Adverse Drug Reactions

A Critical Review

Fred E. Karch, MD, Louis Lasagna, MD

• **The data on adverse drug reactions (ADRs) are incomplete, unrepresentative, uncontrolled, and lacking in operational criteria for identifying ADRs. No quantitative conclusions can be drawn from the reported data in regard to morbidity, mortality, or the underlying causes of ADRs, and attempts to extrapolate the available data to the general population would be invalid and perhaps misleading.**

To evaluate the impact as well as the causes of ADRs, representative populations, including general hospital and ambulatory patients of all medical specialties, must be studied, and operationally defined criteria must be used to establish the presence of an ADR in a prospective study that incorporates appropriate control populations. Similar studies on the benefits of drug use are needed to provide perspective on the risk-benefit aspects of drug therapy. Until such studies are performed, estimates of the nature and scope of the ADR problem can be only guesses.

(*JAMA* 234:1236-1241, 1975)

MUCH attention has been focused on the morbidity and mortality attributed to the use of prescription medications. It has been widely claimed that reactions to drugs have become a major cause of hospitalization, prolonged hospital stays, and even death, with projections of up to 140,000 deaths annually in the United States from adverse reactions to drugs.[1] Clearly, if these projections are valid, adverse drug reactions (ADRs) constitute a major medical problem. It is the purpose of this article to analyze the available data on the scope and nature of ADRs, the statistical validity of making projections from the available information, and to suggest approaches for evaluating and resolving the problem.

For editorial comment see p 1257.

What Is an ADR?

In its broadest sense, an adverse drug reaction is any undesirable effect produced by a drug. However, such a definition would include the effects of intentional overdoses and drug abuse, which are not germane to an analysis of the risks associated with the medicinal use of drugs. The World Health Organization (WHO) has suggested that an ADR is any response to a drug "which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis, or therapy."[2] This would *not* include intentional or accidental poisoning, or drug abuse.

The WHO definition, however, could be interpreted to include therapeutic failures as examples of ADRs. Although it is important to identify the magnitude and impact of therapeutic failures, they should not be lumped together with adverse reactions caused by drugs. The failure of a drug to produce a desired effect is qualitatively distinct from the production of an undesirable effect.

A more appropriate definition would be the following: An adverse drug reaction is any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose.

Although these criteria for evaluating ADRs seem clear, there are major difficulties in discerning whether a particular event in a given patient is the result of a specific medication or part of the patient's underlying illness. The problem is further complicated by the fact that most patients who experience drug reactions often have been receiving many medications and frequently have several underlying illnesses that might account for the particular symptom or laboratory result attributed to the drug. Also, many of the symptomatic complaints often attributed to drugs

From the departments of pharmacology and toxicology, and medicine, University of Rochester School of Medicine and Dentistry, Rochester, NY.

This article is an abbreviated version of a report entitled *Adverse Drug Reactions in the United States: An Analysis of the Scope of the Problem and Recommendations for Future Approaches*, prepared in 1974 for Medicine in the Public Interest, Inc, Washington, DC.

Reprint requests to Department of Pharmacology and Toxicology, University of Rochester Medical Center, 260 Crittenden Blvd, Rochester, NY 14642 (Dr Karch).

—headache, nausea, and dizziness, for example—are totally subjective. Furthermore, many individuals have symptoms of this sort in the absence of drug ingestion. In one study, 81% of presumably healthy individuals not receiving medications had symptomatic complaints (in the 72 hours before questioning) of a type that might be considered to represent adverse reactions to drugs.[3] Similarly, Green[4] reported symptomatic complaints in 13% of patients and 58% of healthy volunteers taking placebos. These studies stress the importance of proper controls in any attempt to evaluate adverse reactions to drugs, and underscore the difficulties in relating specific untoward events to drugs.

