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THE PROMISE OF PHARMACOEPIDEMIOLOGY

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INTRODUCTION

Since the 1930s a series of tragic adverse drug reactions (ADRs) has placed progressively more attention on the new field of pharmacoepidemiology. The stimulus for the 1938 Food and Drug Act was the marketing of elixir of sulfanilamide dissolved in diethylene glycol, which resulted in the death of over 100 children. The resulting public outcry led to stricter requirements for drug safety (1). In the early 1960s the world experienced the notorious "thalidomide disaster." Mothers who ingested this mild hypnotic (available mostly in Europe) during the first trimester of their pregnancy had an increased risk of delivering a child with phocomelia, i.e. one missing one or more limbs or parts of limbs (2). Fortunately the drug had not yet been marketed in the United States. The resulting Kefauver–Harris Amendment to the Food, Drug, and Cosmetic Act strengthened the requirements for testing of safety and added a new premarketing requirement for proof of efficacy. In the latc 1960s and early 1970s Japan experienced an epidemic of subacute myelo-optic-neuropathy (SMON), later attributed to an antimicrobial drug used for prophylaxis and treatment of traveler's diarrhea—clioquinol (3). During the 1970s practolol was recognized as responsible for an oculomucocutaneous syndrome, but only after one million patient-years of worldwide use (4). In the 1980s ticrynafen, benoxaprofen, and zomepirac were all removed from the US market because of serious ADRs, including death.

As these and other problems developed, the potential of pharmacoepidemiology for addressing them became more clear. For years,

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epidemiologists had been developing and refining the techniques necessary to do research on large populations of people. The application of these techniques to the study of the effects of drugs already marketed promised to prove or disprove the many accusations about ADRs. Pharmacoepidemiology can not prevent ADRs, but it can detect them earlier, minimizing their adverse impact. Another important, although often ignored, function of pharmacoepidemiology is that it can document drug safety.

In this paper we review the current status of pharmacoepidemiology, and discuss some of its future prospects and potential problems. Most of the past work in the field applied the techniques of analytic epidemiology to studies of ADRs. We review these techniques, discuss the special methodological problem that differentiates pharmacoepidemiology from other fields of epidemiology, i.e. the large sample size required, and then describe some of the approaches investigators have taken to address this problem. We next review some opportunities for the field that require further investigation, as well as problems that have prevented its further development. Finally, we conclude with some speculation about where the field may go in the future.

BASIC PRINCIPLES OF EPIDEMIOLOGICAL STUDY DESIGN

Epidemiology is the study of the distribution and determinants of diseases in populations. It began with the study of epidemics (infectious diseases in large numbers of people). More recently, it has expanded to include the study of chronic diseases. In the process, it has developed precise and rigorous methodologies for the study of diseases in large numbers of people. Use of these methodologies for the study of drug use and drug effects is the science of pharmacoepidemiology.

Table 1 presents a list of the major epidemiological research designs available. Associations demonstrated by designs at the top of the table are more likely to be causal than those at the bottom of the table. We discuss each in turn, from the least to the most convincing.

A *case report* is simply a report of a single patient with an exposure and an illness, e.g. a report of an oral contraceptive user suffering from a myocardial infarction. This report serves to generate hypotheses for more rigorous study with other techniques; it does not establish whether the patient is typical either of those with that exposure or of those with that illness.

A *case series* is a report of a series of patients who share either a common exposure, e.g. oral contraceptives, or a common illness, e.g. myocardial infarction. Although those patients are presumably typical of those with that exposure or with that illness, respectively, one cannot conclude from a case

Table 1 Study designs used in epidemiology

1. Randomized clinical trials
2. Prospective cohort studies
3. Retrospective cohort studies
4. Case-control studies
5. Case series
6. Case reports

series that their characteristics are unique to that exposure or illness without a concurrent control group.

Analyses of secular trends compare trends in a purported cause to trends in a purported effect, e.g. a coincident rise in oral contraceptive use and myocardial infarction rates (5). Although parallel trends provide evidence for a causal association, this technique cannot separate the causal factor from the many factors whose trends are also likely to occur, e.g. changes in smoking habits.

