A Manual of

Adverse Drug Interactions

J P Griffin
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Third Edition

WRIGHT

A MANUAL OF ADVERSE DRUG INTERACTIONS

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PREFACE TO THIRD EDITION

At the time of completion of this third edition the Medical Defence Union's Annual Report for 1982 was available and to us, as authors of a book on drug interactions; it made interesting reading.

One case settled for £44 000 was due to phenylbutazone-induced potentiation of warfarin, which was followed by an intraspinal haemorrhage resulting in an incomplete tetraplegia at the level of C7.

A second case of a 64-year-old man with a history of cervical spondylosis, hypertension and previous myocardial infarction attended his general practitioner complaining of pain and numbness in his left wrist and fingers. The doctor diagnosed tenosynovitis and prescribed phenylbutazone. Ten days later the patient was admitted to hospital with severe neurological abnormalities. These were subsequently shown to be due to haemorrhage into the spinal cord. The patient had been on long-term anticoagulants and the phenylbutazone had potentiated their effect. The notes held by the general practitioner had the words 'on anticoagulants' written on the folder but when a new folder had been used, this information had not been transferred to it. This case was also settled for £44 000.

One suspects that in the future as patients become more litigation conscious, more claims for drug-induced injury due to drug interaction will be initiated. In the Medical Defence Union's Annual Report for 1982 they discuss this current trend in increased litigation and ask why more claims? Why are damages much higher? The answer is that litigation is easier with increased opportunities to gain legal aid, wages are higher and reimbursement for lost earnings is also higher.

It is interesting that in the first case the solicitor's letter stated that 'Butazolidin is a well known potentiator of coumarin anticoagulants of which warfarin is one' . . . 'the prescribing of Butazolidin for a patient known to be taking warfarin routinely, was a breach of your professional duty to him'.

It is clear from the tone of these and other recent cases that ignorance of drug interactions is likely to result in high financial reimbursement to those that suffer injury. When doctors are prescribing their principle should be 'do not use two if one will do'.

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PREFACE TO FIRST EDITION

The object of this book is to present in a readily accessible and easily understandable form the major drug interactions that are likely to be encountered in practical therapeutics, and to draw attention to some theoretical interactions that could be serious or life threatening. The book is intended as a convenient desk reference book for the prescribing physician and the pharmacist.

A *Lancet* Editorial (19 April 1975) said that 'publication of huge lists and tables will induce in doctors a drug-interaction-anxiety syndrome and lead to therapeutic paralysis'. We are persuaded better things of our colleagues and envisage few will turn into paralysed medical ostriches as a result of this or any other book on the potential hazards of drug therapy. We believe that awareness of possible hazards of medication and possible interactions between drugs on the part of those who use them, both doctors and pharmacists, can only result in better therapeutics with benefit to the patient in terms of both safety and efficacy.

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INTRODUCTION

Today there is much concern about 'Drug Interaction' because many patients receive more than one drug at a time. Many doctors are unaware of the risks to which their patients are exposed when treated with multiple drugs. When Osler, about 100 years ago, referred to the physician who practises 'a sort of popgun pharmacy hitting now the malady and again the patient, he himself not knowing which', he little thought that his words would be applicable today. It has been pointed out that every time a physician adds to the number of drugs a patient is taking he may devise a novel combination that has a special risk hitherto unsuspected. Occasionally these risks are predictable on the basis of known pharmacology, but all too often they have emerged only after the exposure of many patients.

A drug interaction occurs whenever the presence of one chemical substance changes the pharmacological effects of a therapeutically administered drug. The term 'chemical substance' in this context should be extended to include alcohol, foods, insecticides, possibly food additives, environmental chemical agents as well as drugs therapeutically administered, and drugs of abuse such as cannabis and tobacco.

Much of the detailed knowledge of drug interactions has been gained from animal experimentation and although such observations are of undisputed importance it should not be overlooked that the speed and pathway of drug metabolism in man may be quite different from that which has been determined in many species of laboratory animal. Indeed, Brodie (1962) and Modell (1964) have emphasized that trial in man is the only valid way of establishing drug interactions in man and that ideally such studies should be performed during the early stages of drug development. New drug combinations require separate investigation with animal toxicity studies and clinical evaluation in as full a scrutiny as afforded to a completely new drug.

