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Aucune des méthodes d'alarme employées durant cette étude n'a permis d'identifier plus de 60% du total des réactions diagnostiquées.

ADDENDUM

Since completion of the above report, McLamb and Huntley[9] have reported a one-month study of adverse reactions during hospitalization, with comparable results.

We wish to thank the resident and nursing staffs for their co-operation throughout this study.

REFERENCES

1. SCHIMMEL, E. M.: *Ann. Intern. Med.*, **60**: 100, 1964.
2. SEIDL, L. G. *et al.*: *Bull. Hopkins Hosp.*, **119**: 299, 1966.
3. SMITH, J. W., SEIDL, L. G. AND CLUFF, L. E.: *Ann. Intern. Med.*, **65**: 629, 1966.
4. CLUFF, L. E., THORNTON, G. F. AND SEIDL, L. G.: *J. A. M. A.*, **188**: 976, 1964.
5. OGILVIE, R. I. AND RUEDY, J.: *Canad. Med. Ass. J.*, **97**: 1450, 1967.
6. PETROVSKY, C. C.: *Med. J. Aust.*, **2**: 943, 1965.
7. LOURIA, D. B. AND KAMINSKI, T.: *Amer. Rev. Resp. Dis.*, **85**: 649, 1962.
8. KISLAK, J. W., EICKHOFF, T. C. AND FINLAND, M.: *New Eng. J. Med.*, **271**: 834, 1964.
9. MCLAMB. J. T. AND HUNTLEY, R. R.: *Southern Med. J.*, **60**: 469, 1967.

Adverse Drug Reactions During Hospitalization

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SEVERAL studies of adverse drug reactions have been reported recently,[1-4] each emphasizing the need for physician recognition of this hazard of medical care. Some of the epidemiological factors have been ascertained. The reported incidence of reactions is variable, reflecting the different methods of surveillance, populations under study, and habits of medical care. The results of our survey of all hazards of hospitalization have been reported.[5] This report details the findings of one hazard, drug therapy.

METHODS

The methods used are described elsewhere.[5] For a 12-month period from July 1965, all patients admitted to a public medical service of The Montreal General Hospital were surveyed for adverse drug reactions occurring during their hospital stay. An adverse drug reaction was defined as any undesired consequence of drug therapy. Failure to achieve an expected therapeutic result was not considered an adverse reaction. Reports of possible reactions were made in writing by the resident and nursing staffs. Each shift of nurses listed the following information on separate forms: medication alterations; diagnostic and therapeutic procedures, and adverse reactions observed. These reports were used as a daily alerting system whereby one of the authors (R.I.O.) could further investigate, evaluate and record the events. During the study period, the evaluator was resident physician on the ward.

The severity of reactions was classified using a system modified after Schimmel.[1] A minor event was one having a short course and subsiding without specific treatment; an event of moderate severity was one which required specific treatment or prolonged hospitalization; and a major event was one which had continuing effects on the host at the time of discharge, or was life-threatening or fatal.

Reactions were classified according to two types.

I. Adverse reactions due to the action of the drug.

(a) Overdosage—an exaggeration of the desired pharmacological effect of the drug.

(b) Side effect—an undesired pharmacological effect of the drug.

(c) Cytotoxic effect—an effect of the drug causing unwanted morphological changes in tissues.

All of Type I events are quantitative abnormalities in drug effects, usually dose-related and predictable. Host factors determining the concentration of drug at the site of drug action may exaggerate these adverse reactions, but special predisposing factors are not necessary for their production.

II. Adverse reactions due to a combination of the effect of the drug and special predisposing factors:

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(a) Constitutionally induced: These reactions are dependent upon the presence of the drug and special host factors which result in a drug effect not directly related to principal pharmacological actions. Hypersensitivity and allergic reactions, inherited enzyme abnormalities resulting in hemolytic anemias of the "primaquine" type, and unusual reactions to drugs because of the particular susceptibility of tissues in infancy and pregnancy are included in this group.

(b) Disease-induced: These reactions are dependent upon the presence of the drug and a disease which results in an unusual drug effect. The Jarisch-Herxheimer reaction to antisyphilitic therapy is included in this group.

(c) Drug-induced: These reactions are the result of interactions of drugs producing an unusual drug effect. A hypertensive crisis following the simultaneous use of amphetamine and a drug which inhibits monoamine oxidase is an example of this type of reaction.

