Papers and Originals

Intensive Hospital Monitoring of Adverse Reactions to Drugs

NATALIE HURWITZ,* M.B., CH.B., PH.D.; O. L. WADE,† M.D., F.R.C.P.

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Summary: A total of 1,268 patients admitted to hospital wards were kept under surveillance by one observer throughout their stay in hospital. All drugs given to them and the occurrence of adverse reactions were recorded.

Drug reactions were found in 10.2% of the 1,160 patients who received drug therapy. Most reactions were due to known pharmacological actions of the drugs. Though only four reactions were of life-threatening seriousness, 80% of the 129 reactions observed were of moderate severity. Digitalis preparations, bronchodilator drugs, and ampicillin had the highest reaction rates. It is suggested that larger surveys of adverse reactions in relation to drug usage would make a useful contribution to the problem.

Introduction

Although in recent years there has been increasing awareness and anxiety in the United Kingdom concerning adverse reactions to drugs few attempts have been made to measure the incidence of such reactions or their relationship to the use of individual drugs. Several surveys have been carried out in hospitals in the United States of America and Canada, and adverse reactions to drugs have been reported to occur to between 1 and 18% of patients in hospital.

This paper reports the method of recording and the results of a study of the occurrence of adverse reactions in patients in hospital in relation to the use of drugs.

Methods

Seven wards with a total of 179 beds in the Belfast City Hospital, a general hospital, and one ward with 52 beds for patients with mental illness in Purdysburn Hospital were chosen (Table I). All patients admitted to a ward after the start of its period of surveillance were included in the study. The same investigator made daily visits to each patient from admission to discharge. A record of name, age, sex, hospital number, ward, date of admission, and diagnosis was completed for each newly admitted patient. The ward notes of the patient, the letter from the general practitioner, and previous hospital records were examined. Patients were interviewed whenever possible on the day of admission. Inquiry of recent drug therapy, of any previous reaction to drugs, and of allergy, hay-fever, or asthma was made. Coma, the need for emergency surgery, and grave symptoms precluded immediate interview.

In a few patients with illness such as paranoid schizophrenia the answers to questions were unreliable and remained so. For these patients information from relatives, previous hospital notes, and the staff treating the patient was recorded. If a patient was admitted to hospital because of a suspected adverse reaction to a drug details of the dose of drug, route of administration, and symptoms and physical signs were noted. At the end of the period of survey of a ward no further new admissions were seen, but patients already under surveillance were visited daily until their discharge.

TABLE I.—Wards Surveyed

Ward Specialty	No. of Beds	Period of Survey	Length of Survey (weeks)
General medicine	12	1/10/65-5/3/66	52
General medicine	22	1/6/66-31/12/66	47
General medicine	15	1/11/65-2/3/66	3
General surgery	18	1/6/66-31/12/66	16
General surgery	30	11/2/66-5/3/66	16
Dermatology	35	5/7/66-25/10/66	17
Psychiatry	47	1/11/65-2/3/66	9
Psychiatry (psychiatric hospital)	52	29/12/65-2/3/66	16

Recording the Drugs Given to Patients in Hospital

Prescriptions for patients in these hospitals were written in the wards and medicines were dispensed from a stock of drugs sent to the ward from the pharmacy, which had no record of drugs supplied to individual patients. The prescription sheet of each patient was examined daily and the drugs given, the time and route of administration, dosage, and any change in treatment or dosage were recorded. The total amounts of each drug given per day were calculated. In the medical wards this task was made slightly easier because prescription sheets similar to those advocated by Crooks *et al.* (1967) were in use. In other wards the nurses compiled separate "medicine lists." When each patient was visited he was asked whether he had taken the drugs prescribed for him. Only drugs taken in the wards were recorded. Drugs given in operating-theatres, during anaesthesia, or in the radiology department were not recorded, as the logistics were too difficult.

