A Prescription for Monitoring Drugs

Three-year study finds that the United States needs a comprehensive system—outside the FDA—to study drugs on the market

One of those orphans of reform—in this case the drive to make prescription drugs safer—appeared on Capitol Hill in January, and none of its rightful guardians seemed ready to accept custody.

The orphan was a report, released on 23 January, written by the Joint Commission on Prescription Drug Use. It recommends that the United States create a system to keep watch on drugs after they have been approved as safe by the Food and Drug Administration (FDA). This "postmarketing surveillance" of drugs was not being carried out effectively 3 years ago when the Joint Commission began work. Now, the authors of the report say that, although the FDA has improved its monitoring program enormously, more must be done.

The Joint Commission made a second major point. No national institution today studies the use of prescription drugs as a phenomenon in its own right. Most research is directed toward discovering a new commercial product, or meeting regulatory requirements. As a result of this neglect, subtle clues about the unexpected good or bad effects of drugs are being overlooked. Diethylstilbestrol (DES) offers a classic example of the negative side of this problem. This drug was prescribed widely for pregnant women to prevent miscarriages. Although research done as early as the 1950's produced clues that DES might have serious side effects, no definitive case against the drug was presented until the 1970's. It has now been demonstrated that the children of the women who used diethylstilbestrol have a heightened risk of developing cancer or problems of the reproductive system.

Occasionally a familiar drug turns out to have a new and unexpected beneficial effect. One commission member mentioned the sulfanomids, which were originally used to treat bacterial infections. Hospital staffers noticed that the drugs in this family also acted as diuretics, a chance observation that led to the development of modern chemical derivatives used to treat high blood pressure. Propanolol is another example. It was originally approved only for treatment of arrhythmias caused by a vascular tumor. Physicians noticed that it seemed to have other good effects, and it was subsequently approved for use in the treatment of angina and hypertension.

Drugs are so important to the practice of medicine, the Joint Commission concludes, that the United States should create an independent, nongovernmental institution devoted entirely to research on pharmacology. Kenneth Melmon, chairman of the commission and head of Stanford University's department of medicine, said that the cost of the new program would be about $10 million a year—about the price of a freeway interchange in California. The support should not come from any single source, he said, so that the proposed new center for drug surveillance would not be swayed by any particular interest. No one has rushed to accept this opportunity to become a big financer of drug-related research.

One of the report's sponsors, Senator Edward Kennedy (D-Mass.) allowed the Joint Commission to use his hearing room to hold its press conference, but he himself failed to make an endorsement, or even an appearance. (He is chairman of the health subcommittee of the labor and human resources committee.) It was the day after Kennedy lost the Iowa caucus, and he was preoccupied with campaign problems. A staff aide, David Riemer, who spoke in Kennedy's behalf, stopped short of embracing the conclusions. He said that they were "consistent" with the goals of a bill rewriting FDA's authority (S1075) which Kennedy sponsored. The bill, which passed the Senate last fall, gives the FDA authority to monitor and regulate drugs on the market, and asks that the FDA consider Melmon's report when it writes regulations on postmarketing surveillance. Unlike the Joint Commission, Kennedy's bill emphasizes an enhanced FDA and makes no allowance for an independent research agency. Kennedy's bill has been introduced in the House, but it is making no progress.

> Kenneth Melmon, chairman of the commission, said the new program would cost about $10 million a year.

Kennedy is considered the father of the drug study; it was launched after he challenged the drug manufacturers and prescribers to come up with a plan for postmarketing surveillance. The financial support came from eight private medical groups, chiefly from the Pharmaceutical Manufacturers Association. The funds were put into a special trust account to avoid charges of conflict of interest, and commission members were chosen by Kennedy, the secretary of the Department of Health, Education, and Welfare, and the president of the Institute of Medicine (IOM).

The IOM may be the most interested of the three in the commission's recommendations. The government, meaning in this case the FDA, does not seem eager to have another quasipublic agency working within its territory. A spokesman for FDA Commissioner Jere Goyan said that he had not read the report yet. Another FDA official thought it unlikely that the FDA would seek to have the report published in the *Federal Register*, as the authors requested.

Even the Pharmaceutical Manufacturers Association, the chief financer of the study, is taking its time to decide what it thinks. It may not like the recommendation that research be done on the effectiveness of "old" drugs already on the market. The concern expressed by one industry official is that "sooner or later somebody will get into the business of rating drugs—drug A versus drug B—and that would be very controversial." The consumer and public interest groups are leery because they obtain information and wield power through the political system. A drug-monitoring center established outside the government, no matter how well designed, would be less responsive to the consumer lobbies than one run by the bureaucracy. In their view, this is a big flaw in the Joint Commission's proposal.

