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Safety Testing of Poliomyelitis Vaccine

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Much interest and, indeed, concern have lately been expressed about public lack of confidence in science and scientists (*1*). Although such attitudes stem from a variety of causes, many of which are beyond the control of the scientific community, it is important that legitimate grounds for distrust be eliminated. Several observers (*2–8*) have expressed doubts about the propriety of important decisions made in the poliomyelitis vaccine program. Certainly, if these doubts are valid, steps should be taken to prevent the occurrence of similar situations in the future.

When the Salk poliomyelitis vaccine was released for widespread use in April 1955, and despite assurances of safety, a number of vaccinated children developed poliomyelitis. Since most of these cases were associated with lots of vaccine produced by the Cutter Laboratories, this event has come to be known as the Cutter incident. Much has been written about the causes of the Cutter incident and the precautions taken to prevent a recurrence. However, several important questions have not been satisfactorily answered. Why were the intensive scientific preparations inadequate to prevent the distribution of infectious vaccine? And why was the early evidence of unreliability in the inactivation process not publicly acknowledged until after the Cutter incident?

This article reviews some aspects of the poliomyelitis vaccine safety testing program which seem to have important implications for scientists generally. It is based on a study of publicly available documents and papers, as indicated in the references. The most informative sources were the United States Public Health Service "White Paper" (*9*) and the record of testimony before the House of Representatives Committee on Interstate and Foreign Commerce (*10*).

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General Review

The Salk vaccine is prepared by treating live poliomyelitis virus with a killing agent, formaldehyde, which destroys the ability of the virus to infect a human cell while preserving its ability to produce protective antibodies—that is, its antigenicity (*11*). In fact, prolonged treatment with formaldehyde will destroy the antigenic property as well, thereby making the vaccine safe, but worthless. The production of a useful vaccine, then, creates a delicate problem in safety—the vaccine must be treated sufficiently to destroy infectivity but not so much as to destroy or seriously impair antigenicity.

Inactivated virus vaccines against poliomyelitis were first used in this country in the early 1930's. The Kolmer vaccine was known to contain a small amount of live virus capable of infecting monkeys, but it was presumed to be safe for humans on the basis of the unproved assumption that serial passage in monkeys had reduced its pathogenicity for man. This vaccine was clearly implicated as the cause of a number of cases of poliomyelitis. The Brodie vaccine, believed to be completely inactivated, was also suspected of causing several cases of poliomyelitis, but the evidence is much less convincing. At a meeting of the American Public Health Association in November 1935, reports were given on both vaccines. During the discussion of these reports, both vaccines were roundly condemned, particularly by Rivers of the Rockefeller Foundation and by Leake of the U.S. Public Health Service (*12*). Shortly thereafter, Leake published a list of vaccine-associated cases (*13*), and the vaccines were withdrawn from use.

The development of tissue-culture techniques by Enders, Weller, and Robbins (*14*) made it possible to grow virus easily and to obtain an index of its infectivity, thus opening the way to a fresh attack on the vaccine problem. About 1953, Salk developed a process which he believed capable of producing a safe and effective inactivated virus vaccine.

In view of the 1935 experience, the question of safety was a primary issue, and in May 1954, just after the start of the large-scale field trial (*15*), Salk published an account of the theory of the inactivation process which, he believed, guaranteed "absolute safety" of the final product (*16*). To Salk, the theoretical argument was so convincing that he argued against the employment of expensive and difficult procedures which had been suggested for the detection of possible residual live virus in the final product (*16*, p. 568). The theory itself is quite simple. The inactivation was believed to be a first-order chemical reaction and, consequently, the proportion of original virus still infective at time t should be e^{-kt}, where k is the rate constant for the reaction. If the number of infective virus particles at time zero and the rate constant are known, one can specify a time at which the probability of there remaining *any* infective particles is vanishingly small and, for practical purposes, the product could be guaranteed to be free of infective virus. If with this much treatment the material is still highly antigenic, the process can be made to yield a safe, potent vaccine.