Recording Adverse Reactions to Drugs

Daily consultations were made with the medical and nursing staff concerning the occurrence of events which might be adverse reactions to drugs. The reasons for any change in drug treatment and any unusual course of a disease were discussed with reference to their being caused by drug therapy. The nurses' day and night reports were read, as their comments might reveal an adverse reaction to a drug. In the daily visit

* Research Assistant.

† Whitla Professor of Therapeutics and Pharmacology. Department of Therapeutics and Pharmacology, the Queen's University of Belfast.

to the patients, and regardless of whether any adverse reaction had been reported, questions were asked about medicines that had upset them, about any new symptoms or signs, and about reactions that had been reported by the staff. Expected pharmacological reactions were sought and pertinent laboratory findings noted. Those patients who had not been given drugs were similarly visited and questioned to see if they had any manifestations which would otherwise have been mistakenly attributed to a drug reaction.

Analysis of Data

When the survey had been completed a nurse helped with the coding of the data so that automatic data processing could be used in its analysis. A serial number was assigned to each patient, and sex, age, and ward of admission were coded. Individual drugs given were coded by a five-digit code (Inman, 1966; Committee on Safety of Drugs, 1967a). Some additions had to be made to this code to include all the drugs prescribed. If a preparation contained more than one drug its constituent drugs were coded separately. Thus "kaolin and morphine mixture" was recorded as two separate drugs. The number of days each drug was given, total amounts administered, and route of administration were coded. The diseases from which patients suffered were coded according to the International Classification of Diseases (1957) and adverse reactions to drugs by a four-digit code (Committee on Safety of Drugs, 1967b). Basic data were coded for patients whether they did or did not receive drugs in hospital.

The coded information was transcribed on to 80-column graph paper in a predetermined order so that the data could be punched on to cards (International Computers and Tabulators). If a patient had been admitted because of illness due to drugs an "A" card was punched; 64 of these cards were punched. "B" cards were punched for each drug given to each patient; 6,578 B cards were punched.

Definitions and Classifications

A Drug.—Any substance given as therapy or for investigational purposes.

Adverse Reaction to a Drug.—Any adverse response to medication undesired or unintended by the physician (Cluff, Thornton, and Seidl, 1964).

Probability.—Reactions were classified in terms of the probability of their causation by a drug (Seidl, Thornton, and Cluff, 1965). (1) A documented adverse reaction: one commonly known to occur with a definite temporal relationship to taking the drug and a positive rechallenge test or laboratory confirmation. (2) A probable reaction: one commonly known to occur with a definite temporal association and improvement on withdrawal of the drug. (3) A possible reaction: one that is known to occur but the temporal relationship is less clear and other causes are possible.

Severity of Adverse Reactions.—This was classified in three grades (Seidl *et al.*, 1965). (1) Severe: fatal or life threatening. (2) Moderate: required treatment, admission to hospital, or prolonged the stay in hospital by at least one day. (3) Mild: incidental, required no treatment, and did not necessarily call for withdrawal of any treatment.

Type of Reaction.—A classification of the type of drug reaction which takes account of the dose and the possible mechanism of the reaction was used. It is derived from schemes used by Brown (1955), Rosenheim and Moulton (1958), and Rosenheim (1962).

(1) **Overdosage.** Excess intake of drug causing excess predictable pharmacological action.

(2) **Excessive effect.** Therapeutic dose but excess pharmacological action. This might be: (a) a toxic extension of the action of the drug, or (b) conditioned intolerance.

(3) **Side-effect.** Unwanted predictable pharmacological action unrelated to the therapeutic effect and not due to overdosage.

(4) **Hypersensitivity.** Allergic sensitization to a drug by previous exposure to the same drug or a chemically related substance, mediated by antigen-antibody reactions.

(5) **Idiosyncrasy.** Unrelated to known pharmacological actions of the drug and not due to immunological mechanism; possibly genetically determined.