Evaluation of deaths from adverse reactions to drugs is difficult, especially if the patient is suffering from a life-threatening disease. Patients with advanced cancer are usually treated with highly toxic drugs in a last-ditch effort to prolong their lives. Inclusion of such patients in an epidemiological evaluation of adverse drug reactions serves primarily to remind us of the lack of effective drugs for treatment of such diseases as cancer, and adds little to the evaluation of drug toxicity in the less critically ill patient. Nevertheless, since one does not want to ignore adverse reactions in terminally ill patients, perhaps one could include events in patients suffering from terminal illnesses in a separate category.

Cause-Effect Relationship

The fundamental problem in assessing an individual clinical situation for an ADR is establishing a clear cause-effect relationship between the drug and the reaction. This is often difficult or impossible. The interpretation involves complex clinical judgments, usually based on limited data and without the benefit of standardized mechanisms for identifying adverse drug reactions.[5]

In the absence of standardized procedures, one must try to define the firmness of the link between the suspected drug and the specific patient response. Terms like, "definite" or "probable" can be operationally defined, as was done by the Registry of Tissue Reactions to Drugs.[6] The following general definitions seem reasonable:

Definite.—A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues; that follows a known response pattern to the suspected drug; and that is confirmed by improvement on stopping the drug (dechallenge), and reappearance of the reaction on repeated exposure (rechallenge).

Probable.—A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern to the suspected drug; that is confirmed by dechallenge; and that could not be reasonably explained by the known characteristics of the patient's clinical state.

Possible.—A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern to the suspected drug; but that could have been produced by the patient's clinical state or other modes of therapy administered to the patient.

Conditional.—A reaction that follows a reasonable temporal sequence from administration of the drug; that does not follow a known response pattern to the suspected drug; but that could not be reasonably explained by the known characteristics of the patient's clinical state. The function of this category is to retain temporarily those cases that may be manifesting a yet undescribed ADR, and to allow later reclassification of the case when more information becomes available. This category would prevent the loss of previously unsuspected drug reactions, and help identify new ADRs.

Doubtful.—Any reaction that does not meet the criteria above.

Evaluation of ADRs based on "definite" and "probable" reactions tends to underestimate the true incidence of adverse reactions, while data that include "possible" reactions tend to overestimate the incidence.

Pitfalls in Interpretation

Populations.—Almost all surveys on the incidence of adverse drug reactions[7-20] have limited their attention to hospitalized patients on acute medical wards. Such patients represent only a portion of the total hospital population, and the characteristics of this group may differ considerably from those of the whole hospital population. Two studies expanded the hospital patient survey to include other services,[21-24] but only one report[25] has included data from all inpatient services of a general hospital group.

The available data are also, unfortunately, limited to hospitalized patients. There has been no systematic attempt to assess adverse drug reactions in outpatient populations; yet this latter group accounts for the bulk of medicinal use in the United States. One report of ADRs in England and Wales[26] included outpatient data, but the data are fragmentary.

Link Between Drug and Reaction.—In this most difficult step in the analysis of ADRs, there are no standardized guidelines, and the decision rests on the clinical judgment of different physicians in different clinical environments—a situation guaranteed to produce differences of opinion. Consider the example of a young woman who sustained a fractured pelvis in an automobile accident and was essentially confined to bed for the next month. During this period she continued to take her prescribed oral contraceptive pills; one month after the accident she was hospitalized for an acute pulmonary embolus. There was no evidence of thrombophlebitis. Pelvic fractures and the use of oral contraceptive pills have each been associated with pulmonary emboli, but ascribing the embolus specifically to either the fracture or the medication is clearly impossible in this example, a not atypical case.

Another obstacle in determining the link between a drug and an adverse reaction is the frequent administration of several drugs simultaneously to a given patient. Identifying the specific drug responsible for an adverse reaction from several possible candidates is often very difficult. "Challenge" and "dechallenge" experiments are not always feasible or defensible, and do not always work.

