# STUDIES ON THE SAFE ADMINISTRATION OF DRUGS : EVALUATION AND PREVENTION of DRUG INTERACTIONS

by

Brian Whiting, MB. Ch.B.(Glasg) MRCP (U.K.)

Thesis presented to the University of Glasgow
for the degree of Doctor of Medicine

from the

Department of Materia Medica,
University of Glasgow,
Stobhill General Hospital,
Glasgow

submitted

February 1976

# PREFACE

The medical and scientific discipline of clinical pharmacology permits a line of study which is aimed at improving patient care and increasing our knowledge and understanding of drugs. It is hoped that this thesis, to some extent, reflects these aims.

Some of the work has been published or presented to learned societies. Reprints which are available are submitted with the thesis. Collaboration with a number of colleagues has been necessary and this is duly acknowledged in the formal acknowledgements. Except where indicated, the work has been personally carried out by myself.

The writing of this thesis is entirely my own work.

Contents


| | Page Number |
|---|---|
| Preface .. .. .. .. .. .. .. .. .. .. | (ii) |
| Table of Contents .. .. .. .. .. .. .. .. | (iii) |
| List of Figures .. .. .. .. .. .. .. .. | (vii) |
| List of Tables .. .. .. .. .. .. .. .. | (xii) |
| Acknowledgements .. .. .. .. .. .. .. .. | (xiv) |
| Summary .. .. .. .. .. .. .. .. .. .. | (xvi) |
| Chapter 1 : Introduction .. .. .. .. .. .. | 1 |
| Chapter 2 : Background to drug interactions .. .. | 3 |
| 2.1. Historical perspective .. .. .. .. | 3 |
| 2.2. Hospital prescribing and drug monitoring | 4 |
| 2.2.1. Multiple drug therapy in hospital practice .. .. .. .. .. | 4 |
| 2.2.2. International drug surveillance | 5 |
| 2.3. Self-medication .. .. .. .. .. | 8 |
| 2.3.1. Over-the-counter (o-t-c) drugs .. | 9 |
| 2.3.2. Alcohol .. .. .. .. .. | 11 |
| 2.4. Examples of unmonitored multiple drug therapy .. .. .. .. .. .. .. | 12 |
| 2.5. Conclusions .. .. .. .. .. .. | 14 |
| Chapter 3. : Factors modifying drug response in man .. | 15 |
| 3.1. Genetic factors .. .. .. .. .. | 15 |
| 3.2. Environmental factors .. .. .. .. | 18 |
| 3.3. Pathological factors .. .. .. .. | 19 |
| 3.3.1. Renal disease .. .. .. .. | 19 |
| Pharmacokinetic models .. .. | 19 |
| Analogue computer simulation .. | 20 |
| Dosage prediction nomograms .. | 21 |
| Digoxin pharmacokinetics .. .. | 22 |
| Extra-renal mechanisms .. .. .. | 24 |
| 3.3.2. Liver disease .. .. .. .. .. | 25 |

| | | Page Number |
|---|---|---|
| 3.4. | Effect of age and sex .. .. .. .. .. | 26 |
| 3.5. | Biopharmaceutical factors .. .. .. .. | 27 |
| 3.6. | Conclusions .. .. .. .. .. .. .. | 30 |
| Chapter 4. : | Mechanisms of drug interaction .. .. .. | 31 |
| 4.1. | Introduction .. .. .. .. .. .. .. | 31 |
| 4.2. | Interactions in the pharmaceutical phase .. | 32 |
| 4.2.1. | Complex formation .. .. .. .. | 32 |
| 4.2.2. | Pharmacological interference with gastro-intestinal function .. .. | 34 |
| | Analogue computer simulation .. .. | 34 |
| | Modification of gastric function .. | 36 |
| 4.3. | Interactions in the pharmacokinetic phase .. | 38 |
| 4.3.1. | Redistributional interactions .. .. | 39 |
| | Distribution model .. .. .. .. | 40 |
| | Warfarin-phenylbutazone interaction | 41 |
| | General considerations .. .. .. | 43 |
| 4.3.2. | Personal observations : Plasma drug binding in elderly patients .. .. | 45 |
| 4.3.3. | Interactions affecting drug metabolism | 50 |
| | Enzyme induction .. .. .. .. | 51 |
| | Rifampicin and oral contraceptives .. | 52 |
| | Rifampicin and anticonvulsants .. | 53 |
| | Induction and toxicity .. .. .. | 54 |
| | Enzyme inhibition .. .. .. .. | 55 |
| | Sulthiame and phenytoin .. .. .. | 56 |
| 4.3.4. | Personal observations : Effect of acute alcohol intoxication on the metabolism and plasma kinetics of chlordiazepoxide .. .. .. .. | 57 |
| 4.3.5. | Interactions affecting renal excretion .. .. .. .. .. .. | 62 |

| | | Page Number |
|---|---|---|
| 4.4. | Interactions in the pharmacodynamic phase .. | 64 |
| 4.4.1. | Competition for the receptor site .. | 64 |
| 4.4.2. | Synergism at the receptor .. .. | 66 |
| 4.4.3. | Alteration of the receptor .. .. | 67 |
| 4.4.4. | Alteration of other components at the site of action .. .. .. .. .. | 68 |
| 4.4.5. | Modification of the overall biological response .. .. .. .. | 69 |
| 4.5. | Conclusions .. .. .. .. .. .. .. | 69 |
| Chapter 5. : | Initial development of the drug interaction warning system .. .. .. .. .. .. | 71 |
| 5.1. | Introduction - Clinical problems .. .. | 71 |
| 5.2. | Evaluation and organisation of drug interaction information .. .. .. .. | 73 |
| 5.3. | Presentation of drug interaction information .. .. .. .. .. .. .. | 75 |
| 5.3.1. | Reference devices .. .. .. .. | 75 |
| 5.3.2. | Cardboard prototypes of the drug interaction warning system .. .. | 75 |
| 5.4. | The Drug Disc .. .. .. .. .. .. | 76 |
| 5.4.1. | Response to the Drug Disc publication .. .. .. .. .. | 77 |
| 5.4.2. | The Working Party .. .. .. .. | 78 |
| 5.5. | Legal and ethical considerations .. .. .. | 79 |
| 5.6. | Second version of the Drug Disc .. .. .. | 80 |
| 5.6.1. | Modifications .. .. .. .. .. | 80 |
| 5.6.2. | Introduction of coloured symbols .. | 81 |
| 5.7. | United Kingdom Trial version of the Drug Disc .. .. .. .. .. .. .. | 81 |
| Chapter 6. : | United Kingdom Trial of the drug interaction warning system .. .. .. .. .. .. | 83 |
| 6.1. | Phase 1 .. .. .. .. .. .. .. .. | 83 |

Page Number

6.2. Phase 2 .. .. .. .. .. .. .. .. 84

6.3. Phase 3 .. .. .. .. .. .. .. .. 84

6.4. Results .. .. .. .. .. .. .. .. 84

6.4.1. Response .. .. .. .. .. .. 84

6.4.2. Answers .. .. .. .. .. .. 85

6.4.3. Recommendations .. .. .. .. .. 86

6.5. Discussion .. .. .. .. .. .. .. 88

Chapter 7. : Final development of the drug interaction warning system .. .. .. .. .. .. 91

7.1. Adoption of modifications .. .. .. .. 91

7.2. Re-evaluation of drug interactions .. .. 91

7.3. Final version of the drug interaction warning system .. .. .. .. .. .. .. .. 92

7.4. Production and worldwide distribution .. .. 93

Chapter 8. : Conclusions .. .. .. .. .. .. .. 97

References .. .. .. .. .. .. .. .. .. .. 98

List of Publications and Communications .. .. .. .. 125

List of figures

Figure 1. An example of unmonitored multiple drug therapy.

2. Identification of the contents of the bottle shown in Figure 1.

3. The factors which contribute to the response of a patient to a drug.

4. Interindividual differences in steady-state plasma concentrations (8-78 µg/ml) of nortriptyline on days 6-8 in healthy twins given 0.2 mg/Kg. t.i.d. orally for 8 days.

5. Mean nortriptyline plasma concentration on days 6, 7 and 8 in identical twins not previously exposed to drugs.

6. Mean nortriptyline plasma concentration on days 6, 7 and 8 in fraternal twins not previously exposed to drugs.

7. Mean nortriptyline plasma concentration on days 6, 7 and 8 in identical twins exposed to different drugs.

8. Mean nortriptyline plasma concentration on days 6, 7 and 8 in fraternal twins exposed to different drugs.

9. One-compartment open body model.

10. The Limrose AHT 0090 Analog Tutor used to simulate pharmacokinetic processes which change blood and urine drug levels with time.

11. Two Analog Tutors linked and programmed to simulate a complex pharmacokinetic model.

12. Analogue computer programme for a single dose of drug administered into the gut in a one-compartment system.

13. Analogue computer simulation of the effects of changing renal elimination rates ($K_u$ $1h^{-1}$ and $K_u$ $0.2h^{-1}$) on plasma and urine levels.

14. Nomogram for the determination of gentamicin dosage.

15. Three-compartment model for digoxin kinetics.

16. Predicted time course of digoxin levels in the shallow and deep compartments in relation to observed changes in the central compartment (plasma) according to the three-

compartment model.

17. Correlation between phenylbutazone elimination and the galactose elimination capacity of the liver.

18. Dissolution profiles of two different oral digoxin preparations.

19. Serum concentration profiles corresponding to the two digoxin preparations shown in Figure 18.

20. The three phases of drug action.

21. Interference of iron with the absorption of tetracycline in man.

22. Analogue computer simulation of the effect of varying the rate of absorption ($K_a$ 1, 0.5 and 0.2) on (a) plasma levels and (b) urinary excretion.

23. Analogue computer simulation of the effect of varying the fraction absorbed (100%, 75%, 50% and 25%) on (a) plasma levels and (b) urinary excretion.

24. Analogue computer simulation of the relationship between the rate of absorption and the rate of excretion of drugs.

25. Effects of propantheline and metoclopramide on paracetamol absorption in a group of patients and volunteers.

26. Effects of propantheline and metoclopramide on paracetamol absorption in a single subject.

27. Effect of propantheline on digoxin absorption in volunteers.

28. Schematic representation of some mechanisms involved in drug action.

29. Distribution model showing the relationship between the protein binding of drugs in the plasma and the distribution of free drug in the extravascular fluid space.

30. Graphical representation of the relationship between the plasma protein binding of a drug and its distribution throughout the extravascular fluid space.

31. The effect of protein binding displacement on the distribution of drugs.

32. The displacement of warfarin by phenylbutazone demonstrated by sephadex gel filtration.

33. Schematic representation of the phenylbutazone-warfarin interaction.

34. The binding of salicylate, sulphadiazine and phenylbutazone in normal young volunteers receiving no drugs (Group A), young surgical and gynaecological patients receiving drug therapy (Group B), elderly patients receiving no drugs (Group C) and elderly patients receiving drug therapy (Group D).

35. Comparison of plasma albumin concentrations between Groups A, B, C and D.

36. The effect of dilution on the plasma protein binding of salicylate, sulphadiazine and phenylbutazone.

37. The effect of the number of drugs being taken simultaneously on the binding of salicylate in Group C and D subjects.

38. One-compartment model for chlordiazepoxide kinetics, showing its metabolic conversion to desmethylchlordiazepoxide.

39. Observed and predicted plasma levels of chlordiazepoxide and desmethylchlordiazepoxide in normal volunteers following a single 25 mg oral dose of chlordiazepoxide.

40. Observed and predicted plasma concentrations of chlordiazepoxide and desmethylchlordiazepoxide during the first six days of repetitive dosing of an alcoholic patient with chlordiazepoxide.

41. Observed plasma concentrations of chlordiazepoxide during the first five hours of treatment of the patient shown in Figure 40. Included are serial measurements of plasma alcohol concentration which decline linearly at a rate of 40 mg% per hour.

42. Antagonism of guanethidine by desipramine.

43. Antagonism of bethanidine by desipramine.

44. Schematic representation of the mode of action of tricyclic antidepressants at adrenergic neurones and their interference with the actions of other agents.

45. Example of a circular reference disc.

46. Example of a circular reference disc.

47. First cardboard prototype drug interaction warning system showing large disc on the left and small disc on the right.

48. Second cardboard prototype drug interaction warning system showing large disc on the left and small disc on the right.

49. The Drug Disc as published in the Lancet, showing the complete system, and detail of the large disc.

50. Series of coloured symbols considered for use on the Drug Disc.

51. Draft of the United Kingdom Trial version of the Drug Disc, showing both sides.

52. Side 1 of the United Kingdom Trial version of the Drug Disc with detail of the large disc.

53. Side 2 of the United Kingdom Trial version of the Drug Disc with detail of the large disc.

54. Details of the three phases of the United Kingdom Trial of the Drug Disc.

55. Explanatory letter sent out at the beginning of the United Kingdom Trial.

56. United Kingdom Trial : Initial Report.

57. United Kingdom Trial : Follow Up Report.

58. United Kingdom Trial : Evaluation Report.

59. United Kingdom Trial : Graphical representation of the overall response.

60. United Kingdom Trial : details of the response of the major groups participating in the trial.

61. United Kingdom Trial : response of hospital doctors in Scotland.

62. United Kingdom Trial : response of hospital doctors in the Glasgow area.

63. United Kingdom Trial : details of the participants revising their opinion of the Drug Disc during the course

of the trial.

64. Draft of the final version of the Drug Disc : Side I, with detail of the large disc.

65. Draft of the final version of the Drug Disc : Side 2, with detail of the large disc.

66. Details of the design of the final version of the Drug Disc, showing the relative position of the windows on each side.

67. Details of the design of the final version of the Drug Disc, showing the order of printing of drugs on each side of the large disc.

68. Final version of the Drug Disc, Side I.

69. Final version of the Drug Disc, Side 2.

List of tables.

Table 1. International comparison of drug use during hospitalisation from the Boston Collaborative Drug Surveillance Program.

2. International comparison of drug use in medical patients showing the 12 commonest drugs prescribed, from the Boston Collaborative Drug Surveillance Program.

3. Drugs combined with aspirin in single preparations.

4. Drugs combined with paracetamol in single preparations.

5. Commonly available over-the-counter (o-t-c) drugs which may interact with prescribed drugs.

6. Examples of possible interactions between o-t-c drugs and prescribed drugs.

7. Pharmacokinetic parameters obtained from plasma concentration curves after a single 25 mg oral dose of chlordiazepoxide in three healthy volunteers.

8. Calculated pharmacokinetic constants for chlordiazepoxide and desmethylchlordiazepoxide in three healthy volunteers according to the model shown in Figure 38.

9. Pharmacokinetic parameters obtained from plasma concentration curves after repetitive dosing of chlordiazepoxide in four patients with acute alcoholism.

10. Calculated pharmacokinetic constants for chlordiazepoxide and desmethylchlordiazepoxide in four patients with acute alcoholism according to the model shown in Figure 38.

11. List of drugs reported to interfere with established anticoagulant therapy.

12. Drugs frequently implicated in drug interactions.

13. Examples of categories of drug interactions included on the drug interaction warning system, with appropriate references.

14. List of drugs in common use included on the drug interaction warning system.

15. Worldwide response of doctors to articles and reviews about the Drug Disc.

16. Worldwide response of pharmacists to articles and reviews about the Drug Disc.

17. Worldwide response of students and nurses to articles and reviews about the Drug Disc.

18. Worldwide response of official organisations to articles and reviews about the Drug Disc.

19. Worldwide response of pharmaceutical companies and other commercial companies to articles and reviews about the Drug Disc.

20. Additional drugs to be included on the small discs.

21. Examples of the use of coloured symbols on the second version of the Drug Disc.

22. United Kingdom Trial : distribution list.

23. United Kingdom Trial : overall response to questionnaires.

24. United Kingdom Trial : details of the response of the different groups participating in the trial.

25. United Kingdom Trial, Initial Report : analysis of answers.

26. United Kingdom Trial, Follow Up Report : analysis of answers.

27. United Kingdom Trial : changes in assessment of the value of the Disc throughout the trial period.

28. United Kingdom Trial : comparison of the initial and final assessment of the value of the Drug Disc.

29. Final list of drugs shown on the small discs.

30. Geographical distribution of potential users of the Drug Disc.

ACKNOWLEDGEMENTS

Acknowledgements

Much of the work presented in this thesis is the result of fruitful collaboration with many colleagues, all of whom deserve my gratitude.

Professor A. Goldberg has always encouraged me to pursue various aspects of clinical pharmacology, and over the past five years, his experience, criticism and enthusiasm have all proved invaluable. I am greatly indebted for his advice and support, and for placing the necessary facilities at my disposal.

The pharmacokinetic and protein binding studies involved the participation of healthy volunteers in the form of my colleagues at Stobhill General Hospital, and I am most grateful for their forebearance. These studies also demanded scientific expertise and I would like to thank my co-authors Dr. David Sumner and Mr. Allan Russell of the Department of Clinical Physics and Bio-engineering, West of Scotland Health Boards, for their assistance and mathematical support at all times, Miss Susan Wallace for achieving such proficiency with ultrafiltration techniques, Dr. Graham Skellern of the Department of Pharmaceutical Chemistry at the University of Strathclyde, for his skill and patience with the high pressure liquid chromatograph, Dr. Jurg Meier of Sandoz A.G., Basle, Switzerland, for providing kinetic analysis based on the SAAM program, and Dr. John Runcie of the Department of Geriatric Medicine, Stobhill General Hospital, for many stimulating discussions and for permitting the study of elderly patients in his care.

The Biochemistry Department at Stobhill General Hospital has always been willing to provide assistance and I would like to express my thanks for various biochemical estimations including serum proteins and liver function tests.

I am indebted to Dr. David Lawson of Glasgow Royal Infirmary for inspiring an interest in international drug monitoring and for allowing access to data collected for the Boston Collaborative Drug Surveillance

Program.

Many colleagues contributed at various stages in the development and trial of the drug interaction warning system. I am particularly indebted to Mr. Peter Waldie for his co-operation and assistance in the preparation of successive versions of the Drug Disc. The Scottish Home and Health Department were kind enough to support the project from the outset and I am most grateful for the advice and assistance of fellow members of the Working Party. I should also like to acknowledge the contribution made by all who participated in the United Kingdom Trial.

Through collaboration with the Excerpta Medica Foundation I was fortunate in meeting the late Mr. James Cauverien and will always value a friendship which was tragically so brief.

I would like to thank other members of the Excerpta Medica Foundation, Mr. Jaap van Manen of Amsterdam and his colleagues in Princeton, New Jersey, who have been associated with the final development of the Drug Disc.

My sincere thanks go to Mrs. Nancy Thomson for not only typing this thesis, but for her unfailing helpfulness and secretarial assistance throughout all stages of the development of the Drug Disc.

Preparation of the figures was willingly performed by the staff of the Audio-Visual Services Department at Stobhill General Hospital under the expert guidance of Mr. Peter Waldie. I should like to commend Mrs. Christine McCune for her artwork and Mr. Angus Robertson for his colour printing.

Finally, my thanks go to my wife, Jennifer, without whose interest, support and patience this thesis would not have reached this stage.

# SUMMARY

SUMMARY.

The history of drug therapy, from the earliest herbal remedies to the impressive range of drugs available today, has proved the accuracy of the observation made by Sir William Osler in 1891 that "a desire to take medicine is, perhaps, the great feature which distinguishes man from other animals". Modern therapeutics has brought undoubted benefit to the patient, but not without risk. Unwanted effects and adverse reactions have now become an integral part of drug therapy. A small but significant proportion of these adverse reactions can be attributed to drug interactions, the phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another. Drugs may interact in ways not readily foreseeable from the action of either agent alone and may result in increased or reduced therapeutic efficacy, or sometimes toxic or even fatal reactions.

Numerous surveys have proved that in hospital medicine, multiple drug therapy is now common practice and such interactions as have come to light are merely a small indication of an ever increasing problem. The number of over-the-counter drugs which can be purchased indiscriminately by the public complicates matters further because of the difficulty in ascertaining their composition and strength, the dosages employed, and the combinations in which they are taken with prescribed drugs. Alcohol consumption also adds to the therapeutic problems which face the doctor. If safe and effective therapy is to be attained, he must be aware of all the drugs that a patient is taking and carefully review all drug combinations.

Other factors may play an important part in determining the overall response of a patient to a drug, and drug interactions must be seen in this perspective. Genetic, environmental and pathophysiological factors, particularly renal and hepatic disease, together with allergy and idiosyncrasy may all make important contributions to this response.

In addition, variations in the biological availability of drugs due to pharmaceutical factors may assume importance. Assessment of the contribution of these various factors in individual patients is necessary for rational prescribing. Renal impairment, for example, reduces the clearance of drugs such as digoxin which depend on glomerular filtration for their excretion. Pharmacokinetic studies can derive mathematical models which define these changes accurately and predict appropriate dosage adjustments to maintain optimum therapeutic effect. Simulation of the changes can be usefully achieved by analogue computation.

A number of basic mechanisms are responsible for many drug interactions and an appreciation of these mechanisms can greatly facilitate their interpretation, prevention and treatment. Interactions can be viewed in terms of the three phases of drug action, the pharmaceutical phase, the pharmacokinetic phase and the pharmacodynamic phase. Quantitative changes, reflected as alterations in plasma and tissue concentrations, occur during pharmaceutical and pharmacokinetic interactions while qualitative changes at receptor sites modifying onset, intensity or duration of action, or interference with homeostatic mechanisms occur as a result of interactions in the pharmacodynamic phase.

It is virtually impossible for the practising doctor to sustain the mass of detailed information which is now available on drug interactions. To overcome this problem, a simple, portable drug interaction warning system, the Drug Disc, has been developed. It consists of a reversible unit of two concentric superimposed discs which pivot freely about their common centre. Interactions are indicated by symbols which appear in a window cut into the upper disc when individual drugs or drug categories shown on the two discs are brought into alignment. The information presented embraces the majority of drug interactions which have a bearing on therapeutics and different symbols are used to grade interactions

according to their degree of clinical significance. This grading was based on the nature and severity of the interaction, the adequacy of published information, and opinions expressed by the developers of the Disc, including a Working Party established by the Scottish Home and Health Department, and 450 doctors and pharmacists who participated in a trial of the Disc in the United Kingdom. This survey of attitudes about the warning system indicated that the majority of participants found the information provided to be both clinically useful and informative. Subsequent consumer research in other countries has confirmed that the system would be of value both as a practical aid in prescribing and in teaching. The degree of interest and enthusiasm stimulated by the Drug Disc showed that drug interactions are an aspect of modern medicine that cannot be ignored, and suggested that this kind of aid to prescribing was warranted. It is planned to effect a free distribution of the Disc to Health Service Doctors in the United Kingdom and the Excerpta Medica Foundation has accepted responsibility for its worldwide distribution.

Further experience with drug combinations and the introduction of new drugs will largely dictate much of the relevance of drug interactions in the future. The Drug Disc will be subjected to constant review and appropriate changes made whenever necessary. It is hoped that a system of this kind will foster a more critical approach to multiple drug therapy and help to reduce many of the hazards implicit in drug combinations.

# CHAPTER I

# INTRODUCTION

## INTRODUCTION

Combinations of drugs have characterised the practice of medicine in its many forms throughout the ages. Herbal remedies and various concoctions of vegetable or animal material contained mixtures of chemicals, but they were usually administered empirically and little attempt was made to identify individual ingredients. The fact that they might provide a "cure" was sufficient in itself. Modern analytical and synthetic techniques have produced therapeutic agents which have, to a large extent, replaced both the former therapeutic empiricism and the dependence on Mother Nature. A doctor can now choose to use powerful, specific drugs in the treatment of a patient and his knowledge and understanding of drugs and disease should give him complete control over the therapeutic substances he prescribes.

Even now, however, it is rare for patients to receive only one drug at a time. Many surveys of the use of drugs, particularly in the hospital environment, highlight the popularity of multiple drug therapy. There is also little doubt that outside hospital, polypharmacy is even more widespread. In this setting, patients have ready access to over-the-counter medicinal products, but little awareness of their inherent dangers. Modern marketing and advertising have given great incentive and encouragement to self-medication but have failed to stress its main drawback - that any purely symptomatic benefit may be gained at the expense of a carefully prescribed therapeutic regimen.

There is now no doubt that the simultaneous exhibition of several drugs may complicate therapy by presenting the possibility of drug interactions. This implies that a combination of drugs alters the efficacy or toxicity of one or more of the drugs. The proliferation of drug therapy and the introduction of new and more potent drugs will only serve to aggravate this problem unless it can be brought to the

attention of all prescribing doctors. Although there are many excellent reviews of drug interactions, the subject nevertheless presents a complex and profound problem and the practising doctor would find it virtually impossible to sustain the mass of detailed information now available. He should certainly be aware, however, of the potential for interactions and have an appreciation of their clinical significance.

The availability of so many potent drugs, the common practice of polypharmacy and the widespread unmonitored self-medication with over-the-counter products presents drug interactions as an aspect of modern medicine that cannot be ignored. To assist the practitioner in the identification and prevention of clinically significant drug interactions, relevant information should be immediately available in as concise a form as possible. A drug interaction warning system has been conceived and developed to provide this.

# CHAPTER 2

## BACKGROUND TO DRUG INTERACTIONS

# 2. BACKGROUND TO DRUG INTERACTIONS

## 2.1 HISTORICAL PERSPECTIVE

Disease expresses itself as fear, anxiety and pain, and throughout history man has sought to find relief by searching for effective remedies. Indeed, in 1891, in an address to the Johns Hopkins University entitled "Recent Advances in Medicine", Sir William Osler said

> "A desire to take medicine is, perhaps, the great feature which distinguishes man from other animals".

It is fairly certain, however, that until the late 19th Century, most therapeutic regimens were ineffective because they consisted of many agents which were, pharmacologically, virtually inert. Despite this, drugs were traditionally prescribed in mixtures, and there is no doubt that the use of many drugs in the treatment of a single disease or symptom complex had a definite psychological appeal, both to the patient and to the doctor. William Withering's approach to the problem of "dropsy", published in 1785, typified this attitude when he advocated treatment which included "medicines of the deobstruent, tonic, antispasmodic, diuretic and evacuate kinds". Unfortunately, recent surveys of drug usage throughout the world have all testified to the continuing appeal of multiple drug therapy, a practice presumably based on the fallacious premise that "more" is necessarily better than "less".

Drugs, however, are no longer inert substances. While there is no dispute about their tremendous benefits, unwanted effects and adverse reactions are now an integral part of drug therapy and constitute part of the price paid for more effective remedies. Adverse

reactions are inevitable when modern therapeutics demands that drugs modify, stimulate or suppress biological processes. Today, the concept of a "completely safe drug" is unreal, but if sensible precautions are taken, the risks of modern drugs can be minimised. Their abuse, however, by both the public and by doctors can only bring them into unwarranted disrepute.

Multiple drug therapy, whether it has been prescribed or self-administered, is one such area of abuse which cannot be explained on the basis of the action of a single drug, but is due to two or more drugs acting simultaneously. Adverse reactions resulting from multiple drug therapy make up only a small proportion of all adverse drug reactions, but account for a disproportionate number of deaths, and the problem of adverse drug interactions has received increasing attention over the past decade.

## 2.2. HOSPITAL PRESCRIBING AND DRUG MONITORING

### 2.2.1. Multiple drug therapy in hospital practice

Today, the average hospital patient is treated with at least five drugs simultaneously, this figure varying somewhat in different parts of the world. One of the first comprehensive surveys of drug usage in hospital practice was carried out by Smith, Seidl and Cluff (1966). They studied 900 consecutive patients on a 33-bed semi-private medical ward in Baltimore, and reported that 37% of their patients received 0-5 drugs during one hospital admission, 42% received 6-10 drugs, 14% 11-15 drugs, 4% 16-20 drugs and 2% 21 drugs or more. They commented on the impressive relationship between the rate of adverse reactions and the number of drugs administered.

This was the first time that a definite relationship was established between untoward effects and multiple drug therapy. Previously, emphasis had been laid on the toxic effects attributable to individual drugs. Patients given 12 or more drugs were particularly susceptible to adverse reactions, and this suggested that the relationship of rate of reactions to number of different drugs was not simply additive, but more complex and compounded of other factors. Unexpected pharmacological responses were occurring as a result of drug combinations which could therefore be regarded as drug interactions. These combinations included indomethacin and dextropropoxyphene, barbiturates and tranquillisers, tetracycline and mixtures of magnesium and aluminium hydroxide, and reserpine and guanethidine. These observations extended previous reports of drug combinations found to be associated with altered and often adverse drug effects, including digitalis and mercurial diuretics (Lown, Marcus and Levine, 1959), amphetamine and monoamine oxidase inhibitors (Hay, 1962), phenobarbitone and dicoumarol (Cucinell, Conney and Sansur, 1965) and sulphonamide and tolbutamide (Christensen, Hansen and Kristensen, 1963).

More recent studies of drug use during hospitalisation have reaffirmed the medical profession's determination to persist in multiple drug therapy. In a Finnish survey of 1000 consecutive patients in two medical wards, Sotaniemi and Palva (1972) reported that about 70% of the patients received 1-4 drugs regularly, and 21% received 5 or more. Dollery (1973) reported that the average number of drugs per patient stay in a London Hospital was 6, and the maximum 21.

### 2.2.2. International drug surveillance

The Boston Collaborative Drug Surveillance Program (Jick et al, 1970)

reported an average of 8.4 drug exposures per patient, with a range of 5.5 to 10.0. In an editorial on Adverse Drug Interactions (Boston Collaborative Drug Surveillance Program, 1972) analysis of data on 9,900 monitored patients indicated that there had been 83,200 drug exposures and 3,600 reported adverse reactions. Two hundred and thirty four (or 6.9%) of the adverse reactions were attributed to drug interactions. Cumulative pharmacological effects seemed to account for most interaction problems with emphasis being laid on central nervous system depression resulting from the administration of two or more central nervous system depressant drugs. Hypotension, gastrointestinal bleeding, psychotic behaviour and bowel superinfection were also reported complications of combined drug therapy.

In 1969 the Boston Collaborative Drug Surveillance Program began to extend its field of survey outwith North America by including hospitals in Israel, (Hadassah-Hebrew University Hospital, Jerusalem; Beilinson Hospital, Tel-Aviv and Asaf-Harafe Hospital, Tel-Aviv) and more recently, in New Zealand (Auckland Hospital) and Scotland (The Western Infirmary, Glasgow and Stobhill General Hospital, Glasgow). The aim of the Glasgow Drug Surveillance Programme was to collect data from patients admitted to two University Medical Units - the University Department of Medicine at the Western Infirmary and the Department of Materia Medica at Stobhill General Hospital. The present author has, therefore, been fortunate in having an association with this Drug Surveillance Programme since monitoring started in the Department of Materia Medica in 1973.

The main aims of the programme were to:

1. Quantitate clinical drug use
2. Evaluate known or suspected adverse drug effects
3. Detect unsuspected adverse drug effects
4. Assess reports in the literature.

The quantitative analysis of clinical drug use in Glasgow and in other centres has revealed widely differing prescribing patterns throughout the world. A consistent finding has been that patients in North American hospitals receive more drugs during hospitalisation than do their counterparts in Europe, the Middle East or Australasia. On average, medical inpatients in the United States received 9.1 drugs per admission as compared with 7.1 drugs for Canadian, 6.3 for Israeli, 5.8 for New Zealand and 4.6 for Scottish patients (Table 1) (Lawson, Personal communication, 1974).

These differences in prescribing habits merited further analysis and the countries with the highest (United States) and lowest (Scotland) drug use were compared. A large group of American (1442) and Scottish (721) patients in general medical wards were matched for age, sex, survival, primary discharge diagnosis, duration of hospitalisation and various clinical parameters such as blood pressure, renal function and haematological status.

The figures on drug usage already quoted show that American patients received over twice as many drugs as did their Scottish counterparts, and American patients were much more likely to receive at least ten drugs. There is, therefore, little doubt that the Scottish practice reflected by these figures favours relative economy in the use of drugs.

Moir and Hedley (1971) reported similar findings when reviewing a method of prescribing and recording drugs in the Aberdeen General Hospitals Group, devised by Crooks et al (1965 and 1967). The average number of drugs per patient per admission in the whole group including medical, surgical, gynaecological and orthopaedic wards, was 4.5.