Results

During the period of surveillance of these wards 1,268 patients were admitted. Their age distribution is shown in Fig. 1. The youngest patient was aged 11 years, the eldest 93, and the median age was 56 years. The majority of patients (641) were admitted to general medical wards. There were 743 men and 525 women admitted. This male predominance was because the ward observed at Purdysburn Hospital was for male patients.

FIG. 1.—Age distribution of patients

The patients admitted to general medical or surgical wards had a wide variety of diseases, but 139 were admitted with chronic bronchitis, 108 with myocardial infarction, 82 with cardiac failure, and 72 with cerebral vascular disease; 37 had peptic ulcers and 27 had appendicitis. In the dermatology wards 41 had psoriasis, 18 varicose ulcers, and 18 verrucas. Among those admitted for mental illness 45 were suffering from depression and 38 had schizophrenia.

Number of Drugs Administered.—The distribution of all patients according to the number of drugs they received and the length of their stay in hospital is shown in Fig. 2. Drugs were given to 1,160 patients and 108 patients did not receive any drugs during their stay in the wards. Those who stayed in hospital for 22 days or longer were given significantly more drugs than those who did not stay as long (Table II).

Incidence of Adverse Reactions to Drugs.—Of the 1,160 patients who received drugs, 118 (10.2%) had an adverse reaction to at least one drug during their stay in hospital.

TABLE II.—Length of Stay in Hospital and Number of Drugs Given to Patients

Days in Hospital	No. of Drugs		Total
	1-5	6+	
1-21	542 (68.2%)	253 (31.8%)	795
22 +	134 (36.7%)	231 (63.3%)	365

$$\chi^2 = 100.6. \text{ D.F. } = 1. \text{ P } < 0.001.$$

There were no events which might have been mistaken for adverse reactions to drugs observed in the 108 patients who did not receive drugs. Six of the 118 patients who suffered reactions to drugs during their stay in hospital had been admitted because of drug reactions. Two of them had reactions in hospital to the same drug (digoxin) that had been the cause of their admission. One patient who had an adverse reaction to digoxin while in hospital had been admitted on account of self-

FIG. 2.—Number of drugs given to patients

poisoning with pentobarbitone. The 118 patients had adverse reactions to 129 drugs; nine of them had reactions to two drugs during their stay in hospital and a woman of 70 had reactions to three drugs. There were 138 types of reactions observed (Table III). Some patients had more than one type of reaction to the same drug. Thus one patient had a rash attributed to nikethamide, and some days later, when given the drug in larger doses (96 ml.) because he had respiratory failure, he had a twitching and jerking of his limbs. Seven patients had two different reactions to digoxin. The type of reaction which occurred most frequently was the unwanted pharmacological action of drugs. Thus orciprenaline given to relieve bronchospasm caused palpitations. The next commonest type was an excessive effect of the required pharmacological action of a normal dose of a drug.

TABLE III.—Types of Reactions

Overdosage	2
Toxic	30
Conditioned intolerance	2
Side-effect	80
Hypersensitivity	16
Idiosyncrasy	8
	138

Specialty and Reactions.—The incidence of reactions was highest in medical and lowest in psychiatric wards (Table IV).

TABLE IV.—Drug Reactions and Specialty

	Patients Given Drugs	Patients with Reactions	Rate (%)
Medicine	586	96	16.4
Surgery	249	8	3.2
Dermatology	131	10	7.6
Psychiatry	194	4	2.1

Nature of Adverse Reactions to Drugs.—The various manifestations of drug reactions are shown in Table V. Disturbances of consciousness varied from excessive somnolence in a patient who had been given methaqualone and diphenhydramine (Mandrax) to excessive wakefulness in three patients who had received dichloralphenazone (Welldorm). Three patients suffered from hallucinations attributed to methylamphetamine, imipramine, and phenobarbitone.