The ADR literature demonstrates

Table 1.—Adverse Drug Reactions (ADRs) in Hospitalized Patients

Source	Appropriate Definition of ADR	Patient Population	Definition of Link: Drug Reaction	Case Reports	Controlled Study	Reported Incidence of ADRs, %	Interpretation
Seidl et al[10]	±	Medical	+	−	−	13.6	Upper limit estimate
Smith et al[11]	±	Medical	+	−	−	10.8	Upper limit estimate
Hoddinott et al[12]	+	Medical	−	−	−	15	Upper limit estimate
Ogilvie and Ruedy[13,14]	−	Medical	−	−	−	18	Not interpretable
Borda et al[27]	±	Medical	−	−	−	35	Not interpretable
Levy et al[16]	±	Medical	−	−	−	27	Not interpretable
Miller[17]	±	Medical	−	−	−	28	Not interpretable
Gray et al[20]	+	Medical	−	−	−	23	Extreme upper limit estimate
Gardner and Watson[19]	±	Medical	+	−	−	10.5	Moderate estimate
Hurwitz and Wade[21]	±	Medical Surgical Psychiatric	+	−	±	13.5 2.9 2.0	Upper limit estimate
Wang and Terry[24]*	+	Medical-surgical	±	−	−	1.5	Not interpretable
Smidt and McQueen[25]	±	Medical Surgical Obstetrical-newborn Pediatric Gynecologic Psychiatric	−	−	−	6.4 2.0 1.6 1.1 1.3 6.3	Lower limit estimate

*99% male population.

variable concern with the solidity of the drug-reaction link. For example, one report[10] includes reactions that are "documented" or "probable," while another[16] includes reactions described as "definite," "probable," "unknown," and "doubtful." Further, in several studies[16,17,20] these descriptive terms are not clearly defined, and in many reports[7,13,14,18,27] no information is provided on the certainty of the correlation between drug and reaction.

Surveillance Techniques.—Surveillance systems that rely on voluntary physician reporting or retrospective analyses of records will fail to identify many adverse reactions to drugs.[28] Comprehensive prospective surveillance programs have been developed,[8,17,19,27] but intensive prospective monitoring has been utilized only in hospitals, where drug exposures are limited to the pharmaceutical preparations available at that institution. Interpretation of such data should be limited to the specific environment of the study.

Controlled Studies.—There have not been any. Healthy individuals and patients frequently report symptoms that could be interpreted as ADRs if the person were taking a drug.[3,4] Yet the use of controls for this phenomenon has been virtually ignored by articles attempting to evaluate the scope of the ADR problem.

Analysis of Literature

ADRs in Hospital Patients.—The incidence of adverse drug reactions has been variously reported to be between 1.5%[24] and 35%[27] in hospitalized patients, and the differences between these observed incidences reflect differences in sample populations, criteria for evaluating adverse reactions, and surveillance techniques. Table 1 presents a summary analysis of the published reports.

Most of the literature on adverse drug reactions in hospitalized patients has been limited to acute-care medical wards. The incidence of ADRs in hospitalized medical patients ranged from 6% to 15% in those reports that approached the criteria established in this article, but none of these are controlled studies. The limited data available on other hospital services suggest a much lower incidence of ADRs than that observed in medical wards: surgery, 2% to 3%; psychiatry, 2% to 6%; and gynecology, obstetrics and newborn, and pediatrics, 1% to 2% each. The only useful data on the incidence of drug reactions for total hospital populations came from New Zealand, where the overall figure was 3%.

Hospital Admissions Due to ADRs.—Most of the data on hospital admissions due to adverse drug reactions came from the same reports analyzed in Table 1, and the guidelines established in the previous section for cautious interpretation of data apply to this section as well. These reports suggest that approximately 3% of acute-care medical ward admissions[7,11-13,18] and 0.3% of general hospital admissions[25] are due to ADRs.

