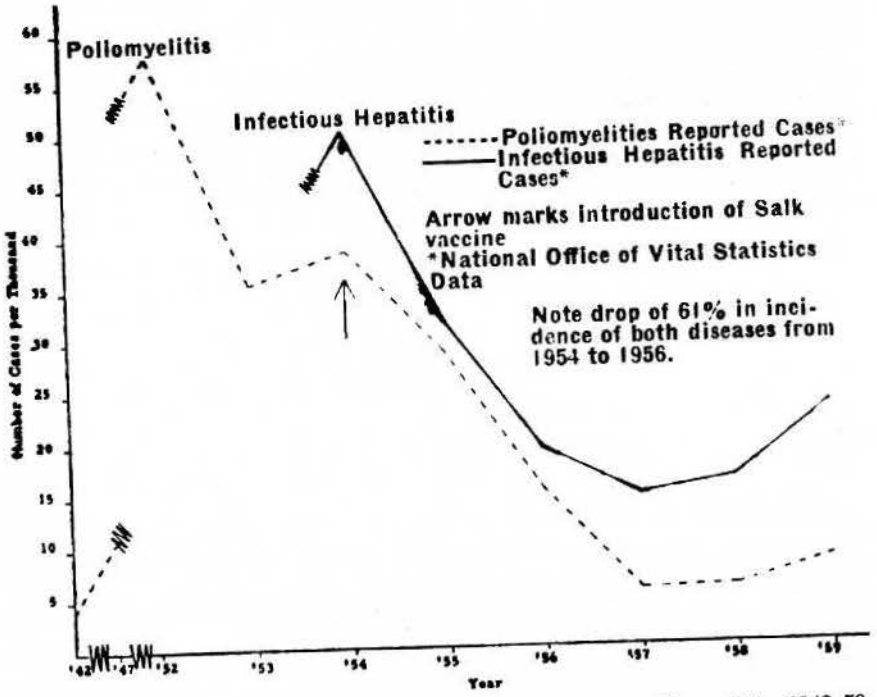


FIGURE 1.—The natural rise and fall of two diseases, poliomyelitis 1942–59, infectious hepatitis, 1949–59.