Unfortunately, Salk's 1954 paper did not give detailed evidence in support of this theory, and the state of knowledge at the time, as judged from other sources, makes the validity of these assumptions appear questionable. The virus suspension from which the vaccine is made is a heterogeneous mixture, containing, for example, considerably more monkey kidney protein than poliomyelitis virus. Even if the rate of inactivation appeared constant over the observable range, the extrapolation beyond the observations would be questionable. Actually, some of the data presented by

Salk in February 1955 (*17*) show a nonconstant rate of inactivation. Inactivation data for the Mahoney strain are shown for lots produced by manufacturers A and B. In each of the nine lots produced by manufacturer A, a decrease in the observed inactivation rate becomes apparent at 72 hours. The change in rate is not evident on the summary graph (*17*, Fig. 5) because the final 72-hour average is omitted. There is no evidence of a systematic change with time in the rates for the nine lots produced by manufacturer B, although it should be noted that the inactivation rates are not determined with very high precision. A recent paper (*18*), reporting the experience of one of the vaccine manufacturers, points out that the inactivation rate undergoes a marked change within the first few hours and, therefore, that first-order kinetics cannot safely be used to extrapolate the inactivation curve. A more detailed analysis of the kinetics of virus inactivation in the preparation of poliomyelitis vaccine is given by Gard (*19*).

Salk's application of his theory also depended on the unstated assumption that a single live virus particle will invariably be detected if tested in a tissue-culture preparation. However, tissue-culture preparations were known to vary widely in sensitivity from batch to batch, and there was some evidence that tissues other than monkey kidney were, on the average, more sensitive (*20*). There was, furthermore, no evidence on the relative sensitivity of children and tissue-culture preparations. To be on the safe side, one had to suppose that a single virus particle might infect a child, so that it was important to estimate the sensitivity of monkey kidney tissue culture in absolute terms. On the basis of electron microscope measurements (*21*), Schwerdt and Schaeffer estimated the chance of infecting a tissue-culture preparation with a single virus particle to be of the order of 0.005, or 1 in 200. This figure is surprisingly low, and there was room for some doubt about its validity (*22*). However, this seems to have been the only experimentally based estimate of the absolute magnitude of tissue-culture sensitivity available in 1954. More refined measurements, reported after the Cutter incident, raise this figure to about 0.02, or 1 in 50 (*23*).

In preparation for the field trial of 1954 (*15*), six drug manufacturers began to produce poliomyelitis vaccine. Their findings made such considerations largely academic. Although they believed that they were following Salk's procedure, residual live virus was found in a number of lots of vaccine from each manufacturer. Thus, whatever the merits of the theory for vaccine made by Salk himself, it clearly could not be applied to the production process used by the manufacturers. At this time, all lots of vaccine were being tested by three laboratories independently—that is, by the manufacturer, by Salk, and by the Public Health Service. In many cases, the presence of live virus was detected by one laboratory, but not by the other two, suggesting the possibility of considerable variability in the sensitivity of the test (*9*).

In April 1954, the Vaccine Advisory Committee of the National Foundation for Infantile Paralysis met with a group of experts from the Public Health Service to decide whether or not to proceed with the scheduled field trial. At this point, only 16 manufactured lots had been tested, and, although four of them had been shown to contain infective virus, the last ten had tested negative. Furthermore, no poliomyelitis had been detected among a group of several thousand children inoculated with vaccine from commercial lots which had passed the tests. The committee decided to proceed with the field trial, using vaccine produced by the two largest manufacturers. No public acknowledgment of the manufacturing difficulties was made at this time, but the Vaccine Advisory Committee released a public statement which was concurred in by the Public Health Service, and which, in effect, gave assurances that the vaccine was safe.

In anticipation of a successful field trial, additional lots of vaccine were produced by all the manufacturers, and residual live virus was again found in occasional lots. Testing in three laboratories was no longer required, and manufacturers varied in the amount of vaccine that they tested (*24*). The Public Health Service Minimum Requirements (*25*) specified only that 0.1 percent of each lot should be tested in tissue culture, but most of the manufacturers tested considerably greater volumes. Tests in monkeys were also required and performed.

