A METHOD FOR MONITORING ADVERSE DRUG REACTIONS

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1. Introduction

A recent international conference on Adverse Reactions Reporting Systems [6] has again underscored the great need for continuing surveillance of therapeutic drugs after they are marketed. Formal clinical drug trials and other premarketing studies are usually too small in scale and too formally structured to detect all of the problems that a drug may cause when it is employed in the varied and complex setting of actual patient care. These drug-caused problems, known medically as *adverse drug reactions*, consist of a wide variety of untoward effects, some of which occur quite rarely.

In the Kaiser-Permanente Department of Medical Methods Research, a computerized medical data system [9] is being developed which now records the essential medical data for patients seen in the Kaiser-Permanente outpatient department in San Francisco. In attempting to minotor the risks of untoward events due to therapeutic drugs, we have employed an analytic method that delves into a relatively unstructured situation in an effort to bring out some orderly and useful observations.

After describing the method we shall discuss the relationship of drug monitoring to studies of the effects on health of environmental pollution, the theme of this part of the Symposium.

2. Data currently available

In contrast to most other drug monitoring programs, we have been working with outpatient data, that is, information about what takes place in outpatient clinics rather than in a hospital ward [3]. Analytic methods applied to inpatient data have been described by others [1], [5], [7], [8].

Because outpatients are not under continuous observation as are hospitalized patients, outpatient data are necessarily imprecise and less complete than inpatient data. Regarding drug usage, in an outpatient setting, one can ascertain

The research activities of this program have been supported in part by the Kaiser Foundation Research Institute, Food and Drug Administration Contract 68-38) and National Center for Health Services Research and Development (Contract HS00288).

that a drug has been prescribed, or even, as in the Kaiser-Permanente system, that a drug has been dispensed. However, one cannot be sure that the drug was taken, without special interviews or tests which are impractical in a monitoring situation. Furthermore, to detect the development of untoward events related to a drug it is necessary in an outpatient setting that the patient report his problem to the physician. Despite these relative deficiencies in the completeness of outpatient data, outpatient surveillance is a necessary component of drug monitoring. Only in this setting can patients receiving chronically administered drugs, such as antihypertensives, antidiabetics, and oral contraceptives, be followed up for the occurrence of long term or delayed side effects.

Our basic outpatient data come from a sequence of visits made by patients to the pharmacy and to various clinics. We have some identifying information about each patient: medical record number, name, sex and month and year of birth. When each clinic visit occurs, the date, the time, the identity of the clinic and the attending physician and the diagnosis made by the physician are recorded and entered into the computer record. Necessary modifiers of the diagnosis are also entered, that is, "new" (meaning that the condition is new or recurrent), "old" (the condition continues from a previous visit) or "worse" (the condition is pre-existing but has worsened since last seen). Certain clinics provide for the entry of procedures such as minor operations, injections and dispensing of drug samples by the doctor. For the clinic visit information to be stored, the patient identifying information must agree with that in the patient computer record, and the date and a diagnosis (or procedure) must be recorded. However, a missing visit time or physician identifying number will not prevent the storage of the visit information.

When a pharmacy visit occurs the dispensing of a prescription is recorded and verified "on-line" by the pharmacist. The stored data include the date and time of the visit, the identity of the doctor who wrote the prescription, the sequential prescription number used by the pharmacy, the name of the drug dispensed (usually the trade name rather than the generic), the form of the drug (for example, tablets, syrup, eye drops, and so on), the strength of the drug (for example, 50 mg. of drug per tablet, or 2 per cent concentration of the drug in the ointment, and so forth), the "sig" or instructions to the patient as to how the drug is to be used, the amount dispensed and the total amount left to be dispensed by subsequent refills.

The various visits are arranged in chronological sequence in the patient's computer record. Such a sequence for an actual patient during three months is summarized in Table I. An example of the greater detail that is available about a prescription is shown in Table II.