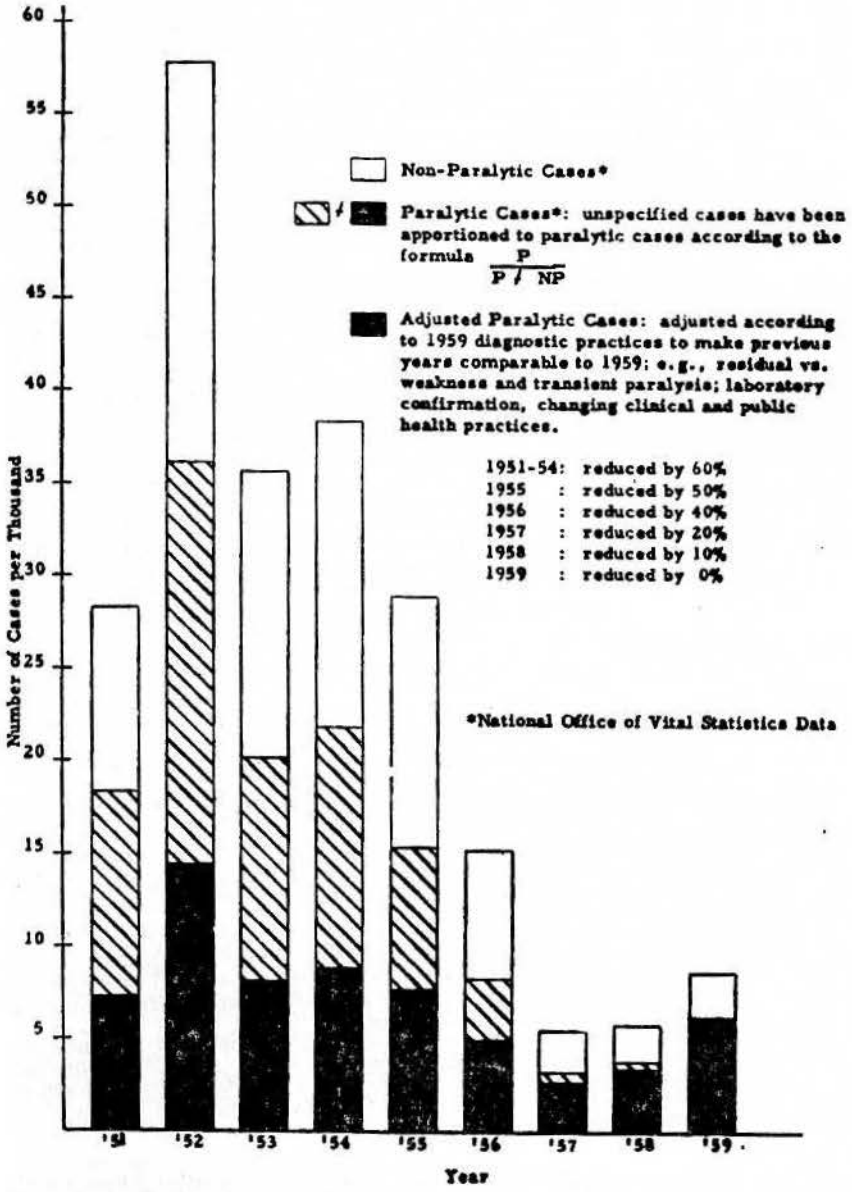


FIGURE 2.—Comparison of the incidence of poliomyelitis, total cases 1951–59.

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.[2] 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 1 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 polio virus before it reaches the central nervous system. One of the major disappointments 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 polio virus in the gut, nor their breakthrough 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 2 years in the incidence rates of paralytic poliomyelitis in the United States. The rate in 1958 was about 50 percent higher than that for 1957, and in 1959 about 80 percent higher than in 1958. If 1959 is compared with low year of 1957, the increase is about 170 percent. 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 a 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.

[2] 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.

One of the most obvious pieces of misinformation being delivered to the American public is that the 50-percent 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 "doubletalk" and an unwillingness to face facts and to evaluate the true effectiveness of the Salk vaccine. It is doubletalk from the standpoint of logical reasoning: If the Salk vaccine is to take credit for the decline from 1955 to 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 2 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 stopgap 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 5 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 percent, 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 percent effective in preventing paralytic poliomyelitis within 1 year, but completely ineffective in preventing nonparalytic poliomyelitis. 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 percent 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. 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. In fact, a report from that unit on December 7, 1955, went so far as to claim that a single inoculation of the vaccine was about 78 percent effective in preventing paralytic poliomyelitis.

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 percent 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 percent reduction among children 5 to 9 years old. The Poliomyelitis Surveillance Unit study had reported about 80 percent 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, 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 percent.

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; sign 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."

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 1955–57. 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 percent 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. 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 percent effectiveness, we found only about 24 percent. 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 percent 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 2 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 percent do not have antibodies to types I and III and that 20 percent lack antibodies to type II polio virus. This is a very disturbing fact. When a phenomenon like this occurs 2 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 polio virus. In 1956 in much of our so-called nonparalytic polio, the etiology turned out to be Coxsackie 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 paraylsis.

I would also like to agree with Dr. Greenberg that the insistence upon a 60-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 60 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. Later, as a bacteriologist at the USPHS, I produced other killed vaccines.

