Polio, Politics, Publicity, and Duplicity

Ethical Aspects of Development of Salk Vaccine

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This paper is an historical account of the discovery, testing, and early distribution of the Salk polio vaccine. The discovery posed fundamental dilemmas of medical research, pharmaceutical production and public health. This paper assesses the ethical problems which arose, and examines critically their resolution.

The great public demand which the discovery of the vaccine generated created a need for federal control which was only partly met. The federal government did not have sufficient institutional and legal mechanisms to assure the safety of the vaccine and protect the public. This discussion illustrates the failure of the government to keep pace with medical technology.

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THE introduction of a new biological pharmaceutical presents a host of medico ethical dilemmas. The debate surrounding the nationwide influenza vaccination programme suggests only a few of the multifarious difficulties involved. Each step in the process—from the initial funding for research to the testing, licensing, commercial production, and distribution of the drug—is wrought with serious judgmental considerations of both a medical and moral nature. If one accepts the public welfare as the preeminent value in the discovery and distribution of a new drug, the role of the government is of primary importance.

The history of the Salk polio vaccine is revealing in this regard. The discovery marks an important episode not only in the growth of immunology, but, most significantly, in the history of public health. The demands made upon the government and the government's response to these demands provide critical insights into the recent course of public health in America. This paper will examine the history of the Salk vaccine in light of the ethical judgments involved.[1]

The vaccine discovered by Salk in 1952 marked the culmination of the efforts of the National Foundation for Infantile Paralysis to secure an immunological agent against polio. The Foundation had grown out of efforts to raise funds for Franklin D. Roosevelt's Warm Springs retreat during the Depression. In consultation with public relations firms, Roosevelt's former law partner, Basil O'Connor, organised a series of "President's Birthday Balls" in 1934 with the slogan: "Dance so that others may walk" (3, p. 16). In 1937 Roosevelt announced the formation of the National Foundation for Infantile Paralysis (NFIP) for the purpose of ensuring "that every responsible research agency in this country is adequately financed to carry out investigations into the cause of infantile paralysis and the methods by which it may be prevented" (5). Basil O'Connor became the president of the new organisation. The creation of the Foundation signaled a major new direction in the history of American medical philanthropy. The appeal for funds now utilised sophisticated public relations techniques (6). Of significance was the dramatic extension of the traditional concept of philanthropy, as the National Foundation now sought funds from everyone, not just the affluent. Radio spots requested that dimes be sent directly to FDR in honor of his birthday on January 30, 1938. More than 2,600,000 dimes "marched" into the White House, inundating the mail room (3, p. 18). Thus was coined the title "March of Dimes."

The Foundation pioneered in the techniques of modern fund raising with its mass appeals, use of media, public relations, and a corps of volunteers. The unprecedented doorbell campaign—the "Mothers' March on Polio"—began in earnest; the Foundation put its cadres into the sheets. Their ability to raise funds, even during the most trying economic circumstances, must be rated remarkable. By the 1950s the National Foundation had developed the perfect form of philinthropy for the burgeoning consumer culture.[2] The concept of philanthropy as consummerism—with donors promised personal benefits—was to a great degree the contribution of the March of Dimes.

Why did poliomyelitis become the rallying point for millions of Americans? One logical answer is, of course, Franklin Roosevelt's personal battle with the disease. Despite FDR's attempts to conceal his infirmity, a new media age made polio the most prominent of diseases. But Roosevelt merely symbolised a more general perception that polio was a peculiarly American malady. More dangerous in affluent nations, polio became America's target although other diseases and medical afflictions were really more common.[3] An increasingly child-oriented society could not tolerate a disease which crippled its young.[4] In addition, the National Foundation had a remarkably powerful influence on the whole direction of American medical research and health care priorities, a topic that demands more attention than is possible here.

There can be little doubt that the Foundation put its funds into the right hands. Through the use of long-term, substantive grants awarded to eminent researchers and institutions, the NFIP insured the continuity of polio research. By 1948 a series of important epidemiological studies had been made under the Foundation's auspices. Most important was the discovery of Drs. John Enders, Thomas Weller, and Frederic Robbins, all of Harvard University, that poliovirus could be cultivated in nonnervous tissue (4, pp. 369-381; 9). This Nobel Prize-winning discovery virtually assured that a polio vaccine could be produced. A race, with bitter political and personal overtones, ensued.

