

# The Present Status of Polio Vaccines\*

## MODERATOR:

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## PANELISTS:

*Herald R. Cox, Sc.D., Pearl River, N.Y.; Bernard G. Greenberg, Ph.D., Chapel Hill, N.C.; Herman Kleinman, M.D., Minneapolis; Paul Meier, Ph.D., Chicago.*

## PART I

**DR. HERBERT RATNER:** In this panel we are first going to discuss the Salk vaccine, later the live virus vaccine. None of us have any commitments or allegiances except to the truth. Dr. Cox, of course, is from a pharmaceutical house, but he is not here to sell you his vaccine. He happens to be one of the world's leading authorities on live virus vaccines, as well as killed vaccines. His reputation for integrity is exceptional and unchallenged. He has devoted 14 years to the development of the live poliovirus vaccine specifically. He is here to share his knowledge with you. You will have full freedom to question and to dispute. Dr. Cox is director of virus research at Lederle, and is at present, president elect of the Society of American Bacteriologists.

Dr. Kleinman is an epidemiologist from the Minnesota Department of Health. He is intimately connected with that department's pioneering field studies on the Cox live poliovirus vaccine. Yesterday, he landed from Russia, where he was an official delegate of the USPHS at a conference on poliovirus vaccines. He was co-author in 1957 with Dr. Leonard Schuman of a paper entitled, *The Efficacy of Poliomyelitis Vaccine with Special Reference to Its Use in*

*Minnesota 1955-1956*, wherein they concluded that "analysis has revealed (that) the use of two doses of Salk poliomyelitis vaccine . . . . . (was) 83% protective against paralytic poliomyelitis."<sup>1</sup>

Professor Meier is a biostatistician from the University of Chicago. In the field of polio, he is best known for his analysis "Safety Testing of Poliomyelitis Vaccine" (*Science*, May 31, 1957), which suggested that a searching study of the entire Salk vaccine program by an appropriate body be conducted. Despite the attempt of the editors to initiate a debate on the crucial issue of safety testing, proponents of the Salk vaccine remained silent.

Professor Greenberg is head of the department of biostatistics of the University of North Carolina, School of Public Health and former chairman of the Committee on Evaluation and Standards of the American Public Health Association. In the past he has presented several papers on methodologic problems in the determination of the efficacy of the Salk vaccine.<sup>2</sup>

The reason for this panel on the present status of polio vaccines is best expressed by a quote from Dr. Alexander Langmuir. He is in charge of polio surveillance for the USPHS, and has been an ardent proponent of the Salk vaccine even prior to the Francis report of 1955. In a symposium on polio in New Jersey last month he stated that a current resurgence of the disease, particularly the paralytic form, provides "cause for immediate concern" and that the upward polio trend in the United States during the past two years "has been a sobering experience for overenthusiastic health officers and epidemiologists alike."<sup>3</sup>

In the fall of 1955 Dr. Langmuir had predicted that by 1957 there would be less than 100 cases of paralytic polio in the United States.<sup>4</sup> As you know, four years and 300 million doses of Salk vaccine later, we had in 1959 approximately 6,000 cases of paralytic polio, 1,000 of which were in persons who had received three, four, and more shots of the Salk vaccine. So you see, expectancy of the Salk vaccine has not lived

*This panel discussion was edited from a transcript. Opinions presented are those of the panel members and do not necessarily represent those of the Society.*

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TABLE 1.—PARALYTIC POLIO CASES IN THE U.S. IN 1957, 1958, 1959, INCLUDING PARALYTIC POLIO CASES IN SALK VACCINES.

	Total	Increase over 1957	Salk Vaccinated		
			1 or More Doses	3 Doses	4 or More Doses
1957	2158 <sup>1</sup>		658 <sup>2</sup>		206 <sup>2</sup>
1958	3122 <sup>1</sup>	45%	571 <sup>2</sup>	237 <sup>2</sup>	10 <sup>2</sup>
1959	5694 <sup>1</sup>	164%	1870 <sup>1</sup>	750 <sup>4</sup>	178 <sup>4</sup>

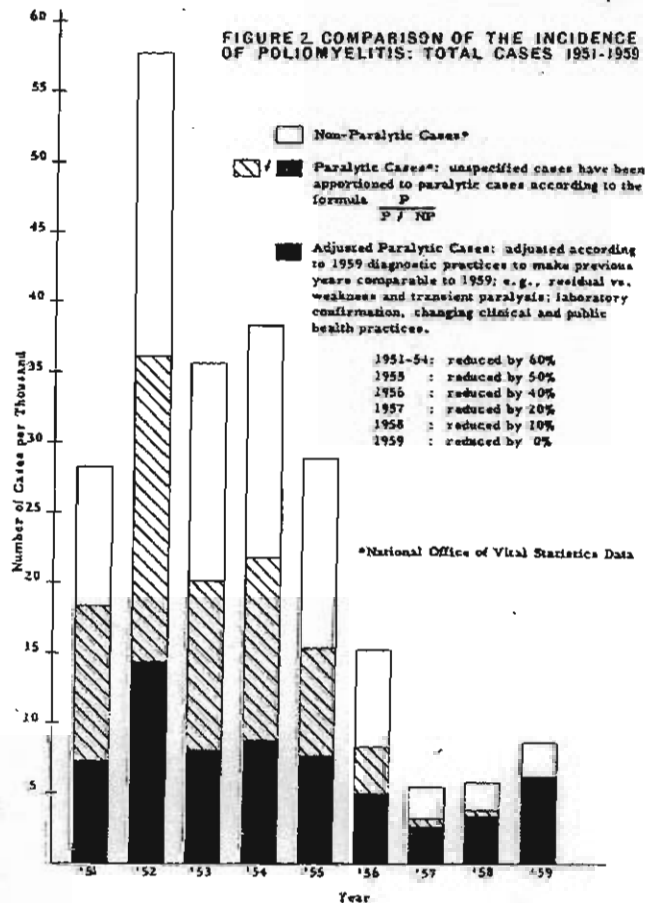
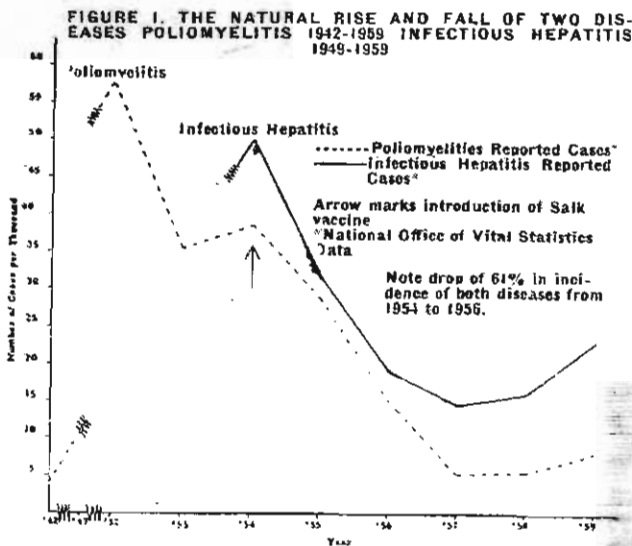
1. National Office of Vital Statistics figures: Morbidity and Mortality. USPHS vol. 8, no. 52 (Jan. 8) 1960.
2. Polio Surveillance figures: Thrupp, Lauri D., et al.: Poliomyelitis in the United States, 1957. Public Health Reports 74:535-545 (June) 1959.
3. Polio Surveillance figures: Polio Surveillance Unit Report No. 160. Dec. 5, 1958. These figures are only through Nov. 20, 1958. Also omitted are cases of paralytic polio among 179 cases for which age and/or vaccination status are unknown. The true figures are higher.
4. Polio Surveillance figures: Polio Surveillance Report No. 197. May 16, 1960.

These figures do not include cases of paralytic polio among 237 cases for which PSU did not receive any separate reports, in 184 cases in which the vaccine status was unknown, and in an unknown number of cases whose original diagnosis was changed as a result of "a 60-day follow-up report which included a verification of the diagnosis, (and) an estimate of the severity of residual paralysis." "The paralytic category (now) includes 4,783 cases with residual paralysis at sixty days plus 689 cases with a preliminary diagnosis of paralytic poliomyelitis for which no follow-up data were received." That the switch from paralytic cases to nonparalytic cases on the basis of the absence of residual paralysis in those with 3 or 4 doses of Salk vaccine is considerable may be gathered by comparing the final report on 1959 (Report 197), which includes follow-up data through Feb. 29, 1960, with the preliminary report in "an earlier PSU Report (No. 193), which includes follow-up data through Jan. 11, 1960. This should be understood in the light of Dr. Langmuir's remark to state epidemiologist in his letter of Sept. 29, 1959, that, "In the final analysis, even a small number of corrections may make crucial differences in the evaluation of effectiveness of vaccine. A revoked diagnosis or a switch of diagnosis from paralytic to nonparalytic, or vice versa, in only 5 to 10% of cases could change basic conclusions remarkably."

up to actuality, and Dr. Langmuir was right when he said the figures of 1959 were sobering.

In preparation for the discussion, it was thought best to review some basic facts of polio: incidence, natural history, the disease, and immunity, all important to the understanding of the vaccine problem. Table 1 presents current data on incidence of paralytic polio. Figure 1 presents the natural variations in incidence of polio and infectious hepatitis. Both diseases were in a natural decline when the Salk vaccine was introduced in 1955. Since the wide acceptance of the Salk vaccine was based primarily on the sharp decline in polio incidence, it is important to keep in mind that infectious hepatitis equally declined following the Salk vaccine.

Figure 2 shows what the incidence of paralytic polio would have been from 1951 through 1959 if the figures were corrected for the radical changes in diagnostic criteria since the introduction of the Salk vaccine. Dr. Greenberg will discuss some of these changes later. The solid columns in figure 2 represent a conservative estimate of what the incidence of paralytic polio would have been in former years if the diagnostic criteria of 1959 had been used. This permits a



more accurate comparison. It also helps us evaluate the progress or lack of progress made since the introduction of the Salk vaccine.

The low incidence of the disease also complicates evaluation of a vaccine. Presently, a community is considered to have an epidemic when it has 35 cases of polio per year per 100,000 population.\* In Oak Park with a population of 61,000, 21 or more cases constitutes an epidemic. Since Oak Park has about 500 blocks, this means one case of polio per year to 25 blocks. We have had only one epidemic of polio in the recorded history of Oak Park. In a high incidence disease like measles, on the other hand, it is common to have 21 cases in a single block. The difficulty in evaluating the efficacy of a vaccine against polio as contrasted to measles is obvious.

Because of the low incidence of polio, neither the private physician nor the local public health physician is in a position to judge the value of polio vaccine from personal experience alone. One central source must collect and evaluate the data. The result will be only as good as the thoroughness, objectivity, and statistical skills of the central source. Part of the difficulty in the evaluation of the Salk vaccine has been that the responsible authorities have not refined the techniques for evaluating high incidence diseases so that they can be applied to low incidence diseases.

We must also distinguish between polio infection and the clinical disease. Tuberculosis, where we have the tuberculin reactor which signifies infection as contrasted to the reportable clinical disease, is the prototype. For every one case of known paralytic polio we have about a thousand cases of subclinical polio infections. The latter accounts for the high degree of natural immunity in adults. Crucial to the understanding of the contemporary vaccine problem is that you can get infection of the gut with or without disease.

The theory of the killed vaccine is that circulating antibodies in sufficient amounts will neutralize poliovirus before it reaches the central nervous system. One of the major disappoint-

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\*Prior to the introduction of the Salk vaccine the National Foundation defined an epidemic as 20 or more cases of polio per year per 100,000 population. On this basis there were many epidemics throughout the United States yearly. The present higher rate has resulted in not a real, but a semantic elimination of epidemics.

ments of the killed vaccine is that circulating antibodies alone do not protect against alimentary infection. Only when the local immunity follows an alimentary infection are we capable of achieving a more consistent immunity against the disease. Circulating antibodies produced by a killed vaccine do not prevent the multiplication of enormous numbers of poliovirus in the gut, nor their break through into the circulatory systems. Protection depends on the presence of circulating antibodies in sufficient titer to offset virus entering the circulatory systems. Immunity of this type is predominantly relative.

This concludes our review. Dr. Greenberg will launch us into our panel discussion.

DR. BERNARD GREENBERG: I agreed, as a participant of this panel, to discuss the present status of the Salk vaccine as a *statistician*. As such, my primary concern, my only concern, is the very misleading way that most of this data has been handled from a statistical point of view.

There has been a rise during the past two years in the incidence rates of paralytic poliomyelitis in the United States. The rate in 1958 was about 50 per cent higher than that for 1957, and in 1959 about 80 per cent higher than in 1958. If 1959 is compared with the low year of 1957, the increase is about 170 per cent. At the same time, the rates for nonparalytic polio have been declining in relation to the 1957 base.

As a result of this trend in paralytic poliomyelitis, various officials in the Public Health Service, official health agencies, and one large voluntary health organization have been utilizing the press, radio, television, and other media to sound an alarm bell in an heroic effort to persuade more Americans to take advantage of the vaccination procedures available to them.

Although such a program might be desirable until live virus vaccines are available to us on more than an experimental basis, the misinformation and unjustified conclusions about the cause of this rise in incidence give concern to those interested in a sound program based on logic and fact rather than personal opinion and prejudice.