Fatal ADRs.—The literature on fatal adverse drug reactions suffers from the same methodological inconsistencies as other aspects of the ADR problem, but some of the confounding elements are more apparent in this area. For example, some reports include suicidal poisonings,[10] and others include reactions to experimental drugs.[10,15] In many of the case reports it is impossible to distinguish an alleged drug-induced effect from the symptoms of the patient's underlying illness,[10,14,15] and therapeutic failures are included as drug reactions by several groups.[10,14,15]

One is struck by the extreme variability reported at different times from the same institutions. At one hospital the incidence of fatal ADRs was first reported as 1.5% of acute-care medical ward patients[10] and later as 0.2%.[11] Another group reported 27 fatal ADRs in the first 6,199 monitored patients (0.44%),[15] but only six fatal ADRs in the next 7,630 (0.08%).[17]

Combining the data within each of these groups, plus the data from other reports, but excluding cases not ful-

Table 2.—Adverse Drug Reactions (ADRs) (%) in Hospitalized Patients

Source	Antibiotics	Digitalis and Quinidine	Hypnotics and Sedatives	Tranquilizers and Antidepressants	Insulin	Antihypertensives	Analgesics	Diuretics
Seidl et al[10]*	21.2	21.2	13.0	...	8.9	8.2	...	6.2
Smith al et[11]*	10.0	13.3	...	23.4	3.9	5.6	6.7	7.8
Ogilvie and Ruedy[14]*	16.1	22.3	<4	<4	16.1	<4	<4	5.7
Hurwitz and Wade[21]†	9.3	30.0	5.4	...	...	...	6.9	...
Smidt and McQueen[25]‡	41.5	6.2	...	15.7	...	...	7.6	...

*Medical patients only.
†Medical, surgical, and psychiatric patients.
‡General hospital population.

filling the criteria presented previously in this article for definite or probable ADRs, the reported range of incidence of fatal drug reactions is 0% to 0.31% of medical ward patients. Since all these data are from university teaching hospital medical services, they give no clue to the rates for hospital services other than the medical wards, or to the rates for nonuniversity hospitals.

Which Drugs Cause ADRs?—The data on this question are deficient in that most studies have been limited to medical wards, and one would anticipate a different pattern of drug use and drug reactions on different hospital services. The available data are summarized in Table 2.

On the medical services, digitalis was the most frequent cause of reported ADRs, while antibiotics caused 41.5% of all reported drug reactions in the general hospital population. No other groups of agents were consistently implicated as causing more than 10% of ADRs in the hospital groups studied, but diuretics, antihypertensives, analgesics, and tranquilizers were frequently implicated.

A slightly different spectrum of agents was commonly implicated in analyzing ADRs as a *cause* of hospitalization on medical wards. These data are summarized in Table 3. Digitalis and antibiotics were again prominent, but aspirin, steroids, and warfarin also were responsible for a considerable number of drug-related hospital admissions.

The available reports of fatal ADRs that approached our criteria for a definite or probable adverse reaction to a drug were analyzed to determine which drugs had been responsible. Twenty-seven cases were analyzed from four studies.[7,10,14,15] Digitalis, insulin, morphine, and potassium chloride were implicated in three cases each, and aspirin, 5% dextrose in water, and heparin each contributed two cases. No other drugs were implicated in more than one case, and a total of 24 different drugs were implicated as contributors to the fatal outcome of these 27 cases. In more than 75% of the fatal cases, the implicated drugs had been available in medical practice for more than 30 years, and all of the reported fatal reactions were well-established risks of therapy. Three of the cases involved over-the-counter medications—aspirin and phenolphthalein.

Table 3.—Drugs Implicated as a Cause of Hospitalization on Medical Wards

Agent	Reported ADR Admissions, %	
	Miller[18]	Caranasos et al[7]
Antibiotics	4.2	18.6
Digitalis	17.7	15.2
Aspirin	11.9	14.1
Steroids	5.8	5.7
Warfarin	5.4	6.8
Diuretics	3.1	13.5
Antihypertensives	6.2	6.2
Tranquilizers and antidepressants	3.1	8.5

ADRs Due to Drug Interactions.—There is little information on the overall incidence of drug interactions causing adverse drug reactions. In the only hospital inpatient studies, Ogilvie and Ruedy[14] suspected drug interaction in two ADRs in 731 acute-care medical ward patients (0.27%), and the Boston Collaborative Drug Surveillance Program[29] reported that 234 adverse reactions in 9,900 monitored patients (2.4%) were attributed by the attending physicians to drug interactions.