We believe that drug reaction studies covering a broad group of drugs should be undertaken in at least two stages. The first stage is a monitoring and screening procedure. This search for drug-event associations can be applied on a large scale to a variety of drugs. It should indicate the presence of statistically significant associations between drugs and subsequent untoward events and provide a meas-

TABLE I

SUMMARY OF A PATIENT'S VISIT DATA DURING JULY 1 THROUGH SEPTEMBER 30, 1969

Patient Number: 1234567 (fictitious number) Sex: Female Birth Date: 03/1895

Date	Time	Visit location	Drug	Diagnosis
July 15, 1969	11:36 a.m.	Pharmacy	pyridoxine	
July 17, 1969	1:30 p.m.	Medical clinic		diabetes mellitus, old arteriosclerotic heart disease, old edema, peripheral, new
July 17, 1969	3:00 p.m.	Pharmacy	lasix	
August 5, 1969	1:36 p.m.	Pharmacy	folic acid orinase	
August 21, 1969	—	Medical clinic		arteriosclerotic heart disease, old arrhythmia, paroxysmal tachycardia, worsening
Sept. 5, 1969	5:00 p.m.	Pharmacy	pyridoxine	
Sept. 16, 1969	11:42 a.m.	Pharmacy	digoxin	
Sept. 19, 1969	4:12 p.m.	Pharmacy	phenobarbital	

TABLE II

ACTUAL STORED DATA CONCERNING AN INDIVIDUAL PRESCRIPTION

(all identifying numbers are fictitious)

Patient number: 7654321		Physician number: 54321
Date: September 3, 1969		Time: 5:06 p.m.
Prescription number	:	174626
Drug name	:	ferrous sulfate
Drug form	:	enteric-coated tablets
Strength	:	3.5 grains
Sig	:	take 1 tablet 3 times a day, before meals as directed
Amount dispensed	:	200
Amount remaining for refills	:	600

ure of the magnitude of the associations. The second stage is more of an *ad hoc* in depth study that is applied to individual drug-event associations to determine the likelihood that the drug actually causes the event and to define better the patient and drug characteristics and other circumstances that foster the adverse reaction.

In order to be broadly applicable, our first stage monitoring uses only the summary data shown in Table I. In Finney's [2] classification of drug monitoring records, these data correspond to class II records, which require patient identification, drugs, events and diagnoses leading to drug prescriptions. To some extent they also meet the criteria for class I records which contain, in addition, patient attributes and past medical history. Some patients have had extensive

multiphasic examinations the results of which are stored in the computer record. These patients have very good class I records, which can be used for detailed second stage studies as can the drug data illustrated in Table II.

3. Monitoring analysis for a particular drug

The first step in bringing some order out of the varying picture of drug usage by outpatients was to establish a *time frame.* The beginning point in chronological time that was imposed on us by technology was the end of June, 1969, when pharmacy data were first entered into the computer. Diagnostic data from most clinics were being entered by that time or soon after. The first large set of data that we worked with was retrieved in January, 1970 and covered the six month period July through December, 1969. We are now beginning to analyze data for the one year period that ended on June 30, 1970.

We define a time period called the "selection interval," during which we identify the patients who received the drug to be studied. Then each patient is followed up for the development of untoward events for a defined period of time called the "follow-up interval." This latter interval begins at the time the patient first receives the drug. Observation of events before the drug is received, extends from the beginning of the selection interval until the time the patient first receives the drug. These intervals are illustrated in Figure 1.

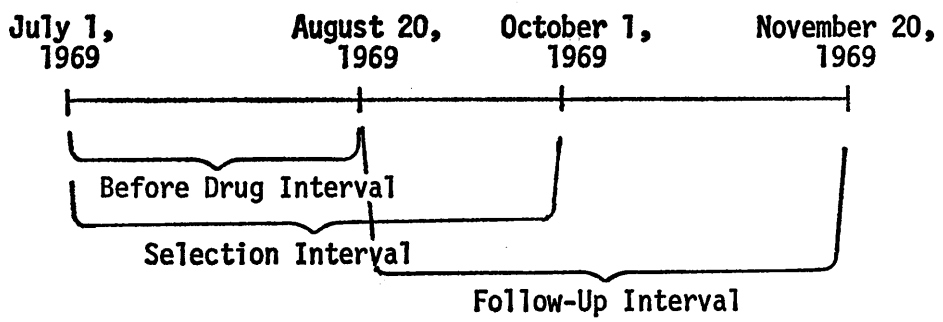

FIGURE 1

Example of "selection" and "follow-up" intervals. For this study, the selection interval is chosen as July through September, 1969. The follow-up interval is chosen as three months. A patient first receiving the drug on August 20 is followed until November 20. Calculation of event incident rate after the drug is based on this follow-up interval. The before drug incidence rate is based on the before drug interval, July 1 through August 20, 1969.