These disparate interests—manufacturers, physicians, consumers—were

0036-8075/80/0222-0853$00.75/0

represented on the Joint Commission; each group nominated its own candidates. They managed to reach unanimous conclusions in the report, but this unanimity is not present in the constituencies that nominated them. There is one general exception. Everyone seems to agree that the nation needs a comprehensive and systematic program to detect unexpected reactions to prescription drugs. That need was brought home again last month.

By coincidence, the same week this report was being released, an apt illustration of the problem it addresses came to light. On 16 January, the FDA decided in an emergency move to pull a drug called Selacryn (generic name: ticrynafen) off the market because it is unsafe. Only 8 months earlier, in May 1979, the FDA had given its approval to the manufacturer, Smithkline & French, to put Selacryn on the market. The company moved aggressively to advertise its product, which is designed to control high blood pressure and fluid retention, because of millions of potential users. During its brief moment in the sun, Selacryn may have been taken by 250,000 American sufferers of hypertension. By mid-January, the FDA and the company had tabulated some unexpected associated casualties: 52 cases of liver damage, including 30 cases of jaundice, and five deaths. It is not clear how many of the deaths were directly caused by the drug.

The FDA and company officials are reluctant to discuss details at present because an investigation is now in progress. The responsible FDA official, Judith Jones, director of the division of drug experience, says that Selacryn appears to have produced bad effects once in every 1000 to 5000 users. She does not think that a more elaborate postmarketing surveillance program would have identified the problem much sooner.

Sidney Wolfe, director of the Health Research Group (a Ralph Nader satellite), thinks that the Selacryn case illustrates the inadequacy of FDA's premarketing as well as postmarketing efforts. Wolfe says the official data he has seen suggest that the drug was tested according to common procedures on only 533 people before it was released. He thinks this was not a large enough population to ensure the safety of the enormous population of potential users. Yet he also says the case is "a good example of how, despite all the handicaps the FDA has, once they got wind of trouble, they moved reasonably quickly."

Wolfe places the burden on the company, for he thinks it should have sent a "red flag alert" to the FDA no later than November 1979 warning that the drug was producing serious reactions. He claims to have spoken with a physician who gave the company strong evidence of trouble in mid-September, and he points out that the company's *routine* quarterly report on Selacryn filed in November mentioned 12 cases of liver damage and 40 cases of renal failure. The law stipulates that a manufacturer must pass along to the FDA within 15 working days any report of unexpected side effects. The alert, it appears, was not raised clearly until December.

A spokesman for Smithkline & French said, "We believe we acted responsibly." He cited an FDA press release given out in January praising the company for its cooperation.

The FDA has several methods, none highly developed, for catching problems after a drug has gone to market. Most of its information comes from the drug companies. They are required by law to report on adverse effects for the first several years after a new drug has been released for general use. Under a separate program, called "spontaneous reporting," physicians are asked to alert the FDA of any problems they encounter with newly released drugs. The FDA receives about 10,000 reports a year from the companies and about 2000 a year from physicians. In addition, the agency has recently commissioned a number of larger than usual studies of drug use through its own contracting authority and through its ability to pressure the drug companies to do safety related research.

The FDA follows these reports as best it can. It tries to sift out the critical warning signs and pass the information along to physicians, but it cannot always stay

Army to Lose Overseas Labs

A government plan to reduce the number of Americans that it employs overseas has landed with disproportionate effect on the tropical disease research programs conducted by the Army and Navy.

Just at a time when a new American military presence overseas has become a distinct possibility, the Office of Management and Budget (OMB) has directed the Walter Reed Army Institute of Research to close down or contract out the work of its six overseas medical research laboratories and the Navy to cut loose its laboratories in Cairo and Manila.

The Walter Reed Army Institute of Research, which has a long tradition of tropical disease research, is somewhat distressed at the prospect of being shorn of its overseas laboratories. The OMB's action will severely limit the military's ability to control infectious diseases and will make it hard to recruit tropical disease specialists in the future, the institute believes.

The military medical laboratories have made important contributions to tropical disease research, many of which have benefitted the host country as well. The laboratories also have a significant diplomatic dimension. The Navy's medical unit in Cairo was the only American presence in Egypt during the critical period before the Yom Kippur war when official relations were severed; the Army's research unit in Bangkok has played a similar role.

The OMB's aim in closing the laboratories is not money: Since most of the work is to be contracted out, savings will be small. The purpose is the high bureaucratic objective of reducing the number of government employees abroad.

The overall goal is to reduce by 5 percent the 11,000 government employees overseas. The Department of Defense was assigned to cut 300 people. About 120 of these cuts were allocated to the military medical laboratories, a distribution which has the evident appearance of being made according to bureaucratic clout rather than merit.

The 5 percent reduction was ordered by the White House primarily because of a belief that there was a duplication of function among the many government agencies with people overseas. It is generally conceded that the military medical laboratories do not duplicate anyone else's work. Nevertheless, to fulfill the bureaucratic form of the President's original intention, though not its substance, the Army and Navy must hand over their overseas medical research laboratories to contractors.—N.W.