Table 2 shows the twelve most commonly prescribed drugs in the United States and in the Glasgow hospitals, with per cent of patients exposed (Wallace and Lawson, personal communication, 1974) and illustrates

| Country | Drugs per admission |
|---|---|
| U.S.A. | 9.1 |
| Canada | 7.1 |
| Israel | 6.3 |
| New Zealand | 5.8 |
| Scotland | 4.6 |

TABLE I International comparison of drug use during hospitalisation from the Boston Collaborative Drug Surveillance Program (Lawson, personal communication, 1974).

| U. S. A. | | SCOTLAND (Glasgow) | |
|---|---|---|---|
| Drug | % patients exposed | Drug | % patients exposed |
| Milk of magnesia | 51 | Nitrazepam | 34 |
| Chloral hydrate | 45 | Potassium chloride | 26 |
| Potassium chloride | 35 | FRUSEMIDE | 21 |
| Propoxyphene | 32 | AMPICILLIN | 14 |
| Dextrose 5% | 32 | Diazepam | 14 |
| Aspirin | 25 | Sodium chloride | 12 |
| DIGOXIN | 23 | | |
| Aluminium and magnesium hydroxides | 21 | Paracetamol | 12 |
| | | DIGOXIN | 12 |
| Multivitamins | 20 | FERROUS SULPHATE | 11 |
| Diphenhydramine | 19 | Milpar | 11 |
| Pentobarbitone | 18 | Dihydrocodeine | 10 |
| Pethidine | 18 | CO-TRIMOXAZOLE | 9 |

TABLE 2 International comparison of drug use in medical patients showing the 12 commonest drugs prescribed, from the Boston Collaborative Drug Surveillance Program (Wallace and Lawson, personal communication, 1974).

the differences in physician attitudes to prescribing in the two countries. The greater enthusiasm with which American physicians prescribe non-specific, symptomatic treatment is obvious. Only one (digoxin) of the twelve most commonly prescribed drugs in the United States has specific therapeutic activity in contrast to five of the Scottish drugs (frusemide, ampicillin, digoxin, ferrous sulphate and co-trimoxazole).

Although there is no way of assessing the relative benefits of the different patterns of drug usage in the United States and Scotland as reflected by these studies, it is certain that drug treatment in America, when compared with that in Scotland, costs the patient more, both in terms of financial outlay and adverse drug effects. Three hundred and seventy (26%) American patients experienced one or more adverse drug effects as compared with 107 (15%) of Scottish patients ($p < 0.001$). The greater frequency of adverse reactions in American patients reflected the practice of multiple drug therapy rather than a greater prevalence of toxicity to individual drugs. This was in agreement with the general principle derived from previous findings that the incidence of adverse drug reactions was directly related to the number of drugs prescribed simultaneously (Seidl et al 1966; Smith et al 1966; Hoddinott et al 1967; Ogilvie and Ruedy 1967; Hurwitz 1969). Thus the increased reaction rate associated with multiple drug therapy may result from drug interactions and an exaggeration of the risks normally associated with drug therapy.

## 2.3. SELF MEDICATION

The data obtained so far by comprehensive drug monitoring has been solely concerned with the situation in hospital practice. Lasagna (1963-1964) speculated that the amount of trouble from drugs which was

publicised represented only the "floating tip of an iceberg" with much of the difficulty remaining hidden beneath the surface of our awareness. Over the past decade, some of the difficulty with prescribed drugs has been uncovered by drug monitoring programmes, but Lasagna's comment still applies to the problem of self-medication with non-prescription drugs.

Concern with the incidence and source of adverse drug reactions in hospital patients has not been as vigorously expressed with regard to outpatients or patients seen in general or private practice. Frequently the ambulatory patient requires greater supervision and surveillance as he usually exercises complete control over self-medication, and this can significantly influence the effectiveness of a prescribed therapeutic regime.

In 1965, the Committee on Safety of Drugs stated that "the public should be made increasingly aware that no effective drug is entirely without hazard, even a drug which can be bought without a prescription, and doctors, for their part, should bear in mind that drug-induced illnesses may be the result of self-medication by the patient".

### 2.3.1. Over-the-counter (o-t-c) drugs.

Non-prescription or over-the-counter (o-t-c) drugs represent special problems to the doctor attempting to avoid therapeutic mishaps:

1. The composition and strength of o-t-c drugs are often vague or cannot be ascertained.
2. They may contain potent pharmacological agents.
3. The same drug, in a somewhat higher dose, may be available only on prescription.

It may, therefore, be very difficult to predict the effect of self-medication on a given therapeutic regimen, and the patient employing an

o-t-c drug without supervision may actually treat himself with doses which would normally only be prescribed, and which could give rise to untoward reactions. It is, therefore, incumbent on the doctor to be aware of all the drugs that a patient is taking if therapeutic mishaps, particularly adverse drug interactions, are to be avoided. It would also be sensible if the same sort of information could be made available to the pharmacist or retail chemist, even although this might encroach upon certain professional and ethical considerations. A suitable treatment card issued to the patient by the general practitioner could be presented when necessary to the pharmacist. Indeed Block and Lamy (1968), in reviewing the responsibility of the pharmacist to the patient, pointed out that the unsuspecting, unquestioning pharmacy customer is a hazard to himself and the pharmacist's maintenance of complete patient record cards, listing drug idiosyncrasies, allergies and current medication would better enable him to fulfil his responsibility to the patient.

The monitoring of o-t-c drugs presents peculiar difficulties because reactions will only be reported by doctors if they are aware that the patient has been treating himself. The incidence of such reactions is rather more difficult to calculate than that of reactions to prescribed drugs, because estimates of consumption of the drugs involved are much less reliable, and very few studies of this have been undertaken. However, one study, conducted about 20 years ago, gave some insight into the size of the problem. Jefferys, Brotherston and Cartwright (1960) surveyed 1399 adults and 1056 children on a post-war working class housing estate with particular reference to the kind of medicines consumed in a four week period. About a quarter of the sample had taken prescribed medicines in this period. The proportion of individuals who had taken or used some medicine which they had obtained without a prescription was very much higher - about two out

of every three individuals. The report was not concerned with adverse drug reactions or drug interactions, but it was interesting to note that the majority of those who took medicine prescribed by their general practitioner supplemented it with self-prescribed remedies.

In a much smaller study of 30 men recently discharged home from hospital, Clinite and Kabat (1969) reported that 83% of subjects had resumed self-medication with non-prescription drugs as a supplement to their prescribed medication within one week of discharge. These observations would tend to reinforce the view expressed about the role and responsibility of the pharmacist in preventing unnecessary drug interactions.

Any accurate assessment of the number of o-t-c products now marketed is virtually impossible. Block and Lamy (1969) referring to the American pharmaceutical market, quoted about 3000 manufacturers, 600 classifications and approximately 6000 products, which gave an indication of the vast number of preparations available. A recent personal survey by the present author of the o-t-c analgesic preparations available in a large city retail chemists revealed 70 preparations, 27 containing aspirin, 26 containing paracetamol and 17 others containing such drugs as codeine and salicylamide. Many aspirin and paracetamol preparations are combined with other drugs, for example barbiturates, antihistamines and sympathomimetic amines, (Tables 3 and 4.) This serves to illustrate the "hidden" dangers of many o-t-c products, as seemingly innocuous drugs may contain potent pharmacological substances.

Table 5 shows the range of o-t-c drugs commonly available together with ingredients which may interact with prescribed drugs, and some examples of reported interactions are given in Table 6.

2.3.2. Alcohol

| Drug(s) | Proprietary Product |
|---|---|
| BUTOBARBITONE | Sol-Tercin |
| CHLORPHENIRAMINE PHENYLEPHRINE | Capriton |
| DEXTROPROPOXYPHENE | Dolasan, Napsalgesic |
| MEPROBAMATE | Equaprin |
| METHOCARBRAMOL | Robaxisal Forte |

TABLE 3 Drugs combined with aspirin in single preparations.

| Drug(s) | Proprietary Product |
|---|---|
| BUTOBARBITONE | Dolalgin |
| DEXTROPROPOXYPHENE | Distalgesic |
| DICHLORALPHENAZONE | Eldo-Sed |
| ORPHENADRINE | Norgesic |
| OXYPHENBUTAZONE | Tandalgesic |
| PHENYLBUTAZONE | Parazolidin |
| PHENYLEPHRINE<br>MEPYRAMINE | Sinulin |
| PHENYLPROPANOLAMINE | Triogesic, Rinurel |
| PHENYLPROPANOLAMINE<br>MEPYRAMINE<br>PHENIRAMINE | Triotussic |
| PSEUDOEPHRINE | Paragesic |

TABLE 4 Drugs combined with paracetamol in single preparations.

| Category | Interacting ingredient(s) |
|---|---|
| Analgesics | Aspirin, salicylates. |
| Antacids | Aluminium, calcium, magnesium, bicarbonate, citrate. |
| Cold cures | Antihistamines, aspirin, belladonna alkaloids, sympathomimetic amines. |
| Cough syrups, elixirs and expectorants | Alcohol, antihistamines, ammonium chloride. |
| Diarrhoea remedies | Kaolin, chalk and other absorbents. |
| Laxatives | Surfactants. |
| Travel sickness preparations | Antihistamines, belladonna alkaloids. |
| Nasal spray and drops | Sympathomimetic amines. |
| Tonics | Alcohol, haematinics. |

TABLE 5 Commonly available over-the-counter (o-t-c) drugs which may interact with prescribed drugs.

| o-t-c drug | Possible interaction with prescribed drugs. |
|---|---|
| Analgesics | Haemorrhage with anticoagulants. |
| Antacids | Decreased absorption, notably of tetracycline. |
| Cold cures | Hypertensive crises with monoamine oxidase inhibitors. |
| Cough syrups, elixirs and expectorants | Excess central nervous system depression with sedatives and tranquillisers. |
| Diarrhoea remedies | Decreased absorption, e.g. with digoxin. |
| Laxatives | Alteration of rate and/or extent of absorption of a variety of drugs. |
| Travel sickness preparations | Excess central nervous system depression with sedatives and tranquillisers. |
| Nasal sprays | Hypertensive crises with monoamine oxidase inhibitors. |
| Tonics | Alcohol content may cause disulfiram-like (Antabuse) reactions with a variety of drugs, excess central nervous system depression with sedatives and tranquillisers and haemorrhage with anticoagulants. |

TABLE 6 Examples of possible interactions between o-t-c drugs and prescribed drugs.

Alcohol, although used almost exclusively for social and not therapeutic purposes, may modify the effect of certain drugs. This may call for considerable restraint in its use. The combination of alcohol and central nervous system depressants has commanded much attention mainly because of its relationship to driving, accidental deaths and suicide. Alcohol may also cause adverse effects in combination with antidepressants, anticoagulants, hypotensive agents, vasodilators, disulfiram-like agents, (e.g. metronidazole and griseofulvin) and hypoglycaemic agents. (Rosinga 1968; Kater et al 1969; Gessner and Cabana 1970; Parker 1970; Rubin et al 1970; Waller 1971; Sellers et al 1972a, 1972b; Gessner 1974; Linnoila et al 1974; Stockley 1974).

An extremely useful annotated bibliography of the scientific literature relating to the interaction of alcohol and other drugs has been prepared by the Canadian Addiction Research Foundation Documentation Department (Polacsek et al 1972).

In view of the risks presented by such combinations, the doctor is obliged to emphasise the dangers of these interactions at the expense of the pleasures of drinking. Even though some control over the utilisation of non-prescription drugs could be exercised by the retail pharmacist, similar consideration could not be expected from the licensee in relation to the sale of alcohol. Nor can any effective control be placed on the supply of drugs and alcohol from other, often misguided but well-meaning sources such as the family, relatives, friends and neighbours. Thus, unless patients are advised by well-informed doctors and pharmacists, the aims of effective therapy may easily be thwarted by the intervention of unnecessary drug interactions.

## 2.4. EXAMPLES OF UNMONITORED MULTIPLE DRUG THERAPY

Varney (1974) drew attention to the confusion and potential harm of unmonitored multiple drug therapy when he graphically described an elderly lady rendered immobile by the large number of drugs which had been prescribed for her. These included (1) dextropropoxyphene and paracetamol ('Distalgesic'), (2) phenylbutazone, (3) aspirin, codeine and caffeine, (4) aspirin, magnesium carbonate and aluminium glycinate, (5) aluminium hydroxide, (6) dicyclomine hydrochloride, doxylamine succinate and pyridoxine hydrochloride ('Debendox'), (7) alkaloids of belladonna leaf, ergotamine tartrate, phenobarbitone and ascorbic acid ('Autergal'), (8) medazepam, (9) prochlorperazine, (10) calcium lactate, (11) sodium chloride, (12) 'Senokot', (13) ferrous sulphate, (14) proteolysed liver and vitamin $B_{12}$, (15) liquid paraffin and (16) chlorpromazine linctus. This elderly lady was, therefore, taking a total of 25 different drugs but was "managing to get them all down". A simple analysis of her treatment shows that she was taking:

| | |
|---|---|
| 6 analgesics | 3 sedatives |
| 3 antacids | 1 hypnotic |
| 2 anticholinergics | 2 laxatives |
| 1 antihistamine | 4 vitamins/haematinics |
| 1 ergotamine preparation | 2 "salts". |

Varney left it to the reader to speculate on the number and variety of possible interactions which could take place from this combination of drugs. It is certain, however, that excessive central nervous system depression was a prominent feature. After admission to hospital all tablets were stopped and ten days later she returned home, fully mobile.

Similar cases have been observed by the present author. The most dramatic example was provided by an elderly lady who presented the bottle shown in Figure 1 to ward nursing staff on her admission to hospital. The bottle contained her current "medicine", a variety

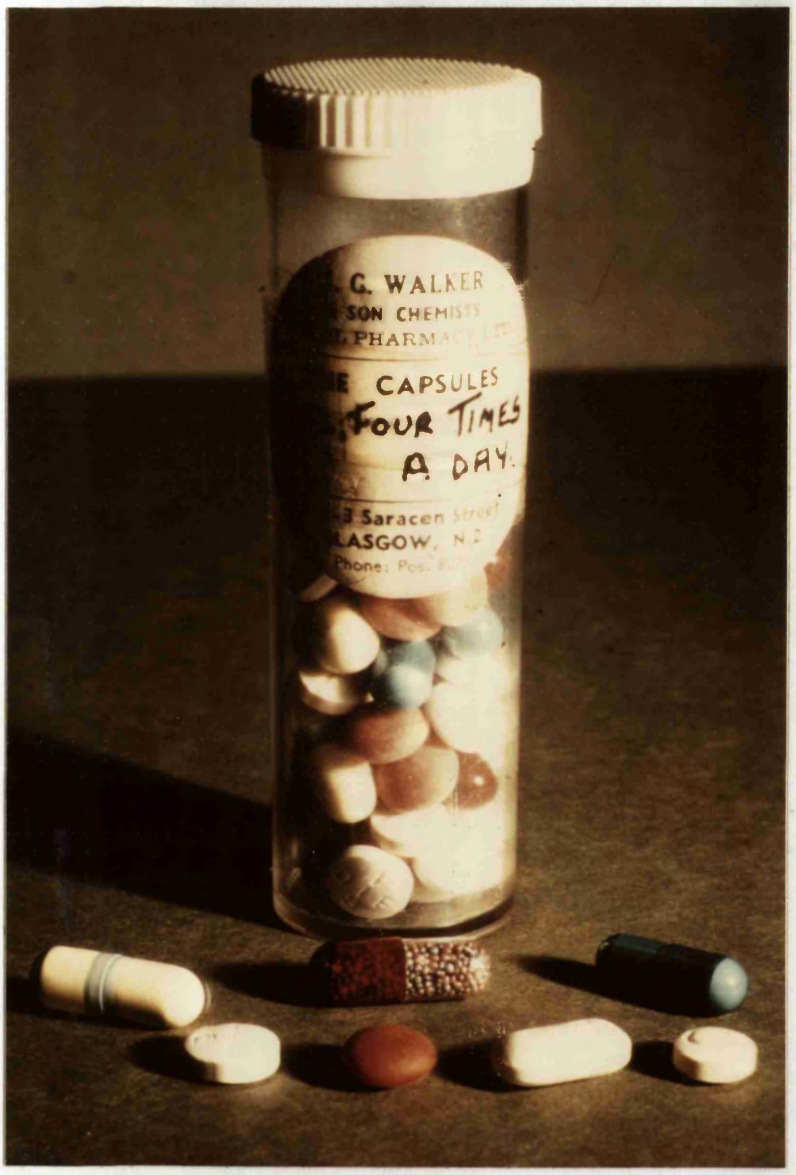



FIGURE I An example of unmonitored multiple drug therapy.

of preparations with the instruction "The Capsules, one four times a day". The patient was obviously totally confused about her treatment, which consisted of the seven preparations shown in Figure 2 namely, indomethacin, a sustained release form of ferrous sulphate, amylobarbitone, dihydrocodeine, "Distalgesic" (a compound preparation of paracetamol and dextropropoxyphene) a sustained release form of glyceryl trinitrate combined with phenobarbitone and one preparation which could not be positively identified, but was probably promazine. Thus the seven preparations contained nine active ingredients. Although no serious adverse effects would have arisen from this particular combination, it was disturbing to find therapeutics reduced to such an arbitrary level.

While it cannot be disputed that the multiple pathology occurring in elderly patients may indicate a number of different therapeutic approaches, Davison (1972) recommended that complicated drug schedules should be resisted, especially for those living alone or suffering from intellectual impairment. Three drugs was the maximum number that an elderly person could be expected to cope with.

## 2.5. CONCLUSIONS

The considerable expansion in the pharmaceutical industry over the last 10-20 years has reflected itself in the proliferation of drug therapy given to individual patients. This has been complicated by the ready availability of non-prescription products and the public's determination to indulge in self-medication. At the same time polypharmacy has been shown to be potentially dangerous because of its association with an increased incidence of adverse drug reactions based partly on drug interactions.

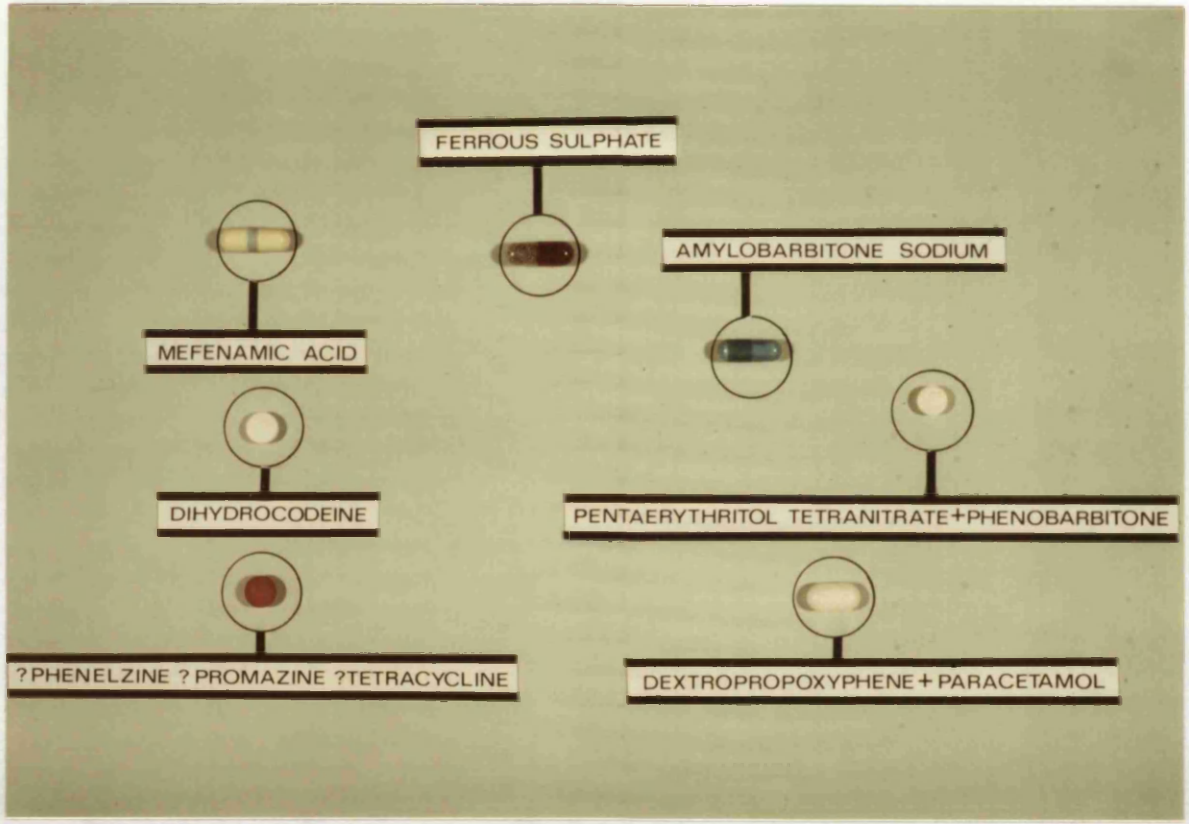



FIGURE 2 Identification of the contents of the bottle shown in Figure 1.

# C H A P T E R 3

## FACTORS MODIFYING DRUG RESPONSE IN MAN

## 3. FACTORS MODIFYING DRUG RESPONSE IN MAN

An understanding of the mechanisms involved in drug interactions is essential for their classification, interpretation, prevention and treatment. It is also essential to recognise that the overall clinical importance of a drug interaction will depend on the interplay of several other factors that modify drug response in man, e.g. genetic, environmental and pathophysiological factors, allergy and idiosyncrasy, age, sex and body weight, and various prescribing factors such as time and route of administration and dosage (Figure 3).

### 3.1. GENETIC FACTORS

The first systematic account of the influence of heredity on drug response was given by Kalow (1962). In the introduction to his book, Pharmacogenetics-Heredity and the Response to Drugs, Kalow stated that not all men react alike to a given dose of a drug, nor do all animals. This variation in response from individual to individual within a species had been regarded for a long time as a nuisance and a stumbling block in the assessment of drug action. Fortunately, the common interest of geneticists and pharmacologists in this subject created the discipline of pharmacogenetics, which has attempted to define precisely the hereditary influences that modify drug response, and also the genetically determined conditions which may be precipitated by drugs, e.g. the acute attack of porphyria caused by barbiturates (Eales and Linder 1962). Genetic factors, therefore, may effect drug metabolism and response, giving rise to an important source of individual variability.

An excellent example of this was provided by Hammer and Sjöqvist (1967). They gave the tricyclic antidepressants desmethylimipramine

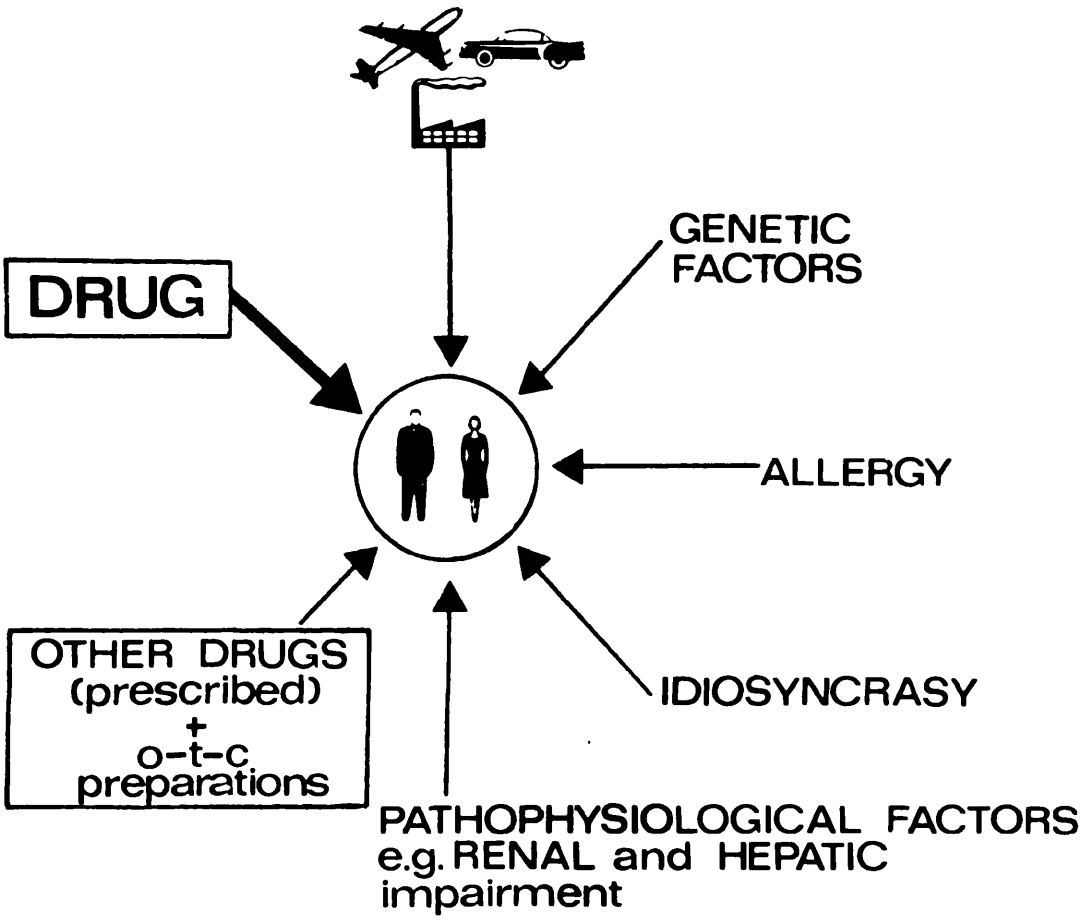



FIGURE 3 The factors which contribute to the response of a patient to a drug. The small cartoon at the top of the figure represents the environment.

and nortriptyline in standard doses to a group of patients, and measured steady-state plasma concentrations. Marked interindividual differences were found, with 30-fold differences in the steady-state levels attained. This was taken to indicate large individual differences in the activity of drug metabolising enzymes in the patients studied. Subsequent work showed that the steady-state plasma level, rather than the dose employed, determined the pharmacological effect of tricyclic antidepressants in individual patients (Freyschuss, Sjöqvist and Tuck 1970; Åsberg et al 1970, 1971.) The mechanisms behind these interindividual differences were explored further by Alexanderson, Sjöqvist and Price Evans (1969) when they undertook a pharmacogenetic study in a group of healthy twins from the Stockholm area. Their aim was to assess the relative contribution of genetic and environmental factors, particularly concomitant drug therapy, to the determination of steady-state levels of nortriptyline. Nineteen identical (monozygotic) and 20 fraternal (dizygotic) sets of twins between 45 and 51 years of age were given nortriptyline orally in a dose of 0.2 mg/kg body weight three times daily for eight days. Steady-state plasma concentrations of nortriptyline were determined at the end of this period. The entire group showed a 10-fold difference in these levels (8-78 µg/ml) (Figure 4).

Identical twins not treated with other drugs showed no significant differences between steady-state plasma concentrations (Figure 5) in contrast to a similar group of fraternal twins who showed significant intrapair differences (Figure 6). Identical twins who were on treatment with various other drugs during the study (Figure 7) lost the intrapair similarity shown by their counterparts not taking other drugs, and fraternal twins exposed to other drugs (Figure 8) showed even greater differences in steady-state levels than those not exposed.

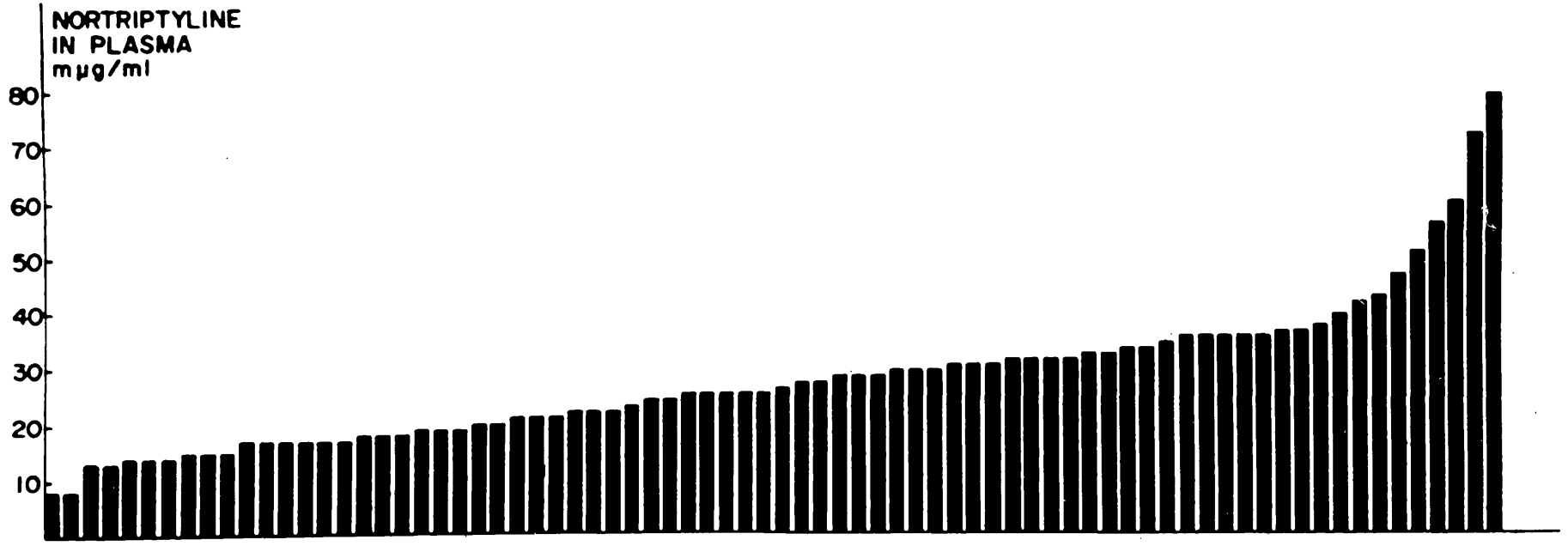



FIGURE 4 Interindividual differences in steady-state plasma concentrations (8-78 μg/ml) of nortriptyline on days 6-8 in healthy twins given 0.2 mg/Kg t.i.d. orally for eight days.

Figures 4-8 from Sjöqvist and Alexanderson 1972, by kind permission of Professor F. Sjöqvist and Excerpta Medica. (Original source : Alexanderson et al 1969).

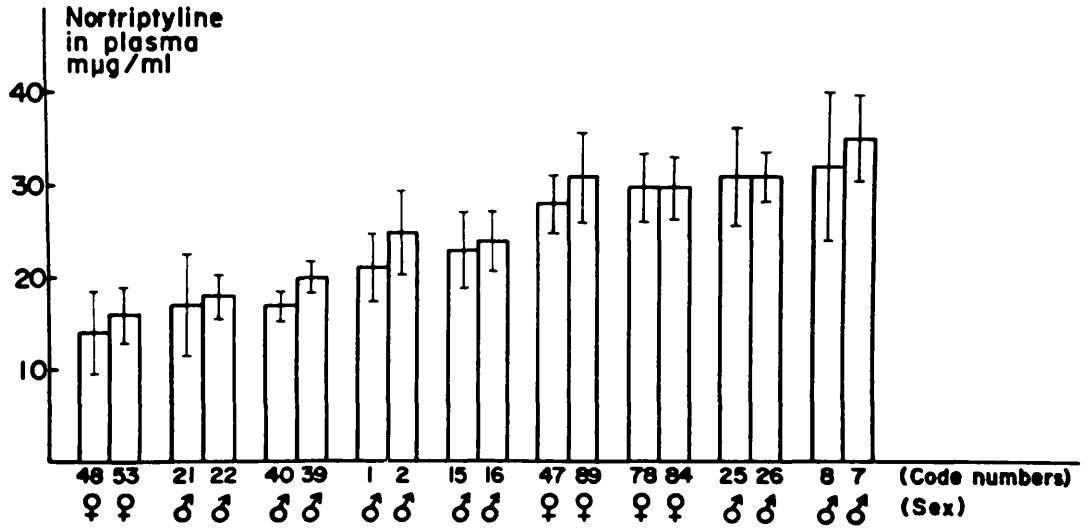



FIGURE 5 Mean nortriptyline plasma concentration on days 6, 7 and 8 in identical twins not previously exposed to drugs.

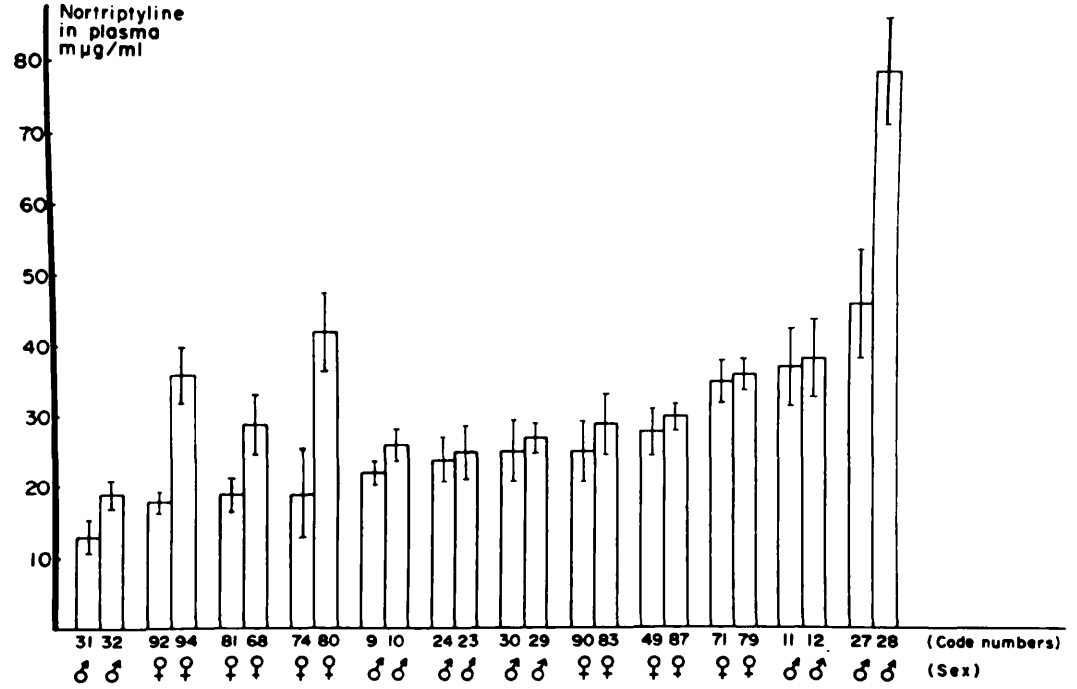



FIGURE 6 Mean nortriptyline plasma concentration on days 6, 7 and 8 in fraternal twins not previously exposed to drugs.