This has been the time frame that we have most often used so far. The selection interval can be made as long as desired within the constraints of the duration covered by the available data and the minimum duration of follow-up desired. The follow-up interval is less easily selected. For chronically used drugs one

would desire as long a follow-up as the data would allow. For drugs used for a short duration (about one day to two weeks) or for a medium duration (up to a few months) one view is that the period of usage of the drug should be computed from the detailed dispensing data and patients should be followed for that time only. However, we feel that this would be too cumbersome from a computational point of view, particularly since patients often do not follow instructions exactly and since some adverse reactions may occur after the drug is stopped. It seems more prudent to select a reasonable follow-up interval based on the type of drug. For short term antibiotics we used a one month period. For long term drugs we used three months to follow-up. As more data become available we will use longer and longer periods of follow-up but after three or six months have elapsed it would seem desirable in many cases, to require continuing evidence that the patient is still using the drug.

4. Incidence of untoward events

The occurrence of any "new" or "worse" diagnosis is considered an untoward event that is worth at least some initial scrutiny as to whether it is or is not related to the drug. In this way we are open to the discovery of previously unsuspected reactions. Any patient receiving the drug who develops the event at least once during follow-up is counted. The incidence rate for each event is the proportion of drug users who develop the event per unit of time of follow-up.

While we have generally used a fixed after-drug follow-up period, this is not a requirement. Where follow-up duration varies from person to person the incidence rate can be expressed in terms of person-days of observation.

In traditional prospective epidemiologic studies the presence or absence of a disease under investigation is ascertained at the onset by special study. Only those certified to be free of the disease are considered at risk for the development of the disease and only they are used in the denominator of an incidence rate. In a large scale monitoring program concerned with a wide variety of untoward events this approach obviously is not practical. Instead, we have depended on the doctors' determinations as to whether conditions are new or worsening. Naturally, errors may occasionally occur, particularly in situations when a patient changes physicians or when the old chart is not readily available at the time the patient is seen.

5. Comparison groups

5.1. *Nonusers.* To evaluate the observed incidence rates of events in users of the drug one needs some basis of comparison. Our primary comparison group to date has been those persons who came to the clinic or pharmacy during the selection interval but who did not receive the drug. The incidence of the untoward events observed in these nonusers is computed in an analogous fashion to that in the users.

We considered using the entire Kaiser Health Plan population residing in San Francisco as our basic study group and source of nonuser incidence rates. However, there was some doubt as to whether all of these persons consistently used the San Francisco facility for their care since Health Plan members are free to use facilities in other locations or to utilize non-Kaiser physicians. It seemed more prudent to require that nonusers show evldence of visiting the data collecting facility as do users. This would provide some assurance that untoward events developing in users and nonusers have a reasonably equal chance of being detected by the monitoring system.

The users' follow-up begins when they first were known to have received the drug. We begin the nonusers' follow-up when they first were seen at the pharmacy or any clinic during the selection interval.

There are, of course, a number of possible sources of bias that should be considered when users of a drug are compared with nonusers. For example, it occurred to us that there might be a substantial difference in the distribution of starting times between users and nonusers of a particular drug. In the study of events with a seasonal variation substantial differences between users and nonusers as to the timing of follow up might introduce artificial differences that have nothing to do with the drug. An example of a seasonal condition in our data is Acute Bronchitis which had a relatively low frequency during the summer months but increases through autumn and winter (Table III).

TABLE III

MONTHLY FREQUENCIES OF MEDICAL CLINIC DIAGNOSES OF "ACUTE BRONCHITIS—NEW"

Month	Number of diagnoses	
	Total	Per 1000 visits
July	64	8.5
August	58	8.3
September	84	10.9
October	112	14.6
November	122	15.4
December	142	18.3

We examined the distributions of starting times for users and nonusers of various drugs. Anticipating longer periods of data for analysis we assumed that the entire six month period, July 1 through December 31, 1969, was a selection interval and computed the percentage of users and nonusers that began follow-up each week. The nonuser distribution curves for all drugs were quite similar since the users of even the most popular drugs comprise only a small proportion of patients, leaving the vast bulk of the population as nonusers. Nonuser starting times tended to be most frequent early in the period with a gradual decrease as time passed. This is what would be expected since patients with more than one visit during the period would be started at their earliest visit. Incidentally, there

were the expected dips in the distribution curve for the weeks with holidays in them (Figures 2 and 3).

For chronically used drugs such as oral contraceptives (Figure 2) the distributions of starting times for users and nonusers were quite similar. This was not the case for antibiotics, such as penicillin, used on a short term basis (Figure 3). These showed a gradual rise in percentage starting each week until a peak was reached at the end of October. With drugs of this nature we will have to be concerned about spurious associations due to seasonal trends.

