higher proportion of individuals who are, for perhaps still unknown reasons, prone to come down with Guillain-Barré disease. That latter theory may prove difficult to explore.

The extent of Guillain-Barré cases among the vaccinated caught federal health officials by surprise. Before launching the immunization campaign, they had conducted the largest clinical trials in the history of vaccination drives—ultimately involving some 7000 individuals—and had seen no reason to expect much in the way of side effects beyond transient fevers and sore arms. They had also conducted a survey of the medical literature since the early 1950's and found only about a dozen reports of neurologic disorders in temporal association with influenza vaccination. According to Sencer, nothing prepared him for the extent of Guillain-Barré syndrome that has now been found. That should serve as a sobering reminder that mass vaccination campaigns aimed at tens or hundreds of millions of people may cause side effects that can't be detected in clinical trials of a few thousand individuals. Some observers suspect that previous vaccination efforts—aimed at other diseases as well as influenza—may have caused cases of Guillain-Barré syndrome that were simply not detected.

The decision to suspend the campaign was made easier by the absence of significant influenza activity anywhere in the country. No one is quite certain what to make of the fact that very few cases of influenza, either swine flu or other strains, have been detected this winter. (Those "flu" cases that keep felling one's friends and family are apparently not bona fide cases but "flu-like" ailments.) Some experts believe that, as each week passes with no appreciable flu, the chances of an epidemic diminish. Others predict that an epidemic—probably of swine flu—will break out in the coming months. But critics predict that the vaccine won't work. "We were told we had a safe and effective influenza virus vaccine," says J. Anthony Morris, a former federal vaccine scientist. "We now know that it isn't safe. And if a swine influenza epidemic occurs, we will then learn that it is not effective."

If no epidemic occurs soon, the immunization campaign is apt to be over for all practical purposes no matter what the Guillain-Barré investigation reveals. The program was running out of steam anyway and this latest controversy is not apt to energize an apathetic public to get shots. Many health leaders fear that the troubles of the influenza campaign may cause a public backlash against other vaccination programs, many of which are already lagging. But office wits at CDC see a silver lining in their cloud of troubles. They joke that abandonment of the influenza campaign will free them to devote full energies to their next major project—a massive drive to immunize all Americans against Guillain-Barré syndrome.—PHILIP M. BOFFEY

Adverse Drug Reactions: Monitoring Needed of Drugs on Market

"We simply don't know how different kinds of doctors use different categories of drugs; we don't know the true incidence of adverse reactions nor do we appreciate the very real benefits of appropriate drug usage," Senator Edward M. Kennedy (D–Mass.) declared recently while announcing the formation of a Joint Commission on Prescription Drug Use* which is supposed to find a solution to the problem. "Millions of dollars, public and private, are spent to assure that a product is safe and effective for a specific purpose *before it is marketed*," Kennedy observed, but "once marketed, a physician may use a drug in any dosage, for any purpose—whether or not that purpose has been scientifically evaluated."

Although the idea for it was Kennedy's, this commission is a nongovernmental body with most of its money coming from the very people who make the drugs that sometimes cause adverse reactions—the drug industry via the Pharmaceutical Manufacturers Association (PMA). To preclude charges that the commission is stacked steps were taken to minimize the industry's role in selecting members and to ensure that PMA cannot withdraw its support if commission decisions seem to be going against it. As a result most observers are satisfied that the commission begins with neither a strong pro- nor anti-industry bias.

Drug laws in this country are predicated on the assumption that, if regulations governing premarket clearance are sufficiently stringent, then all drugs that make it to the marketplace automatically will be safe and effective as promised. Unfortunately, that assumption simply is not valid. In fact, there is abundant evidence to support the observation that, once a drug enters widespread use, it is likely that unanticipated side effects or unexpected benefits will be observed. Kenneth L. Melmon, who was chosen chairman of the commission at its first meeting on 30 November, notes, "No system in the world will reveal all activities of biological importance of a drug pre-marketing."

Melmon, a clinical pharmacologist at the University of California Medical School in San Francisco, has long favored the development of a system to monitor drugs in general usage—a so-called phase IV study. In an interview with *Science*, he cited a few examples of drugs with unanticipated toxicity or efficacy that might have been detected reasonably soon after marketing had there been a workable program of drug surveillance.

