DES: A Case Study of Regulatory Abdication

A restaurant worker in New York was so fond of chicken that he had for his supper each night the necks left over from the birds consumed by the patrons. At that time, in the 1950's, the poultry industry was producing a particularly tender-meated chicken called a caponette, whose soft flesh was the result not of castration, as in the capon, but of the implantation of a pellet of diethylstilbestrol, or DES. The DES, a synthetic chemical that mimics the action of the natural female sex hormones, was implanted in the young chickens' necks. On his diet of caponettes' necks, the New York restaurant worker attained immortality as a medical textbook example of gynecomastia—the growth of female-sized breasts on a man. Last year DES itself made medical history in what the *New England Journal of Medicine* described as a "unique situation in human oncology." A hitherto extremely rare kind of vaginal cancer was noticed in eight young women admitted to a Massachusetts hospital. Their only point in common was that some 20 years previously they had all, as fetuses, been exposed to DES (in one case to a related chemical) when their mothers were treated with it to prevent a threatened abortion.

DES is a chemical of bizarre and far-reaching properties, chief of which is that it is a spectacularly dangerous carcinogen. Some 22 countries have taken steps to ensure they do without DES in their food supply. The hormone is a regular ingredient of the American diet because the federal government permits its use as an additive in cattle feed. Fed to some 75 percent of the 30 million cattle slaughtered each year, DES makes the animals fatten faster and on less grain, thereby saving cattlemen some $90 million yearly. In the past 9 months, the chemical has enjoyed a crescendo of notoriety—culminating in hearings last week before Senator Kennedy's health subcommittee—because residues of DES in possibly cancer-causing quantities continue to this day to appear in beef.

The attempts of the Food and Drug Administration (FDA) and the Department of Agriculture (USDA) to protect the consumer from DES form an illuminating case study of the use of scientific information in regulatory decision-making. The DES case also illustrates the gulf between the present law and rational policy, as well as the basic and as yet unresolved dilemma of food protection: Is there a "no effect" level at which a carcinogen can safely be allowed in food?

The history of the attempt to control DES is a record that includes negligence, deception, and suppression by the USDA and prevarication by the FDA. DES was first approved for use in cattle in 1954, with the condition that it be withdrawn from feed 48 hours before slaughter so that none would remain in the meat. Under the law, the FDA was supposed to recommend a method for detecting DES in meat, and the USDA was to inspect meat. For 11 years, until 1965, neither agency bothered to check meat for DES on a regular basis. This abdication was in spite of the clearest warning signals. For example, in 1959 the National Cancer Institute advised that "it would seem the better part of reason to exclude this known potent carcinogen from our diet and to eliminate such food additive practices as have been shown to lead to any detectable residues . . . in our food."

The methods available in 1959 were good enough to pick up DES residues in poultry but not in sheep or cattle. The Delaney anticancer law of 1958 says unambiguously that no known carcinogen shall be allowed in food, so the FDA had no option but to prohibit the use of the hormone in poultry. It was clearly only a matter of time before detection methods improved sufficiently to pick up DES residues in beef and mutton. The FDA was not hurrying, however, and in 1962 someone persuaded Congress to emasculate the Delaney law as it affected DES. The new clause, a piece of fine-print chicanery known as Section 512 (d) (1) (H) of the Food, Drug, and Cosmetic Act, said that it is okay to feed carcinogens to meat animals, as long as no residue is left in the meat when the chemical is used according to label directions that are "reasonably certain to be followed in practice." In other words, if you find DES in meat, that's the fault of the farmer for disobeying the "reasonable" regulations. So don't ban DES, jail the farmer.

The loophole didn't face any test until 1965, the first year the USDA started to check beef regularly for DES. Even then, the USDA's anxiety about DES remained less than extreme, as is illustrated by the case of John N. S. White, a former USDA meat inspector in Los Angeles. Noticing that cows fed particularly heavy doses of DES developed anatomical abnormalities, White prepared a scientific article suggesting that DES should be more strictly controlled. He was told not to publish it. When he persisted he received the following encouragement in a letter from a USDA personnel officer:

> I have before me a file disclosing that you acted contrary to supervisory instructions by offering for publication an article entitled 'The Effect of Feeding Stilbestrol to Beef Cattle.' . . . You are hereby reprimanded for failure to follow supervisory instructions and conduct causing embarrassment to the Department. You are also warned that a repetition of this type of offense could result in severe disciplinary action and very possibly removal.