Even more basic than starting times, however, is the question of whether users are really users and nonusers are really nonusers. The limitations of outpatient data for determining whether patients actually use drugs, have been mentioned above. Regarding nonuser status we carried out some validation studies using

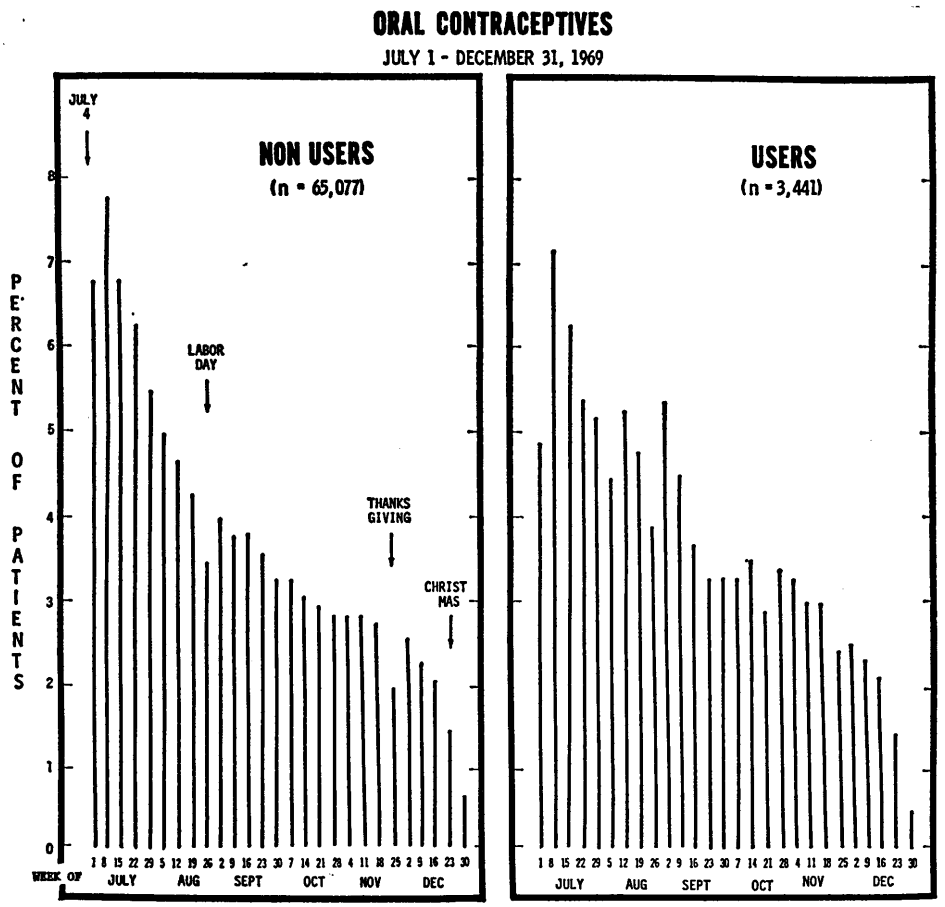

FIGURE 2

Distribution of starting times for follow-up: oral contraceptives.