*The members of the Joint Commission on Prescription Drug Use, and the organizations that nominated them, are:

American Academy of Family Physicians: John F. Derryberry, Chairman, Public Relations Committee, AAFP, and Phillip D. Cleveland, Commission on Health Care Services, AAFP

American Medical Association: F. Gilbert McMahon, Tulane University School of Medicine, and Daniel Freedman, University of Chicago

American Society for Pharmacology and Experimental Therapeutics: Daniel L. Azarnoff, University of Kansas Medical Center, and Kenneth L. Melmon, University of California, San Francisco

American Society for Clinical Pharmacology and Therapeutics: Edward A. Carr, Jr., State University of New York, Buffalo, and Marcus M. Reidenberg, Cornell University Medical School

American Hospital Association: William E. Hassan, Jr., Peter Bent Brigham Hospital, and Robert N. Heyssel, Johns Hopkins Hospital

Phamaceutical Manufacturers Association: Foster B. Whitlock, Johnson & Johnson, and Monroe Trout, Winthrop Laboratories

American Pharmaceutical Association: William R. Bacon, President, APhA Academy of Pharmacy Practice (1972–73) and practicing pharmacist, and Harold H. Wolf, University of Utah College of Pharmacy

American Society of Hospital Pharmacists: R. David Anderson, Waynesboro University Hospital, Virginia

Public Members: Marcia Greenberger, Attorney, Center for Law and Social Policy, Washington, D.C., Patricia King, Georgetown University Law Center, and Anthony Robbins, Colorado Department of Public Health.

● Diethylstilbestrol (DES): In the 1950's, DES was given to pregnant women to prevent miscarriage. Now it is known that this drug caused vaginal cancer in the teen-aged daughters of many of those women. The lag time between the giving of the drug and the recognition of its ill effects on offspring was close to 20 years. Granting that in this particular situation some lag is inevitable—the daughters, after all, did have to grow into teen-agers—many pharmacologists be-

Briefing

Breeder, Arms Sales Are Targets of New Lobby Group

New Directions, the new world affairs lobby modeled on the citizens' lobby Common Cause, has announced a first set of priorities that should keep it busy for some time.

First, it wants to mount a campaign that will culminate in a prohibition on nuclear reprocessing in this country, a halt to the development of the breeder reactor, and pursuit of a "soft energy" economy based primarily on solar energy. Second, it wants a reduction of arms sales by this country, whose volume has grown from $1 billion in 1970 to $13 billion in 1976. Finally, it wants to get the world's poor better fed through various means such as increased food aid, rural development in poor countries, and more support for population programs.

Despite these grand aspirations, the press releases bearing the news sank without leaving a trace in the daily press, much to the surprise of New Directions president Russell Peterson. However, as the organization expands it may get more attention, particularly since its announced goals are not far out of line with what Jimmy Carter talked about during the presidential campaign.

Peterson, former chairman of the Council on Environmental Quality, says things have moved apace since the group was launched on 1 October. It has picked up close to 1000 members so far. Plans call for a huge direct mail campaign that is expected to bring in another 99,000 members within a year. The group is looking for a lobbyist to send to Capitol Hill, and has four volunteer lawyers drafting legislation for introduction by friendly members of Congress. A giant meeting of all the New Directions task forces is planned for April in Washington. The organization also intends to establish a membership group in every one of the 435 congressional districts.

While the ideas New Directions wants promoted are hardly new, they are enjoying unprecedented support judging from the 60-member board, which is studded with famous names associated with science, the environment, overseas development, and world peace. And among the founders of the organization is Cyrus R. Vance, the next Secretary of State.

—C.H.

Tosteson New Harvard Dean: Chicago Bitter About His Leaving

Harvard University president Derek Bok, completing a months long inventory of the nation's medical talent, has decided upon Daniel C. Tosteson of the University of Chicago as the next dean of Harvard Medical School. Tosteson will succeed Robert Ebert who is retiring from the job.

Bok's search for a new medical dean was an unusually personal one in a day when academic leaders are often selected by committees carefully put together to represent the interests of everyone who could possibly have a stake in the choice. In an address to the faculty last spring, Bok, a lawyer who has taken considerable interest in medical affairs, made it clear that there would be no search committee. Although he would seek advice, the decision would be his alone.

