOR LIVE VIRUS Example A	Example B
1	1,200,000 ml	1,500 ml	0	0
2	2,400,000	3,000	+	0
3	3,600,000	4,500	0	0
4	4,800,000	6,000	+	0
			Negative tests are less significant in proportion to the number of positives	Negative tests are of increasing significance as cumulative experience is extended

Figure 2—Significance of a Sequence of Negative Tests on Trivalent Vaccine Prepared from "Negative" or Presumably Monovalent Pools

in negative tests consistently (Example B) as compared with one in which positives are encountered from time-to-time (Example A).

The summary in Figure 3 emphasizes the elements of a negative safety test: (1) the reliability of the test system itself, and (2) the significance of a negative test for judging safety. The degree of *reliability* of any one negative test is dependent (a) upon the sensitivity of the testing system itself, which includes volume of sample as well as the demonstrated capacity of the system to detect trace amounts of infectious virus; and (b) upon physical homogeneity, since the latter can affect the validity of sampling, especially if virus were present in more than one physical phase, i. e., a fluid phase as well as a solid phase that could settle out of suspension. The degree of *significance* of a negative test, for an interpretation of safety, depends to a great extent, therefore, upon consistency of performance of the manufacturing process.

Each of the elements that contribute to reliability of testing and to significance for safety can be influenced and controlled by attention to certain practical details that are considered in charts that will follow: for example, the time at which samples for safety tests are taken, in relation to the rate at which virus is inactivated, as is illustrated in Figure 4. This simplified diagram shows that it is possible, routinely, to demonstrate the rate at which virus infectivity is destroyed in the early stages of inactivation; and it illustrates the way in which the reaction continues, as is demonstrable under experimental circumstances. On the basis of such observations a theoretical projection can be made which can be further verified by experience accumulated in the course of testing samples from successive batches of vaccine. If the samples removed at any of the intervals indicated (i. e., 6, 9, 12 days) are negative for infectious virus, and if such were the case in a succession of experiences, this would tend to validate the conception of the theoretical projection. This was, in fact, demonstrated in the course of preparing material for use in the field trial.[11]

The results of the field trial experience are illustrated in Figures 5 and 6. Figure 5 contains a comparison of the original and present interpretations of the available facts. The difference is due to the interpretation of the significance of lesions found in histologic sections of monkey CNS tissue. Three lots were suspect and, therefore, not used,

