of the military situation on the eve of Mao's takeover. Some Americans (a total of 27 went to China under this program) had to evacuate to places farther south almost as soon as they arrived in Peking in order to escape the Communists coming down from the north. Nonetheless, according to Wilma Fairbank's book *American's Cultural Experiment in China*, the program resulted in studies that remain of great value for Westerners. Two scholars, for example, translated books on Chinese philosophy and society in collaboration with the authors, who subsequently repudiated their work for the revolution. Thus, writes Fairbank, the program offered a chance to absorb the views of significant Chinese thinkers "while they were still addressing us in our terms."

Now they are addressing us in their terms, and few people have a very good idea of what that is ultimately going to mean.—CONSTANCE HOLDEN

The Phenformin Ban: Is the Drug an Imminent Hazard?

Phenformin is the only drug ever removed from the market as an imminent hazard

On 25 July 1977, Health, Education, and Welfare Secretary Joseph Califano banned phenformin, an oral anti-diabetes drug, as an "imminent hazard to the public health." This was the first, and so far the only, time an HEW secretary has exercised his power to remove a drug from the market, and Califano's action is being legally contested by a group who says it was unwarranted. The action "opened the door for more drugs to be banned as imminent hazards," says Richard Merrill, who is now at the University of Virginia Law School and who was chief counsel for the Food and Drug Administration (FDA) at the time phenformin was banned. Merrill cautions that it is not clear how wide the door is open, and, in fact, Califano recently denied a petition that the drug Darvon be similarly banned (*Science*, 2 March, p. 857). But since the phenformin case set a precedent, it is worth recounting.

In banning phenformin, Califano acted in part at the urging of Sidney Wolfe, a physician who heads Ralph Nader's Health Research Group. In April 1977, Wolfe hand delivered a petition to Califano demanding that phenformin be immediately removed from the market and estimating that 17 people had been killed by the drug in the past 6 months. Wolfe had become impatient with the pace of the federal bureaucracy. Six months before he wrote his petition, the FDA's advisory committee had recommended that phenformin be removed from the market because of a serious side effect called lactic acidosis, which is sometimes associated with the drug. But it could take 2 years before the drug would be removed if normal procedures were followed. The delay is mainly due to hearings and appeals.

Lactic acidosis had been known for several years to be a side effect of phenformin, although the mechanism by which the drug causes the disorder is unknown. The condition was first discovered 20 years ago, and some doctors suspect that reports of its increased incidence may reflect increased attention to and detection of it. As its name suggests, lactic acidosis results from an excess production of lactic acid by the body's tissues. It is accompanied by weakness, lethargy, rapid breathing, abdominal pain, nausea, and vomiting. It is fatal in about half the cases, but patients who recover have no lingering effects. In addition to being caused by phenformin, lactic acidosis can also be caused by diabetes itself or it can occur in patients who do not have diabetes but have other serious disorders such as heart failure or shock.

Wolfe kept hammering home his contention that patients were dying while the FDA delayed taking action. At that time, the drug was being taken by more than 300,000 Americans and had annual sales of $25 million. The result of Wolfe's actions was a hearing before an FDA advisory committee on the question of whether the drug was an imminent hazard.

Shortly after the hearing, Marion Finkel, the FDA's associate director for new drug evaluation, recommended in a memo that the imminent hazard clause not be invoked. Finkel said the FDA had calculated that phenformin caused lactic acidosis at an annual rate of 0.0125 to 2.0 per 1000 users—a rate 5 to 80 times higher than side effects of other drugs that cause fatal reactions. Yet Finkel admitted that these estimates were shaky and that a new warning label that had been placed on the drug in February of 1977 might have decreased the incidence of this disorder. The new warning label halved the recommended maximum dose (higher doses are more likely to cause lactic acidosis), it mentioned, as did a previous warning label, that the drug is contraindicated in patients with certain conditions such as heart and kidney disease, and it advised doctors to consider phenformin a drug of last resort for use in patients with symptoms of diabetes.