(d) Environmentally induced: These reactions are the result of interaction of a drug and an environmental factor. Superinfection complicating broad-spectrum antibiotic use, due in part to the interaction of drug and normal flora and photosensitivity reactions, are examples of this type of reaction.

Type II adverse reactions are dependent upon a change in the host which alters his response to the drug so that the effect of the drug differs qualitatively from the principal pharmacological effects. These reactions are often not dose-related and are not as readily predicted as are Type I reactions. Some overlap exists between reactions in different categories.

Statistical significance was determined using the Student 't' and chi square tests.

TABLE I.—TYPES OF ADVERSE DRUG REACTIONS

Type I. Due to action of the drug	*Number*	*Per cent*
Overdose	86	44.6
Side effect	52	27.0
Cytotoxic effect	18	9.4
	156	81.0

Type II. Due to combined action of the drug and special predisposing factors	*Number*		*Per cent*
Constitutionally induced			
Allergic 12	15	6.1	7.5
Unknown 3		1.4	
Disease-induced	9		4.6
Drug-induced	2		1.3
Environmentally induced	11		5.6
	37		19.0
Total	193		100.0

RESULTS

One hundred and thirty-two of 731 patients (18%) suffered 193 adverse reactions to drugs in hospital during the one year of study. Reactions present at the time of admission were not included in this incidence.

The majority of reactions (81%) were due to the pharmacological action of the drug—Type I reactions (Table I). Overdose was responsible for 44.6% of all reactions, side effects for 27.0%, and cytotoxic effects for 9.4%. A minority of reactions (19%) were due to the interaction of the drug with special predisposing factors—Type II reactions: 7.5% were constitutionally induced, 4.6% disease-induced, 1.3% drug-induced and 5.6% environmentally induced.

TABLE II.—ADVERSE DRUG REACTIONS: DRUGS IMPLICATED

	Number		*Per cent*
Cardiovascular drugs:			
Digoxin 41	43/193	21.0	22.3
Quinidine 2		1.3	
Antimicrobials	31/193		16.1
Insulin	31/193		16.1
Diuretics	11/193		5.7
Total	116/193		60.2

Digitalis, antibacterial drugs, insulin and diuretics caused 60% of the reactions (Table II). Analgesics, sedative-hypnotics, antidepressants, antihypertensives, hormonal agents other than insulin, radiographic dyes, anticoagulants and bronchodilating agents each caused less than 4% of the reactions.

TABLE III.—AGE OF PATIENTS

	Number of patients	*Average age (years ± S.D.)*
All patients in hospital	731	57.0 ± 23.1
All non-reactors	554*	56.6 ± 22.5
All drug reactors	132*	57.9 ± 15.8

*Number of patients does not include those admitted with an adverse drug reaction.

Characteristics of Reactors

The age of patients who had reactions was not different from the age of other patients ($p > 0.5$) (Table III), and the incidence of adverse reactions for each decade from age 20 to 90 was similar (Fig. 1). There were too few patients beyond these age groups for evaluation. The incidence of reactions in males (17.8%) was not different from that in females (18.5%) ($p > 0.7$).[7]

A marked difference in the incidence of adverse drug reactions in patients in different ad-

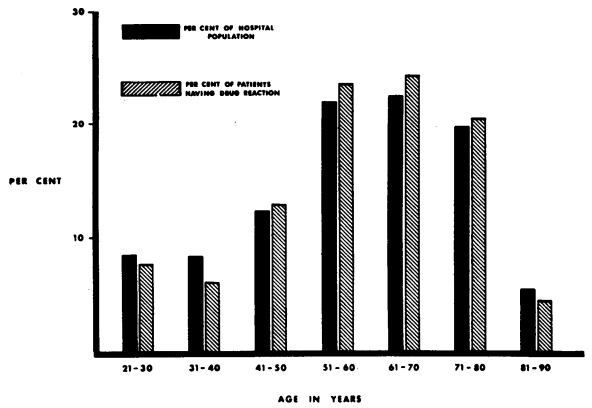

Fig. 1

mission categories was recorded. Patients with a chronic illness alone showed an incidence of 9.0%, those with an acute illness alone, 13.8%, and those with an acute and chronic illness, 31.8% ($p < 0.0005$).

Effect of Reaction on the Patient

The effect of adverse reaction on the patient was assessed by recording the length of hospital stay of patients and by using the classification of severity already described.