On 12 April 1955, the results of the field trial were made public. The findings were interpreted as convincing evidence of the safety of the vaccine as well as proof of its effectiveness. The six manufacturers were immediately licensed, and all but one of them began to distribute poliomyelitis vaccine. However, the vaccines used in the field trial, which were produced by two of the manufacturers, had been extensively tested in three laboratories and had been found negative for live virus. Many of the lots of vaccine released after the field trial had been produced by other manufacturers and had been tested only by the producer. Therefore, the safety of these lots could not properly be judged from the results of the field trial. All manufacturers had rejected some lots because live virus had been found in them, and therefore Salk's theory that safety was guaranteed by the method of preparation obviously did not apply. The final tissue-culture and monkey tests were the only safeguards provided against the release of lots containing live virus, and the sensitivity of these tests was not known. Within a week or two of the mass distribution of vaccine, it became evident that the experience of 1935 had been repeated —a number of cases of poliomyelitis were clearly associated with the administration of certain lots of vaccine—and within the next few weeks all poliomyelitis vaccine was withdrawn. In subsequent weeks, production processes and safety test procedures were revised, and vaccine distribution was gradually resumed.

Modifications of the Program

When, on 12 April 1955, the Salk vaccine became a licensed product, the Public Health Service became responsible for the establishment of minimum requirements for its potency and safety. Such requirements had been established before 12 April so that the licensing of the vaccine would not be delayed if the field trial proved successful. However, when the Cutter incident was recognized, the advice of a number of experts was sought, and on 26 May 1955, the Technical Committee on Poliomyelitis Vaccine was formed as a permanent advisory group. The committee was to advise the Public Health Service on the release of individual lots of vaccine and to give continuing guidance on vaccine production and testing.

In June 1955, the Public Health Service released the White Paper, a technical report on the Salk vaccine (*9*). The White Paper reviewed the entire experience with vaccine production and thus made public the fact that live virus had been found in lots of vaccine produced by each of the manufacturers. The White Paper also presented an analysis of the safety test procedure, with recommendations for a considerably more stringent testing program.

The analysis of the test procedure rested on two basic assumptions. First, the live virus was supposed to be present in particulates (single virus particles or, possibly, aggregates of virus particles) which were randomly distributed throughout the lot of vaccine. Second, it was assumed that if such a particle were included in the test sample its presence would be detected with certainty. From these assumptions, it follows that if a lot contains r such infective particulates per liter and v liters are tested, the probability of detecting the presence of live virus is given by $(1 - e^{-rv})$. A test of only 0.1 percent of, say, a 40-liter lot might easily fail to detect infectivity at the level

of 10 particulates per liter, since the probability of detecting infectivity in such a case is only 0.33, or one chance in three. The White Paper recommended that 1.5 liters be tested from each of the three single-strain vaccines and that 1.5 liters be tested from the mixed final vaccine, regardless of the lot size. According to this theory, each of these tests should independently have a probability better than 0.999 of detecting the presence of live virus at the level of 5 particulates per liter.

It has been pointed out that the ability to reject defective lots with high probability does not guarantee that all infective lots in a long sequence are rejected. However, if the frequency with which lots are rejected is found to be low, it can be shown that the average infectivity of the lots accepted will also be quite low (*26*).

The choice of 5 particulates per liter is arbitrary. In view of the low annual incidence of paralytic poliomyelitis (about 50 per 100,000 at the most susceptible ages, *27*), the "acceptable" level of infectivity for a poliomyelitis vaccine would have to be very low indeed. If each particulate injected did cause a case of paralytic poliomyelitis, the injection of 1 milliliter of a vaccine containing 5 particulates per liter could cause up to 500 cases per 100,000 vaccinated. Of course, it is now clear from the Cutter incident that, as with natural infection, most individuals do not develop paralytic poliomyelitis when they are inoculated with live virus. The cases of poliomyelitis among contacts of children inoculated with Cutter vaccine (*9*) give evidence for the existence of numerous inapparent infections caused by the vaccine (*28*).