Tosteson, who has a reputation as a first-rate investigator in the field of pharmacology and membrane biochemistry and physiology, is also well known as an active player in the world of medical politics. He is a member of the Institute of Medicine and is a former chairman of the Association of American Medical Colleges. Although unwilling to discuss in detail his plans for Harvard Med, Tosteson told *Science*, "Medicine and medical education are going to occur in a changing environment in the years ahead. It is the responsibility of Harvard to shape that change."

Tosteson, who for many, many years was at Duke University, has been at Chicago since 1 July 1975 as dean of the Pritzker School of Medicine and vice president of the university for the medical center. His relations there have been more than successful—indeed, the faculty apparently thought highly of his administrative and leadership abilities—until the day his move to Harvard was announced in Cambridge. Finding a dean these days is not easy, and the Chicago faculty has not taken kindly to the idea of losing a good one after only 18 months. It leaves them, as one of Tosteson's colleagues put it, "with a feeling of having been ditched." Said another, "The reaction to Dan's leaving Chicago has been more bitter than anything I've seen in medicine in a long, long time."

Tosteson said in an interview, "I am leaving because I could not refuse the call of my alma mater. I went to Harvard College and Harvard Medical School. In spite of the great respect I have developed for this institution during the past year and a half, my intellectual roots are in Boston. Also, I have a sense of symmetry, of going back. And I have respect for the tradition of scholarly work at Harvard." And besides, infuriating as it may be, there is a mystique about Harvard that sets it apart. If you happen to want to be a dean, it would be awfully hard to turn down an offer to be chief dean if it came your way.

A week after Tosteson's move to Harvard was announced he went on leave as dean and vice president of Chicago and will spend his time from now until July writing papers—as many as 15—on work he and his colleagues have been doing in his lab. One project of particular interest, Tosteson says, involves analysis of the transport of lithium across cell membranes. Some individuals who suffer from mania have an inherited disorder that precludes normal transport of lithium across red blood cell membrane. This disorder leads to a disequilibrium in the lithium concentration between the cell interior and the surrounding plasma. Lithium, of course, is the drug that, although controversial, has been used with some success in treating manic-depressive disease. Tosteson notes that it is too early to generalize the observations about lithium and membrane transport to clinical questions, but the findings are certainly intriguing. He intends to establish a lab of his own in Boston and is going to try to continue his research. "Otherwise," he says, "you'd go crazy."—B.J.C.

lieve the problem could have been spotted earlier with a good drug reporting system. Vaginal cancer is extraordinarily rare, and so even a handful of cases in young women nationally would constitute a warning blip in the system. But as it was, the problem went undetected until a conspicuous cluster of six or seven cases turned up at one hospital in Boston.

● MER-29: Several years ago a drug called MER-29 was marketed as a cholesterol-lowering agent, the idea being that it would reduce the incidence of myocardial infarction among individuals who were prone to heart attacks. Premarket testing demonstrated that MER-29 did, indeed, lower the concentrations of cholesterol in the blood. What was not apparent then, however, was that it led to the buildup of cholesterol deposits that, in turn, contributed to the lethal infarcts that MER-29 was supposed to prevent. In the absence of a workable surveillance system, the toxicity of the drug was not detected until the problem reached tragic proportions because most physicians whose patients died said, in effect: Isn't that too bad. He had an infarct even though we'd gotten his cholesterol down. Bad luck.

● Propanolol: On the more positive side of the issue, there is the story of the drug propanolol. It was originally approved by the Food and Drug Administration (FDA) for use in this country to treat arrhythmias caused by pheochromocytoma, an unusual vascular tumor. The drug was so effective that subsequently it was approved for control of arrhythmias of whatever origin. That resulted in fairly widespread usage, and with time physicians observed it had other beneficial properties as well. First in Europe and eventually in this country—after much debate and pressure—propanolol was approved for control of the pain of angina and for hypertension. Now, Melmon notes, there are data indicating it may be useful in preventing myocardial infarctions, but it has not been approved for that yet. Here again, Melmon contends, with a good drug surveillance system, the benefits of propanolol could have been noted and proved far more efficiently and quickly than they were.

It is in the context of these situations, times thousands of drugs, that the joint commission must work to design a system for finding out what is going on. Its charge is "to design and recommend the details of a postmarketing drug surveillance mechanism for the gathering of data on adverse drug reactions and new drug uses; and to develop a format, using available data, for reporting annually or every six months on trends in drug prescribing and drug usage."