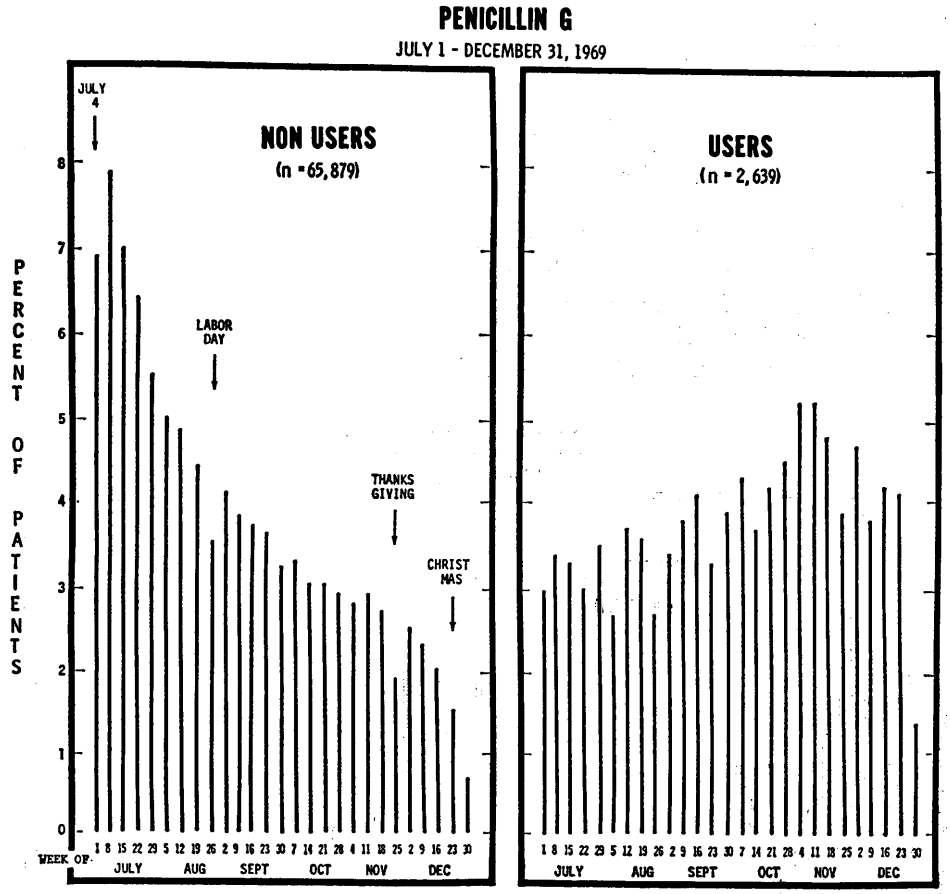

FIGURE 3

Distribution of starting times for follow-up: penicillin G.

patient charts after the computer data had been collected for two months. We asked whether there was any evidence in the chart suggesting that the patients whom we called nonusers by virtue of their computer-stored data were actually users. Had they probably been taking the drug during the two month period because it was prescribed then, or prescribed previously with instructions to continue taking it during the period in question?

For penicillin, which is generally used on a short term basis for acute infections, 2 per cent (7/297) of the persons whom we had called nonusers probably were users as evidenced by notes in their charts. For thiazide diuretics, which are usually used on a medium term or long term basis, 6 per cent (14/225) of "nonusers" aged 15 and over probably were users. For oral contraceptives, which are usually used on a long term basis, 11 per cent (11/97) of "nonuser" women aged 15–54 probably were users. So, it appeared that our computer records for

a two month period were reasonably good at identifying nonusers. They were less accurate for oral contraceptives, but prescriptions for these drugs are usually given every three or six months, so that longer interval computer records would be expected greatly to increase the accuracy.

5.2. *Users before receiving the drug.* Another comparison group that should be suitable for monitoring comprises the drug users themselves, looked at before they received the drug. A distinct advantage in using this group is that many of the important characteristics that might differ between users and nonusers, such as age, sex and socioeconomic status are automatically matched. However, people do change over time and the fact that they have just obtained a drug suggests that they have developed a new disease or have arrived at a new stage in their disease or have changed doctors, all of which can change the likelihood of new untoward events being reported. Furthermore the problem of seasonal changes in event rates previously mentioned would be a very important consideration in the before-after comparison.

Because we have dealt primarily with the earliest data collected, there is considerable doubt as to what has occurred before the first recorded issuance of a drug for a patient. Therefore, to say that before the first recorded issuance is really before the drug was given, would not be appropriate. In the chart review studies for the first two month period, we also checked to see whether there was evidence that patients who were called users were also taking the drug during the period before the first recorded dispensing. For penicillin, 6 per cent (1/16) of users had received the drug before the first recorded dispensing. For thiazides, the drug was used before by 53 per cent (10/19) of users and for oral contraceptives, by 77 per cent (10/13) users. Thus the before-after comparison would be quite unsatisfactory in our early data for medium term and long term drugs.

However as more data are collected we will be able to look farther back from the time of issuance of a drug to determine that the patient had indeed not received it before. With this in mind we have begun to use a "search-back" procedure on data collected over a one year period or more. This places the "selection" interval later in the available time period, to be preceded by a "search-back" interval, during which period the use of the drug being studied is again checked. Users and nonusers are defined during the "selection" interval as before. However, any evidence of use of the same drug during the "search-back" interval will result in the exclusion of users from the before-after comparison. Furthermore any nonusers who received the drug during the "search-back" interval will be excluded from the nonuser comparison group. This modified study design is illustrated in Figure 4 where the first three months of a one year period are allotted for "search-back," the second three months for "selection" and the remainder for follow-up.

