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NEWS AND COMMENT

Division of Biologics Standards: Reaping the Whirlwind

On 27 October 1963, a Philadelphia housewife named Mary Jane Griffin swallowed a sugar cube impregnated with live poliovirus vaccine. The vaccine, it was to appear, came from a production lot in which the virus had changed back into a virulent form. A month later, Mrs. Griffin awoke from a coma to find herself in an iron lung, with a priest administering the last rites.

She survived, but the polio has left her confined to a wheelchair and almost totally paralyzed in all four limbs. The most active movement she can manage is to bend her right arm at the elbow, but only enough to touch her nose, not to reach her head or comb her hair. Her left shoulder, unless the nurses dressing her are careful, is easily pulled out of its socket, causing severe pain. Her diaphragm is two-thirds paralyzed; she has learned to breathe again, but she cannot cough. Otherwise, she is healthy in mind and body and has the normal life expectancy of a 50-year-old woman—another 28 years.

Last November, deciding a case that had taken 7 years to prepare, a Philadelphia judge awarded Mrs. Griffin and her husband just over $2 million in damages against the United States government. (The government is still deciding whether to appeal the ruling.) Mrs. Griffin's disease, the judge ruled, "was caused by the negligence of the Division of Biologics Standards [DBS]," the government agency that regulates vaccines. The DBS's own test results indicated that the lot from which Mrs. Griffin's dose was derived exceeded the legally established safety limit for neurovirulence.

Significantly, a quite separate inquiry into DBS affairs has also found evidence that agency officials ignored their own regulations. The General Accounting Office, the investigatory arm of Congress, recently published a report on the DBS's supervision of adenovirus vaccine, concluding on the basis of the agency's own records that about half the vaccine lots the DBS approved were less potent than required by regulation.

The DBS, formerly a part of the National Institutes of Health, is now the Bureau of Biologics of the Food and Drug Administration. The agency was transferred to the FDA last July, following criticisms of its scientific and regulatory management (*Science*, 3 and 17 March 1972). The polio and adenovirus cases concern events that are now ancient history. But they are indicative, and maybe representative, of a period of regulatory management which came to an end only last year, and the full repercussions of which may not yet be evident.

The Griffin decision is also important because of others similar to it. About 100 other cases occurred, and more than 20 people filed claims against the manufacturer. Most were lost or settled for small sums. A principal reason for their lack of success, according to Mrs. Griffin's attorneys, was testimony by DBS officials to the effect that the vaccines had passed the DBS safety tests. But polio vaccine victims seeking to reopen or initiate claims now would run into difficulty with the statute of limitations.

The unique feature of the Griffin case is that Mrs. Griffin's attorneys brought suit against the government as well as against the manufacturer and were thus able to obtain a court order compelling the DBS to release all its relevant files. From the files they were able to construct a case that the DBS had violated its own rules for dealing with the vaccine in several important instances. Their suit, brought under the Federal Tort Claims Act, represents the first time that the government has been held liable for the release of a biological product. Mrs. Griffin's attorneys, Avram G. Adler and Stanley P. Kops, of the Philadelphia firm Freedman, Borowsky, and Lorry, say they spent some 7 years preparing the case.

Mrs. Griffin's contraction of polio from Sabin type III vaccine could not have come as a total surprise to those knowledgeable in the field. Several cases associated with the vaccine occurred soon after it was introduced, and the Surgeon General's committee on polio decided at a meeting in September 1962 to recommend that adults not take the type III vaccine unless they were at special risk. In December 1962, by a 6 : 4 vote, the committee reversed

its decision. Between these two decisions, according to Mrs. Griffin's attorneys, the manufacturer informed the DBS it would cease to produce the vaccine unless the restriction on adults was lifted.

To test the safety of the vaccine, DBS officials used to inject a batch of monkeys with vaccine from each production lot and compare the extent of brain damage with that caused in other monkeys by a standard reference virus. A lot is to be judged satisfactory, states the Code of Federal Regulations, only if the neurovirulence of the vaccine virus under test can be demonstrated not to exceed that of the reference virus.

With the vaccine lot from which the judge decided Mrs. Griffin had received her dose, Pfizer lot 56, four out of 30 monkeys injected were found to have developed mild to severe brain damage, and one of the four was paralyzed.

Why then was lot 56 passed for release? At the trial, DBS officials argued that the actual number of monkeys affected (severity of damage apart) was within the range of that experienced with the reference virus; that because of biological variation it was within the regulations to release anything judged to fall within the variation expected; that the type III virus was known in any case to be more neurovirulent than other types; that the survival of 26 of the monkeys showed that the vaccine was not too bad; that the monkey test was, anyway, not a reliable guide to the virus's behavior in humans; and, finally, that it lay within the discretion of DBS officials to use their judgment and experience in deciding what to release and what not to release. The judge bought none of these arguments.