TABLE V.—Nature of Adverse Reactions in 118 Patients

System	No. of Manifestations	Manifestations	No.
Gastrointestinal	63	Nausea and vomiting	59
		Diarrhoea	1
		Glossitis, stomatitis	1
		Dryness of mouth	1
		Heartburn	1
		Disorientation	2
		Excessive wakefulness	6
		Excessive somnolence	3
		Hallucinations	3
		Euphoria	1
Neuromuscular	33	Tremulousness	7
		Muscular twitching	4
		Major epilepsy	2
		Myopathy	1
		Parkinsonism	2
		Headache	2
		Arrhythmia	16
Cardiovascular	19	Palpitations	3
		Maculopapular rash	12
		Pruritus and rash	2
Cutaneous	19	Erythema	2
		Erythema and rash	1
		Neurodermatitis	1
		Alopecia	1
		Hypoglycaemia	2
Metabolic	8	Hyperglycaemia	1
		Electrolyte disturbance	1
		Fluid retention	4
		Haematuria	1
Haematological	2	Postoperative bleeding	1
Pulmonary	1	Respiratory failure	1
Renal	1	Retention of urine	1
Total	146		

Objective and Subjective Reactions.—An objective reaction can be regarded as one in which physical signs have been observed, such as rash or respiratory failure, and a subjective reaction as one in which no physical signs were observed and there are only symptoms—for example, nausea, hallucinations. Six men and eight women out of 118 patients had subjective reactions without physical signs.

Severity and Probability Grading of Adverse Reactions.—Of the 129 reactions to drugs that occurred, 4 were classified as severe, 103 as moderate, and 22 as mild. Two of the severe reactions occurred in patients aged 61 and 68 years who had hypoglycaemia caused by insulin given as part of the glucose, insulin, and potassium regimen for myocardial infarction. The other two severe reactions occurred in a man aged 65 with cor pulmonale who went into respiratory failure after he was given Omnopon and in a 75-year-old woman who had severe postoperative bleeding after cholecystectomy. The reaction in the latter patient was thought to be due to heparin given for deep venous thrombosis. Six reactions were classified as “documented” and 118 as “probable.” Five reactions were considered “possible” because for each patient in the context of their disease an alternative cause of their condition could be postulated.

Time from Administration of Drug to Appearance of Reaction.—Fifty-five reactions occurred during the first day of treatment with the drug to which the reaction was thought to be due. Sixteen occurred within one hour of administration of the drug and 13 between one and eight hours after the drug had been given (Fig. 3). Eighty-eight per cent. of reactions occurred during the first eight days of treatment with the drug.

Hospital Day on which Reactions Occurred.—Sixty-two per cent. of reactions occurred during the first eight days of hospital stay (Fig. 4).

Drugs Causing Adverse Reactions

There were 6,470 prescriptions for 309 drugs for 1,160 patients. Forty-seven preparations were responsible for 129 adverse reactions in 118 patients. It was realized that a valid comparison of liability of individual drugs to produce adverse reactions might not be obtained with this method of prospective personal surveillance unless a very large number of patients were studied. However, it was possible to draw some provisional

conclusions regarding the reaction rates of a few drugs where moderate numbers of patients had received them.

Cardiac Glycosides.—Digoxin was given to 192 patients, digitoxin to three, and lanatocide C to two. Thirty-nine patients (19.8%) had reactions—37 to digoxin, one to digitoxin, and one to lanatocide C; 16 of them suffered cardiac arrhythmias. Table VI shows that elderly patients and women had the most reactions. Patients who had reactions received a mean total dose of 6 mg. of digoxin during an average period of 15.9 days. Patients with no reactions had a mean of 7.25 mg. during an average of 16.7 days. During the period of survey 1,371.75 mg. of digoxin were taken by 192 patients and the risk rate of a reaction might be expressed as one reaction per 37 mg. administered, or, if the average dose is considered to be 0.25 mg., one reaction for 148 doses. A high proportion of patients who were given digitalis were also given diuretics.

FIG. 3

FIG. 3.—Period of time from administration of drug to appearance of reaction.