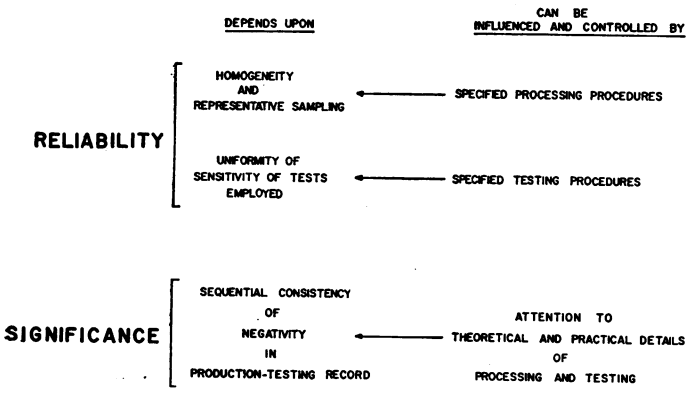


Figure 3—Reliability and Significance of a Negative Safety Test

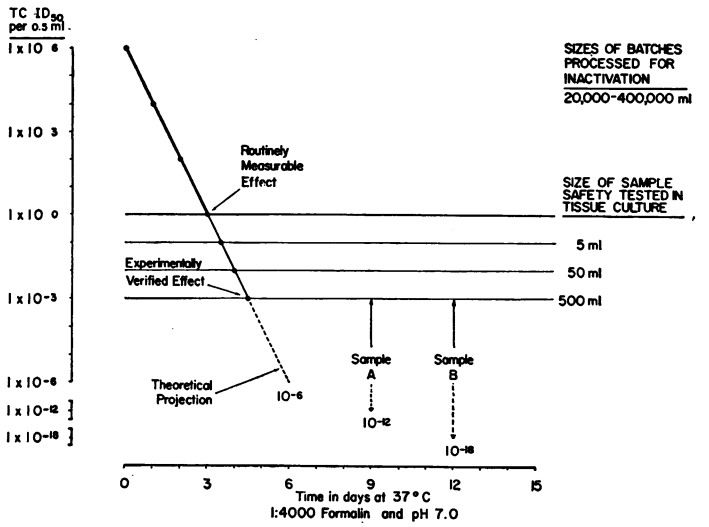


Figure 4—Combination of Processing and Safety Control

Relationship Between the Measured Rate of Virus Inactivation and the Time of Removal of Samples for Safety Test

even though the monkeys showed no signs of paralysis nor was live polio virus found in the tissue culture test. The findings in the CNS were incidental to the histologic examination of surviving animals; that the lesions were not due to poliomyelitis virus infection is the present opinion of Dr. David Bodian, who reviewed the histologic sections.

Although the cumulative experience in Figures 5 and 6 suggests that vaccine can be made in a consistently reliable manner and that the theoretical considerations (that were under test in the 1954 application) * were valid, it is

* Reference has been made [1] to the experience of a third manufacturer that did not, at first, achieve a similar degree of consistency during preparation of material that might have been used in field trial. It was recognized at the time this occurred that certain technical factors could explain the early difference in performance between manufacturers. The production of this manufacturer was not considered for use in the field trial because of inconsistency in achieving a negative test after treatment for the inactivation of virus.

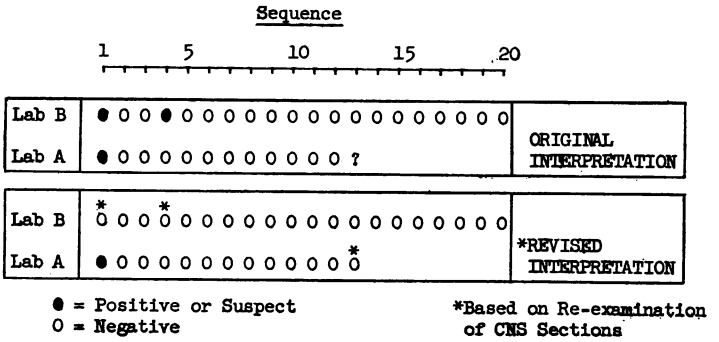


Figure 5—Experience of Two Laboratories in Inactivation of Virus for 1954 Field Trial Vaccine

Lab.	Lots	Trivalent Vaccine	Tested in T.C. and Monkeys	Monkeys Inoculated
	No.	Volume	Volume	No.
A	12	1,400,000 ml	3,312 ml	648
B	20	3,000,000 ml	5,520 ml	1,080
Total	32	4,400,000 ml	8,832 ml	1,728

Figure 6—Accumulated Consecutive Experience of Two Laboratories in Preparation of Vaccine for Field Trial Use

also known that in the beginning certain manufacturers experienced inconsistencies.[1] This fact has been interpreted several ways. One interpretation was that the theoretical considerations in processing and testing were not wholly sound[1]; that fundamentally it is not possible to prepare a killed vaccine safely[12]; another interpretation is that technical factors were responsible for the inconsistencies that were observed, but that the fundamentals were sound.[10]

Factors that Could Cause Inconsistency in Production

The fact that not all manufacturers experienced the same degree of inconsistency, and that the experiences of some did coincide with what was expected theoretically tended to support the view that the difficulties were due to technical factors. Further support[13] for this view was derived (1) from an analysis of manufacturing practices and experiences, (2) from tests upon fluids from certain of the manufacturing laboratories, and (3) from the effects upon the record of consistency, when specific attention was directed to certain technical details. This has been more fully discussed by the Public Health Service Technical Committee on Polio Vaccine in a report[13] to the Surgeon General. The discussion that follows is drawn, in part, from the substance of this report.