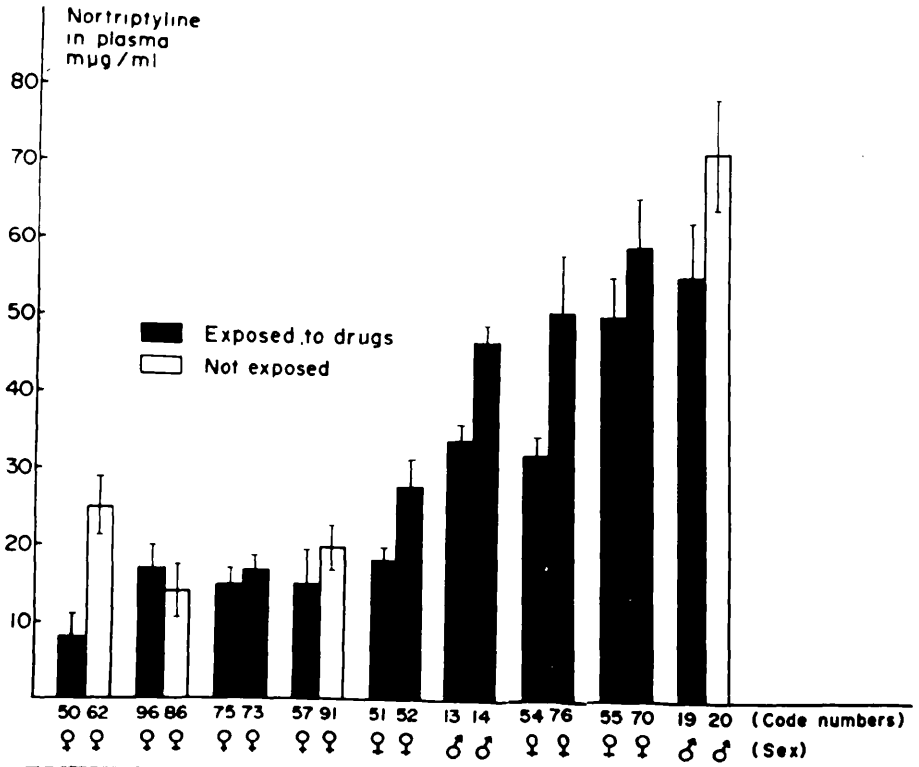



FIGURE 7 Mean nortriptyline plasma concentration on days 6, 7 and 8 in identical twins exposed to different drugs.

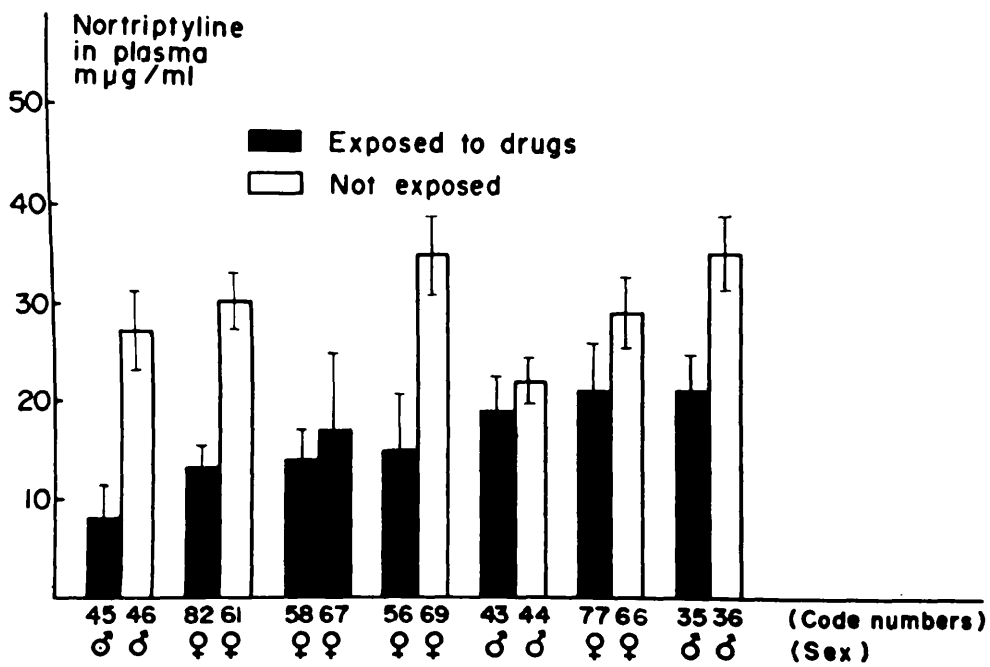



FIGURE 8 Mean nortriptyline plasma concentration on days 6, 7 and 8 in fraternal twins exposed to different drugs.

Furthermore, identical twins treated with various drugs containing barbiturates had considerably lower steady-state plasma concentrations of nortriptyline than untreated control twins.

The marked differences between identical and fraternal twins not previously exposed to other drugs indicated that most of the variability in nortriptyline steady-state levels was genetically determined, probably a reflection of individual rates of drug metabolism. Exposure to other drugs also influenced the steady-state plasma concentration of nortriptyline, which in a given patient may therefore be determined by a combination of genetic and environmental factors.

The Stockholm study confirmed the results of a series of studies on normal adult Caucasian twins living in the Washington D.C. area. (Vessell and Page, 1968a, 1968b, 1968c; Cascorbi et al 1971; Vessell, Page and Passananti 1971; Vessell et al 1971). Single oral dose studies were performed with phenylbutazone, antipyrine, bishydroxycoumarin and ethanol, a group of agents known to be handled almost exclusively by biotransformation rather than by excretion of unaltered parent drug. Plasma half-lives, rather than steady-state levels, were measured because chronic administration of these agents would produce an increase in activity (induction) of the hepatic microsomal drug-metabolising enzymes, (Conney 1967; Breckenridge and Orme 1971). This would, of course, obscure any genetically determined differences in rates of drug metabolism. Intratwin differences in half-lives were appreciably greater in fraternal than identical twins, and it was concluded that genetic rather than environmental factors maintained large individual differences in metabolic rates of elimination of these drugs.

It is clear, therefore, that genetic factors may be responsible for large intraindividual differences in rates of metabolism and

elimination of many commonly used drugs. Unless these factors are taken into account, inappropriate doses of some drugs may be prescribed, which could lead to unexpected results, including adverse drug interactions. As Price Evans (1969) has pointed out, pharmacogenetic studies have emphasised the necessity of treating patients on as personal a basis as possible with respect to choice of drugs and dose schedules.

## 3.2. ENVIRONMENTAL FACTORS

Sjöqvist and Alexanderson (1972) placed drugs in an environmental perspective by referring to their overconsumption as a form of "internal pollution". External, or atmospheric pollution, may also exert a considerable influence on rates of drug metabolism. It has been established that a variety of chemicals found in the environment, such as chlorinated hydrocarbons and insecticides can stimulate drug metabolism, (Hart and Fouts 1963; Conney 1967, 1969; Conney et al 1967).

Kolmodin, Azarnoff and Sjöqvist (1969) found that workers who were occupationally exposed to a mixture of insecticides, including D.D.T., chlordane, and lindane, had shorter plasma antipyrine half-lives than unexposed controls. This suggested induction of antipyrine metabolism and supported similar findings in experimental animals exposed to chlorinated insecticides (Kolmodin-Hedman, Alexanderson and Sjöqvist, 1971). Thus environmental factors may play a role in regulating the rate of drug metabolism, and may lead to unexpected variations in the plasma level and tissue content of some drugs. This may in turn make a contribution to the evolution of drug interactions.

## 3.3. PATHOLOGICAL FACTORS

Against this background of individual variability due to genetic factors and the environment must be set the effects of disease. For many years, dosage regimes have been derived from the study of normal healthy volunteers, but there may be no comparison between such volunteers and ill patients with respect to their drug handling.

### 3.3.1. Renal disease

The importance of renal function in the determination of drug dosage is clearly documented for many antibiotics and other drugs, such as digoxin, that are excreted mainly unchanged in the urine. If the clearance of a drug is largely dependent on renal excretion, its plasma half-life will be prolonged in patients with renal impairment. Thus changes in renal function will modify a number of pharmacokinetic processes which may lead to unanticipated drug effects or drug interactions. The dosage schedule must, therefore, be modified in such a way, that the drug level resulting in patients with kidney disease is the same, and is reached after a similar time interval as in patients with normal renal function, (Dettli, Spring and Ryter 1971).

Pharmacokinetic models

Simplified pharmacokinetic models can be used to avoid drug toxicity due to accumulation in such patients, provided that the renal function is known. The simplest description of the time course of circulating drug levels is provided by the one-compartment open model (Figure 9) where $K_u$ and $K_m$ are first order rate constants for

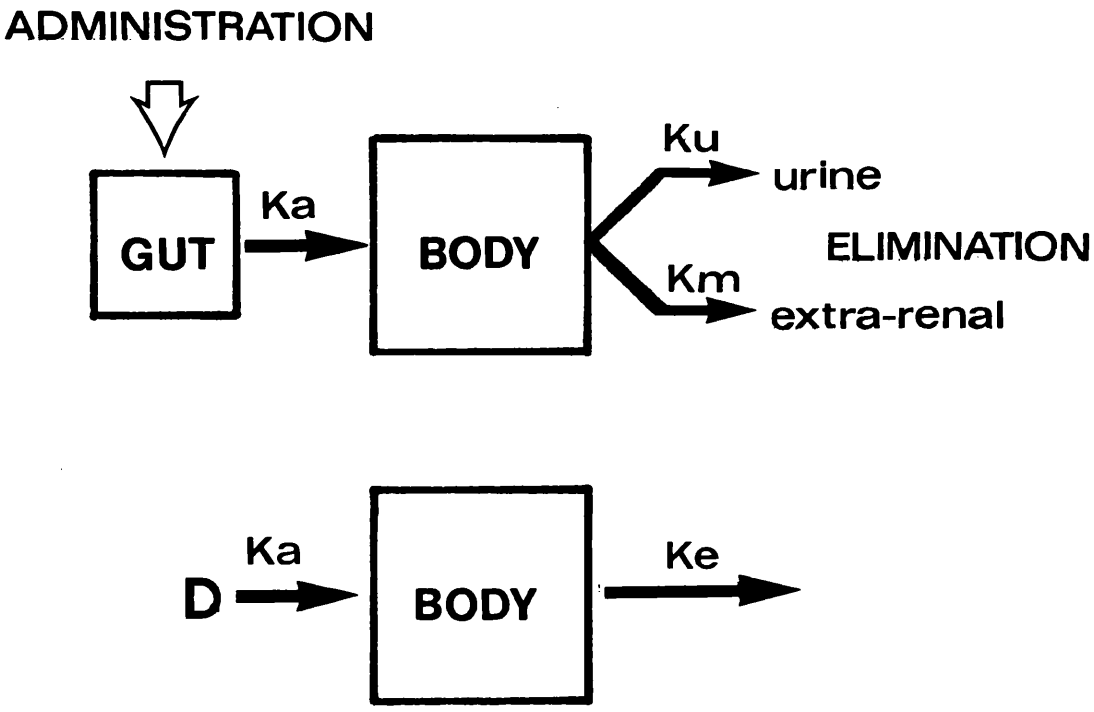



FIGURE 9 One-compartment open body model. $K_a$ is the rate constant for absorption of drug (D) from the gut into the body. $K_e$ in the simplified lower diagram is the sum of the rate constants $K_u$ and $K_m$ which characterise drug elimination by renal and extra-renal routes respectively. It is assumed that all drug transfer processes are first-order, i.e. are concentration dependent.

excretion of unchanged drug by the kidneys, and drug elimination by all other extra-renal routes respectively. It follows that $K_u + K_m = K_e$, the overall elimination rate constant, and it is assumed that the reduction of the overall elimination rate in patients with renal disease is entirely due to a reduction of the renal elimination rate, while the extra-renal elimination rate remains unaltered. In severe renal impairment, $K_u$ approaches zero, and the overall rate constant for drug elimination approaches $K_m$.

## Analogue Computer Simulation

The effect of altered renal function on circulating drug levels and urinary excretion, based on the one-compartment model, can be simulated by analogue computation. Using a Limrose AHT 0090 Analog Tutor (Figures 10 and 11), programmed as shown in Figure 12 the relationships shown in Figure 13 were derived to demonstrate these effects. Analogue computation differs from digital computation in that it deals with continuously varying voltages rather than discrete integers or digits. The input of the analogue computer is a voltage (i.e.(D) in Figure 12, representing the dose of a drug) that subsequently varies with time, determined by setting potentiometers in the circuit ($K_a$, $K_m$ and $K_u$ in Figure 12, set to the control rates of absorption, extra-renal elimination and renal elimination respectively). The output is also in the form of a voltage which changes with time, visualised either as a repetitive sweep on an oscilloscope, as shown in Figure 11, or as a graph traced on a suitable plotter. Figure 13 was prepared from such a graph. A single dose, D, in the gut at time zero is absorbed into, and lost from, the body at a rate proportional to the residual drug concentration according to the following relationships (extra-renal elimination is ignored for

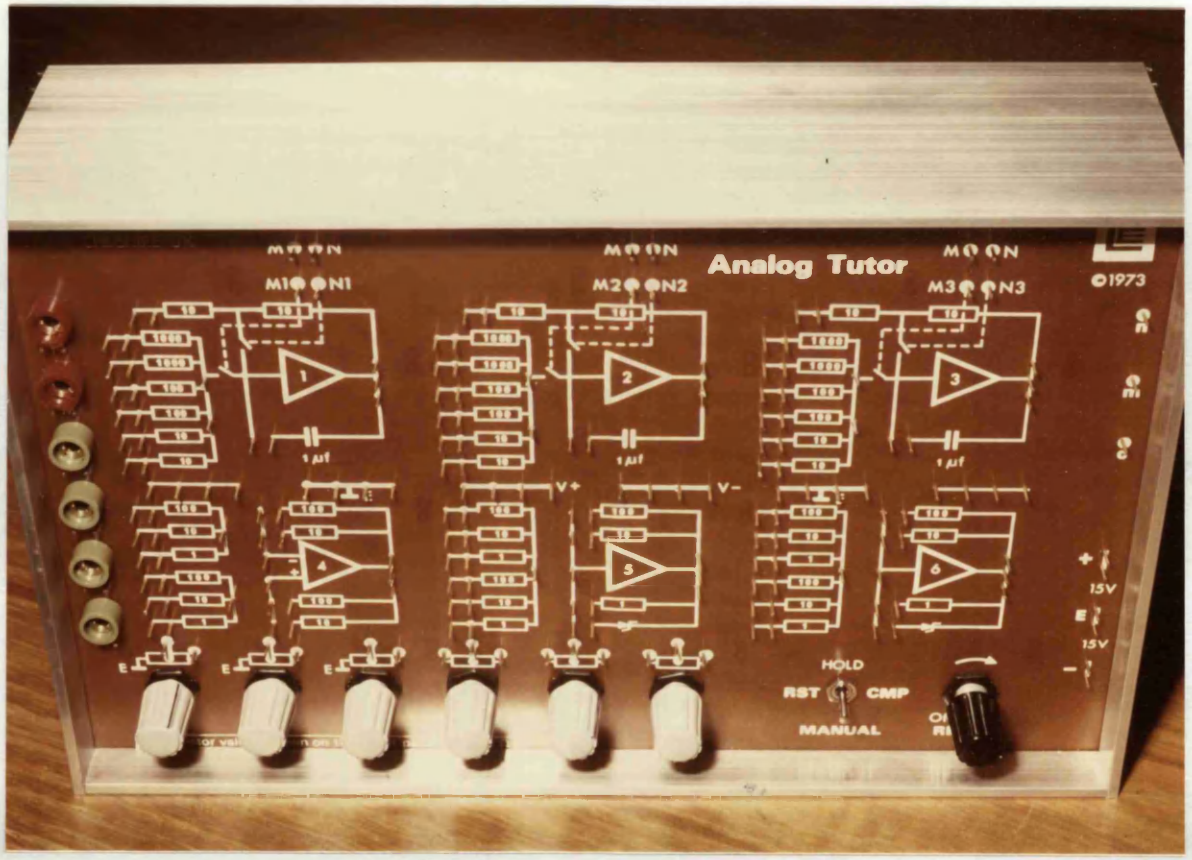



FIGURE 10 The Limrose AHT 0090 Analog Tutor used to simulate pharmacokinetic processes which change blood and urine drug levels with time.

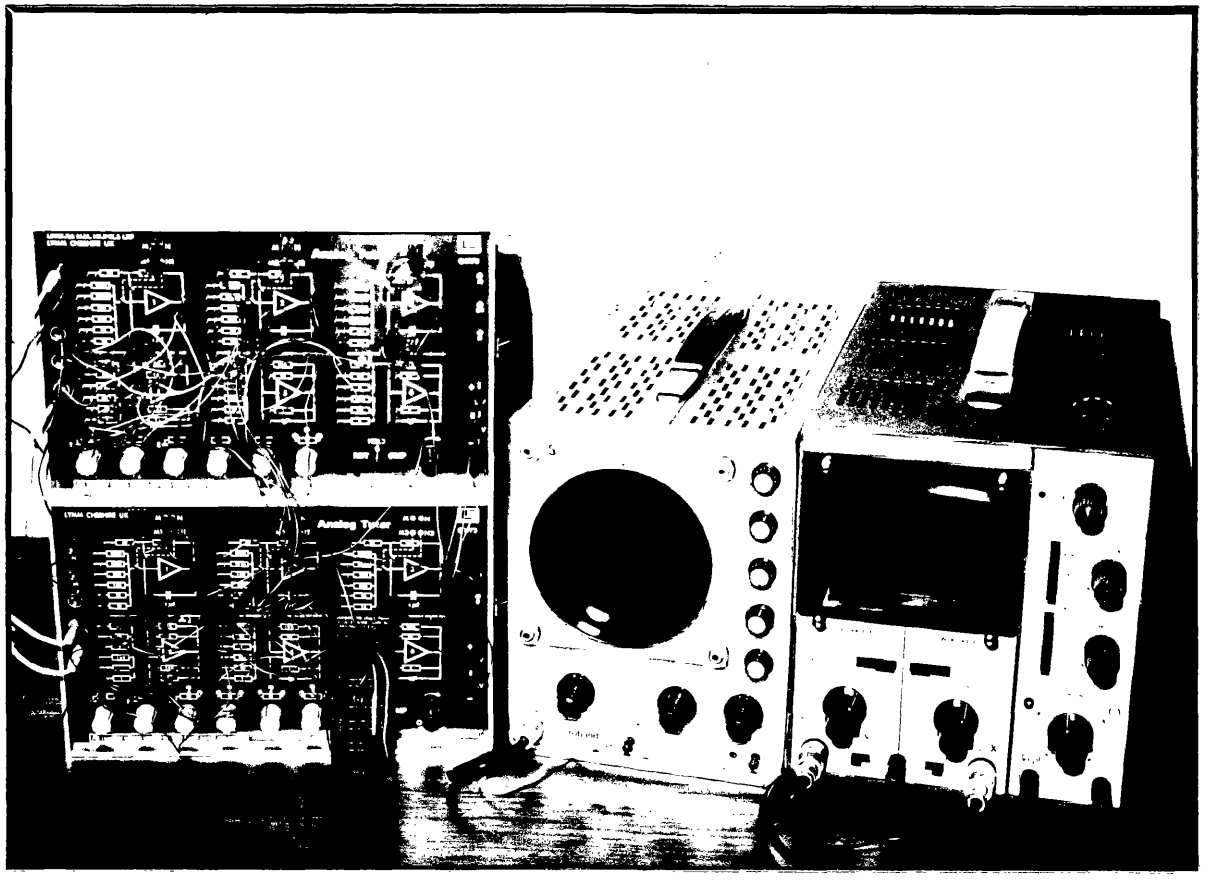


FIGURE 11 Two Analog Tutors linked and programmed to simulate a complex pharmacokinetic model. Relevant outputs are visualised on the oscilloscopes shown.

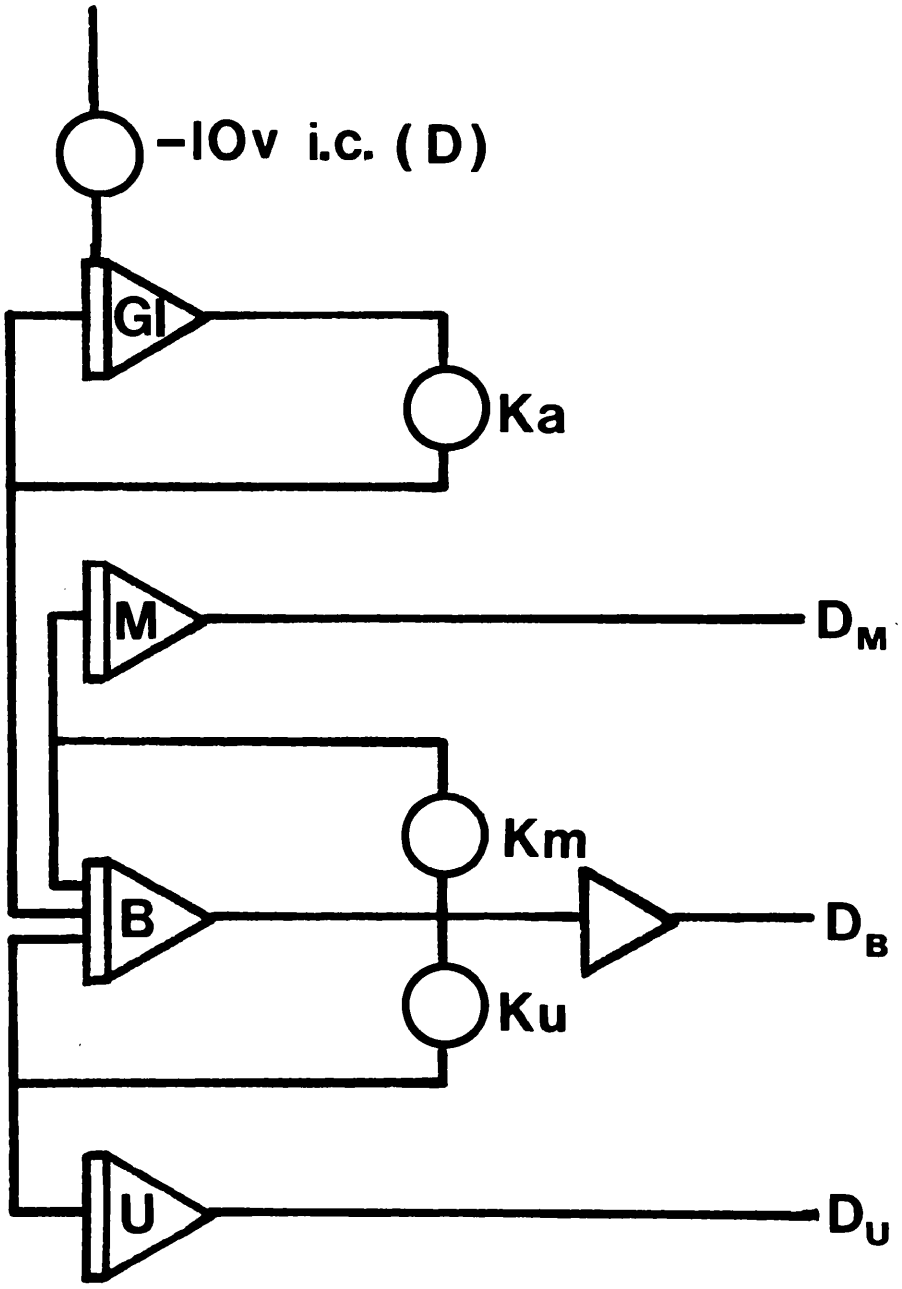



FIGURE 12 Analogue computer programme for a single dose of drug administered into the gut in a one-compartment system. i.c. (D) is the potentiometer connected to a constant voltage (-10v) which determines the dose. $K_a$, $K_m$ and $K_u$ are potentiometers which determine absorption, extra-renal and renal elimination rates (cf. rate constants in Figure 9). $D_B$, $D_M$ and $D_U$ are integrator voltage outputs which vary with time and reflect changes in the amount of drug in the body and the amount eliminated by extra-renal and renal routes respectively. GI, M, B and U are operational amplifiers acting as integrators.

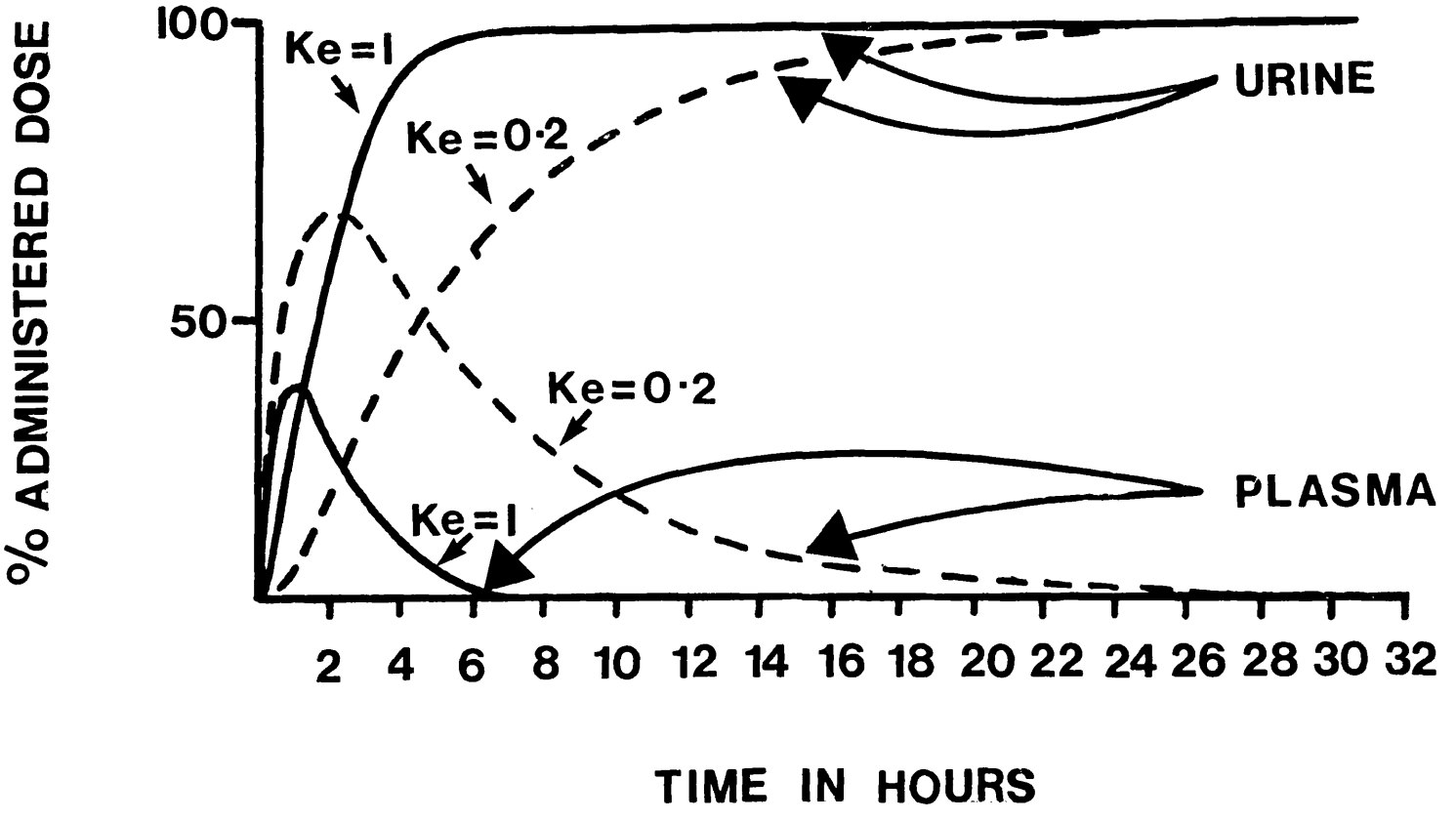



FIGURE 13 Analogue computer simulation of the effects of changing renal elimination rates ($K_u 1h^{-1}$ and $K_u 0.2h^{-1}$) on plasma and urine levels. Any contribution from extra-renal elimination is ignored. $K_u$ is therefore equivalent to $K_e$, the overall elimination rate. i.c.(D) and $K_a$ remain constant. Instantaneous equilibrium of drug between tissues and plasma in the body compartment is assumed.

the sake of simplicity).

$$\frac{dD(gut)}{dt} = -K_a D(gut)$$

$$\frac{dD(body)}{dt} = K_a D(gut) - K_u D(body)$$

$$\frac{dD(urine)}{dt} = K_u D(body)$$

The computer programme resulting from these equations is seen in Figure 12. After an identical dose, reduction of renal function by a factor of 5 (corresponding to $K_u$ values of 1 and 0.2) caused a significant increase in the amount and persistence of drug in the plasma. The respective half-life values were 42 minutes and $3\frac{1}{2}$ hours.

Dosage prediction nomograms

In a subject with normal renal function, the fraction of absorbed dose excreted unchanged in the urine, f, is given by:

$$f = \frac{K_u}{K_u + K_m}$$

The values of $K_u$ and $K_m$ can be readily calculated from the observed elimination of unchanged drug in the urine of subjects with normal renal function, and this information has recently been utilised by Welling, Craig and Kunin (1975) to construct nomograms which relate the elimination of a drug to renal function, as assessed by the endogenous creatinine clearance.

Similar measures have been proposed by Dettli and his colleagues to derive elimination rate constants in individual patients that can be used to calculate dosage adjustments (Dettli 1970a, 1970b; Dettli, Spring and Ryter 1971) and by Mawer and his colleagues, specifically

in relation to the use of gentamicin in renal impairment (Mawer et al 1974a, 1974b). The latter group designed a nomogram based on simple bedside parameters such as age, weight, sex and plasma creatinine level, (Figure 14).

All these methods are based on assumptions derived from the one-compartment open model (Figure 9), in particular that drug clearance is linearly related to creatinine clearance. Halkin et al (1975), however, have suggested that digoxin clearance may be more closely related to that of urea than to that of creatinine.