FIG. 4

These patients had a higher incidence of adverse reactions to digitalis than patients who received no diuretic (Table VII). Thirteen patients had steroids as well as digitalis (five without diuretics) and four had reactions. The influence of the diuretics and steroids on digitalis toxicity could not be accurately assessed, partly because the number of patients was small and because many of the patients were receiving several other drugs at the same time.

TABLE VI.—Reactions to Digitalis

Age of Patients	No. Given Drug		No. with Reactions	
	Male	Female	Male	Female
20-39	7	1	0	1
40-49	2	4	0	0
50-59	11	18	1	5
60-69	30	30	2	4
70-79	26	40	6	13
80-89	14	14	2	5
Total	90	107	11	28

TABLE VII.—Reactions to Digitalis and Diuretics

	Patients Given Drugs	Reactions to Digitalis	Reaction Rate (%)
Digitalis + frusemide	79	16	20
Digitalis + hydroflumethiazide ..	23	8	35
Digitalis + frusemide + hydroflumethiazide	18	6	33
Digitalis + other diuretics	24	4	17
Total	144	34	24
Digitalis (no diuretics)	53	5	9

Antibiotics.—Ampicillin was given to 103 patients and eight had reactions (Table VIII). Benzylpenicillin was given to 143 patients and there were no reactions associated with its use. There were also no reactions related to other penicillins given to 24 patients. The patients who had reactions to ampicillin had extensive maculopapular pruritic rashes with slight or moderate fever. In six the rash appeared between one and eight days after ampicillin had been started and while they were still receiving the drug. In two the rash appeared eight and nine days, respectively, after ampicillin had been discontinued. A patient who had glandular fever developed a reaction to ampicillin. The mean age of patients who had reactions to ampicillin was 67 years and of those who did not, 59 years. Patients who had reactions were given a mean daily dose of ampicillin of 2.2 g. for an average of 7.4 days and those who had no reactions had a mean dose of 2.1 g. daily for an average

of 7.3 days. During the period of surveillance 1,548 g. of ampicillin were given to 103 patients and the risk rate of reactions can be expressed as one reaction per 193.5 g. administered, or, if the average dose is considered to be 0.5 g., one reaction for 387 doses.

TABLE VIII.—Drugs and Adverse Reactions

Drug	No. of Patients Given Drug	No. of Adverse Reactions	Rate (%)
Ampicillin	103	8	7.8
Other penicillins	167	0	0
Tetracycline	37	1	
Sulphadimidine	21	1	
Nitrofurantoin	13	1	
Chloramphenicol	9	1	
Orciprenaline	74	6	8.1
Choline theophyllinate	100	5	5.0
Methoxyphenamine	133	1	0.8
Dichloralphenazone	245	4	1.6
Phenobarbitone	68	1	1.5
Other barbiturates	240	0	0
Methaqualone and diphenhydramine ..	22	2	
Glutethimide	22	0	
Chloral hydrate	10	0	
Morphine	90	5	5.6
Methadone	78	2	2.6
Opium alkaloids	57	1	1.8
Pethidine	200	0	0.5
Dihydrocodeine	76	0	0
Codeine	38	0	
Paracetamol	128	0	0
Acetylsalicylic acid	27	0	

Bronchodilator Drugs.—The incidence of adverse reactions for three oral bronchodilator drugs is given in Table VIII. It was customary for patients with bronchitis to be given all three of these bronchodilator drugs for short periods consecutively. Aminophylline, which was given intravenously to 151 patients,

caused reactions in five (3.3%), and in all patients the injection was given very slowly.

Hypnotic Drugs.—Dichloralphenazone was the most widely used hypnotic and had a low reaction rate, similar to that of phenobarbitone (Table VIII). Other barbiturates which were widely used had no adverse reactions. There were two adverse reactions from methaqualone and diphenhydramine which was given to 22 patients.

Analgesic Drugs.—None of the patients with reactions had more than the usual therapeutic doses. Many patients were given several analgesic preparations together. Patients given morphine for premedication were frequently given pethidine for postoperative pain or paracetamol for incidental discomfort and headache.