We have formalized our comparison of incidence rates in users *versus* nonusers, and after *versus* before the drug, by looking at the ratio of two rates (commonly known in epidemiology as the *relative risk*) and by looking at the difference between two rates (commonly known as the *attributable risk*). The 95

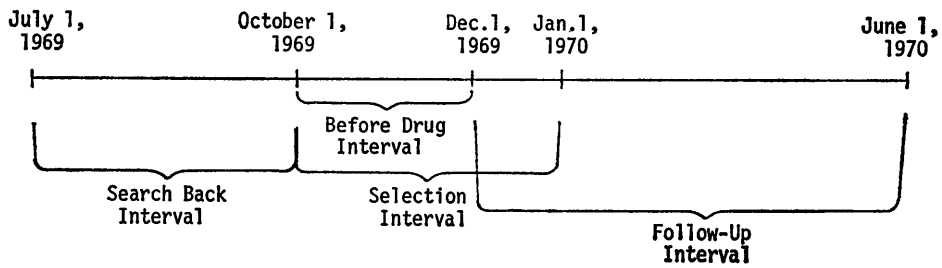

FIGURE 4

Example of time intervals resulting from the use of a "search-back" procedure. For this study the selection interval is chosen as October through December, 1969. The follow-up interval is chosen as six months. The search-back interval is July through September, 1969. A patient first receiving the drug during the selection interval on December 1, 1969 is followed until June 1, 1970. If he also received the drug during the search-back interval he is excluded from the before-after comparison but not from the user-nonuser comparison. Calculation of the event incidence rate after the drug is based on the length of the follow-up interval. The incidence rate before the drug is based on the length of the before-drug interval, October 1 through December 1, 1969. A nonuser during the selection interval, is excluded from the nonuser comparison group if he received the drug during the search-back interval.

per cent and 99 per cent confidence limits of the difference were examined to see if they included zero difference. If not, then one or two asterisks were placed on the computer output next to the event, indicating a significant association deserving further scrutiny.

As an example of our screening analyses, Table IV shows our current findings concerning a particular drug-event relationship, that is, between oral contraceptives and anxiety reaction. While the results varied among age groups, the over all six month incidence of physician-diagnosed anxiety reaction in oral contraceptive users was similar to the age adjusted incidence in nonusers (12.9/1000 and 15.4/1000 respectively). The apparent lack of association between anxiety reaction and oral contraceptive usage illustrates another value of population based drug monitoring. In addition to detecting adverse drug reactions, monitoring may provide valuable negative results. Some conditions are not brought about by a drug, despite their reported occurrence in some users of the drug.

The use of the relative risk, attributable risk, statistical significance tests and medical judgment to determine which drug-event associations should be pursued further have been discussed in detail elsewhere [4].

6. Refining user versus nonuser comparisons

Since users and nonusers may differ greatly in characteristics that influence the event rates it is important to control for these characteristics in the analysis

TABLE IV

EXAMPLE OF A USER—NONUSER COMPARISON
Oral Contraceptives and Anxiety Reaction

(Women aged 15–54; drug use and nonuse ascertained during October–December, 1969; follow up for six months; search-back during July–September, 1969)
* Age adjusted. The overall proportion with an event for nonusers is a weighted average of the proportions for individual age-sex subgroups. The weighting is according to the proportion of *users* who fall into each age-sex subgroup.

	Total number		No. developing anxiety reaction		Incidence/1000 of anxiety reaction		Relative risk	Attributable risk per 1000
Age group	Users	Non-users	Users	Non-users	Users	Non-users	(User/nonuser)	(User − nonuser)
15–24	905	3,798	7	30	7.7	7.9	.98	−0.2
25–34	1,261	3,816	9	64	7.1	16.8	.43	−9.7
35–44	539	3,265	13	76	24.1	23.3	1.04	0.8
45–54	241	4,165	9	80	37.3	19.2	1.94	18.1
15–54	2,946	15,044	38	250	12.9	15.4*	.84	−2.5

whenever possible. Control by randomization is not possible in the observational monitoring situation. We control for age and sex differences by adjustment, that is, in computing the overall nonuser rate, weighting the rates for nonuser subgroups according to the proportions of users that fall into each corresponding subgroup. However, more control of extraneous variables is often needed to make a fair comparison. Ideally one would like to control for many different variables with each separate drug-event association but this is not feasible in the first screening stage of monitoring. That is why we favor applying a second stage detailed study to selected drug-event associations.

We have had some experience controlling for a third variable in our screening analyses, that is, the disease being treated. For example, we have restricted some of our analyses concerning antidiabetic drugs to patients with diabetes mellitus. In this way users and nonusers are matched for an important variable.