## Digoxin pharmacokinetics

Compartmental analysis of digoxin kinetics (Sumner, Russell and Whiting 1976) demonstrated that digoxin conforms to the three-compartment model shown in Figure 15. It can be seen that this is rather more complex than the single compartment model. In parallel with the central compartment, which represents plasma water and those fluid spaces with which free (non protein bound) drug achieves rapid equilibrium, are two "side" compartments, referred to as the shallow and deep compartments. These represent various body tissues, and while no definite anatomical significance can be attributed to them, they denote tissues in which the myocardial receptors, sensitive to the action of digoxin, are located. $K_a$ is the absorption rate constant, $K_u$ the renal elimination rate constant, and $K_m$ the extra-renal elimination rate constant, largely accounted for by biliary excretion. $K_1$, $K_2$, $K_3$ and $K_4$ are rate constants which identify the rates at which digoxin diffuses into and out of the tissues, and the rates of binding to, and dissociation from, drug receptors. Even this model could be improved by introducing "feed-back" loops to represent the entero-hepatic circulation of digoxin and its salivary

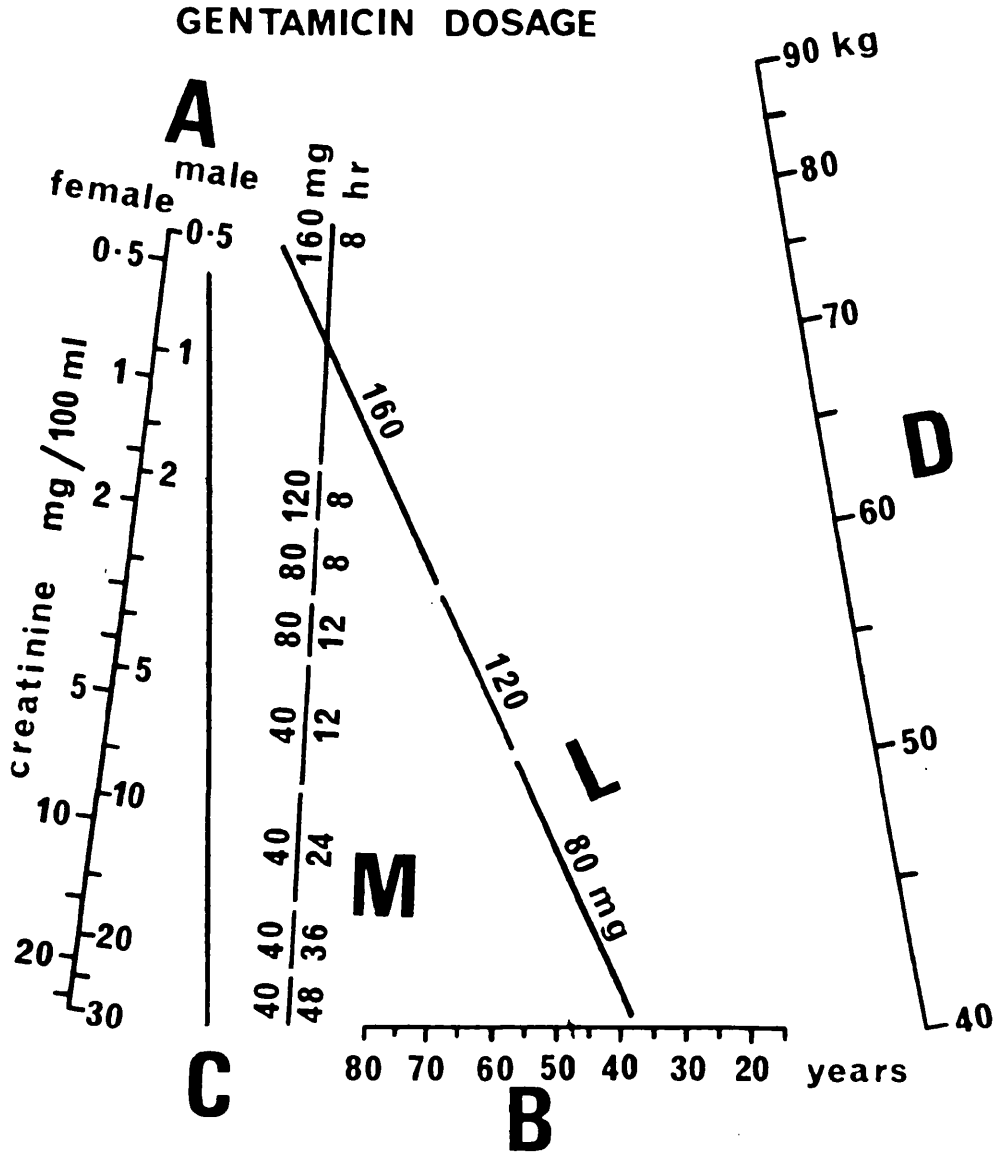



FIGURE 14 Nomogram for the determination of gentamicin dosage. A straight line is drawn between serum creatinine concentration (scale A) and age (scale B). The point of intersection on line C is marked. A straight line is then drawn between this point and the body weight (scale D). The points at which this line cuts the dosage lines L and M are marked and the appropriate loading dose (mg), maintenance dose (mg) and interval (hr) are read off.

From Mawer et al 1974, reproduced by kind permission of Professor G.E.Mawer and the publishers, Macmillan Journals Ltd.

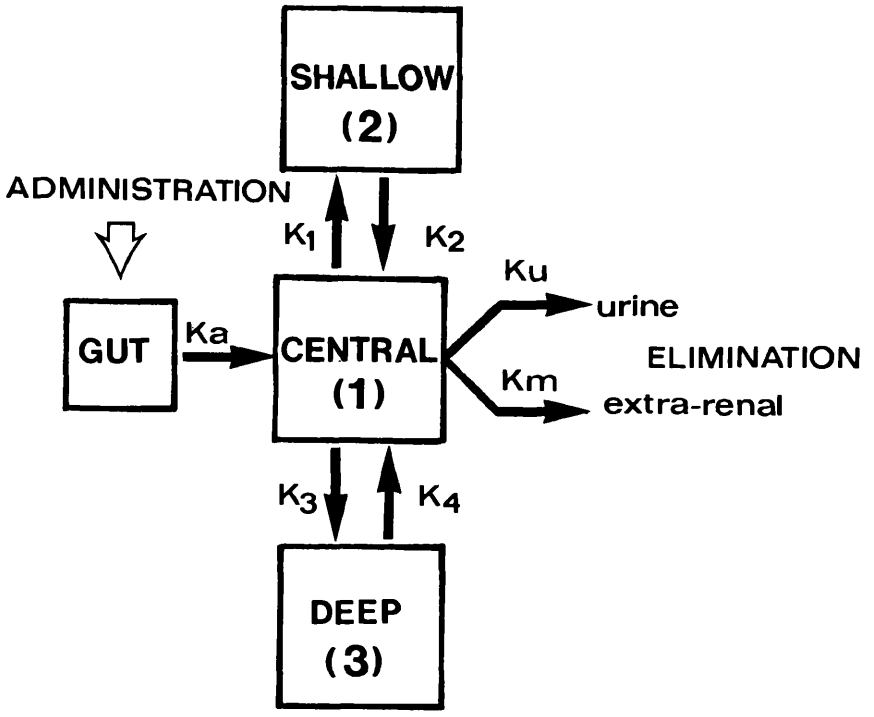



FIGURE 15 Three compartment model for digoxin kinetics. See text for description of compartments. All rate constants are assumed to be first-order; $K_a$, $K_u$ and $K_m$ as in Figure 9, $K_1$, $K_2$, $K_3$ and $K_4$ describe uptake and release from the shallow and deep compartments.

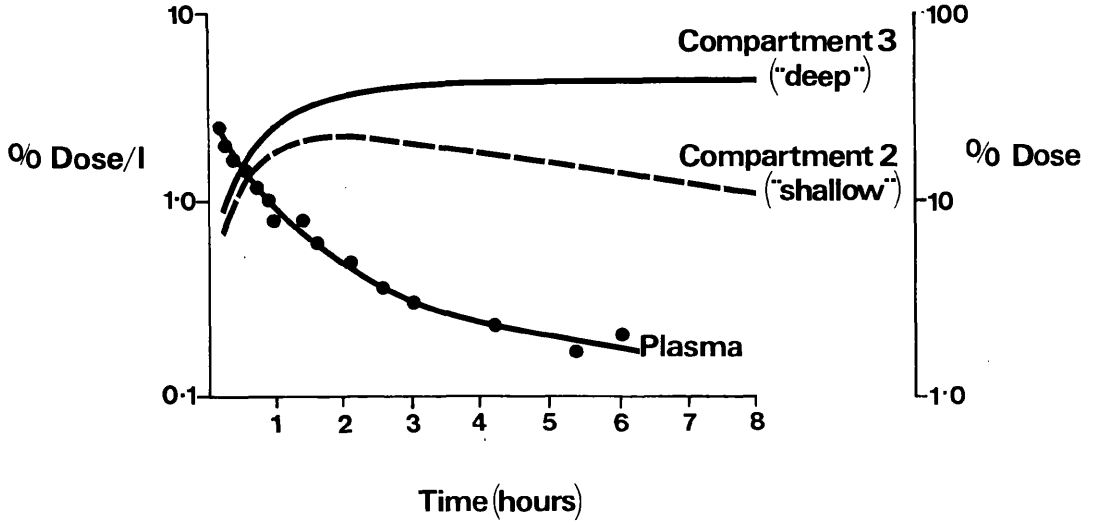



FIGURE 16 Predicted time course of digoxin levels in the shallow and deep compartments (R.H. scale) in relation to observed changes in the central compartment (plasma, L.H. scale) according to the three-compartment model shown in Figure 15.

excretion.

Thus the time course of circulating drug is determined by the movement of digoxin between the various compartments and does not depend solely on absorption and elimination. An important rate limiting step is the release of drug from the deep compartment, characterised by the rate constant $K_4$. Overall clearance from the body appears to depend largely on glomerular filtration, but a significant contribution is made by extra-renal routes, notably the bile.

The predicted time course of digoxin levels in the shallow and deep compartments, in relation to the central compartment, is shown in Figure 16, derived from mathematical analysis of the concentration-time relationships of $^3$H-digoxin in blood, urine and faeces, following its intravenous administration to four healthy male volunteers, aged between 27 and 35 years. The intravenous plasma concentration data were fitted to the triexponential function

$$c_1e^{-\lambda_1 t} + c_2e^{-\lambda_2 t} + c_3e^{-\lambda_3 t}$$

using a non-linear least squares fitting programme, BMD X85 (BMD Biomedical Computer Programs, 1968) on an IBM 370/158 computer. It was found that three exponentials were required to give a satisfactory fit to the data, and therefore any compartmental model used to fit the data had to contain a minimum of three compartments, excluding the gut. The model shown in Figure 15 was considered to be consistent with this analysis.

The changes in digoxin concentration in the tissue compartments shown in Figure 16 correlated well with the pharmacodynamic effects of the drug observed by other workers (Weissler et al 1972; Davidson and Gibson 1973; Reuning, Sams and Notari 1973) which lends support to the validity of this model.

Analysis of this type can subsequently be used to calculate individual dosage regimes to suit varying degrees of renal function.

Extra-renal mechanisms

The extra-renal elimination of drugs, which assumes increasing importance in renal failure, may not remain constant and may be subject to individual variations. Reidenberg and Katz (1973), for example, described a uraemic patient with an 8-day half-life for digoxin, compared with the 4.4 days normally found in uraemic patients. This indicated substantial slowing of the extra-renal elimination of the drug, and was probably due to coexisting liver disease. Previous studies by Bloom and Nelp (1966) and Doherty and Flanigan (1967) had also shown substantial individual variation in faecal excretion of digoxin.

Other processes which may be altered by uraemia are drug metabolism (Reidenberg, James and Dring 1972; Reidenberg 1974), drug plasma protein binding (Odar-Cederlof, Lunde and Sjöqvist 1970; Reidenberg et al 1971; Reidenberg and Affrime 1973; O'Malley et al 1975) and tissue sensitivity to drugs (Reidenberg 1971).

In uraemic patients, however, in whom dose adjustment is most important, it is acceptable to assume a linear relationship between drug elimination and creatinine clearance or glomerular filtration rate when a drug is normally eliminated principally by the kidneys. Impaired renal function may, however, modify a number of pharmacokinetic processes, and predictions based on this linear relationship must be seen as only a first approximation to ideal dosage. It is clear, therefore, that unless the influence of renal function on the clearance of many drugs is recognised, accumulation may lead to toxicity per se or to drug interactions as a result of altered kinetic processes and abnormally high concentrations of drugs.

### 3.3.2. Liver disease

The role of liver disease in altering rates of drug metabolism in man is controversial. Studies are hampered by the considerable overlap in kinetic variables (which reflect drug metabolism) between normal patients and patients with liver disease. Two approaches have been used to study this problem, the measurement of drug metabolising enzyme activity in liver biopsies, and the study of drug kinetics in patients. Schoene et al (1972) estimated the content of cytochrome P-450 in liver biopsies taken from patients with severe hepatitis or cirrhosis. A reduction in cytochrome P-450 was demonstrated, together with a reduction of the demethylating activity of the drug-metabolising enzymes. Leewy et al (1970), on the other hand, could not correlate hepatic pentobarbital hydroxylase activity with liver function in viral hepatitis or alcoholic liver disease. Such in vitro studies, however, do not take into account the total hepatic capacity of drug metabolism, and are probably of limited value. Another difficulty is shown by the lack of correlation between hepatic enzyme content and variations in rates of drug metabolism when different species are compared.

In vivo studies in hepatic disease have also yielded conflicting results, with reports of prolongation of the half-life of some drugs not confirmed by others. The inconsistency of these results has been attributed to the lack of reliable methods for the quantitative estimation of reduced liver function, and to genetically determined interindividual variations in drug metabolism.

Hvidberg, Andreasen and Raneck (1974) attempted to define the position more clearly by using a more sensitive index of liver function, the galactose elimination capacity (G.E.C.) (Tygstrup, 1964).

Reduction of G.E.C. in patients with liver disease (alcoholic and idiopathic cirrhosis) was significantly correlated with changes in the apparent elimination rate constant (or plasma half-life) of phenylbutazone, which undergoes almost complete metabolic transformation in the liver (Figure 17).

These results provided preliminary evidence for a correlation between liver function and the rate of metabolism of a drug, but further research is needed to assess the contribution of other factors such as changes in plasma protein binding and alterations in the disposition of drugs in liver disease. As Wagner (1971) has pointed out, changes in plasma half-life need not necessarily reflect changes in the rate of drug metabolism, and there is now an increasing amount of evidence to show that the binding capacity of serum proteins for various drugs is reduced in patients with liver disease (Powell and Axelsen 1972; Affrime and Reidenberg 1973; Reidenberg and Affrime 1973; Reidenberg 1974; Hooper et al 1974; Affrime and Reidenberg 1975; Wallace and Brodie 1976).

## 3.4. EFFECT OF AGE AND SEX

Apart from the major factors already discussed, drug response may be partly dependent on basic physiological factors such as age and sex. No sex difference in drug metabolism had been found until O'Malley et al (1971) reported a significant reduction in antipyrine metabolism in a group of men, aged 17-52 (mean 27.4) years compared with a group of women aged 16-49 (mean 25.3) years. These workers also observed a reduced capacity for drug metabolism in elderly patients. More recently, alterations in warfarin protein binding and phenytoin clearance have also been described in the elderly (Hayes, Langman and Short 1975a, 1975b). This will be discussed further in Chapter 4.

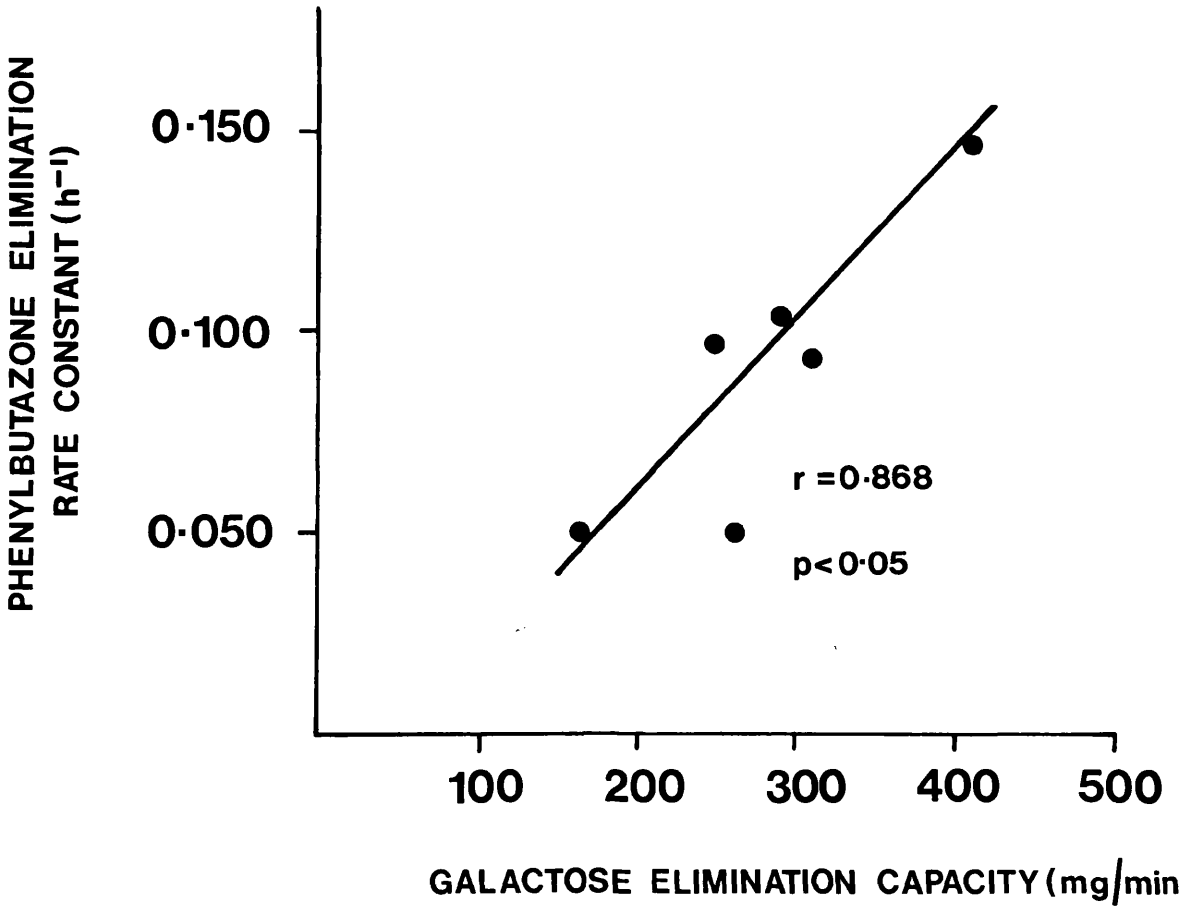



FIGURE 17 Correlation between phenylbutazone elimination and the galactose elimination capacity of the liver. Redrawn from Hvidberg et al 1974, by kind permission of the authors and publishers, The C.V. Mosby Company.

## 3.5. BIOPHARMACEUTICAL FACTORS

Variation in drug absorption may also assume considerable importance and a great deal of attention has been focussed recently on the influence which some physico-chemical properties of drugs exert on their behaviour in the gastro-intestinal tract. Release and availability of a drug from its pharmaceutical formulation in vivo depends on a number of factors:

lipid solubility
water solubility
degree of ionisation
chemical stability
molecular weight
pharmaceutical formulation.

These factors largely determine the amount of drug available, the rate of its release from the dosage form, and the rate of absorption through the intestinal mucosa. Different preparations of a drug containing the same amount of active chemical are regarded as "chemically equivalent", but they cannot be considered "generically equivalent" unless they have identical biological activity under clinical conditions.

A major advance in pharmacotherapy during the last few years has been the demonstration of lack of generic equivalence, implying incomplete and variable biological availability (bioavailability) of drug products. This has had important repercussions on both the pharmaceutical industry and clinical practice. Variations in the bioavailability of drugs obviously placed clinicians in an untenable position, especially when dosage was relatively critical - as in the case of digoxin. The first suggestion that digoxin tablets from several sources might show differing bioavailabilities was made in

Finland by Manninen, Melin and Hartel (1971). Shortly after Lindenbaum et al (1971) in the United States, provided further evidence for this lack of equivalence, and many other studies have subsequently confirmed this. Even variations in the bioavailability of digoxin from the same manufacturer provided a degree of consternation (Stewart and Simpson 1972; Whiting, Rodger and Sumner 1972). It was soon recognised that this variability was largely related to the rate of dissolution of digoxin tablets (Lindenbaum et al 1973; Johnson et al 1973) and standardisation of this pharmaceutical determinant of bioavailability was urgently required. (The rate of dissolution characterises the rate at which a drug dissolves in gastro-intestinal fluid following its release from solid dosage form). For sparingly water-soluble drugs like digoxin the dissolution rate was shown to be an important rate limiting step in absorption and subsequent biological availability (Beckett and Cowan 1972; Fraser, Leach and Poston 1972).

A convincing demonstration of the correlation between dissolution rate measured in vitro, and bioavailability assessed in vivo by measuring the area under the six hour concentration/time curve in healthy volunteers was presented by Fraser et al (1973). Shaw et al (1973) performed a similar study in patients, and evaluated seven types of digoxin (0.25 mg tablets) in common use in the United Kingdom. They concluded that measurement of in vitro dissolution rates appeared to be a valid method of ensuring that different brands of digoxin were equally effective. Figures 18 and 19 show typical dissolution profiles and corresponding serum concentration/time curves respectively, (from Fraser et al 1973).

The marked differences in bioavailability revealed by these reports was due to the effect of different production methods on the particle size of digoxin (Jounela and Sothmann 1973; Shaw et al 1973;

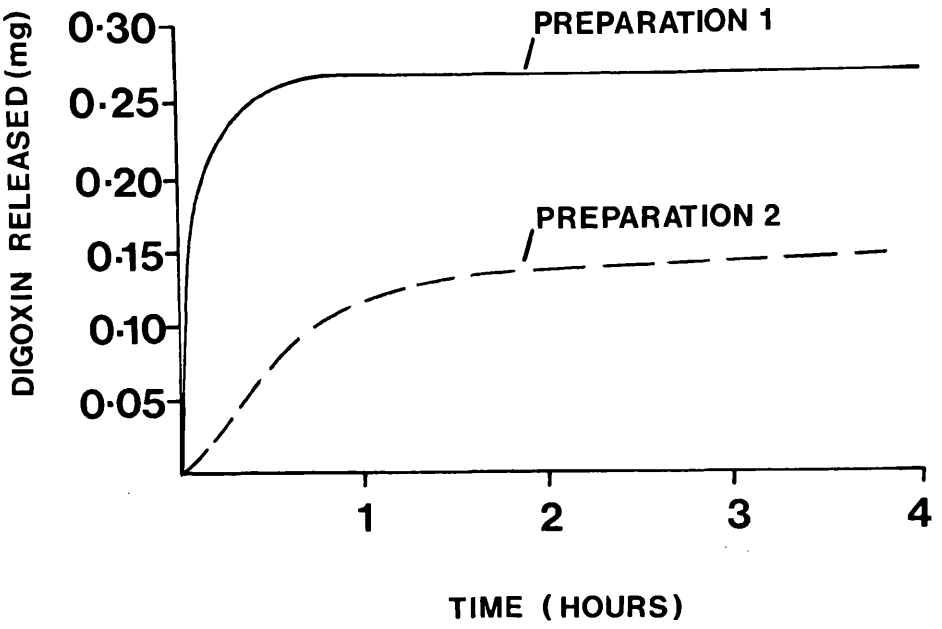



FIGURE 18 Dissolution profiles of two different oral digoxin preparations. Redrawn from Fraser et al 1973 by kind permission of the authors and the Journal of Pharmacy and Pharmacology.

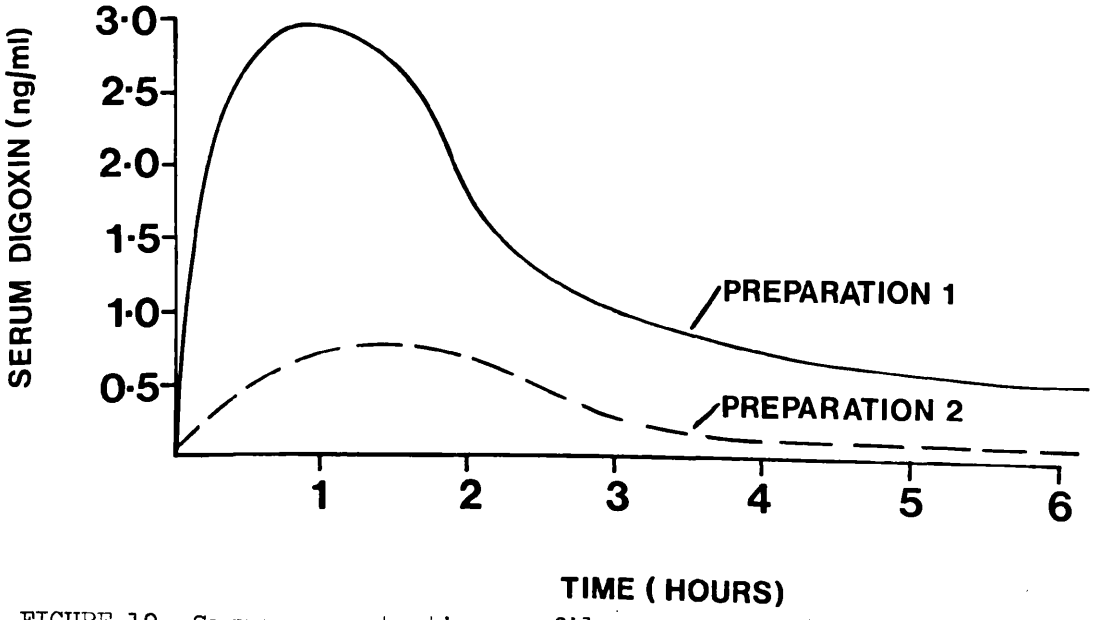



FIGURE 19 Serum concentration profiles corresponding to the two digoxin preparations shown in Figure 18. Redrawn from Fraser et al 1973, by kind permission of the authors and the Journal of Pharmacy and Pharmacology.

Jounela, Pentikäinen and Sothmann 1975) and the problem has now been resolved by the introduction of a new standard ensuring a uniform rate of release of digoxin, i.e. at least 75% of the stated tablet content of digoxin should be released within one hour.

In 1972, Doluisio stated "At present, there are no enforced standards which will insure **bioavailability**". Experience with digoxin inequivalence has been of considerable value as it has led to some improvement in this situation and a greater awareness of the problem as a whole. This is important as every effort should be made to minimise variations in drug availability due to pharmaceutical factors, as such variations may be compounded by a number of other factors. Koch-Weser (1974) identified the following important ones:

1. Drug characteristics such as interaction before gastro-intestinal absorption, biotransformation in the intestinal wall or in the liver ("first-pass effect") and incomplete absorption.
2. Interaction with other substances in the gastro-intestinal tract, such as food and drugs.
3. Patient characteristics such as gastro-intestinal pH, motility, perfusion, flora, structure and malabsorption states.

Genetic factors have even been implicated, as Levy and Hollister (1964) described "slow" and "rapid" absorbers of aspirin and Prescott and Nimmo (1971) observed a similar phenomenon with phenacetin, paracetamol and tetracycline. Numerous references relate to generic inequivalence with a variety of other drugs including chloramphenicol, nitrofurantoin, nortriptyline, phenylbutazone, phenytoin, tetracyclines, tolbutamide and warfarin.

It is clear, therefore, that drug response in man is determined by the interplay of several important factors and if drug interactions are

to be interpreted correctly they should be regarded as one contributory factor to this response.

## 3.6. CONCLUSIONS

The individual patient given a combination of drugs presents a unique set of conditions under which the drugs may interact. The effects of renal and hepatic disease, age, sex, genetic influences and bioavailability are some of the factors which must be taken into account and may often assume greater importance than the effects of drug interaction itself. Indeed, the same combination of drugs may produce an adverse effect in one patient and no observable effect at all in another.

# CHAPTER 4

## MECHANISMS OF DRUG INTERACTION

# 4. MECHANISMS OF DRUG INTERACTION

## 4.1. INTRODUCTION

A true appreciation of the significance of drug interactions demands (a) an awareness of their contribution to the overall drug response in man and (b) a knowledge of their mechanisms. The factors responsible for (a) have already been discussed, and drug interactions have been placed in their correct perspective. Because of the multiplicity of factors involved, it is not surprising that some interactions may not be recognised and may fail to attain much clinical significance. They may also be obscured by a large therapeutic index or a therapeutic effect which is difficult to measure quantitatively. But interactions will be obvious if they occur with drugs which have readily measured effects, or which require regular monitoring, e.g. anticoagulants and hypoglycaemic agents. Moreover, the recent availability of assays for measuring plasma levels of several drugs with low therapeutic indices and difficult end points has allowed recognition and investigation of several important drug interactions, including those with digitalis glycosides, anti-arrhythmic agents and antiepileptic drugs. Although toxicity may be a relatively dramatic outcome of a drug interaction, a decrease in effect may be just as important. Thus, loss of hypotensive effect or failure to control an arrhythmia or epileptic seizure can be as serious a result of drug interactions as drug toxicity.

Drug interactions can occur in any of the three main phases of drug action shown in Figure 20.

The pharmaceutical or drug release phase relates to the physical processes which release the drug in a molecular, dispersed form from the pharmaceutical preparation, and make it available for absorption.

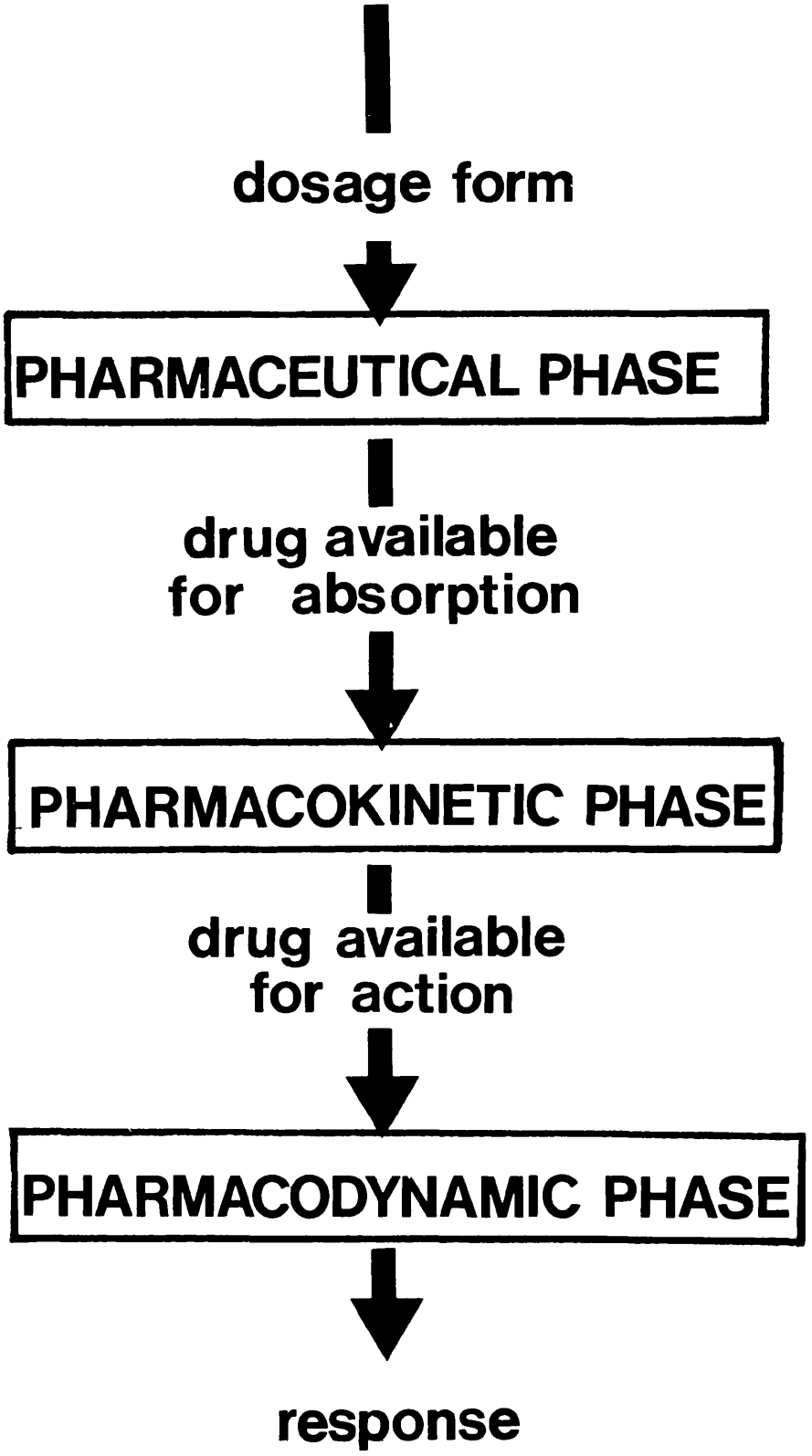



FIGURE 20 The three phases of drug action.

The pharmacokinetic phase comprises the processes involved in the distribution and elimination of a drug, either by biotransformation or excretion, and determines the level of a drug in the body fluids and tissues.

The pharmacodynamic phase comprises the induction of effect and subsequent response in target tissues.

Thus drug interactions can conveniently be referred to under three headings - pharmaceutical, pharmacokinetic and pharmacodynamic.

## 4.2. INTERACTIONS IN THE PHARMACEUTICAL PHASE

The rate or amount of drug absorbed may be significantly altered by interactions in the gastro-intestinal tract. Two mechanisms may be responsible for this:

(a) Complex formation

(b) Pharmacological interference with gastro-intestinal function.

### 4.2.1. Complex formation

Many organic drug molecules can form relatively weak reversible associations with one or more molecules of another drug, surfactant or protein (Martin, Swarbrick and Cammarata 1969). This results in drug complexes which may differ appreciably from the free drug with respect to such physical-chemical characteristics as solubility, diffusivity, size, electrical charge and lipoid-water partition coefficient. Such differences imply corresponding differences in the absorbability of the free drug and drug complex from the gastro-intestinal tract. Unintentional and unanticipated interactions of drugs with other constituents of their dosage form, with ingested food or with other drugs may lead to the formation of poorly absorbed complexes and

consequent relative unavailability or drug inactivation. Two examples of such adverse interactions are the poor absorption of tetracycline in the presence of calcium (Kunin and Finland 1961), iron and milk (Price et al 1957; Neuvonen et al 1970; Mattila et al 1972) and the ineffectiveness of an orally administered iron-carbohydrate complex (Diamond et al 1963). In their study Mattila et al (1972) derived important implications for this type of interaction. There was no doubt that ferrous sulphate interfered with tetracycline absorption (Figure 21, from Neuvonen et al 1970). The two drugs administered simultaneously would result in reduced plasma levels of the antibiotic. But Mattila and colleagues pointed out that if the drugs were given separately with an interval of about three hours between them, this interaction could be avoided.