White eventually got his article published, by the expedient of quitting the USDA.

When the USDA did start looking for DES residues in meat, it used an analytical method capable of detecting DES down to levels of 10 parts per billion (ppb). Only the year before, in 1964, DES had been shown to cause tumors in mice when fed at a level of 6.5 ppb, and the "no effect" level, if any, had not been discovered, then or since. Hence even meat shown to be clear of DES by the USDA's method could still contain dangerous quantities of DES. Little wonder that a senior USDA chemist described the method as a "regulatory control chemist's nightmare."

It was the nightmare, nonetheless, which allowed the DES issue to slumber on for 7 years more. Maybe because of the coarseness of the detection method, the USDA did not bother to test more than a perfunctory number of samples each year, even though DES turned up in a suggestive quantity. In 1966, the USDA found DES in 1.1

percent of 1023 samples. Since some 30 million cattle are slaughtered each year, 1023 is not too healthy a sample from which to draw statistically valid conclusions. A reasonable step to ensure that DES was not contaminating the public's beef might have been to increase the sample size. Yet in 1967 the USDA tested only 495 samples, 2.6 percent of which contained DES. In 1968 545 samples were taken, in 1969 505, and in 1970 only 192.

The USDA's sampling program showed every appearance of dwindling to the vanishing point in a few more years. For 1971, however, the USDA actually increased its sample size to 6000, yet by some strange circumstance found DES residues in none. That, at least, is what USDA Assistant Secretary Richard Lyng told Senator William Proxmire (D-Wis.) on 31 August. The truth was that DES had been detected in ten animals, in quantities up to 37 parts per billion ppb, but a lower official had ordered these results to be suppressed. The explanation proffered when this became known was that the residues were not to be reported until confirmed by a second method of analysis. No second method was available, so the results had not been reported. In his letter of apology to Senator Proxmire, Lyng called the episode an "inexcusable error" and a "gross malpractice."

In a critique of the DES case, Harrison Welford, of Ralph Nader's Center for the Study of Responsive Law, concludes that up until April 1971, some 17 years after DES was first approved for use in cattle, "neither the USDA nor the FDA could make a serious estimate of how much DES was getting into the nation's beef. This result is an object lesson in the ways bureaucracy can silently evade the consumer protection mandates of Congress," Welford says.*

The cases of vaginal cancer discovered in April 1971 suggested that the silent evasion policy had nearly outrun its usefulness. When the USDA admitted in October that it had, after all, been finding DES in beef, the FDA had a crisis on its hands. For a start, the Natural Resources Defense Council filed a suit requiring the FDA to ban DES. The residues of DES being found in beef were confined to the liver and averaged typically 2 ppb—the lower limit of the new detection technique. This concentration of DES amounts to about 0.3 microgram for a 150-gram serving of liver, a quantity that represents an appreciable addition to a woman's own natural supply of estrogen. Whether or not regular exposure to such quantities of DES represents a cancer hazard no one knows, but witnesses from the National Cancer Institute and elsewhere have advised that it would be prudent to avoid such exposure.

The FDA's response to the crisis last October was not to ban DES, but to lengthen from 2 to 7 days the mandatory period between the withdrawal of DES from a cow's feed and the time of the animal's slaughter. The continuing presence of DES residues in beef could have been either because it took longer than 2 days for DES to be cleared from an animal's system or because some cattlemen were breaking the law by neglecting to withdraw DES before slaughter. Which explanation had the FDA acted on? If the latter, a cattleman who neglected to withdraw DES had just the same chance of being caught—about 1 in 5000—whether the withdrawal period was 2 days or 7. Did the FDA then have scientific evidence to indicate that the 2-day withdrawal period was insufficient? Apparently not. In a hearing on 11 November before Congressman L. H. Fountain's (D–N.C.) subcommittee on intergovernmental relations, the commissioner of the FDA, Charles C. Edwards, explained that "sound scientific data" supported the belief that DES is cleared from an animal's system within 2 days. This may have been belief at the top of the FDA hierarchy; at humbler levels there was doubt if even the new 7 day period was long enough for DES to be cleared. According to a position paper drafted on 8 February 1972 by A. J. Kowalk and R. L. Gillespie, scientists in the FDA's Division of Toxicology, a single experiment formed "practically the only evidence to support a 7-day withdrawal period." This study is "weak scientific justification," Kowalk and Gillespie said, because only one animal was used, only a single dose of DES was fed, and

* H. Welford, *Sowing the Wind* (Grossman, New York, in press).