One of the most obvious pieces of misinformation being delivered to the American public is that the 50 per cent rise in paralytic poliomyelitis in 1958 and the real accelerated increase in

1959 have been caused by persons failing to be vaccinated. This represents a certain amount of "double talk" and an unwillingness to face facts and to evaluate the true effectiveness of the Salk vaccine. It is double talk from the standpoint of logical reasoning: If the Salk vaccine is to take credit for the decline from 1955-1957, how can those individuals who were vaccinated several years ago contribute to the increase in 1958 and 1959? Are not these persons still vaccinated?

The number of persons over two years of age in 1960 who have not been vaccinated cannot be more, and must be considerably less, than the number who had no vaccination in 1957. Yet, a recent Associated Press release to warn about the impending threat referred to the idea that the "main reason is that millions of children and adults have never been vaccinated." If they were never vaccinated, undoubtedly many more than were reported were unvaccinated during 1955, 1956, and 1957 when the same officials were claiming that reduction in rates was due to the vaccine.

Could it be that the vaccine has been only a temporary stop-gap and that the effect is now wearing off because the vaccinated individuals are not maintaining their antibody status through subclinical exposures and booster doses?

One cannot answer this question in the negative with real assurance because such a possibility is certainly a real one. The reduction of antibody titer with time is well documented and may explain why some individuals vaccinated five years ago have lost their immunization status. On the other hand, officials urging vaccination have taken the stand that the rate increased because large segments of the American population, about 49 per cent, have had no vaccine at all!

A scientific examination of the data, and the manner in which the data were manipulated, will reveal that the true effectiveness of the present Salk vaccine is unknown and greatly overrated.

The remainder of this paper documents this statement.

#### Effectiveness of Salk vaccine

All here will remember that the field trials in 1954 showed that the vaccine used was 72 per cent effective in preventing paralytic poliomyelitis within one year, but completely ineffective in preventing nonparalytic poliomyelitis.<sup>5</sup> It

must be remembered that these figures apply to the vaccine used in 1954, and, therefore, all the Francis report really tells us is that the Salk vaccine of 1954 was 72 per cent effective in preventing paralytic poliomyelitis for that one season.

For the 1955 vaccine, certain changes in the manufacture and testing for safety were introduced. The vaccine did not contain merthiolate as did the 1954 product. Live viruses were found in several lots, and the foundation of Salk's theory of inactivation was questioned. We were alarmed by the variation in antigenic potency of different lots from different manufacturers especially for a product that was to be administered on a mass basis. The Cutter incident and the "White Paper" are clearly remembered by those of us who, at that time, questioned the wisdom of the program as it was being conducted. To insure "absolute safety," an extra filtration step was introduced in November, 1955.<sup>7</sup> Perhaps Dr. Cox will comment on what this extra filtration step may do to the antigenic potency of the vaccine.

The result of that change, as well as the preceding ones, upon the effectiveness of the present vaccine is unknown. At that very time—November, 1955—the Poliomyelitis Surveillance Unit of the Communicable Disease Center published a paper which purported to show that in 1955 the vaccine was still as effective as in 1954.<sup>8</sup> In fact, a report from that unit on Dec. 7, 1955, went so far as to claim that a single inoculation of the vaccine was about 78 per cent effective in preventing paralytic poliomyelitis!<sup>9</sup>

In care and precision, the method of study in this Public Health Service report was not at all comparable to that of the field trials of 1954. There were no controls, the data were retrospective, and there were no rigid diagnostic criteria that could be supervised on a national basis. The claim that one inoculation was 78 per cent effective was too much for anyone to accept.

We were able, fortunately, to conduct a more intensive study in North Carolina, but it was subject to the same limitations of no real controls, and of retrospective design. Our purpose was simply to learn the magnitude of the bias introduced by faulty statistical manipulations in the Poliomyelitis Surveillance Unit study. We found that one dose was practically ineffective and two doses would produce a figure of only

about 60 per cent reduction among children 5 to 9 years old. The Poliomyelitis Surveillance Unit study had reported about 80 per cent effectiveness in North Carolina for a single shot. Why this discrepancy of figures in the two studies?

In a paper on the results of our study delivered before the Biometric Society and Institute of Mathematical Statistics in April, 1956,<sup>10</sup> I pointed out that the discrepancy was purely a statistical one. There were two biases in the way the Public Health Service had calculated its rates of attack among the vaccinated and the unvaccinated.

First of all, the unvaccinated population figure for 5 to 9 year old children used in the Public Health Service report was the number given in the 1950 census minus the number of children vaccinated. The number of children aged 5 to 9 in 1955 was estimated, however, to be 101,000 more than it was in 1950. The Public Health Service did not take this increase into account. The omission of 101,000 children from the unvaccinated population would have increased the latter roughly from 236,000 to 337,000 children. Hence, the attack rate for unvaccinated children was overestimated by about 40 per cent.

The second bias in the way the Public Health Service had calculated rates involved the period of exposure for the vaccinated children. As the children were vaccinated each month, they were transferred to the vaccinated group piecemeal. Before children can be moved to the vaccinated status, however, one must consider the length of time they remained in the nonvaccinated group before transference. In the adjustment process, the seasonal incidence of the disease also must be considered. To obtain correct estimates of the population who had "one and only one" inoculation of vaccine, this adjustment process must be used, not only to transfer first vaccinees into that group, but also to transfer out those children who obtained second inoculations. Failure to do so by the Public Health Service accounted for the remainder of bias between the two studies. Hence, as far back as 1955 and before the extra filtration step was introduced, the question of whether the Salk vaccine was really as effective as it was in 1954 could not be answered.

#### Reasons for recent increase

If the vaccine was not as effective, one might wonder why the tremendous reduction occurred

in the 1955, 1956, and 1957 reported rates. Here, again, much of this reduction was a statistical artifact.

Prior to 1954 any physician who reported paralytic poliomyelitis was doing his patient a service by way of subsidizing the cost of hospitalization and was being community-minded in reporting a communicable disease. The criterion of diagnosis at that time in most health departments followed the World Health Organization definition: "Spinal paralytic poliomyelitis: Signs and symptoms of nonparalytic poliomyelitis with the addition of partial or complete paralysis of one or more muscle groups, detected on two examinations at least 24 hours apart."<sup>11</sup>

Note that "two examinations at least 24 hours apart" was all that was required. Laboratory confirmation and presence of residual paralysis was *not* required. In 1955 the criteria were changed to conform more closely to the definition used in the 1954 field trials: residual paralysis was determined 10 to 20 days after onset of illness and again 50 to 70 days after onset. The influence of the field trials is still evident in most health departments; unless there is residual involvement at least 60 days after onset, a case of poliomyelitis is not considered paralytic.

This change in definition meant that in 1955 we started reporting a new disease, namely, paralytic poliomyelitis with a longer lasting paralysis. Furthermore, diagnostic procedures have continued to be refined. Coxsackie virus infections and aseptic meningitis have been distinguished from paralytic poliomyelitis. Prior to 1954 large numbers of these cases undoubtedly were mislabeled as paralytic poliomyelitis. Thus, simply by changes in diagnostic criteria, the number of paralytic cases was predetermined to decrease in 1955-1957, whether or not any vaccine was used. At the same time, the number of nonparalytic cases was bound to increase because any case of poliomyelitis-like disease which could not be classified as paralytic poliomyelitis according to the new criteria was classified as nonparalytic poliomyelitis. Many of these cases, although reported as such, were not nonparalytic poliomyelitis. If this inaccurate number of cases of nonparalytic poliomyelitis reported in 1957 is accepted as accurate and considered as a base for subsequent comparisons, it is no wonder that we now say nonparalytic cases went down in 1958.



There is still another reason for the decrease in the reported paralytic poliomyelitis cases in 1955-1957. As a result of the publicity given the Salk vaccine, the public questioned the possibility of a vaccinated child developing paralytic poliomyelitis. Whenever such an event occurred, every effort was made to ascertain whether or not the disease was truly paralytic poliomyelitis. In fact, I am certain that many health officers and physicians here will ask routinely if a child has been vaccinated when signs of poliomyelitis are present during the summer months. We have been conditioned today to screen out false positive cases in a way that was not even imagined prior to 1954.

As a result of these changes in both diagnosis and diagnostic methods, the rates of paralytic poliomyelitis plummeted from the early 1950's to a low in 1957.

Why then has there been a recent increase since 1957?

Why have the improved methods of diagnosis not prevailed during 1959 and 1960?

The improved methods of diagnosis have prevailed. The present increase, I believe, is caused by a long-term, increasing trend in the incidence of the condition or disease we now call paralytic poliomyelitis. Without doubt, the increasing trend has been reduced to some extent by the Salk vaccine. Nevertheless, the Salk vaccine has limited effectiveness in its ability further to reduce this trend. The reduction at the outset appeared to be much more effective than it was, because the early years of the vaccine's use were clouded by reduction in reported incidence by the elimination of the false positives. However, any future substantial reduction in this trend will require a more potent vaccine, not simply vaccinating more people. If there were no other vaccine, complete vaccination of all susceptible persons in the population with Salk vaccine would be justifiable.

Delays in accepting the new live virus vaccines may result in a continuation of the trend observed in 1959. Today it may be a serious mistake to be ultraconservative in accepting the new live virus vaccines under the impression that there is no hurry because an almost equivalent immunizer exists in the Salk vaccine. A delay in accepting and promoting better vaccines will be a costly one. There must be immediate pressure applied to determine whether or not the new

vaccines are more effective, so that we do not cling, for sentimental or personal reasons, to an older vaccine whose true effectiveness is today unknown.

QUESTION: Are antibody levels any indication of the reliability of the effectiveness of the vaccine?

DR. COX: The only way you really can determine vaccine effectiveness is by direct challenge. Obviously, in polio you cannot make a direct challenge on man. We know, however, from experience with other vaccines that the most accurate indirect method we have is measuring the levels of neutralizing antibodies in the blood, and that's what we're checking.

It is well accepted now that this method represents a spillover of antibodies produced in the tissue. We do not know, however, the exact level of neutralizing antibodies necessary to protect against paralytic polio. There is increasing evidence that antibody levels as low as 1:4 are significant. Complement-fixing antibodies, on the other hand, are not a reliable index of effectiveness, nor do they necessarily correlate with neutralizing antibodies.

DR. KLEINMAN: Dr. Ratner has put me in the position of Devil's Advocate, being the only one on the panel who at one time committed himself in writing that the Salk vaccine was quite effective. Back in 1958 we showed, or thought we showed, that two doses of Salk vaccine was 83 per cent effective in preventing paralytic polio. We thought this was done rather carefully using a Life Table method of analysis which recognizes that the population at risk changes week by week and month by month. We did not, however, as Dr. Greenberg suggested, give special weight to those months of the year in which the risk of contracting polio is greatest.

We repeated this study of 1955 and 1956 by projecting the same type of statistical analysis into 1957.<sup>12</sup> Lo and behold, we found that two doses of Salk vaccine was not nearly as effective in 1957 as we thought it was in 1956. Instead of 83 per cent effectiveness, we found only about 24 per cent. Further, in 1957 we found that it took three doses to come close to the effectiveness that we had demonstrated with two doses in 1956.

But let's leave that aside. Let me tell you why, aside from the statistical standpoint, I'm getting nervous about the Salk vaccine. My first reason is the definite increase in paralytic polio. In Minnesota we have found that 20 per cent of our 1959 paralytic experience has occurred in triple and quadruple vaccinates. At present, I am an agnostic as far as the efficacy of the Salk vaccine is concerned because I do not *know* how effective it is. I believe it has some degree of effectiveness, but I do not know the extent because I cannot get proper denominators. A denominator which consists of a point determination of the number of vaccinates as compared to the unvaccinates is absolutely useless because it ignores the changing character of the risks involved. These risks vary from day to day depending upon the seasonal peculiarities of polio infection and the changing character of the Salk vaccinated population.

Laboratory findings are another reason why I am getting nervous. If polio antibodies mean anything in respect to protection, then I am forced to conclude that much of the Salk vaccine we have been using is useless. For two years now we have done antibody titrations on children who have received three or more doses of Salk vaccine. These titrations show that over 50 per cent do not have antibodies to Types I and III and that 20 per cent lack antibodies to Type II poliovirus.<sup>13</sup> This is a very disturbing fact. When a phenomenon like this occurs two years in a row, one has reason to believe that the material we are injecting is not an antigenic preparation.

I should also like to emphasize Dr. Greenberg's remarks on the changing concepts of polio. It is now extremely difficult to get a Minnesota physician to make a preliminary diagnosis and report of nonparalytic polio. We now know that aseptic meningitis has a much broader etiology than poliovirus. In 1956 in much of our so-called nonparalytic polio, the etiology turned out to be Cocksackie B-5 virus, and in 1957 a staggering outbreak turned out to be Echo 9 virus. It is no wonder then that the average doctor does not want to make a diagnosis of polio in the absence of frank lower motor neuron flaccid paralysis. As a result, the only polio that's being reported today are cases with frank paralysis.

I would also like to agree with Dr. Greenberg that the insistence upon a sixty day duration of paralysis for paralytic polio is absolutely silly.