Discussion

If modern potent drugs are to be used in medicine it is inevitable that adverse reactions will occur. The purpose of this pilot survey was to obtain a reliable estimate of the incidence of adverse reactions and it was hoped that some indications of the risk rate of individual drugs might be determined. Cluff *et al.* (1964) thought that the method most applicable to the study of adverse drug reactions in hospitals required detailed, personal, and daily professional examination of patients, and this method of prospective surveillance was used in the present study.

Reidenberg (1967) and Weston (1968) commented that in previous surveys there had been no control observations of the symptoms and signs of patients before administration of drugs. It is not possible in a survey of this type to defer the administration of drugs, but all patients were interviewed daily whether they were or were not given drugs. The 108 patients who did not receive drugs did not report drug reactions or illness of a type which, had they been having drugs, might have been attributed to them. As the investigator knew that no drugs had been taken as placebos, bias may have been introduced in this assessment.

Cluff *et al.* (1964), Seidl, Friend, and Sadusk (1966), Seidl, Thornton, Smith and Cluff (1966), and Smith (1966) stress the value of information on drug usage which they obtained automatically from the pharmacy where prescriptions were billed. Data-processing equipment used in hospital pharmacies would ease the burden of collecting data on all drugs given to a patient, including those given in operating-theatres and the radiology department. It might still not provide information on the drugs actually taken by the patient.

A criticism of the present survey is that the direct questioning by the adverse reactions officer may have influenced the report-

ing of subjective symptoms by suggesting to patients an adverse reaction to a drug. An improvement in a future study might be a panel of observers to decide on the occurrence of an adverse reaction, and if several observers could be employed the size of the survey could be increased.

Incidence of Adverse Reactions to Drugs

The incidence of adverse reactions found in this survey is compared with the findings of other observers in Table IX. MacDonald and MacKay (1964) and Reidenberg (1968) found only 1% or less of patients admitted had adverse reactions to drugs, but their ascertainment of reactions depended on the continued collaboration of many workers in the hospital who were asked to submit report cards. Slone *et al.* (1966) reported a rate of 8.4% for drugs causing adverse reactions in relation to the total number of drugs prescribed. Sarkany (1968) referred to a recent study based on the dermatology department at the Royal Free Hospital, London, where 45 adverse reactions were observed in 1,846 patients.

The surveys most comparable to the present study in definitions and methods were those at the Johns Hopkins Hospital, Baltimore (Smith, Seidl, and Cluff, 1966; Seidl *et al.*, 1966), and at a university hospital in London, Ontario, by Hoddinott, Gowdey, Coulter, and Parker (1967) and Simmons, Parker, Gowdey, and Coulter (1968). These surveys were of medical wards only and adverse reactions to drugs were reported to occur to between 11 and 15% of patients admitted. They included in their calculations only those reactions to drugs they classified as "documented" or "probable." In the present survey 586 patients admitted to the three medical wards received drugs and 16.4% of them had adverse reactions, or, if three reactions which were classified as "possible" are omitted, 15.9%. Considering the small size of these surveys, the different character of the three hospitals, and the heterogeneity of reactions, the figures are notably similar. Such an incidence of reactions to drugs may pass almost unnoticed in the hospital community unless a special survey is undertaken, but it is widely accepted that if the benefits of modern drug therapy are to be exploited the occurrence of adverse reactions to drugs has to be accepted. Intensive drug monitoring would give valuable information about the risk rate of individual drugs and the relationship between drug dosage and adverse reactions.

Seidl *et al.* (1966) reported more adverse drug reactions on the first hospital day than on any other, whereas in the study by Ogilvie and Ruedy (1967) the incidence was almost identical for each of the first nine days in hospital. In the present study there were more adverse reactions on the first two hospital days than on any others.