Briefing

Michigan Approves Equal Pay

Cheryl Clark, the soft-spoken woman research associate at the University of Michigan, who 18 months ago began to protest that she should receive the same salary as a man in her research group, last week finally won her case.

In a landmark decision for university salary policy at Michigan and elsewhere, a three-member university panel, which was appointed only after lengthy procedural negotiations, ruled that Clark should receive a retroactive salary adjustment based on a salary of $10,500. She had complained that she was only receiving $9,000 while a male research associate in the same group with comparable and, if anything, fewer responsibilities was being paid $12,500 (see *Science*, 16 July 1971).

The Clark case has been eyed by university administrators all over the country as a key test of salary policies toward women academic employees, who are not now, as it happens, covered by federal wage-hour laws. Significantly, the head of the university panel was labor arbitration specialist Russell A. Smith, and the university's president, Robben Fleming, who accepted the panel's decision, is also known for his work on labor practices.

The Smith panel made two rulings which favored Clark's cause and the cause of university women generally. One was that Clark did not need to prove that her superiors intended to discriminate on the basis of sex. All that needs to be proved is that "a salary differential unfavorable to a female employee exists." The second point was that the burden of proof was on the university, not on the woman bringing suit. Asked for their reaction, a university's women's rights spokeswoman said happiness was not the word for it. "Our general reaction has been whoopee"

However the arbitration panel also ruled that the university was entitled to base salaries on factors including educational background. Since the male employee to whom she compared herself holds a master's degree and she doesn't, Clark then will still be paid somewhat less than he. Asked what she would do with her back pay when she got it, Clark quipped "for tuition to get that master's degree—what else?"—D.S.

half the drug could not be accounted for. And far from justifying a 7-day withdrawal period, the data even from this experiment could be interpreted to indicate that residues of DES will remain in the animal for longer than 7 days.

The practical value of the FDA's 7-day withdrawal period was no less contentious than its scientific basis. Roy Hertz, of Rockefeller University, an adviser to the FDA at the time that DES was banned from use in poultry, opined to the Fountain subcommittee last October that the new 7-day withdrawal period would be even harder to enforce than the 2-day period. He categorized the FDA's new procedures as "unfeasible and impractical and ill-advised" because they would increase rather than reduce the hazards of exposure to DES. The only justification for using DES in cattle would be under threat of famine, Hertz said.

"We are absolutely convinced that, if we do have and enforce sound controls, DES can be used safely and effectively," Edwards proclaimed. But it was Hertz's predictions that were correct. DES, which appeared in 0.5 percent of the samples tested in 1971, is at present being found in 2 percent (admittedly the USDA's testing procedure has also grown more sensitive over the same period). In the week ending on 24 June, DES was found in an astounding 10 percent of all samples tested. As for the threat of famine, under which the saving of grain by use of DES might make some sense, the present wheat surpluses are the highest in a decade, even though farmers were paid $1 billion this year not to grow wheat.

At the hearings before Fountain's subcommittee on 11 November and 13 December, the FDA's basic game plan was to rely on Section 512 (d) (1) (H) the specially created loophole for DES. To objections that, legalisms aside, a potent carcinogen was nevertheless getting into people's food, the FDA's response was, first, that DES is no more carcinogenic than the natural estrogens and, second, that a carcinogen ingested in small enough doses can reasonably be regarded as safe. When it was pointed out that Congress had passed the Delaney clause specifically to protect the public against this kind of judgment, the FDA scuttled back into its Section 512 (d)(1)(H) bolthole. And when asked what would happen if the new regulations failed to prevent DES from turning up in food, Edwards stated categorically that he would have no choice but to ban DES immediately.