There isn't a doctor in this room who hasn't seen a case of frank paralytic polio which has not recovered within sixty days, or at least recovered sufficiently so that you could not estimate with clinical certainty that there was some residual paralysis.

I would like, then, to have my position understood, at least on this panel, as that of an agnostic so far as the Salk vaccine is concerned. I am not against it. I think it is the only medium we have which has some degree of reliability; but I think there are better methods, and I think we should take advantage of these methods if it seems at all reasonable.

DR. RATNER: Dr. Cox, what has been your experience with antibody findings in triple or quadruple Salk vaccinates?

DR. COX: First let me say that I am convinced that living virus vaccine is going to be the final answer. I base this statement on my experience in the virus field since 1928. I am not against killed virus vaccines. I was the first person to prove that they could be made. This was at the Rockefeller Institute, where I developed a killed vaccine against eastern equine and western equine encephalomyelitis.<sup>14</sup> Later, as a bacteriologist at the USPHS, I produced other killed vaccines.<sup>15</sup>

I want to emphasize, however, that everything done in the field of virology has to be quantitative. This applies to living as well as killed virus vaccines. Unless you have quantitative methods and know what you are putting into a vaccine product, you have nothing. The reason our company refused to make the killed Salk vaccine was because we knew it was impossible to produce enough virus by known tissue culture methods to make a good killed poliovirus vaccine. We knew the quantitative requirements for vaccine as far back as 1934. Dr. Salk has admitted this past year that this principle is true. This basic quantitative principle is precisely applicable to polio. I am anxious to tell you what we know.

There are very few things that you can generalize upon in this field, but one thing you can depend on is that you've got to have at least 100 million particles per dose to make a killed vaccine that's worth anything. The only single exception is Rocky Mountain spotted fever vaccine, which has by far the best antigen that

anybody has ever found, either in rickettsiology or virology. With spotted fever you can make a good killed vaccine with between 10 and 30 million rickettsial particles, but in the case of viruses you must have 100 million virus particles, as a minimum, and preferably a higher concentration.

We have found that in production—all the manufacturers have found this—you never get much above 10 to 30 million poliovirus particles per cc. by tissue culture methods. Accordingly, we told our company that to make a good killed virus product we would have to concentrate the vaccine from five to tenfold for a product that would meet our standards. Otherwise, we would be producing a product that a true scientist could not be proud of, and we didn't want to be in a position where we could not back the product. It costs the manufacturer around 39 cents a cc. to make the present killed vaccine. If you multiply that by five to tenfold and include the additional labor costs, you can see that the product would be costly. We predicted this back in 1950 when we decided not to produce Salk vaccine.

We are now learning, not only in the United States but in Israel, England, and Denmark, that the killed product does a fairly good job of producing antibodies against Type II poliovirus. But Type II represents only about 3 per cent of paralytic cases throughout the world. The killed vaccine does a poor job against Type I, however, which causes 85 per cent of paralytic cases, and against Type III, which causes about 12 per cent. In other words, the killed vaccine is doing its best job against the least important type. It took time to find this out. It was proven in Israel in 1958, when it had its big Type I epidemic.<sup>16</sup> They did not see any difference in protection between the vaccinated and the unvaccinated. Last year in Massachusetts during a Type III outbreak, there were more paralytic cases in the triple vaccinates than in the unvaccinated.<sup>17</sup> Actually, there is a very good but little known immunological explanation for this.

Dr. Kleinman, in referring to the Minnesota studies, did not specify that in the triple Salk vaccinates 57 per cent had antibody titers of less than four to Type I poliovirus, 20 per cent had the same lack of antibody titers to Type II poliovirus, and 77 per cent had titers of less than four to Type III poliovirus, as of January

and February, 1958. We found the same thing in Pearl River personnel.<sup>18</sup> The amazing thing is that when you analyze these 1,100 people scattered in northern New Jersey and southern New York, you find no appreciable difference between the response of the unvaccinated and the vaccinated, following three or four injections, to Type I or III poliovirus.

QUESTION: At what intervals after the last injection did you make these antibody studies?

DR. COX: These vary, but they're all within a period of 18 months. Of course, the claim has been made that a good killed Salk vaccine should give a longer duration of immunity. I don't know of any killed vaccine that gives a longer duration of immunity. I do know that in Rocky Mountain spotted fever, which has a mortality rate of 95 per cent, the vaccine has eliminated mortality, provided booster doses are taken once a year. The same thing is true with epidemic typhus vaccine. Both of these are very good killed vaccines. I know of none better; yet the immunity they provide is of short duration and requires yearly boosters.

DR. RATNER: Dr. Cox, would you relate the effect of the additional filtration step, which was introduced as a necessary safety measure in November, 1955, on the production of a potent Salk vaccine?

DR. COX: The extra filtration step was introduced because the amount of formalin used in preparing the vaccine did not inactivate the poliovirus. We found residual live virus for as long as 42 consecutive days of inactivation. It is common knowledge in the industry that the regulations requiring incubation for 10-day intervals did not eliminate residual live virus. The manufacturers, through difficulties encountered in production, soon learned of this and, to be sure there was no live virus, extended the period of cooking to 30 days or more. Even then they had to throw out batches, because polio is one of the most difficult viruses to inactivate with formalin.

The second filtration step was picked out of thin air with no experimentation to back it up. Because it was thought that residual live virus particles encased in a mass of killed particles were getting through, the filtration step was introduced in the hope that it would remove this aggregate. We've known for years, however, that



any time you introduce an additional filtration step you lose antigen. Actually, the Israelis found they lose from 10 to 30 fold in virus content by a second filtration step.<sup>19</sup> If you have a small amount of antigen to start with, additional filtration will only reduce it still further. Certainly, this vaccine has been most confused because of many vested interests, but on a scientific basis any virologist will agree that I'm telling you the absolute gospel.

QUESTION: Do you know the variation of the potency of the Salk vaccine on the market?

DR. COX: Unfortunately, that varies considerably. The manufacturers are unable to quantify virus particles in the killed vaccine because it is too costly. A good killed vaccine requires a standard, consisting of the number of virus particles of the strain being used. This standard, of course, will vary with the strain used in both killed and live vaccines. From experience we know that it is wise to have a highly virulent strain for good antibody response. That's why the Mahoney strain, which is highly virulent in monkeys, was chosen as the Type I component of the Salk vaccine. As little as five virus particles of Mahoney injected intramuscularly will paralyze monkeys.

This virulent strain, however, was responsible for the vaccine-induced outbreaks in the spring of 1955. In Idaho, where the people were polio virgins, the vaccine caused numerous cases of polio. In New Mexico, Arizona, and elsewhere, where natural immunity was present, there were few or no cases.

DR. RATNER: Some specific data on the variation in potency may be of interest. New York State Health Department investigators reported in September, 1956, that there was a six-hundredfold variation in the potency of commercial Salk vaccine on the market.<sup>20</sup> Other unpublicized USPHS data showed a sixtyfold variation.<sup>21</sup> Today many inoculations of the Salk vaccine are needed to accomplish the same results that were claimed in 1955 with one inoculation. In the history of drug therapy there are few drugs, if any, which become progressively inferior with increasing years.

DR. COX: I would like to repeat that good vaccine, whether living or killed, has to be quantified. Our living poliovirus vaccine, which

I hope to tell you about very soon, is quantified. We keep very careful control of the exact amount of virus in every drop we produce.

In virology you have to deal with both quantity and quality. If both are under control, you're on solid ground. If they are not under control, you don't know where you are.

DR. RATNER: To close the discussion on potency, back in May, 1957, the largest producer of Salk vaccine in the United States had several million dollars worth of vaccine on hand which did not pass the minimum potency requirements of the USPHS. Subsequently, the Division of Biological Standards reinterpreted the minimum requirements to make possible the commercial utilization of this vaccine.<sup>22</sup>

We would now like to spend a little time on the safety factor.

DR. MEIER: The thing that impresses me most about this question of polio vaccine is a problem that has been discussed only by indirection. How is it that today you hear from the members of this panel that the Salk vaccine situation is confused; yet what everybody knows from reading the newspapers, and has known since the vaccine was introduced, is that the situation as far as the Salk vaccine is concerned was and is marvelous? The reason for this discrepancy lies, I think, in a new attitude of many public health and publicity men. It is hard to convince the public that something is good. Consequently, the best way to push forward a new program is to decide on what you think the best decision is and not question it thereafter, and further, not to raise questions before the public or expose the public to open discussion of the issues.

My own contact with this attitude came when I was a member of the Department of Biostatistics at Johns Hopkins, where I had an opportunity to talk with some of the people who were connected with the vaccine. My interest was stimulated by several papers<sup>23</sup> on the safety of the vaccine written by Salk preparatory to the 1954 field trials.

The general theory that Salk was working on was a very simple and old one: that the inactivation of poliovirus by formalin would proceed in a straight-line, first-order reaction. This means that in  $x$  hours of contact with formalin, half the virus particles would be inactivated, that

an equal number of additional hours would inactivate another half of the remaining live virus particles and so on. By extending the period of inactivation, a product would result in which the amount of living virus remaining was necessarily so minute as to have no practical significance. This was Dr. Salk's built-in-safety factor to insure complete safety.

Although this theory applies to many cases, whether it applies to the Salk vaccine remains an empirical question. What troubled me greatly was that it appeared from actual data which Salk presented that the theory did not apply. Assuming there was some error in my understanding or in Salk's, I inquired of the people who knew about this. The answer I consistently received was "I see what you mean. I haven't thought about it very carefully myself, but there are many important and competent people who are taking care of this. Don't worry. After all, this is merely a paper for the public and not the real technical goods." The answer as it emerged later, of course, was no one was taking care of it.

The problem of making a new vaccine, or adopting any public health measure, will always be difficult. We have to be prepared to move ahead in face of the risk of error. In this particular issue, what troubled me was moving ahead when the error was there before us in the paper that undertook to demonstrate safety.

The reason for this unhappy situation lies first in the attitude I referred to earlier: that dissent and discussion in public are unwelcome. Secondly, I think it lies in the diffusion of responsibility that has resulted from the committee system of promoting new measures. In this case a large committee was involved, but no single member took it upon himself to check the problem all the way through. Although Dr. Salk felt he had, no one else double checked him. Even more serious evidence than that which Salk provided in public emerged later: the presence of live virus in vaccine manufactured in strict accordance with the protocols.<sup>24</sup> To be sure, these lots of vaccine were not distributed for the field trials in 1954. Notwithstanding, this experience demonstrated unequivocally that the method itself was not safe. Furthermore, most of you know that the triple safety checking of the vaccine used in the field trials by the manufacturer, Dr. Salk's laboratory, and the Public Health Service was dropped in the licensing procedure. Most of the lots distributed in 1955 were tested only by the manufacturer. It was no surprise, then, that we had a spring outbreak of vaccine-induced cases. The only surprise was that there weren't more.

(To be concluded)

#### REFERENCES

A bibliography is available on request.

## Health man-power only one-tenth physicians

The latest *Health Man-power Chart Book* of the United States Department of Health, Education, and Welfare states, "Nearly two million persons are employed in occupations considered in the health field." Among these are dentists,

public health nurses, health engineers, health educators, medical and psychiatric caseworkers, nutritionists, sanitarians, and laboratory technicians. Of the nearly two million health workers, perhaps less than two hundred thousand are practicing physicians. *Hugh A. Matthews, M.D. The Role of a Physician in a Changing Society. North Carolina M.J. Feb. 1960.*

# The Present Status of Polio Vaccines\*

(concluded)

## MODERATOR:

Herbert Ratner, M.D., *Oak Park.*

## PANELISTS:

Herald R. Cox, Sc.D., *Pearl River, N.Y.;*

Bernard G. Greenberg, Ph.D., *Chapel Hill,*

*N.C.;* Herman Kleinman, M.D., *Minne-*

*apolis;* Paul Meier, Ph.D., *Chicago.*

## PART II

### Vaccine safety (*Continued*)

QUESTION: How many lots were accepted as safe for licensing on manufacturer's protocol alone?

DR. HERALD COX: Not all lots were checked by laboratories other than the manufacturers'. They were random sampled. The director of the Laboratory of Biological Controls was aware of safety testing problems but was unsuccessful in obtaining a clarification from Dr. Salk.

QUESTION: Didn't the director grant the license?

DR. COX: He did not want to grant the license, but his decision was overruled.

DR. HERBERT RATNER: In March, 1954, 10 of the 48 lots of vaccine produced for field trial use were positive for live virus by tissue culture or monkey tests. In only 2 of these 10 was live virus detected by all three laboratories: that of the manufacturer, the National Institutes of Health, and Dr. Salk. In 7 of the positive lots live virus was found by a single laboratory but not by the other two.<sup>25</sup> As Krumbiegel pointed out at this Society's annual meeting in 1956, "The real cause for alarm was the knowledge that there was no correlation of positive test results among the different laboratories . . . and practically none within the same laboratories insofar as results of tissue culture and mon-

key inoculation tests were concerned . . . the results of the tests served to prove the inadequacy and unreliability of the testing procedure."<sup>26</sup> Notwithstanding, on the basis of Dr. Salk's report in April of no adverse effects following the vaccination of 7,507 children with commercially prepared vaccines, the 1954 field trials were allowed to proceed.