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 every 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 cubic centimeter 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 fivefold 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 cubic centimeter to make the present killed vaccine. If you multiply that by fivefold 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 percent of paralytic cases throughout the world. The killed vaccine does a poor job against type I, however, which causes 85 percent of paralytic cases, and against type III, which causes about 12 percent. 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. 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. 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 percent had antibody titers of less than four to type I poliovirus, 20 percent had the same lack of antibody titers to type II poliovirus, and 77 percent 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. 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 injuection 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 percent, 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 tenfold to thirtyfold in virus content by a second filtration step. 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 600-fold variation in the potency of commercial Salk vaccine on the market. Other unpublicized USPHS data showed a sixtyfold variation. 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.

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 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 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. Second, 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 doublechecked 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. 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.

PART II[a]

VACCINE SAFETY

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 seven of the positive lots live virus was found by a single laboratory but not by the other two. 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 monkey inoculation tests were concerned * * * the results of the tests served to prove the inadequacy and unreliability of the testing procedure." 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 percent (seven-fiftieths) of the lots submitted for licensing were subjected to both tests; the majority, 64 percent (thirty-two-fiftieths), 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 percent (eleven-fiftieths) of the lots submitted for licensing were not tested by NIH at all. 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.

To bring this issue of the safety of the Salk vaccine to a close, the following

[a] Reprinted from Illinois Medical Journal, September 1960.

information is pertinent. In 1953, experienced investigators from the Michael Reese Hospital in Chicago failed to produce a safe vaccine by the Salk formula. Their findings were dismissed by the backers of the Salk vaccine.

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. This manufacturer discontinued production of Salk vaccine and did not resume 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-percent effectiveness. 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. A member of the USPHS also found live virus in commercial vaccine other than that admitted by the USPHS to have induced cases. 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. Epidemiologic evidence of unsafe vaccine from manufacturers not named by the USPHS has been reported by Anderson, Redeker, and others.

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, Brown, and others, 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.

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, and secondly, because of unrefined criteria for the determination of safety; for instance, insistence on correlation of initial paralysis at the site of inoculation, and discontinued reporting of satellite cases.

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 fivefold to tenfold into the range of 100 million to a billion organisms per cubic centimeter 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.

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 percent of the paralytic cases occurred in those who had three or more injections of the Salk vaccine. The lower incidence of paralytic polio (37 percent) 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 1,000 to 4,000 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

When measured against its killed counterpart, a live virus vaccine is always a superior vaccine. It invariably cost 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 percent 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 nonantigenic; 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 cubic centimeter 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 10 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 percent 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. Although the killed vaccine does

induce antibodies in the blood, this does not prevent the person from becoming a carrier and shedding poliovirus. 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 10 days to as long as 6 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 feeding and over 1.5 million people with trivalent vaccine. The vaccine now has over a 90 percent take, and over 90 percent 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 polio-virus infection. This is something we have to continue to study. In this country it is unusual to find antibody titers as high as 1,000 to 2,000; but in South America it is not unusual to find pregnant women with titers in excess of 8,000 to 10,000, 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. They had over 1,000 cases in a total population of approximately 1 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 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 3 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 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 percent antibody response in vaccinated individuals and about a 14 percent increase in antibodies in the placebo group. We dis-

covered 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 in 1958, and the tail end of type II (surprisingly enough it was type II) in Managua, 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 8 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 3 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 6 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 6 weeks. We find circulating antibodies in the blood on about the 9th or 10th day, and they reach a maximum peak in about 30 days. By the end of 1 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 3 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 percent to types I and III, which independently confirms our conversion figures.

Other findings are of interest. In Cuba we carried out a study 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 percent, and converted 65 of the 76 children to a triple positive status for a conversion rate of 86 percent.

In western Massachusetts where we tested 123 paired bloods, 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 percent, and 56 out of the 67 persons were converted to a triple positive stage for a conversion rate of 84 percent.