The regulation governing the testing, Judge Clarence C. Newcomer ruled, was not discretionary. It required the test results to demonstrate that the test lot did not exceed the reference vaccine in neurovirulence. In the judge's opinion, the test data demonstrated the very opposite. The severity of the nerve damage caused by lot 56 in monkeys was clearly greater than anything ever encountered with the reference vaccine. As to the DBS argument that what counted was only the quantity, not the quality, of the nerve lesions, Newcomer commented: "There is no real evidence . . . that the DBS ever honestly thought that the quantity of lesions was the only important factor in determining neurovirulence. It was, however, the only factor which could be used at the time to get any of the lots to pass."

Newcomer again referred to the concern to get vaccine lots passed when dismissing a statistical argument proposed by the defense. When it was found in 1963 that the reference vaccine provided, in effect, too high a safety level for the test vaccine to meet, the DBS statistician devised acceptance tables based on a different vaccine. "These tables," Newcomer noted, "are perfect examples of the DBS–Surgeon General's Committee propensity to blithely violate the regulations to get type III lots to pass rather than working to change the regulations while doing their duty by failing the lots."

Newcomer was also unimpressed with the belief of the DBS's chief expert on monkey neurovirulence that the test results were required to be *comparable* to that of the reference virus, whereas the law in fact requires that they should not exceed it. The faulty lot was passed for release, the judge concluded, "either because the personnel of DBS charged with enforcing the regulation failed to read the regulation carefully or because they did not understand or failed to take seriously the strict duty imposed upon them by regulation. Either circumstance constitutes negligence."

Problems with Licensing

Even the original licensing of the Sabin types I, II, and III polio vaccines came under question in court. The Sabin strains were selected by the Surgeon General's committee on live polio vaccine before any regulations had been finalized and before the necessary test data had been gathered, Newcomer observed. The regulations as finally adopted called for the vaccine to be tested on at least 100,000 susceptible people before general release. No one called upon to do so at the trial—including the then Surgeon General, the director of the DBS, and Dr. Albert Sabin—could document the tests in which this had been done. (According to plaintiff's counsel, failure to conduct large-scale field trials of Sabin vaccine in the United States was part of the reason given by Merck and Company, original manufacturer of the Sabin seed strains prior to licensure, for declining to produce the Sabin vaccines on a commercial scale. Counsel also pointed out that, in such field trials as were undertaken, the vaccine used was contaminated with SV40, a monkey virus that in fact reduces the natural neurovirulence of the Sabin type III vaccine. The SV40 was later discovered and removed, but the decontaminated vaccine was never given fresh field tests, as required by regulation, to see if removal of the SV40 had increased its neurovirulence.)

In assessing damages, Newcomer awarded Mrs. Griffin a total of $1,759,946.25 for medical expenses, loss of earning power, and past and future suffering, and her husband $300,000 for loss of consortium. In fixing the amount for pain and suffering, Newcomer observed that Mrs. Griffin "cannot leave her home except on rare occasions . . . suffers excruciating pain from time to time . . . undergoes the kind of mental suffering that only a quadriplegic who had lived an active life beforehand can know . . . is completely aware . . . has become completely dependent on other persons, even to her bowel and bladder functions . . . has become her husband's jailer . . . [and suffers] ever-present and continuing agony."

Newcomer's judgment was delivered on 7 November last year. Later he ruled that the damages he awarded need not be reduced in view of compensation Mrs. Griffin had won in a previous case against Pfizer. The manufacturers are reputed to have paid her between $300,000 and $400,000.

The study of adenovirus vaccine was occasioned by a request to the General Accounting Office from Senator Abraham Ribicoff (D–Conn.). Last April the GAO released a report on the DBS's regulation of influenza vaccine, which disclosed that substantial amounts of vaccine had been below the required potency (*Science*, 7 April 1972). The GAO report issued last month reveals a similar situation with adenovirus and combined adenovirus-influenza vaccine.

The DBS paid rather haphazard attention to the potency requirements for adenovirus vaccine, according to the GAO report. In one instance, a manufacturer applying for a license to produce the vaccine submitted six lots, five of which were subpotent, a circumstance which the manufacturer even noted on his protocol. The DBS official who reviewed the protocols also observed that the five lots were subpotent. The manufacturer received his license. Two other manufacturers submitted six lots each, none of which passed. They too were licensed by the DBS. This being the basis on which licenses were handed out, it is perhaps

surprising that only 47 of the 97 lots of adenovirus released on the market failed to meet the required potency.