Development of Salk Vaccine

Dr. Jonas Salk began his research on polio immunisation in 1951 under a grant from the National Foundation. Within a year he had successfully immunised monkeys in his laboratory at the University of Pittsburgh. Confident that he had found the key to immunisation in a killed virus vaccine, Salk proceeded to test his discovery on human subjects.

The first of these experiments was conducted on children from the D. T. Watson Home for Crippled Children. Risk was reduced by vaccinating these children, who had already had polio and were thus immune prior to injection. Salk inoculated 43 children with no adverse reactions. He later commented, "When you inoculate children with a polio vaccine, you don't sleep well for two or three months" (1, p. 139).

Salk continued his experiments at the Polk State School, where he again inoculated children with his test vaccine. Unlike the polio victims at the Watson Home, these children, who were mental defectives, had no history of polio and thus much lower antibody titer, significantly increasing the danger of the test. The ethical standards applied here, though in no way unusual in the 1950s, must be questioned. Dr. Tom Rivers, one of the most eminent virologists in the history of modern immunology, in reviewing an experiment similar to Salk's, voiced concern about the morality of such a test (10, pp. 466-467):

> I think that if someone wants to use adults as volunteers to try out a new drug or vaccine, that is perfectly all right, provided that the adult has been told about the nature of the disease he is exposing himself to, has been completely informed about the nature of the agent he is to receive, and has been told the chances for success or failure ... An adult can do what he wants, but the same does not hold true for a mentally defective child. Many of these children did not have mommas or poppas, or if they did their mommas didn't give a damn about them.

Fortunately, Salk's confidence in the vaccine was borne out by the results of these initial human tests. But Dr. John R. Paul, in his definitive history of poliomyelitis, pointed out what failure may have entailed (4, p. 418):

> Had the experiments gone wrong at this point there might have been a tremendous outcry. Some would have called it unnecessarily hasty to use so many subjects all at once... And others would have called it a crime to subject helpless children and adults to this sort of experimentation.

It would seem from this analysis that an experiment on human subjects is ethical if successful, unethical if a failure—a dubious formulation. No government guidelines or requirements for human testing existed at that time.

Salk's success buoyed his faith in the vaccine. In presenting his findings to the medical community, he was, however, more cautious (11):

> Although the results obtained in these studies can be regarded as encouraging, they should not be interpreted to indicate that a practical vaccine is now at hand. ... It will now be necessary to establish precisely the limits within which the effects here described can be reproduced with certainty.

The task of establishing the effectiveness and consistency of the new vaccine would not be Salk's alone.

Planning Field Trials

By the middle of 1953 the National Foundation had begun devising plans for a mass nationwide trial, the largest of its kind ever attempted. The Foundation established a Vaccine Advisory Committee (VAC) of eminent physicians and researchers headed by Tom Rivers to oversee the field trials. The NFIP's decision to conduct such a field trial meant that serious consideration of other forms of immunisation, particularly the attenuated vaccine, no longer was possible (4, pp. 423-425). The Foundation's position, though clearly understandable in light of the embryonic nature of attenuated vaccine research, sparked controversy and aroused bitterness. From this time onward, criticism of the Salk vaccine would be an indeterminate mixture of scientific judgment and personal animosity.[5]

The National Foundation conducted affairs on a grand scale; the field trials slated for early 1945 were to be no exception. The NFIP with its newly created Vaccine Advisory Committee proceeded to design the trials in a direct, almost autocratic manner. After his initial discovery, Salk found his influence diminishing over subsequent decisions concerning testing, as did a host of other scientific advisers to the Foundation. Basil O'Connor, anxious to move forward with all possible speed within the bounds of safety, pushed the VAC in the singular direction of conducting a definitive test (10, pp. 495-500).

Scientific advisers dashed over the design of the trials. Originally, the Foundation planned to vaccinate volunteers and compare the rate of paralytic polio among this group to a control group of nonvaccinated children. This format had the advantage of being easy to administer and evaluate, and in addition gave all volunteers the potential benefit of the vaccine. The Vaccine Advisory Committee insisted, however, that a "double-blind" test was necessary to eliminate the socioeconomic bias of the volunteer group and thus provide a scientifically unassailable evaluation. Under this test, half the volunteers would receive vaccine, half placebo.