0036-8075/80/0222-0854$00.50/0

on top of events. The agency lacks the staff, the mechanical support, and the mandate to do what it would like.

Melmon thinks the government responded well in the Selacryn case, but he said, "Three years ago, this particular situation wouldn't have been detected as quickly." The FDA has "definitely tuned up" its monitoring of new drugs, Melmon said, largely because of the attention focused on the problem by the Joint Commission and others.

The commission's real concern, Melmon said, was with more subtle matters: delayed side effects, rare effects, the interactions between drugs and combinations of diseases, unexpected therapeutic effects, and the unhurried, objective study of common patterns of drug use. The FDA is not, and cannot afford to be, interested in these things, but an independent research agency could be, he said.

Melmon summarized the commission's reasons for wanting these areas of study assigned to a private institution. First, a private outfit would be more flexible and less goal-oriented than a government agency. It would not be required to justify research in terms of immediate rewards or law enforcement needs. Second, it would be able to tap specialists who, under present conflict-of-interest laws, would not be able to work for the government. Melmon mentioned that most of the members of the Joint Commission would now be barred from serving even as advisers to the FDA because of the government's strict new policy on professional conflicts. The proposed drug surveillance center would be more flexible and better able to solicit expert opinion. Third, the center would be funded from a variety of sources, so as to avoid coming under the sway of any clique or interest group. Fourth, a private institution would have to compete for funds each year more intensely than government agencies must do, and this, he thought, would make the new center a more vigorous intellectual creature. Finally, because it would not be involved in enforcement, the new center would be trusted more readily, both as a recipient of sensitive information and as a provider of sophisticated advice. Speaking of the FDA, Melmon said, "You're always grateful to have a cop around, but you don't want to ask him for societal advice."—ELIOT MARSHALL

Rand Issues Final Alcoholism Report

Authors persist in contention that for less severe cases controlled drinking may be feasible

A few years ago a group of Rand Corporation researchers kicked off a furor in alcoholism treatment circles by suggesting that is is possible for some alcoholics to develop a pattern of moderate drinking.

Now, these researchers have pulled back somewhat on that assertion. In a 4-year follow-up study of their population of 780 male drinkers, the group contends that some alcoholics can return to controlled drinking, but only the ones who were not heavily dependent on alcohol to begin with.

The 361-page, $549,000 report,* paid for by the National Institute on Alcohol Abuse and Alcoholism, leaves room for considerable controversy. The authors say the results are "consistent with our first study"; however, NIAAA officials have been saying that it pretty much confirms what they have always believed: that alcoholics shouldn't drink at all.

The Rand group's original study population was 922 men admitted to eight NIAAA treatment centers in 1973. By the time the 4-year follow-up study was complete, 14.5 percent of the group had died. Of the remaining 780, 28 percent were abstinent, 54 percent still had serious drinking problems, and 18 percent were drinking but without ill effects (nonproblem drinkers). Of these, a little more than half were still drinking a lot—more than four drinks a day—and the rest less than four drinks, or about 2 ounces of ethanol, a day.

The authors assign the problems associated with drinking to two categories. They outline six symptoms of "dependency": morning drinking, tremors (both of which indicate withdrawal), missing meals because of drinking, drinking continuously for 12 hours or more at a time, blackouts, and "loss of control" over drinking. Then there are the "consequences" of drinking—alcohol-related diseases and accidents, and serious problems with jobs or social life.

In their earlier report, the authors were rather liberal in assigning nonproblem (or "normal" as they then called it) status to alcoholics who continued to drink, including in the group men who still showed occasional signs of dependency. In the follow-up study they acknowledge that this was too optimistic, saying they "now realize it would be imprudent to treat any alcoholic with dependence symptoms as in a favorable condition." The authors also make a sharper distinction between "short-term abstainers"—those who stay off the bottle for a period of less than 6 months—and long-term abstainers. They now portray the short-term abstainers as the most erratic and unsuccessful group of those who have changed their drinking habits at all. (An NIAAA official says that it would be more accurate to refer to these people as "short-term drinkers.")

But the study leaves room for considerable controversy.

But despite their new-found caution, the Rand group continues to maintain that "for some alcoholics, especially those under 40 and less dependent on alcohol, nonproblem drinking can be regarded as a form of remission."

That statement is sharply at odds with beliefs prevailing in the government and in private groups concerned with alcoholism. Says Loran Archer, assistant to NIAAA director John DeLuca, "our ma-

*Copies of the report, *The Course of Alcoholism: Four Years After Treatment*, can be obtained for $10 each from the Rand Corporation, 1700 Main Street, Santa Monica, Calif. 90406.

0036-8075/80/0222-0855$00.50/0