Adverse drug reactions occur more frequently than suspected. Various methods have been employed to study this problem and, although each method has limitations, all can provide useful information. In this sense adverse drug reactions represent a problem in noncommunicable disease amenable to epidemiologic methods. General principles are illustrated with data from The Johns Hopkins Hospital.

EPIDEMIOLOGICAL STUDIES OF ADVERSE DRUG REACTIONS

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STUDIES have been made on the epidemiology of adverse drug reactions in patients admitted to The Johns Hopkins Hospital. It has been stated that reported adverse reactions underestimate a common problem producing significant morbidity and mortality. Quantitative estimates of the risks involved in administering drugs are currently unavailable, and although for most drugs the incidence of adverse reactions is probably low, valid incidence data on the risk of adverse reactions may assist the physician who must make practical therapeutic decisions daily.

The methods we have used to study adverse reactions heavily draw upon the informative investigations of staphylococcal infections in The Johns Hopkins Hospital in collaboration with the Epidemic Intelligence Service of the U. S. Public Health Service.[1]

In the study of infections, numerator data on cases are often more easily obtained than denominator data on populations from which they arise. In drug reaction epidemiology, however, the denominator data can be obtained more readily than the numerator data. The greatest single problem in accurately determining the quantitative incidence of drug reactions is the failure of physicians to report adverse reactions in their patients as they occur.

Charge drugs, which include nearly all injectable medicines, all antibiotics, diuretics, phenothiazines, and other comparatively expensive drugs, are now billed to patients by means of IBM automatic data-processing equipment. Ward-stocked usually inexpensive drugs, such as aspirin, digitalis leaf, thyroid, and phenobarbital, are not charged for in this way. When billing is completed, the cards can then be sorted to obtain accurate data on the number of patients at risk, i.e., who have received a given medication within the study period. Thus, denominator data can be obtained with relative ease. The role of automatic data-processing methods is vital, however, because between 15,000 and 20,000 drug charge cards are processed each month.

We have collected data on drug usage within the hospital since July, 1963, and it has been instructive to note the differences in drug usage within the hospital (Tables 1, 2, 3). A valuable feature of this program is the permanent recording on magnetic tape of all drugs received by every hospitalized patient, making it possible to calculate the actual incidence of adverse reactions.

Table 1—Usage of Penicillins—October-November, 1963

Drug	Total No. of Patients	Hospital-Wide Incidence Usage (per 100 Pts.)	Incidence Usage (per 100 Pts.) Leading Services*
Procaine Penicillin G	567	11.4	Osler–20.2 Halsted–16.0
Penicillin G (Aqueous)	321	6.4	HLH–11.8 Halsted–10.2
Penicillin V tablets	127	2.5	HLH–10.0
Methicillin (Staphcillin)	124	2.5	HLH– 6.2 Halsted– 5.5
Oxacillin (Resistopen)	63	1.3	HLH– 3.8
Penicillin G tablets	43	0.9	HLH– 1.8 Osler– 1.5
Bicillin for injection	43	0.9	Osler– 1.8 Wom.Cl.– 1.7 HLH– 1.5
Pen-Tids	3		
	1,291		

* Osler–Public Medicine, Halsted–Surgery, HLH–Pediatrics, Wom. Cl.–Ob.–Gyn.

As mentioned previously, detecting reactions and then identifying the etiologic agent has been a difficult task (Table 4). For three years, a report-of-drug reaction card has been used at The Johns Hopkins Hospital in reporting adverse reactions by the staff. Although bizarre, serious, and unusual reactions are sometimes reported on these cards, which are attached to each patient's record on admission and completed at discharge, the number of reactions reported has been few, and data obtainable from a review of these cards have been unreliable in indicating drug reaction incidence.

During a period of active surveillance of the medical service recently, the number of reactions detected on a 150-bed service was four times that reported from the entire 1,100-bed hospital for the same period. Curiously, a similar card reporting system *has* been reasonably effective in detecting infections occurring in The Johns Hopkins Hospital. Because of poor reporting of reactions by the general hospital staff, more intensive studies in the surveillance of drug reactions in smaller groups have been undertaken. Patients receiving a given drug, patients with a particular disease, or those in a defined area of the hospital, can be intensively surveyed to detect adverse reactions. We have used these technics in the following ways.

Methicillin Pilot Study

All patients in the hospital for whom methicillin was ordered from the pharmacy were followed daily from the time the drug was begun until they left the hospital. A number of facts were uncovered (Table 5). The average num-

Table 2—Use of Multiple Antibiotics in Patients, April-May-June, 1964

Received	No. of Patients	Per cent of All Patients
One antibiotic	1,178	15.6
Two antibiotics	639	8.5
Three antibiotics	268	3.6
Four antibiotics	85	1.1
Five or more antibiotics	32	0.4
		29.2

Table 3 — Comparative Hospital-Wide Drug Usage by Quarter

Figures stand for per cent of *all* patients discharged from Johns Hopkins Hospital who have received the drugs listed during their hospitalization.