As Melmon is well aware, the difficulties associated with monitoring drugs in widespread use are tremendous. For starters, the commission will try to find out what information already exists on the prescribing habits of practicing physicians—the epidemiology of prescription drugs. "Industry may already have a lot of this kind of information," Melmon notes. Then, the commission will have to design a protocol for picking up characteristic effects of drugs nationally. Says Melmon, "We frankly don't know if we can do it. It will be damn hard."

Foreign experience tends to bear out Melmon's observation. Britain, for example, has a post-marketing reporting system but its efficacy is questionable. A case in point involves practolol, a relatively new drug meant to do what propanolol does—regularize abnormal heart rhythms—without its side effects. However, it now appears that practolol produces more serious side effects but that physicians, equipped though they were with forms for reporting adverse reactions, failed at first to notice a connection between patients' complaints and the fact they were taking a new drug. A report in the New Scientist (2 December) offers this explanation: ". . . there appears to be evidence that prescribers either ignored their patients' complaints, or failed to consider the possibility that their symptoms (sometimes involving serious damage to sight, hearing, or the gastro-intestinal tract) might be due to the medicine in question."

In order to do its job, the Melmon commission first will have to define the limits of the information it wants and establish criteria for defining drug effects, good or bad. Clearly, every idiosyncratic reaction cannot be taken into account. There needs to be a framework in which to identify patterns. Therefore, the commission members will have to decide how to measure morbidity per X ten thousand or hundred thousand (X to be determined) drug takers. And they will need to devise some way of getting physicians to (i) pay attention to side effects and (ii) report them. Obviously, there is no way to have an effective monitoring system if physicians do not cooperate by reporting adverse effects. Yet, in this litigious climate, there is great fear that physicians will shy away from involvement in anything that might land them in court.

Just defining the problem of adverse drug reactions is, itself, a monumental task. Melmon, who wonders whether willingness to join the commission makes one an "optimist"—believing the job is doable—or just plain "crazy," had this to say about the scope of the definition back in 1971 in the 17 June issue of the *New England Journal of Medicine*: "A drug reaction includes all unwanted consequences of drug administration, including administration of the wrong drug (or drugs) to the wrong patient in the wrong dosage (form, amount, route or interval), at the wrong time and for the wrong disease. Any single 'wrong' may result in unwanted effects. . . ."

A lot has been written about adverse drug reactions during the past several years. There have been estimates, for example, that 18 to 30 percent of all hospitalized patients have an adverse reaction to some drug they are given, that they stay in the hospital twice as long as they otherwise would because of this, and that between 3 and 5 percent of all persons who are admitted to the hospital are admitted *because* of an adverse reaction to a prescription drug they were taking at home. The Department of Health, Education, and Welfare (HEW) has guessed that it costs about $3 billion a year to take care of individuals who suffer toxic side effects from drugs prescribed for them by their physicians.

Are these figures accurate? No one knows for sure. Suppose they are correct, at least approximately. What is anybody doing about it? Not much. Certainly, practicing physicians are encouraged to report adverse reactions to the FDA, but this practice is neither mandatory nor customary and not many do it. Some hospitals—particularly those with strong departments of clinical pharmacology—make a concerted effort to keep track of adverse reactions among their patients. But at best what we have is scattered, anecdotal evidence that all is not well, plus the occasional major fiasco as with DES or MER-29.

The joint commission has 3 years to complete its work. It will not attempt to do any actual monitoring—just try to figure out how to go about it, a task commission members believe to be monumental in itself.

For the past 2½ years, the Senate health subcommittee, of which Kennedy is chairman, has been investigating prescription drug use with an eye to drafting some new legislation governing FDA. Among the legislative proposals is one for the establishment of a National Drug Science Board, composed of nationally recognized experts, to advise the director of FDA on some of the kinds of problems the joint commission is addressing now. But Kennedy recognizes

that it will be a year, maybe two, before the legislation he envisions can work its way through both houses of Congress, while "the problem is with us now." The joint commission should be seen as a way of getting on with the task while the legislative process wends its way.

Kennedy first proposed creation of the commission last May in a speech before the PMA, which represents most of the nation's drug manufacturers. And PMA, trying hard to shed its "bad guy" image with Congress and the public, decided it would not do much harm to sponsor an independent commission to look into things.