Effect of ADRs on Hospitalization.—Many studies[10,12,14,21] have reported that patients experiencing adverse drug reactions are hospitalized, on the average, for longer periods than patients without drug reactions; but this does not mean that the hospitalization was prolonged as a result of the ADR. Certainly, longer hospitalization allows for more exposure to more drugs.

Only three studies have attempted to evaluate the impact of a drug reaction on the length of hospitalization. None describes the criteria for determining that hospitalization had been prolonged. In two reports from the Boston Collaborative Drug Surveillance Program,[16,17] an ADR was thought to have prolonged the hospital stay of about 1.5% of medical service patients. In contrast, the experience at the Shands Teaching Hospital of the University of Florida[19] suggested that the hospital stay was prolonged in 11% of acute medical ward patients because of ADRs.

None of the studies determined how long hospitalization was prolonged. The essential data for assessing the impact of the drug reaction on the hospitalization are missing; a priori, it would seem extremely difficult to estimate when, and for how long, hospitalization is prolonged by an ADR.

Preventable ADRs.—None of the published studies of the adverse drug reaction problem have addressed the question of what drug reactions are preventable. Since case reports have not been presented for the majority of ADRs, the data cannot be evaluated to determine if the reported reactions were preventable.

Symptoms and Severity of ADRs.—

Minor functional gastrointestinal disturbances are the most frequently reported reactions in all studies that describe the observed drug-related symptoms[9,16,17,21]; together with rash, itching, drowsiness, insomnia, weakness, headache, tremulousness, muscle twitching, and fever, they account for 60% to 71% of ADRs. Interpretation of these data is impossible because of the lack of control groups in the study populations, especially since one or more of these symptoms are frequently experienced by the majority of healthy individuals taking no medications at all.[3] Similarly, Green[4(p264)] has shown the ability of placebo administration to elicit and intensify symptoms "to a degree where they become regarded as 'side effects' of the medication being given." Thus, many of the described ADRs may be merely manifestations of underlying conditions or placebo effects.

Implications of ADR Data

Estimates of the morbidity, mortality, and cost of adverse drug reactions abound in the medical literature[1,2,30,31] and the lay press (Von Hoffman N: Deadly prescriptions. *New York Post*, May 28, 1974, p 33). In the United States the annual cost of ADRs has been estimated at more than $4.5 billion for hospital rooms alone,[32] and 30,000 to 140,000 patients have been estimated to suffer fatal drug reactions.[1,32] The claim has been made that the length of hospitalization is doubled as a consequence of drug reactions,[31] and that to a great extent these ADRs are avoidable.[31] In contrast, estimates of 160,000 hospitalizations and 2,000 to 3,000 deaths annually have been claimed in other reports.[30] What portion of the claims represents fact, and what portion is conjecture?

Estimates of the number of deaths due to ADRs have generally proceeded as follows. The gross estimate of fatal adverse reactions in one report was 0.44% of medical patients.[15] Since there are approximately 32 million hospital admissions annually in the United States, the total number of deaths (0.44%×32 million) would be 141,000. This reasoning is clearly unacceptable. Our analysis suggests that 0.44% exceeds the upper limit of the range of reported mortalities from drug reactions. Also, the data were obtained from medical wards of university medical centers and cannot be extrapolated to the general hospital population, which includes 75% to 80% nonmedical patients. It is indeed questionable whether such data can validly be applied beyond the institutions where they were obtained.

Hospital costs from ADRs have been estimated along similar lines. At least 18% of hospitalized patients have been said to have a drug reaction, and the hospital stay is alleged to be doubled as a consequence.[31] If there are 30 million hospitalizations annually in the United States, and the average hospital stay is ten days at $90/day, then the total additional cost would be $4.8 billion. Neither the 18% estimate for drug reactions nor the alleged doubling of hospital stay has been substantiated by our analysis of the literature. The reported incidence of adverse drug reactions on medical wards ranged from 6% to 15%, and 10% seems to be a reasonable approximation. However, the only available data on the incidence of ADRs in a general hospital population suggest an incidence of 3%. We were unable to document the doubling of the period of hospitalization as a consequence of ADRs. There was some evidence that hospital stays are prolonged by a drug reaction in 1% to 11% of cases but no data on how much the hospitalization was prolonged.