An analysis[13] of information on manufacturing practices and experiences available to the U. S. Public Health Service's Technical Committee on Poliomyelitis Vaccine suggested the likelihood that virus incorporated in a solid phase, and out of contact with formalin, could be responsible for incompleteness of inactivation; this surmise was confirmed by direct test upon fluids obtained from different sources. A schematic presentation of these test observations, and of their interpretation, is shown in Figure 7 in which is illustrated the effect of the existence of virus-containing sediment that prevented contact between virus and formalin. It is clear that under such circumstances virus could not be expected to be destroyed by the formalin with which it had had no contact. It was for reasons, such as this, that the original requirements stated that filtration be done before inactivation; the purpose being the removal of particles of such size as might incorporate and protect virus from interaction with formalin.[9]

Still further investigation[13] revealed that filtration was not always carried out shortly before the inactivation step; at times, weeks or months elapsed between filtration and formalin treatment. During such periods of storage precipitates tend to form. Failure to remove such precipitates, with incorporated virus, could result in incomplete interaction between formaldehyde and all of

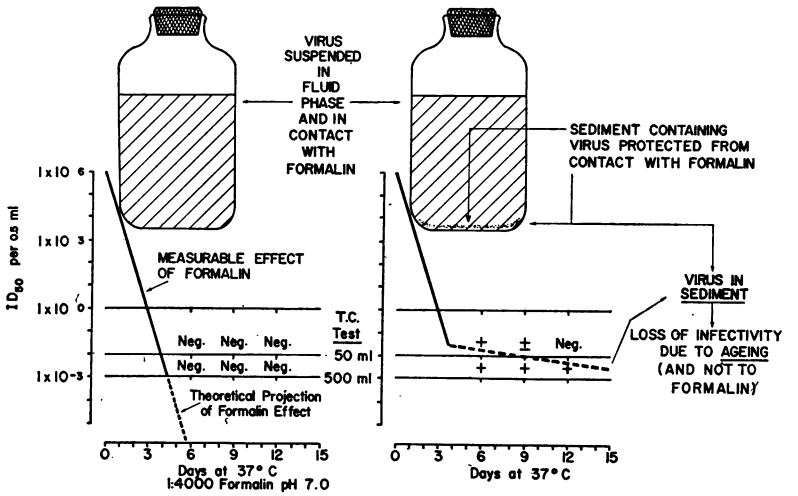


Figure 7—Effect of Virus-Formaldehyde Contact Upon Rate of Destruction of Virus Infectivity

the virus and could readily account for incompleteness of inactivation.

Other facts that emerged from these inquiries were that there existed differences in the kind of filter system used, as well as differences in filtration practices, so far as elapsed time of storage between the harvesting of fluids and filtration. These details are to be described by the Technical Committee whose study correlated these observations.

Essentials for Consistency in Production

A great deal was learned from the different processes in effect, and as a result certain practices were recommended and others were required to obviate such variation. Those required to accomplish basic uniformity are summarized graphically in Figure 8. It may be seen here that a filtration is required within 72 hours of beginning inactivation. Another filtration step has been added as a further requirement against the contingency of the formation of precipitates, or of protected virus particles, or aggregates, before inactivation is completed. This additional filtration is to be carried out at a point in the process when virus infectivity has been reduced to levels that are not readily detectable, which is sometime between the third and sixth days. The continuation of treatment for the predetermined time should be as effective in destroying infectivity as is suggested by the "theoretical projection," and this is verified by tests upon samples as is indicated in Figures 7 and 8.