It is rather difficult to assess the overall clinical significance of the iron-tetracycline interaction when tetracycline is often prescribed for infections which are not responsive to this antibiotic. However, simultaneous therapy with tetracycline and iron, whether in "tonic" form or tablets, may be instituted in prolonged or recurrent infections, and proper timing of these drugs will be important, particularly in debilitated patients who need adequate antibiotic levels.

It is also interesting to note that Greenberger, Ruppert and Cuppage (1967) demonstrated that iron absorption may be interfered with as well when in combination with tetracycline. Experiments performed in rats, both in vivo and in vitro, showed that the inhibitory effect of tetracycline was dose dependent, and was only observed after large doses. Both complex formation and impaired intestinal iron transport were implicated. Iron preparations also form poorly soluble precipitates when combined with antacids or phosphates.

Adsorbents such as activated charcoal and kaolin, and astringents, may delay or inhibit absorption from the intestine. A good example

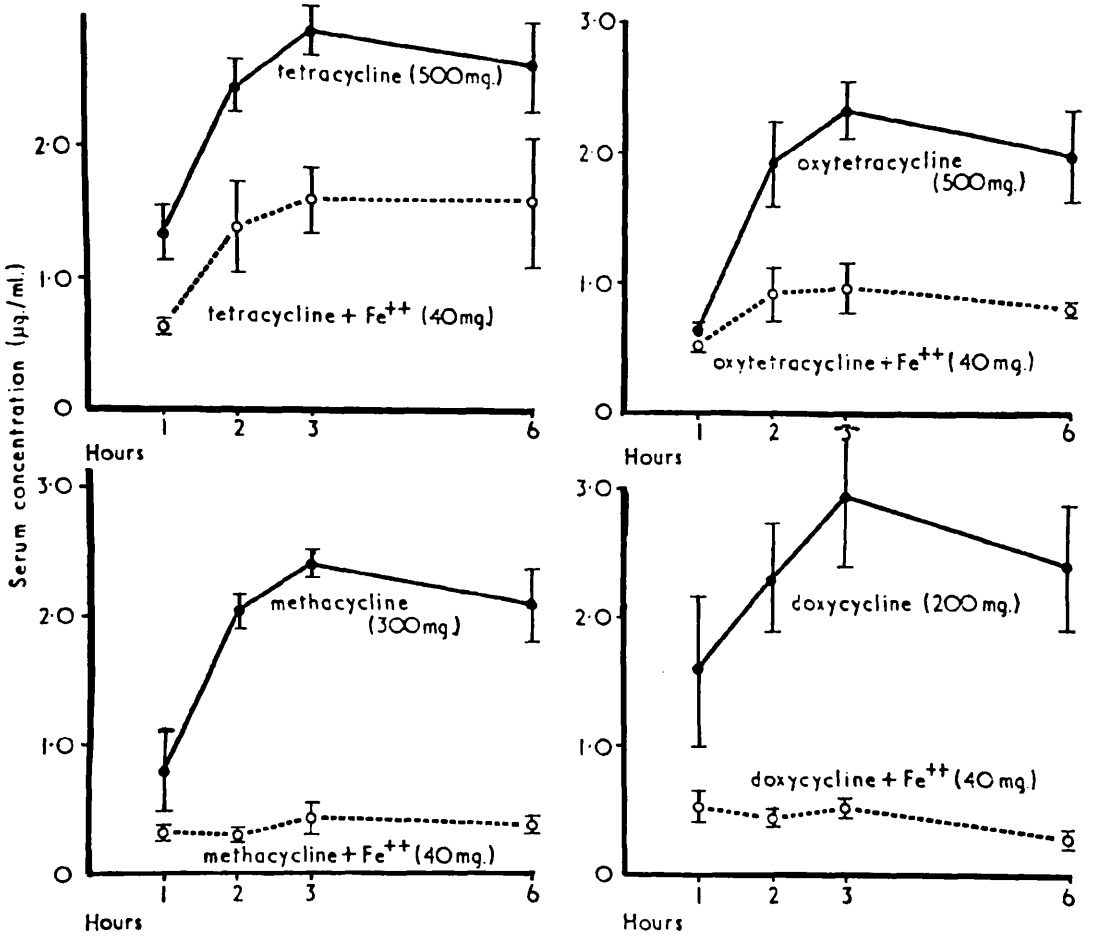



FIGURE 21 Interference of iron with the absorption of tetracycline in man. Mean serum levels (± S.E) after single doses of tetracycline preparations taken either alone or simultaneously with 200 mg of ferrous sulphate. (Five subjects in each group). From Neuvonen et al 1970, by kind permission of the authors and the Editor of the British Medical Journal.

was provided by Wagner (1966) when he demonstrated the delay in lincomycin absorption when combined with the intestinal adsorbents kaolin and pectinic acid. More recently, Hinnion and McDermott (1972) suggested that the absorption of digoxin could be interfered with by the antacid preparation "Maalox" and the antidiarrhoeal preparation "Kaopectate". Both these preparations adsorbed digoxin in vitro and preliminary human studies showed a marked effect on blood digoxin levels when digoxin tablets were administered with these two medicines.

### 4.2.2. Pharmacological interference with gastro-intestinal function

An important distinction must be made between interactions that alter the rate of drug absorption and those that increase or decrease the total amount of drug absorbed, since the consequences may be quite different.

#### Analogue computer simulation

This distinction can be conveniently demonstrated by analogue computation and Figures 22 and 23 were derived from the computer programme shown in Figure 12 to demonstrate the effect of changes in the rate constant of absorption ($K_a$) and the fraction absorbed on blood levels and urinary excretion. Figure 22 shows that changes in the rate of absorption with $K_a$ values of 1, 0.5 and 0.2 do not influence the actual amount of drug absorbed, but delay and reduce the peak plasma concentrations attained. The urinary excretion curves reflect the different rates of absorption but show that there are no differences in the total amount excreted. It is obvious from Figure 23 that a decrease in the fraction absorbed is equivalent to a decrease in the dose given, with obvious clinical implications. Complex formation will

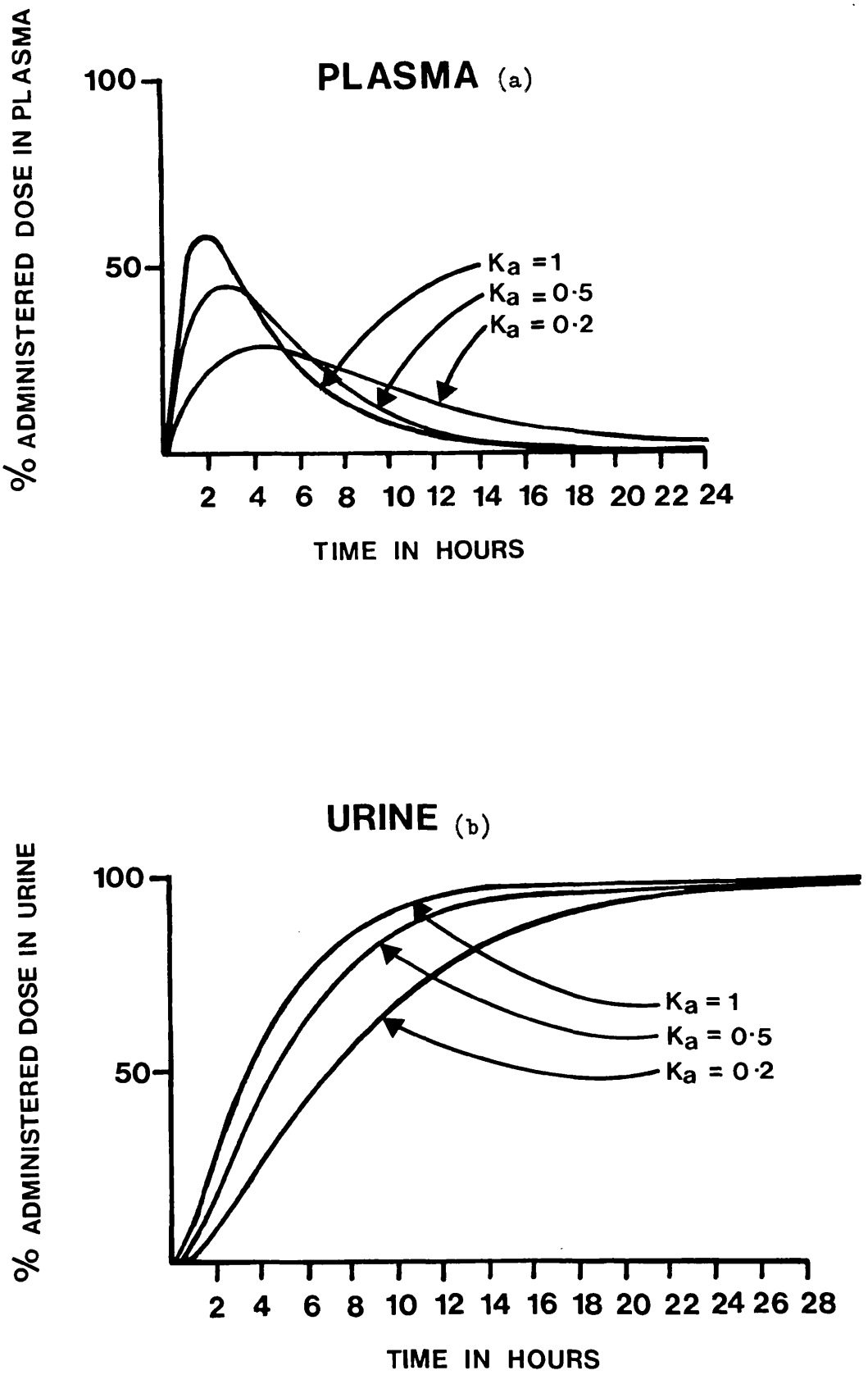
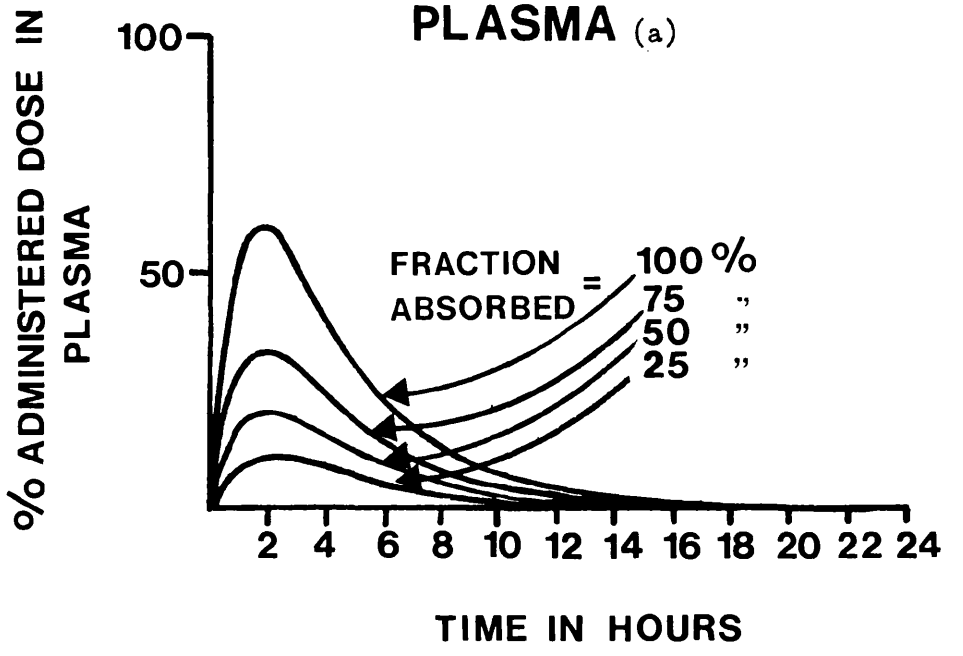



FIGURE 22 Analogue computer simulation of the effect of varying the rate of absorption ($K_a$ 1, 0.5 and 0.2) on (a) plasma levels and (b) urinary excretion. i.c. (D) and $K_e$ remain constant.



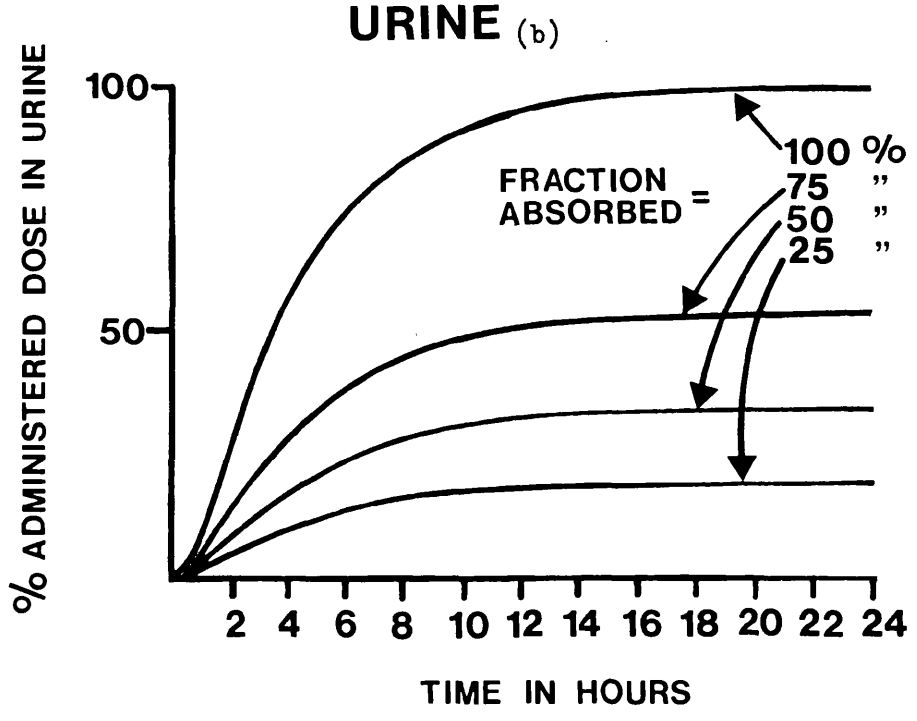




FIGURE 23 Analogue computer simulation of the effect of varying the fraction absorbed (100%, 75%, 50% and 25%) on (a) plasma levels and (b) urinary excretion, achieved by progressive reduction of i.c. (D). $K_a$ and $K_e$ remain constant.

have this effect.

Although a drug may eventually be completely absorbed, it may be absorbed so slowly that:

(a) it may never reach effective blood levels

(b) the rate of onset of effect may be delayed

(c) the effect may be unduly prolonged.

An important distinction must be made between types of drugs and clinical situations when decreased rates of absorption are clinically significant and those where this type of interaction may occur but is of little or no concern. In general, delayed absorption is usually important for drugs that are given as a single dose in clinical situations requiring a rapid onset of effect, e.g. analgesics or hypnotics. Delayed absorption may also be important in the case of drugs with a short biological half-life (or rapid elimination) such as procainamide, as therapeutic concentrations may never be attained. Figure 24 was derived on the analogue computer to demonstrate this. Drug A has a relatively short half-life of 42 minutes compared with drug B which has a half-life of seven hours. Absorption rates differ by a factor of 2.5, i.e. each drug is shown with $K_a$ values of 1 and 0.4. The slower rate of absorption ($K_a$ = 0.4) has had much less effect on the peak attained by drug B, which is reduced by 21%, than on that attained by drug A, which is reduced by 41%. Thus if the absorption of a rapidly eliminated drug is delayed for any reason, its therapeutic effect may be seriously compromised. On the other hand the rate of absorption of compounds with relatively long half-lives such as digoxin, has little influence on the blood levels achieved. The mean steady-state blood level in these circumstances depends much more on the fraction of drug absorbed than on the relative rate of absorption. Two circumstances in which aspirin is used will illustrate these points. Food affects the rate of absorption of aspirin but not the total amount absorbed. This

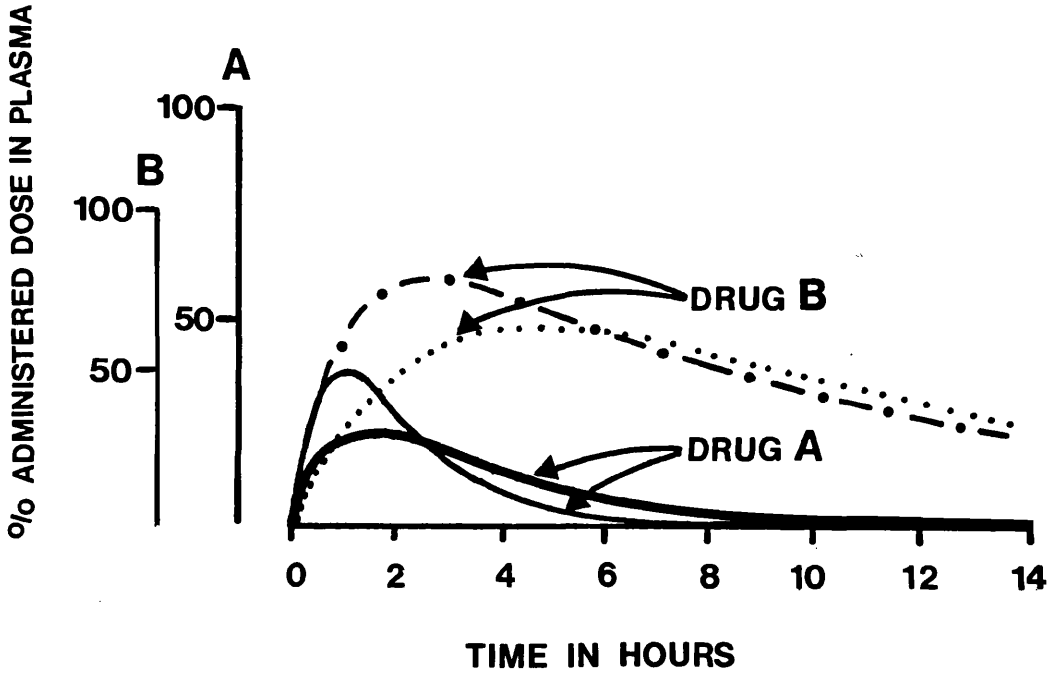



FIGURE 24 Analogue computer simulation of the relationship between the rate of absorption and the rate of excretion of drugs.

$K_e(A) = 1h^{-1}$, $t_{\frac{1}{2}}$ 42 minutes

$K_e(B) = 0.1h^{-1}$, $t_{\frac{1}{2}}$ 7 hours

Absorption of both drugs is reduced by 60% :

A _____ $K_a = 1$ ; ▬▬▬ $K_a = 0.4$

B -.-.-.-.-. $K_a = 1$ ; ..... $K_a = 0.4$

Peak height A is reduced by 41%

Peak height B is reduced by 21%

might vitiate the treatment of a headache but not the management of rheumatoid arthritis where multiple doses are given to achieve a relatively constant plasma level.

Modification of gastric function

Prescott (1974) reviewed the mechanisms of drug absorption interactions and highlighted the part played by the stomach. It is not of itself an important site of drug absorption, but the rate of gastric emptying may limit the rate of absorption from the upper small intestine. This is important in the context of interactions as the rate of gastric emptying can be influenced by many drugs, e.g. anticholinergics, antihistamines, tricyclic antidepressants, narcotic analgesics and metoclopramide. This was clearly demonstrated by Nimmo et al (1973) who studied the effect of propantheline and metoclopramide on the absorption of the weak acid paracetamol, whose rate of absorption in man had been shown to be directly related to the rate of gastric emptying (Heading et al 1973). Propantheline and metoclopramide were known to delay and accelerate gastric emptying respectively and would therefore illustrate pharmacological interference with gastro-intestinal function resulting in drug interactions.

Figure 25 (right hand graph) shows that gastric emptying was prolonged by propantheline, (six convalescent hospital patients) with a significant reduction in the rate of paracetamol absorption, peak plasma paracetamol concentration and the time taken to reach the peak. There was also a reduction in the 0-12 hour urinary excretion of total unchanged and conjugated paracetamol but the total amount excreted in 24hours was unchanged. Thus, propantheline delayed gastric emptying and reduced the rate of paracetamol absorption but did not reduce the total amount absorbed, (cf. analogue computer simulation, Figure 22).

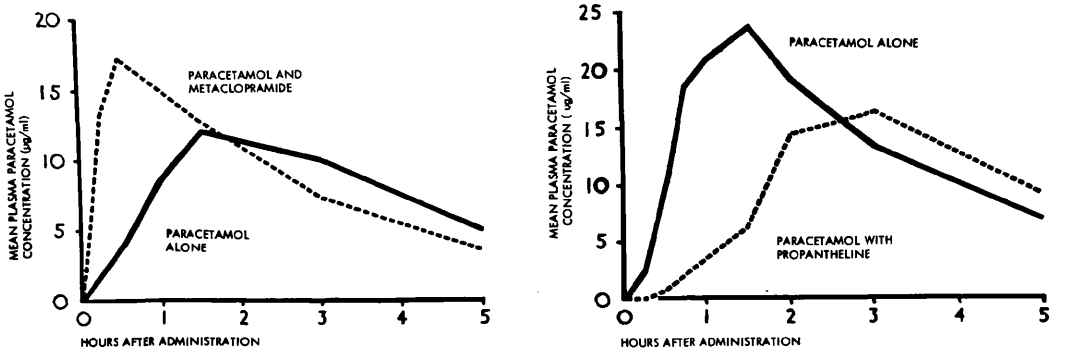



FIGURE 25 Effects of propantheline (right) and metoclopramide (left) on paracetamol absorption in six patients and five healthy volunteers respectively.
From Nimmo et al 1973, by kind permission of the authors and the Editor of the British Medical Journal.

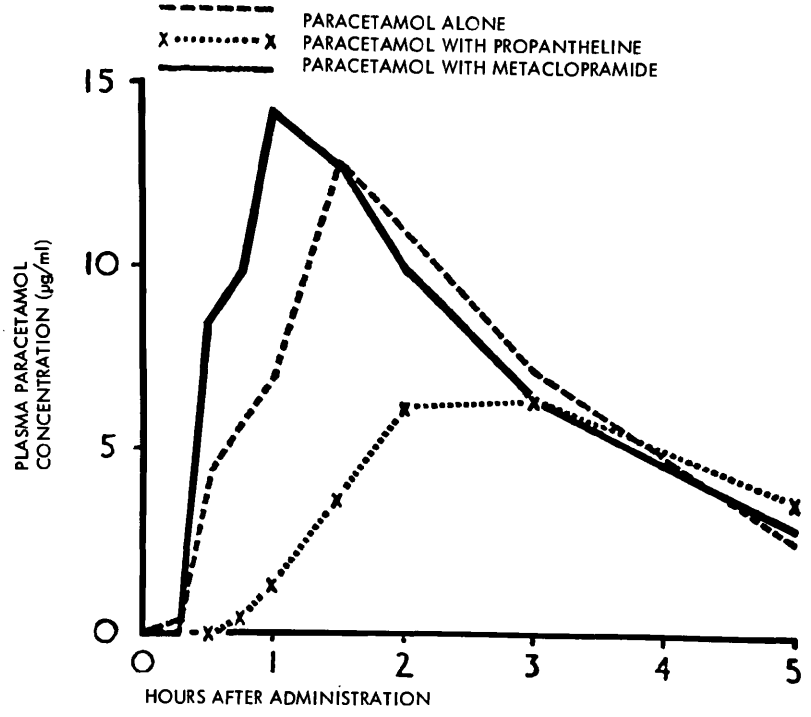



FIGURE 26 The effect of propantheline and metoclopramide on paracetamol absorption in a single subject. From Nimmo et al 1973, by permission as in Figure 25.

The opposite effect was shown by metoclopramide, Figure 25 (left hand graph) which significantly increased the rate of paracetamol absorption. The mean maximum plasma concentration (five volunteers) was increased and the mean time to peak concentration decreased (cf. analogue computer simulation, Figure 22). Figure 26 shows that these observations could be repeated in the same individual.

These experiments were designed to show the effect of modified gastric motor function on drug absorption. The dose, timing of administration, and duration of action of the drugs concerned were factors which were of crucial importance in determining the outcome. Lengthening the time interval between the administration of paracetamol and propantheline or metoclopramide would undoubtedly reduce and finally abolish the effects on paracetamol absorption. This, of course, reinforces the point that drug interactions may often be avoided by intelligent adjustment of dose and/or timing interval.

Atropine and metoclopramide were used in similar studies by Gothoni et al (1972) to show, respectively, delayed and accelerated absorption of pivampicillin and tetracycline. But Manninen et al (1973) obtained paradoxical effects with digoxin. In patients on maintenance digoxin therapy, propantheline increased serum digoxin concentrations while metoclopramide lowered them. The results with propantheline were confirmed in healthy volunteers taking digoxin tablets, but absorption of digoxin in liquid form was unaffected by propantheline (Figure 27).

The discrepancies in the results obtained by these workers could probably be explained on the basis of the dissolution characteristics and absorption properties of digoxin. When ingested in tablet form, disintegration, dissolution and absorption in the upper gastro-intestinal tract determine the bioavailability of digoxin. Rapid gastro-intestinal transit induced by metoclopramide could reduce the effective time for

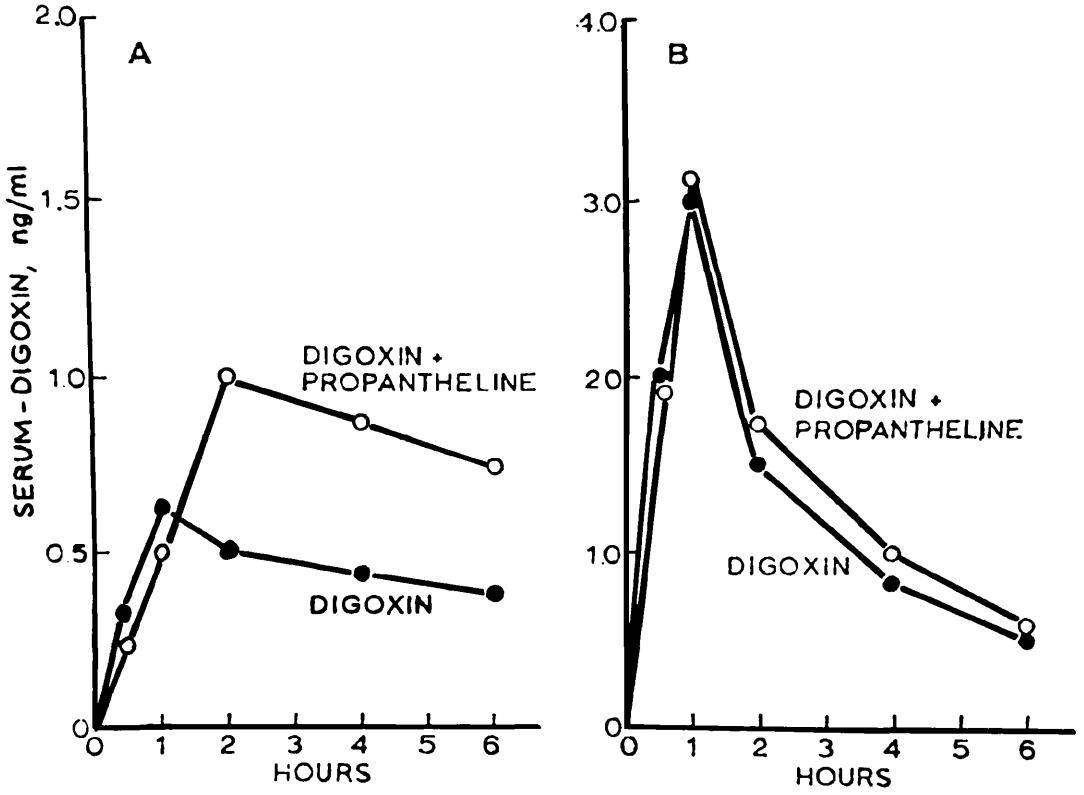



FIGURE 27 Effect of propantheline on digoxin absorption in volunteers.
Mean serum digoxin concentrations in healthy medical students.
A. 0.5 mg digoxin ingested in fasting state in tablet form.
B. 0.5 mg digoxin ingested in solution with a small amount of water.
Propantheline (30 mg in tablets) was administered 30 minutes previously. Four students in each group.
From Manninen et al 1973, by kind permission of the authors and the Editor of the Lancet.

dissolution and absorption whereas propantheline would have the opposite effect by lengthening the effective absorption time.

A number of other studies have attested to the effects of drug-induced alterations of gastro-intestinal function on drug absorption. Levy, Gibaldi and Procknal (1972) showed that propantheline delayed the absorption of riboflavin, but greatly increased the total amount absorbed. Adjepon-Yamoah, Scott and Prescott (1973) observed a marked delay in the absorption of orally administered lignocaine in patients premedicated with atropine prior to laparoscopy and Consolo et al (1970) demonstrated that desmethylimipramine delayed the absorption of phenylbutazone.

Absorption of drugs from the gastro-intestinal tract is clearly a complex process. The rate of gastric emptying may often be an important rate-limiting step, and may itself be determined by pharmacological factors. This, together with more generalised changes in gastro-intestinal motility and peristalsis, may modify tablet disintegration and dissolution and increase or decrease the contact time between drug and absorptive mucosa.

## 4.3. INTERACTIONS IN THE PHARMACOKINETIC PHASE

The basic factors affecting transit to and from receptor sites which can be altered by drug interactions can be summarised as follows:

(a) Factors affecting transit of active drug to site of action

i. Rate and extent of absorption of drug (discussed under "Interactions in the pharmaceutical phase")

ii. Distribution of active drug from plasma to tissues and site of action.

iii. Metabolism of inactive drug to biologically active metabolites.

(b) Factors affecting removal of active drug from site of action

i. Redistribution from site of action to other tissues.

ii. Metabolism of active drug to inactive metabolites.

iii. Excretion of drug and metabolites, principally in the urine and bile.

A schematic representation of these mechanisms is shown in Figure 28. The pharmacokinetic components which may be modified by drug interactions are therefore:

1. Distribution
2. Metabolism
3. Excretion.

## 4.3.1. Redistributional interactions

Drugs are present in the plasma in two forms - free and protein bound. Transfer across cell membranes can only be achieved by the free drug, which is therefore regarded as the pharmacologically active component. Binding occurs principally to albumin and is easily reversible. Drug molecules associated with albumin will be readily liberated as the free concentration in the plasma declines. Reversibility and lack of specificity of binding enable plasma albumin to act as a transport organ designed to regulate the distribution of the majority of drugs throughout the body. Many acidic drugs share the same limited number of binding sites on plasma albumin and can displace one another under certain conditions. The increased concentration of free drug may then lead to enhanced drug effects and toxicity.