As you may know, in February this year Dade County including Miami began a countywide mass vaccination program with our trivalent vaccine. The data

from there are actually the best we've seen. 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 percent) 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 percent of paralytic polio cases. We filled in 19 of the 25 gaps for type II, which accounts for 3 percent of paralytic polio, for a conversion rate of 76 percent. And we filled in 23 of the 25 gaps for type III, which accounts for about 12 percent of paralytic polio, for a conversion rate of 92 percent. 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 percent; in type II 70 of 79 gaps filled, 89 percent; and in type III, 80 of 85 gaps, 94 percent. We filled in a total of 247 out of 263 antibody gaps for an overall conversion rate of 94 percent on a single 2 cubic centimeter 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 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 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 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 percent 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 unequivocably 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 percent, 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 through 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 percent of the adults, and in 63 to 75 percent of the children tested. 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.

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 lifelong, 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 his 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 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, the U.S. Public Health Service 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.

[Reprinted from the Journal of the American Medical Association, Feb. 25, 1961]

POLIOMYELITIS IMMUNIZATION

TO THE EDITOR: If we assume that a yearly booster injection of poliomyelitis vaccine is needed because of the lack of potency in the present injectable vaccine, are we not inconsistent in principle to say that the patient who had the last injection—be it the third or the fourth—2 to 4 years ago can get the same protection by only one booster injection as the one who had the last injection 1 year ago? Furthermore, is it true that by next year the oral vaccine will have solved this problem.

M.D., *Wisconsin.*

ANSWER: The question rightly recognizes that recommendations of additional injections of the Salk vaccine relate to its low and variable potency. On April 19, 1955, only 7 days after the Francis report and the promulgation of minimal requirements for the licensing of the vaccine, the U.S. Public Health Service found it necessary to reduce potency standards by two-thirds. The problem worsened late in 1955 when, to insure safety, it was necessary to introduce additional filtration during inactivation. This additional filtration resulted in a 10- to 30-fold loss in antigen (Illinois Med. J. 118: 83–93, 1960; and 118: 160–168). Kelly and Dalldorf (Amer. J. Hyg. 64: 243–258, 1956) reported a 600-fold variation in the potency of the Salk vaccine on the open market from negligible potency upward. The difficulty became enhanced when, on May 17, 1957, the Division of Biological Standards permitted lots of vaccine which had failed to meet minimum potency requirements to be retested, so that if the manufacturer then obtained a positive potency test, earlier negative tests could be disregarded. It is now generally recognized that much of the Salk vaccine used in the United States has been worthless.

It follows, then, that the true issue for the physician and patient is not how many injections, or how often, but whether the vaccine given or to be given contains dependable amounts of viral antigen. With the Salk vaccine this cannot be determined because it is an unstandardized product of an unstandardized process. Therefore, for the physician who prefers to know what he is giving, the choice rests with either the recently licensed killed poliovirus vaccine which is concentrated to a known and optimal weight of inactivated virus antigen, and which has substituted the Parker strain for the dangerous Mahoney strain, or with the standardized attenuated live poliovirus vaccine promised for next spring. In either instance, a complete course of vaccination is indicated, irrespective of the number of injections of the Salk vaccine given.

HERBERT RATNER, M.D.

[From the Chicago Sunday Tribune magazine, Mar. 5, 1961]

THE TRUTH ABOUT THE POLIO VACCINES

Do Salk Shots Really Prevent Polio? Should We Keep Using Salk Inoculations? How Good Are the New Oral Vaccines? Here Are the Facts

(By Joan Beck)

Behind glowing reports of the Salk polio vaccine's success and even rosier predictions about the new, live, oral Sabin vaccine rages a storm of medical controversy that seldom reaches the ears of parents.

Many serious criticisms have been leveled at the Salk vaccine. These are now being acknowledged—at least indirectly—in announcements praising and promoting the new oral vaccines.

Yet all is not yet sweetness and accord among developers of the live, oral vaccines, either. At least three different types have been developed and—according to their producers—proved safe and effective in tests, chiefly in foreign countries, but also in the United States.