Similarly, the claim that the majority of drug reactions are avoidable is not substantiated by the available literature.

Conclusions and Recommendations

Our analysis of the ADR literature suggests the following:

1. Estimates of the magnitude of the problem of adverse drug reactions are characterized by a data base that is incomplete, arbitrary, unrepresentative, and uncontrolled, and by cost estimates whose accuracy is questionable.

2. Most reported drug reactions, whether minor or serious, seem to be due to older, standard, and relatively unpromoted drugs.

3. It is not clear how much of the problem results from inept prescribing by physicians, and how much is preventable by decreasing such prescribing or by educating doctors and patients about drug-drug interactions, drug-disease interactions, and scrupulous adherence to directions.

4. Most drug reactions are difficult to categorize unequivocally as to cause, except in the case of gross overdosage, accidental or intentional. This is due to the nonunique character of the reactions, the taking of multiple drugs, and the failure or inability to perform definitive cause-effect tests. Although there are certainly drug reactions that are unsuspected and unreported, there is also assuredly a percentage of "drug reactions" that are unrelated to drugs or blamed on the wrong drug.

These problems require a great deal more information than has been presented in the literature, and we recommend a moratorium on reckless statements and estimates until such information is available. Specifically, we need in-depth analysis of the following:

1. The operational identification of drug reactions.

2. A method for assigning a reaction causally to a specific drug. No one has described a logical system for assigning blame to a drug for an untoward event. What is needed is a systematic approach—perhaps an algorithm that would analyze each case in an accurate and reproducible fashion—to assure agreement on what constitutes a valid drug reaction. Such a system will not be easy to devise, since it would require precise knowledge not only about the drugs but about the diseases they are prescribed for and about the patients who take them. It would also need constant modification. Until such a system is devised, the identification of ADRs will remain arbitrary.

3. The problems involved in evaluating the causes of drug reactions.

4. The extent to which adverse reactions are a reflection of inherently imperfect drugs rather than of improper use.

5. The need for data on control groups for estimates of the "back-

ground noise" that should be subtracted from the observed incidence.

6. Stratification of populations, since the nature of the drugs, the risk-benefit situations, etc, will differ greatly (eg, a cancer hospital is obviously different from an obstetrical hospital).

7. Quantification of the benefit derived from drugs, and the costs of underprescribing drugs.

On the basis of the data gathered from such studies, comprehensive educational programs could be launched. The data presently available are grievously inadequate. Without better data, no one can know whether the ADR problem is trivial, moderate, or worse than the most gloomy current estimates.

Alvan Feinstein, MD; Daniel Azarnoff, MD; Jan Koch-Weser, MD; Paul Meier, PhD; Kenneth Melmon, MD; and Leighton Cluff, MD, aided in the preparation of the original manuscript.

References

1. Talley RB, Laventurier MF: Drug-induced illness. *JAMA* 229:1043, 1974.

2. International drug monitoring—the role of the hospital, World Health Organization. *Drug Intelligence Clin Pharm* 4:101, 1970.

3. Reidenberg MM, Lowenthal DT: Adverse nondrug reactions. *N Engl J Med* 279:678-679, 1968.

4. Green DM: Pre-existing conditions, placebo reactions, and "side effects." *Ann Intern Med* 60:255-265, 1964.

5. Feinstein AR: Clinical biostatistics: XXVIII. The biostatistical problems of pharmaceutical surveillance. *Clin Pharmacol Ther* 16:110-123, 1974.

6. Irey NS: *Diagnostic Problems and Methods in Drug-Induced Diseases: Part I* (1966); *Part II* (1967); *Part III* (1968). Washington, DC, American Registry of Pathology, Armed Forces Institute of Pathology.