The average stay for all patients was 13.7 days. Those who experienced an adverse drug reaction during hospitalization stayed 20.5 days. All other patients averaged 11.6 days in hospital.

Of the 193 reactions, 52 were minor, 74 were of moderate severity and 67 were major. Seventeen of the latter were fatal and 12 had continuing effects on the host at the time of discharge. The mortality rate for all patients experiencing a reaction was 13.2% (22/132), almost twice that of all others in the study group ($p < 0.005$). The average age of patients with fatal reactions was not different from other patients dying in hospital ($p > 0.5$).

Digitalis preparations caused a total of 41 reactions—21% of all adverse drug reactions. On 11 occasions the reaction was manifested by anorexia, nausea, vomiting or diarrhea and on 30 occasions by a cardiac arrhythmia. There were 12 fatal adverse reactions to digitalis. An attempt was made to elucidate some of the factors underlying these adverse reactions, including the presence of renal insufficiency or hypokalemia, and the method of digitalization. Renal insufficiency indicated by an elevated concentration of urea nitrogen in the blood was present in one-half of all patients who showed signs of digitalis toxicity. Hypokalemia induced by diuretic agents was present on six occasions. These factors become more striking in considering the 12 fatal reactions to digitalis. Nine of the 12 patients who died had renal insufficiency and four had serum hypokalemia due to diuretic use. Nine of the 12 patients who died of digitalis toxicity had received an excessive "loading" dose for digitalization. Digitalis toxicity was predictable in a majority of the fatal reactions. Laboratory confirmation of the renal insufficiency or hypokalemia was available in 10 of the 12 patients who died before the intoxication occurred. In six cases, either ventricular tachycardia or fibrillation or supraventricular rhythm was diagnosed by electrocardiography; in four cases cardiorespiratory arrest occurred and at the time that cardiac monitoring was initiated, asystole had occurred. The final two cases had no electrocardiographic or monitoring evidence of normal or abnormal cardiac rhythm. Although the evidence is circumstantial in all cases, we believe that the evidence is sound enough to accept digitalis intoxication as the likely cause of death (see Appendix).

Antibacterial drugs were implicated in 31 reactions. One-third of these reactions were superinfections, defined as invasion or overgrowth by organisms resistant to the drugs in use. Four patients died with overwhelming superinfection. Their average age was 77 years. They remained in hospital 33 days compared to 20.5 days for all reactors. All of these patients received more than one antimicrobial agent. The original bacterial culture before drug use was considered to be a significant growth in only two patients. Death followed severe pneumonia due to *Klebsiella pneumoniae* in one patient, pneumonia due to *Staphylococcus aureus* in another, enterocolitis due to *Staphylococcus aureus* in a third patient, and septicemia due to *Pseudomonas aeruginosa* and *Escherichia coli* in the fourth patient. In these four patients, concurrent disease and other therapy were important factors: one patient with myelogenous leukemia was receiving vincristine, aminopterin, methotrexate and prednisone; one had bronchogenic carcinoma, another had chronic chest disease and parkinsonism, and one patient had severe decubitus ulcers.

Other reactions caused by antimicrobial agents included eight gastrointestinal upsets due to drugs of the penicillin group, tetracyclines or nitrofurantoin. Phlebitis followed intravenous administration of penicillin on four occasions. Allergic reactions followed the use of penicillin, nitrofurantoin and nalidixic acid on one occasion each. There was a Herxheimer reaction during penicillin therapy for syphilis, a grand mal seizure after a high dose of intravenous penicillin, a thrombocytopenia after sulfisoxazole and a pancytopenia after chloramphenicol.

TABLE IV.—RECOGNITION AND REPORTING OF ADVERSE DRUG REACTIONS IN HOSPITAL

Severity	Number of reactions	Method: Intern-resident reporting	Method: Nurse reporting	Method: Medication changes
Minor	52	21	42	10
Moderate	74	32	53	17
Major	67	56	20	16
	193	109 (56.5%)	115 (59.5%)	43 (22.3%)
All major reactions				
Continuing effects at time of discharge	12	12	0	2
Life-threatening	38	27	17	11
Lethal or contributing to death	17	17	2	3
	67	56 (84.0%)	19 (28.5%)	16 (24.0%)

Figures in parentheses refer to the percentage of total reactions.