Case-control and cohort studies both include concurrent control groups (see Figure 1). *Cohort studies* select patients on the basis of the presence or absence of an exposure and then look for subsequent disease, e.g. they might compare oral contraceptive users to nonusers and look for a difference in myocardial infarction rates (6). Cohort studies are generally used to calculate the relative risk of developing a disease, i.e. the ratio of the incidence of disease in the study group to that in the control group. A relative risk greater than 1.0 means the study subjects are more likely to develop the disease than the control subjects, or that the exposure appears to cause the disease. A relative risk of less than 1.0 means the study subjects are less likely to develop the disease than the control subjects, or that the exposure appears to prevent the disease. A relative risk of 1.0 means there is no association between the exposure and the disease.

Case-control studies select patients on the basis of the presence or absence of a disease and then look for antecedent exposures, e.g. they might compare patients suffering from myocardial infarctions to normal controls and look at the relative rates of antecedent oral contraceptive use (7). Although both case-control studies and cohort studies suffer from many of the same limitations, including difficulty in the control of extraneous factors (e.g. family history), the choice of a control group is more difficult for a case-control study than for a cohort study. Many investigators, therefore, consider case-control studies less definitive than cohort studies. Case-control studies are generally used to calculate odds ratios, estimates of relative risks.

Finally, an *experimental study,* or randomized clinical trial, is one in which

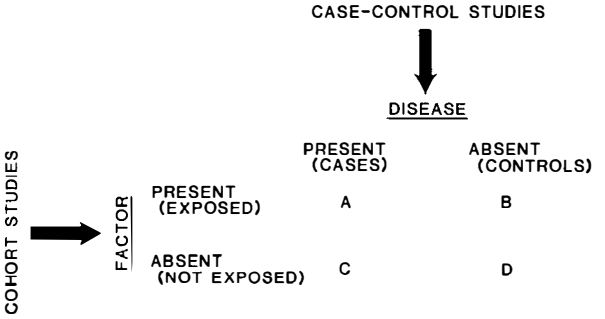

Figure 1 A cohort study compares patients with an exposure to patients without an exposure or with a different exposure, looking for differences in disease incidence. A case-control study compares patients with a disease to patients without a disease, looking for differences in drug exposure.

subjects are randomly assigned to alternative exposures and differences in outcome are observed. For example, women might be randomly assigned to either oral contraceptives or IUD's and the resulting myocardial infarction rates would be determined. The experimental design is by far the most powerful, but as the example demonstrates, it can create logistical and ethical difficulties.

NUMBERS—THE SPECIAL METHODOLOGICAL PROBLEM

Most drugs are studied in 500 to 3000 subjects prior to being marketed (8). This regulation is enforced, even if drug efficacy can be proven in 20 or 30 patients, to ensure the reliability of detecting adverse effects that occur at least once in 100 exposed patients. Therefore, most postmarketing case series, cohort studies, or randomized clinical trials need to include at least 10,000 subjects in order to add sufficient sensitivity to be worth attempting. This requirement obviously raises considerable logistical problems in designing and conducting such studies. Before we explore past solutions to these problems, however, we illustrate how sample size calculations are made for epidemiological studies. We separately present the approach one would use for: (*a*) a case series, (*b*) a cohort study or randomized clinical trial, and (*c*) a case-control study.

In a case series in pharmacoepidemiology, one generally investigates whether a disease occurs more frequently than some predetermined incidence in exposed patients. Most often the predetermined incidence is zero, and the researcher looks for any occurrences of a rare illness. To establish drug safety, a study must include a sufficient number of subjects to detect the

elevated incidence, if it exists. More precisely, one needs to examine the upper limit of the 95% confidence interval for an observed frequency of zero. In most case series, researchers assume a Poisson distribution (i.e. that the frequency of the event is vanishingly small) and use that to calculate confidence intervals. (See Ref. 9 for published tables.) A helpful guide is the "rule of threes," which states that if no event of a certain kind in a population of size X is observed, a 95% certainty exists that this event occurs no more than $3 \div X$ (10). For example, if 500 drug-exposed subjects are studied prior to marketing of a particular drug, and no reactions are observed, then a 95% certainty exists that any unobserved medical event occurs in fewer than 3 in 500 subjects, or that it has an incidence less than 6 in 1000. A postmarketing study of 10,000 subjects could exclude events that occur in more than 3 in 10,000, or 1 in 3333, subjects.