In a review, Orme (1972) claimed that drug interaction formed only a small part of adverse reactions to drugs as a whole; this type of statement unfortunately reflects the ignorance that surrounds the epidemiological aspects of adverse drug effects in general, and drug interaction in particular. It is true that data of the type required are not plentiful, and it is doubtful if in many of these the reporting is complete. Smith et al. (1966) investigated the incidence of drug-induced adverse effects in a 33-bed medical ward between 1 January and 31 December 1965. Nine hundred patients were included in the survey, and adverse reactions were detected in 10·8 per cent of them. Reactions were most common in patients who were seriously ill and who had received many drugs. The correlation with adverse effects and multiple drug therapy appears to indicate the presence of drug interaction.

In 1967 Ogilvie and Ruedy surveyed adverse drug reactions in 731 patients admitted to a general medical unit over a 12-month period; 193 patients (26·4 per cent) suffered adverse consequences of drug therapy. Sixty-seven deaths occurred in the unit and a quarter of the deaths were drug induced. Most of the reactions (81 per cent) were caused by the primary pharmacological action of the drug; these effects could be shown to be dose related and predictable. Nineteen per cent of reactions were due to drug interaction or were related to special predisposing factors that were constitutionally induced, disease induced, drug induced or environmentally induced.

The Boston Collaborative Drug Surveillance Program collected such quantitative

information on consecutive patients admitted to medical wards. In 1968 they published an article which reported the first 830 patients monitored in a chronic diseases hospital. There were 7078 drug exposures and 405 reported adverse reactions, 22 per cent of which were thought to be due to a drug interaction. The definition of drug interaction used in that publication was similar to one which is widely used, namely a 'pharmacological response which cannot be explained by the action of a single drug but is due to two or more drugs acting simultaneously'. This definition is broad and includes two fundamental types of adverse interactions—those in which two or more drugs with similar pharmacological actions have a cumulative effect which is toxic, and those in which the interaction is 'indirect', i.e. two or more drugs interact in such a way that there is an alteration in the pharmacological effects of one or other of the drugs.

In 1972 the Boston Group re-examined their data on 9900 monitored patients. There were 83 200 drug exposures and 3600 (36·4 per cent) reported adverse reactions. A total of 234 (6·9 per cent) of the adverse reactions were attributed by the attending physicians to a drug interaction (as defined above). This is a considerably lower frequency than that which was previously reported. The change was probably due to the fact that all of the nine hospitals added to the Surveillance Program since the initial report have been acute diseases hospitals. In virtually all cases (230 out of 234) the reported interaction resulted from cumulative pharmacological effects.

In 1973 the Group's total of monitored patients had reached 11 526; there were 103 770 drug exposures and the adverse reaction rate was 28·1 per cent (Miller, 1973). In 1974 the patients numbered 19 000 with 171 000 drug exposures; the reaction rate had seemingly stabilized at 30 per cent (Jick, 1974). It is interesting to notice that during the six years or so of this study, awareness of the relatively high incidence of adverse reaction rate had not altered clinical practice in so far as multiple drug therapy was concerned. Patients at the beginning and at the end of the study received, on average, nine drugs during their stay in hospital.

Members of the Boston Group have also reported on 24 drug-related deaths in hospitalized medical patients (Porter and Jick, 1977a); this latter study monitored more than 26 000 acutely ill patients in seven countries, and in this sense presented some insight into the attendant hazards of drug therapy in the more advanced countries. Such data must not, however, be considered in isolation, or out of context of the diseases from which the patients were suffering. In the Boston Group study, most of the patients who died from drug therapy (in part at least) were suffering from severe terminal illness such as cancer, leukaemia, pulmonary embolism and cirrhosis. Viewed retrospectively (*British Medical Journal*, 1977a) only 6 out of 24 deaths occurring in 26 000 consecutive patients could have been prevented, and in only 3 cases did death result from treatment of patients who were otherwise only mildly unhealthy. The prevalence of *preventable* deaths in this group of medical in-patients was 1 per 10 000, and the drugs responsible were predominantly intravenous fluids and the common additive, potassium chloride.

Similar conclusions have been reached on the results of other studies on adverse reactions and associated deaths. Irey (1976) from the US Armed Forces Institute of Pathology classified 827 autopsied cases of adverse drug reactions and found that only 25 were due to therapeutic errors that were unjustifiable and could have been prevented. Two hundred and twenty cases (26·6 per cent) were unexpected adverse drug reactions, and although these reactions might not have been preventable, since they were not anticipated, the number could perhaps have been reduced by more careful selection and use of anti-infective and anaesthetic agents since these were associated with more than half the deaths (*Journal of the American Medical Association*, 1976). The results of other studies and retrospective reviews have also confirmed that deaths associated with therapeutic drugs in in-patients and out-patients

are uncommon and usually occur in the terminally ill (Böttiger et al., 1974; Girdwood, 1974; Armstrong et al., 1976; Caranasos et al., 1976; *Journal of the American Medical Association*, 1977).