Drugs may interact at plasma protein binding sites by competitive and non-competitive mechanisms, the latter probably being due to configurational changes in the protein molecule (O'Reilly and Aggeler,

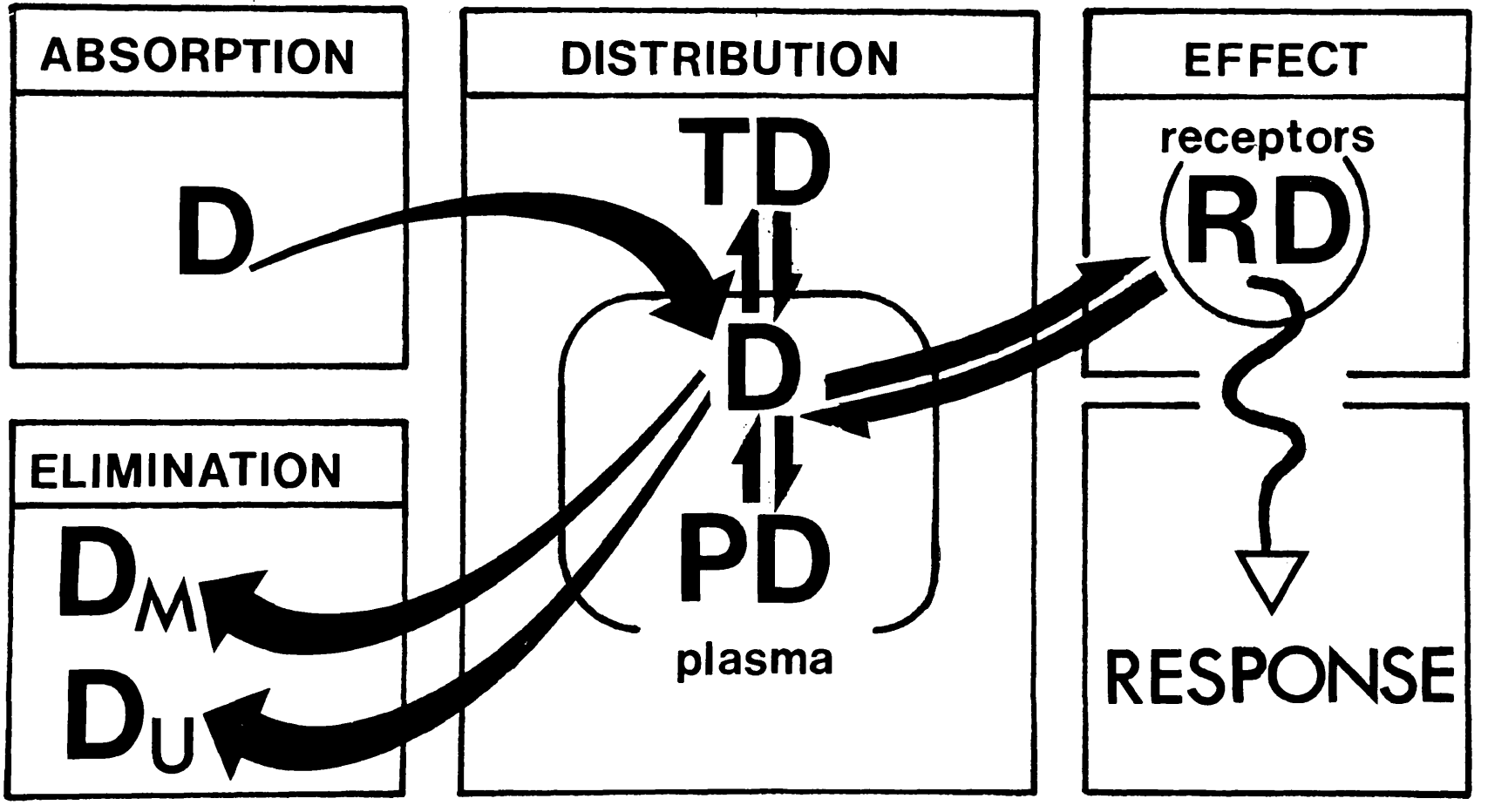



FIGURE 28 Schematic representation of some mechanisms involved in drug action. D is free (unbound) active drug, PD is drug reversibly bound to plasma proteins, TD is drug reversibly bound to tissue, RD is drug reversibly bound to the "receptor site", $D_M$ is drug eliminated by drug metabolising enzymes and $D_U$ is drug eliminated by excretory pathways such as the urine and bile.

1970; Levy 1970). The chemical structure of drugs cannot predict whether or not they are likely to participate in such interactions, but when they do, important changes in drug effects will only occur with drugs which are normally highly bound to plasma protein (>90%), since even a small change in binding will then have a disproportionate effect on the concentration of unbound drug.

Distribution model

Hasselblatt (1972) has proposed a simple model to illustrate the relationship between the degree of binding of a drug and its distribution and this can be used to visualise the effects of displacement interactions. The model assumes that drug molecules which are not bound to plasma proteins are in equilibrium with drug molecules freely distributed throughout the whole of the body water. They will then leave the blood and enter a space thirteen times as large as the plasma volume (Figure 29). If, for example, 70% of a drug within the blood is bound, 85% of the total amount of drug present in the body at equilibrium will be free. On the other hand if a drug is 98% bound, only 22% of the total amount will be free. This relationship between bound drug and the distribution of free drug at equilibrium can be computed over a wide range of theoretical binding values and the results expressed graphically as in Figure 30. The shape of the curve clearly illustrates that in this model system, redistribution of a drug is only likely to be of significance when initial binding values are high (>90%). Figure 31 examines two portions of this curve in detail. Typically, a change of binding from 98% to 95% would be associated with an 18.8% rise in the free content of drug, whereas even a relatively large change at a lower level, e.g. 30% to 20%, would lead to no significant change in distribution (approximately 1%). This would apply to a drug such

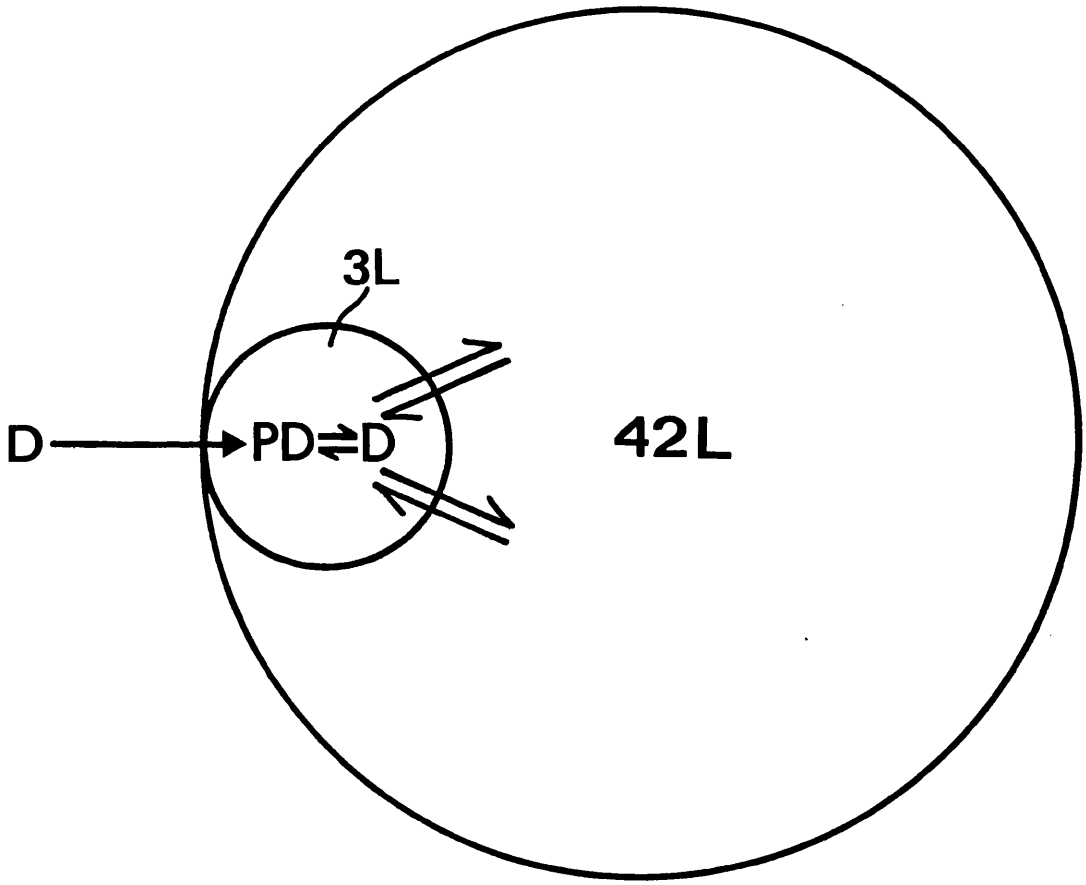



FIGURE 29 Distribution model showing the relationship between the protein binding of drugs in the plasma and distribution of free drug in the extravascular fluid space. (Plasma volume = 3L; whole body water volume = 42L). Assumptions made : binding occurs only on plasma proteins, free drug molecules are distributed throughout the body water space. D is free, active drug and PD is drug reversibly bound to plasma proteins.

Redrawn from Hasselblatt 1972, by kind permission of the author and Excerpta Medica.

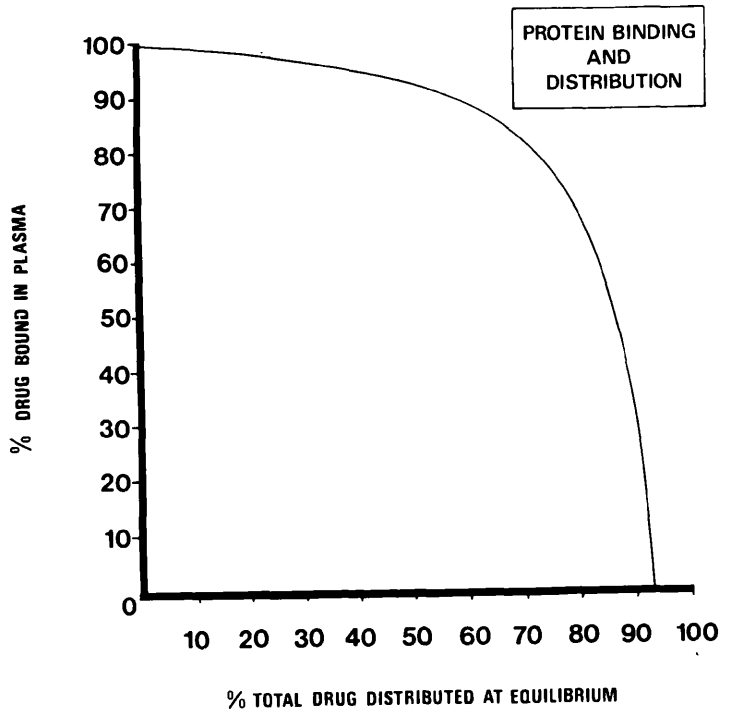



FIGURE 30 Graphical representation of the relationship between the plasma protein binding of a drug and its distribution throughout the extravascular fluid space.

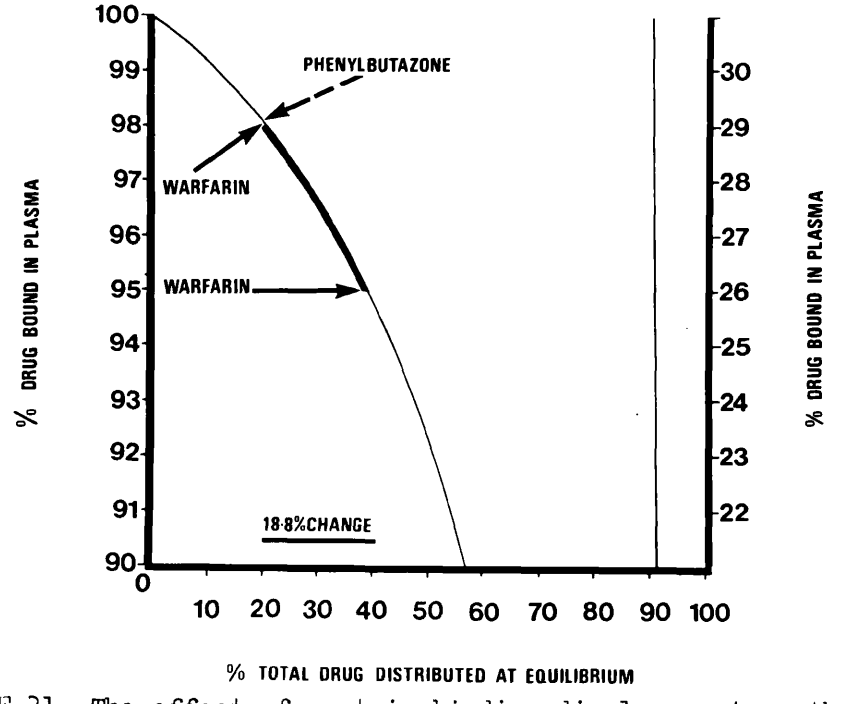



FIGURE 31 The effect of protein binding displacement on the distribution of drugs. Two portions of the curve shown in Figure 30 are examined : L.H. scale and curve for binding values in the 90-100% range and R.H. scale and "curve" for binding values in the 20-30% range.

See text for further details.

as digoxin with binding values of 30-40% at therapeutic concentrations (Wallace and Whiting 1974). It is relatively easy to demonstrate changes like this in the test tube with human plasma, but this should constitute only the first rudimentary step in the evaluation of displacement phenomena.

Warfarin-phenylbutazone interaction

Much emphasis was formerly placed on the interaction between warfarin and phenylbutazone at plasma protein binding sites (Aggeler et al 1967) and warfarin displacement with a rise in free concentration could be readily demonstrated by such in vitro techniques as ultrafiltration (Solomon and Schrogie 1967). The present author set up a comparable system using Sephadex Gel filtration and was able to demonstrate the displacement of $^{14}$C-warfarin from albumin by phenylbutazone (Figure 32, author's unpublished observations).

Sephadex gel filtration separates substances in solution according to their size and molecular weight. The relationship between the size of, e.g. drug molecules and the interstices of the gel set up in a vertical column determines the rate at which the drug molecules gravitate down the column. Fractionation can be achieved by collecting the effluent from the column over a period of time. Substances of relatively high molecular weight gravitate first while lighter molecules tend to be retained. Figure 32 shows that warfarin is almost totally associated with the protein (albumin) fraction in plasma (left hand upper and lower graphs) but when phenylbutazone is added, a proportion of the warfarin is displaced and retained to appear later as free drug (right hand upper and lower graphs). The relevance of these observations to the clinical situation, however, must be examined.

Wardell (1974), in his critical review of putative clinical examples

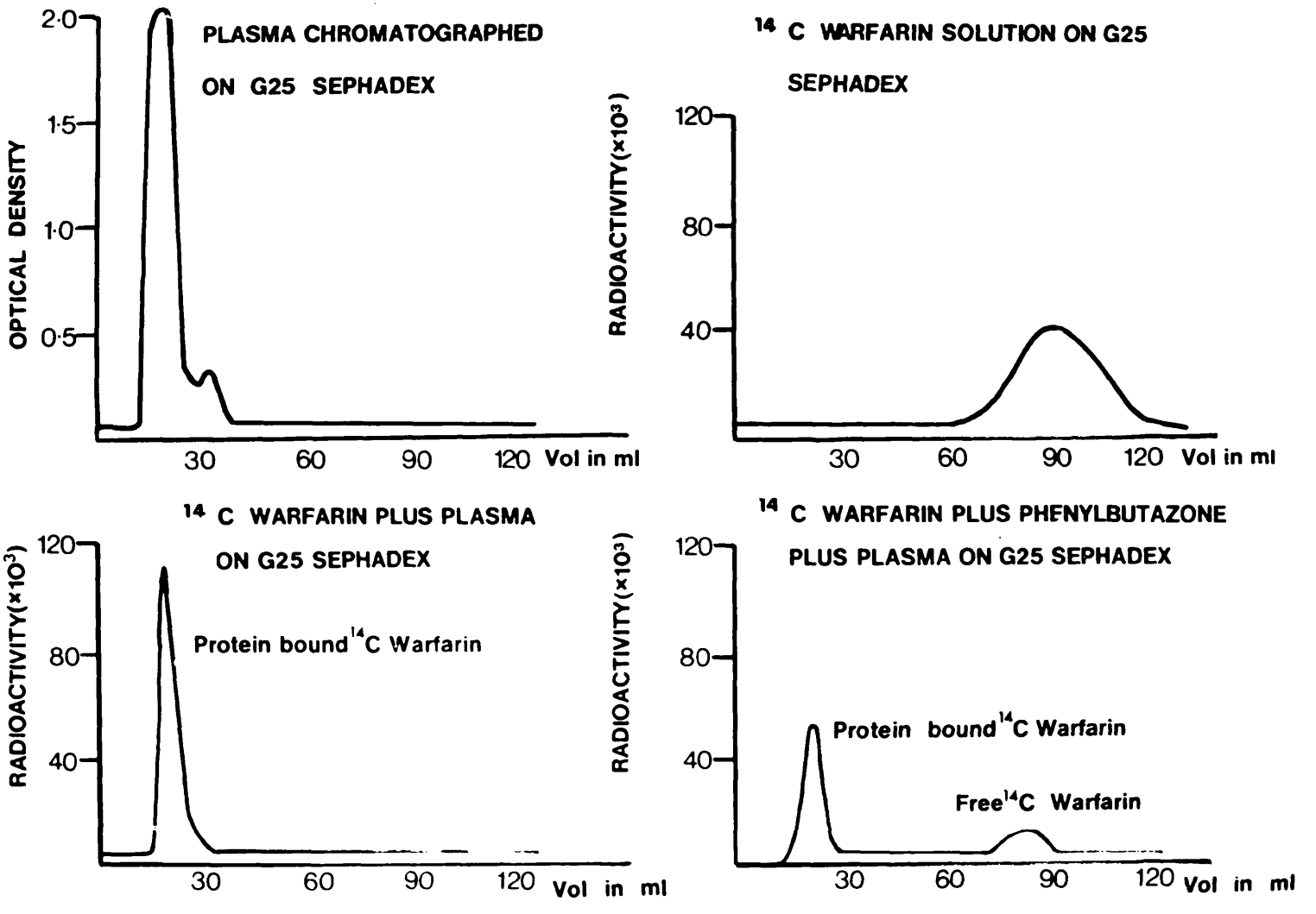



FIGURE 32 The displacement of warfarin by phenylbutazone demonstrated by sephadex gel filtration. For details, see text.

of redistributional drug interactions, stresses a number of criteria which should be applied to the analysis of such interactions. In vitro experiments should be followed by a demonstration that redistribution actually occurs in human subjects. Plasma samples should be assayed for both total and free concentrations of displaced drug and should show a fall in total concentrations consistent with a fall in bound drug partially offset by a rise in the free concentration. A quantitative assessment of the overall pharmacokinetic changes should be made to see whether redistribution alone can wholly account for the changes or whether other mechanisms need to be invoked. The transient nature of many in vivo binding interactions underlines the complex dynamic processes with which they may be associated, e.g. alterations in drug metabolism and elimination. Thus the demonstration of warfarin displacement by phenylbutazone is now known to be only one component of the interaction between these two drugs.

A consideration of the stereochemical configuration of warfarin led to findings which indicated a much more subtle and complex interaction than had been previously supposed (Lewis et al 1974). Warfarin was known to exist in two isomeric forms, (R)(+)Warfarin (R Warfarin) and (S)(-)Warfarin (S Warfarin), the clinically available formulation being a mixture of equal parts of these isomers (a racemate). An examination of the metabolic fate of each isomer (Lewis and Trager 1971) revealed that they were metabolised by different routes, and previous work had demonstrated that S Warfarin was five times more potent as an anticoagulant than the R isomer, both in man (O'Reilly 1971) and the rat (Elbe, West and Link 1966; Breckenridge and Orme 1972). This meant that the configuration of warfarin would greatly influence its pharmacological effect. Moreover, the metabolic fate of each isomer might show different susceptibilities to the influence of other drugs, suggesting that interactions with warfarin might be manifest

stereospecifically. Lewis et al (1974) reported a reduction in the plasma clearance of S Warfarin and an increase in the plasma clearance of the R isomer after phenylbutazone. The rate of clearance of the racemic mixture, however, was unaffected as the depressed S isomer clearance was effectively masked by the stimulated clearance of the R isomer (Figure 33). The impaired metabolism of the more potent S Warfarin, therefore, provided evidence of another important mechanism by which phenylbutazone augments warfarin induced anticoagulation.

General considerations

A great number of drugs have been implicated in protein displacement interactions notably acidic compounds such as non-steroid anti-inflammatory agents including aspirin, uricosuric drugs, sulphonamides, penicillins, nalidixic acid, oral anticoagulants, clofibrate, methotrexate, sulphonylureas, diazoxide, ethacrynic acid, barbiturates, phenytoin and trichloracetic acid. Many in vitro studies attest to protein displacement interactions with these drugs, but the evidence for a redistributional mechanism in man is less secure. As with the phenylbutazone-warfarin interaction, initial enthusiasm for protein binding displacement to explain the potentiation of tolbutamide induced hypoglycaemia by phenylbutazone or sulphaphenazole has been tempered by subsequent work which demonstrated inhibition of tolbutamide metabolism (Christensen et al 1963).

Strong circumstantial evidence however has been presented for a redistributional mechanism as being partly responsible for warfarin potentiation by chloral hydrate - or more accurately by its major metabolite, trichloracetic acid. Sellers and Koch-Weser (1970) showed that trichloracetic acid accumulated during chloral hydrate therapy, displaced warfarin from its binding sites, and caused a fall in the

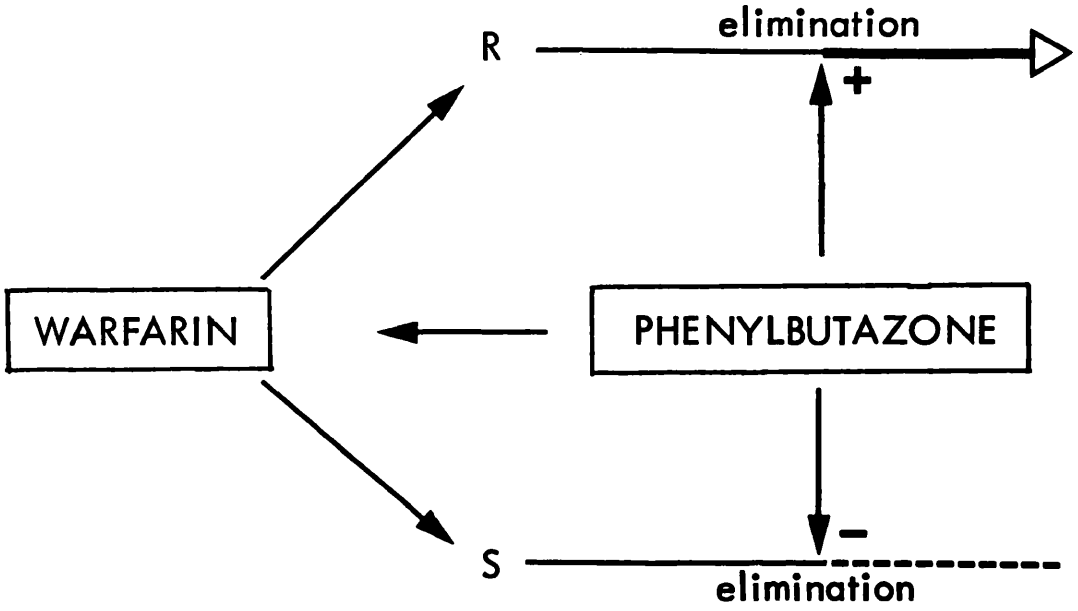



FIGURE 33 Schematic representation of the phenylbutazone-warfarin interaction. Elimination of R-warfarin is increased and that of S-warfarin decreased by phenylbutazone.

total plasma concentration of warfarin. An associated increase in prothrombin time reflected the greater amounts of warfarin available at receptor sites and the increased distribution also made more warfarin available for metabolism and so reduced its half-life.

The dynamic nature of these changes - the liberation of an excess amount of pharmacologically active drug on the one hand and its increased metabolism on the other - re-emphasises the transient nature of these interactions, but as Sellers and Koch-Weser (1971) have pointed out, there is sufficient potentiation of warfarin activity for the interaction to be of clinical significance. Of 52 hospitalised patients who received warfarin and chloral hydrate concomitantly, 13 showed significant potentiation of anticoagulation. It is interesting to note, however, that in a much smaller series of five patients taking warfarin and chloral hydrate, Breckenridge et al (1971), although they demonstrated a fall in plasma warfarin concentration failed to detect any commensurate changes in anticoagulation. Thus the relationship between redistribution and detectable changes in pharmacological activity can be somewhat tenuous.

Further understanding of these interactions will depend on the application of more rigorous criteria. Any displacement that occurs will always invalidate concentration-effect relationships based on the measurement of total plasma concentrations, and this problem could be overcome by the routine measurement of free drug concentrations in plasma ultrafiltrates.

4.3.2. Personal observations :

## PLASMA DRUG BINDING IN ELDERLY PATIENTS

Many protein binding studies, especially those carried out exclusively in vitro, have failed to relate experimental findings to the clinical situation. One particular problem which seemed to demand a combined clinical and experimental approach was the increased susceptibility to drug toxicity in the elderly (Hurwitz 1969). This signified that ageing may be associated with some alteration in drug handling. Convincing evidence of this was lacking until O'Malley et al (1971) found that the half-lives of antipyrine and phenylbutazone were prolonged in a group of elderly patients. Evidence has also been presented for increased phenytoin clearance in an elderly group (Hayes et al 1975b) which correlated inversely with reductions in both plasma phenytoin binding and albumin levels. Reduced albumin levels were also thought to contribute to reduced warfarin binding in the elderly (Hayes et al 1975a). It was therefore of interest to study the various factors which may be responsible for changes in protein binding in the elderly and assess the contribution made by both decreased albumin levels and multiple drug therapy (Wallace, Whiting and Runcie 1976).

### Patients and methods

Sixty nine subjects were studied, divided into the following groups:

(a) Sixteen healthy volunteers, aged 19-40 years (mean 27 years) taking no drugs. (Group A)

(b) Fifteen surgical and gynaecological patients, aged 14-39 years (mean 30 years), not acutely ill but taking sedatives, analgesics and a variety of other drugs, including antibiotics. (Group B)

(c) Sixteen elderly patients, aged 69-85 years (mean 79 years) taking no drugs. (Group C)

(d) Twenty two elderly patients, aged 74-92 years (mean 84 years) taking one or more drugs at the time of the study. (Group D)

Blood samples (10 ml) were withdrawn from hospital patients approximately two hours after the first morning drug administration round, and collected into tubes containing lithium-heparin as anticoagulant. Plasma was immediately separated by centrifugation, an aliquot reserved for routine biochemical tests, including serum proteins, and the rest was stored at -20°C until use.

Aliquots of plasma (1 ml) from each subject were incubated for 30 minutes at room temperature with three "test" drugs - salicylic acid (280-400 μg/ml) sulphadiazine (300-500 μg/ml) and phenylbutazone (75-200 μg/ml). The plasma was then subjected to ultrafiltration (Amicon Centriflo membrane cones or the Amicon Multi-Micro Ultrafiltration System) and samples of the original plasma-drug solution and ultrafiltrate were analysed for total and free drug respectively. Salicylate was determined by the method of Trinder (1953)[1], sulphadiazine by the method of Bratton and Marshall (1939)[2] and phenylbutazone by the method of Andreason (1973)[3].

1. Trinder, P. (1953) Rapid determination of salicylate in biological fluids. Biochemical Journal, 57, 301-303.

2. Bratton, A.C. and Marshall, E.K. (1939) A new coupling component for sulphanilamide determination. Journal of Biological Chemistry, 128, 537-550.

3. Andreason, F. (1973) Protein binding of drugs in plasma from patients with acute renal failure. Acta Pharmacologica et Toxicologica, 32, 417-429.

A separate series of experiments was performed to determine the effect of plasma dilution on the binding of the three test drugs. Serial dilutions of 1:5, 1:20 and 1:100 were made of normal plasma using Sørensen's phosphate buffer (pH 7.4). The three drugs were added as described above, the samples ultrafiltered, and total and free concentrations measured as before.

## Results

Figure 34 shows the relative amounts of free drug in the plasma of all subjects. Significant increases in free salicylate, sulphadiazine and phenylbutazone were found in elderly patients taking drugs (Group D) when compared with Group A. A similar increase in free phenylbutazone was seen in young hospital patients and elderly patients not on drug therapy (Groups B and C).

Elderly subjects showed a significant reduction in plasma albumin levels ($p < 0.001$ for Groups C and D compared with Groups A and B, Figure 35).

The effect of in vitro plasma dilution on the binding of all three drugs is shown in Figure 36. The binding of phenylbutazone decreased dramatically with increasing dilution but for both salicylate and sulphadiazine a considerable reduction in plasma protein concentration was necessary before any real increase in unbound drug occurred.

Figure 37 shows that a highly significant increase in free salicylate concentration ($p < 0.001$) was detected in the plasma of elderly patients taking two or more drugs. A similar result was observed with sulphadiazine.

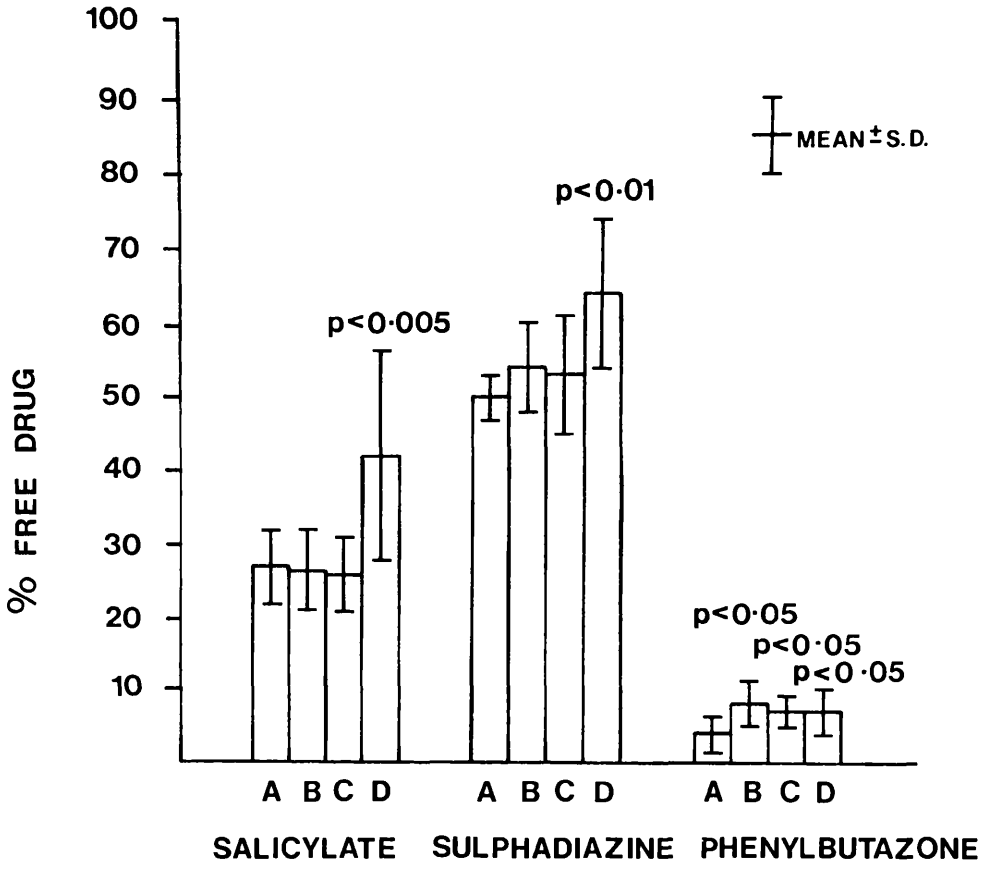



FIGURE 34 The binding of salicylate, sulphadiazine and phenylbutazone in normal young volunteers receiving no drugs (Group A), young surgical and gynaecological patients receiving drug therapy (Group B), elderly patients receiving no drugs (Group C) and elderly patients receiving drug therapy (Group D). Groups B, C and D are compared to Group A.

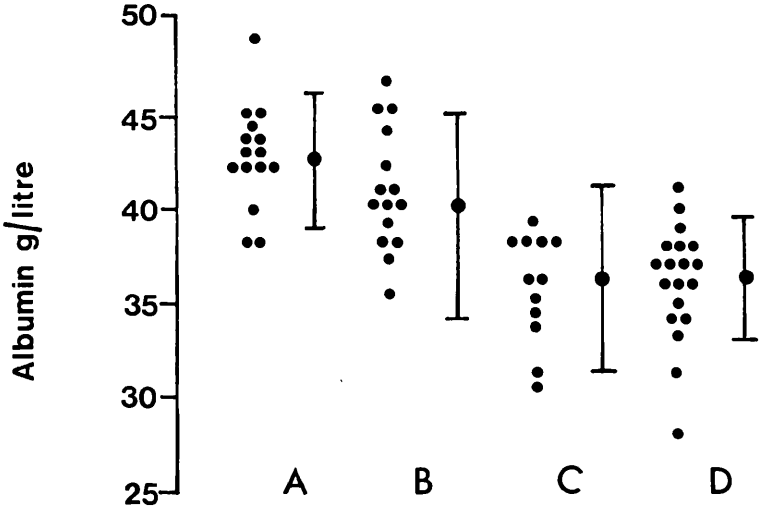



FIGURE 35 Comparison of plasma albumin concentrations between Groups A,B,C and D. Vertical bars indicate mean ± S.D. Groups C and D are significantly different ($p < 0.001$) from Group A.

