A Manual of

Adverse Drug Interactions

Fourth Edition

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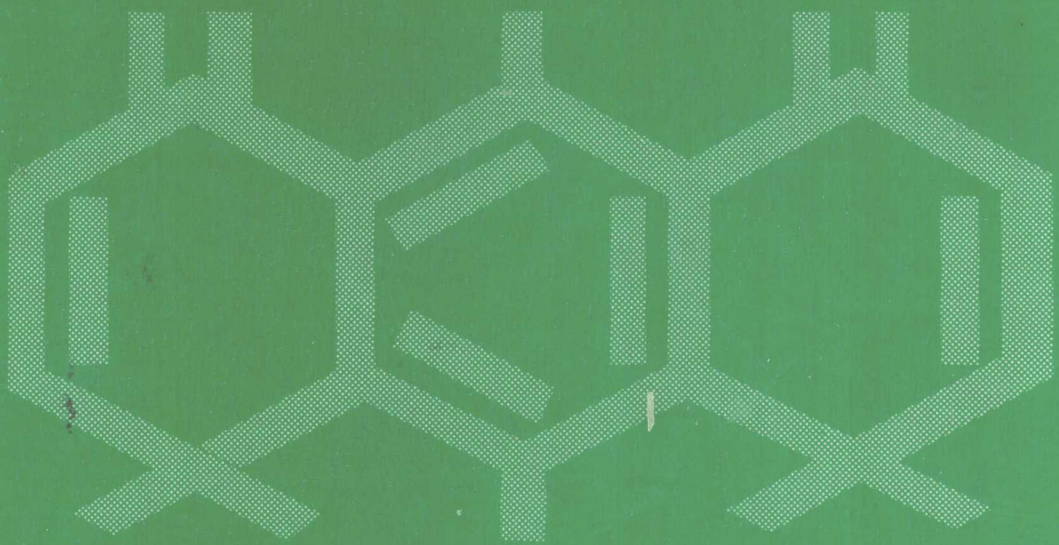

WRIGHT

A MANUAL OF ADVERSE DRUG INTERACTIONS

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PREFACE TO FOURTH EDITION

In the preparation of this edition we are pleased to welcome Dr Chris Speirs as a co-author.

It is becoming very clear that the literature in the field of interactions is also requiring some judgemental element to be exercised as to its clinical significance when therapeutic judgements are being made. We have attempted to do this by indicating by the boldness of typeface the relative importance that should be given to various reports. We are also aware that there are drawbacks to this approach since, rarely, for some unfortunate individuals a reaction may have unexpected severity; for them such interactions are therefore very significant. It is because of this awareness that we have not excluded reference to some usually clinically unimportant interactions.

Finally, we would wish to reiterate the warnings we gave in the preface to the Third Edition regarding the increasing level of medicolegal litigation and have therefore taken the step of reproducing the Preface to the Third Edition.

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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 was of a 64-year-old man with a history of cervical spondylosis, hypertension and previous myocardial infarction who 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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ACKNOWLEDGEMENTS

In the preparation of the fourth edition of this book, one of the final tasks is the writing of the acknowledgement section. During the current revision we have been reminded of how many people have contributed to one or other of the earlier editions which has led to the evolution of the current edition, and we would like to reiterate our thanks to all those acknowledged in previous editions. For particular mention in this context we would mention Professor J. W. Dundee and Mrs Marian Balaam.

We would particularly like to thank two ladies for their expert secretarial help on this and the previous editions, Mrs Vera Markey and Mrs Catherine Fowler.

We are grateful to various authors and their publishers for permission to reproduce figures from their works in our text. We acknowledge the cooperation of Sandoz for the literature search for interactions with cyclosporin.

Our publishers have continued to give their expertise and support in the manner we have now come to expect of them.

Finally, we are as usual indebted to our respective wives for their long suffering patience in allowing us the time to prepare this volume and for their many assistances in its preparation.

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, trial in man is the only valid way of establishing drug interactions in man and 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 1972 review, Orme claimed that drug interaction formed only a small part of adverse reaction reports to drugs as a whole; this type of statement is unfortunately equally true today and reflects the paucity of information that surrounds the epidemiological aspects of adverse drug effects in general, and drug interaction in particular. Under-reporting of adverse drug reactions and interactions and the absence of a finite denominator of patients prevents any true calculation of incidence or prevalence (Griffin and Weber, 1985, 1986). It is a problem in all countries, even those with sophisticated drug regulatory bodies.

The Boston Collaborative Drug Surveillance Program have collected 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).

In a more recent study on the intensive drug monitoring of surgical patients, Danielson et al. (1982), also from the Boston Group, monitored 5232 patients in selected wards in five hospitals in the United States, Scotland and New Zealand from 1977 through 1981. Patients received on average nine drugs on the ward and adverse reactions were associated with 2·2 per cent of these drug orders. Of the 1150 drug-attributed adverse reactions, only 62 were considered to be 'major' by the attending physicians, and 35 (affecting 20 patients) were termed 'life-threatening'. There were, however, no drug-attributed deaths.