The required tests in tissue culture are made during the first three days of treatment to establish the degree of inactivating effect of formaldehyde upon virus, and, again, during the last three days of treatment to verify the completeness with which the inactivating effect has been accomplished. Thus, there is built into the manufacturing and testing process a measure of safety that far exceeds in significance merely the isolated results of a set of tests upon a particular lot that is being considered for use in man. This is accomplished by relating treatment time and the time of selection of safety-test samples to the rate of virus inactivation and by considering the consistency with which

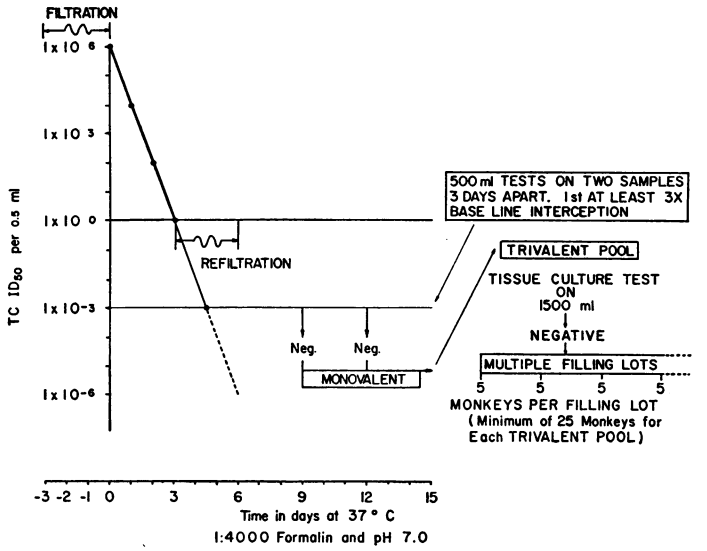


Figure 8—Guarding Safety by a Combination of Requirements for Processing and Testing

negative tests are obtained in successive lots.

In addition, further tests are required on the trivalent mixture. The report that a mixture made of three negative monovalent pools sometimes has revealed live virus has led some to speculate about the possibility of reactivation of virus believed to be inactivated. This could occur readily where virus is contained in sediment in the monovalent pool, only to be revealed in samples removed shortly after stirring of sediment upon admixture of the three strain pools.

After a negative tissue culture test of the trivalent pool, still another safety test is performed—this one in monkeys. This is done on samplings of the different filling lots. It has been recognized not only that the monkey test is less sensitive than the tissue culture test for detection of small amounts of virus, but that difficulties can occur as a result of so-called "false-positives" (Figure 5). This problem has now been reduced by changes in the manner of performance of the monkey test and in the criteria for establishing the significance of histologic changes, especially when these are not accompanied by signs of paralysis. The greater sensitivity of the tissue culture test does not obviate the need for a test in monkeys at this stage of experience.

Since a number of months are normally required for completing the testing of a lot of vaccine, after completion of the inactivation process, information is available on consistency, not only for the period preceding the start of manufacture of any one lot, but for a period of several months that follow, and before the lot is ready for release. Thus, the value of the consecutive record, as a safety guide, is enhanced by the availability of information on inactivation *after* preparation of the lot of vaccine that is considered for release, as well as *before* its manufacture was begun. Although the significance and importance of this was not as thoroughly appreciated before, as it is now, this concept was the basis for

the statement about consistency that has been retained through several amendments to the Public Health Service's Minimum Requirements for Preparation of Poliomyelitis Vaccine.[14]

The purpose of the information and analyses just presented is to help answer the question "How is vaccine safety determined?" Each of the several elements that are part of the question of safety must be applied with equal vigilance, regardless of the pathogenic characteristics of the strains used for inclusion in the vaccine.