More frequently pharmacoepidemiologists study more common diseases to determine if any of them has a higher incidence in patients taking a study drug than in control patients. This research requires a cohort study, comparing a drug-exposed study group to a control group. To calculate the required sample size, one must specify four variables (11, 12): (*a*) the α, or type I error that is tolerable, i.e. the probability of declaring there is an association when in fact one doesn't exist, conventionally set at 0.05; (*b*) the β, or type II error, that is tolerable, i.e. the probability of declaring there is no association when in fact one exists, conventionally set at 0.1 or 0.2; (*c*) the smallest relative risk one wants to be able to detect; and (*d*) the incidence of the outcome in the control population. Table 2 presents the sample sizes needed for each of the two study groups in a cohort study for various incidence rates in the control group and for possible values of relative risk one might want to be able to detect, assuming an α of 0.05 (two tailed) and a β of 0.2. For example, if one wants to detect a doubling of risk (a relative risk of 2.0) of a disease with an

Table 2 Sample sizes for cohort studies[a]

Relative risk	Incidence of outcome in control group					
	1/50,000	1/10,000	1/5,000	1/1,000	1/500	1/100
2.0	1,177,645	235,500	117,732	23,518	11,741	2,319
2.5	610,627	122,108	61,043	12,191	6,084	1,199
3.0	392,544	78,496	39,240	7,835	3,909	769
5.0	147,201	29,432	14,711	2,935	1,463	285
7.5	78,969	15,788	7,890	1,572	782	151
10.0	53,304	10,656	5,324	1,060	527	100

[a]Calculations are based upon a two-tailed alpha of 0.05, a beta of 0.2, and 1 control subject per expoed subject. Calculated using the formulas presented in Ref. 11 and 12.

incidence in the control group of 1 in a 100, a cohort study would require 2319 subjects in each study group. If this disease occurred in only 1 in a 1000 subjects in the control group, then 23,518 subjects would be needed in each group. If one wanted to detect only a relative risk of 5.0, then the corresponding sample sizes would be 285 and 2935, respectively.

To calculate sample sizes for a case-control study, one similarly needs to specify four variables: (*a*) α, (*b*) β, (*c*) the smallest relative risk you want to be able to detect, and (*d*) the prevalence of the drug exposure in the undiseased control group (11, 12). Table 3 presents data similar to those in Table 2, but for a case-control study. As the prevalence of exposure in the control group and/or the relative risk one wishes to detect increases, the sample size needed generally decreases. Importantly, a case-control study often requires fewer subjects than a cohort study, since the prevalence of a drug exposure of interest is often more common than the incidence of a disease of interest.

CURRENTLY AVAILABLE SYSTEMS

Traditionally, postmarketing studies of drug effects have been performed by physicians voluntarily reporting ADRs in the medical literature, to pharmaceutical companies, or to governmental agencies. This approach has the disadvantages of case reports listed above. However, it is inexpensive, it is useful for generating hypotheses about ADRs, and it is currently the only feasible method of detecting very rare ADRs. In the United States, pharmaceutical manufacturers who receive reports of ADRs are obligated to report in turn to the FDA. The FDA's spontaneous reporting system receives over 11,000 adverse drug reports annually from physicians and pharmaceutical companies: 80% of these reports come from pharmaceutical companies (13).

Table 3 Sample sizes for case-control studies[a]

Relative risk	Prevalence of drug exposure in control group					
	1/1000	1/100	5/100	10/100	25/100	50/100
2.0	23,596	2,398	516	283	152	137
2.5	12,239	1,247	272	151	85	81
3.0	7,870	804	177	100	58	58
5.0	2,954	305	70	41	27	31
7.5	1,587	165	39	24	17	22
10.0	1,072	113	28	18	14	19

[a]Calculations are based upon a two-tailed alpha of 0.05, a beta of 0.2, and 1 control subject per diseased subject. Calculated using the formulas presented in Ref. 11 and 12.