Analgesics caused seven reactions, one of which was fatal. A 73-year-old man with chronic pulmonary emphysema and possible bronchogenic carcinoma was admitted with dyspnea and aching chest pain, without electrocardiographic evidence of myocardial damage. Administration of 15 mg. of morphine sulfate subutaneously was followed by apnea and death.

Insulin-induced hypoglycemia occurred on 31 occasions. Chlorpropamide caused symptomatic hypoglycemia once. One reaction occurred in a non-diabetic patient given a "small dose" of insulin before meals to stimulate appetite.

Adverse reactions caused by diuretic agents included an elevated concentration of urea nitrogen in the blood in four patients, hepatic coma in three patients with hepatic cirrhosis, acute gout in two patients, alkalosis after ethacrynic acid therapy in one patient, and digitalis intoxication in one patient. There were five other episodes of digitalis intoxication in which the use of diuretic agents was considered contributory to the development of the reaction.

Time of Occurrence of Drug Reactions

In 114 patients whose first reaction was an adverse drug reaction, the median number of days in hospital preceding this initial reaction was 6.9 days. On each of the first nine days of hospitalization, eight or more patients experienced their first drug reaction (total of 85). Only 29 initial reactions to drugs occurred at a later time.

Recognition and Reporting

The events recognized and reported by the three monitoring systems used have been enumerated in Table IV. None of the systems identified more than 60% of all events. The nursing staff was more efficient in reporting events of minor and moderate severity than the intern-resident staff. Surveillance of medication changes proved to be inadequate because nurses did not complete the report forms fully.

The number of events reported each month of the study was similar. There was no decline in incidence with increasing experience of the intern staff.

Patients Admitted with an Adverse Reaction

This special group was not included in the overall incidence although the number of patients is large. Forty-eight patients were admitted with an adverse effect from drug therapy, and 15 of these had further reactions in hospital. The 31.2% incidence of second reactions in this group was similar to the incidence of second reactions in patients suffering reactions during hospitalization. Both incidences were higher than the 18% incidence of a single adverse reaction ($p < 0.001$). The mean age was similar to that of all other hospitalized patients, but the average stay was 14.4 days compared to 20.5 days for reactors in hospital. Three-quarters of the events recognized on admission were of major severity. Sedative-hypnotic, antidepressant and antipsychotic drugs were implicated in 12 events, digitalis in nine, antimicrobials in five and diuretic agents in four. Nine of these patients died in hospital; five deaths were directly related to the drug reaction present on admission, and three were associated with digitalis intoxication incurred in hospital.

DISCUSSION

The importance of adverse reactions to drugs in the hospital care of patients has been emphasized in three recent studies[1-4] which reported that between 10 and 13.6% of patients suffer such reactions (Table V). The 18% incidence in our patients is higher than the previously reported attack rates. The reason for this higher

TABLE V.—INCIDENCE OF ADVERSE DRUG REACTIONS DURING HOSPITALIZATION

	Present study, 1965 - 1966	*Smith, Seidl and Cluff,[3] 1965*	*Seidl et al.[2], 1964*	*Schimmel,[1] 1960 - 1961*
Patients in hospital	731	900	714	1014
Patients with one or more drug reactions	132 (18.0%)	97 (10.8%)	97 (13.6%)	103* (10.0%)
Total adverse drug reactions	193	—	146	119*

*Reactions to therapeutic drugs only.

TABLE VI.—SEVERITY OF ADVERSE DRUG REACTIONS

	Present study, 1965 - 1966	*Seidl et al.*[2] *1964*	*Schimmel*[1] *1960 - 1961**
Minor	52 (27.0%)	65 (44.6%)	61 (51.2%)
Moderate	74 (38.4%)	71 (48.6%)	44 (37.0%)
Major	67 (34.6%)	10 (6.8%)	14 (11.8%)
	193 (100.0%)	146 (100.0%)	119 (100.0%)

*Therapeutic drugs only.

TABLE VIII.—INCIDENCE OF THE TWO PRINCIPAL TYPES OF ADVERSE DRUG REACTIONS IN HOSPITAL

	Present study, 1965 - 1966	*Seidl et al.*[2] *1964**	*Schimmel*[1], *1960 - 1961**
Due to action of the drug	156 (81.0%)	114 (78.0%)	78 (65.5%)
Due to combined action of the drug and special predisposing factor(s)	37 (19.0%)	32 (22.0%)	41 (34.5%)
Total	193 (100.0%)	146 (100.0%)	119 (100.0%)

*Figures from these studies are estimates only.

incidence was not a more frequent reporting of reactions of minor significance in our study (Table VI). Inclusion of diagnostic as well as therapeutic drugs, the use of three methods of surveillance simultaneously, and differences in patient populations and in medical care habits may partially explain the greater occurrence of adverse drug reactions in our patients.