This decision infuriated the increasingly confident Salk who called the double-blind test a "fetish of orthodoxy..." Salk clearly exposed the ethical dilemma of using a placebo in an impassioned letter to O'Connor (1, pp. 191-192):

> ...if we are aware of the fact that the presence of antibody is effective in preventing the experimental disease in animals and in man, then what moral justification can there be for the purpose of determining whether or not a procedure that produces antibody formation is effective...[?] I would feel that every child who is injected with a placebo and becomes paralysed will do so at my hands.

Such an experiment, argued Salk, "would make Hippocrates turn over in his grave."

It is not difficult to sympathise with Salk's viewpoint. With a double-blind test the effectiveness of his vaccine would essentially be proven by the contraction of polio among those children who received placebo. But the emotional content of Salk's plea would also seem to indicate the importance of removing the test from the hands of the discoverer. In a sense, Salk favored an early limited distribution of his vaccine as a test for efficiency, not a carefully controlled, scientifically conducted examination. Sure of the safety and effectiveness of his vaccine, he actually jeopardised its full acceptance in the medical community. This is not to question Salk's scientific ethics or his personal morality, but rather to suggest the difficulties of participating in the evaluation of one's own researches.

Though the National Foundation took full responsibility for the field trials, the VAC commissioned Dr. Thomas Francis of the University of Michigan to evaluate the trials. Francis, a pioneer in the fields of microbiology and immunology, commanded unquestioned respect in the scientific community. The Foundation assured the University of Michigan ample funds to assist in Francis' evaluation. He demanded complete control of the evaluation—with no outside pressure, timetable, or supervision—and O'Connor agreed to these stipulations. Francis also insisted on an injected control

group in at least some states. The decision to have Francis assess the vaccine insured an irreproachable trial.

Before a trial could be attempted, however, the difficult transition from an experimental, laboratory-produced vaccine to a consistent, commercially manufactured vaccine had to be negotiated. Until commercial laboratories could produce vaccine, all talk of a field trial was really premature. Although the National Foundation contacted five major pharmaceutical companies to produce vaccine for the field trials, a complete draft of the requirement for production did not evolve until early 1954, only several months before the trials began (1, pp. 207-211). The Vaccine Advisory Committee supervised the shift to commercial production, making two critically important recommendations. First, the Committee required that Salk conduct an initial trial on at least 5,000 children using commercially produced vaccine before undertaking nationwide trials. And secondly, *all* commercial vaccine for the field trials had to undergo safety tests in three laboratories—the producers', Salk's and the U. S. Public Health Service's Division of Biological Control (12).

The decision to test commercial vaccine in the federally operated lab represents the difficulty of the government's position. The government had no legal role in the trial; no licence was required for such an experiment. The Food and Drug Administration only required that the test drug be safe, not necessarily effective(13). A major medical advance was in the making, with the government's only capacity an essentially extralegal one. Moreover, when it came time for the licensing of the vaccine, the Public Health Service would be in the dark. "We wouldn't know enough about the vaccine and the ins and outs of its manufacture", remarked a Public Health Service official. "We would not be able to act on licence applications for months. But the public would want action in hours" (1, p. 209).

With no official role in the testing of the vaccine but badly needing most information, the Public Health Service gladly accepted the functions allocated by the Vaccine Advisory Committee of the National Foundation. Indeed, the Division of Biological Control, under the direction of Dr. William Workman, scrutinised procedures to the point of threatening the trials. Workman and other government officials realised that, although they had no legal sanctions, they had the responsibility of insuring a safe, effective vaccine (1, p. 208). Moreover, the National Foundation recognised the importance of having the blessing of the Public Health Service before conducting its trials.