The Boston group believe that the current interest in manuals and information systems that emphasize interactions of the indirect type focuses attention on only a small part of the problem of drug interactions. More attention should be given to toxicity resulting from the use of multiple drugs with similar pharmacological actions. It is also true to say that of the many reported drug interactions in the literature many are anecdotal and have not been confirmed, nor does there exist any well-established pharmacological principle for believing that they could occur. Nevertheless, individual variability is such that factors such as pharmacogenetic differences and effects of disease states may have contributed to a unique reaction. Environmental factors such as smoking and atmospheric pollution or even the hardness of the water supply have also been reported to influence drug metabolism and may also be involved in contributing to a drug interaction as may also dietary factors and particularly herbal remedies which are increasing in their usage by the population due to the mistaken belief that they are free of adverse effects, when in fact their usage is surrounded by ignorance of their pharmacology and toxicology (Dukes, 1977). Discussion is given to these points later in the text.

It is certain that not all adverse drug reactions or interactions are reported to official bodies; indeed the Committee on Safety of Medicines has repeatedly reminded doctors to fill in their 'yellow cards' on which the official statistics are dependent. In the United States there may be a further complication in collecting accurate statistics; the FDA report of 1966 suggested that physicians were becoming increasingly fearful of reporting drug-induced adverse reactions and deaths because of the fear of legal reprisals. In their excellent survey *Medicines in the 1990s*, the Office of Health Economics (1969) predicted that more rational attitudes to adverse reactions were likely to develop, and that a sounder epidemiological approach with better monitoring at the local level would identify more precisely the risks of adverse reactions occurring with particular medicines. Many groups have done, or are now doing, precisely this; for example: Hurwitz and Wade (1969) 'Intensive hospital monitoring of adverse reactions to drugs'; the Boston Collaborative Drug Surveillance Program (1972a) 'Adverse drug interactions', (1972b) 'Adverse reactions to the tricyclic antidepressant drugs', (1972c) 'Interaction between chloral hydrate and warfarin'; Stewart and Cluff (1974) 'Gastrointestinal manifestations of adverse drug reactions'; New Zealand Rheumatism Association Study (1974) 'Aspirin and the kidney'; Boston Collaborative Drug Surveillance Program (Levy, 1974) 'Aspirin use in patients with major upper gastrointestinal bleeding and peptic ulcer disease'; Medicines Evaluation and Monitoring Group (Wood et al., 1974) 'Central nervous system effects of pentazocine'; Boston Collaborative Drug Surveillance Group (1974) 'Regular aspirin intake and acute myocardial infarction'; Sanders et al. (1974) 'Adverse reactions to cephalothin and cephapirin'; Caranasos et al. (1974) 'Drug induced illness leading to hospitalization'; Lawson (1974) 'Adverse reactions to potassium chloride'; Boston Collaborative Drug Surveillance Program (1974) 'Allopurinol and cytotoxic drugs. Interaction in relation to bone marrow depression'; Petrie et al. (1974) 'Drug interaction in general practice'; Janerich et al. (1974) 'Oral contraceptives and congenital limb-reduction defects'; Williams et al. (1976) 'The effects of concomitantly administered drugs on control of long-term anticoagulant therapy'; Bleyer (1975) 'Surveillance of pediatric adverse drug reactions'; McKenney and Harrison (1976) 'Drug-related hospital admissions'; 'Patient compliance especially in the elderly patient' (Smith, 1976; Waters et al., 1976; Wandless and Davie, 1977); 'Drug-induced deafness, anaphylaxis, convulsions and extrapyramidal symptoms' (Porter and Jick, 1977b); 'Oral contraceptives and