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 (Buurma and Vulto, 1984; Vulto and Buurma, 1984). 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; today this is only too apparent and indeed fear of litigation is affecting the whole structure of medical care in America.

Griffin (1986) has surveyed the spontaneous adverse drug reaction reporting schemes in 15 countries and concluded that there was a gross under-reporting of ADRs. The rate of spontaneous reporting of ADRs associated with individual drugs could be influenced by a number of factors not necessarily directly related to the safety of the product, e.g. media bias, monitoring bias.

National differences in volume of usage of individual drugs vary and there are also national differences in the susceptibility to the toxicity of a drug which may vary qualitatively as well as quantitatively.

Griffin (1986) has especially recommended that National Drug Regulatory authorities should make their adverse drug reaction data available to each other. He warned, however, that they should have regard to the heterogenicity of the data collected and realize that extrapolation of ADR data from one country to another may be unjustified. Interestingly, the national awareness of the medical profession to the possibility of ADRs is greater in countries with more conservative prescribing habits than in those countries in which drugs are prescribed more liberally.

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', (1972) '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 Practitioners' 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 outpatient 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'; Halsey and Cardoe (1982) 'Benoxaprofen: side-effect profile in 300 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'; D'Arcy (1983a) 'Reactions and interactions in handling anticancer drugs'; Black and Somers (1984) 'Drug-related illness resulting from hospital admission'; Royal College of Physicians (1984) 'Medication for the elderly'; Stewart et al. (1984) 'Drug use and adverse reactions in an ambulatory elderly population; A review of the Dunedin Program'; D'Arcy (1984a) 'Vaccine–drug interactions'; D'Arcy (1984b) 'Tobacco smoking and drugs'; Danielson et al. (1984) 'Drug-induced blood disorders'; Stern et al. (1984)' Life-threatening drug overdose: Precipitants and prognosis'; Curb et al. (1985) 'Long-term surveillance for adverse effects of antihypertensive drugs'; Durrence et al. (1985) 'Potential drug interactions in surgical patients'; D'Arcy (1985b) 'Drug interactions and reactions update: nitrofurantoin'; White and Ward (1985) 'Drug-induced adverse pulmonary reactions'; Bigby et al. (1986) 'Drug-induced cutaneous reactions'; Griffin (1986) 'Survey of the spontaneous adverse drug reaction reporting schemes in fifteen countries'; D'Arcy (1986a) 'Drug interactions with oral contraceptives'; Lumley et al. (1986) 'Under-reporting of adverse drug reactions seen in general practice'; Walker and Lumley (1986) 'Attitudes of general practitioners to monitoring and reporting adverse drug reactions'; Ridout et al. (1986) 'Knowledge of and attitudes to medicines in the Southampton community'; and International Agranulocytosis and Aplastic Anemia Study (1986) 'Risks of agranulocytosis and aplastic anemia; their relation to drug use with special reference to analgesics'.

It is with systematic surveys and reviews 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. There also is no doubt that other systems of adverse reaction monitoring should be developed and should operate alongside national spontaneous adverse reaction reporting systems (see reviews by Griffin and Weber, 1985, 1986). Foremost among these systems are Prescription Event Monitoring as developed at Southampton University by Inman (1981a, b); the Record Linkage schemes of Skegg and Doll (1981) in the Oxford Region; Crombie (1984) in the Dundee Region; the Medicaid Pharmaceutical Analysis and Surveillance System, Compass (Morse, 1984); and the well- and long-established Boston Collaborative Drug Surveillance Programs which now have international ramifications (Jick, 1984).

Communication about the extent and nature of adverse drug reactions is of critical importance if safety in drug use is to improve. Within this sphere it is vital for physician, pharmacist and other health-care professionals to be aware of, and knowledgeable about, drug interactions. It is with this latter requirement 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. Clinical significance is indicated by boldness of typeface.

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 a few 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.

It will also be evident from this text that most of the drugs that are involved in clinically important interactions are those on which patients are carefully stabilized for long periods. Past experience has shown that it is these drug-stabilized patients who are at special risk from any interaction that will influence the potency or availability of their medication. This is especially so for the elderly patient who is at substantially greater risk than the younger patient of experiencing adverse reactions to medication.

It should be clearly understood, however, that drug interactions *per se* are no threat to the patient; most of the adverse events that they cause are capable of speedy reversal. Their real threat is the practitioner's ignorance either through lack of knowledge of the interaction, or through lack of adequate observation of the patient and the proper interpretation of new events. It is under such circumstances that interactions become dangerous.

References are included on pp. 65–75.