Opposition to Trials

Scientific opposition to Salk's vaccine remained formidable as the trials approached. Some scientists had difficulty duplicating Salk's inactivation process in their own labs, while others questioned the viability of a killed virus vaccine. Dr. Albert Milzer had been unable to reproduce the Salk vaccine in his laboratory at the University of Chicago. He repeatedly found live virus in the vaccine—an ominous result. Dr. Albert Sabin, at work on an oral, attenuated vaccine, became Salk's chief antagonist. Only one month before the field trial was set to begin, Sabin called the test "premature". Salk and the National Foundation attempted to combat the criticism: "I give every possible assurance I can and that medical science can that the antipolio vaccine will be safe. I will personally be responsible for the vaccine", declared Salk (14, 15).

More troublesome than this criticism, however, were the continued difficulties of the commercial producers in their attempts to replicate Salk's vaccine *en masse*. Scientists at the Public Health Service's Division of Biological Control harbored serious doubts about the abilities of the manufacturers to produce consistently safe vaccine. This reflected, in part, inexperience in the histopathology of polio (10, p. 513). But it also revealed a very real production problem. In March 1954, Dr. William Workman suggested that the field trials be postponed:

> I again come to the conclusion that the specifications and minimum requirements. . .are inadequate to assure the reasonable regularity of production of a vaccine of acceptable safety to be used in the field study. Under the circumstances, I cannot escape the feeling that an occasional lot. . .which does pass the test, may actually contain living virus and be unsafe for use. My recommendation is that the proposed field studies be postponed until—(1) specifications and minimum requirements can be revised to give greater assurance of the safety of the final product; (2) it has been shown that the vaccine prepared in accordance with such specifications meets acceptable criteria for safety (1, p. 221).

It should be emphasised, however, that the government had no legal means of postponing the trials. The National Institutes of Health and the National Foundation agreed that, rather than revising the safety tests themselves, companies must produce eleven *consecutive* lots of safe vaccine for any to be acceptable for use. With this agreement, plans proceeded for the field trials.

Despite the persistent opposition within the scientific community, the National Foundation and the press stimulated public optimism for the vaccine's success. The dual role of the National Foundation—philanthropic and scientific—created tensions. The profusion of positive press release, essential to fill the Foundation's coffers, jeopardised scientific judgments (3, pp. 82-85). The National Foundation announced publicly the plans for a mass field trial months before a commercial laboratory had produced any vaccine (16).

The press played upon the drama of the situation; no medical discovery before or since has been covered as intensely. Beginning in 1953, progress in the vaccine's development was regularly front-page news in the *New York Times*. Press reports were often filled with speculation (17):

> If the vaccine fulfills the hope that at last a way has been found to cope with poliomyelitis as effectively as public health officers cope with smallpox or typhus, Dr. Salk will have scored one of the greatest triumphs in the history of medicine.

Although Salk and the National Foundation attempted to discourage such optimistic conjecture, Basil O'Connor's euphoria could not be contained. He declared that the development of the vaccine had brought the fight against polio to the "verge of victory" (18). The *New York Times Magazine* called the trials the "climax of a stirring medical drama" (19).

The vaccine's notoriety undermined the control of the scientific community. The public now clamored for the vaccine, making it increasingly difficult for scientists with reservations to resist the demand for mass testing. Sabin's attacks on the vaccine, became more personal in nature: "Let us not confuse justifiable optimism with achievement" (20). And Salk's defence became less scientific: "I have the courage of

my convictions. I couldn't do it unless I was more critical of myself than others are of me. It is courage based on confidence, not daring, and it's confidence based on experience" (21). Salk continued to announce that he would take "personal responsibility" for the safety of the inoculation—a courageous, if ill-advised stand (22). The *New York Times* felt qualified to endorse the trials, remarking (23):

> No matter how important a medical discovery may be, there are always skeptics who try to strip it of importance. We need these skeptics, but sometimes they may be nuisances.

At this point the skeptics were threatening the test. Several states withdrew, from cooperation in the trials after Walter Winchell announced on national television and radio that the vaccine "may be a killer" (24).