One of these new oral vaccines, developed by Dr. Albert Sabin with National Foundation research funds, has been OK'd by the U.S. Public Health Service for manufacture. But there are problems remaining to be solved in its production and, according to acommittee of experts headed by Dr. Roderick Murray, of the National Institutes of Health, dangers to be considered in its use by the general public (although it has been given to a reported 77 million Russians and to at least 300,000 Americans. Russian Prof. Mikhail Chumakov, who directed a 2-year program of inoculations with the Sabin vaccine, says he is convinced polio epidemics have been eliminated in the Soviet Union). Licensing is not expected until this spring. Quantities of the vaccine are not expected to be available for communitywide use until November.

"Both 'live' (Sabin) and 'killed' (Salk) polio virus vaccines will be needed to combat poliomyelitis in the near future, U.S. public health officials declared at the AMA clinical meeting," the Journal of the American Medical Association reported in December 1960. "The new oral poliomyelitis vaccine developed by Dr. Albert Sabin and approved for future use in this country will not be the complete solution as far as can be predicted now, the Public Health Service experts said."

Evaluating the true effectiveness of the Salk vaccine and the new oral vaccines has been difficult for several reasons. Polio is a relatively rare disease in the United States. Because so few persons get it in its paralyzing form, success of an immunizing agent is hard to determine.

The definition of polio also has changed in the last 6 or 7 years. Several diseases which were often diagnosed as polio are now classified as aseptic meningitis or illnesses caused by one of the Coxsackie or Echo viruses. The number of polio cases in 1961 cannot accurately be compared with those in, say 1952, because the criteria for diagnosis have changed.

Even the Salk vaccine itself is not a constant, standard product. Since the first field trials of 1954, the vaccine has been changed several times. The first alternations were aimed at increasing the vaccine's safety by changing the method of killing the polio virus and by adding an extra filtration step. Newer changes are intended to increase the vaccine's effectiveness. The success of the Salk vaccine necessarily varies, depending upon which Salk vaccine is being considered.

Ever since the public was first informed about the Salk vaccine in the Francis report of April 12, 1955, the National Foundation has praised its effectiveness and urged parents to have themselves and their children vaccinated. Although some physicians remained skeptical about the original theories behind the vaccine, about the techniques used in its evaluation, and about its success in combating polio, these objections seldom reached the general public. With the resurgence of paralytic polio in 1958 and 1959, the criticisms increased.

These views were summed up by five experts in a panel discussion on the "Present Status of Polio Vaccines" presented before the Illinois State Medical Society in Chicago, in May 1960, and published in the August and September issues of the Illinois Medical Journal. To make parents aware of the controversy about the Salk vaccine and the problems involved in developing an effective oral vaccine against polio, here is a report of that discussion:

Moderator of the panel was Herbert Ratner, M.D., director of public health in Oak Park, and associate clinical professor of preventive medicine and public health, Stritch School of Medicine, Chicago.

Dr. Ratner noted the upward trend in polio, particularly in the paralytic form, in the United States during 1958–59. He quoted Dr. Alexander Langmuir, in charge of polio surveillance for the U.S. Public Health Service, as saying this resurgence is "cause for immediate concern."

"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," commented Dr. Ratner. "Four years and 300 million doses of Salk vaccine later, we had in 1959 approximately 6,000 cases of paraltic polio, 1,000 of which were persons who had received three and more shots of Salk vaccine. Salk vaccine hasn't lived up to expectations."

Dr. Sabin says the number of cases in 1960 was less than in 1959, but that 23 percent are now occurring in persons who have had three or more doses of Salk vaccine.

Dr. Ratner next reviewed some basic facts about polio. Paralytic polio occurs in cycles and was in a natural decline when the Salk vaccine was introduced in 1955, he pointed out.

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. Now, an epidemic is defined as 35 cases per year per 100,000. This change has resulted in a statistical—but not necessarily a real—drop in polio epidemics.