The effects of adverse drug reactions on the patients may be studied by observing the length of stay in hospital of patients suffering reactions as well as by estimating the severity of the reactions. Patients who had a drug reaction had a longer hospital stay in all the study groups reported (Table VII). It may be that adverse reactions were not the cause of this prolonged stay but that the patients susceptible to drug reactions were also the patients requiring long hospitalization. In studying the severity of drug reactions in our patients it was found that 73% of them were moderate or major; that is, they required specific treatment, prolonged hospitalization, had continuing effects on the patient at the time of discharge, or were life-threatening or fatal. Other studies have reported a higher proportion of minor reactions (Table VI).

TABLE VII.—STAY IN HOSPITAL

	Hospital stay (average in days ± S.D.)		
	Present study, 1965 - 1966	*Seidl et al.*[2] *1964*	*Schimmel*[1] *1960 - 1961*
All patients in hospital	13.7 ± 10.3	14.3	12.0
Non-reactors	11.6 ± 7.8	11.4	—
Reactors	20.5 ± 12.3	28.7	20.8

Whether or not these untoward events can be prevented is the most critical question. Are the reactions predictable or are they for the most part unusual and unexpected reactions? Are the reactions chiefly to drugs that have been introduced recently into practice? Do many different drugs or do only a few drugs contribute to the high incidence? Can susceptible patients be characterized and special precautions used in these patients?

Most reactions were due to the pharmacological action of the drug (Table VIII). In our study 81.0% of reactions were due to these Type I reactions of overdosage, side effects or cytotoxic effects. These effects are quantitative abnormalities of drug effects, dose-related and predictable. Physician awareness and care in the use of drugs should eliminate many of these reactions. A better knowledge of dose requirements, recognition of factors which potentiate drug action and awareness of side effects of drugs should aid in decreasing the incidence of these reactions. A reduction in the number of drugs used, and a greater pharmacological knowledge of the agents used should help the physician to avoid these reactions.

It is remarkable that 38% of all adverse drug reactions in our patients were due to three agents which have been used in medical practice for over 30 years—digoxin, quinidine and insulin (Table II). If reactions to other drugs such as acetylsalicylic acid, phenobarbital, paraldehyde, adrenalin, heparin, thyroid extract and purgatives are added, the percentage of reactions caused by these "old" drugs was over 50%. The majority of remaining reactions was due to drugs which have been in use for more than 10 years. It cannot be said that the high incidence of reactions was due to new drugs with which the medical profession has had little experience. Four drugs or drug groups—digitalis and quinidine, antimicrobials, insulin and diuretics—caused 60% of reactions (Table II).

TABLE IX.—DETAILS OF REACTIONS TO DIGITALIS PREPARATIONS

Severity	*Number of patients*	*BUN > 20 mg.%*	*Diuretic-induced hypokalemia*	*Average age (years)*
Minor	6	2	0	51.1
Moderate	13	5	1	64.5
Major:	22			
(a) Life-threatening	(10)	7	1	66.7
(b) Fatal	(12)	9	4	68.1
Totals	41	23	6	

Because of the high incidence of reactions to digitalis preparations, a closer look was taken at these reactions (Table IX). Toxic reactions to digitalis comprised 21% of all drug reactions and 18% of all deaths in patients on the study;

TABLE X.—PATIENTS ADMITTED WITH ADVERSE DRUG REACTIONS

	Present study, 1965 - 1966	*Seidl et al.,*[2] *1964*
Patients admitted with adverse drug reactions	48/731 (6.6%)	34/714 (5.0%)
Patients having further adverse drug reaction during hospitalization	15/ 48 (31.2%)	11/ 36 (30.4%)
Number of deaths	9	8
Deaths related to reaction present on admission	5	5
Deaths related to reaction during hospitalization	3	3

all were dose-related. Factors known to increase drug action, such as renal insufficiency and hypokalemia, were present in over half the patients. Three-quarters of the fatal reactions were predictable on the basis of existing renal disease, hypokalemia or an excessive loading dose for digitalization. Our familiarity with digitalis preparations does not obviate the need for reappraisal of our use of these agents.