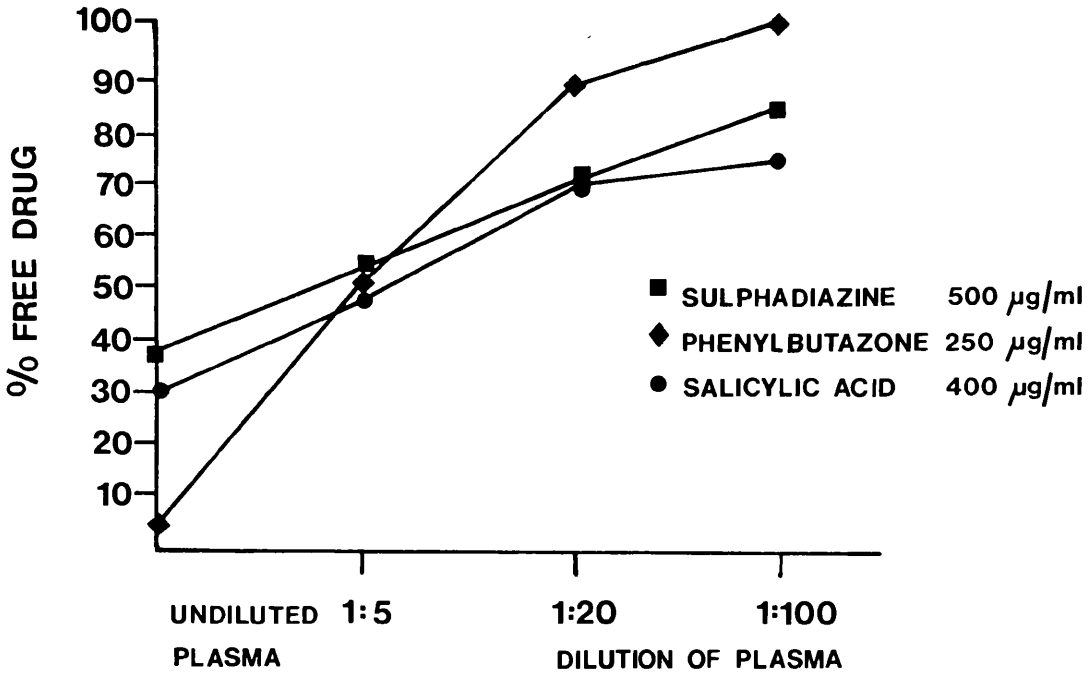



FIGURE 36 The effect of dilution on the plasma protein binding of salicylate, sulphadiazine and phenylbutazone.

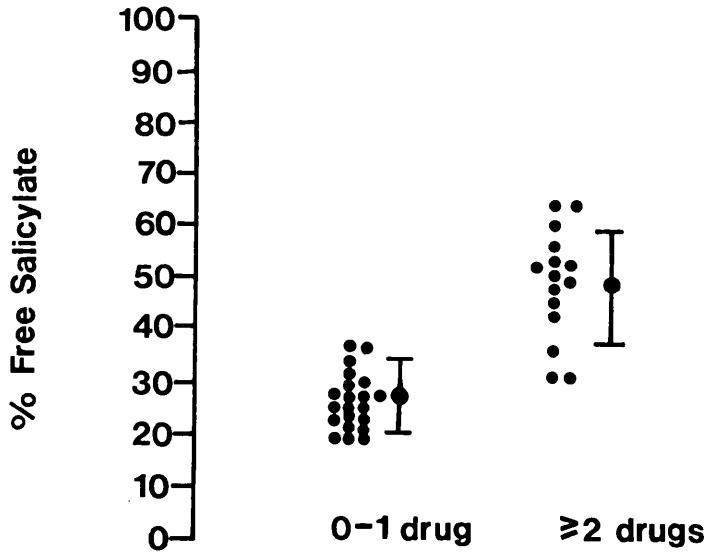



FIGURE 37 The effect of the number of drugs being taken simultaneously on the binding of salicylate in Group C and D subjects. The difference between the two groups is significant ($p < 0.001$). Vertical bars indicate the mean ± S.D.

## Discussion

The changes in plasma protein concentration with age noted in this study agreed with previous findings (Woodford-Williams et al 1964). The pattern generally found has been a fall in albumin and a rise in gammaglobulin levels, seemingly related to decreased mobility in elderly people (Woodford-Williams et al 1964). This reduction in albumin could lead to altered drug distribution characteristics.

This study demonstrated a significant reduction in the plasma protein binding of phenylbutazone in the elderly and the plasma dilution experiments indicated that phenylbutazone binding - normally about 98% - is particularly susceptible to changes in albumin concentration. Neither of the two less extensively bound drugs, salicylate and sulphadiazine showed significant reductions in binding in elderly patients not receiving drugs and plasma dilution curves indicated that changes in albumin levels did not have such a pronounced effect on the binding of these drugs.

The relationship between plasma albumin concentration and competitive binding effects has received relatively little attention, but Anton and Corey (1971) showed that competition may be enhanced when the plasma albumin concentration is reduced. Our findings were related to both young and elderly patients, with significantly different albumin levels, receiving a variety of drugs. Binding of salicylate, sulphadiazine and phenylbutazone was significantly lower in elderly patients receiving drug therapy compared to normal healthy young adults, and also to elderly drug free subjects. Only phenylbutazone binding was significantly reduced in young hospitalised patients receiving drugs, and the mean albumin level of this group did not differ significantly from that of healthy young adults.

It appears, therefore, that the combination of low albumin levels

and multiple drug therapy may be responsible for the observed reduction in binding of the three test drugs in the elderly group receiving drug therapy. It is also apparent that low albumin levels per se can cause significant increases in the free concentration of phenylbutazone and other highly bound drugs.

The group of young patients receiving drugs had albumin levels within the normal range and only phenylbutazone binding was significantly reduced. It is probable that the relatively high (normal) albumin concentrations encountered in this group reduced the susceptibility to competitive effects.

Evidence of the tenuous nature of the relationship between altered drug distribution and pharmacological effect has already been presented in this thesis. The data presented here could not be analysed directly in terms of altered pharmacological effect, but provided additional evidence for altered drug handling in the elderly.

It is difficult to say whether or not this would make a significant contribution to the increased susceptibility to drug toxicity which has been shown to occur in the elderly, but it is certainly important to recognise that protein binding relationships alter with age and possibly modify the redistributional effects of a protein binding interaction. In these circumstances, it would be sensible to exercise particular caution when a combination of highly bound drugs was being used. It might even be advisable to test each individual's plasma for its ability to bind the drugs in question.

No definite relationship between the type of drug taken by elderly patients in Group D and the observed effects on protein binding could be demonstrated. The drugs included hypnotics, tranquillisers, iron preparations, analgesics and antibiotics.

4.3.3. Interactions affecting drug metabolism.

The excretion of many drugs by the kidney is limited by their lipid solubility and would proceed at a very slow rate if the liver had no capacity to convert lipid soluble drugs into more water soluble, polar compounds. Fortunately, the smooth endoplasmic reticulum in liver cells contains enzymes which can effect this conversion by a variety of oxidative, reductive, and conjugation mechanisms including hydroxylation, dealkylation, deacetylation and glucuronidation (Brodie, Gillette and La Du 1958). The polar metabolites which are formed are usually less toxic than the parent compound because their reduced lipid solubility precludes transfer across cell membranes to potential sites of action. Occasionally, however, despite increased polarity, a derived product may gain pharmacological activity which is not present in the parent compound if the conversion unmasks or produces a new functional group.

Many chemicals and lipid soluble drugs can increase the rate of their own metabolism and the metabolism of other pharmacologically and chemically unrelated compounds by inducing an increase in the size and enzyme content of the smooth endoplasmic reticulum. This non-specific phenomenon has been observed in many mammalian species and can be viewed as an adaptive process which protects the organism against the effects of excessive amounts of foreign compounds (Remmer 1964, 1967, 1972; Conney 1967; Conney and Burns 1962). In therapeutic terms, induction of drug metabolism by one drug may increase the rate of metabolism of other drugs, thereby reducing their therapeutic and toxic effects. The original response may be regained by an increase in dose but this may lead to a problem when the inducing drug is withdrawn. Metabolism then returns to normal with the risk of an exaggerated response or toxicity if the dose is not reduced.

The activity of drug-metabolising enzymes can also be inhibited by certain compounds, which presents the opportunity for mutual inhibition of metabolic inactivation. Thus one drug may inhibit the metabolism of another and cause cumulation and toxicity.

Two basic mechanisms, therefore, may underlie interactions affecting drug metabolism - (a) enzyme induction, and (b) enzyme inhibition.

Enzyme induction

The number of drugs which can significantly induce drug metabolism during therapy is relatively small and includes phenobarbitone, the most widely recognised example, other barbiturates, phenytoin, carbamazepine, meprobamate, glutethimide and alcohol.

Individuals differ in their response to inducing agents because the degree of induction is under genetic control (Vessell and Page 1969). Some people have no alteration in drug metabolism; others have striking effects. Unfortunately, it is difficult to predict the response of an individual to enzyme induction, although in general, the greatest effect is seen in persons who initially show the slowest metabolism (Nies 1974). Interactions involving enzyme inducers, therefore, may or may not reach clinical significance but their foreknowledge should facilitate dosage adjustments to maintain a desired effect.

The drug which has been investigated most extensively in this regard is warfarin, whose metabolism can be increased and effects diminished by inducing agents (Levy et al 1970; Breckenridge et al 1971; Koch-Weser and Sellers 1971). As accurate control of anticoagulation is essential, any acceleration of metabolic inactivation of warfarin has important therapeutic consequences. The daily dose required for adequate suppression of prothrombin-complex synthesis

is increased and necessitates careful adjustment if loss of adequate therapeutic effect is to be avoided. The exact dosage increase required to balance the induction effect varies greatly and is unpredictable, but may exceed 100 per cent. Furthermore, it is very difficult to achieve stable anticoagulation in the presence of enzyme inducers, particularly hypnotics and alcohol which patients may take in a somewhat erratic fashion. Finally, withdrawal of the inducing agent may cause bleeding from excessive hypoprothrombinaemia if appropriate reduction of warfarin maintenance dose is not anticipated.

Unlike digoxin, which is excreted largely unchanged in the urine, digitoxin undergoes extensive metabolism and Solomon and Abrams (1972) showed that steady-state levels of digitoxin in the plasma could be lowered by phenylbutazone and phenytoin, both acting as inducing agents. Discontinuation of these drugs resulted in a return of plasma digitoxin levels to control values.

Rifampicin and oral contraceptives

Another interesting and important example of the consequences of enzyme induction was provided by Reimers and Jezek (1971) when they reported that simultaneous administration of rifampicin and oral contraceptives resulted in an increased incidence of "spotting" and breakthrough bleeding. Rifampicin, introduced relatively recently for the treatment of tuberculosis, was subsequently shown to be a potent enzyme inducer (Remmer, Schoene and Fleischmann 1973) and a further study by Nocke-Finck, Breuer and Reimers (1973) showed that five pregnancies occurred in 88 rifampicin-treated women receiving oral contraceptives. These clinical observations, combined with a study of urinary oestrogen excretion, suggested that rifampicin may cause partial or total failure of oral contraceptive therapy by

altering the biogenesis and/or inducing the metabolism of oestrogens. Bolt, Kappus and Bolt (1975) have recently clarified the position by demonstrating a four-fold increase in the hydroxylation of ethinyloestradiol and oestradiol by human liver microsomes in vitro after only several days of rifampicin treatment. These authors were satisfied that the in vitro findings could be extrapolated to the in vivo situation because hydroxylation constituted the only metabolic route of quantitative significance for the oxidative inactivation of ethinyloestradiol. Moreover, the oral effectiveness of ethinyloestradiol depended on its relatively slow rate of inactivation when compared with oestradiol, known to be ineffective when given by mouth (Reed, Fotherby and Steele 1972; Fotherby 1973). The results presented by Bolt et al (1975) indicated that induction by rifampicin would shift the half-life of ethinyloestradiol towards that of oestradiol, thus rendering oral ethinyloestradiol ineffective. The wisdom of low dose oestrogen oral contraceptive therapy cannot now be disputed but women on rifampicin obviously deserve special consideration. Future clinical surveys should determine whether higher doses of oestrogen are required to maintain effective oestrogen activity.

Rifampicin and anticonvulsants

A problem encountered recently also illustrated the induction properties of rifampicin. A man of 36 with epilepsy, normally well controlled on the combination of phenobarbitone, ethosuximide and phenytoin, developed frequent major fits soon after starting rifampicin therapy for tuberculosis. Measurement of the serum steady-state phenytoin concentration by radioimmunoassay revealed a level of 0.9 µg/ml, well below the accepted therapeutic range of 10-20 µg/ml. This raised the possibility of induction of phenytoin metabolism from the combined

induction effects of phenobarbitone and rifampicin as phenobarbitone itself is known to reduce phenytoin levels (Morselli, Rizzo and Garattini 1971). The introduction of rifampicin probably exaggerated this effect. It was important to obtain evidence of microsomal enzyme induction and this was provided by measurement of the plasma antipyrine half-life. Antipyrine is suitable for this purpose since it is almost completely metabolised in the liver (Brodie and Axelrod 1950) and is not bound to plasma proteins (Soberman et al 1949). The rate of antipyrine metabolism in man has been shown to be under genetic control (Vessell and Page 1968a) and to increase with exposure to drugs (Vessell and Page 1969). The half-life is measured by giving a standard oral dose (18 mg per Kg) in aqueous solution and assessing the decline in antipyrine concentration, measured by the method of Brodie et al (1949), over a period of 24 hours in either plasma or mixed saliva samples.

The patient's antipyrine half-life was 5.17 hours, compared with 12.4 ± 2.04 (S.D) hours in a group of normal control subjects. This highly significant shortening of the anitpyrine half-life, therefore, provided good evidence of microsomal enzyme induction. Gradual increase in the daily dose of phenytoin over a period of four weeks produced a therapeutic level of 11 μg/ml with resolution of the fits. This, of course, stressed the importance of anticipating careful reduction of phenytoin dosage on completion of rifampicin therapy to avoid phenytoin intoxication.

Induction and toxicity

Instead of reducing the therapeutic effect of a drug, the administration of an inducing agent may have the opposite effect and lead to increased toxicity. Relatively few clinical examples are

known but this type of interaction is potentially of great significance. The formation of active intermediary metabolites has been considered to be one of the mechanisms by which a number of experimental drug toxicity reactions have occurred. For example, the hepatoxicity of carbon tetrachloride can be increased by pre-treatment of animals with inducing agents such as phenobarbitone or D.D.T., and protection against hepatic necrosis can be achieved by inhibition of carbon tetrachloride metabolism by hypothermia, anti-oxidants, the inhibiting drug SKF 525-A or a previous small dose of carbon tetrachloride itself (Marchand, McLean and Plaa 1970; Glende 1972). Inducers have also been implicated in carcinogenesis. Prescott (1970, 1973) suggested that the renal pelvic tumours observed in analgesic abusers with renal papillary necrosis were caused by carcinogenic hydroxamino metabolites resulting from induction of phenacetin metabolism by concurrently administered antipyrine. Since so many drugs, dietary constituents and environmental chemicals are known to be inducing agents, potentiation of drug toxicity and carcinogenesis caused by microsomal enzyme induction may assume considerable importance.

Enzyme inhibition

Several drugs have been shown to inhibit the metabolism of other drugs in man with important clinical consequences. In contrast to the genetic variability of enzyme induction, enzyme inhibition seems to be less affected by genetic differences and will probably occur in all patients given certain combinations (Nies 1974). Microsomal enzymes may be involved but other enzymes which inactivate drugs may also be inhibited. Allopurinol, chloramphenicol, dicoumarol, disulfiram, isoniazid, methylphenidate, monoamine oxidase inhibitors, phenyramidol and sulphaphenazole all inhibit the metabolism of several drugs, notably

coumarin anticoagulants, phenytoin and tolbutamide. Such interactions have declared themselves relatively easily because of the low therapeutic ratio of the inhibited drugs and their obvious toxic manifestations.

Sulthiame and phenytoin

The introduction of sulthiame in the treatment of focal or major epilepsy was soon followed by reports of an intoxication syndrome similar to that produced by phenytoin (La Veck, de la Cruz and Thomas 1962; Ingram and Ratcliffe 1963; Gordon 1964) and closer examination of these reports revealed that in fact the syndrome was always associated with the combination of sulthiame and phenytoin. Hansen, Kristensen and Skovsted (1968) showed that sulthiame caused an elevation of the serum concentration of phenytoin and suggested that the metabolism of phenytoin by liver microsomal enzymes was inhibited because they found a prolongation of the serum half-life following addition of sulthiame to the patients' treatment. These results have been confirmed more recently in a series of studies by Houghton and Richens (1973, 1974a and 1974b) when they showed unequivocally that sulthiame or one of its metabolites inhibits the parahydroxylation of phenytoin by hepatic microsomal enzymes.

Thus, despite the fact that phenytoin is an excellent drug in the treatment of epilepsy, interaction with other anticonvulsants, e.g. phenobarbitone and sulthiame, may leave many patients without the full benefits of treatment. The availability of plasma level measurements of phenytoin should make it possible to tailor and adjust dosage regimens for individual patients so that therapeutic efficacy can be maximised and the risk of adverse effects from interactions minimised. But although the range of therapeutically effective concentrations of

phenytoin has been established (Kutt and McDowell 1968), this may not be entirely relevant to the common practice of treating patients with combinations of several anticonvulsants. Knowledge of this range does, however, identify plasma concentrations which are associated with toxicity.

4.3.4. Personal observations

EFFECT OF ACUTE ALCOHOL INTOXICATION ON THE METABOLISM AND PLASMA KINETICS OF CHLORDIAZEPOXIDE.

Enzyme inhibition may be related to the length of exposure to a drug. Many inducing agents cause an initial inhibition followed by stimulation. Acute ethanol intoxication, for example, is associated with impairment of pentobarbitone and meprobamate metabolism (Rubin et al 1970) whereas drug metabolism is accelerated in chronic alcoholics (Kater et al 1969). As it is common practice to use relatively large doses of the benzodiazepine chlordiazepoxide in the suppression of delerium tremens in acute ethanol intoxication, it seemed pertinent to investigate the effect of acute alcoholism on the metabolism of this drug.

## Patients and methods

In a relatively small, preliminary study, two groups of subjects have been studied:

(a) Three healthy male volunteers, and

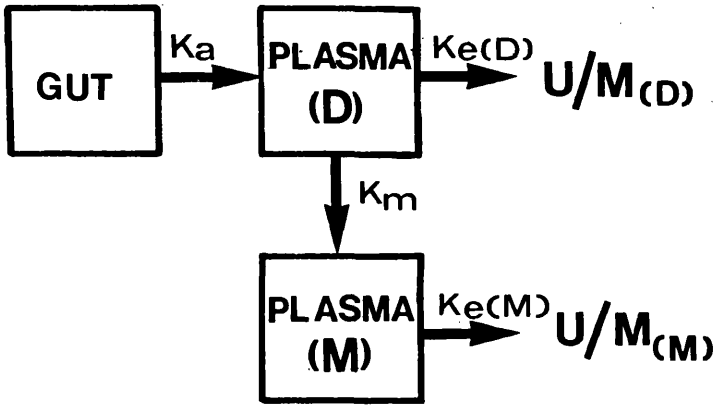
(b) Four adult male patients admitted to the Psychiatric Department of Stobhill General Hospital, Glasgow, with a diagnosis of acute alcohol intoxication.

The volunteers were given a single oral dose of 25 mg chlordiazepoxide and 10 ml blood were withdrawn into lithium-heparin anticoagulant at the following times: pre-dose (control) and $\frac{1}{2}$, 1, 2, 4, 6, 8, 12 and 24 hours after the dose. Plasma was separated by centrifugation and stored at -20°C until required for analysis of chlordiazepoxide and its desmethyl metabolite by high pressure liquid chromatography (H.P.L.C) (Skellern, Meier and Whiting 1976).

Once it had been established that chlordiazepoxide would be appropriate in the management of the alcoholic patients, informed consent was obtained for the study, a control blood sample was withdrawn, the first dose administered, and samples then taken at the following times: 1, 2, 3, 4, 5 and 6 hours after the first dose, then once daily for 4-5 days, immediately prior to the second morning dose. Plasma was separated, stored at -20°C and subsequently analysed as indicated above. An aliquot of the control sample was also reserved for routine biochemical assessment of liver function. A careful record was made of the time of administration and amount of each dose, and the precise times of each blood sample. The daily dose of chlordiazepoxide during the study period ranged from initial high doses of 200 mg to lower doses of 30 mg given in three or four equally divided doses.

## Evaluation of the data

For all subjects the disposition kinetics of chlordiazepoxide after oral dosing could be described by a one-compartment open model (Figure 38) with metabolic conversion of chlordiazepoxide to its desmethyl metabolite and subsequent renal elimination and/or further metabolism of both parent drug and metabolite. Pharmacokinetic parameters were obtained by digital computation using SAAM (Berman and Weiss 1968) a non-linear regression analysis programme.




**PLASMA (D) =CHLORDIAZEPOXIDE in plasma**
**$U/M_{(D)}$ =urine/further metabolism**

**PLASMA (M) =DESMETHYL-CHLORDIAZEPOXIDE in plasma**
**$U/M_{(M)}$ =urine/further metabolism**

FIGURE 38 One-compartment model for chlordiazepoxide kinetics, showing its metabolic conversion to desmethylchlordiazepoxide. All rate constants are assumed to be first-order, i.e. concentration dependent. $K_a$ is the absorption rate constant for chlordiazepoxide. $K_m$ is the metabolic rate constant characterising the conversion of chlordiazepoxide to desmethylchlordiazepoxide. $K_e(D)$ and $K_e(M)$ are overall elimination rate constants for chlordiazepoxide and desmethylchlordiazepoxide respectively.

## Results

### (a) Normal volunteers

Plasma concentration/time curves for chlordiazepoxide and desmethylchlordiazepoxide are shown in Figure 39 which also demonstrates the closeness of fit between calculated and experimentally derived data. The corresponding pharmacokinetic parameters are shown in Table 7. These results yield a mean chlordiazepoxide elimination half-life of 6.98 ± 2.51 (S.D) hours and a mean desmethylchlordiazepoxide elimination half-life of 13.1 ± 2.6 (S.D) hours. Calculated values for the rate constants shown in the proposed model are presented in Table 8.

### (b) Alcoholic patients

A typical example of the effect of multiple dosing on plasma concentrations of chlordiazepoxide and desmethylchlordiazepoxide is shown in Figure 40, which also illustrates the predicted drug and metabolite concentrations in relation to each dose, according to the proposed pharmacokinetic model. Figure 41 shows the plasma concentrations of chlordiazepoxide in the first five hours of treatment following the initial dose of 50 mg. Also included in this figure are serial plasma concentrations of alcohol (measured by gas liquid chromatography) which decline linearly as expected with a clearance rate of 40 mg% per hour. Table 9 shows the pharmacokinetic parameters of the patients studied. The mean chlordiazepoxide elimination half-life was 13.0 ± 3.0 (S.D) hours and the mean desmethylchlordiazepoxide elimination half-life was 15.2 ± 6.5 (S.D) hours. Corresponding rate constants are presented in Table 10. On the basis of the routine

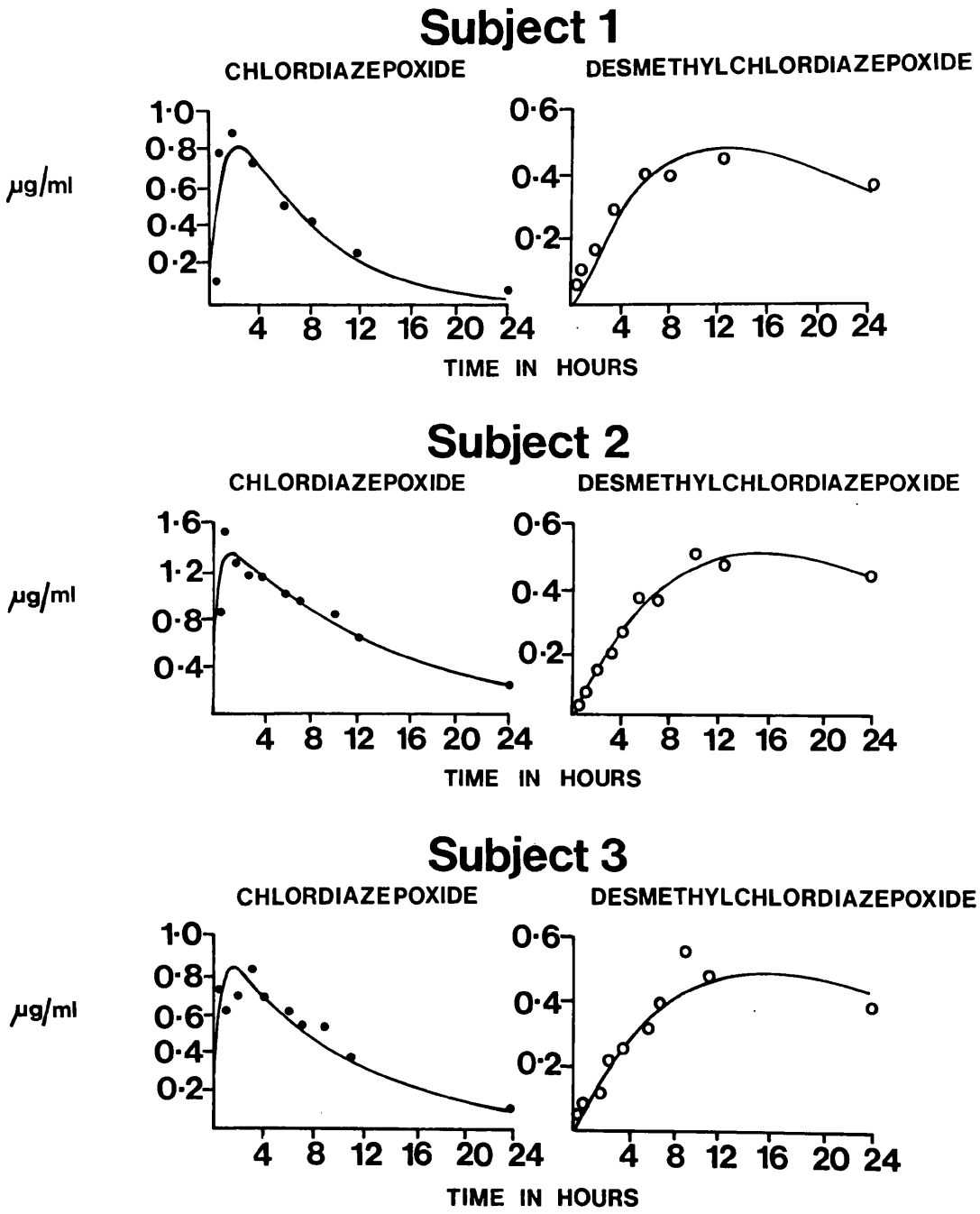



FIGURE 39 Observed and predicted plasma levels of chlordiazepoxide and desmethylchlordiazepoxide in normal volunteers following a single oral dose of chlordiazepoxide. (•) and (o) are concentrations of drug and metabolite measured by HPLC; the continuous lines are concentration/time relationships predicted by kinetic analysis based on the model shown in Figure 38.

| Parameter | Subject 1 | Subject 2 | Subject 3 | Mean ± S.D. |
|---|---|---|---|---|
| $t_{\frac{1}{2}}$ Absorption (h) | 0.84 | 0.32 | 0.35 | 0.50 ± 0.29 |
| $t_{\frac{1}{2}}$ Elimination of Chlordiazepoxide (h) | 4.33 | 9.33 | 7.27 | 6.98 ± 2.51 |
| $t_{\frac{1}{2}}$ Elimination of Desmethylchlordiazepoxide (h) | 13.4 | 10.3 | 15.5 | 13.1 ± 2.6 |

TABLE 7 Pharmacokinetic parameters obtained from plasma concentration curves after a single 25 mg oral dose of chlordiazepoxide in three healthy volunteers ($t_{\frac{1}{2}}$ values derived from the relationship $t_{\frac{1}{2}} = 0.693/k$).

| Rate constant ($h^{-1}$) | Subject 1 | Subject 2 | Subject 3 | Mean ± S.D. |
|---|---|---|---|---|
| $K_a$ | 0.826 | 2.14 | 1.97 | 1.65 ± 0.71 |
| $K_e(D)$ | 0.0511 | 0.0105 | 0 | 0.021 ± 0.027 |
| $K_m$ | 0.109 | 0.0638 | 0.0953 | 0.0894 ± 0.0232 |
| $K_e(M)$ | 0.0516 | 0.0676 | 0.0446 | 0.0546 ± 0.0118 |

TABLE 8 Calculated pharmacokinetic constants for chlordiazepoxide and desmethylchlordiazepoxide in three healthy volunteers according to the model shown in Figure 38.

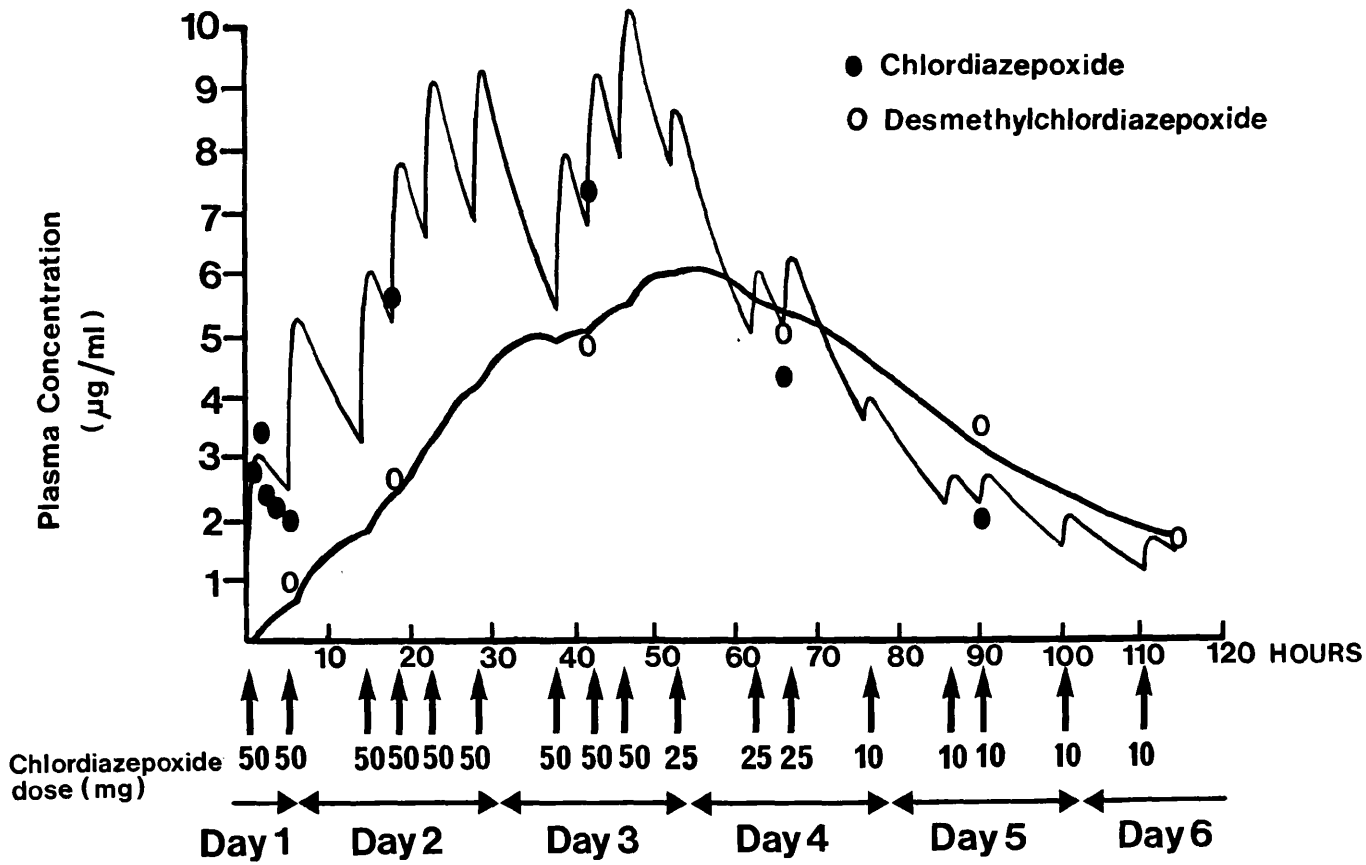



FIGURE 40 Observed and predicted plasma concentrations of chlordiazepoxide and desmethylchlordiazepoxide during the first six days of repetitive dosing of an alcoholic patient with chlordiazepoxide. The continuous lines are concentration/time relationships predicted by kinetic analysis based on the model shown in Figure 38.