Mahoney Strain

The use of the Mahoney strain in the initial investigations in animals, and in the initial studies in man, was determined by a number of deliberate considerations: (1) At first, of all of the Type I strains examined in the initial attempts to find viruses that would grow well in tissue culture, this strain surpassed all others.[15] With further developments in tissue culture technics differences between strains, in this respect, have been considerably reduced. (2) Since the monkey was more sensitive for the detection of Mahoney virus than the earliest tissue culture systems, while for detecting MEF–1 and Saukett the tissue culture system was more sensitive than the monkey,[3] it seemed wise to work with viruses of both types to permit the development of methods that would destroy virus more readily detectable in either system. Such methods could then be applied to viruses of any variety in accordance with the needs of the problem. Further developments have now made the tissue culture test more sensitive than the monkey test for all three strains. (3) In the absence of direct knowledge of the relationship between virulence and antigenicity it seemed desirable to investigate the effectiveness of a vaccine made from a particularly virulent strain. The decision to orient the investigation in this way was influenced by the knowledge that a vaccine made from the virulent Phase I pertussis organisms is more effective than vaccine made from less virulent varieties. Moreover, there are other similar examples in the field of immunology[16] and this consideration seemed worthy of further investigation.

Also, there was the basic scientific question of proof that a killed-virus vaccine can actually induce immunity. For proving this point the Mahoney strain was best suited, since this would then leave no doubt that monkeys vaccinated successfully, without the development of disease, would have, in fact, developed their immunity from the killed virus. The successful vaccination of human subjects, without the induction of disease—either in the subject himself or in his familial associates or community contacts—provided the desired proof that antibody could, in fact, be induced by a nonliving form of the poliomyelitis virus and gave further support to the hypothesis that living virus was not needed for immunization against this disease.[17] Furthermore, it appeared that with due care, vaccine with this strain—a particularly virulent one—could be prepared safely. If this be so, then surely, the fundamental scientific question of safety and effectiveness of a killed-virus vaccine could be answered decisively.[5] This, I believe, has been done.[6]

If the Mahoney strain had not been used, the significance of the scientific proof might have been questioned. In fact, even today, there are some who are of the opinion that the only reason antibody is formed after vaccination with a killed-virus vaccine is because of the presence of traces of live virus or of virus that becomes "reactivated" after injection. For these hypotheses no proof has been presented, and the weight of evidence is to the contrary.

The Question of Strain Change

The wisdom of continuing the use of Mahoney strain for preparation of vaccine on a large scale has been questioned [18] understandably. The existence of defective vaccine was first revealed because of the effect of this component in those who received such vaccine. The opinion that vaccine should not be made with the Mahoney strain still left unresolved the reasons for the defections in the vaccine preparation and testing process that permitted this to occur. The solution of the basic problem would solve simultaneously the problem of the Mahoney strain, since this same solution would be applicable to any virus, regardless of its potential pathogenicity for man. If the basic problem has, in fact, been solved, then the question of change of strain is being considered for reasons other than that it is essential for the preparation of a safe vaccine; the hazards of any living polio virus are to be avoided.

A change was contemplated over a year ago as a result of observations which revealed the lesser stability of Mahoney, in the presence of merthiolate—hence the poorer showing for Type I as compared to Types II and III in the field trial.[4] When this observation was made [11] a study was instituted to select another Type I strain.

The problem of the instability of the Mahoney strain—and of the other strains as well—in the presence of merthiolate was controlled promptly in a number of ways. These have all been put into practice; preservatives may be omitted entirely; merthiolate used in combination with versene,[4] or any one of a number of other preservatives can be used. The practice in the United States is to use a preservative, while in other countries it is omitted.

Even though the stability problem seemed to have been resolved, the study of strains was continued because of interest in the basic question of the interrelationship, if any, between virulence and antigenic capacity. It is now evident that degree of virulence and degree of antigenic capacity are independent variables; each can be cultivated separately or together. The problem has now been sufficiently far advanced to indicate that a group of strains exist, within each type, that are in the lower range of virulence for animals, and that are equal to or better, antigenically, when compared with strains of higher virulence.

It has been established, also, in the course of these studies [19] and by others [20, 21] that virus populations that are dominantly avirulent can give rise to offspring that are virulent. For this reason, the assurance of the absence of infectious virus is of first importance in preparing vaccine.