This is not to argue that the press and public should have no role in a medical discovery, but rather that, in this kind of atmosphere, where public demands and expectations are great, sound scientific judgment may be jeopardised. *The Salk vaccine was sold to the public before its safety and efficacy were proven.*

The National Foundation must bear some of the responsibility for the public fervor which surrounded the field trials. Perhaps the most objectionable of all the Foundation's pronouncements was that the test was exclusively designed to test the efficiency of the vaccine. According to the Foundation, safety had already been conclusively demonstrated. In light of the production difficulties, this was a particularly bold assertion. The NFIP struck the word "experiment" from its literature; this was a "trial" vaccine, not an "experimental" vaccine. Although the test was conducted on a voluntary basis, the *quality* of informed consent is thus highly questionable.[6]

On April 25, 1954 the Vaccine Advisory Committee set up final guidelines, giving its approval for the trials. The United States Public Health Service issued the following statement (26):

> We believe that the judgment of the Vaccine Advisory Committee is sound and that the National Foundation for Infantile Paralysis is justified in proceeding according to the Committee's recommendation.

The next day the field trials began. With more than 1,800,000 children participating, the trials mark the largest clinical test using human subjects in the history of medical science. No medical experiment ever held such public attention. According to a Gallup Poll conducted in May 1954, 90 per cent of the American people knew of the field trials, more than could identify the full name of the President of the United States (1, p. 268).

The test, conducted in 45 states, used placebo controls in 84 areas and observed, nonvaccinated controls in 127 areas. More than 400,000 children received three injections; about 200,000 of these actually received salt-water placebo injections rather than the test vaccine. Along with blood samples to test antibody titer, Dr. Thomas Francis now had the information needed for a conclusive evaluation of the vaccine (1, pp. 238-261).

Speculation was rampant concerning the results of the field trials, but Francis promised no annuoncements until the spring of 1955. He had more than 144 million pieces of information to assemble and review. Some days the Evaluation Center's morning mail filled an entire elevator (1, p. 255).

A critical problem faced the National Foundation during this interim period while awaiting Francis' report. Without a federal licence (which could not be obtained until the vaccine was finally evaluated) and without advance orders, the pharmaceutical companies could not afford to continue to produce vaccine. It was not difficult to foresee a situation in which the vaccine would be found to be safe and effective, and yet there would be no vaccine available for the 1956 polio season. Basil O'Connor, with typical boldness, ordered $ 9 million worth of vaccine from six pharmaceutical companies—an expensive gamble on the vaccine's approval. Of course, if the Congress had been willing to allocate funds, this risk could have been avoided. But the government seemed content to let the National Foundation carry the ball.

On April 12, 1955, the tenth anniversay of Franklin Roosevelt's death, Francis released his evaluation, one of the most comprehensive epidemiological studies ever conducted. According to Francis, the safety of the vaccine was "powerfully affirmed" (27, 28). This is an interesting observation in view of the National Foundation's reluctance to consider the trials a test of safety. Francis found the vaccine 80 to 90 per cent effective in placebo-controlled areas, slightly less in observed controlled districts (28, pp. 15-19). In short, the vaccine appeared to be a tremendous success. The nation celebrated; for many parents, it seemed, the anxious summers were over.

The successful development of the polio shot characterised the Eisenhower years as the moon shot did a later era. The image of the scientist-hero, unhampered by government intervention, held great appeal. The press proclaimed Salk a national demigod, while some colleagues, resentful of all the attention he received, suspected him a demagogue. The vaccine became a perfect cause for an age in which ideology was suspect.[7] The scientific atmosphere of the 1950s was wrought with Cold War overtones. The vaccine, an affirmation of American scientific and technological progress, was viewed as a triumph of the American system. American science, pragmatic and purposeful, demonstrated the continued viability of the promise of American life.

In Washington, Ms Olveta Culp Hobby, Eisenhower's Secretary of Department of Health, Education, and Welfare, signed licences for six companies to produce vaccine. These companies had, of course, been producing vaccine all along; the licences gave them authority to distribute it.[8] The National Foundation's vaccination programme for school children began immediately, with youngsters who had received placebo during the field trials given top priority. For all intents and purposes this should have been the dramatic conclusion to the conquest of polio. Unfortunately, it was not.

The Cutter Crisis

On April 26, 1955, two weeks after Francis' Ann Arbor proclamation of safety, five cases of paralytic polio were reported among children who had just received vaccine. All five victims, it was found, had received vaccine from the Cutter Laboratories in California. Surgeon General Leonard Scheele requested that Cutter recall all its vaccine pending an investigation. Remarkably, the government had no power to order the Cutter Labs to withdraw the vaccine, but Cutter readily complied. The infamous "Cutter Incident" would, however, eventually encompass 25 states and Hawaii, 260 cases of polio, and 11 deaths (1, p. 316).