When we compared the results of restricting the analysis in this manner to using an unselected nonuser comparison group certain differences were noted as expected. There were reductions in the total number of users available for study since not all users had had the disease in question recorded during the six month study period. This problem will be largely solved by longer periods of data collection. Corresponding to the decrease in the number of users there were fewer different events in users to be studied, but the decrease in the number of different events was proportionally much less than the decrease in the number of users. The main discernible benefit that resulted from restricting the analysis to users and nonusers with a specific disease was a reduction in the number of events which appeared to be associated with the drug but were actually related to the basic disease being treated by the drug.

7. Relationship of drug monitoring to studies of the effects on health of environmental pollution

Medically prescribed drugs are not customarily thought of as environmental pollutants. However, there are a number of analogies between drugs and pollutants as well as similarities in the requirements for their study.

Many environmental pollutants are chemicals and so are drugs. Perhaps if drugs or medicines were referred to as "chemicals" they would not be so eagerly sought by some patients.

The harmful consequences of environmental pollutants, are, like those of drugs, unwanted byproducts of socially useful or desirable inventions. Just as the physician must consider the potential benefits *versus* risks of each drug he prescribes, decisions resulting from studies of the effects of pollution on health will involve weighing benefits and undesired side effects.

Both in the study of environmental pollution and in drug monitoring, one will encounter a very complex situation in attempting to measure degree of exposure. Quantities of pollutants or drugs and the time patterns of exposure are quite variable. Reasonable systems for classifying exposure, will have to be developed in order to compare population subgroups. While the presence or absence of gross exposures may be relatively easy to determine, some individuals may be exposed to small quantities of drugs or pollutants which go undetected or unquantified. For example, very little is known about the exposure of humans to antibiotics or other drugs given to the animals they eat; and what, if any, role these exposures might play in promoting or preventing adverse reactions to the same drugs prescribed medically.

Just as it is wished to have objective measures of health and disease it is also important to have objective measures of exposure. Interview or questionnaire data about drug usage are often inadequate because of the unfamiliarity of some people with what medications they are taking. Furthermore many people are unwilling to admit that they are not taking the drugs prescribed for fear of displeasing their physician. Periodic health examinations may provide the means of measuring blood levels or other objective indices of exposure of a population to drugs and environmental contaminants such as trace metals.

8. Interpretation and evaluation of findings

Monitoring of drug reactions and of the health effects of environmental pollutants involves primarily observational rather than experimental study. The investigator cannot control the situation and randomly allocate persons to exposed and nonexposed groups. Thus the problem of self-selection, already discussed in this symposium, must be reckoned with. We must be concerned with all of the ways that users of a particular drug might differ from nonusers and that those exposed to a particular pollutant might differ from those not exposed. Occasionally there will occur a "natural experiment" in which an exposure is so

universal or haphazard that the influence of self-selection or other important confounding variables seems quite remote. Usually, however, this will not be the case.

The critic of an observational study can usually think of additional reasons why an observed association might have been fortuitous or explained by a third variable. Ultimately it becomes a matter of judgment as to how far this skepticism should be allowed to proceed. While the investigator has the major responsibility for testing and defending his findings the critic should be able to provide some evidence that his questions and doubts are reasonable. This is particularly true in the case of findings affecting human health and safety. Often it will be most prudent for the decision maker to act on the basis of incomplete evidence from observational studies even before some of the reasonable questions have been answered.

The difficulty and expense of long term observational studies of human populations should also be kept in mind. The classical approach in laboratory science of other investigators verifying findings by repeating experiments may be impractical for the kinds of studies we are talking about. Other means of confirmation may have to be sought. Existing vital statistics data can often be explored at little expense, to test hypotheses that are generated by findings of large scale population studies. For example, if a pollutant appears associated with a particular fatal disease, known time trends or geographic differences in exposure to this pollutant should be correlated with similar trends and differences in the mortality rates for this disease.

Large scale population monitoring studies may well involve follow-up periods measured in decades. Many of the adverse health effects of drugs or environmental pollutants may take long periods to develop even after exposures of short duration. The offspring of the exposed should also be studied.

It would be unfortunate if the value of a large scale population surveillance program were judged solely by the number of hazards that were detected. Just as with medical checkups to detect early disease, it is also desirable to find out that there is nothing wrong. The study should be judged according to its ability to detect problems if they exist. If it has this ability and no problems are detected, this reassuring information is well worth the expense and effort in our changing environment.

9. Conclusion

An epidemiologic method for monitoring adverse drug reactions has been described. It is clear that some of the decisions as to how the data are to be analyzed are arbitrary and will be modified by future experience. The conditions that are imposed by a real medical care program are less than ideal for formal scientific study. However, the medical care situation is a crucial setting for monitoring the harmful effects of drugs.