Seidl *et al.*[2] found that female patients and patients over the age of 50 years had a higher incidence of adverse reactions to drugs. We found no age or sex predilection. Seidl and his colleagues[2] also reported more adverse reactions on the first hospital day than any other. Our incidence was almost identical for each of the first nine days in hospital. Our patients with concurrent acute and chronic illnesses suffered reactions more frequently than did others. It is possible that these patients were exposed to more drugs than were other patients. Further studies should be made of the incidence in relationship to the exposure rate.

Because our results are taken from a study of patients in hospital it might be said that the high incidence of adverse reactions to drugs is only a hospital phenomenon and does not occur outside of hospital. Not included in the overall incidence in our study, however, were 48 reactions in patients which occurred outside of hospital and with which the patient was admitted to hospital (Table X). The drugs implicated, the severity of the reactions and the percentage of fatal reactions in this group were similar to those incurred in hospital. This suggests that adverse drug reactions are a health problem outside as well as inside our hospitals.

Present methods of predicting drug reactions are unsatisfactory.[8-10] Further study of monitoring systems for the recognition and reporting[4, 6, 7, 11] of adverse drug reactions should be made.

Summary For a 12-month period from July 1965, all patients admitted to a public medical service of The Montreal General Hospital were surveyed for adverse drug reactions occurring during their hospital stay. Three methods of surveillance were used. Of 731 patients, 18% suffered unintended or undesired consequences of drug therapy. Most reactions were major or of moderate severity, that is, required specific treatment, prolonged hospitalization, were life-threatening or fatal. One-quarter of 67 deaths on the service were the result of adverse drug reactions. Of the 193 reactions the majority were caused by drugs that have been in use for many years; 60% were caused by digitalis, quinidine, antimicrobials, insulin and diuretics. Most of the reactions (81%) were caused by the pharmaceutical action of the drug, overdosage, side effects or cytotoxic effects. These reactions were usually dose-related and predictable. Fewer reactions (19%) were due to the interaction of the drug with special predisposing factors that were constitutionally induced, disease-induced, drug-induced or environmentally induced. Nursing staff and resident staff each reported less than 60% of the reactions that occurred. Nurses recognized more events of minor and moderate severity than the resident staff. The average age of patients who experienced reactions did not differ from that of other patients, and attack rates did not differ among the various decades. Reactors remained in hospital for 20.4 days; all other patients, for 11.6 days. Most patients had their first adverse reaction during the first week of stay in hospital. There was a higher incidence of a second reaction in reactors than a first reaction in the total population.

Résumé A partir de juillet 1965, les auteurs ont entrepris, pendant une période de 12 mois, une enquête systématique sur les réactions médicamenteuses défavorables survenant pendant la durée de leur hospitalisation chez tous les malades qui on été admis dans un service médical public du Montreal General Hospital. Ils ont appliqué trois systèmes distincts de surveillance. Parmi ces malades, au nombre de 731, 18% ont présenté des symptômes qui étaient la conséquence inattendue ou indésirable de la médication. La majorité des réactions étaient graves ou modérées, c'est-à-dire qu'elles ont exigé un traitement spécifique, ont prolongé la durée du séjour à l'hôpital, ont menacé la vie des malades ou leur ont été fatales. Un quart des 67 décès enregistrés étaient la conséquence de réactions médicamenteuses défavorables. Des 193 réactions notées, la majorité était le fait de médicaments employés en thérapeutique depuis fort longtemps, 60% ayant été causées par la digitale, la quinidine, des antimicrobiens, l'insuline et des diurétiques. La plupart des réactions (81%) ont été causées par l'action pharmacologique propre du produit, une posologie excessive, des réactions secondaires ou des effets cytotoxiques. Ces réactions étaient généralement liées à la dose et parfaitement prévisibles. Un nombre moins élevé de réactions (19%) étaient causées par l'inter-réaction entre le médicament et

certains facteurs prédisposants qui étaient constitutionels, ou provoqués par la maladie, le médicament lui-même ou le milieu. Le personnel infirmier et les médicins résidents n'ont signalé qu'à peine 60% des réactions. Les infirmières, pour leur part, ont pu diagnostiquer plus de réactions bénignes ou modérées que les résidents. L'âge moyen des malades ayant présenté des réactions ne différait guère de celui de malades d'autres groupes et la fréquence des réactions n'a pas différé entre les diverses périodes. Les victimes de ces réactions ont séjourné à l'hôpital, pendant une moyenne de 20.5 jours, alors que tous les autres étaient restés pendant 11.6 jours. La majorité des malades ont présenté leur première réaction défavorable pendant la première semaine de l'hospitalisation. La fréquence d'une seconde réaction a été plus élevée que celle d'une première réaction dans l'ensemble de la population.