These cases of polio cast an ominous cloud over the Salk vaccine, the National Foundation, the pharmaceutical companies, and the National Institutes of Health. What had gone wrong with the most rigorously tested drug in medical history? The most obvious cause of the problems was that the careful triplicate testing of the field trials had not been continued for the licensed vaccine (12, pp. 329-331). Written protocols submitted by the manufacturers to the Division of Biological Control were the only legal requirement. The Division had the right to make spot checks, but did not exercise this option. Moreover, the consistency standards of repeated safe batches which had been devised for the field trials were not required of licensed vaccine. In brief, safety precautions for commercially produced, licensed vaccine fell far short of the guidelines used for the field trials.

During a series of meetings of top virologists and advisers called together by Surgeon General Scheele, it was decided to let the vaccination programme continue. But this consensus began to erode quickly. Dr. John Enders, regretting his approval for continuing the programme, wrote to Dr. William Sebrell, the Director of the National Institutes of Health (32):

> I am forced to conclude that active virus might be present in certain finished lots of vaccine prepared by any or all of the manufacturers concerned. I cannot, therefore, longer assert my confidence that the poliomyelitis vaccine now being distributed and injected consists solely of inactivated vaccine and in consequence, of harmless virus.

On May 7, Scheele *requested* that the national vaccination programme be suspended pending further studies.

Scientific criticism of the Salk vaccine intensified. In June, Enders and Sabin testified before a House subcommittee investigating the crisis that the vaccination programme should be stopped and the licences withdrawn until safety could be conclusively proven. But they were overruled by an equally eminent group of scientists who expressed confidence in the quality of the vaccine if properly produced (33).

On June 9, Scheele released a Public Health Service "Technical Report" on the Salk vaccine, an attempt to explain and correct the problems which produced the Cutter crisis. The "white paper", though not a complete whitewash, was carefully written to avoid directing blame (34).

> The Salk vaccine applies new principles in the production of vital vaccines. The speed of its development, which reflected the increased tempo of all medical research, created problems in biologics control amenable to solution only with the accumulation of knowledge and experience. It is likely that problems of equal complexity will be raised by the development of other new vital vaccines.

This analysis obscured the inadequate preparations made by the Public Health Service for testing the vaccine. Despite the easily predictable demand for the vaccine, the Bureau of Biologics staff remained at only 35, insufficient to carefully scrutinise the commercial production process. Moreover, the protocols required of manufacturers did not provide enough information for proper safety-evaluation. The contrast between the careful tripartite testing of the trial vaccine and the testing of the commercial product is a remarkable example of the lackadaisical attitude of the government toward biological control.

The irresponsibility of the Cutter Laboratories must not be overlooked in evaluating the crisis. Repeated difficulties in producing safe vaccine were experienced by the Cutter Labs; 9 out of 27 lots produced had contained live virus and were discarded. Yet Cutter failed to report this inconsistency to the Bureau of Biologics; the company only submitted protocols for batches which passed their safety test (34). Cutter officials never asked for assistance from NIH or Salk. *Their ethical commitment to produce safe vaccine must thus be seriously questioned. But it must also be remembered that they acted entirely within the letter of the law.* The NIH had no consistency requirement and did not require reports on discarded vaccine or production difficulties.

The Public Health Service's "white paper" explained the manufacturing problems in terms of inadequate sensitivity of the safety tests (34, p. 17):

> Each producer had had difficulties in processing and testing materials at various stages of production. Because some lots were obviously unsatisfactory they were not submitted for release, and therefore no protocols on them were submitted by the manufacturers. These experiences showed the need for more sensitive and better controlled testing methods, and for greater attention to the history of consecutive lots.

The Public Health Service revised the minimum requirements for production in light of the Cutter incident, making them mandatory standards. The Division of Biological Control was reorganised, becoming the Division of Biologics Standards with larger facilities and a fourfold increase in staff.