When compared to three uncontrolled case series, the FDA's spontaneous reporting system identified most of the same information (14). In Great Britain, the comparable system involves physicians' identifying potential ADRs and then completing and submitting a yellow business reply card. This yellow card system identified the increased risks of thromboembolism from oral contraceptives, hepatitis from methyldopa, jaundice from halothane, and extrapyramidal side effects from metoclopramide (15, 16). Importantly, however, it did not detect the practolol-induced oculomucocutaneous syndrome (4). Other countries have similar programs, and the World Health Organization collects and combines this information from multiple countries. Also, case reports in the medical literature continue to be an important source for suspected ADRs, although these ADRs are frequently not confirmed on subsequent study (17), and in one review of the literature only 19% of the reports had all of the necessary information (18). A checklist of data that should be included in any published case report has been developed (19).

In response to the practolol problem, Dr. William Inman, who had run the yellow card system, recently developed the innovative "Prescription Event Monitoring" system in Great Britain (20). Copies of all prescriptions for drugs of interest are obtained from the Prescription Pricing Authority and used to identify patients who had received the drug of interest. Questionnaires are then sent to the prescribers, requesting information regarding all medical events following drug exposure. The frequency of these diagnoses is compared to that in a control group of patients exposed to a similar drug, or to the same patients before or after cessation of their exposure. Preliminary experience with this system suggests that it will be useful.

Hospital-based cohort studies of short-term expected and unexpected ADRs in hospitalized patients have been conducted by the Boston Collaborative Drug Surveillance Program (BCDSP) (21, 22). These studies have provided important information about relatively common short-term ADRs. However, this system cannot be used to study medium- or long-term drug effects, to study drugs used primarily in outpatients, to study uncommon drugs or diseases, or to study new drugs, as data collection has largely ceased.

The Boston University Drug Epidemiology Unit has extended the hospital-based approach of the BCDSP, by collecting lifetime drug-exposure histories and performing hospital-based case-control studies (23). This program has provided much high-quality information on relatively uncommon ADRs. This system can only study hospitalized patients and is thus limited to illnesses that result in inpatient care. In addition, it can be used only for case-control studies and therefore cannot be used to calculate the incidence of diseases. Also, the manner in which the drug history is collected makes this system potentially subject to recall and interviewer biases.

Finally, ad hoc case-control and cohort studies may be performed if special

circumstances make the described systems inadequate. The advantages of studies designed to address the question at hand are that the research methodology, patient population, and clinical setting can be tailored to fit the needs of the study question. The disadvantages are that these studies are much more expensive to perform and often will take longer to complete than would the use of an existing system. As an example, large-scale "cohort" studies conducted ad hoc by pharmaceutical companies have been conducted. Typically, a company's sales force is asked to recruit 2000 cooperative physicians, each of whom is then asked to report on the experience of five patients who received the drug (24). This approach is extremely expensive, generally well over a million dollars (25), and is open to biased reporting because of the mechanism of recruitment. Most importantly, though, is that such studies generally lack control groups, making the judgement about whether or not a medical event is likely to be due to a drug arbitrary and the detection of new ADRs unlikely. Certainly a control group could be added, but this addition would double the cost.

As an attempt to reduce the cost of pharmacoepidemiology studies, a recent trend has been to take advantage of billing databases. The BCDSP has used data from the Group Health Cooperative of Puget Sound. This HMO serves 300,000 patients and has computerized drug and hospital-discharge information. Both case-control and cohort studies can be performed using these data. While many useful studies have been carried out using this resource (26), outpatient diagnoses are not computerized and relatively uncommon drugs and illnesses cannot be studied because of the limited size of the database.

Northern and Southern California Kaiser Permanentes each have one to two million patients enrolled in their Health Maintenance Organization. Drug information and diagnostic data, both inpatient and outpatient, are linked in the same record. However, retrieval requires medical-record review; only discharge diagnoses are computerized, although Southern California Kaiser is computerizing its drug data, which will greatly increase its potential utility for pharmacoepidemiology studies. Both case-control and cohort studies can be performed on this system. Its advantages include high-quality data and a working, middle-class, and middle-age population. Its disadvantages are that it is not completely computerized, it has a limited formulary and only moderate sample size, and data cannot be collected directly from patients.