In her memo, Finkel argued that phenformin should not be removed from the market entirely because it is useful for a small group of patients. These are people who have symptoms of diabetes and who do not respond to sulfonylureas, the only other type of oral anti-diabetes agents sold, and who are unable to take insulin, either because they have a physical disability such as blindness, or because they have jobs in which they cannot risk becoming unconscious from hypoglycemic shock following an accidental overdose of insulin. Finkel discussed various options available to the FDA, concluded that an imminent hazard ban would be upheld by the courts, but recommended that the phenformin manufacturers be asked to voluntarily restrict the drug's distribution under threat of removal of the drug as an imminent hazard if the restrictions failed.

> The importance of the phenformin ban is that the FDA is now convinced that the imminent hazard provision is a tool it can use.

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Califano "preferred the option of calling the drug an imminent hazard," Finkel says. Legally, this meant that phenformin's New Drug Application (NDA) was suspended, thus forcing the manufacturers to withdraw the drug from the market. Then an expedited hearing was held to justify continuing the suspension of the NDA. If the imminent hazard ban were not invoked, the hearings would come before the NDA was suspended.

In his order suspending phenformin's NDA, Califano cited four sources of evidence that the drug is hazardous: data submitted by the drug's manufacturers, foreign clinical data, data from a prospective study in the United States, and reports from individual hospitals in the United States, Australia, and Sweden. These various sources of data led to quite different estimates of death rates from phenformin, which is why the FDA's calculated death rate was so imprecise. The argument was that even the lowest estimated death rate was too high.

Opponents of the phenformin ban, who include a group of about 250 doctors and patients that calls itself the Committee for the Care of the Diabetic (CCD), stress the weakness of all of these data. They point out that, at the expedited hearing following Califano's suspension of phenformin's NDA, Administrative Law Judge Daniel J. Davidson dismissed most of Califano's evidence that the drug is harmful. For example, he dismissed as incomplete the foreign clinical data. These data had been obtained by a few trans-Atlantic telephone calls made by the staff of the FDA's general counsel.

Judge Davidson dismissed the data from the prospective study, known as the University Group Diabetes Project (UGDP), after hearing testimony on these data from Samuel B. Beaser, professor emeritus at Harvard University and former chief of the diabetes clinics at Massachusetts General Hospital and Beth Israel Hospital in Boston. Even though two FDA witnesses said at the hearing that the UGDP data were the best available because they came from a prospective study, Beaser argued that the government's "pivotal case" from the UGDP was virtually a textbook example of a person in whom use of the drug was contraindicated.

Davidson dismissed as unreliable the manufacturers' estimates of the risks of lactic acidosis. He accepted, however, data from one U.S. hospital, which were obtained by Frank Davidoff of the University of Connecticut School of Medicine. Davidoff estimated the expected

Soviet Jailings Hit by 2400

Years of hard labor and close quarters are the fate of Yuri Orlov, 55, and Anatoly Shcharansky, 31, two Soviet scientists who were condemned to long prison terms last summer for monitoring Soviet adherence to international agreements on human rights (*Science*, 17 November 1978, p. 731).

Now, in the largest protest of its kind, 2400 U.S. scientists have pledged to end or restrict their cooperation with the Soviet Union until the two prisoners are released. And these protests, according to several U.S. scientists, have already had an impact.

The group, known as Scientists for Orlov and Shcharansky (SOS), includes 13 Nobel laureates and 113 members of the National Academy of Sciences (NAS). They announced their protest at a press conference in Washington, D.C. on 1 March. More than 70 percent of the 2400 signed a pledge "to withold all personal cooperation with the Soviet Union until Orlov and Shcharansky are released." The rest do not foreclose their participation in existing exchange programs, but commit themselves to passing up international conferences in the Soviet Union, to opposing the enlargement of U.S.-Soviet exchanges, and to campaigning against the transfer of sophisticated technology to the Soviets.