Drug \ Year	1963		1964	
Quarter	3rd	4th	1st	2nd
	%	%	%	%
Any penicillin	11.1	18.6	21.2	14.7
Procaine penicillin	3.3	11.3	13.0	10.0
At least one antibiotic	29.1	37.2	37.6	29.3
Three or more antibiotics	3.8	5.1	6.4	3.6
Tetracycline	9.4	10.6	9.4	7.7
Streptomycin	8.3	8.8	10.0	8.7
Chloramphenicol	5.3	5.3	5.9	5.7
Digoxin	4.8	5.6	5.7	5.0
Prednisone	3.6	3.5	3.5	3.3
Heparin	1.8	2.2	2.5	1.4
Coumadin	1.5	1.3	1.4	1.2
Metaraminol	1.4	1.8	1.6	1.0
L-Norepinephrine	0.9	1.2	0.8	0.5

ber of medications these patients received was 14. They also previously or concurrently had received an average of four other antibiotics. (One desperately ill patient received 32 medications including ten other antibiotics.) Although in 37 patients, only two reactions probably caused by methicillin occurred, 18 patients suffered adverse reactions to one or more of the other medications received.

Methicillin therefore acted as an indicator drug, often selecting seriously ill patients who received many medications and had a drug reaction incidence approaching 50 per cent.

Warfarin Record Review

The records of all patients receiving warfarin over a three-month period were reviewed for indications for therapy and evidence of adverse reactions—chiefly bleeding. Fifteen per cent of patients receiving warfarin under "routine" conditions had overt adverse reactions probably related to it, and another 21 per cent had at least one prothrombin determination below 10 per cent, an arbitrarily chosen hazardous range. Such retrospective investigations are wholly dependent on the diligence with which hemorrhagic complications are sought, detected, and recorded, and therefore underestimate the incidence of adverse reactions.

Medical Service Study

During the first three months of 1964, each of six wards on the medical service was visited daily and nurses and physicians questioned about the occurrence of any untoward reactions in patients, possibly related to drugs. The working definition of a drug reaction was any adverse response to medication undesired or unintended by the physician (Table 6). Having been reported as suffering from a possible drug reaction, the patient was followed throughout his hospitalization. Suspected reactions have been listed as proved or probable, possible, or doubtful, and also classified by severity, probable mechanism, body system involved, and responsible drug (Tables 7, 8).

Although our analysis is incomplete, it appears that about 5 per cent of

Table 4—Methods Employed in the Surveillance of Adverse Drug Reactions

1. Report card method
2. Surveillance of drug usage
3. Retrospective chart review
4. Prospective studies
   (a) All patients receiving a particular drug
   (b) All patients on a particular service

Table 5—Surveillance of Patients Receiving Methicillin—Johns Hopkins Hospital, August 12-September 12, 1963

Total number patients receiving methicillin		38
Average duration of therapy	11 days (range: 1–44 days)	
Indication for therapy		
Staphylococcal infection with positive culture		16
Staphylococcal infection suspected, not proved		16
Prophylaxis after surgery		6
Average total number of medications received	14 (range: 6–32)	
Average number of other antibiotics received in addition to methicillin	4 (range: 1–10)	
Adverse reactions possibly caused by methicillin	2	5% incidence
Adverse reactions to all drugs in these patients	10	47% incidence

all admissions to the public medical service were directly caused by drug reactions, including digitalis excess, sulfadiazine crystalluria, bromism, erythema multiforme caused by phenolphthalein, penicillin, "serum sickness," thrombocytopenic purpura attributed to sulfisoxazole, glutethimide-induced coma, and hypokalemic dehydration caused by chlorothiazide.

An additional 15 per cent of all patients admitted acquired an adverse drug reaction while hospitalized. The patients who suffered drug reactions in this study were compared with the population of all patients from which they were drawn. Although reactions were more common in the 41-70 age group, the age distribution of drug reaction patients paralleled the age distribution for the entire medical ward. There seemed to be no racial predilection for developing drug reactions. On the other hand, women, though making

Table 6—Definition and Classification of Reported Drug Reactions

An Adverse Reaction—Any Adverse Response to a Medication *Undesired* or *Unintended* by the Prescribing Physician

Classifications

Probability	Severity	Mechanism
1. Documented or probable	1. Severe	1. Toxic
2. Possible	2. Moderate	2. Side-reaction
3. Doubtful	3. Mild	3. Allergic
		4. Idiosyncratic
		5. Unclassified

up but 45 per cent of the population, accounted for about 62 per cent of the drug reactions detected.