The opinion has been expressed that vaccinations should cease pending the production of vaccine containing "avirulent" strains for all three types or that there be a halt until the Mahoney strain is replaced.[22] This opinion can be questioned in terms of the relative importance (1) of safeguards based upon rigid requirements for production and testing as compared with safeguards based upon strain composition and (2) in terms of the advantages that could result from the availability of a supply of properly produced and tested vaccine as compared with a lesser supply that could be expected as a result of an abrupt change-over. These two alternatives must be considered in proper perspective to guide the judgment of those who have the responsibility for the decisions involved in vaccine manufacture, vaccine application, as well as those for safeguarding the public health.

Factors Related to Effectiveness

Evidence continues to accumulate indicating that the prevention of paralysis is mediated through the action of anti-

body. On the basis of this evidence the presence of antibody in the circulating blood could be regarded as synonymous with immunity. However, it seems that if antibody was once present, but has declined to nonmeasurable levels, that a state of immunity continues. The mechanism that appears to be operative is that of a hyperreactive antibody response.[23] Although it is known that the presence of a measurable level of antibody will prevent paralytic polio in the lower primates,[17, 24] and probably in man,[25] it is not known what degree of hyperreactivity, in the absence of measurable circulating antibody, is sufficient for prevention of paralysis. It appears from studies reported elsewhere [23] that the degree of hyperreactivity of the immunologic mechanism required is very little; more precise information should be forthcoming from studies now in progress.

Thus, the primary objective of an immunization program is that of inducing the formation of a measurable level of circulating antibody in all vaccinated subjects—and in so doing to have stimulated the immune mechanism in such a way that the resulting hyperreactive state will persist throughout life, even though in the course of time antibody levels decline; this occurs whether antibody is the result of vaccination or natural infection.[4] The basic goal is the initial production of antibody, since this would reflect the effectiveness of the primary stimulation that accompanies the initiation of the hyperreactive state. The use of secondary, or booster stimulation, is to assure further the full development of the hyperreactive state and to serve as a third opportunity to induce primary stimulation if this may have failed on both previous occasions for any one of a number of reasons—relative insensibility of the vaccinated subject, or because of the use of vaccine of low potency.[4]

The goal is to achieve the maximal effect with the minimal amount of treatment. The critical factors are (1) antigenic mass,[10] i.e., potency of vaccine and volume inoculated, and (2) the number of inoculations and the spacing between each.[4, 10] Vaccine potency and stability are the most critical factors in this regard.

While the degree of antigenic potency of vaccine can be established technically in any of a number of ways the significance of any laboratory test can be established only by comparison between the vaccine under test and a reference vaccine,[4] the performance of which has been standardized in fully susceptible children.[10] Such a reference vaccine has been established and standardized and is being used.

Correlation between level of potency of lots of vaccine used in areas where epidemics occurred in 1955, and the degree of effectiveness observed after a single dose, will contribute considerably to the establishment of a rational limit of potency to be required for maximal effectiveness. From such correlations it should be possible, also, to gain further insight into the requirements for persistence of vaccine effectiveness in terms of level of antibody associated with immunity to paralysis.

In view of certain details in the Francis Report[5] questions have been raised about the immune response in relation to age. The answers to these questions may be seen in Figures 9 and 10 which show, respectively, antibody response to infection and to vaccination in individuals of different ages. It would appear from these data that, over the age range studied, there are no significant differences in terms of antibody response to the two different kinds of antigenic stimulation.

No further developments have occurred to warrant changes in the recommendation for two doses, spaced not less than two weeks apart and, preferably, four to six weeks apart. A third dose

Figure 9—Antibody Response in Relation to Age

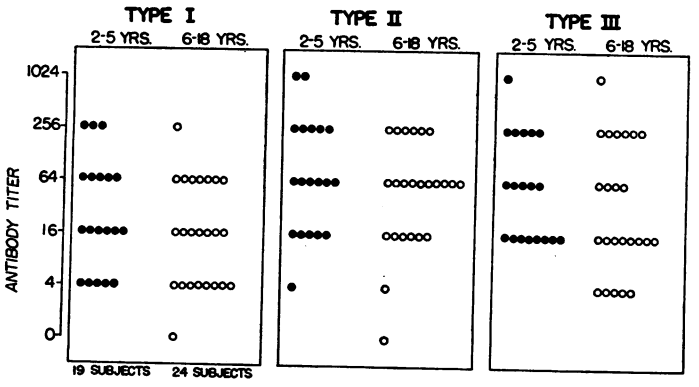
Type I Antibody Levels in a Group of 87 Recently Paralyzed Convalescents (1952—Pittsburgh)