7. Caranasos GJ, Stewart RB, Cluff LE: Drug-induced illness leading to hospitalization. *JAMA* 228:713-717, 1974.

8. Cluff LE, Thornton GF, Seidl LG: Studies on the epidemiology of adverse drug reactions: I. Methods of surveillance. *JAMA* 188:976-983, 1964.

9. Cluff LE, Thornton G, Seidl L, et al: Epidemiological study of adverse drug reactions. *Trans Assoc Am Physicians* 78:255-268, 1965.

10. Seidl LG, Thornton G, Smith JW, et al: Studies on the epidemiology of adverse drug reactions: III. Reactions in patients on a general medical service. *Bull Johns Hopkins Hosp* 119:299-315, 1966.

11. Smith JW, Seidl LG, Cluff LE: Studies on the epidemiology of adverse drug reactions: V. Clinical factors influencing susceptibility. *Ann Intern Med* 65:629-640, 1966.

12. Hoddinott BC, Gowdey CW, Coulter WK, et al: Drug reactions and errors in administration on a medical ward. *Can Med Assoc J* 97:1001-1006, 1967.

13. Ogilvie RI, Ruedy J: Adverse reactions during hospitalization. *Can Med Assoc J* 97:1445-1450, 1967.

14. Ogilvie RI, Ruedy J: Adverse drug reactions during hospitalization. *Can Med Assoc J* 97:1450-1457, 1967.

15. Shapiro S, Slone D, Lewis GP, et al: Fatal drug reactions among medical inpatients. *JAMA* 216:467-472, 1971.

16. Levy M, Nir I, Birnbaum D, et al: Adverse reactions to drugs in hospitalized medical patients. *Isr J Med Sci* 9:617-626, 1973.

17. Miller RR: Drug surveillance utilizing epidemiologic methods: A report from the Boston Collaborative Drug Surveillance Program. *Am J Hosp Pharm* 30:584-592, 1973.

18. Miller RR: Hospital admissions due to adverse drug reactions: A report from the Boston Collaborative Drug Surveillance Program. *Arch Intern Med* 134:219-223, 1974.

19. Gardner P, Watson LJ: Adverse drug reactions: A pharmacist-based monitoring system. *Clin Pharmacol Ther* 11:802-807, 1970.

20. Gray TK, Adams LL, Fallon HJ: Short-term intense surveillance of adverse drug reactions. *J Clin Pharmacol* 13:61-67, 1973.

21. Hurwitz N, Wade OL: Intensive hospital monitoring of adverse reactions to drugs. *Br Med J* 1:531-536, 1969.

22. Hurwitz N: Predisposing factors in adverse reactions to drugs. *Br Med J* 1:536-539, 1969.

23. Hurwitz N: Admissions to hospital due to drugs. *Br Med J* 1:539-540, 1969.

24. Wang RIH, Terry LC: Adverse drug reactions in a Veterans Administration Hospital. *J Clin Pharmacol* 11:14-18, 1971.

25. Smidt NA, McQueen EG: Adverse reactions to drugs: A comprehensive hospital inpatient survey. *NZ Med J* 76:397-401, 1972.

26. Girdwood RH: Death after taking medicaments. *Br Med J* 1:501-504, 1974.

27. Borda IT, Slone D, Jick H: Assessment of adverse reactions within a drug surveillance program. *JAMA* 205:645-647, 1968.

28. Koch-Weser J, Sidel VW, Sweet RH, et al: Factors determining physician reporting of adverse drug reactions. *N Engl J Med* 280:20-26, 1969.

29. Adverse drug interactions, Boston Collaborative Drug Surveillance Program. *JAMA* 220:1238-1239, 1972.

30. Stetler CJ: Drug-induced illness. *JAMA* 229:1043-1044, 1974.

31. Melmon KL: Preventable drug reactions—causes and cures. *N Engl J Med* 284:1361-1368, 1971.

32. Silverman M, Lee P: *Pills, Profits and Politics*. Berkeley, University of California Press, 1974.