Said Nobelist Paul A. Samuelson of the Massachusetts Institute of Technology, one of the signatories: "Recent acts of bureaucratic repression of scholarship and science have done tremendous harm not only to the fabric of the international scientific community but to the power interests of the Soviet Union itself. . . . They [the Soviet authorities] misjudge the realities if they think that, after a brief period of agitation, emotions will settle down and scientists abroad will forget."

One of the organizers of SOS, Kurt Gottfried of Cornell University, said that "scientists were perhaps the first Americans to cross the chasms of the Cold War . . . we are now curtailing these contacts with the deepest reluctance, but the actions of the Soviet government appear to leave us no other alternative."

Since the convictions of Orlov and Shcharansky, says Gottfried, several international meetings in the Soviet Union have had to be canceled, and many others have had greatly reduced attendance. The transfer of technology, especially computers, added Joseph Weizenbaum of MIT, has also suffered. And according to Dan McCraken, president of the 40,000 member Association of Computing Machinery (ACM), the ACM Council has decided "not to cooperate with or cosponsor any meetings held in the U.S.S.R."

Others, however, were skeptical. Said one State Department source: "I personally doubt that a boycott will have the desired effect. Computer sales will be picked up by the Japanese and Germans, and the Soviets will go out of their way to show that they cannot be bullied."

One of the most prominent scientists to get out of the Soviet Union, Veniamin G. Levich, speaking in New York, said that Western critics of Soviet repression should be more careful to avoid exaggerated accusations, because Moscow seeks to undermine the credibility of criticism by exposing exaggerations. "Things in the Soviet Union are bad enough without having to make them seem worse," he said. "Also, when you demand Soviet respect for human rights, you have to be very specific what you mean, because the Soviet authorities constantly praise human rights themselves. But they mean something quite different from what you mean."

And there were other criticisms. Said Larry Mitchell, who runs NAS's U.S.-Soviet Inter-Academy program: "To cut off relations, in the long run, is probably counterproductive. It punishes individual Soviet scientists for circumstances over which they have no control."

But members of SOS, at their press conference, said that the Soviets used exchange programs as rewards for politically orthodox scientists, and that the work of these scientists was often mediocre.

Added Christian Anfinsen, a Nobel laureate biochemist at the National Institutes of Health, "The Orlov and Shcharansky cases were the last straw."—WILLIAM J. BROAD

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annual death rate from lactic acidosis in this country by extrapolating from the number of such deaths in 2 years at the 400-bed Beth Israel Hospital in Boston. Although Davidson concluded that the rate of lactic acidosis is "not susceptible to quantification," he recommended that the phenformin ban should remain in effect.

Donald Kennedy, current FDA commissioner, had to make the final decision, and in November of 1978 he decided to uphold the phenformin ban. This decision and the entire administrative proceedings are being appealed by the CCD. This group was formed 10 years ago in order to contest the controversial UGDP (*Science*, 9 March, p. 986). The CCD, which retains Boston lawyer Neil Chayet, maintains in its appeal that "the Secretary did not meet the statutory conditions for suspension. He failed to recognize the depth of the controversy over the very existence of an undue safety hazard with phenformin and the degree to which information he cited was seriously impeached or grossly unverified by his agency."

The CCD and other opponents of the phenformin ban say that the dangers of the drug are greatly overexaggerated and that the drug is important for overweight adult-onset diabetics who do not respond to sulfonylureas. Of course, these opponents say, overweight diabetic patients should be urged to diet. Weight loss alone can usually control their diabetes. But many of these patients find it extremely difficult to change their eating habits.

In its argument that phenformin is an unnecessary and toxic drug, the government said that if overweight diabetics fail at dieting and if they don't respond to the sulfonylureas, there is always insulin to relieve their symptoms. But, critics argue, insulin is not such a benign drug. Not only is it emotionally difficult and inconvenient for many patients to inject themselves, but the drug may also have undesirable effects. Many medical scientists suspect it causes atherosclerosis. It also may cause weight gain, thereby aggravating the patient's diabetes.