For every case of known paralytic polio, there are about a thousand "subclinical polio infections," so mild they pass unnoticed, Dr. Ratner explained. These mild cases account for the high degree of natural immunity in adults You can have a polio infection in the intestines without having paralytic polio or nonparalytic polio with enough symptoms to be diagnosed.

The theory of the Salk vaccine, made with killed polio virus, is that it will produce enough antibodies circulating in the blood to neutralize polio-virus before it can reach the central nervous system. But "one of the major disappointments of the killed vaccine" is that these circulating antibodies do not protect an individual against getting a polio infection in the intestines, nor its breakthrough into the circulatory system, said Dr. Ratner. Protection against paralysic polio depends upon the presence of enough circulating antibodies to offset the virus, he explained.

Discussing the "very misleading way" in which the Salk vaccine data has been handled, was Bernard G. Greenberg, Ph. D., 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.

"There has been a rise during the last 2 years in the incidence rates of paralytic poliomyelitis in the United States," stressed Dr. Greenberg. "The rate in 1958 was about 50 percent higher than that for 1957, and in 1959 about 80 percent higher than that in 1958. If 1959 is compared with the low year of 1957, the increase is about 170 percent.

"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 utilitizing the press, radio, and 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," said Dr. Greenberg.

"Although such a program might be desirable until live virus vaccines are available to us on more than an experimental basis, the misinformation and 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-percent 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 doubletalk and an unwillingness to face facts and to evaluate the true effectiveness of the Salk vaccine," said Dr. Greenberg.

The number of persons over 2 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, Dr. Greenberg pointed out. Then how can it be claimed that it is the large number of unvaccinated persons who are causing the increase in polio, when there were a larger number of unvaccinated individuals in 1957 when the vaccine was given credit for reducing rates of the disease?

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

Why was there such a tremendous reduction in reported rates of paralytic polio in 1955–57? Much of this highly publicized decrease was a statistical illusion, said Dr. Greenberg.

Prior to 1954, any physician who reported a case of paralytic poliomyelitis was doing his patient a favor because funds were available to help pay his medical expenses. At that time, most health departments used a definition of paralytic poliomyetis which specified "partial or complete paralysis of one or more muscle groups, detected on two examinations at least 24 hours apart." Laboratory confirmation and the presence of residual paralysis were not required.

In 1955, these criteria were changed. Now, unless there is paralysis lasting at least 60 days after the onset of the disease, it is not diagnosed as paralytic polio.

During this period, too, "Coxsackie virus infections and aseptic meningitis have been distinguished from paralytic poliomyelitis," explained Dr. Greenberg. "Prior to 1954 large numbers of these cases undoubtedly were mislabeled as paralytic polio."

Thus, because the definition of the disease was changed and two similar diseases virtually ruled out, the number of cases of polio reported was sure to decrease in the 1955–57 period, vaccine or not. Then, too, physicians are reluctant today to diagnose paralytic poliomyelitis in a vaccinated child without thorough laboratory tests, thus eliminating most of the false positive cases commonly reported in the pre-1954 period.

"As a result of these changes in both diagnosis and diagnostic methods, the rates of paralytic poliomyelitis plummented from the early 1950's to a low in 1957," said Dr. Greenberg. The recent increase in the disease, despite improved diagnostic methods, he believes, is due to a long-term, increasing trend in the occurrence of polio.

"Without doubt, the increasing trend has been reduced to some extent by the Salk vaccine" explained Dr. Greenberg. "Nevertheless, the Salk vaccine has limited effectiveness in its ability further to reduce this trend. * * * Any future substantial reduction in this trend will require a more potent vaccine, not simply vaccinating more people.

"Today it may be a serious mistake to be ultraconservative in accepting the various new live 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."