CONTENTS

PART 1

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 bioavailability 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 and tissues 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 on *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, tissue 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

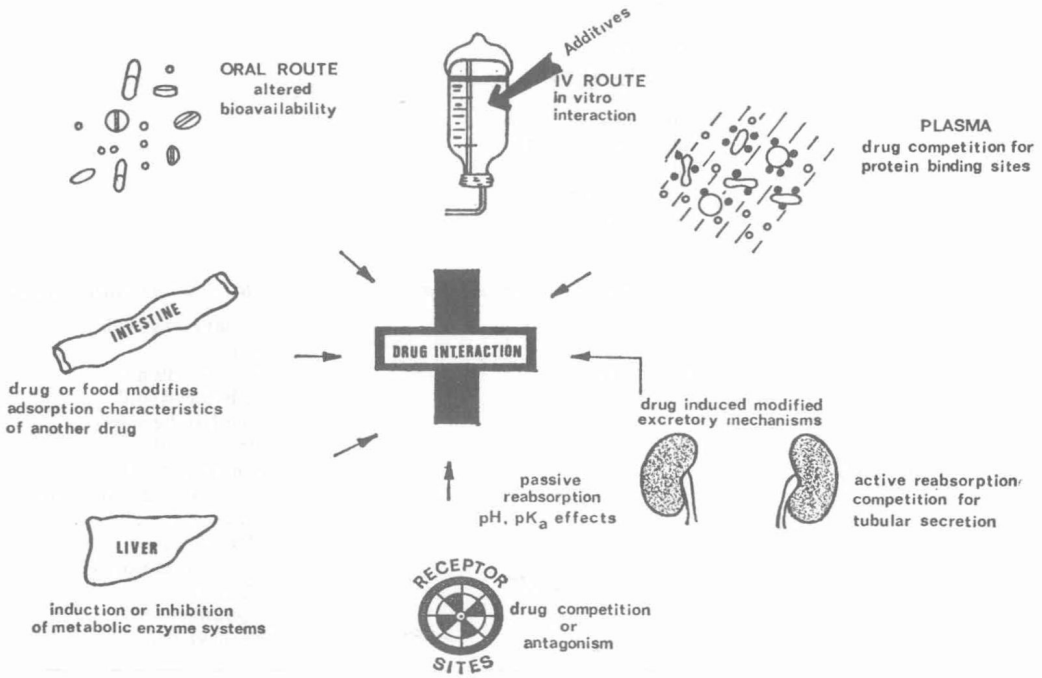

Fig. 1. The possible sites of drug interactions.

Table 1. DRUG INTERACTIONS WITH ANTICOAGULANTS (COUMARINS)

Drugs which antagonize the therapeutic response:

By enzyme induction

Barbiturates
Carbamazine
Chloral hydrate
Dichloralphenazone
Ethchlorvynol
Glutethimide
Griseofulvin
Meprobamate
Nafcillin
Phenytoin
Rifampicin
Sulphinpyrazone
Sulphonylurea hypoglycaemics

By reduced absorption

Activated dimethicone
Antacids
Barbiturates
Cholestyramine

By increasing clotting factor synthesis

Acetomenaphthone
Enteral feeds containing vitamin K
Foods rich in vitamin K (e.g. *Brassica* vegetables)
Oral contraceptives
Phytomenadione
Vitamin K

Drugs which potentiate the therapeutic response:

By enzyme inhibition

Alcohol (ethanol)
Allopurinol
Amiodarone
Chloramphenicol
Cimetidine
Co-trimoxazole
Dextropropoxyphene
Disulfiram
Erythromycin
Influenza vaccine
MAOIs
Methylphenidate
Metronidazole
Phenyramidol
Sulphinpyrazone
Tricyclic antidepressants

*By displacement from protein binding**

Amiodarone
Aspirin
Azapropazone
Chloral hydrate
Co-trimoxazole
Diazoxide
Diflunisal
Erythromycin (?)
Ethacrynic acid
Flurbiprofen
Indomethacin
Ketoprofen
Mefenamic acid
Nalidixic acid
Naproxen
Phenylbutazone
Phenytoin
Salicylates
Sulphinpyrazone (?)
Sulphonylurea hypoglycaemics
Sulphonamides
Tolbutamide

By increased receptor site affinity

Clofibrate
D-Thyroxine
Norethandrolone

By reducing availability of vitamin K

Acetomenaphthone
Cephaloridine
Chloramphenicol
Co-trimoxazole
Kanamycin
Liquid paraffin
Neomycin and oral broad-spectrum antibiotics
Streptomycin
Sulphonamides
Tetracyclines

By inhibiting platelet function

Aspirin
Diflunisal
Flurbiprofen
Latamoxef sodium

By reducing clotting factor synthesis

Anabolic steroids
e.g.
drostanolone
ethyloestrenol
methandienone
stanozolol
and other C-17 alkylated androgens
Danazol
Paracetamol (acetaminophen)
Quinidine
Quinine
Salicylates

*Coincident mechanisms of interaction may also apply.