diseases of the circulatory system' (Royal College of General Practitioner's Oral Contraception Study, 1977; Vessey et al., 1977; *British Medical Journal*, 1977b); Hull et al. (1978) 'Potential anticoagulant interactions in ambulatory patients'; Stanaszek and Franklin (1978) 'Potential drug interaction incidence in an out-patient clinic'; Wightman (1978) 'Medicine interactions observed in a year of ward pharmacy'; Jick and Porter (1978) 'Drug-induced gastrointestinal bleeding'; 'Hospital admissions due to adverse drug reactions' (Hutcheon et al., 1978; Wiser et al., 1978; Levy et al., 1979); Lawson et al. (1979) 'Life threatening drug reactions amongst medical in-patients'; Burkholder (1979) 'Adverse drug effects and their impact on patient care'; Martys (1979) 'Adverse reactions to drugs in general practice'; Williamson and Chopin (1980) 'Adverse reactions to prescribed drugs in the elderly'; Armstrong et al. (1980) 'Analysis of drug–drug interactions in a geriatric population'; Shehadi and Toniolo (1980) 'Adverse reactions to contrast media'; Williams et al. (1981) 'Awareness of potential drug interactions with anticoagulants'; Danielson et al. (1981) 'Drug-associated psychiatric disturbances'; Jusko (1981) 'Smoking and drug response'; Vessey et al. (1981) 'Mortality in oral contraceptive users'; Somogyi and Gugler (1982) 'Drug interactions with cimetidine'; McElnay et al. (1982) 'Interactions involving theophylline kinetics'; Yosselson-Superstine and Weiss (1982) 'Drug related hospitalization in pediatric patients'; D'Arcy and McElnay (1983) 'Adverse drug reactions and the elderly patient'; Addy et al. (1983) 'Risk factors in phenytoin-induced gingival hyperplasia'; The Centers for Disease Control Cancer and Steroid Hormone Study (1983a) 'Long-term oral contraceptive use and the risk of breast cancer'; (1983b) 'Oral contraceptive use and the risk of ovarian cancer', and (1983c) 'Oral contraceptive use and the risk of endometrial cancer'.

It is with systematic surveys of this type, rather than haphazard and incomplete reporting, that the underlying mechanisms of adverse drug reactions and interactions will be revealed and thus become better understood. This better understanding should allow a more accurate prediction of the reactions and interactions and as a result should reduce their potential hazard. There is, however, a clear need to improve the effectiveness of communication about adverse drug interactions if unnecessary iatrogenic disease is to be avoided.

It is with these requirements in mind that this present volume was prepared. Mechanisms of drug interactions are given in essential detail only to provide a basic background for the better understanding of the drug interactions that are presented in the tables.

The entries in the tables have been carefully selected, and as far as possible interactions in experimental or purely animal studies have been avoided unless they specifically and significantly contribute to the understanding of a clinical problem.

Where possible, details of *in vitro* drug–drug or drug–fluid interactions have also been included in the tables of interactions. This information is likely to be of value in the ward, where it is now a relatively common practice to give drugs as additives to intravenous infusions.

In some instances, drug interactions have been predicted on the basis of established pharmacology, even though examples have not been reported in the clinic. No excuse is offered for this crystal-ball' approach since it is obviously preferable for the clinician to be warned in advance of a potential (albeit theoretical) hazard than for the patient to contribute a new account to the literature on drug interactions.

References are included on pp. 55–63.

CONTENTS

PART 1

Basic Mechanisms of Drug Interactions

PART I

Basic Mechanisms of Drug Interactions

1. BASIC MECHANISMS

Drug interactions can occur inside or outside the body. They can occur before administration when drugs are added *in vitro* to an intravenous drip, or they can have origins in a tablet or capsule when one component of the formulation alters the subsequent bio-availability of the active drug. They can occur in the intestine before absorption when a drug or food component modifies the absorption characteristics of another drug. They can occur after absorption either from drug competition for protein-binding sites in the plasma or from drug competition at binding sites or antagonism at receptor sites in the tissues at which they arrive.

Interactions may modify the degradation of a drug by inducing or inhibiting metabolic enzyme systems, especially those associated with liver microsomes. They may intervene in the excretory processes of the drug in the kidney tubules; indeed there is no phase from formulation to elimination where drug interactions are excluded (Griffin and D'Arcy, 1974).

The many possible sites of drug interactions are shown in *Fig.* 1; this illustrates clearly the extent of the problem which, in this present account, is discussed under the following main headings: drug interactions *in vitro*; drug interactions at the absorption site; drug interactions and drug-metabolizing enzymes; drug interactions at plasma and receptor-binding sites; drug interactions in excretory mechanisms, and other factors in drug interactions.