In 1955 two rather than three groups participated in safety testing: the manufacturers and the National Institutes of Health. The manufacturers ran both tissue culture and monkey tests on the vaccine they submitted for licensing. At the NIH laboratories only 14 per cent (7/50) of the lots submitted for licensing were subjected to both tests; the majority, 64 per cent (32/50), were subjected to only one test—the tissue culture test. This was done despite the fact that it was known from the 1954 testing experience that monkey tests on some trivalent material were positive even when each of their monovalent components (Types I, II, and III), before pooling, had been found negative by tissue culture tests. Twenty-two per cent (11/50) of the lots submitted for licensing were not tested by NIH at all.<sup>28</sup> These figures indicate that the vaccine used in 1955 was inadequately tested. Therefore, it is not surprising that there were cases of vaccine induced polio in the spring of 1955.<sup>29</sup>

To bring this issue of the safety of the Salk vaccine to a close, the following information is pertinent. In 1953, experienced investigators from the Michael Reese Hospital in Chicago failed to produce a safe vaccine by the Salk formula.<sup>30</sup> Their findings were dismissed by the backers of the Salk vaccine.<sup>31</sup>

In the spring of 1955 one of the manufacturers using safety tests more rigid than those required by the USPHS found live virus in its own vaccine, in another manufacturer's vaccine on the open market, and in one of Dr. Salk's vaccine preparations used as a standard for commercial vaccines.<sup>32</sup> This manufacturer discontinued production of Salk vaccine and did not re-

*This panel discussion was edited from a transcript. Opinions presented are those of the panel members and do not necessarily represent those of the Society.*

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sume until an alternative method (ultraviolet irradiation) was developed in the fall of 1955. Some of the released vaccine of this manufacturer, however, had already been used in Massachusetts, which experienced an epidemic, and some of the same lots were used in New York, and in Minnesota, where, as Dr. Kleinman has said, he found 83 per cent effectiveness.<sup>33</sup> Of course, many of us thought the effectiveness of the 1955 vaccine was due primarily to the fact that it did contain live virus.

One other manufacturer found live virus in another of Dr. Salk's standard vaccines.<sup>34</sup> A member of the USPHS also found live virus in commercial vaccine other than that admitted by the USPHS to have induced cases.<sup>35</sup> The findings were not published. The Massachusetts State Polio Advisory Committee, which included among others, John F. Enders, Thomas H. Weller, and Maxwell Finland, temporarily banned the vaccine despite USPHS licensing because of its knowledge of these findings.<sup>36</sup> Epidemiologic evidence of unsafe vaccine from manufacturers not named by the USPHS has been reported by Anderson,<sup>37</sup> Redeker,<sup>38</sup> and others.<sup>39</sup>

It should also be stressed that safety testing was inadequate when Dr. Salk developed his vaccine and when the vaccine was commercially prepared for the field trials of 1954 and for licensing and use in 1955. The claim of long duration of effectiveness, then, as measured by antibody levels reported by Salk<sup>40</sup>, Brown<sup>41</sup>, and others<sup>42</sup>, really applies to a vaccine which did not exclude the presence of live virus. It does not apply to current vaccine in which potency has been sacrificed for safety. There is internal evidence in the papers of Salk and Brown that some of the antibody response to the vaccine was too pronounced to be explained by a killed virus.<sup>43</sup>

At present, epidemiologic methods employed by the USPHS to assure safety of the vaccine are inadequate: first, because of the failure to thoroughly survey untoward reactions,<sup>44</sup> and, secondly, because of unrefined criteria for the determination of safety; for instance, insistence on correlation of initial paralysis at the site of inoculation,<sup>45</sup> and discontinued reporting of satellite cases.<sup>46</sup>

QUESTION: Has any state health department recommended that Salk vaccine not be used?

DR. RATNER: I know of no state health department that refuses to issue it now, although earlier this was not the case. This is a question of whether a state health department is in a position to oppose mass propaganda and the public opinion that has been formed by it.

DR. HERMAN KLEINMAN: There is only one thing we can do in Minnesota and that we are doing. There is no known way of preventing polio with a licensed product at the present time except through the use of the Salk vaccine. While I am an agnostic about the effectiveness of the Salk vaccine, I still believe it does something in preventing paralysis. So we owe it to the public to recommend its use. On the other hand, if we are going to act not only as public health physicians but as scientists, we must continue our investigations into the truth about the Salk vaccine. On the basis of the facts as I know them, we must look for something better.

DR. PAUL MEIER: It seems to me that the state and local health officers are at levels different from USPHS and in much the same position as my children's pediatrician. He said, "We are very disappointed in the Salk vaccine; we are very unhappy with it; but what can we do? The people who have the evidence, who have the knowledge, who should be able to judge, say use it. I am in no position to second guess them and to make a different decision. I have to recommend it and I have to use it."

This is no position for public health officers to be in, but there isn't any question that is the position. All the facts have never been discussed. The great pressure of publicity has been exerted. It would be a health officer with great self-confidence who would say that on the basis of the little he knows he is prepared to make a judgment different from that of the USPHS and to decide not to give it. On the other hand, I don't consider it convincing evidence of the efficacy of Salk vaccine that all, or almost all, health officers have gone along with it.

DR. BERNARD GREENBERG: I would like to second that comment to make sure that my position is understood. I'm an agnostic like Dr. Kleinman. I am sorry that I do not know what the effectiveness of the Salk vaccine is. Since nothing else is available, there seems to be no alternative but to push the use of it. I don't think we should do so in ignorance, nor too complacently, believing that as long as we have

something partially effective there is no need to have something better. The USPHS is, in effect, saying, "Let's face it: we were burned the last time by getting into this business too quickly; so this time we are going to be more cautious." By being more cautious, we may make a mistake by accepting a better polio vaccine too slowly. And that's what I am trying to emphasize: They must realize they are making this mistake possible. The issue must be pursued.

QUESTION: Dr. Cox, are we doing any harm by using a low antigen titer Salk vaccine?

DR. COX: I have data which I have never published, because at the time I didn't fully understand the significance of it. While working with the USPHS in Montana many years ago on the development of killed vaccines for Rocky Mountain spotted fever and epidemic typhus fever, I observed that vaccinated guinea pigs challenged with Rocky Mountain spotted fever or typhus would sicken and die before the controls. I couldn't find anything about this in the literature, and it bothered me for about a year. I learned that by increasing the antigen five to tenfold into the range of a 100 million to a billion organisms per cc. of vaccine, this adverse effect was corrected and an effective product obtained.

We had the same experience at Lederle with Japanese B vaccine. Lots of vaccine which had less than 100 million virus particles invariably would cause the vaccinated mice to die before the controls when challenged. The same thing happened to us when we tried to produce a vaccine against lymphocytic choreomeningitis. During the war the Division of Biological Standards made the same observation with Japanese B encephalitis vaccines.

I mentioned this observation and correlation in a paper in 1954, namely, that with a low antigen killed vaccine you stand the danger of actually doing more harm than good.<sup>47</sup>

The first field evidence we've had that there may be something to this clinically was the Type III polio epidemic in Massachusetts last year, where 47 per cent of the paralytic cases occurred in those who had three or more injections of the Salk vaccine.<sup>48</sup> The lower incidence of paralytic polio (37%) in the unvaccinated group raises the question as to whether we have produced a greater sensitivity in the

vaccinated individual. If the investigators have correctly estimated the numbers of vaccinated individuals, the clinical finding confirms what we've seen in the laboratory. It is hard to be sure that this is the case. But we have supporting laboratory experience that susceptibility is increased by sensitization with low antigen vaccines. This is an immunologic fact supported by USPHS findings. I advised against the manufacture of the Salk vaccine because I knew from experience that one to four thousand formalin would not kill the poliovirus and that high concentrates of antigen are necessary for an effective killed vaccine. With low concentrates of antigen you may do more harm than good.

#### Live poliovirus vaccine

DR. COX: When measured against its killed counterpart, a live virus vaccine is always a superior vaccine. It invariably costs about half of that of a killed vaccine. The only reason for not making a live typhus vaccine, for instance, is that technical problems of sterility would be difficult to overcome on a production basis.

We chose the oral route for live poliovirus vaccine because polio infects through the oral route. We also knew from our work with other viruses that the best way to immunize is to follow nature where possible. Since nature was immunizing 999 persons out of a 1,000 against polio without any trouble, the idea was to follow nature's example but to cut the risk down as much as possible.

The work we did on Newcastle disease in chickens was a perfect model in every respect for polio. Although the Department of Agriculture had previously stated that they would not license a single live virus product, today it is hard to find a killed virus product in veterinary medicine. They too found out that living virus vaccines are superior. They give a higher degree of longer-lasting immunity. They cost less to make and administer.

Polio is unique because many more people get the infection than the disease. When you think about it, theoretically it should be the easiest of all viruses to modify. Rabies, by comparison, is 100 per cent fatal when introduced into the brain tissue of any warm blooded animal. Yet, we are able to modify the rabies virus so that we can inoculate it directly into the



brain of warm blooded animals with no sign of the disease. When challenged with virulent strains of rabies, these animals will withstand 100,000 lethal doses inoculated directly into the brain. If we can do this with rabies, we certainly should be able to modify polio, which produces clinical signs of the disease in so few people.

A complicating factor in polio was that we were dealing with three different types, each of which had to be modified. Furthermore, we felt that we had to modify these viruses by adaptation to a foreign host. In making yellow fever vaccines, we learned that when you take a virus and adapt it to an unnatural host, it loses its virulence for the original host. This central basic principle was observed by Jenner also, when he found that cowpox had the ability to immunize against smallpox. In yellow fever, therefore, scientists purposely adapted these strains to new hosts, first, by adaptation to the brain tissues of suckling mice, then to mixed tissues of suckling mice in tissue culture, then to chick embryo tissue cultures, and finally to the chick embryo in the egg itself. Even though it has been claimed that you cannot grow polio in chick embryo, we succeeded in growing all three strains in chick embryos. The reason we desired this was that experience has shown the absence in chick embryo of extraneous virus contaminants which cause illness. Chick embryo for all practical purposes is a pretty sterile package.

The only thing that balked us after we got the polio strains in chick embryo was their poor antigenicity. Type I was completely non-antigenic; Type III was so poor that its cost would have been prohibitive; the only one that was half-way antigenic was Type II. In other words, we learned that it is unwise to continue passage in nonmammalian tissue for long periods of time. The big danger in modifying live virus is not stopping at the right point. If you carry it too far, you overmodify and lose what you're after. It's safe but it won't immunize.

We have developed our strains of virus so that they are nonvirulent to monkeys in the range of 100,000 to a millionfold. We know that in some instances as little as two tissue culture particles of some wild strains of polio when placed in the brain, or as little as five tissue particles inoculated intramuscularly, will paralyze monkeys.

It's most unusual, however, for our modified strains in undiluted form with a concentration range from 30 to 40 million virus particles per cc. to paralyze monkeys by direct intracerebral inoculation.

Since the chance of getting paralytic polio from a natural infection of wild virulent viruses is only one in a thousand, modified poliovirus adds an additional safety factor of at least 100,000, reducing the risk to about one in 100 million or ten in a billion. Furthermore, we don't need 30 million virus particles for an infecting dose. We need only somewhere in the range of a 1.5 million to 3 million virus particles. We do not have to concentrate anywhere from five to tenfold, as in the killed vaccine; instead we dilute.

A live poliovirus vaccine needs many more virus particles to establish an immunizing infection than any other live virus vaccine I know. This may be due in part to the destruction of virus by gastric juices. It could be because our strains may be modified more than they need to be. At any rate, all of these factors must be worked out quantitatively, for we have to know just how many virus particles we're feeding if we are to come out with a better product.

The Type I and III components of our vaccine are now standardized to contain at least 1,200,000 to 1,500,000 live virus particles. In our Type II, which has been overmodified, we need 3 million virus particles for a 90 per cent immunizing dose. Now we are in the process of increasing Type II's power to infect. We do this by feeding the virus to man, having him shed the virus as long as possible, recovering the virus in the stool, and obtaining pure strains through tissue culture. Then we test the recovered viruses in monkeys and isolate those with minimal virulence. Such strains then have the ability to infect human cells, which is what is needed, because you cannot immunize unless you can infect.

It must be remembered that you cannot immunize the gastrointestinal tract with killed vaccine, even in large amounts.<sup>49</sup> Although the killed vaccine does induce antibodies in the blood, this does not prevent the person from becoming a carrier and shedding poliovirus.<sup>50</sup> One can recover wild poliovirus strains as well as modified virus strains in Salk-vaccinated persons.

The principle of the live virus vaccine in polio is analagous to protecting your house against the

weather. You don't fill the rooms with concrete. All you do is paint the outside walls because they are the site of exposure. In the case of a natural polio infection, if you are one of the 999 lucky ones out of a thousand who does not get the disease, the virus grows in the cells of the gut, and viruses are shed anywhere from ten days to as long as six months without symptoms. During this process antibodies appear in the blood. As a result of this infection the cells of the gut become resistant for varying periods of time, depending on the number of cells infected. I have an example of this in my three grandsons. The older ones, who had been vaccinated more than once, did not shed Type II on refeeding. The youngest one, however, who was immunized only once, a year earlier, shed virus for several consecutive days and then stopped.