The Commission on Professional and Hospital Activities' Professional Activities Survey represents another data source, containing data on 35–40% of hospital discharges in the United States (27). While this system has great potential to find cases for case-control studies, the process of determining prior exposure requires obtaining consent from many individual hospitals, then individual physicians, and then patients, with resulting logistical difficulties and low participation rates.

The Saskatchewan Health Plan has 10 years of billing data on one million residents of that province in Canada. This system is just beginning to be used for pharmacoepidemiology studies, but appears to hold great promise because it is population-based and has a relatively representative and stable population. Both cohort and case-control studies can be performed. This system suffers from a limited formulary; limited outpatient diagnosis information, since these diagnoses use only 3 of the available 5 digits of the diagnosis codes; limited inpatient diagnosis data, which include only 4 of the available 5 digits of the diagnosis codes; the fact that physician reimbursement is dependent on the diagnosis, which might bias these data; and its moderate sample size. Inasmuch as it has not been organized or used for pharmacoepidemiology studies, further evaluation awaits additional experience.

Over the past ten years, the Food and Drug Administration has funded the development and testing of Medicaid billing data for pharmacoepidemiology studies. The Computerized On-Line Medicaid Pharmaceutical Analysis and Surveillance System (COMPASS) is composed of over six million patients from ten U.S. states. Case-control and cohort studies can be performed. The advantages of this system are that it is population based, very large, and relatively inexpensive to use. The principal disadvantage is that the validity of the diagnosis data has been questioned (28). We recently reviewed this issue in detail and concluded that the data are sufficiently valid to be useful for pharmacoepidemiology studies (29). Care must be taken, however, to ensure that all potential confounding factors of interest are available on the system and that diagnoses under study are chosen carefully, since the validity of the diagnosis data is still an issue.

OPPORTUNITIES

To date, most research in pharmacoepidemiology has focused on the study of drug effects, particularly adverse effects. As of the end of phase III clinical testing, considerable gaps remain in our information about drug effects. Areas needing further development include identification and quantitation of less common adverse effects, even serious ones; identification and quantitation of delayed adverse effects; evaluation of the efficacy and toxicity of drugs in types of patients usually excluded from premarketing testing, e.g. children, the elderly, and pregnant women; evaluation of the efficacy and toxicity of drugs used in patients with other illnesses and/or ingesting other drugs; evaluation of the efficacy and toxicity of drugs relative to the other drugs used for the same purpose; and evaluation of efficacy and toxicity for indications other than those initially tested. In this section of the paper, we review the opportunities for pharmacoepidemiological research, including both work underway and promising areas for future research.

Studies of drug effects can be divided into four categories, each with different implications for research. In the first category, research is directed toward discovering unanticipated adverse effects of drugs. This type of research can be done with an experimental study, but is better addressed with a cohort study that focuses on the drug; a case-control study (if searching for drug causes of a certain disease); or voluntary case reports. The opposite of this research is, in fact, an overlooked but extremely important role for pharmacoepidemiology---documenting drug safety by searching for unanticipated adverse effects and not finding any. Documenting safety is particularly important in light of recent drug withdrawals in response to reports of serious adverse effects that could not at the time be quantitated, e.g. zomepirac (30), and in light of the considerable litigation resulting from adverse drug effects (31).

The second set of questions relates to adverse effects of drugs that have been or could have been anticipated, either because of the pharmacology of the drug, preclinical results of animal testing, or premarketing clinical testing. The major research question to be addressed for this category is quantitative: how often does this adverse effect occur? This kind of investigation can be made with an experimental study, a cohort study, or even a case series, but not with a case-control study, as one needs an identifiable denominator. An example is the study conducted of first-dose syncope from prazosin. This adverse effect was known prior to U.S. marketing from both the prior experience in Europe and premarketing clinical testing. However, the former suggested an incidence rate of 1% and the latter, an incidence rate of 0.1%. A "Phase IV cohort study," actually a case series, was conducted by the manufacturer in response to a request by FDA. This study measured the incidence of first-dose syncope more precisely, recruiting 10,000 patients through prescribing physicians, via sales representatives. The result confirmed the premarketing suggestion of a 0.1% incidence, and was thought to be lower than that found in Europe because the latter led to marketing of a lower dosage form of the product and a recommendation to give the first dose at bedtime (25).