TABLE IX.—Incidence of Adverse Drug Reactions During Hospital Stay. Comparison with Other Surveys

Authors	Year of Study and Hospital	Duration of Survey	Total Patients in Survey	Patients who Developed Reactions in Hospital	Reaction Rate (%)	Methods
Schimmel (1964)	1960-61. Grace New Haven Community, Yale Univ. Service, New Haven, Conn., U.S.A.	8 months	1,014	103	10	House officer reports
MacDonald and Mackay (1964) ..	1962. Mary Fletcher, Burlington, Vermont, U.S.A.	1 year	9,557	98	1	Report cards and investigation
Seidl <i>et al.</i> (1966)	1964. The Johns Hopkins, Baltimore, Maryland, U.S.A.	3 months	714	97	13.6	Prospective surveillance
Reidenberg (1968)	1964-6. 5 Philadelphia hospitals, U.S.A.	2 years	86,100	772 reactions	0.9	Report cards
Smith <i>et al.</i> (1966)	1965. The Johns Hopkins, Baltimore, Maryland, U.S.A.	1 year	900	97	10.8	Prospective surveillance
Ogilvie and Ruedy (1967) ..	1965-6. Montreal General, Canada	1 year	731	132	18.0	Report cards and investigations
Hoddinott <i>et al.</i> (1967) ..	1966. A univ. hospital, London, Ontario, Canada	59 days	104	16	15	Prospective surveillance
Simmons <i>et al.</i> (1968) ..	1967. A univ. hospital, London, Ontario, Canada	90 days	219	27	12.3	Prospective surveillance
Present survey	1965-6. Belfast City and Furdysburn, N. Ireland	1 year	1,160* (586)	118 (96)	10.2 (16.4)	Prospective surveillance

* Total number of patients given drugs. The number and reaction rate for patients given drugs in medical wards are in parentheses.

Risk Rates of Individual Drugs

The risk rate of individual drugs for producing adverse reactions can be assessed in two ways. The proportion of all patients who receive a given drug and who get reactions can be calculated, or the total amount or the number of doses of a drug administered or dispensed per adverse reaction can be estimated. The grouping together of heterogeneous and very different reactions to individual drugs makes comparisons between drugs of doubtful validity. A drug which has a high-risk rate of minor reactions may be preferable to a drug with a low incidence of more serious reactions.

Others have noted the frequency of adverse reactions to digitalis (MacDonald and MacKay, 1964; Ogilvie and Ruedy, 1967). Seidl *et al.* (1965) reported that 11.8% of patients given digitalis had reactions. In this survey 19.8% of patients had reactions and the risk rate was greater if patients were also given diuretics, a finding in accord with the known pharmacology of these drugs.

Reaction rates for patients who received ampicillin of 3.8% (Co-operative Controlled Trial, 1966), 10.4% (Kennedy, Wallace, and Murdoch, 1963), and 22% (Sleet, Sangster, and Murdoch, 1964) have been reported. The last-mentioned workers thought the high incidence was related to the high dose, 6 g./day, which they used. In the present study, where the reaction rate was 7.8%, the mean dose of ampicillin was 2.2 g./day. In a larger survey the relationship of the dosage of drugs to the incidence of adverse reactions might become accessible to investigation.

REFERENCES

- Brown, E. A. (1955). *J. Amer. med. Ass.*, **157**, 814.
Cluff, L. E., Thornton, G. F., and Seidl, L. G. (1964). *J. Amer. med. Ass.*, **188**, 976.