The White Paper thus proposed a test procedure which was designed to provide a known degree of protection. Unfortunately, the assumption of perfect sensitivity for tissue-culture preparations was not in accord with the experimental evidence. Even if one takes the more recent estimate (*23*) that the probability of infection by a single particle is about 0.02, one would have to multiply all test volumes by 50, a wholly impractical requirement, to achieve the degree of protection described in the White Paper.

Shortly after the Cutter incident, the Laboratory of Biologics Control of the Public Health Service requested outside laboratories to assist in testing incriminated and other lots of vaccine for the presence of live virus. The results of these tests were reported in the July 1956 issue of the *American Journal of Hygiene* (*29*). Of 16 Cutter lots tested, six had been clearly incriminated epidemiologically and ten had not. Since the supply of these vaccines was limited, none of the lots could be tested in tissue culture to the extent specified in the revised minimum requirements. Nonetheless the results were surprising. The tissue-culture test, previously believed to be considerably more sensitive than tests in monkeys, gave completely negative results in two of the three laboratories, and in the third laboratory it gave positive results for only two lots, one of which was not epidemiologically incriminated. However, two of the laboratories also made tests in monkeys pretreated with cortisone. All incriminated lots were found to infect a substantial proportion of the treated monkeys, and two additional nonincriminated lots were also found to contain live virus. Check tests showed that virus not treated with formaldehyde was more easily detected in tissue culture than in cortisone-treated monkeys. Evidently something happens in the process of treatment with formaldehyde which reduces the ability of virus to infect a tissue-culture preparation more than its ability to infect cortisone-treated monkeys. Although the reason for this phenomenon is not known with certainty, a mechanism which could give rise to such a result was described by Veldee in September 1955 (*5*).

At present, tests in coritsone-treated monkeys are incorporated into the minimum requirements. Thus, the epidemiologically incriminated Cutter lots would almost certainly not have passed the present safety test. However, the number of live virus particulates per liter which might plausibly escape detection by the present safety test is not known.

In addition to the review and revision of the safety test requirements, the Public Health Service initiated a study to determine the cause or causes of the failure of the manufacturing process to inactivate completely all of the virus. Each manufacturing plant was visited by a team of experts, and some changes in manufacturing procedures were introduced. In November 1955, the Public Health Service Technical Committee issued an interim report (*30*) in which it was stated that "the Committee is of the opinion that the principal factors which were involved in manufacturing difficulties have been identified and corrective measures have been taken." Precipitates had been found in some vaccine lots at various stages of production, and it was argued that virus might become trapped in a speck of precipitate and thus be shielded from the formaldehyde. The corrective measures proposed consisted of the addition of further filtration steps at certain stages in the inactivation process. The report offers no experimental evidence to support this theory, nor does it give evidence to show that improvement resulted from the introduction of the new filtration steps.

Meanwhile, it was considered desirable to revive the vaccination program as soon as possible. Throughout the summer and fall of 1955, lots were considered individually by the Public Health Service Technical Committee and released when the committee was satisfied that the lot in question had been adequately tested and proved safe. The criteria actually used for releasing lots under this system are not described in the report of the technical committee (*30*).

Discussion

The introduction of any new vaccine on a mass basis is always accompanied by a certain amount of risk that the vaccine may not be entirely safe. The degree of risk which ought to be tolerated depends, of course, on the incidence of the disease in question and the amount of benefit which the vaccine is supposed to offer. In view of the low average annual incidence of paralytic poliomyelitis —approximately 50 per 100,000 at the most susceptible ages—the introduction of a poliomyelitis vaccine can be justified only if the risk of acquiring poliomyelitis from the vaccine itself is known to be very small. Indeed, Salk himself has said that no vaccine could be justifiably introduced for which there existed any measurable risk at all (*16*). In view of the known deficiencies of the tissue-culture test and the inability of the manufacturers to produce consistently safe vaccines, the original decision to proceed with the field trial seems, in retrospect, unwise. Considering how little was known about the susceptibility of children to virus introduced by inoculation, one could not have ruled out the possibility that a vaccine containing live virus might produce more paralytic cases in a few weeks than would be expected from natural infections in many years. In practice, fortunately, it turned out that the clinical cases later produced by defective Cutter vaccine were only a very small proportion of the number infected (*9*).