The most accurate way we have of determining the effectiveness of vaccine (except by direct exposure to the disease) is to measure the levels of neutralizing antibodies in the blood, explained Herald R. Cox, Sc. D., director of virus research at Lederle Laboratories and president-elect of the Society of American Bacteriologists. We do not know, he said, the exact level of antibodies necessary to protect against paralytic polio.

Herman Kleinman, M.D., an epidemiologist from the Minnesota Department of Health, pointed out that in antibody studies on children who have received three or more doses of Salk vaccine, he has found more than half do not have antibodies to two of the three types of polio strains used in the Salk vaccine. Twenty percent lack antibodies to a third type.

"This is a very disturbing fact," said Dr. Kleinman. "If polio antibodies mean anything in respect to protectiion, then I am forced to conclude that much of the Salk vaccine we have been using is useless."

Dr. Kleinman also commented on the "changing concept to polio" and said physicians were reluctant to diagnose the disease without overwhelming evidence. He called the insistence on a 60-day duration of paralysis in defining paralytic polio "silly."

Dr. Cox, who has worked in the virus field since 1929 and was the first person to prove that a killed vaccine could be made, commented on some of the problems of producing a potent, killed-virus 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," said Dr. Cox. "But type II represents only about 3 percent of paralytic cases throughout the world. The killed vaccine does a poor job against type I, however, which causes 85 percent of paralytic cases, and against type III, which causes about 12 percent.

"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. 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."

There have been problems, too, in the production of the killed Salk vaccine. An extra filtration step was added in November 1955, Dr. Cox said, "because the amount of formalin used did not inactivate the poliovirus. We found residual live virus for as long as 42 consecutive days of inactivation."

Dr. Cox went on to assert that the second filtration step was "picked out of thin air with no experimentation to back it up," and that the extra filtration cut down on the effectiveness of the vaccine.

Mass vaccination with the Salk product started in April 1955 and by April 26 there were reports of paralytic polio among vaccinated children, with deaths occurring in Idaho and California. Then came cases of polio among family members of vaccinated children. Live virus was discovered in the supposedly killed vaccine, although it had been produced by the Salk procedure.

Dr. Ratner cited numerous instances in which live viruses were found in vaccine which was presumably safe, even in Dr. Salk's own standard vaccines. "It should be stressed that safety testing was inadequate when Dr. Salk developed the vaccine and when the vaccine was commercially prepared for the field trials of 1954 and for licensing and use in 1955," said Dr. Ratner. He added that in current vaccine, potency has been sacrificed for safety and that "at present, epidemiologic methods employed by the U.S. Public Health Service to assure safety of the vaccine are inadequate."

Should the Salk vaccine continue to be used?

"There is no known way of preventing polio with a licensed product at the present time except through the use of the Salk vaccine," answered Dr. Kleinman. "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."

Other panel members agreed, pointing out that because all of the facts about the Salk vaccine have not been made public, physicians and public health officials find it difficult to resist the great pressures of public opinion built up through an unprecedented publicity campaign urging the public to be vaccinated.

"Since nothing else is available, there seems to be no alternative but to push the use of it," commented Dr. Greenberg. "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. By being more cautious, we may make a mistake by accepting a better polio vaccine too slowly."

"When measured against its killed counterpart, a live virus vaccine (using modified virus which stimulate the production of antibodies but do not cause the disease) is always a superior vaccine," asserted Dr. Cox. He said it invariably costs much less. And it gives a higher degree of longer lasting immunity. Dr. Cox has developed a live vaccine which was tested on thousands of schoolchildren and adults last year in Dade County, Fla., and also on thousands of persons in foreign countries.

Another live, oral polio vaccine has been developed by Dr. Hilary Koprowski, of Philadelphia's Wistar Institute, and has been tested on approximately 9 million individuals.

Dr. Koprowski has challenged the U.S. Public Health Service decision last August to grant approval only to the Sabin vaccine. In a letter in the January 14 Journal of the American Medical Association, he said, "Although it is a step forward that the principle of live virus immunization in poliomyelitis has