- Committee on Safety of Drugs (1967a). *Adverse Reaction Code*. London.
Committee on Safety of Drugs (1967b). *Drug Numbers*. London.
Co-operative Controlled Trial (1966). *Brit. med. J.*, **1**, 1329.
Crooks, J., *et al.* (1967). *Lancet*, **1**, 668.
Hoddinott, B. C., Gowdey, C. W., Coulter, W. K., and Parker, J. M. (1967). *Canad. med. Ass. J.*, **97**, 1001.
Inman, W. H. W. (1966). *Proceedings of European Society for the Study of Drug Toxicity*, **7**, 191. *Excerpta Medica Congress Series*, No. 115.
International Classification of Diseases (1957). *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, vol. 1 and vol. 2, 7th Revision. Geneva.
Kennedy, W. P. U., Wallace, A. T., and Murdoch, J. McC. (1963). *Brit. med. J.*, **2**, 962.
MacDonald, M. G., and MacKay, B. R. (1964). *J. Amer. med. Ass.*, **190**, 1071.
Ogilvie, R. I., and Ruedy, J. (1967). *Canad. med. Ass. J.*, **97**, 1450.
Reidenberg, M. M. (1967). *Lancet*, **2**, 892.
Reidenberg, M. M. (1968). *J. Amer. med. Ass.*, **203**, 31.
Rosenheim, M. L. (1962). *Proc. roy. Soc. Med.*, **55**, 7.
Rosenheim, M. L., and Moulton, R. (editors) (1958). *Sensitivity Reactions to Drugs: A Symposium*. Oxford.
Sarkany, I. (1968). *Proc. roy. Soc. Med.*, **61**, 891.
Schimmel, E. M. (1964). *Ann. intern. Med.*, **60**, 100.
Seidl, L. G., Friend, D., and Sadusk, J. (1966). *J. Amer. med. Ass.*, **196**, 421.
Seidl, L. G., Thornton, G. F., and Cluff, L. E. (1965). *Amer. J. publ. Hlth*, **55**, 1170.
Seidl, L. G., Thornton, G. F., Smith, J. W., and Cluff, L. E. (1966). *Bull. Johns Hopk. Hosp.*, **119**, 299.
Simmons, M., Parker, J. M., Gowdey, C. W., and Coulter, W. K. (1968). *Canad. med. Ass. J.*, **98**, 175.
Sleet, R. A., Sangster, G., and Murdoch, J. McC. (1964). *Brit. med. J.*, **1**, 148.
Slone, D., *et al.* (1966). *Lancet*, **2**, 901.
Smith, J. W. (1966). *Hospitals*, **40**, 90.
Smith, J. W., Seidl, L. G., and Cluff, L. E. (1966). *Ann. intern. Med.*, **65**, 629.
Weston, J. K. (1968). *J. Amer. med. Ass.*, **203**, 35.

Predisposing Factors in Adverse Reactions to Drugs

NATALIE HURWITZ,* M.B., CH.B., PH.D.

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Summary: Predisposing factors were sought in 118 patients who developed adverse drug reactions in hospital. Significantly more patients of 60 years and over, and more women than men, developed adverse drug reactions. Patients with reactions had more drugs before the development of the reaction than patients who did not develop reactions. A previous adverse drug reaction and a history of allergic disease were significant factors, while a history of jaundice or the presence of diabetes mellitus and renal disease was not.

Introduction

In a prospective study of adverse reactions to drugs in hospital patients it was found that 10.2% of 1,160 patients who were given drugs had adverse reactions (Hurwitz and Wade, 1969). During the survey information was obtained on factors which may have predisposed the patients to the development of these reactions.

* Research Assistant, Department of Therapeutics and Pharmacology, the Queen's University of Belfast.

Methods

Only the first admission of each patient was considered in the analysis, so that there was no duplication of patients. Of 1,160 patients who were given drugs, 118 developed adverse reactions.

The results were analysed with the use of a standardization technique for four variants—age, sex, length of stay in hospital, and number of drugs received. This analysis was based on comparisons of the observed distribution of patients with and without adverse reactions with those expected. It is postulated that the distribution of patients with and without adverse drug reactions is the same in groups defined by age, sex, length of stay in hospital, or number of drugs, when the other variants are held constant.

The method of standardization described by Elwood, Pemberton, Merrett, Carey, and McAulay (1965) of the expected distributions has been used in the present study. This standardization technique was also applied for age and sex to assess the separate influences of a history of previous drug reactions, allergic disease, or jaundice and the presence of diabetes mellitus and renal disease on the distribution of patients with adverse