A medical report in 1998 estimated that adverse reactions to prescription drugs are killing about 106,000 Americans each year -- roughly three times as many as are killed by automobiles.[1] This makes prescription drugs the fourth leading killer in the U.S., after heart disease, cancer, and stroke. The report included only drugs that were given properly and under normal circumstances, excluding drugs that were administered in error or taken in attempted suicides. (When errors of administration are included, the death toll may be as high as 140,000 per year.[2] Such errors include prescribing the wrong drug or the wrong dosage; giving medications to the wrong person; giving medications to the right person but in the wrong quantities or the wrong frequencies, and so forth.)

According to the 1998 report, which analyzed the data from 39 separate studies conducted over the last 32 years in U.S. hospitals, 3.2 out of every 1000 (or 3200 per million) hospital patients die from adverse reactions to prescription drugs. Of the 106,000 people killed each year by prescription drugs in the U.S., 41% (43,000) were admitted to the hospital because of an adverse drug reaction; the other 59% (63,000 people) were hospitalized for some other cause but developed a fatal reaction to prescription drugs they received while hospitalized. In the U.S. in 1994, there were 33,125,492 hospital admissions.

The sale of prescription drugs has more than doubled in the U.S. during the past 8 years. In 1990, Americans spent $37.7 billion on prescription drugs; in 1997, national spending on prescriptions reached 78.9 billion.[3] Prescription drugs are the fastest-growing portion of health-care costs, having risen at the rate of 17% per year for the past few years.[3]

Urging physicians to prescribe particular drugs -- especially new drugs -- is a huge business. According to the NEW YORK TIMES, the sales force of the largest 40 drug companies has “exploded” in recent years.[3] In 1994, there were 35,000 full-time “detail people” employed by drug companies to visit doctors and describe pharmaceutical products; by 1998, the number had grown to 56,000 -- one sales person for every 11 physicians.[3] Drug companies spent $5.3 billion in the first 11 months of 1998 sending their “detail people” into doctors’ offices and hospitals, plus another $1 billion putting on “marketing events” for doctors.

Not all adverse reactions to new drugs can be anticipated or avoided under the present system, according to medical experts. “It is simply not possible to identify all the adverse effects of drugs before they are marketed,” say three physicians writing in the NEW ENGLAND JOURNAL OF MEDICINE.[4] In fact, “Overall, 51% of approved drugs have serious side effects not detected prior to approval.”[5]

Side effects from new drugs cannot be anticipated for 2 main reasons: (1) Individuals vary greatly in their reactions to chemical substances; and (2) drugs are tested on only 3000 or 4000 people before they are marketed, so rare side effects may not appear in such a small group but may become painfully obvious when millions of people start taking the drug. Even a few years ago, drugs reached a mass audience slowly, providing time for unexpected side effects to show up in relatively small numbers of people. But today drugs are marketed directly to consumers via TV, so a huge market for a new product can be created quickly and side effects can appear in large numbers of people. The sexual potency drug, Viagra, provides an example of this phenomenon. Within a few months of its introduction, several million people began taking Viagra, and many serious side effects, including fatalities, suddenly appeared.

Despite the widespread knowledge that half of all new drugs will cause serious side effects in some people, neither the government nor the drug companies systematically collect information on adverse reactions to new drugs. Even when it is recognized that a new drug will be given to many patients for many years, rarely are systematic post-marketing studies carried out.[4]

In the U.S., there is no formal procedure for monitoring drug safety. If physicians became aware that a new drug had killed or maimed one of their patients, or caused an allergic reaction, they may report it but they also may not. As reports filter into the U.S. Food and Drug Administration (FDA) in hit-or-miss fashion, FDA can revoke the approval of a drug, and sometimes does, but almost never quickly. In December, 1997, the popular nonsedating antihistamine terfenadine was withdrawn from the market because a safer alternative existed without terfenadine's danger of a potentially fatal heart arrhythmia (irregular heart beat). However, by that time terfenadine had been on the market 12 years. Last September the FDA took the diet drugs fenfluramine and dexfenfluramine off the market because of heart valve damage to 31% of those who took the drugs in combination with another diet pill, phentermine (a combination known as fen/- phen) Fenfluramine could also damage heart valves when taken alone. By the time fenfluramine was banned, it had been on the market for 24 years.

A recent commentary by three doctors, published in the NEW ENGLAND JOURNAL OF MEDICINE, contrasted prescription drug safety with airline safety.