The decision to remove phenformin as an imminent hazard, then, was hardly clear-cut. The American Medical Association criticized Califano's move, and recently the ban was criticized by Charles Edwards, who was FDA commissioner when the UGDP results were first accepted by that agency in 1970. Edwards told the *Medical Tribune* that he finds Califano's action "logically and semantically unintelligible. Imminent hazards are very clear-cut things. When you have a soup contaminated with botulism, that's an imminent hazard. The thalidomide episode posed an issue of imminent hazard. But how can anyone, on the basis of any available evidence, assert that phenformin was an imminent hazard to life? And to do so in the face of scientific controversy about the very nature of the evidence?"

FDA officials argue that Califano's action is not without legal precedent. In three cases involving pesticides, the courts interpreted an "imminent hazard" to include a "substantial likelihood that serious harm will be experienced during the year or two required in any realistic projection of the administration process." Thus, even though the phenformin ban may well have seemed logically and semantically unintelligible, it was not legally so.

Ironically, as many as 3000 patients are still taking phenformin. The drug is now available free of charge to doctors who file an investigatory new drug (IND) application for each patient. Henry Dolger of Mt. Sinai School of Medicine, for example, has 263 patients (out of a total of about 1000 diabetic patients) taking a combination of phenformin and a sulfonylurea. Dolger fills out so many IND forms that the FDA suggested he photocopy his own. He says he has never seen any toxic effects from the drug because he is careful to control the dose. He uses phenformin for patients who no longer respond to sulfonylureas alone. Calling phenformin an investigatory new drug is the FDA's way of restricting its distribution, Finkel says.

The only countries besides the United States that have banned phenformin are Canada and Norway, and these countries allow on the market another similar drug for patients who do not respond to sulfonylureas.

Critics of the phenformin ban say that it was a completely political decision. On the other hand, Kennedy argues that the adverse reaction data on the drug are very clear, that the manufacturers of phenformin are not contesting the decision, and that the University of Pennsylvania, Yale, and Emory University had already stopped using phenformin before the ban. The CCD and the Joslin Clinic in Boston are the only ones still pro-phenformin, Kennedy says.

At this time, the issue is, or seems, dead. The drug is off the market and there is very little chance it will come back on. But, Merrill says, the importance of the phenformin ban is that the FDA is now convinced that the imminent hazard provision is a tool it can use.

—GINA BARI KOLATA

Yankee Know-How and the Oil of Olé

One well-publicized outcome of President Carter's recent 3-day visit to Mexico was the agreement between countries to start negotiations on the price of oil and natural gas. Yet more than that came out of Mexico City. Carter and Mexican President José Lopez Portillo also struck a series of agreements giving Mexicans freer access to Yankee technology.

According to Benjamin Huberman, assistant Director of the White House Office of Science and Technology Policy (OSTP), one set of agreements will cover energy. Included will be the exchange of conservation techniques and of research findings on fossil, nuclear, solar, and geothermal energy sources. Projects will range from prospecting for uranium by satellite to the use of the *Glomar Explorer* for deep-sea oil exploration.

Another set of agreements will cover the development of arid lands and the control of desertification—a common problem over vast areas of the U.S.-Mexican border. Still another will give Mexicans access to U.S. research and development work in the industrial sector (including programs of the U.S. Bureau of Standards), work on railroads, and work on new agricultural products.

One such product with potential for both countries, says Huberman, is made by jojoba (*Simmondsia chinenis*), a desert bush that produces a wax that can substitute for sperm whale oil—an important ingredient of perfumes. Another is the desert shrub guayule (*Parthenium argentatum*). It produces a natural rubber that can be used for airplane tires and radials, and it grows in both Mexico and the United States. Congress recently passed a bill that would sink some $30 million into guayule research and development (*Science*, 27 October 1978). The U.S.-Mexican accords, says Huberman, would make that research a joint venture.

Responsibility for carrying out the accords will fall mainly to the U.S. Institute for Technological Cooperation, an agency proposed by Carter that will, when established, aid in the movement of U.S. technology into de-

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