If you proceed gradually, and quantitatively, and imitate the norms of nature as a model for improvement, you are on solid ground. In this connection we have benefited from experience with 10 or 12 live virus vaccines used routinely in the United States in veterinary medicine.

Using live virus vaccine is the only possible way to eliminate wild virulent strains in nature. The gastrointestinal tract must be made so resistant that wild strains cannot get a foothold. This cannot be done with a killed vaccine. We know this from hog cholera. In the 35 states that have prohibited the use of anything but live virus vaccine, the wild strains of hog cholera have disappeared because the swine have become resistant to infection.

In the beginning we moved slowly and cautiously. We started with my immediate family—my daughter was the first pregnant woman ever immunized. Then we included neighbors, then employees at our Pearl River plant and their families. At present we have immunized over 900,000 people in something like 20 different countries on four continents with monovalent feedings and over 1.5 million people with trivalent vaccine. The vaccine now has over a 90 per cent take, and over 90 per cent of those missed, whether it be Type I, II, or III, can be immunized by a second feeding.

We do not claim that this product will result in life-long immunity. One does not even get life-long immunity on a mild exposure to a natural poliovirus infection. This is something we

have to continue to study. In this country it is unusual to find antibody titers as high as one to two thousand; but in South America it is not unusual to find pregnant women with titers in excess of 8 to 10 thousand, because they are constantly being battered by reinfecting doses.

Live polio vaccine will be cheap enough so that you can afford it once a year, however, if it turns out that it's needed that often. This is important because the United States is not the only country in the world that needs polio vaccine, and in other countries low cost is more important. Polio vaccine is needed particularly in the tropics where there is plenty of polio even though it has been said for years that the tropics are not affected by this disease. One of the most severe epidemics of Type I polio in medical history occurred in Costa Rica in 1954.<sup>51</sup> They had over 1,000 cases in a total population of approximately one million.

We began our basic clinical investigations in Minnesota particularly because University of Minnesota and state health department physicians felt as we did that killed vaccine was not the answer. We began in 1957 and are now in our fourth year. We gave them all of the facts of our product. We held back nothing. We let them know the unanswered questions.

We learned from our initial studies<sup>52</sup> on 25 babies that babies shed virus in quantities as high as a million virus particles per gram of stool. Some of these babies shed virus as long as three months. Practically every member of the family picks up this polio infection whether they've been Salk-vaccinated or not. The important thing is that there were no signs of illness, neither in the babies fed, in the family contacts, nor in the community.

In 1958 we did a larger scale double-blind study<sup>53</sup> in the university community of Como Village in Minneapolis with coded vaccine. Only the state statistician knew the code. Neither the doctor, nor the patient, nor those at the State Laboratories who ran the bloods and stools of these 550 people knew who had received the vaccine and who the placebo. When the code was broken, we found that we had about a 90 per cent antibody response in vaccinated individuals and about a 14 per cent increase in antibodies in the placebo group. We discovered that the infection caused by modified viruses is essentially a household disease just as polio is normally.

We went into two epidemics, a Type I in Colombia<sup>54</sup> in 1958, and the tail end of Type II (surprisingly enough it was Type II) in Managua,<sup>55</sup> the capital of Nicaragua, in 1958. The Type I epidemic was caused by an exceptionally virulent strain—two virus particles paralyzed monkeys. Fifteen verified cases had already been reported. We vaccinated over 7,000 children with monovalent Type I followed by Types II and III. Within eight days no more cases were reported, and not a single case has been reported since then. But we cannot make the claim that we broke the epidemic because we have no way of knowing what the future of that outbreak would have been.

In Nicaragua in a highly virulent Type II epidemic 254 paralytic cases had been reported. Of the 251 cases in children under age 10, 217 were under age 2. We went into Managua and vaccinated over 42,000 children under age 10 during a 12 day period with Type II, and then later fed Type I and III. Even though polio had been reported in Managua every month since 1949, with the exception of three months following the 1953 Type I epidemic, they had a 10½ month period without a single case reported. Polio has come back to Nicaragua this year in the outlying districts, but it has spared Managua. This year we moved into the outlying districts and fed 35,000 doses of trivalent vaccine. Within six days there wasn't a single case of polio reported.

Here again we may have been hitting the tail end of an epidemic, but it seemed to break right in the middle. We can't conclusively say one way or the other that we did or did not stop the epidemic, but we do know that a person who is fed this vaccine will begin to show the presence of virus in the stools on the third or fourth day after feeding indicating that the cells in the gut are infected. Type II sheds for a maximum period of two weeks; Type I for about a month; and Type III stays within the norm of six weeks. We find circulating antibodies in the blood on about the ninth or tenth day, and they reach a maximum peak in about 30 days. By the end of one year they start to decline gradually.

We have fed this vaccine under all kinds of conditions. We fed it in Finland, and in West Germany where presently we are immunizing West Berlin. We started the latter on May 12. I checked this morning and they have already fed

271,000 children and estimate that by the middle of June they will have fed about 450,000 under 11 years of age. We've worked in France, Spain, Italy, Israel, slightly in Argentina, on a rather good scale in Montevideo, in Peru, Colombia, Nicaragua, Costa Rica, Haiti, heavily in Cuba, in California, Minnesota, New York, New Jersey, and Florida, and in Canada, Japan, and Taiwan.

In Latin America we have worked with the approval of the local health officer and the Pan-American Sanitary Bureau. This year the entire country of Costa Rica has been singled out to be vaccinated because of the severe epidemic they experienced in 1954. About three weeks ago I heard from the Costa Rican minister of health that they have succeeded in feeding trivalent vaccine to 281,000 children of an estimated 460,000 under the age of 11. There's no point in going above that age, because by the time Costa Rican children are 10 or 11 years old, they have all had experience with the three types of polio. He reports a conversion rate of about 93 per cent to Types I and III, which independently confirms our conversion figures.

Other findings are of interest. In Cuba we carried out a study<sup>56</sup> with Dr. Juan Embil, Jr., who fed trivalent live poliovirus vaccine to children with acute infectious diseases such as, measles, mumps, influenza, and even typhoid fever to determine contraindications to the use of the vaccine. We found none.

Out of 360 pairs of blood (pre- and post-vaccination) that we tested from Cuban children of school age, we found 76 children who lacked antibodies to one type or another. Actually they had 91 antibody gaps in their Type I, II, and III antibody structures. A single feeding of trivalent vaccine filled in 80 of the 91 gaps for a conversion rate of 88 per cent, and converted 65 of the 76 children to a triple positive status for a conversion rate of 86 per cent.

In western Massachusetts where we tested 123 paired bloods,<sup>57</sup> 67 individuals started out with 115 antibody gaps. A single feeding of trivalent vaccine filled in 104 of the 115 gaps for a conversion rate of 90.4 per cent, and 56 out of the 67 persons were converted to a triple positive stage for a conversion rate of 84 per cent.

As you may know, in February this year Dade County including Miami began a county-wide

mass vaccination program with our trivalent vaccine. The data from there are actually the best we've seen.<sup>58</sup> That's partly because we corrected the Type II component, which has been giving us comparatively poorer results, by doubling the quantity of Type II virus in the vaccine. To give us an idea of the results, they sent us 300 coded pairs of blood. We received them in lots of 20, and all we knew was that each lot included 10 matching pairs.

After the code was broken, we found they were all from young adults at the University of Miami. Of these 300 students, 161 were not triple positives and 25 (8%) were actually triple negatives — they had no antibodies at all. This was a surprising fact because in Florida's subtropical climate they should have had plenty of experience with natural polio infections, as well, perhaps, as exposure to Salk vaccine.

In the polio virgins we filled in 25 of the 25 gaps for Type I, the type responsible for 85 per cent of paralytic polio cases. We filled in 19 of the 25 gaps for Type II, which accounts for 3 per cent of paralytic polio, for a conversion rate of 76 per cent. And we filled in 23 of the 25 gaps for Type III, which accounts for about 12 per cent of paralytic polio, for a conversion rate of 92 per cent. These gaps in the antibody structure of 25 triple negative, polio virgins were filled in by a single feeding of trivalent vaccine.

In the group of 161 students not triple positives, the conversion rates were as follows: In Type I 97 of 99 gaps filled, 98 per cent; in Type II 70 of 79 gaps filled, 89 per cent; and in Type III 80 of 85 gaps, 94 per cent. We filled in a total of 247 out of 263 antibody gaps for an over-all conversion rate of 94 per cent on a single 2 cc. oral dose of trivalent modified live poliovirus vaccine.

I've talked long enough. The only other thing I can say is that the live poliovirus vaccine is coming. It takes time. The one thing I am sure of in this life is that the truth always wins out.

DR. RATNER: Dr. Cox's vaccination figures deserve comparison with the 1954 field trials of the Salk vaccine. The Cox live poliovirus vaccine has now been used by many investigators in over 2.5 million people with millions more in the process of being vaccinated. The other two live virus vaccines under study have been used in

additional millions. The question of safety has been paramount in the minds of these investigators. On the other hand, the Salk vaccine was used in only 400,000 persons in a single field trial in a study<sup>59</sup> which assumed safety and was primarily designed to determine effectiveness. These figures reinforce Dr. Greenberg's thesis that the USPHS was premature in licensing the Salk vaccine and is now excessively overcautious in licensing the live virus vaccine.

Dr. Kleinman, will you bring this discussion to a close? Dr. Kleinman has recently spent several months in Latin America studying firsthand the results of field trials there.

DR. KLEINMAN: I want to make a few points by taking you out of the laboratory and away from the statistician's computer without raking up the ghosts of long dead monkeys and waving their shrouds in your faces. In the final analysis the important issue is What does this vaccine do to people and among people? Our Minnesota studies demonstrate a number of things. I would like to bring these to your attention because I feel work such as this must go on on the American scene within groups of people who have the same way of life to which you and I are accustomed.

First of all, the Minnesota studies are American in the sense that we're using the vaccine in people who are living in a way we are accustomed to describe and to understand. Secondly, the Minnesota studies were the first to put these modified poliovirus strains into a community whose nature approximated our normal way of living. Prior to this, these strains were used in isolated individuals and in institutional environments. Thirdly, the Minnesota studies prove what has previously been denied: that it is possible to do a controlled study with the oral live poliovirus vaccine. Finally, the Minnesota studies demonstrate that it is possible to secure definitive results in a population which has had considerable experience with the Salk vaccine.

The importance of the Minnesota studies does not lie in their number, but rather in their design. I want to emphasize the word study. Even though we have involved 100,000 people in 1960, we still firmly believe we are *studying* the oral polio vaccine strains. Although the numbers are large, we are not carrying out a mass immunization program.



Important characteristics of our design are (1) Our studies are placebo controlled. This includes the 100,000 people we are studying in 1960. (2) Our subjects receive complete public health nursing and medical surveillance. We do not feed and forget. We feed and follow through. (3) Our studies are double-blind. Only one person, the statistician, knows who is getting the vaccine and who is getting the placebo. On the basis of our experience<sup>60</sup> I can assure you that in your own community you can make a scientific and controlled study.

Now, briefly, what have we found in Minnesota?

We have found that these strains are good antigens. They will produce a conversion from titers of less than four to an appreciably higher titer in 90 per cent of cases. Type II is the poorest. Type I and III are both excellent.

We have found, within the limits of our numbers, that these vaccines are perfectly safe to use. Because our studies have been controlled, we can unequivocally state that there have been no reactions. Before I left Minnesota for Russia, more than 50,000 persons had been fed the vaccine in Minneapolis and St. Paul, and we had checked out all reports of illnesses that occurred shortly after feeding. I did this personally. In Minneapolis, where more than 30,000 were fed, I had to make only 15 housecalls. What I saw was run of the mill. There was no central nervous system disease, just prodromes of measles, follicular tonsillitis, atopic dermatitis, and other conditions you normally find in a community.

We have found there is no great community spread of these viruses. Concern for spread has been a bugbear to many individuals. While these viruses will spread fairly rapidly and thoroughly within any one family, they will spread from household to household within the neighborhood only to the extent of 5 to 14 per cent, depending upon the type. So you don't have to worry about creating an epidemic secondarily through the spread of viruses you originally fed.

We have found, by taking time out to study their natural behavior, that these modified viruses do everything that wild viruses do except produce the disease. In a certain percentage of vaccinees the virus can be recovered from the stool, of course. The fed strains can also be recovered from the pharynx, even though the person has circulating polio antibodies in the

blood to begin with. And the virus can be recovered in the blood, which indicates a viremia following the feeding of these vaccines. Those persons with virus in the pharynx and in the blood have no subjective symptoms, however, and the examiner can see nothing objectively.

How long does the immunity last? We don't know. In those that we have studied we know that after a year, even though there is a general drop in titer from the originally induced titer, the antibodies persisted in 50 to 80 per cent of the adults, and in 63 to 75 per cent of the children tested.<sup>61</sup> This is in individuals in whom we are certain that it was we who produced the original antibody change. We are not including those who started with either natural antibodies or Salk-produced antibodies. Other data show that the presence of the latter have no additional effect.<sup>62</sup>

My experience in Latin America is this: Nobody can say that an epidemic was stopped. There were no controlled studies there. But over a million people have been completely vaccinated without any incident at all and, in the countries of Latin America where temperaments are mercurial, emotions excitable, and health departments political, I'm sure that if an incident had occurred it would have come to our notice and to everybody else's notice. The conversion rates in Colombia and other places are remarkably close to the conversion rates we achieved in Minnesota. I've gone over the Costa Rica data carefully. I am satisfied that they have done a good job of surveillance, because the central nervous system disease that they have categorized at the end of a year's observation is remarkably the same in content to what we have found in Minnesota.