Complexity of drug interactions

In the following account of the basic mechanisms of drug interaction it is purely for simplicity that the varied sites of possible interaction are discussed separately; it must be very obvious,

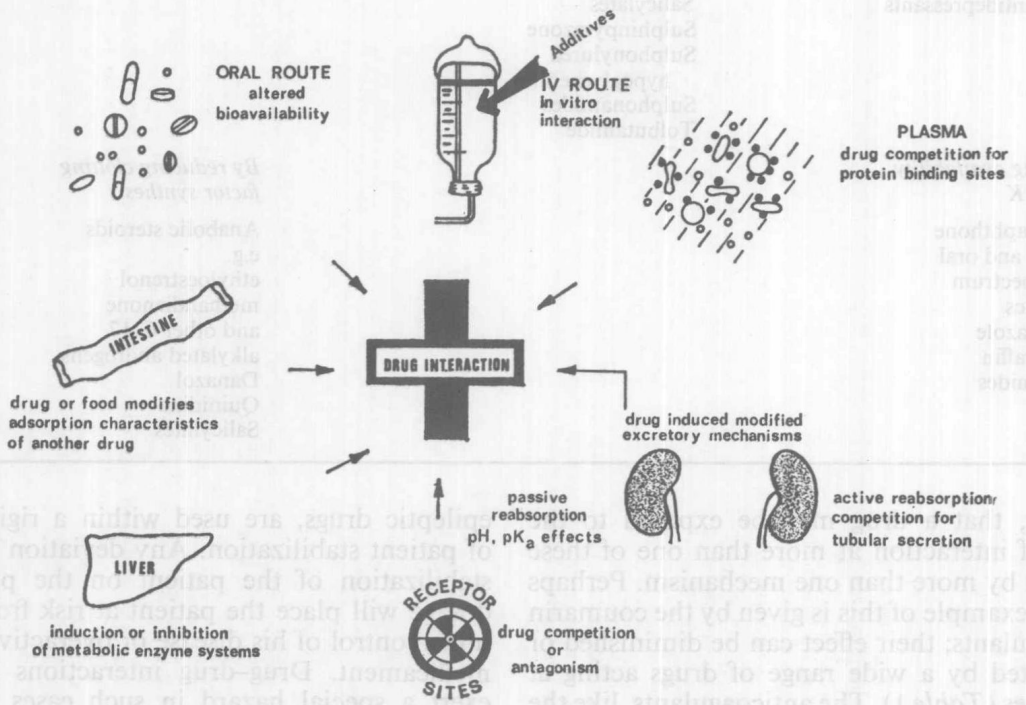

Fig. 1. The possible sites of drug interactions.

Table 1. DRUG INTERACTIONS WITH ANTICOAGULANTS (COUMARINS)

Drugs which antagonize the therapeutic response:

By enzyme induction	*By reduced absorption*	*By increasing clotting factor synthesis*
Barbiturates	Activated dimethicone	Oral contraceptives
Carbamazine	Antacids	Vitamin K
Dichloralphenazone	Cholestyramine	(Pregnancy)
Ethchlorvynol		
Griseofulvin		
Meprobamate		
Rifampicin		
Sulphinpyrazone		
Sulphonylurea hypoglycaemics		

Drugs which potentiate the therapeutic response:

By enzyme inhibition	*By displacement from protein binding*	*By increased receptor site affinity*
Allopurinol	Amiodarone	Clofibrate
Amiodarone	Azapropazone	D-thyroxine
Cimetidine	Chloral hydrate	Norethandrolone
Chloramphenicol	Co-trimoxazole	
Co-trimoxazole	Diazoxide	
Dextropropoxyphene	Ethacrynic acid	
Disulfiram	Indomethacin	
Ethanol	Ketoprofen	
Influenza vaccine	Mefenamic acid	
MAOIs	Nalidixic acid	
Methylphenidate	Naproxen	
Metronidazole	Oxyphenbutazone	
Phenyramidol	Phenylbutazone	
Tricyclic antidepressants	Salicylates	
	Sulphinpyrazone	
	Sulphonylurea hypoglycaemics	
	Sulphonamides	
	Tolbutamide	

By reducing availability of vitamin K	*By reducing clotting factor synthesis*
Acetomenaphthone	Anabolic steroids e.g. ethyloestrenol methandienone and other C-17 alkylated androgens
Neomycin and oral broad-spectrum antibiotics	Danazol
Co-trimoxazole	Quinidine
Liquid paraffin	Salicylates
Sulphonamides	

however, that a drug may be exposed to the effects of interaction at more than one of these sites and by more than one mechanism. Perhaps the best example of this is given by the coumarin anticoagulants; their effect can be diminished or potentiated by a wide range of drugs acting at many sites (*Table* 1). The anticoagulants, like the antihypertensives, antidiabetics and the anti-epileptic drugs, are used within a rigid sphere of patient stabilization. Any deviation from the stabilization of the patient on the prescribed dosage will place the patient at risk from either undercontrol of his disease or overactivity of his medicament. Drug–drug interactions therefore exert a special hazard in such cases (D'Arcy, 1974).