APPENDIX

CASE SUMMARIES OF THE 12 PATIENTS WITH FATAL INTOXICATIONS DUE TO DIGITALIS

Mr. S.N., aged 68. This patient was on no known digitalis therapy when he was admitted to hospital with acute chest pain and shortness of breath. A diagnosis of acute myocardial infarction, atrial fibrillation and congestive heart failure was made. The patient was given 2.75 mg. digoxin intramuscularly during a three-day period, then 0.25 mg. orally daily. On the fifth day of digitalis treatment, the electrocardiogram (ECG) showed sinus bradycardia with multilocular ventricular premature beats. Blood urea nitrogen (BUN) had risen from 20 to 25 mg. per 100 ml. On the 10th day of digitalis treatment, the ECG showed ventricular tachycardia and fibrillation. This responded to electrical countershock. Digitalis therapy was discontinued and potassium given. On the 12th day, ventricular tachycardia and fibrillation recurred and the patient died.

Mrs. V.M., aged 77. This patient with acute chest pain was admitted with no known previous digitalis therapy. A diagnosis of acute myocardial infarction was made. Four days later mild congestive heart failure ensued. Diuretics and digoxin were administered. The patient was given 3.5 mg. digoxin orally over a four-day period, then 0.25 mg. orally daily. On the fourth day of digitalis treatment, the patient complained of anorexia, nausea, vomiting and diarrhea. BUN had risen from 18 to 27 mg. per 100 ml. Digoxin was withheld for one day. On the 11th day, the ECG showed runs of bigeminal and nodal rhythm with a wandering atrial pacemaker. Five episodes of ventricular fibrillation followed, each terminated by electrical countershock. Digitalis therapy was discontinued and potassium was given. The patient died eight days later.

Mrs. A.L., aged 71. This patient with previous hypercalcemia owing to a parathyroid adenoma, diabetes mellitus and chronic renal insufficiency, on no known digitalis treatment before admission to hospital, was admitted with complaints of shortness of breath. A diagnosis of congestive heart failure was made. Diuretic therapy failed to ameliorate her condition. BUN remained over 30 mg. per 100 ml. Potassium was given to correct hypokalemia. The course was complicated by pulmonary edema and the patient was given 2.0 mg. of digoxin intravenously over a period of 12 hours, followed by 0.25 mg. orally daily. Two days after starting treatment with digoxin, the patient complained of nausea and vomiting. Anorexia persisted. Digitalis treatment was continued. The patient died suddenly 13 days later.

Mr. A.K., aged 70. This patient with arteriosclerotic heart disease, chronic congestive heart failure and Stokes-Adams attacks was admitted to hospital with anorexia and nausea. A diagnosis of digitalis intoxication was made and maintenance therapy with digoxin 0.25 mg. daily was discontinued. BUN was 24 mg. per 100 ml. Increasing shortness of breath occurred despite frequent administration of diuretics. Six days after admission, the patient was given digoxin 2.0 mg. orally over a two-day period, then 0.25 mg. daily. Four days after starting digitalis treatment, the patient had three episodes of ventricular tachycardia, each treated by electrical countershock and potassium. Ventricular fibrillation and death followed.

Mr. M.B., aged 68. This patient with arteriosclerotic heart disease and intractable congestive heart failure was admitted to hospital and continued on diuretics and digoxin 0.125 mg. orally daily. While in hospital, the BUN rose from 40 to 112 mg. per 100 ml. Seven days after admission, cardiorespiratory arrest occurred with ECG evidence of asystole unresponsive to resuscitative measures.

Mr. J.F., aged 55. This patient was admitted with acute chest pain and dyspnea with no known digitalis intake before admission. A diagnosis of acute myocardial infarction and pulmonary edema was made. The patient was given lanatocide C 0.8 mg. intravenously during a two-hour period. One-half hour later, the ECG showed a supraventricular tachycardia and atrioventricular block. Electrical rhythm reversion was attempted. Cardiac standstill and death ensued.