Money for the commission—guaranteed at $250,000 a year for the 3 years, with a more than reasonable chance of more if necessary—is being put into what amounts to a blind trust. Each of PMA's approximately 130 member companies will be assessed, according to sales volume, for a total PMA contribution of about $200,000 annually (no one is going to go broke at that rate), with the remainder coming from the American Academy of Family Physicians, the American Medical Association, the American Hospital Association, the American Pharmaceutical Association, and the American Society of Hospital Pharmacists. It gets almost everyone into the act, at least a little.

So did the process of selecting commission members—there are 18—which was designed to preclude its being weighted by any special interests. Thus, a number of organizations, including each of the commission's sponsors, two scientific societies, and a public interest group, submitted nominations and a broad range of points of view are represented among the members who were finally selected. Each nominating group was entitled to one or two representatives on the commission with the exception of the "public interest"—it has three representatives. The final decisions were made by Kennedy, Theodore Cooper, assistant secretary for health, and David A. Hamburg, president of the Institute of Medicine.

Conspicuous by their absence from the group are consumer representatives of the Nader organization, particularly the Washington-based Health Research Group from which Sidney Wolfe, an M.D., and Anita Johnson, a lawyer, watch over both the drug industry and the FDA, which is also notably absent from any involvement with the commission. It is reliably said that PMA president Joseph Stetler was adamant in his opposition to having either Wolfe or Johnson on the commission on grounds that he would "never be able to raise a nickel" from drug companies if they were members, but it is not clear that he actually exercised any veto power on the subject.

Johnson, who says she knows nothing of PMA's opposition, reports that she was asked if she would consider joining the commission, though she does not know whether it was a firm invitation or just a request to put her name on a list. In any case, Johnson says she declined any connection with the group which she expects will issue recommendations that represent a compromise. "I don't see my role as working out a compromise. My job is to defend the consumer," she said, adding that it "clouds the issue" to have so many people on the commission and that it is "ludicrous to think these issues can be batted out in an industry-sponsored panel." Johnson observed that if PMA wanted to do something about adverse reactions, they could more appropriately do it themselves, but then conceded that she would be unlikely to accept industry actions—leaving PMA in a damned if it does and damned if it doesn't position, it would seem, as far as her consumer group is concerned.

Most observers, however—including Johnson—believe that the three public interest members of the commission have impeccable credentials in their defense of consumer affairs.

Just how the joint commission will turn out is anybody's guess but it seems to be off to a satisfactory start. Certainly, its potential for significantly affecting the process by which drugs are regulated in this country is great. And, referring to the commission as a "unique coalition of private and public groups," Kennedy has blessed it in rhetoric with even greater potential. "I believe this must be viewed as an important national experiment," he declared grandly. "Our country is too small to maintain an intransigent approach to the solution of national problems. Neither consumers nor industry, neither government nor academia, has enough talent and expertise to solve our domestic problems alone."

—BARBARA J. CULLITON

Nuclear Partners: Adversity Breeds Trouble Between Dow and Utility

Nearly 10 years ago, in 1967, Michigan's Consumers Power Company and the Dow Chemical Company reached an agreement looking to construction of the world's first and largest major dual-purpose nuclear plant for the generation of electricity and industrial process steam. Consumers Power was to build the nuclear facility at Midland and supply steam to Dow's large and expanding industrial complex there. The two companies hailed the project as innovative and progressive. Its supposed benefits included at least a modest improvement in energy efficiency.

But, impeded by regulatory hurdles and financial difficulties, the project fell far behind schedule. Originally to have been finished by 1975, it is still only about 20 percent completed today, and it will not be fully operating before 1982, if then. Moreover, the warm spirit of collaboration that once marked relations between Consumers Power and Dow has now vanished. As a Dow attorney noted recently at an embittered regulatory hearing, their relationship has become "adversarial and antagonistic," with each company warning that it will sue the other if contractual commitments are not kept. Environmental intervenors have been trying since 1970 to stop the project. They are now convinced that Dow would renounce its contract with Consumers Power except for an implied threat by Consumers to file huge damage claims if, because of such action by Dow, the construction permit is revoked.

But the company takes a risk in standing by the contract, too. The company-owned fossil-fuel boilers with which Dow is now generating power and process steam are old and must be replaced by 1984 if breakdowns that could seriously cripple Dow's Midland operations are to be avoided. Furthermore, the variance in air pollution control standards under which these boilers are being oper-