The decision to proceed with the field trial may have been influenced by the fact that, of the 16 vaccine lots tested, the last ten had appeared to be free of live virus. However, continued production of vaccine while the field trial was in progress showed that both the inactivation process and the tissue-culture and monkey safety tests were unreliable. In any event, the assumption that the safety of the triple-tested vaccines used in the field trial was evidence for the safety of vaccines tested only by the manufacturer was not justified. In a recent paper (*31*), Salk suggests that improvements in the quality of vaccine production make possible the abandonment of the expensive safety tests with cortisone-treated mon-

keys. This weakening of the safety test would be extremely dangerous. Even if manufacturers are able to produce safe vaccine consistently, an adequate safety test is essential to guard against manufacturing accidents.

The adequacy of the present safety standards is difficult to judge. In view of all that remains unknown about the interaction of poliomyelitis virus and animal cell systems, a theoretical demonstration of the adequacy of even the present safety test requirements seems to be out of the question. However, testing procedures now incorporated into the minimum requirements have been able to detect the presence of live virus in the incriminated Cutter lots and also in some lots with which no cases of poliomyelitis were known to be associated. Although these findings by no means guarantee the adequacy of the current test requirements, they do provide some reassurance. The decision to proceed with the field trial and later to continue the vaccination program through the summer of 1955 seems, on the basis of the published evidence, to have been a gamble. Whether a gamble of this kind was warranted in this situation is a matter on which opinions will differ.

Perhaps the most disturbing element of the entire program has been the disparity between the risks that were known to be involved and the repeated assurances of safety. Before Salk's papers on safety testing had appeared (*16, 17*), it had become clear that this theory of inactivation did not in fact apply to the vaccine then being produced. Likewise, the implication that the experience in the field trial was strong evidence for the safety of the vaccine subsequently distributed was misleading. Finally, the statement that the fault in production had been determined and corrected seems, on the basis of the evidence presented in the report of the Public Health Service Technical Committee, a conjecture, rather than an experimentally determined fact.

The tendency to minimize the actual difficulties is not limited to these major instances. Many of the technical reports and publications which have appeared both before and after the Cutter incident have been vague about those facts which might open the status of the program to criticism. For example, the public statement preceding the field trial did not mention the finding of live virus, but asserted that ". . . the possibility of infectious activity remaining in any vaccine meeting the specifications and Minimal Requirements has been reduced to a point below which it cannot be measured by practicable laboratory procedures" (*9*). Without an assessment of the sensitivity of the practicable laboratory procedures, the statement is essentially meaningless. Nonetheless, the statement was issued without further explanation. More recently, Ratner has pointed out (*3*) that the report on revised production methods (*30*) fails to indicate that the vaccine made by these methods was not available at the time the report was released and that the only vaccine that would be available for several months had been manufactured without the new safeguards and had been subjected to safety tests whose extent was not described. No reply to this letter or to Ratner's earlier article (*2*) seems to have been published.

If we consider the information which actually reaches the general public, the reports distributed to physicians by the National Foundation for Infantile Paralysis are probably more important than the technical reports of the Public Health Service committees. Although the reports of the National Foundation for Infantile Paralysis are ostensibly designed to explain the status of the program to physicians who will in turn give advice to parents, a rather biased picture emerges. All doubts about the safety of the vaccine are dismissed. It is said to be "as safe as any biologic product can possibly be," and it is stated that the safety of the vaccine "has become a question for historians rather than clinicians" (*32*, no. 3). To the query, "What is the estimated calculated risk of inducing poliomyelitis infection by the inoculation of vaccine under present safety standards?" the foundation reply is, "None. No risk" (*32*, no. 3). Despite the unresolved questions on the safety of the vaccine and the very small risk to any individual of acquiring paralytic polio in a single season, the foundation described the need for vaccinating as many children as possible before the 1956 polio season as "akin to a medical emergency" (*32*, no. 2).