Although the FDA is supposed to be protecting the consumer against the manufacturer no less than vice versa, FDA witnesses at the Fountain hearings seemed to be grasping at any straw to defend DES, even the assertion that to ban DES would create more animal excrement, leading to the eutrophication of lakes and streams. A less absurd bulwark of the FDA's defense is the contention that, for any carcinogen, there exists a dose sufficiently low that, for all practical purposes, it is safe. On this issue a diversity of voices is heard. On the one hand, two committees of independent experts have advised that, once a substance is agreed to be a true carcinogen, then none, or for all practical purposes none, of it shall be allowed in food.†

How Little Is Enough?

On the other hand, the Food Protection Committee of the National Academy of Sciences (NAS) states in a 1969 report that under certain conditions people of sound toxicological judgment can ascertain "toxicologically insignificant" levels of a chemical. Any claim by the NAS food protection committee to be an independent, unbiased, and representative body of experts must be weighed against the fact that it is supported by grants from the food, chemical, and packaging industries, and five of the nine scientists who prepared the 1969 report were employed by food or chemical companies.

Which side did the FDA favor., Fountain asked during the DES hearings. "We cannot, with confidence determine what a practical safe level would be of a carcinogen," the FDA said in written response. "However . . . we must be pragmatic." The FDA "accepts and endorses the Delaney clause." On the other hand, "arbitrarily to ban foods that contain miniscule amounts of known [cancer-]inducing factors would lead to chaos and an inordinate waste of vitally needed food." Who could doubt just where the FDA stood on this vital issue?

"If we find the new program is not going to work," FDA commissioner Edwards told Fountain last December, ". . . we will take immediate steps to ban this particular drug from the animal food supply." Five months later, when DES residues had not decreased but quadrupled, it was time for the FDA to deliver on its promise. On 16 June, Edwards announced that he would hold a public hearing in order for the FDA to "make absolutely certain it has all the facts." The only legal mechanism for holding a hearing is for the FDA to propose to withdraw the drug, as has been done. But formalities apart, it appears that even now the FDA has not decided to ban DES. "We have not yet concluded that withdrawal of approval for DES is the appropriate course of action," Edwards said in his 16 June announcement.

The FDA's decision to hold hearings on DES did not please everyone. Fountain dismissed it as "merely a tactic for delaying the regulatory action which the law requires." And the new head of the National Cancer Institute, Frank J. Rauscher, courageously took public exception to the policy of his fellow bureaucrat. Anything that adds to man's carcinogenic burden should be eliminated if possible, Rauscher told Morton Mintz of the Washington *Post*, and it would be "prudent" to eliminate DES pending the outcome of the FDA's public hearing.

Why has the FDA invested so much credit in the defense of a mediocre and probably unwinnable cause? Cynics have observed that the Administration has been visibly concerned about the rising price of meat in an election year, and the banning of DES would cause a small but perceptible rise—3.85 cents per pound—in the price of beef. The circumstance that the FDA's present course of action will probably not lead to a decision on DES until shortly after 7 November does not in itself invalidate this explanation. Another consideration the FDA may have in mind is that if they cannot hold the line with DES, which has a legal loophole tailored for it, a lot of other chemicals may fall domino-like into the jaws of the Delaney clause: "DES will not be the only substance to generate these kinds of issues," Edwards complained darkly to Kennedy's subcommittee. More important, perhaps, the defense of the carcinogenic food additive is a self-sustaining activity, from which the FDA can withdraw only at the price of admitting that the critics were right all along.

—NICHOLAS WADE

† The two committees are the Ad Hoc Committee on the Evaluation of Low Levels of Environmental Chemical Carcinogens, which reported to the surgeon general on 22 April 1970, and the Panel on Carcinogenesis of the FDA Advisory Committee on Protocols for Safety Evaluation, which reported in December 1969. The former committee, chaired by Umberto Saffiotti of the National Cancer Institute, said zero carcinogens should be allowed in food; the latter committee, chaired by Norton Nelson of the New York University Medical Center, opted for "levels which are the practical equivalent of zero."