The third set of questions concerns unanticipated beneficial effects of drugs. An example is the beneficial effect of aspirin, given for treatment of rheumatoid arthritis, in preventing myocardial infarction (32). This result is a side effect, even if beneficial. Similar to that with unanticipated harmful effects, researchers in this area seek to discover these beneficial effects. Study design alternatives for both categories are also similar.

Finally, the fourth set of questions about drug effects concerns anticipated beneficial effects of drugs. This research determines whether a drug works as expected. Although drug efficacy needs to be established prior to marketing, multiple questions of efficacy remain after the drug is marketed (33).

These questions include the efficacy of the drug in the face of variations in drug regimen, e.g. dose per unit time, distribution of dose over time, and duration; variations in characteristics of the indication, e.g. severity, subcategories of the illness, and changes in the indication over time; and variations in characteristics of the patient being treated, e.g. age, sex, race, genetics, geographic location, diet, nutritional status, compliance, other illnesses, and use of other drugs, including tobacco and alcohol. Other questions of efficacy remaining at the time of marketing include the efficacy of the drug when used for indications other than those initially evaluated and the efficacy of the drug relative to other drugs used for the same purpose. In general, studies of drug efficacy require randomized clinical trials. However, recent work indicates that clinical trials are not always needed (34), and that the exceptions occur more often than one might have anticipated (35). This field is a new one in pharmacoepidemiology, which deserves more attention in the future.

To a large degree, the field of pharmacoepidemiology began with descriptive studies of how physicians use drugs and determinants of good prescribers vs bad prescribers (36). Subsequently, studies of drug utilization were considered more important for marketing purposes than for academic purposes, and commercial firms have done most such work recently. These firms sell their data to industry to support its marketing efforts. A number of these firms have been very generous, however, in supplying these data, without charge, to investigators as well, in support of academic research efforts (33, 35). Even more recently, there has been a resurgence of interest in academic studies of drug utilization, especially international studies (37). With the development of computerized databases, as described above, such studies are likely to increase in frequency.

A relatively undeveloped field in pharmacoepidemiology is the study of drug interactions. Only a few nonexperimental studies of drug interactions have been done (38). These studies require techniques similar to those described above for the study of other drug effects. For example, one could perform a cohort study comparing patients receiving aminophylline and digoxin to those receiving only aminophylline or only digoxin, and look for differences in the frequency of various outcomes.

A new and rapidly growing field in pharmacoepidemiology applies the principles of health economics to the study of the implications of drug use (39). As society has become more concerned with the costs of medical care, investigators have begun to conduct a series of cost-benefit or cost-effectiveness analyses, examining the financial implications of drug use. These implications involve much more than the costs of the drugs but include the costs of drug administration, the costs of adverse drug reactions, decreases in costs because of other treatments that are not used, etc. This work was

markedly advanced by Smith Kline and French, who used it to support its marketing effort for cimetidine, by funding a series of studies that compared the costs of the drug to the savings from reduced peptic ulcer surgery (40). Cost-effectiveness studies of other drugs have followed, and many more are underway.

Another field of clinical epidemiology not yet applied much to the study of drug effects is the field of clinical decision making. Investigators are beginning to examine more rigorously how physicians make clinical decisions (41). Although the field of clinical decision making has been applied frequently to the evaluation of diagnostic tests, it has only rarely been applied to therapeutic decisions. Better understanding of prescribers' decision making could be useful, among other things, in understanding their choices about whether or not to treat. A better understanding of this process might provide a clearer understanding of when therapy is indicated, which is the major obstacle in expanding the use of nonexperimental study designs to address questions of drug efficacy (34).

Drug utilization review (DUR) has been performed for years. However, DUR programs generally focus exclusively on abuse or overuse of drugs, or they focus on the use of costly drugs in an attempt to reduce expenditures on drugs. More recently a new approach to DUR has been developed. This approach focuses on preventing the adverse effects resulting from inappropriate, excessive, or therapeutically incompatible drug use, thus reducing costs by preventing adverse effects from drugs (42). Other similar programs are needed, the efficacy of which must be evaluated rigorously.