Although we expected to find a correlation between duration of hospitalization and incidence of drug reactions, simply owing to a longer period at risk, we found that the majority of reactions occurred within first few days of hospitalization (Table 9). Forty-one per cent of all reactions occurred in the first three days of hospitalization, and 75 per cent within the first 11 days. On a medical service this is when the patient is usually acutely ill, subject to the intensive diagnostic and therapeutic endeavors of the staff—and at risk to more procedures and drugs given simultaneously. Similarly, most of the reactions detected occurred within a few days after initiation of therapy with the suspected offending agent, 33 per cent on the first day the drug was given (Table 10). Further analyses are presently being conducted to compare, for example, the distribution of primary diagnoses in the drug reaction group with the total population. We plan to calculate the exact incidence of reactions to specific drugs and drug combinations as well.

The difficulties in studying drug reactions in this way are several. Daily surveillance of medical wards is time-consuming and tedious. The total number of different medications a patient receives in the hospital is impressive; in this instance, an average of 13 different medications. The number of medications he receives in the hospital before the appearance of his first ad-

Table 7—Further Drug Reaction Classification

Drug Reaction Probability
Documented — adverse reaction commonly known to occur, clear-cut temporal association, positive re-challenge test or laboratory confirmation
Probable—adverse reaction commonly known to occur, clear-cut temporal association, improvement on withdrawal of medicine
Possible—adverse reaction known to occur, temporal relationship less clear, other etiologies also possible
Doubtful—other cause of adverse reaction judged more likely
Drug Reaction Severity
Severe—fatal or life threatening
Moderate—requires antidote drug, hospitalization, or prolongs hospitalization by at least one day
Mild—incidental, no antidote required, suspect medicine may or may not be stopped

Table 8—Mechanisms of Adverse Drug Reactions

Toxic—excessive degree of desired pharmacologic effect
Side-reaction—unintended pharmacologic effect of medication, often dose-related
Allergic—prior sensitization usually required, accelerated response often noted, manifestations are allergic in nature, e.g., fever, rash, adenopathy, urticaria, anaphylaxis, arthralgia, vasculitis
Idiosyncratic—rare adverse reactions, prior sensitization unnecessary, not dose-related, probably genetically controlled
Unclassified

Table 9—Per cent of All Drug Reactions in Relation to Days in the Hospital

Days after Admission	Per cent of All Reactions	Cumulative Per cent
0– 3	41	41
4– 7	18	59
8–11	22	81
12–15	4	85
16–19	3	88
20–23	7	95
24+	5	100

Table 10—Duration of Suspected Therapy When Drug Reaction Recognized

Days Receiving Therapy	Per cent of All Reactions	Cumulative Per cent
One	33	34
Two	16	49
Three	14	63
Four	8	71
Five	4	75
Six	4	79
Seven	7	86
Eight	—	86
Nine	3	89
Ten-plus	9	99

verse reaction is also large—nine in our patient sample. These figures must be compared with a matched population not having an adverse reaction in order to decide whether a direct relationship exists between numbers of drugs given and adverse reactions. Schimmel[2] has suggested such a relationship. A final difficulty in most cases is that a confirmatory laboratory test to aid in the diagnosis of an adverse reaction is seldom available, and the diagnosis must rest on the clinical findings, drug history and, where pertinent, a re-challenge.

Summary and Conclusion

The investigations illustrate several general principles pertinent to a discussion of epidemiology in the hospital. Adverse drug reactions represent another noninfectious disease problem amenable to study using epidemiologic methods, thus broadening the scope of the duties of the hospital epidemiologist. Patients are given many drugs when hospitalized, and at least 15 per cent develop adverse reactions, ranging from incidental to fatal ones. The characteristics of those patients suffering adverse reactions can be identified.

Various methods for surveillance of adverse drug reactions have been used. Although each method has certain deficiencies, all can provide useful information. Surveillance of drug reactions providing uniformity of reporting and satisfactory detection can best be accomplished by one or a few particularly interested physicians. Detailed study of persons given specific drugs to detect any clinical phenomenon, even though apparently unassociated with the drug given, is necessary. The method most applicable to surveillance of the general problem of adverse reactions in hospitals requires detailed, individual, daily examination of large numbers of patients.

In this way, adverse reactions to many drugs can be surveyed in several hospitals simultaneously. If complete clinical and drug usage data are available, the incidence of both adverse reactions and factors predisposing patients to them can be determined rapidly and accurately.

REFERENCES

1. Cluff, L. E.; Thornton, G. F.; and Seidl, L. G. Studies on the Epidemiology of Adverse Drug Reactions. I. Methods of Surveillance. J.A.M.A. 188:976-983 (June 15), 1964.
2. Schimmel, E. M. Hazards of Hospitalization. Ann. Int. Med. 60:100-110 (Jan.), 1964.

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