The relationship between the commercial producers and the federal government lay at the heart of the Cutter incident. This association became the target of serious investigations in the days following the tragedy. Victor Haas, the Director of the National Microbiological Institute, a division of NIH, evaluated the government-pharmaceutical connection in a series of memos to Sebrell in May 1955.[9] Haas argued that the responsibility for safety must ultimately rest with the manufacturers, and that the government could not (and should not) participate intensively in the safety testing of biologic products (35):

> It has been the principle of operation that this intensive participation in what is essentially a part of the manufacturing process, properly should be only a temporary activity for the Laboratory of Biologics Control. Once it has been established that manufacturers can produce safe material (and production experience and field trials of last summer formed the basis for licensing manufacturers for polio vaccine), this principle of operation would assume that periodic plant inspection, knowledge of the capabilities of supervisory personnel, review of protocols, and spot-testing of materials would suffice to assure us of continuing acceptability of any product within the limits imposed by available knowledge and human acceptability to error.

Intensive and continuous testing in government laboratories, Haas believed, would destroy industrial initiative and responsibility. According to his evaluation, more testing and inspection would not have prevented the Cutter incident. This is a dubious assertion, for certainly the manufacturing difficulties experienced by Cutter and the other pharmaceutical companies would have been revealed, raising questions of safety.

Finally, Haas suggested that it would be improper to overreact to the Cutter incident by revising existing standards of control. He ascribed the current fervor to the tremendous publicity which the polio vaccine had generated (35):

> Had the poliomyelitis vaccine been used on the same quantitative scale that applies to other biologicals and had an incident occurred, there would have been very little attention given it other than by the constituted authorities. The many factors which have gone into creating a demand for a safe and effective poliomyelitis vaccine, which would be available at the earliest possible time, should not force us to abandon careful and sound judgment as to what is the best method for the operation of biological control over the years.

The Cutter incident exposed the inherent weakness in the

argument for governmental laissez-faire with regard to biologics control and pharmaceutical production. The limited role of the federal government clearly reflected the Eisenhower political philosophy. Olveta Culp Hobby eventually lost her job, largely because of the vociferous criticism of her handling of the vaccine programme. In addition, the government's action was circumscribed by the miniscule legal powers of the Public Health Service, essentially unrevised since 1902, a time of relatively primitive pharmaceutical production. The government continued to assume that industrial interest in producing a safe product would ensure the public's safety.

In view of the federal government's minor role, the National Foundation assumed massive responsibilities in the development and distribution of the vaccine. Combining the functions of fund-raising, research, testing, and distribution, the National Foundation often found its multiple roles conflicting. Although well-intentioned, the publicity mill created an atmosphere in which demand threatened to outstrip sound scientific decision making. In such an environment, ethical questions can become obscured. The field trial, for example, though brilliantly engineered and promoted, and meticulously evaluated, lacked truly informed consent.

The ethical aspects involved in the development and distribution of the Salk vaccine are varied and complex, and the historian must be leery of second-guessed, overarched generalisations. But three key issues which demand continued attention emerge. First, testing with human subjects presents a series of problematic considerations, from the suspect use of mentally defective children to the use of healthy, parent-volunteerd youngsters. High ethical standards for defining risk-benefit ratios must be exercised in such investigations; use of placebos complicates such assessment. Moreover, informed consent is liable to compromise (36). Second, the obligation of pharmaceutical companies to manufacture safe products cannot be assumed, especially when pressures to market a new drug become intense. The third point is most striking: the federal government's minimal role in a major scientific advance. Although the government cannot be the final arbiter of ethical medical judgment, it is the only body which can provide a central direction and standard for these practices. By abdicating a more active role, the government invited the possibility for crisis. The Salk episode seems to indicate a less than complete commitment by the government to the public welfare.

In the years since the discovery of the Salk vaccine, the problems of pharmaceutical control have expanded rather than diminished. The capacity of the government has remained limited in overseeing industry. The Government Accounting Office, Congress' investigative arm, recently attacked the lax attitude of the Food and Drug Administration's drug testing (37, 38). According to the GAO's report, human subjects are exposed to unnecessary risks and the FDA has approved new drugs for public use on the basis of highly questionable data. FDA attempts at self-investigation have proven largely useless (39). The FDA has failed to enforce its standards and, according to many reports, has served as a lackey to the major pharmaceutical companies (40). In its mission of public protection, the FDA, by any standards, has proven to be grossly inefficient.