Antibody Titer	Age Group 1-2-3 yr.	4-5-6 yr.	7-8-9 yr.	10+yr.
2048		●		
1024	●●●●	●	●	
512	●●●	●●●●●●	●●●●	●●●
256	●●●●●●●●●	●●●●●●●●●●●	●●●●●●	●●●●●
128	●●	●●●	●●●	●●●
64	●●●	●●●●	●●●	●●●●●●●●
32		●		●
16				●●
8				
No. Subjects	21	27	17	22

is required for producing the full effect; this can be approximated by administration of the third dose at least seven months after the second. Whether or not reinoculation will be required preschool, for maintenance of immunity, for children first vaccinated early in life, or additional inoculations to compensate for low potency—if found to be less than optimal—will be determined by continued study; appropriate recommendations will be suggested.

Figure 10—Antibody Response in Different Age Groups with No Demonstrable Preantibody for Any Type

Two Doses of Vaccine Given 4 Weeks Apart (1 ML.-I.M.)



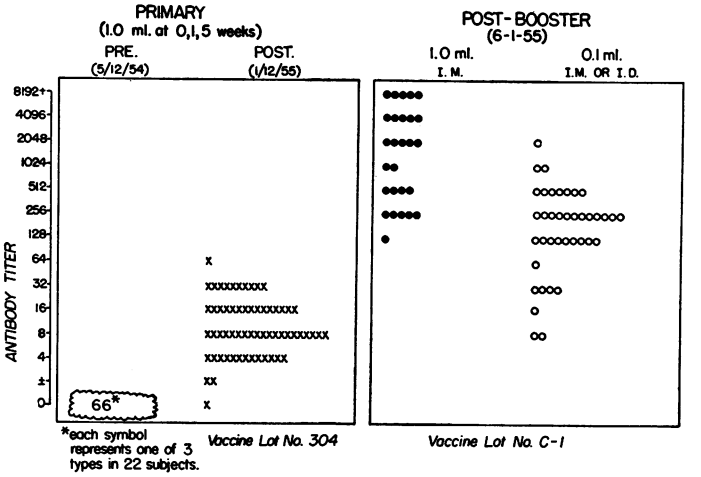


Figure 11—Influence of Dose on "Booster" Response in 22 Children with No Demonstrable Preantibody for Any Type

Until such time, the schedule recommended can be regarded as optimal and the dose for all ages is 1 ml, given either *intramuscularly* or *subcutaneously*. Although the intramuscular response is perceptibly better than the subcutaneous, this is not sufficiently great to be so significant as to warrant the use of one route to the exclusion of the other.

The only limitation in the usefulness of the *intradermal* route is the amount of antigen that can be so administered. Any demonstrable immunologic advantage of the intradermal route, in terms of efficiency of antibody formation, is so slight as to be offset by the limitation in volume that can be given in this way as compared with the subcutaneous or intramuscular routes. This does not mean to say that administration of smaller volumes intradermally will not be effective—it merely says that there are quantitatively demonstrable immunologic advantages to the use of larger doses which can be given more readily either intramuscularly or subcutaneously. The relative degree of response elicited by a small "booster" dose given intradermally or intramuscularly as compared with a larger dose given intramuscularly is shown in Figure 11.

Future Developments

Even though we have continued to study different methods of inactivation, there have been no developments in our laboratory, nor in any others of which we are aware, to indicate that there are improved ways of inactivating virus.