The regulations stated that adenovirus vaccines were to equal or exceed the reference vaccine in potency. DBS officials told the GAO that, because of the variability of the potency test, they passed vaccines which showed at least a third of the reference vaccine potency. But the officials were unable to produce any documentary basis for this practice. Even if they had, it would have been at variance with the regulations. And the agency's records showed that at least ten lots that had been passed were less than a third of the required potency.

Production of adenovirus vaccine was halted by the DBS in October 1964 because of the discovery that the vaccine was irremediably contaminated with SV40, the same virus that had turned up in early polio vaccine. The GAO auditors were unable to find any evidence that the DBS had at the same time considered withdrawing any contaminated lots that might still be on the market. But if there was enough evidence to tell manufacturers to halt production, the GAO opined, "the same evidence should have suggested that DBS determine if any vaccines remained on the market and, if so, take action to have them withdrawn."

It is still open to the government to appeal the Griffin case. The decision rests with the Department of Justice, but the FDA is understood to have advised against appeal. One reason is for fear that the appeal judge would broaden the verdict and increase the government's liability toward those it fails to protect. Another, maybe, is the evident feeling among FDA staff that Newcomer's verdict was only fair. As one senior official remarked, "I have never met the lady but having read the judge's report I feel I know her. If you figure everything she's been through, I think the poor damn woman deserves every cent she gets."

Harry M. Meyer, director of the Bureau of Biologics since the reorganization last June says he is unable to comment on the specifics of the Griffin case while there is a possibility of a government appeal. But discussing the GAO report, which cites the same failing brought out in the Griffin case—the ignoring by DBS officials of their own regulations—Meyer told *Science*: "I think that as a regulatory agency we were properly faulted. There was a tendency at that time to make informal interpretations of rules. That was a loose and sloppy system, neither logical nor legally sound. We should be writing regulations that say what we mean, and if we don't mean them we shouldn't write them." Since July, Meyer has been reexamining the bureau's rule book in order to remove ambiguities and ensure that regulations accord with practice.

The attitude of the DBS toward its rule book is to some extent understandable. The legal test for the potency of adenovirus vaccine was to measure its antigenicity in guinea pigs, a property which some experts believed had little or no relation to its antigenicity in man. As for the polio case, the details that emerged in the trial suggest that the full story of the Salk and Sabin polio vaccines and their delivery to the public has yet to be told. It seems evident, at least, that the DBS was acting under considerable pressure at the time. Yet why should prudence have been thrown to the winds? In rushing the Salk vaccine onto the market in 1955, there was the excuse of lack of defenses should a polio epidemic strike. There was no such excuse in 1962 because Salk vaccine, however imperfect, was available. Adler, the senior attorney in the Griffin case, theorizes that a political decision was taken to hurry the Sabin vaccine out: "Sabin had his vaccine field-tested in Russia and it was widely bruited about that if the government didn't pass the Sabin vaccine the Russians would come out with it first. This was at a time when the Sputnik mentality still prevailed." Adler also observes that, "To give the devil his due, the DBS only got into the testing business because they did not trust the drug companies. The tragedy is that they did not then act in the best scientific tradition."

However difficult the DBS's position, it seems in retrospect foolhardy to have ignored its own rule book instead of trying to get the rules changed. The practice can hardly have strengthened the agency's posture toward the manufacturers it was supposed to regulate. It left DBS officials without the protection of their regulations should something go wrong. And, or so the judge was persuaded, it lead to the case of Mrs. Griffin.

—NICHOLAS WADE

POINT OF VIEW

Research Style and the Entrepreneur

The threat to biology posed by the dangers of scale and the advent of the entrepreneurial system is discussed by S. E. Luria in the current issue of Daedalus.* *Luria is professor of biology at the Massachusetts Institute of Technology.*

The pursuit of scientific research varies depending on external circumstances, with regard not only to the contents of research but to the way it is carried out—its style. The charming snootiness of the physicists as intellectuals, for example, did not survive the pressure to associate with the military crowd during the 1940's. . . . A medium-big scale, not quite that of physics, but relatively substantial all the same, has overtaken biology. Some biologists have joined the jet set, and reports—less carefully documented than articles—are written in the first-class sections of airplanes. . . .

But the entrepreneurial system does lend itself to opportunism. . . . A subtle change in ethical standards follows: not necessarily a loss of integrity, but a shift of responsibility from the scholar to the entrepreneur. One sees signs of such a change taking place in biology, in which substantial research support dates only from two decades ago. For example, if someone published some good work, other scientists used to allow him to develop it alone at least for a few years. Now eager researchers rush back from professional meetings to perform the obvious experiments that a speaker had not yet had time to do. Nothing strictly unethical, of course—not according to the ethics of competitive enterprise.

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