Finally, the federal government has recently eased the process by which generically equivalent drugs can be approved for marketing, after expiration of the patent on the original product. Now, generically equivalent drugs can be approved after a single study in a small number of normal subjects, documenting roughly equivalent bioavailability (43). Whether or not generically equivalent drugs are in fact therapeutically equivalent has been controversial for years (44). In response to these new regulatory changes, and recent expirations of the patents of a number of products, an unusual number of generic drug products have recently been marketed (45). Studies are needed to evaluate whether these new drug products are in fact therapeutically equivalent to the trade-name predecessors.

PROBLEMS

The field of pharmacoepidemiology is also facing a number of methodological and logistical problems. Methodologically, the first problem is that no effective and reliable technique has yet been developed to study rare effects of infrequently used drugs. The sample sizes needed have been impossible to

attain. Second, it remains difficult to study delayed drug effects in a reliable and efficient manner. None of the available databases have been in existence long enough for this, and even once they are, attrition from each database will probably make this type of study impractical. The only useful technique now available is the use of ad hoc case-control studies, but determining whether drug exposures occurred years previously is obviously difficult.

The third major methodological problem that remains to be addressed is how to screen for adverse drug effects. To date, virtually all adverse drug effects have first been noted as case reports, reported to the medical literature, the manufacturer, or a regulatory body. Most of the databases and the Drug Epidemiology Unit's case-control surveillance have the ability to screen for drug effects, looking for associations between drug exposures and disease occurrence. However, the number of statistical tests involved in such a screen guarantees false positive findings. If an α level of 0.05 is used, 1 out of 20 tests will be positive, purely by chance. Yet, if a smaller α is used, the screen will be insensitive. This problem has led to a reluctance to conduct such screens.

The field of pharmacoepidemiology also has two major logistical problems: funding and manpower. Obvious sources of funding for such research are the FDA, the pharmaceutical industry, and NIH. However, the FDA's budget for extramural research is extremely small, and is used only to address questions of particular regulatory importance. Although this budget for pharmacoepidemiology research was recently increased significantly, even more recently, in response to the first Gramm–Rudman budget cut of 4.3%, the budget for extramural research was reduced by 40%.

The pharmaceutical industry continues to support such work, but its needs are very short term and defined, so it does not represent a feasible source of either long-term salary support for investigators or support for studies of clinical importance that are not of marketing or regulatory importance.

Finally, NIH is organized by organ system. Any set of pharmacoepidemiology studies generally crosses organ systems, making NIH funding awkward. Although the Pharmacological Sciences Program of the National Institute of General Medical Sciences provided pivotal support of the Boston Collaborative Drug Surveillance Program at its initiation, it currently supports only basic research. It was in response to this and other problems that the Joint Commission on Prescription Drug Use, an interdisciplinary commission charged to study the opportunities and problems of pharmacoepidemiology, suggested in 1980 the formation of an independently funded, academically based Center for Drug Surveillance (25). However, such a Center has not been founded.

The other logistical problem is manpower. There are currently very few investigators in the field, and few obvious ways of training new individuals.

First, fellowship programs in Clinical Pharmacology generally do not have faculty with epidemiologic expertise. Second, Master of Public Health programs generally do not have faculty with clinical pharmacology expertise. Third, most of the current investigators in the field are not affiliated with active training programs. Obviously, the funding problems described above make recruiting new individuals into the field even more difficult. As some of the pioneers in the field approach retirement age, this problem will become more acute. The Burroughs Wellcome Foundation has established a Burroughs Wellcome Scholar Award in Pharmacoepidemiology, with the hope of attracting people into the field. Its success remains to be evaluated.

THE FUTURE

Pharmacoepidemiology is a unique new field, bridging clinical pharmacology and clinical epidemiology. There is a tremendous need for a large expansion of research in pharmacoepidemiology, both more research of the type now underway and new types of research. However, there are significant methodological and logistical obstacles that need to be overcome. If all goes well, the future is likely to see a huge expansion of the field, with an increased use of databases; more emphasis on drug safety and drug efficacy, in addition to the current emphasis on drug toxicity; and more emphasis on the financial implications of drug use. The promise of pharmacoepidemiology appears great. Time will tell whether it will be fulfilled.

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