Airplanes are built, licensed and flown according to standards set by the Federal Aviation Administration (FAA). But whenever a plane crash occurs, a different agency (the National Transportation Safety Board, or NTSB) steps in to establish the facts and make recommendations for avoiding future crashes. The assumption is that a second, independent agency is needed because the FAA would have a conflict of interest investigating crashes of planes it had approved and licensed.

In drug safety, on the other hand, there is only one agency. The Food and Drug Administration (FDA) approves pharmaceuticals and it also has responsibility for investigating injuries and deaths caused by those pharmaceuticals. As we have seen, FDA has a very limited capacity to conduct surveillance studies, so, in fact, they rely on the drug companies to provide data on deaths and illnesses caused by their own products.

As mentioned above, the diet drug dexfenfluramine was taken off the market in 1997 because, combined with phentermine (the fen/- phen diet- pill combination), it damaged heart valves.[4] When the FDA learned that dexfenfluramine was dangerous, the agency had no good data on the total number of people harmed. At the time, the director of FDA's Office of Epidemiology and Biostatistics said, "We've done what is necessary to determine there is a problem. Other information is up to American Home Products [which marketed dexfenfluramine] to find out." Of course American Home Products had little incentive to investigate the number of problems caused by its product.

The three doctors comment, "Given the litigious climate surrounding issues of drug safety, information from investigations conducted by parties with vested interests is unlikely to be impartial and is seldom publicly available to improve future decision making."

The three doctors say an independent drug safety board -- analogous to the National Transportation Safety Board -- is needed to study deaths and illnesses from drugs. They point out that FDA officials spend up to a year of their lives evaluating a drug before approving it for marketing "and it is unlikely that those who recommended a drug for approval could later conduct a dispassionate evaluation of possible harm due to that drug."

According to a recent commentary in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, a competent drug safety program would have four parts:

1. A program to monitor all adverse effects from prescription drugs and annually report the number of injuries and deaths and their likely causes. Currently no one keeps such statistics.
A program to monitor side effects from new drugs. Presently, the FDA's Division of Pharmacovigilance and Epidemiology (DPE) has a staff of 52 people, but only 8 of those have MD degrees and only one has a Ph.D. in epidemiology. This small group collects anecdotal information about side effects of new drugs, but hasn't the resources to be systematic or thorough.

The problem with anecdotal information is that only about 1% of adverse drug reactions get reported in this way. For example, the FDA received an average of 82 reports each year about adverse reactions caused by the drug digoxin. This relatively small number of reports seemed to indicate that digoxin was not a big problem. However, a systematic survey of Medicare records revealed 202,211 hospitalizations for adverse reactions to digoxin during a seven-year period.

When FDA's DPE identifies a drug problem, they can only pass the information along to the division of FDA that approved the drug. That division can require the manufacturer to develop additional information. However, "The most common corrective action is a change in the product disclosure label or package insert."[5] The question then becomes, are such warnings effective?

The third part of a competent drug safety program would make sure that safety information is being disseminated and heeded by physicians. FDA currently has no such program. "The limited information available, however, suggests that some important safety information--such as boxed warnings on drug disclosure labels--either was not received or had little effect. For example, one outcome of the protracted debate over the safety of the sedative triazolam was a new drug label warning that it should be prescribed for only 7 to 10 days. Several years later an FDA task force reported that 85% of the prescriptions were being written for longer periods.... Neither the FDA nor any other agency has an organized program to find out whether the important warning messages are achieving their intended purpose of protecting the public and, if not, discovering the cause."[5]

The fourth part of a competent drug safety program would aggressively seek out information about unsuspected adverse reactions to drugs. Instead of waiting passively for anecdotal information to filter in, the government needs to aggressively look for drug involvement in reported birth defects, heart problems and other common disorders that are frequently caused by prescription drugs. In the same way that the world's public health specialists aggressively seek out new strains of influenza, FDA needs to be aggressively seeking out new side effects of drugs.

Rather than strengthening the U.S. government's drug safety programs, the present Congress has recently diminished the powers of the FDA to monitor drug safety. Congress now allows drug companies to pay fees which FDA uses to speed up the approval process for new drugs. As a result, during 1996-1997, FDA approved 92 new drugs for market -- twice the previous rate. However, Congress specifically prohibited FDA from using any of the new money for monitoring drug safety.[4]

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Descriptor terms: pharmaceutical drugs; hospitals; drug industry; fenfluramine; dexfenfluramine; airline safety; phentermine; fda; faa; ntsb; fen/phen; fen-phen; drug safety;