The history of the Salk vaccine, from the initial research through testing and production, speaks clearly to the present. The institutional connections through which a new drug is channelled from laboratory to market remain uncertain, subject to frequent short-circuit. The time between discovery and production has steadily decreased, augmenting the difficulties implicit in regulation. Most importantly, the federal government has failed to keep pace with the rapid innovations in medical and pharmaceutical practice, at great cost to the public welfare.

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Notes

1. Several studies of the development of the Salk vaccine have been written, although none is definitive. The most comprehensive of these is *Breakthrough: The Saga of Jonas Salk* by Richard Carter (1). Rich in detail, though weak in analysis, this book was particularly helpful in my study. Also recommended are Jo[illegible] R. Wilson's *Margin of Safety* (2) and Aaron K. Klein's *Trial By Fury: The Polio Vaccine Controversy* (3). The definitive medical history of poliomyelitis is *A History of Poliomyelitis* by John R. Paul (4).

   The archives of the National Foundation have unfortunately been closed to researchers. This rich collection of materials contains valuable information pertaining to the development and distribution of the Salk vaccine.
2. For a more extended analysis of the implications of consumer culture, see reference 7.
3. Nations with high standards of sanitation and personal hygiene actually prove to be more susceptible to enteric viral infections such as poliomyelitis (4, pp. 364-365).
4. For an explanation of attitudes toward children in the postwar era, see reference 8.
5. See references 1 and 2 for extended discussions of the bitter relationship between Salk and Dr. Albert Sabin of the University of Cincinnati.
6. Parental consent was required for a child to participate in the trial. Excellent essays on informed consent and human testing are contained in reference 25.
7. Excellent discussions of political and cultural life in the 1950s are contained in references 2 and 30.
8. One of the six companies was the Cutter Laboratories of Berkeley, California. The Region Oral History Office of the University of California at Berkeley recently completed an oral history memoir with individuals from this organisation, documenting its involvement with the vaccine (31).
9. These memoranda, marked "confidential" have only recently been opened to researchers as a result of a Freedom of Information suit. They are a highly valuable source for deciphering the government's view of its role in the development of the vaccine (35).

References

1. Carter, R. *Breakthrough: The Saga of Jonas Salk*. Trident Press, New York, 1966.
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Pharmaceutical Industry in Latin America

BOTH the transnationalisation and oligopolisation of the pharmaceutical industry is well known. A few companies occupy a large percentage of the worldwide market. In 1985, the fifteen largest companies in the world were responsible for 37 per cent of the total pharmaceutial sales (US $ 79.8 billion).

This same phenomenon can be witnessed in Latin America, which accounts for 7 per cent of the world pharmaceutical market, or approximately US $ 5.5 billion. In 1985, the 10 leading companies in Latin America—all transnationals—captured 30.5 per cent of the pharmaceutical market in the seven countries studied (Argentina, Brazil, Columbia, Chile, Mexico, Peru and Venezuela). Sales in these countries reached US $ 4.13 billion that year.

The largest markets for pharmaceuticals in Latin America are Brazil, Mexico and Argentina, which are also the countries with the largest populations. In 1985, the total market in Latin America was valued at US $ 5.5 billion; 69.3 per cent of these products were sold in these three countries.

The most frequenfly sold products in the region are antibiotics, cough preparations, antirheumatics, analgesics and vitamins. This illustrates well the pattern of pharmaceutical consumption in this part of the world. On the one hand, while it is true that there is a high-incidence of infectious illnesses justifying the use of antibiotics, these products are often used indiscriminately. Of more concern, however, is the fact that "cough and cold preparations", many of which are simply useless for the purpose intended, occupy second place on the list of sales. Analgesics and antirheumatics—symptomatic drugs—also occupy a preferential place, while products containing vitamins represent a considerable proportion of the sales, thanks to promotional campaigns which try to present them as a solution to the nutritional problems of the Latin American population.

The most startling fact, however, may be that "Novalgina", produced by HOECHST, occupies first place in the sales list, in spite of the fact that its principal active ingredient—Dipirona or Metamizole—has been withdrawn from the markets of many countries because it can produce agranulocytosis, a sometimes fatal blood condition.

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