There are a lot of important things we don't know about this vaccine. Although we know that it's a good antibody producer, we can't actually say it will protect against polio until we can measure it against a direct challenge by the disease. This has not yet been done. Reasoning by analogy, however, we can assume, because of the antibody responses, that it should protect against the direct challenge by polio itself.

I am not sure that we yet know the optimum dosage schedule. It may be that one feeding is not sufficient, just as one wild polio infection may not completely immunize a child. I don't



think we are quite sure how long the immunity is going to last. As Dr. Cox stated, it is not going to be life-long, but what it's going to be in terms of years I don't think anybody can tell. These are things for the future to disclose.

In the meantime, let me assure you from my direct experience in Minnesota and from my vicarious but close contact in Dade County, Fla., and from my experience in South and Central America, that these strains are safe. From the laboratory standpoint they are potent antigens. The Cox live poliovirus vaccine is worthy of the consideration of people who are working in preventive medicine and public health. I do hope that more people will pay more and more attention to their use in this country, because it is the data gathered in this country that will ultimately count in granting the license and in gaining universal use of this particular preparation.

DR. RATNER: We have attempted in this panel discussion to present you with a sober, candid exposition of the facts as we know them and as

they relate to current questions surrounding decisions to be made in the use of Salk, and oral live virus vaccines. I hope you recognize that the panelists have shown unusual freedom from extra-scientific considerations and pressures.

During the 1960 polio season, epidemics may occur. To dramatize the urgency of the decision involved, remember the futility of using the Salk vaccine to combat epidemics despite its proven ineffectiveness<sup>63</sup> in epidemics simply because it is the only vaccine available to us. An objective and fearless evaluation of the Salk vaccine is needed, for this is the necessary ingredient of an intelligent decision as to when the live virus vaccine should be licensed. Obviously, if the Salk vaccine is simultaneously safe and highly effective,<sup>64</sup> the USPHS can take its time about licensing the live virus vaccine. If, on the other hand, polio and polio epidemics remain with us, and children become paralyzed despite three, four, five, and six inoculations of Salk vaccine, and vaccinees die, we cannot take our time.

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## Community hospitals and medical education

Except for this possibility of house staff shortage, the educational picture is bright. Throughout the country programs are being developed that are really valuable, and in many hospitals the enthusiasm for this work is very encouraging. The American Association of Directors of Medical Education, an organization of rapid growth and great vitality, is doing its part. In New England, for example, more than half of the 62 community hospitals which support interns and/or residencies have appointed either full- or part-time directors of medical education, and sound programs of training are being carried out in almost all of them. *Editorial. Alex. Burgess, Sr., M.D. Medical Education in Community Hospitals. Ann. Int. Med. June 1960.*

## Therapy for Raynaud's disease

Vasospastic conditions of the upper extremity generally termed Raynaud's Disease present a challenge to the medical profession. This disease involves the digital arteries and arterioles. These patients have an increased sensitivity to cold as compared to normal persons. The sympatholytic drugs are of value in many of these patients and have a real range of usefulness. If there is failure of response to conservative measures, sympathectomy is indicated, recognizing that even with adequate denervation, the condition may recur. The severity of the disease and the amount of disability should form the basis for the therapeutic range. In the mild and nonprogressive types, sympathectomy is not indicated. *George H. Yeager, M.D. Factors Influencing Therapy in Peripheral Vascular Disease. Virginia M. Month. March 1960.*

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"There is no doubt that a severe type I poliovirus epidemic occurred among vaccinated children in Israel in 1958... Although Israel practiced wide-scale vaccination against poliomyelitis in 1957 and 1958--- with apparent success in 1957--- a severe epidemic in 1958 overrode the immunity attained... From the available evidence, it appears that if vaccinated children from the United States or elsewhere were subjected to the same virus exposure that the children of Israel had in 1958, severe epidemic poliomyelitis would break out among them."
- Note: The National Foundation for Infantile Paralysis has prided itself on keeping the public and physicians informed about the Salk vaccine. During 1955 and 1956, for instance, the Foundation distributed to all physicians in the U.S. four booklets entitled New Information for Physicians on the Salk Poliomyelitis Vaccine. The purpose, as is expressed in these booklets, is as follows (Introduction, No. 2, Jan. 1956): "Since every physician must decide for himself how extensively he wishes to participate in... endeavors to provide protection against paralytic poliomyelitis, a background of scientific information on the Salk vaccine is essential." That they have kept Dr. Melnick's report "restricted" and "confidential" confirms the belief of critical observers that their true purpose is to present a favorable picture of the Salk vaccine through a one-sided, biased selection of materials. An additional example of such selection is documented in an editorial in Northwest Medicine, 56:680, June 1957.
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Note: The Salk vaccine was licensed by the USPHS on April 12, 1955, as a product which was safe. Shortly, thereafter, it was evident that the vaccine was not safe. This was not simply a matter of the lack of safety of a few lots of one manufacturer but of many lots of most, if not all, manufacturers. The attempt to attribute this to one manufacturer failed when a jury listening to expert testimony under oath concluded that there was no failure or negligence on the part of this manufacturer. (Cutter Trials, 1 Civil Nos. 18413, 18414. In the District Court of Appeal, State of California, First Appellate District, Division 2.).

The evidence is equally clearcut that the Salk vaccine which the USPHS also licensed to be effective, i. e. potent, is not potent. This is borne out by the following admissions and observations.

"A year ago emphasis was principally on the technical details concerned with the production of a safe vaccine. This year emphasis is on technical details concerned with effectiveness---or potency." (Nov. 13, 1956) (J. E. Salk: Poliomyelitis Vaccination in the Fall of 1956, Am. J. Pub. Health, 47: 1, 1957).

"It is now clear that considerable variation in the potency of different batches of vaccine still exists. The improvement of the means for controlling potency of the vaccine may seem to be a technical detail, but on this detail rests the most important remaining problem of the vaccine." (July 8, 1957) (D. Bodian of the Public Health Service's Technical Advisory Committee on Poliomyelitis Vaccine: Control of the Manufacturer of Poliomyelitis Vaccine, 4th IPC 1957, p. 84).

"Two injections of ordinary commercial vaccine leave a high proportion of 'triple negative' children without detectable Type 1 and 3 antibodies." (July 8, 1957) (R. Murray, Director of the Bureau of Standards, USPHS: Discussion, 4th IPC 1957, p. 104).

"The data... give cause for some concern as to the antigenic content of vaccines now being released in the United States. It should be noted that the vaccine which is really under test is the single, unselected lot used for primary vaccination. The important findings is that this lot not only failed... but it also failed in most cases to condition the nonresponders to the later booster dose of selected and presumably potent vaccines." ("the booster was from a commercially prepared lot of vaccine selected with the advice of the Division of Biologic Standards as being of maximal potency.") (J. P. Fox: Epidemiology of Poliomyelitis in Populations Before and After Vaccination with Inactivated Viruses, 4th IPC 1957, p. 147).

"The situation that presently exists with respect to vaccine potency, and that is revealed by these observations and analyses, has for some time been known and appreciated by those who have been close to the problem. The present state may be regarded as a normal condition..." "Those who have the responsibility for manufacture and control of vaccine are fully aware of the need and are making every effort to assure the availability of material that may be expected... to induce effects of an order of magnitude that might well bring about a condition for type 1 and 3 poliomyelitis that vaccination may already have induced for type 2 poliomyelitis." "It is not difficult to see that vaccines with potency levels that are so low as to cause a response in only a small proportion of the population after administration of the first dose may also have a potency too low to be more than partially effective even after the second dose and, perhaps, after a third and fourth and even beyond. The point is too obvious to dwell on further..." (J.S. Salk: Poliomyelitis Vaccine Preparation and Administration, J.A.M.A. 169: 1829, April 18, 1959).

The latter paper was presented at a symposium at the Univ. of Mich. School of Public Health, Ann Arbor, Jan. 6, 1959. Time Magazine (Jan. 19, 1959), reporting on this symposium concluded that "much of the material used in about 200 million U.S. inoculations has been no good."

There are several peculiarities which attach themselves to these series of admissions and observations which carry us through four years of the Salk vaccine program and are still unresolved at the practical level. First, the Salk vaccine is still an unstandardized product. Secondly, the vaccine has been made safer primarily through the removal of polio viral antigen---a dubious achievement. Lastly, the claims of high effectiveness of the Salk vaccine by the Poliomyelitis Surveillance Unit continues unabated despite the absence of antigen. Naturally, the claims add additional incredulity to the epidemiologic conclusions of the P.S.U.

22. R. Murray, Director, Division of Biologics Standards, to Manufacturers of Poliomyelitis Vaccine, May 17, 1957. The interpretation follows in full: "Interpretation of Results when Multiple Potency Tests are Performed . - A number of situations have recently occurred in which it has been necessary for manufacturers to repeat potency tests on individual lots of poliomyelitis vaccine because of failure of an initial test to show potency ratios for one or more types which meet the minimal acceptable levels set forth in Section 73.103 (e) of the Regulations. Recognizing that the health of the animals used in these tests may be a factor in this problem, the Division of Biologics Standards will use the following conventions in interpreting the results of multiple potency tests.
1. Repeat antibody titrations within a single monkey test will be averaged.
  2. A series of tests will be acceptable if the average potency for each type is at a passing level.



3. A test may be ignored if a repeat monkey test is satisfactory for all three types and shows a rise of not less than four-fold for each type.
  4. If two successive individually satisfactory monkey tests are available, earlier tests may be ignored."
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b. Cutter Trials: 1 Civil Nos. 18413, 18414, In the District Court of Appeal, State of California, First Appellate District, Division 2, Reply Brief for Cutter Laboratories Dec. 21, 1959, Parker Printing Company, 180 First Street, San Francisco 5. "All the vaccines that

were released (prior to the events of April 1955) were tested, and by tests then available were safe. We know in retrospect they still contained active virus" (Reporters Transcript. 2890:13-17) (Testimony by Wendell M. Stanley, M.D. p. 35).

- c. H. Ratner: The Devil's Advocate and the 1955 Salk Poliomyelitis Vaccine Program, A Contribution Toward an Objective Evaluation, Bull. of the Am. Assoc. of Pub. Health Physicians, 2:5, Nov. 1955. "The impression has been given that the only pre-May 27th 1955 Salk Vaccine which contained live virus was that in several lots of one manufacturer's product. It is common knowledge, however, amongst many working intimately in poliomyelitis that by additional testing live virus was detected in other manufacturer's products used in children."  
"This vaccine contained unknown amounts of live virulent virus varying with manufacturers and lot numbers."  
"The Salk Vaccine Post Inoculation Poliomyelitis Phenomenon confirms the proposition that the pre-May 27th 1955 Salk Vaccine used on the majority of children in the N.F.I.P. program contained poliomyelitis producing virus."
- d. Ibid. Bibliography and Notes. 2:5, Dec. 1955. "The increase due to the SVPIPP would be approximately 72% or roughly 770 cases." (Note 36).
- e. H. Ratner: Letter - Poliomyelitis Vaccine, J.A.M.A. 160:231, Jan. 21, 1956. "Such vaccines (1955 Salk vaccines) were admittedly the product of a process in which there were 'fundamental weaknesses in the safety testing procedures' (Scheele, Aug. 25, 1955), which did not have the benefit of the more sensitive coriisone-treated monkey tests...and which did not have the advantage of crucial filtration procedures that followed the recognition of 'the absolute need for removal of particles within which virus may be protected from inactivation by formaldehyde.' (Scheele, Nov. 17, 1955). There is substantial evidence indicating that manufacturers' vaccine, other than Cutter's, had varying amounts of live virus in it and that what is being measured for effectiveness is not Salk's killed virus vaccine but a live virus vaccine labeled Salk...."
- f. H. Ratner: Letter, Stalking the Salk, GP, Vol. 15, May 1957. "The program was initiated with the alleged demonstration that the vaccine was absolutely safe, that it contained built-in safety, and that it was 'one of the simplest biological preparations to make.' (Salk). Shortly after the launching of the mass inoculation program in 1955, however, it was evident that these claims were not true. The vaccine was not safe. All spring 1955 Salk vaccine had variable amounts of live virus in it. It did not contain a 'built-in' safety factor (Scheele, Shannon, Gard, Stokes, Guenther, Timm) and it was found to be 'one of the most complex biological preparations ever to be made.' (Scheele and Folsome.)"