As a matter of general policy, the failure to make complete information available and to answer serious criticisms seems unfortunate on several counts. For one thing, it makes it difficult if not impossible to have effective interaction between the scientific workers participating in the program and other scientists. It is not an uncommon finding, after all, that problems which are new in one field are familiar in another, though perhaps in a slightly different guise. Yet most researchers are unwilling to comment forcefully on what they know to be a limited portion of the evidence. If it had been generally recognized before the field trial that no guarantees of safety existed other than those outlined in Salk's paper in 1954 (*16*), individuals who remained silent might have made known their concern and urged a review of the safety testing program.

From the viewpoint of the relationships between scientists and the general public, the consequences of this policy may be much more serious than the harm done by faulty vaccine. It is understandable that, having decided to proceed with a program, all concerned should wish to have it presented in the most favorable light. However, failure adequately to inform the public, more particularly the physicians who must largely accept the responsibility for advising the rest of the public, seems likely to lead to the deterioration of the confidence and respect which scientists should enjoy.

In view of the questions raised about the general policies adopted in the safety-testing program for poliomyelitis vaccine, a searching study of the entire program conducted by an appropriate body, such as the National Academy of Sciences, seems called for. Such a study could lead to recommendations for future programs which would provide for more complete access to information and, consequently, to more adequate protection from errors in judgment.

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Origins and Status of American Botanists

Charles J. Lyon

Scientists should learn more about themselves than is possible through personal observations. As a basis for maintaining the proper supply of trained men in each of the special fields, we should have accurate information about the number, ages, and professional preparation of the workers in each area. Such items as their academic origins and present fields of employment are also of considerable interest to many administrative officers.

In the absence of a central authority to regulate standards of training and the number of men in each field of science, the responsibility for advising students rests largely with individuals who depend too often on personal impressions and experience. They and the various planning agencies that can influence careers through fellowships and grants-in-aid should have information about the fields that require more men and about where these men can be trained to advantage.

With the exception of the *National Register of Scientific Personnel*, the records for the biological sciences are few and quite out of date. The only recent analysis of the numbers and origins of professional botanists was reported in 1955 by Greulach (*1*), but it was based on the facts for 1943, as assembled in the seventh edition of *American Men of Science*. It was also limited in its objectives, with emphasis on the academic origins of 2015 workers. The publication of the ninth edition, in 1955, with the biological scientists in a separate volume (*2*), has provided the opportunity for a second study of the same group of mature scientists, now grown to more than 2700 in number. In addition to an analysis for some of the points that were developed in the Greulach study, the botanists of 1955 have been tabulated by age classes and nature of employment. The entire group has also been divided into the three major subgroups of (i) plant pathologists, (ii) plant physiologists, and (iii) the other botanists.

For the purposes of this study, a botanist has been defined as a scientist who lists his or her primary professional interest as being in one or more of the plant sciences other than the applied sciences. Botanists are thus taken to include workers in plant nutrition, forest pathology, and economic botany, but the tabulation did not include geneticists, bacteriologists, foresters, horticulturists, agronomists, or plant breeders. Arbitrary decisions were made in the cases of scientists who were identified with some such field as cytology or biology; such a person was rated as a botanist only if a primary interest and activity in plant science was indicated by research titles, by membership in professional societies, or by his department in the organization by which he was employed. For the subdivisions of botany, a worker who indicated two such special fields as plant physiology and plant pathology was tabulated as having a primary interest in the area that he named first.

In tabulating such items as age, academic origin, and type of employment, certain other arbitrary decisions were necessary. For example, the age of an individual for whom no date of birth was recorded was taken to be about 21 years when the bachelor's degree was awarded. Only the first bachelor's degree, master's degree, and doctorate were tabulated. When only the advanced degree was reported, it was assumed (probably sometimes in error) that the bachelor's degree had been taken at the same institution. The occupation of a retired botanist was considered to be that shown by his last position before retirement. An important distinction had to be made in the many cases of botanists who were employed by the state colleges and universities; although most of them do research to some degree, they were tabulated under "education" if their official titles indicated that they were instructors in formal classes.

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