Mrs. A.S., aged 63. This patient with arteriosclerotic heart disease and congestive heart failure received diuretics and digoxin 0.25 mg. daily before admission for increasing dyspnea. In hospital, the BUN rose from 27 to 45 mg. per 100 ml. The patient was given 1.5 mg. digoxin parenterally during one day, then 0.25 mg. daily. Nine days later cardiorespiratory arrest occurred with ventricular fibrillation recorded on ECG. Death followed.

Mr. F.L., aged 77. This patient with no known previous digitalis intake was admitted with increasing dyspnea. A diagnosis of arteriosclerotic heart disease and congestive heart failure was made. Diuretics and digoxin were given. The patient was given 3.0 mg. digoxin orally during a four-day period, then 0.25 mg. daily. BUN of 30 mg. per 100 ml. on admission had risen to 87, then to 292 mg. per 100 ml. Seventeen days after digitalis treatment was started, ventricular tachycardia followed by fibrillation unresponsive to treatment occurred and the patient died.

Mrs. S.C., aged 66. This patient with diabetes mellitus and arteriosclerotic heart disease was admitted for control of congestive heart failure. Maintenance therapy of 0.25 mg. digoxin as well as diuretic therapy daily was continued in hospital. BUN of 19 mg. per 100 ml. rose to 26 mg. per 100 ml. five days after admission, at which time the patient complained of anorexia. ECG showed a sinus bradycardia. Hypokalemia was corrected with oral potassium salts, and digoxin was withheld for one day. Anorexia persisted. Eleven days after admission, cardiorespiratory arrest occurred with ECG evidence of asystole, and the patient died.

Mrs. N.B., aged 73. This patient with hypothyroidism had received diuretics and digoxin 0.125 mg. daily before admission for increasing dyspnea. A diagnosis of congestive heart failure was made. BUN was 18 mg. per 100 ml. The patient was given diuretics. Two doses of digoxin totalling 0.75 mg. were given intramuscularly over a four-hour period. Two hours after the last dose of digoxin, the patient died.

Mr. H.C., aged 58. This patient with intractable congestive heart failure of unknown etiology, previously treated with diuretics and 0.25 mg. digoxin daily, was admitted with increasing dyspnea. Within one hour of the administration of lanatocide C 0.4 mg. intravenously, numerous runs of supraventricular arrhythmia were recorded. BUN was 21 mg. per 100 ml. Hypokalemia was treated with oral potassium. No digitalis preparation was given on the second day in hospital. During the following two days, the patient was given 0.625 mg. digoxin, and then 0.25 mg. daily. Anorexia, nausea and vomiting increased in intensity. Cardiorespiratory arrest occurred on the 10th hospital day with an ECG record of asystole, and the patient died.

Mr. J.B., aged 77. This patient with severe dyspnea was admitted with a diagnosis of congestive heart failure. The patient was given 1.0 mg. digoxin orally and 0.4 mg. lanatocide C intravenously during a 12-hour period. Cardiorespiratory arrest occurred 45 minutes after the last dose of digitalis with an ECG record of asystole, and the patient died. Subsequently, it was learned that the patient had received diuretics and 0.25 mg. digoxin daily before admission. The BUN on admission was 245 mg. per 100 ml.

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REFERENCES

1. SCHIMMEL, E. M.: *Ann. Intern. Med.*, **60**: 100, 1964.
2. SEIDL, L. G. *et al.*: *Bull. Hopkins Hosp.*, **119**: 299, 1966.
3. SMITH, J. W., SEIDL, L. G. AND CLUFF, L. E.: *Ann. Intern. Med.*, **65**: 629, 1966.
4. CLUFF, L. E., THORNTON, G. F. AND SEIDL, L. G.: *J. A. M. A.*, **188**: 976, 1964.
5. OGILVIE, R. I. AND RUEDY, J.: *Canad. Med. Ass. J.*, **97**: 1445, 1967.
6. FINNEY, D. J.: *J. Chronic Dis.*, **18**: 77, 1965.
7. CARR, E. A., JR.: *Clin. Pharmacol. Ther.*, **5**: 141, 1964.
8. BARNES, J. M. AND DENZ, F. A.: *Pharmacol. Rev.*, **6**: 191, 1954.
9. LITCHFIELD, J. T., JR.: *J. A. M. A.*, **177**: 34, 1961.
10. *Idem*: *Clin. Pharmacol. Ther.*, **3**: 665, 1962.
11. SLONE, D. *et al.*: *Lancet*, **2**: 901, 1966.