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30. A. Milzer, H.J. Shaughnessy et al: Immunogenicity Studies in Human Subjects of Trivalent Tissue Culture Poliomyelitis Vaccine Inactivated by Ultraviolet Irradiation, presented at the 81st Annual Meeting, Am. Pub. Health Assoc., New York, N.Y., Nov. 10, 1953. "We followed very rigidly the conditions of formalin inactivation as outlined by Salk... For reasons not apparent to us we were not successful in consistently completely inactivating the virus with formalin, residual infectivity being manifest both in tissue culture tests and monkey inoculations... Before undertaking a field study to evaluate a poliomyelitis vaccine, we feel that it would be advisable to proceed cautiously in order to be certain that there are no ill effects and that no risks are taken, for we must avoid the tragic consequences that have accompanied poliomyelitis vaccine research in the past."
31. The New York Times, Nov. 11, 1953, p.28, col. 3. Dr. Van Riper, Medical Director of NFIP said, "The method used by Dr. Salk for making a safe polio vaccine requires that the virus be killed. This is established by most exacting laboratory tests both in animals and tissue cultures. Failure of some scientists to reproduce Dr. Salk's results for making a safe polio vaccine is due to the fact that they have not followed his exact methods." Dr. Salk said, "...we can state flatly that the vaccine as prepared by us is devoid of any infective virus and that no human being has been, or ever will, in any field trials, be inoculated with any material that has the remotest suspicion attached to it."
- Note: Dr. Salk here and through the whole subsequent course of the Salk vaccine dispute keeps insisting on the infallible ability of his laboratory to assure a vaccine devoid of any infective virus. This infallibility is belied by the 1954 testing of field trial Salk vaccine for the presence of live virus. Dr. Salk's laboratory was one of three laboratories testing for live virus in the vaccine. In five instances (Lilly lot 301, Parke Davis Lots 501 and 504, and Wyeth lots 207 and 208), Dr. Salk's laboratory failed to find live virus either by monkey test or tissue culture test though live virus was found with these tests by the manufacturer and/or the NIH (White Paper Appendix C). This confirms other evidence that Dr. Salk did not in fact know whether vaccine prepared by him---so called 'properly prepared vaccine'---contained live virus or not. Because of this his many publications, including the paper to be presented in Copenhagen in 1960, claiming persistence of antibodies stimulated by his 'killed' vaccine, are invalid.
32. The report of the finding of live virus in Dr. Salk's Reference Vaccine A was made at a meeting of pharmaceutical representatives. Note: Naturally, it is not possible to find published references to these findings. Scientists of commercial firms and in government are not always free to make public the results of their work. Other scientists, particularly grantees, do not always feel free in some circumstances to make public some of their findings. "The charge of secrecy and restriction of pertinent data to a small handful of

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selected physicians is not a new one. It has been made twice by Dr. Wendell M. Stanley, Nobel Prize winner: First, before the Congressional Hearings of the Priest Committee in June, 1955, and later at a meeting of Nobel Prize winners in Lindau, Germany. Dr. E. M. Krumbiegel, health commissioner of Milwaukee; Professor Dr. Redeker, chief of the Federated Health Services of West Germany; and Dr. Sven Gard, vice-chairman of the Poliomyelitis Committee of the World Health Organization have also made this charge." (H. Ratner Letter. GP Vol. XV, No. 5, May 1957).

- a. supra 29
- b. A Report on the Salk Vaccine by two Nobel Prizewinners and Eighteen Other Polio Experts. The Text of the Jan. 9, 1956 Meeting of the Massachusetts State Advisory Committee on Polio Vaccine. Saturday Review, March 24, 1956. "Criticism has questioned the right of the committee to rest its explanation of delay on 'knowledge from authoritative sources' that live virus has been found in the vaccine prior to November 1955. Scientists both in government and private manufacturing firms are often forbidden to divulge the results of their work...these scientists meeting in privacy discuss their difficulties hoping for mutual help in their problems. There are members of the committee who have received such confidential information."
- c. S. Gard: Prophylactic Vaccination Against Poliomyelitis. Svenska Lakartidningen 53: 121. 1956. "Simultaneously with the inoculation (in Massachusetts) a violent epidemic erupted which up to now has numbered 4,000 cases. According to non-official statements live virus has been demonstrated in several batches of vaccines used."
- d. H. Ratner: Letter - Poliomyelitis Vaccine, J.A.M.A. 160: 231, Jan. 21, 1956. "They urged mass inoculation despite the fact that one of the two major producers of the vaccine since the field trials of 1954 had begun to find live virus in the vaccine back in May, by using testing procedures more stringent than those required by the government."
- e. Cutter Trials: 1 Civil Nos. 18413, 18414. In the District Court of Appeal. State of California. First Appellate District. Division 2. Opening Brief of Defendant and Appellant. Nov. 3, 1958. Pernau-Walsh Printing Co., San Francisco. "The parties to the instant case were unable to obtain information as to tests conducted on the vaccines of other manufacturers, as Dr. Murray, a successor to Dr. Workman as present head of the Division of Biological Standards, declined to produce this information..." (From Opening Brief of Defendant and Appellant Cutter Laboratories by Keith, Creede, & Sedgwick et al. of above trial, page 60. Pernau-Walsh Printing Co., San Francisco, November 3, 1958).

Note: The fact that such knowledge was refused by Dr. Murray on the witness stand in answer to Cutter's lawyers indicates that knowledge of live virus in other vaccines was known, otherwise the answer would have been "there was none."

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33. A.S. Pope et al: Evaluation of Poliomyelitis Vaccination in Massachusetts, Preliminary Report, New Eng. J. Med., 254:110, Jan. 19, 1956. (This study was made under a grant from the N.F.I.P. A final report has never been published to my knowledge).
34. Note: Live virus was found in Salk Reference Vaccine J. Unfortunately, my knowledge of this is confidential and, at present, the finding cannot be referenced in further detail. Independent corroboration of the presence of live poliovirus in Vaccine J arose at a meeting of virologists at the National Institute of Health, Washington, D.C. At this meeting virologists using Vaccine J were attempting to correlate chick and potency tests on killed poliovirus vaccines with human potency tests. When it was proposed that the correlation could be established by using Vaccine J in human subjects a staff member of N.I.H. stated that this could not be done because Vaccine J was unsafe.
35. Note: This finding, as well as other similar findings, was repressed by the USPHS. A similar suppression of data occurred when live virus was found in the Salk vaccine manufactured for the field trial of 1954. Even consultants who had to advise on the continuance of the Salk vaccine program following the vaccine induced poliomyelitis outbreaks of early 1955 were kept in ignorance of these manufacturing difficulties. It was only under severe public and scientific pressure that the USPHS made these manufacturing difficulties known to the medical profession who had the responsibility for administering the inoculations. (White Paper). The practice of withholding data unfavorable to the Salk vaccine continues in both the Division of Biologics Standard and the Poliomyelitis Surveillance Unit.
36. Supra 32, b.
37. G. Anderson: Modern Medicine, May 15, 1956.
38. H. Redeker: Experience with the Salk Vaccine in the U.S. and Critical Evaluation of the Results. Report of the Federated Health Board of West Germany, pp. 1-86, 22 charts, Coblenz, Germany, Feb. 1956.
39. a. Supra 29, c, d, and e.  
b. L.J. Taubehaus: Salk Vaccine and Poliomyelitis. Mimeographed Report, Brookline, Mass. Health Department, 1955. "In a study of the relationship between Salk vaccine injections and the occurrence of poliomyelitis in Brookline in 1955, 80% of cases occurring within nine weeks of the vaccination program gave a history of a close contact with the vaccine, while only 8% of the cases occurring after 9 weeks give such a history.  
Note: A personal communication from Dr. Taubehaus (Nov. 21, 1955) states, "I have made a study of our Brookline cases and have been able to confirm the Salk vaccine post-inoculation poliomyelitis phenomena." The Pope Report (supra 33) which discussed the "possibility that live virus in the vaccine used in May and June initiated the epidemic" makes no mention of this study.  
c. Supra 29 a. "A careful study of the epidemiologic course of polio in the United States for 1955 yields indications of grave significance.



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In numerous states of the U.S.A., typical early epidemics developed in connection with the immunizations in the spring of 1955... These early epidemics had such a bearing on the over-all polio incidence curve for the U.S.A. in 1955 that this over-all polio incidence curve reveals an early peak. ... This abnormal course of the curve indicates a special cause for the occurrence of these early epidemics."

40. a. J.E. Salk: Studies in Human Subjects on Active Immunization Against Poliomyelitis, *J.A.M.A.* 151: 1081, March 28, 1953.  
 b. Ibid. Present Status of the Problem of Vaccination Against Poliomyelitis, *Am.J.Pub. Health* 45:285, March 1955.  
 c. Ibid. Antigenic Potency of Poliomyelitis Vaccine, *J.A.M.A.* 162: 1451, Dec. 15, 1956.
41. C. Brown & S. Smith: Serologic Response of Infants and Preschool Children to Poliomyelitis Vaccine, *J.A.M.A.*, 161: 399, June 2, 1956.
42. a. R. Bateson et al: Response of the young infant to poliomyelitis vaccine given separately and combined with other antigens. *Pediatrics*, 21: 1, 1958.

Note: Satisfactory antibody response to unselected commercially available vaccine was obtained. The estimated date of the manufacture of the vaccines, however, indicates that they did not conform to the requirements for safety of Nov. 11, 1955 (supra 7). It does not follow, then, that these findings apply to subsequent unselected commercial vaccines. It should be emphasized that as Salk vaccine has become safer it has become less potent. Antibody studies made on these infants 12 months later showed "a definite and striking decline in antibody level." (*Pediatrics*, March 1959).

- b. L.L. Coriell: Vaccination Against Poliomyelitis, *A.M.A.J.Dis. Chil.*, 95: 349, 1958.

Note: Here, as in Bateson's work, the vaccine used to establish effectiveness in preschool children was a "pre-Nov. 11, 1955" vaccine. (supra 7).

43. a. Supra 40 a.

Note: At the time of these studies safety tests were grossly undeveloped. Furthermore, no stool studies were made to rule out a vaccine induced subclinical infection. The fact that Dr. Salk's 161 subjects developed no signs of illness attributable to the inoculations is inconsequential because of the low incidence of clinical disease outbreaks of vaccine induced poliomyelitis. It would also be important to know whether there were any illnesses, since Idaho follow-up studies on the 1955 Salk vaccine-induced epidemic showed that 32.7% of vaccinees not reported to have illness attributable to the inoculations did in fact have an illness compatible with abortive poliomyelitis within three to 25 days after vaccination. (*Am.J.Dis. Chil.*, 96: 58, July 1958).

In these studies two 0.1 cc primary doses were highly effective in producing high titers of antibodies corresponding to "that found in recently paralyzed patients." This is in contrast to present ex-

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perience where two 1.0 c.c. doses of Salk vaccine which have passed modern safety tests produce detectable antibodies in only about half the recipients. Dr. Salk refers to the high antigenicity as "rather unexpected findings."

b. Supra 40 b.

Note: In this study Dr. Salk expresses awareness that "quantities of virus that were generally considered to be too small to be effective" were shown to be "surprisingly active...in inducing antibody formation."

c. Supra 40 c.

Note: This article deals with further work on antigenicity of Reference Vaccines A and J from which live poliovirus has been obtained. (Supra 32, Note; 34, Note). Antibody response to Reference Vaccine A was found to be equivalent to that found in lots 028061, 029028 & 028349 used in Mass. in 1955. At the time of this vaccines' use the manufacturer discontinued the production of Salk vaccine because of the detection of live virus in its vaccine through safety tests more sensitive than that required by the USPHS.

d. Supra 41.

Note: The vaccines used in these studies were Cutter E 5721, Wyeth 23401 and Lilly 309. These vaccines were manufactured prior to the spring outbreaks of vaccine-induced poliomyelitis cases in 1955. The Lilly vaccine which had previously been used in the field trials of 1954 proved to be non-antigenic because of the viricidal effects of merthiolate. The Cutter and Wyeth vaccines were vaccines of the same manufacturing process that subsequently were epidemiologically associated with polio cases in vaccinees by the USPHS. (White Paper).

In Brown's studies some of the high titers of antibody achieved were of the same magnitude as the high titers found in Idaho children who were infected by the Salk vaccine but not diseased. He also obtained contradictory findings. In one series two shots of the same lot of vaccine produced a significantly greater antibody response than three shots. In another group of children who had no preexisting antibodies he found that "the booster effect of the secondary vaccination (with Cutter vaccine) upon the development of antibodies (was) marked" but that "no appreciable increase in titer was observed in those having antibodies prior to vaccination." He admits, "the explanation for this is not clear."

ADDENDUM: IT IS NOW KNOWN FROM THE CUTTER TRIALS THAT CUTTER VACCINE LOT E 5721 CONTAINED LIVE VIRUS. SEE PLAINTIFF'S EXHIBITS IN EVIDENCE 9 THROUGH 15, AND PAGE 378, LINE 19, OF REPORTER'S TRANSCRIPT IN GOTTSANKER VS. CUTTER LABORATORIES, CIVIL NUMBER 18413, IN THE DISTRICT COURT OF APPEAL, STATE OF CALIFORNIA. THIS SECTION SHOWS THAT CUTTER LABORATORIES AFTER RECALLING AND RETESTING ITS VACCINE RECOVERED LIVE VIRUS FROM BULK MANUFACTURER'S LOT NUMBER MO 19460. THE EXHIBITS IN EVIDENCE SHOW THAT CUTTER FILLING LOT E 5721 WAS A

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FILLING LOT OF MO 19460. THIS FINDING INVALIDATES DR. BROWN'S CONCLUSION THAT "INFANTS AND PRESCHOOL CHILDREN RESPOND WELL TO (KILLED) POLIOMYELITIS VACCINATION AND THAT THE VACCINE SHOULD BE EFFECTIVE IN THESE AGE GROUPS."