Drug monitoring is, in many ways, similar to studying a population for the

effects of environmental pollutants. In both instances the methods are observational rather than experimental, and exposures may be difficult to detect and classify.

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Discussion

Question: John R. Goldsmith, Environmental Epidemiology, California Department of Public Health

Time trends in needs or demands for drugs used to treat bronchospasm can be of great value in environmental epidemiology since they may be the most sensitive index of the buildup of pollutants causing respiratory irritation. Many patients would not be aware of such a possible relationship.

Epidemiological study of effects of drugs of abuse requires more than the customary examination of vital statistics to find evidence of increased fatality among young people due to overdose or increased prevalence of hepatitis. What is more difficult and more urgent is the need for longitudinal studies of such possible effects as fetal loss or birth defects. The empaneling of populations of drug abusers is, therefore, also necessary for a program of drug monitoring which is comprehensive.

Another type of study is based on the retrospective examination of drugs used by individuals with causes of death commonly related to drug ingestion (such as blood dyscrasias, and certain renal or skin conditions). Unfortunately, many serious drug reactions are only beginning to be reflected in morbidity and systems of medical records. Those at Kaiser have an unusually important role to play

in defining the parameters in studying morbidity reactions in follow-back investigations.

Reply: G. Friedman

Regarding the study of time trends in the usage of bronchodilators, our pharmacy data might be a very good source of this kind of information. This is because the dispensing of prescription refills is recorded even if not immediately preceded by a physician visit. Patients in distress might go directly to the pharmacy for a refill of their medicines.

At this time our monitoring system only deals with prescription drugs and not with the drugs of abuse such as marijuana, heroin, and so on. We thought that by looking for persons at the upper ends of the distributions of numbers of prescriptions dispensed, the monitoring system might be able to detect previously unsuspected abusers of drugs such as tranquillizers and analgesics. However a preliminary review of the records of some of the patients who had received many prescriptions for these drugs indicated that they were using these drugs for good medical reasons and that their physicians were well aware of their heavy drug usage.

We agree that the retrospective method of investigation may play an important role in drug monitoring, particularly when one is dealing with rare events.

Question: Alexander Grendon, Donner Laboratory, University of California, Berkeley

You were in a position to use a control group which, unlike the environmental pollutant case, was not exposed to *any* "pollutant" drug; yet your "nonusers" apparently might have been using other drugs, so long as they were not using the drug you were investigating. Would it not have been better to select as controls nonusers of *all* drugs, who came to your clinic for medical care not requiring treatment with drugs?

Reply: G. Friedman

Your suggestion is an interesting one and perhaps deserves to be tried out. However, there has been much concern that users of a drug might receive more intensive follow-up medical care and might therefore be more likely to have untoward events detected, than might those who are not receiving any drug at all. The comparison would then be biased in the direction of finding higher event rates in users than in nonusers.

Question: E. B. Hook, Birth Defects Institute, Albany Medical College

In a conference such as this devoted to planning a comprehensive program, it is worth emphasizing that the drugs dispensed by a hospital pharmacy represent only a small proportion of chemicals ingested by the population, and about which we should have some concern. In a sense they are relatively easy to study compared to such agents as:

(1) Over the counter, self administered preparations: aspirin, vitamin C (in high doses), and so on.

(2) Illicit drugs: LSD, amphetamines, and so on, as well as their multitudinous contaminants.

(3) Food additives and preservatives: monosodium glutamate, sodium benzoate, and so on.

This list of categories is not exhaustive, but it illustrates that whatever the population studied, very detailed scrutiny of these and other "occult" agents which may represent "cocarcinogens," "coteratogens," or just "cotoxins," would be required.

Reply: G. Friedman

So far our outpatient monitoring involves only prescription drugs. It would certainly be desirable to be able to study as well the items that you have mentioned.

Question: Colin White, Department of Public Health, Yale School of Medicine

What are the unique contributions of a monitoring program? In particular, when should a designed study be preferred to monitoring? Monitoring may fall into disrepute if it is used for investigations that ought to be carefully planned rather than made on an observational basis.

Reply: G. Friedman

We regard monitoring as an initial screening process to provide clues and hypotheses that can later be studied more carefully. By covering a large number of drugs and events, even though superficially, monitoring provides a means of detecting previously unsuspected reactions. We wish to emphasize the limitations of the data we have presented. They certainly are not meant as a substitute for well controlled studies.