It has been said that the interval between destruction of infectivity and destruction of antigenicity is very critical and that extension of treatment time tends to impair potency. I should like to point out the extent to which antigenicity is retained during a period of overtreatment, after destruction of virus infectivity. This is illustrated in Figure 12 which shows (1) the rate of destruction of infectivity of each of the three strains of virus (Mahoney, MEF–1, and Saukett) and, by comparison, (2) the relative stability of the antigenicity of each, in the course of more than three weeks of treatment with 1:4,000 formalin, at pH 7.0, and at 37° C. It is evident that the Mahoney strain is slightly

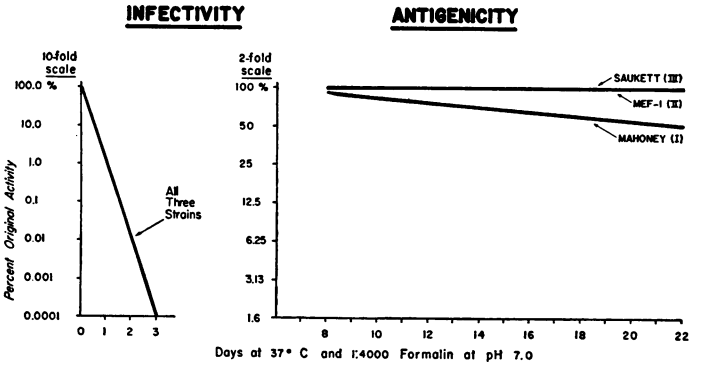


Figure 12—Rates of Destruction of Infectivity and of Antigenicity of Three Strains of Polio Virus

less stabile than the other two, but this difference is not of practical significance. More importantly, there is no evidence, whatever, to indicate that a narrow or critical margin exists between destruction of infectivity and the beginning of destruction of antigenicity. However, further treatment under these conditions will, in time, impair antigenic activity.

The developments that can be foreseen now are technologic and in relation to the quantity of virus that can be obtained per monkey. Since the virus yield per tissue culture cell is relatively constant, the principal change can come from increasing the number of cells in the tissue culture flask. In our own laboratory the efficiency has been increased measurably—as is no doubt true in industry—and in this way we have been able recently to prepare vaccines that are, in general, more potent than vaccines prepared earlier. The problem is simply one of efficient tissue cultivation.

In answer to the question as to whether or not a "new vaccine" can be expected soon, it appears now that developments or changes for the immediate future will most likely deal with variations in detail rather than fundamentals.

Summary

The discussion of vaccine safety contained in this report may be summarized as follows: The safety test has a twofold purpose: (1) as a test of a given lot of vaccine, and (2) as a test of the manufacturing process. Since the information on the lot in question gives a positive answer only with respect to a relatively small fraction of the entire lot, the answer to the question of the safety of the remainder of the lot from which the sample is drawn is had from the results of the test of the manufacturing process. While the safety of a batch of vaccine is determined by the presence or absence of infectious virus in a sample submitted to test, safety of a much higher order of magnitude is assured by a continuing examination of the manufacturing process as reflected by consistency of performance.

The discussion of vaccine effectiveness reiterates the concept of relationship to antigenic mass and this as a function of potency and dose as well as spacing between inoculations. Data on the influence of age upon antigenic response are also presented.

The question of future developments is discussed briefly and reasons given why these will be of technologic detail rather than of fundamentals.

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"This (the Hill-Burton) hospital construction program brought about the addition of more than 100,000 hospital beds and more than 500 community health centers. Most of these hospital beds have been built in rural areas and their availability has attracted scores of young physicians to practice in those areas. It is also gratifying to note that of the two billion dollars which has gone into this program, more than two-thirds has been contributed by state, local, and private sources. In the true democratic fashion, the people have taken hold of this program and shaped it to meet their needs."

(Excerpt from the address by Harry S. Truman, November 17, 1955, on the occasion of the annual presentation of the Albert Lasker Awards at the 83rd APHA Annual Meeting, Kansas City, Mo.)