Also in the following account, emphasis has been somewhat biased towards the adverse drug interactions that may occur when another drug is *introduced* into a therapeutic regimen. It must be emphasized, however, that a very severe, even fatal, adverse effect may occur when a drug which causes acceleration of drug metabolism is *withdrawn* from such a regimen. In such a case, the daily intake of the remaining drug, previously well tolerated, is transformed into a virtual overdose due to its normal but slower metabolism.

The coumarins again provide a classic example of this with the increased prothrombin time and spontaneous massive haemorrhage that can occur when phenobarbitone, an enzyme inducer, is withdrawn from a patient on coumarin anticoagulant therapy.

2. DRUG INTERACTIONS *IN VITRO*

Drugs may interact prior to administration; it is in the lore of pharmacy that medicaments may be incompatible with each other in the bottle. This was a frequent, but well-recognized hazard in the bygone days of the elaborate compound prescription. Incompatibility was the only drug interaction that caused concern then, but times have changed, and the unit dosage from the bottle of medicine has been largely replaced by the tablet, capsule or injection of the newer therapeutic agent. The understanding of how drugs can interact with each other inside the body has gradually been augmented, but this specific problem of *in vitro* drug interaction has been forgotten for over a quarter of a century. It has now come back into prominence as a result of the common vogue of adding multiple drugs at patient level in the ward to commercially prepared standard i.v. infusions, and also as a result of the gradual realization that the formulation of the solid dosage form, the tablet or capsule, can have pronounced effects on the bio-availability of the active component.

It is with these two separate problems that this account is concerned; although quite distinct in their origins and their nature, these two problems are nevertheless linked in that their basic cause lies in the chemical or physical–chemical interaction between formulation components.

Additives to i.v. fluids

At the start of such a discussion on the dangers of haphazard addition of drugs to i.v. fluids it is useful to consider the reasons for such additions. There are many reasons for such practice, for example, either where absorption of a drug by the oral route is unpredictable due to vomiting or other reasons, or where it is quite impracticable due to the patient being unconscious. Absorption from the intramuscular site may be erratic as in impaired circulation, or it may be impracticable because of other circumstances, notably intensive anticoagulant therapy. The addition may be an adjunct to fluid therapy, or it may be to facilitate a smooth and continuous administration of a drug, or the number of veins available for drug administration may be limited. There is good reason to believe, however, that in many instances it is just a matter of convenience to use the infusion fluid for the administration of another drug. There is also good reason to believe that many drugs are given via an infusion bottle without due regard to the stability and therapeutic integrity of such combinations.

It is inevitable that the number of situations in which drugs are added to infusion fluids is increasing; this practice reflects the expanding use of a wide range of i.v. fluids. In a survey of 10 hospitals in Ulster, carried out during a 1-month period in January 1972 or January 1973, D'Arcy and Thompson (1974) found that of a total of 7900 separate i.v. infusions documented, 3096 (39·2 per cent) had drugs injected into the infusion container, and in a considerable proportion of these the additives were multiple. Harrison and Lowe (1974) have also published a ward study of i.v. additives and showed that 44 per cent of i.v. solutions used contained drug additives, and that multiple additives were present in 17–24 per cent of the fluids containing additives. Interestingly, Brodlie et al. (1974) found that single drugs were added to fluids for medical patients, whereas for surgical patients 15 per cent of the additives contained two or more drugs. Other surveys within hospitals in the British Isles have shown similar results. These have been reviewed by D'Arcy (1976, 1982) and it is apparent that the addition of drugs to the containers of intravenous infusion fluids is a common practice. The percentage of drug additions made to containers ranged from 14·3 to 45 per cent. Such additions were made mainly on the wards by nursing or medical personnel who were not fully aware of the inherent problems of incompatibility or instability of the admixtures that they were preparing.

There is growing evidence that some drugs will not retain their integrity and efficacy in certain fluids if they are added alone or with other drugs.