DR. BROWN IN A FOOTNOTE STATES THAT CUTTER VACCINE LOT E 5721 WAS "GRACIOUSLY SUPPLIED BY DR. JONES E. SALK AND REPRESENTED (A LOT) USED BY HIM IN CHILDREN IN PENNSYLVANIA." DR. SALK UTILIZED THE FINDINGS BASED ON THE USE OF THIS LOT TO CONCLUDE 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" (i. e. "AS A RESULT OF AN INFECTION WITH PARALYTIC CONSEQUENCES.") NATURALLY, THE INOCULATION OF A VACCINE CONTAINING LIVE VIRUS CAN BE EXPECTED TO MATCH OR TO EXCEED THE ANTIBODY RESPONSE RESULTING FROM A NATURAL INFECTION. THESE FINDINGS WERE GIVEN TO THE SCIENTIFIC WORK ON APRIL 12, 1955 ON THE OCCASION OF THE PRESENTATION OF THE FRANCIS REPORT. (J. Salk: Vaccination Against Paralytic Poliomyelitis, Performance and Prospects, Am. J. Pub. Health, 45: 575, May 1955).

THIS EVIDENCE REAFFIRMS THE NEED FOR DR. SALK TO REPEAT ALL OF HIS EARLY STUDIES, 'ESTABLISHING' THE SAFETY AND EFFECTIVENESS OF A 'KILLED' FORMALIN-INACTIVATED VACCINE, WITH PRESENT DAY TECHNIQUES FOR DETECTING LIVE POLIOVIRUS IN INACTIVATED VACCINE BEFORE HIS CONCLUSIONS CAN BE ACCEPTED. THIS PARTICULARLY APPLIES TO HIS CONCLUSIONS ON PERSISTENCE OF IMMUNITY AFTER ADMINISTRATION OF THE SALK VACCINE AS WELL AS TO THE EVIDENCE THAT LEADS HIM TO BELIEVE IN THE CREDIBILITY OF A ONE DOSE LONG TERM IMMUNITY.

44. I speak here as a practicing health officer who has followed their work carefully. The following are three types of examples.

The first deals with K.S., a three year old girl, a relative of a resident in my community, who within a week following a second inoculation with Lilly Salk vaccine died in a respiratory chamber No. 19, 1955. The Florida Death Certificate (State File No. 29264) lists ACUTE PARALYTIC POLIOMYELITIS as the cause of death, and records that the autopsy findings were compatible with the diagnosis. This case was neither listed as polio, nor as a neurological complication, nor as a case occurring within 30 days of inoculation by the P.S.U.

The second relates to cases of poliomyelitis in vaccinees following inoculation with Lilly #676316 and #679909. Eight cases of polio occurred within fifteen days after inoculations with #676316 (P.S.U. Miss. #41 & 42; Ill. #133; N.Y. #243, #249, #250, #251; Wash. #11). Two cases were the first two cases of an epidemic in Hattiesburg, Miss. The Ill. case was correlated, i. e., the first paralysis was at the site of inoculation. Three of the four N.Y. cases were post-

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seasonal (Nov. 5 & 6) at a time when there were only six additional cases in the entire state for that week. P.S.U. dismissed the Hattiesburg epidemic with a sketchy report from a recent medical school graduate, designated as an Epidemic Intelligence Service Officer, who stated, "that this outbreak represents direct person to person transmission and that vehicles or vectors are not incriminated." (PSU Rpt. 105, Feb. 8, 1957).

Lot No. 679909 was associated with 18 cases of polio occurring within 18 days of inoculation. These included cases in Miss., N.Y., and Md. One case was correlated. Of six additional cases inoculated in the arm, three had bulbar paralysis, one had initial paralysis in the neck, one had an opposite arm correlation, and one had an unlisted first paralysis. Two of the cases occurred post-seasonally in Maryland when the total incidence of reported cases in the state over the two week period within which these cases occurred, was five.

PSU makes no published reference to the association of these cases with these two lots of vaccine (H. Ratner, from Unpublished Studies on the Salk Vaccine, Feb. 12, 1957).

The third relates to one of several cases reported by me directly to the Polio Surveillance Unit, D.S., an eight year old girl, daughter of a physician, had an onset of paralytic polio four days following her third shot (Lilly lot No. 649 345) on Feb. 14, 1956. Paralysis was observed in the left peroneals, the left gastrocnemius and the left deltoid. Subsequently atrophy was observed in the left calf muscle. The paralysis was confirmed by electromyographic studies at Northwestern Medical School. This case was never accepted by the P.S.U. either as a case of polio, or as a neurological complication.

Several other cases associated with these lot numbers were also known to have occurred in Chicago. One was of particular interest because the intern diagnosed this four year old boy as a hemiplegia probably caused by an aneurysm whereas the attending physician, Dr. Archibald Hoyne, an international authority on communicable diseases, diagnosed it as paralytic poliomyelitis. The intern's diagnosis was accepted. None of these cases were included in the study of the 1956 Chicago epidemic although they were Chicago residents.

45. Note: The only admissions made by PSU of unsafe lots of vaccine have been in this instances obvious to the man on the street. The epidemiologic concern, however, is to detect unsafe vaccine not obvious to the layman. This is the work of the specialist. PSU's insistence that criteria of all unsafe vaccines should conform to their own delineation of characteristics of the Cutter outbreaks has no experimental or epidemiologic justification.

An illustration of this is their insistence on the critical importance of correlation of first paralysis with the site of injection. The Bodian data with monkeys which PSU quotes in support of its thesis is only superficially relevant. Bodian's monkeys received heavy doses of polio-virus compared to the trace amounts present in the Salk vaccine.

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Bodian's subjects were immunologically inexperienced whereas the majority of human vaccinees are experienced. Again, in Bodian's experiment 100% of the animals developed paralysis. But this incidence is hardly characteristic of vaccine-induced cases in man. In Idaho the rate was one case per 1600 vaccinees.

Syverton's findings in monkeys with the actual vaccine is in sharp contrast to Bodian's. In contrast to Bodian's 100% paralysis only 3.6% (1/28) of Syverton's monkeys developed paralysis, but 39.3% (11/28) of the monkeys developed asymptomatic identified polio viremias. Syverton's findings are in greater conformity to the true field findings with the incriminated lots of Salk vaccine.

In Idaho, Peterson presents data to show that the number of asymptomatic infections, as detected by satellite cases, was more than twice the number of known vaccinee cases. More significantly, Peterson reports that "A study of antibody response to the one injection of vaccine in a representative sample of children receiving the vaccine has indicated that very high levels of antibody were obtained." He concludes that "The fact that these children have developed high antibody titers against all three types is additional evidence that the vaccine used in Idaho contained living...virus." His findings indicate that a representative group of children experienced an incidence of infection of 79.4%. Melnick, who did complement fixation studies on 27 children following inoculations with another lot of incriminated vaccine, reports that 10 of these had a high titer of complement fixation antibodies signifying a recent infection. This is an infective rate of 37%.

The indices of correlated cases to infections as obtained from the above data is roughly as follows: a.) Assuming that Syverton's paralyzed monkey was correlated, the index is 1 to 8; b.) in Idaho the index is 1 to 6.5 as determined by satellite cases; c.) using Peterson's antibody studies the index is 1 to 2,540; and d.) using Melnick's figures of high complement fixation titers and other data the index is 1 to 1,504. (H. Ratner. Unpublished Studies on the Salk Vaccine 1957)

Sunada's clinical study of 425 Idaho poliomyelitis vaccine recipients in 1955 (Am. J. Dis. Child., 96: 58, July 1958) gives further support of the thesis that PSU's insistence on the critical importance of correlation in detecting unsafe vaccine is unfounded. Sunada and his co-workers report that 32.7% (139/425) of vaccinees gave a history of illness compatible with abortive poliomyelitis within 3 to 25 days after vaccination.

Finally, it must be recalled that the USPHS only incriminated six lots of Cutter vaccine epidemiologically. Yet, they admit the finding of live virus in a 7th lot, and Syverton reports live virus in 9 lots. It becomes obvious that PSU's epidemiological techniques for determining the presence of live virus in a vaccine is not sufficiently refined.

46. The Idaho studies give unequivocal proof of the importance of surveilling satellite cases. The Massachusetts State Polio Advisory Committee, which includes John Enders and other leading virologists, stresses



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the importance of detecting satellite cases as the key to an unsafe vaccine, especially as we make progress in reducing the danger of the vaccine. (Letter, New Eng. J. Med., Dec. 1, 1955). Leading epidemiologists and virologists in West Germany emphasize "the main danger which is entailed by immunization with incompletely inactivated vaccines. This danger is not the fact that certain vaccinated subjects may contract the disease on account of vaccination, but rather that the vaccinated persons can excrete virus and in turn produce epidemics." (Supra 29 a.).

Suffice it to say that most of the large epidemics that have occurred in this country since the introduction of the Salk vaccine have followed the wide scale use of the vaccine and have been characterized by an uncommon early seasonal onset. To name a few, there is the Massachusetts epidemic of 1955 ("the rapid upward swing began three or four weeks earlier than usual." Supra 33); the Chicago epidemic of 1956 ("Early in the course of the epidemic several unusual features became apparent: an early seasonal rise of incidence..." Am. J. Hygiene, 70: 107, Sept. 1959) and the Des Moines epidemic of 1959 ("characterized by an unusually early seasonal onset." J. F. Speers et al: to be published).

The careful reader of polio reports cannot help but note the many individual cases and small outbreaks that seem attributable to a recently vaccinated contact.

Yet PSU decided to drop the reporting of satellite cases in 1955.

It is another sign of the double standard approach of PSU (one standard for those who have received the Salk vaccine and another standard for those who have not) that they have reintroduced the reporting of satellite cases in 1960, not for the Salk vaccine, however, but "...in cases ... who may have had contact with one who has had vaccination with live poliovirus." (as transmitted through the Illinois State Health Department, May 23, 1960).

47. H. R. Cox: Living Modified Viruses as Immunizing Agents, Brit. Med. J. 2:259, July 31, 1954.
48. Supra 17.
49. a. D. M. Horstmann: 4th IPC 1957. "It has been suggested that higher levels of vaccine-acquired... antibodies may be capable of preventing alimentary infection. At present, however, there is no indication that this is the case." (p. 154).
- b. A. B. Sabin: Present Position of Immunization Against Poliomyelitis with Live Virus Vaccines. Brit. Med. J. 1:663, March 14, 1959. "..... high levels of antibody produced in some children by four doses of Salk vaccine failed to influence in any way the extent of viral multiplication in the intestinal tract...."
50. H. Koprowski: Vaccination with Modified Active Viruses. 4th IPC 1957. p. 112.  
"In marked contrasts... subjects who had been vaccinated with inactivated virus, or were nonimmune, developed an alimentary infection which lasted from 1 to 3 months" (p. 122).

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51. J.M. Quirce et al: Vaccination with Attenuated Polioviruses in Costa Rica. 1st LPVC 1959, p. 510.
  52. M. Martins da Silva: Studies of Orally Administered Attenuated Live Virus Poliomyelitis Vaccine in Newborns and Infants Under Six Months, Univ. Minn. Med. Bull. 29: 133, Dec. 15, 1957.
  53. R.N. Barr et al: The Use of Orally Administered Live Attenuated Polioviruses as a Vaccine in a Community Setting: A Controlled Study, 1st LPVC 1959, p. 369.
  54. H.A. Comez et al: Vaccination of 133,000 Children under 10 years of Age with Live Attenuated Poliovirus in Medellin, Columbia-Preliminary Report, *ibid*, p. 458.
  55. M. Martins da Silva et al: The Use of Attenuated Poliovirus in an Epidemic Area, *ibid*. p. 464.
  56. J. Embil, Jr. et al: A Clinical and Serological Study of the Response of Cuban Children to Oral Vaccination with Attenuated Poliovirus Vaccines, *ibid*. p. 593.
  57. Unpublished data.
  58. Unpublished data.
  59. *Supra* 5.
  60. *Supra* 53 and large scale studies presently being conducted in Minneapolis, St. Paul and Duluth.
  61. 1st LPVC 1959: p. 405.
  62. *Ibid*.
  63. a. R.S. Poos & N. Nathanson: Use of poliomyelitis vaccine under epidemic conditions. Report of Outbreak of Poliomyelitis Among Naval Personnel and Dependents in Hawaii, *J.A.M.A.*, 162: 85, 1956.  
 b. N. Nathanson et al: Epidemic Poliomyelitis During 1956 in Chicago & Cook County, Illinois, *Am.J.Hygiene*, 70: 107, Sept. 1959.  
 c. "It seems probable, however, from experience in this (Des Moines Epidemic of 1959) and other recent epidemics, that the mass use of the vaccine at the time of the epidemic does little to alter the course of the epidemic." (J.F. Speers et al: to be published).
- Note: Vaccinating during epidemics not only does no good but the harm it it may do is considerable. As in other areas of Salk vaccine evaluation epidemiologic techniques and practice in this area have been wanting.
64. The fact of the matter is that it is not simultaneously safe and highly effective (*Supra* 29 e.). Today the Salk vaccine available to practicing physicians is in part more safe because it has less viral antigen (*Supra* 21). Furthermore, it has a low and an extremely variable potency.

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