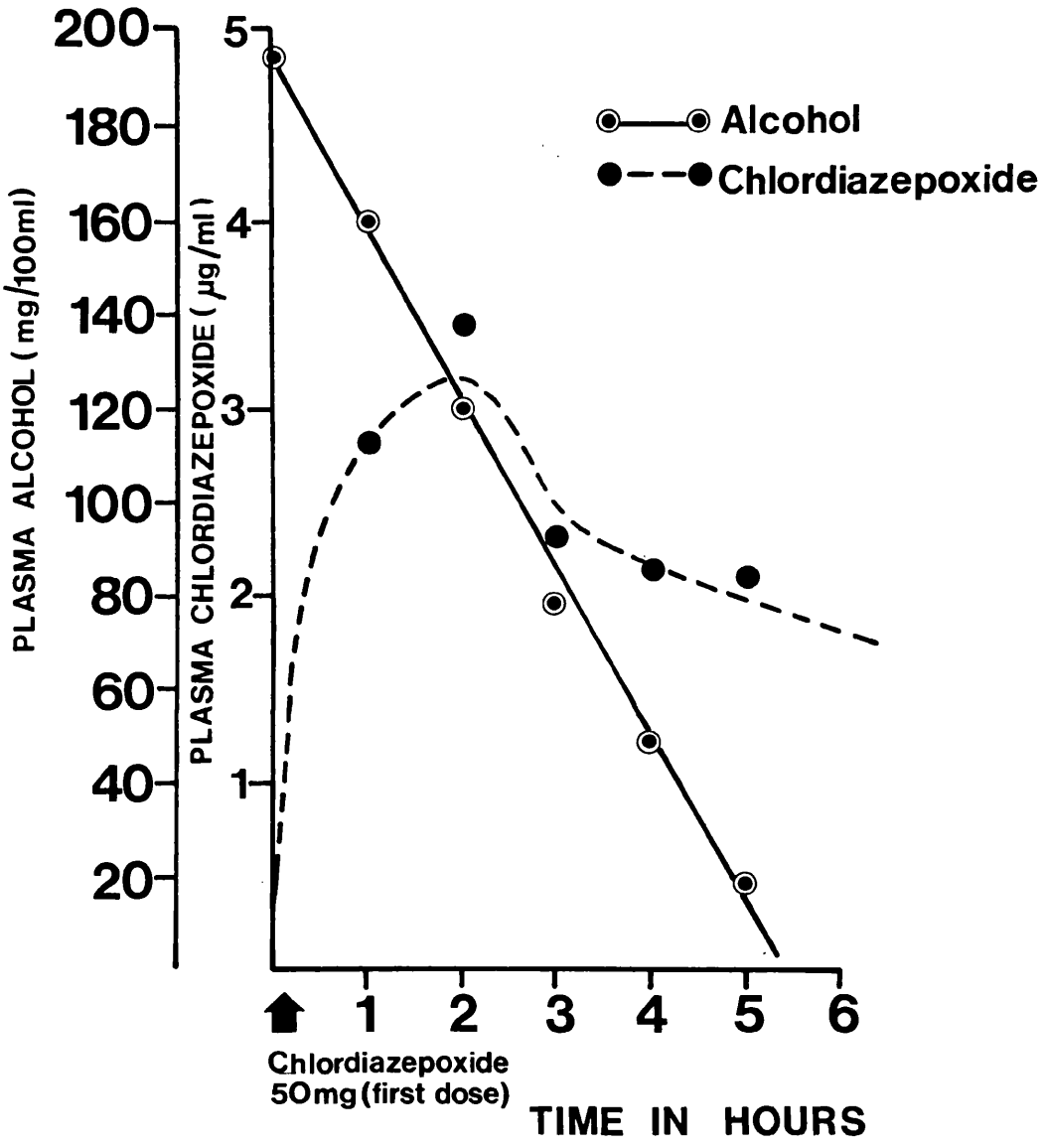



FIGURE 41 Observed plasma concentrations of chlordiazepoxide during the first five hours of treatment of the patient shown in Figure 40. Included are serial measurements of plasma alcohol concentration which decline linearly at a rate of 40 mg% per hour.

| Parameter | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Mean ± SD |
|---|---|---|---|---|---|
| $t_{\frac{1}{2}}$ Absorption (h) | 0.285 | 0.613 | 0.420 | 0.115 | 0.358 ± 0.211 |
| $t_{\frac{1}{2}}$ Elimination of Chlordiazepoxide (h) | 10.7 | 10.1 | 15.5 | 15.8 | 13.0 ± 3.0 |
| $t_{\frac{1}{2}}$ Elimination of Desmethylchlordiazepoxide (h) | 10.5 | 11.6 | 14.0 | 24.8 | 15.2 ± 6.5 |

TABLE 9 Pharmacokinetic parameters obtained from plasma concentration curves after repetitive dosing of chlordiazepoxide in four patients with acute alcoholism.

| Rate constant ($h^{-1}$) | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Mean ± S.D. |
|---|---|---|---|---|---|
| $K_a$ | 2.43 | 1.13 | 1.65 | 6.04 | 2.81 ± 2.22 |
| $K_e(D)$ | 0.0130 | 0 | 0 | 0 | 0.0033 ± 0.0065 |
| $K_m$ | 0.0518 | 0.0689 | 0.0446 | 0.0439 | 0.0523 ± 0.0116 |
| $K_e(M)$ | 0.0660 | 0.0597 | 0.0496 | 0.0279 | 0.0508 ± 0.0167 |

TABLE 10 Calculated pharmacokinetic constants for chlordiazepoxide and desmethylchlordiazepoxide in four patients with acute alcoholism according to the model shown in Figure 38.

biochemical tests, none of the patients had any significant degree of hepatic impairment.

## Discussion

The limited amount of data presented in this preliminary study demonstrated the suitability of the one-compartment open model for describing the disposition kinetics of chlordiazepoxide and its metabolic conversion to the desmethyl form after oral administration. The lack of any significant divergence between predicted and measured concentrations of drug and metabolite attested to the adequacy of the model.

The major elimination pathway for chlordiazepoxide has been shown to be almost exclusively biotransformation to desmethylchlordiazepoxide (Koechlin et al 1965). Almost no unchanged chlordiazepoxide is excreted in the urine, and this places considerable emphasis on the metabolic rate constant, $K_m$, shown in the model. The decline of chlordiazepoxide levels in the plasma therefore depends on this constant and any change in chlordiazepoxide metabolism will be reflected by changes in this constant. Volunteers who received single doses of chlordiazepoxide had a mean $K_m$ value of $0.0894 \pm 0.0232$ (S.D)$h^{-1}$ compared with a mean $K_m$ value of $0.0523 \pm 0.0116$ (S.D)$h^{-1}$ in the alcoholic patients. This was reflected by significant differences in the elimination half-lives of chlordiazepoxide in the two groups. The half-life in the alcoholics (mean $13.0 \pm 3.0$ (S.D) hours) was approximately double that found in the volunteers (mean $6.98 \pm 2.51$ (S.D) hours) and this provided good evidence of slower metabolic conversion of chlordiazepoxide to desmethylchlordiazepoxide in the acutely intoxicated patients.

The range of half-lives observed in this study, 4.33 - 9.33 hours

in the control group and 10.1 - 15.8 hours in the alcoholic group emphasises a degree of variability which may be genetically controlled. It is also evident that previously reported half-lives of chlordiazepoxide of 20-24 hours (Koechlin and D'Arconte 1963) were over-estimated as the result of an assay procedure which could not distinguish between chlordiazepoxide and desmethylchlordiazepoxide. As Figures 39 and 40 show, the metabolite rises to appreciable levels with time and would artificially prolong the measured half-life of the parent drug if it could not be identified separately.

The elimination of desmethylchlordiazepoxide, characterised by the rate constant $K_e(M)$ in the model, has been shown to involve further biotransformation to the metabolite demoxepam (Kaplan et al 1970). Thus desmethylchlordiazepoxide is an intermediate in the biotransformation of chlordiazepoxide to demoxepam. $K_e(M)$ had similar values in the two groups with corresponding mean elimination half-lives of 13.1 ± 2.6 (S.D) hours in the volunteers and 15.2 ± 6.5 (S.D) hours in the alcoholics. It appears, therefore, that alcohol dependent enzyme inhibition is confined to the first step in the metabolism of chlordiazepoxide.

These preliminary observations were sufficiently encouraging to warrant further study and additional subjects have now been included in each group. Further pharmacokinetic analysis will be improved by the inclusion of plasma levels of demoxepam measured by H.P.L.C.

From a clinical point of view, the decreased elimination of chlordiazepoxide in patients with acute alcohol intoxication does not seem to be a disadvantage, but it does demonstrate that enzyme inhibition is associated with this condition. Paradoxically, the rate of alcohol clearance is increased, in keeping with heavy drinking (Kater, Carulli and Iber 1969; Kater et al 1969). The patient illustrated in Figures 40 and 41 had an alcohol clearance rate of 40 mg% per hour, the upper limit of normal being 20 mg% per hour (Forney and Harger 1969). This

increase may well represent an adaptive response to excessive amounts of alcohol. Despite the relatively high plasma chlordiazepoxide concentrations observed and predicted, (cf. peak concentrations in volunteers after a single dose and concentrations attained on day three in the patient illustrated), drowsiness was not a feature of the treatment and the patients remained alert and relatively mobile during the day. However, the anxiety and agitation associated with delerium tremens was effectively suppressed.

It appears, therefore, that delirium tremens presents a challenge to the psychopharmacological effects of relatively high doses of chlordiazepoxide in that it over-rides any significant sedative effect which the drug would normally exert at much lower plasma concentrations. Fortunately, the distressing symptoms of anxiety and agitation usually respond satisfactorily. The exact relationship between the suppression of delirium tremens and plasma concentrations of chlordiazepoxide and its metabolites remains to be determined. By definition, alcohol will always play an important part in this relationship.

### 4.3.5. Interactions affecting renal excretion

Interactions that modify the renal excretion of drugs only assume importance when a drug or its active metabolite is excreted largely unchanged in the urine. Three mechanisms are responsible for renal elimination: glomerular filtration, tubular reabsorption and active tubular secretion.

Glomerular filtration produces an ultrafiltrate of plasma containing free drug molecules and is not significantly affected by other drugs. Disease states do, however, modify glomerular filtration (See Chapter 3) and its reduction may greatly increase the half-life of some drugs.

Many weak acidic drugs are transported from the tubular capillaries

across the proximal tubular cell into the tubular urine against a concentration gradient by an active process. These drugs include the penicillins, most anti-inflammatory agents including salicylate, phenylbutazone and indomethacin, uricosurics such as probenecid and sulphinpyrazone, thiazide diuretics and some oral hypoglycaemics including chlorpropamide. In general, the administration of such acidic drugs will slow the tubular secretion of other concurrently administered acidic drugs. Similarly, the administration of a base will slow the tubular secretion of other bases. The effect of probenecid on the elimination of penicillin is well known and has been exploited therapeutically. Probenecid has also been shown to decrease the renal excretion of indomethacin (Skeith, Simkin and Healy 1968; Brooks et al 1974) with a corresponding rise in indomethacin plasma levels. It remains to be determined whether or not this interaction could be exploited in the management of rheumatoid arthritis. For example, an adequate level of indomethacin maintained throughout the night by delay in its elimination might well help to suppress the distressing symptoms of morning stiffness.

Adverse interactions based on this competitive mechanism include methotrexate toxicity as a result of its delayed excretion by salicylate (Liegler et al 1969) and the potentiation of the hypoglycaemic effect of acetohexamide by phenylbutazone (Field et al 1967). In the latter case, excretion of the active metabolite hydroxyhexamide is delayed but there is no effect on the parent compound.

Drug molecules in the tubular fluid are progressively concentrated and may be reabsorbed into the blood as the glomerular filtrate passes down the nephron. The extent of this reabsorption depends on a number of factors including the lipid solubility of the drug - determined largely by its degree of ionisation - and the urine pH. An alkaline urine favours the excretion of acidic drugs such as aspirin and phenobarbitone

while basic drugs such as amitriptyline and quinidine are more readily excreted in acid urine (Goldstein, Aronow and Kalman 1969). The manipulation of the pH of the glomerular filtrate and the degree of ionisation of a drug can, therefore, significantly influence its rate of elimination and this forms the basis of the use of forced alkaline diuresis in the management of aspirin and phenobarbitone poisoning (Waddell and Butler 1957; Lassen 1960; Milne 1965).

## 4.4. INTERACTIONS IN THE PHARMACODYNAMIC PHASE

A number of complex mechanisms may be responsible for interactions in the pharmacodynamic phase which may involve various types of drug antagonism or synergism. These mechanisms include:

(a) competition for the receptor site

(b) synergism at the receptor

(c) alteration of the receptor

(d) alteration of the other components at the site of action

(e) effects on a different biological system which has similar or opposite effects leading to augmentation or diminution of the overall biological response.

### 4.4.1. Competition for the receptor site

Many pharmacologically active substances compete for common receptor sites, e.g. metabolites and antimetabolites, cholinergic and anticholinergic agents, histaminergic agents and antihistamines, beta adrenergic and beta adrenergic blocking agents, etc. Competitive antagonism signifies that the antagonist has affinity for the sites of action but lacks any intrinsic activity. The agonist has both affinity for and intrinsic activity on the specific receptors.

Adverse drug interactions based on competition between drugs at receptor sites are relatively rare. As an example, it has been suggested that the reduced hypoglycaemic action of the sulphonylureas in the presence of thiazide diuretics may be partly due to inhibition of insulin secretion from the pancreas by the chemically related thiazides (Goldner, Zarowitz and Akgun 1960; Samaan, Dollery and Fraser 1963; Hicks et al 1970; Levine 1970).

The loss of response to indirectly acting adrenergic agents, which release noradrenaline from stores at nerve endings, and to compounds which deplete those stores by release of noradrenaline, constitute further examples of antagonistic interaction at receptor sites. Typical is the interaction between adrenergic neurone blocking antihypertensives and tricyclic antidepressants. Leishman, Matthews and Smith (1963) suggested that imipramine blocked the action of guanethidine in hypertensive patients. This was confirmed by Mitchell, Arias and Oates (1967) when they showed that the antihypertensive effect of guanethidine was significantly reversed by two tricyclic antidepressants (desipramine and protriptyline) and that this reversal was not immediate, but required many hours before maximum antagonism was seen. Furthermore, after discontinuation of the antidepressant, a latent period of about five days was required before re-establishment of effective anti-hypertensive activity (Figure 42). Similar interactions have been reported with other guanethidine-related drugs, such as bethanidine and debrisoquine (Figure 43) (Mitchell et al 1967, 1970) and more recently with clonidine (Briant, Reid and Dollery 1973).

The pharmacological effect of these antihypertensives has been shown to depend on their transport to sites of action within adrenergic neurones by the transport system that is responsible for the uptake of noradrenaline, the noradrenaline "pump". This system also transports several indirectly acting adrenergic agents such as ephedrine and the

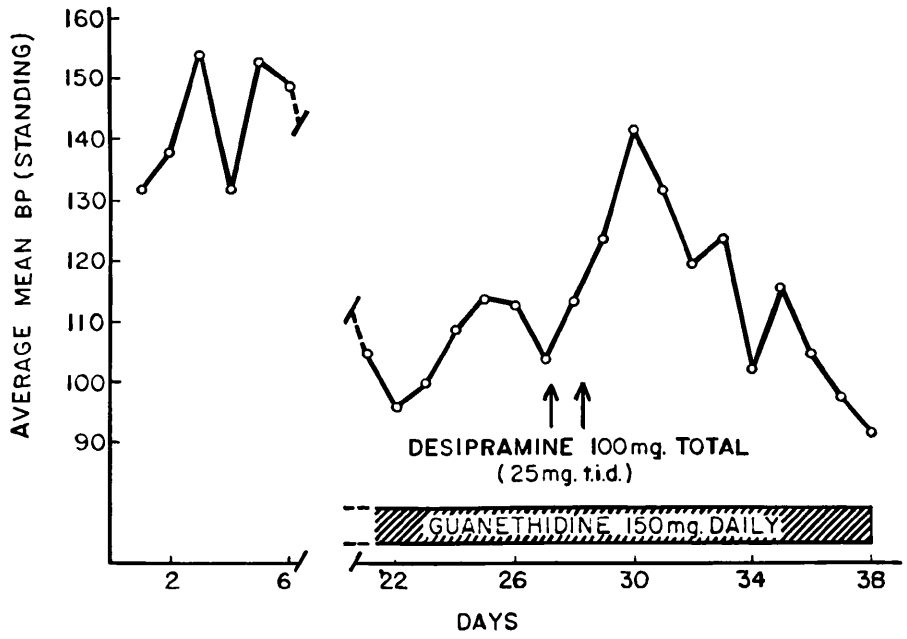



FIGURE 42 Antagonism of guanethidine by desipramine. Guanethidine was given in increasing doses between days 6 and 21 until blood pressure was controlled (150 mg daily). Dose was maintained during experimental period. Desipramine administered between arrows.

From Mitchell et al 1967, Journal of the American Medical Association, 202, 973-976, by kind permission of the authors and the Editor. Copyright 1967, American Medical Association.

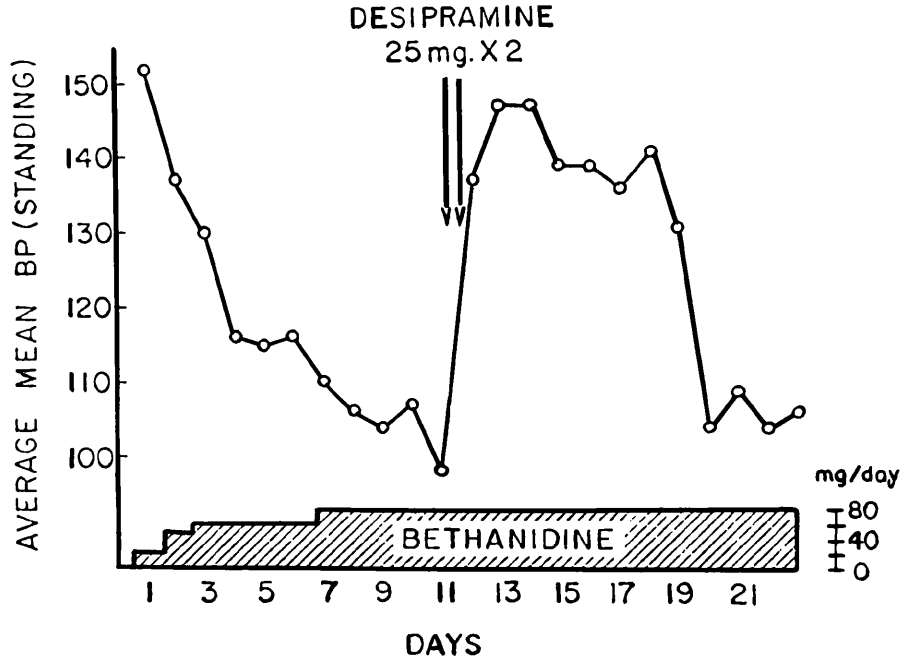



FIGURE 43 Antagonism of bethanidine by desipramine. Bethanidine was given in increasing doses until blood pressure was controlled (80 mg daily). Dose was maintained during experimental period. Desipramine administered between arrows.
From Mitchell et al 1967, by permission as in Figure 42.

amphetamines to their respective sites of action, (Gulati et al 1966). It is probable that the tricyclic antidepressants block the action of this pump, and the uptake of the antihypertensives (Figure 44). The hypotensive action of methyldopa, however, is not usually affected because it enters the neurone by a completely different mechanism. Nevertheless, there has been one unexplained and isolated case in which antagonism apparently occurred. White (1965) reported that amitriptyline produced agitation, a fine tremor in the hands and tachycardia and reduced the antihypertensive effect of methyldopa in a single patient. Animal studies have subsequently provided further evidence for this interaction (Kale and Satoskar 1970).

### 4.4.2. Synergism at the receptor

Rather than participating in competition at receptor sites, two drugs with similar intrinsic activities may act on common receptors or sites of action to produce an enhanced response. For example, if anticholinergic agents are combined, or if anticholinergic agents are used with other drugs which have an anticholinergic component in their action, such as various antiparkinsonian drugs or tricyclic antidepressants, excess anticholinergic activity may result. This effect was observed by the present author when the combination of a small dose of an anticholinergic drug and a tricyclic antidepressant (imipramine) produced troublesome urinary hesitancy and retention in a 60 year old female patient. Withdrawal of the anticholinergic drug restored normal bladder function.

But this interaction has been associated with a much more dramatic and even fatal outcome. Warnes et al (1967) reported eight cases of chronic constipation with faecal impaction due to treatment with a phenothiazine, a tricyclic antidepressant, an antiparkinsonian drug or a combination of these drugs. Excessive anticholinergic activity had

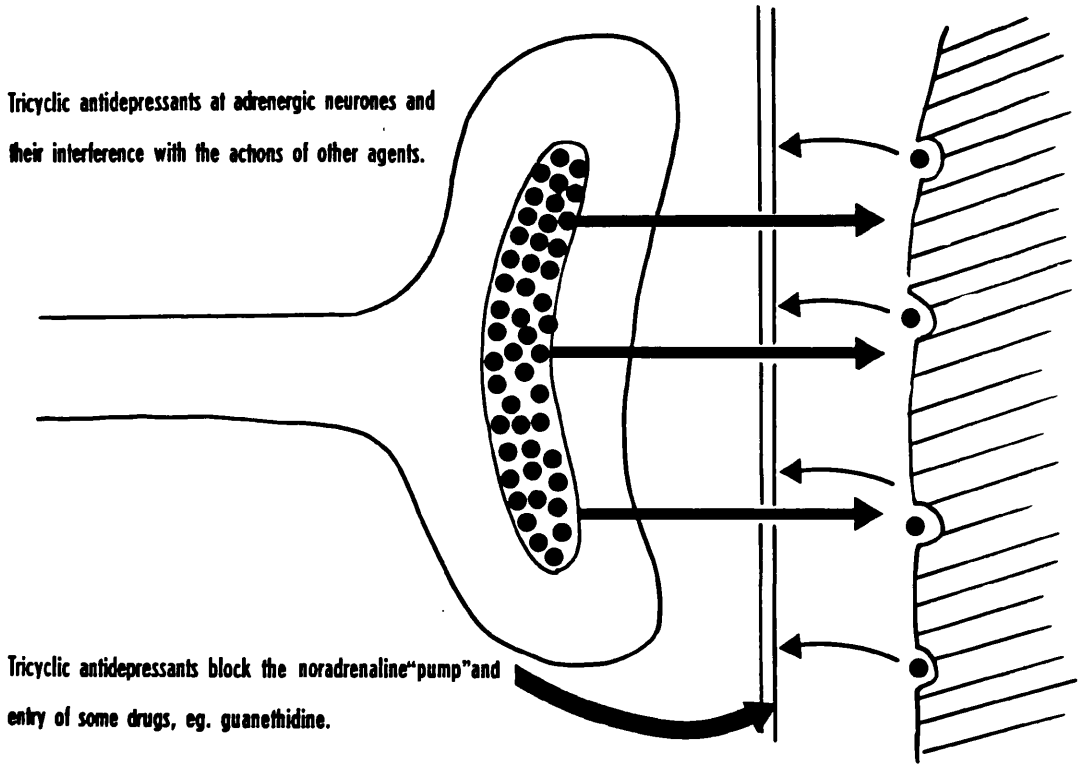



FIGURE 44 Schematic representation of the mode of action of tricyclic antidepressants at adrenergic neurones and their interference with the actions of other agents. A highly simplified nerve ending is shown discharging noradrenaline whose re-uptake, and that of some hypotensives (e.g. guanethidine and bethanidine) is blocked by tricyclic antidepressants.

resulted in adynamic ileus. Five patients were treated successfully by disimpaction, nasogastric suction, intravenous fluid therapy and enemas but recognition of the condition was too late in three cases and a fatal outcome could not be prevented.

Dramatic results have also been reported when aminoglycoside antibiotics (e.g. gentamicin, kanamycin, neomycin and streptomycin) have been administered in the presence of surgical neuromuscular blocking agents. Prolonged muscular paralysis and apnoea have followed this combination as a result of synergistic interaction. Pittinger, Eryasa and Adamson (1970) reviewed more than 80 such incidents which had been recorded in the literature over the period 1955-1970. Many studies have shown that the aminoglycosides themselves produce neuromuscular blockade which may enhance the blockade of skeletal muscle relaxants.

### 4.4.3. Alteration of the receptor

Interactions based on alteration of the receptor usually involve some kind of sensitisation mechanism typified by digitalis toxicity occurring as a result of hypokalaemia and hypomagnesemia induced by concomitant diuretic therapy. Digitalis glycosides are believed to exert part of their cardiac effect by inhibition of ATPase which reduces the intracellular concentration of potassium. If this concentration is reduced further by diuretic-induced hypokalaemia, the ATPase system of myocardial cells is subjected to greater digitalis inhibition and the possibility of digitalis intoxication is markedly increased (Goodman and Gilman 1970; American Pharmaceutical Association 1973b). Hypomagnesemia predisposes to digitalis toxicity because it also augments the inhibition of ATPase induced by digitalis (Seller et al 1970).

Alteration of the receptor has also been proposed as the mechanism underlying the potentiation of the anticoagulant effect of warfarin by

thyroxine. Schrogie and Solomon (1967) and Solomon and Schrogie (1967b) suggested that a change in anticoagulant receptor site affinity induced by thyroxine might be responsible.

### 4.4.4. Alteration of other components at the site of action

Alteration of other components involved at the site of action is exemplified by the inhibition of monoamine oxide by monoamine oxidase (MAO) inhibitors. The increase in noradrenaline levels in various tissues which results from MAO inhibition is responsible for the hypertensive crises observed with combinations of MAO inhibitors and drugs which act by releasing noradrenaline, e.g. the indirectly acting adrenergic agents ephedrine (Low-Beer and Tidmarsh 1963; Elis et al 1967) phenylephrine (Elis et al 1967) and phenylpropanolamine (Tonks and Lloyd 1965; Cuthbert et al 1969; Humberstone 1969; Mason and Buckle 1969). The excess amounts of noradrenaline which accumulate during MAO inhibition are released by these adrenergic agents causing massive stimulation of receptors and an exaggerated pressor response. This has led to fatal intracranial haemorrhage.

Similar interactions may occur with drugs which possess MAO - inhibition as a side effect, e.g. isoniazid and furazolidone. In the latter case this is due to a metabolite of furazolidone - a hydrazine derivative - which has an appreciable amount of MAO inhibitory activity, comparable to that of pargyline (Stern et al 1967). Furazolidone is normally used as an antibacterial agent only for periods of up to five days. This period is not long enough for sufficient metabolite to accumulate to exert significant MAO inhibitory activity (Pettinger, Soyangco and Oates 1968). If used for longer periods, however, furazolidone may behave like an MAO inhibitor and good experimental evidence from human studies has been presented to support this (Stern et al 1967).

### 4.4.5. Modifications of the overall biological response

Certain combinations of drugs may act on different sites of the same system or different systems to modify the overall biological response. This type of pharmacodynamic interaction is responsible for the enhanced depression of the central nervous system which occurs relatively commonly with combinations of narcotic analgesics, tranquillisers, neuroleptic agents, sedatives and hypnotics (Boston Collaborative Drug Surveillance Program 1972). A similar mechanism underlies the synergism between alcohol and various central nervous system depressants. A rather more complex mechanism is thought to be responsible for potentiation of the hypoglycaemic action of insulin and oral hypoglycaemics of the sulphonylurea type by beta adrenergic blocking agents (Abramson, Arky and Woeber 1966; Kotler, Berman and Rubenstein 1966; Annotations 1967). Part of the homeostatic response to hypoglycaemia is glycogenolysis and mobilisation of glucose due to sympathetic stimulation mediated by beta receptors in skeletal muscle (Abramson and Arky 1968). Beta adrenergic blocking agents, therefore, may interrupt this component of the glucose regulatory system and leave the hypoglycaemic action of insulin and the sulphonylureas unopposed. This may have particular clinical significance when hepatic glycogen stores are depleted or unavailable, for example, in badly controlled diabetes or following starvation.

## 4.5. CONCLUSIONS

Based on mechanism of action it is impossible to classify many of the interactions reported in the literature. Good experimental evidence is often lacking. Some may be explained only in terms of a number of different mechanisms which may embrace all three phases of

drug action. But perhaps more important than classification is the detection and systematic documentation of interactions which are of clinical significance. Knowledge of these interactions should then foster a critical approach to the therapeutic efficacy of drug treatment in general. This would not only avoid adverse drug interactions in terms of overdosage and toxic responses but also loss of drug response which may assume greater importance in the individual patient than the well-known adverse drug interactions. These were the considerations that dictated the development of a drug interaction warning system.

# CHAPTER 5

# INITIAL DEVELOPMENT OF THE DRUG INTERACTION WARNING SYSTEM

# 5. INITIAL DEVELOPMENT OF THE DRUG INTERACTION WARNING SYSTEM

## 5.1. INTRODUCTION - CLINICAL PROBLEMS

A therapeutic problem encountered on a routine medical ward round provided the initial stimulus to develop some form of drug interaction warning system.

An elderly lady with a deep venous thrombosis had been admitted for anticoagulant treatment and had been established on warfarin. It was subsequently noted that some instability in her anticoagulant control had developed, the result of which was an enhanced anticoagulant effect which carried the inevitable risk of haemorrhage. A survey of her drug treatment revealed that with the onset of a painful, superficial thrombophlebitis, phenylbutazone had been added to her therapy and the instability dated from the introduction of this second drug. This suggested that an interaction between phenylbutazone and warfarin had led to the difficulties in anticoagulant control and this was endorsed by the experimental and clinical evidence already reviewed in Chapter 4 of this thesis. It was obvious that combined phenylbutazone and warfarin therapy posed serious haemorrhagic threats to all patients in whom it was used, and it had been recommended that the combination should be avoided (American Pharmaceutical Association 1973a). This experience served to highlight the necessity of creating a system which would alert doctors to the dangers of prescribing certain other drugs with warfarin. Simple bed-side methods were explored, for example, the word INTERACTION could be stamped in bold, red capital letters on a patient's bed-head progress chart, to act as a daily reminder, but this was rejected largely on the grounds that it was uninformative and could alarm both the patients and their relatives. As it was essential

to incorporate useful information into any warning system, a list of drugs which were known to interfere with established anticoagulant therapy (Table 11) was compiled, which could be placed at the bed-side of any patient on anticoagulant therapy or carried on the ward trolley during ward rounds. It was immediately apparent, however, that anticoagulants represented only one part of the interaction problem and it would, therefore, be necessary to widen the concept to embrace other groups of drugs known to be implicated in drug interactions, for example antihypertensives, anticonvulsants, tricyclic antidepressants, oral hypoglycaemics and monoamine oxidase inhibitors. This resulted in a dossier of papers which could only be presented in booklet form and this was thought to be somewhat unwieldly and impracticable. It did not represent any real advance over literature on the subject already published. It was also important to recognise that the problems presented by drug interactions were not confined to hospital practice and that any warning system would be equally relevant to general practitioners and pharmacists. It thus became obvious that it was essential to condense the necessary information on to some easily portable system which could be rapidly referred to and read at a glance.

Two important questions presented themselves:

1. How much information should be incorporated on to a system which was primarily intended to serve as a guide to possible drug interactions?
2. How could the information already assembled be presented in as concise a form as possible?

In answer to question 1, it seemed essential to draw attention to well-documented interactions and to stress when a combination of drugs was potentially dangerous. No details of pharmacological mechanisms would be incorporated but the effects of an interaction on drug activity would be shown, as this would be highly relevant to the clinical situation.

| | |
|---|---|
| ANTICOAGULANTS (WARFARIN) are INHIBITED by: (i.e. activity is reduced) | BARBITURATES<br>CHOLESTYRAMINE<br>DICHLORALPHENAZONE<br>GLUTETHIMIDE<br>GRISEOFULVIN<br>"MANDRAX"<br>MEPROBAMATE<br>ORAL CONTRACEPTIVES<br>PRIMIDONE |
| ANTICOAGULANTS (WARFARIN) are POTENTIATED by: (i.e. activity is increased) | ALCOHOL<br>ANABOLIC STEROIDS<br>ASPIRIN<br>BROAD SPECTRUM ANTIBIOTICS<br>CHLORAL HYDRATE<br>CLOFIBRATE<br>ETHACRYNIC ACID<br>GUANETHIDINE<br>INDOMETHACIN<br>MEFENAMIC ACID<br>NALIDIXIC ACID<br>OXYPHENBUTAZONE<br>PHENYLBUTAZONE<br>PHENYTOIN<br>SULPHONAMIDES<br>THYROXINE |

TABLE 11 List of drugs reported to interfere with established anticoagulant therapy.

In drawing up the list of drugs which could interfere with anticoagulants, a simple classification had been used to divide the drugs into those which could inhibit anticoagulants, i.e. reduce their activity, rendering them less effective, and those which could potentiate anticoagulants, i.e. increase their activity, possibly to the point of toxicity. This simple classification seemed appropriate for the presentation of all drug interaction data in a concise form, and provided a solution to the problem presented by the second question. Certain interactions, however, had been associated with relatively serious, sometimes fatal consequences, and such drug combinations would require a separate "dangerous combination" category.

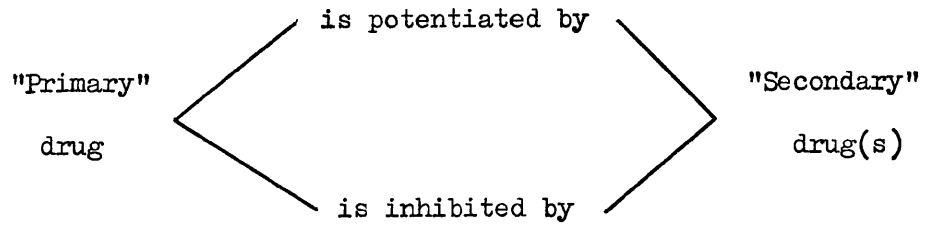
## 5.2. EVALUATION AND ORGANISATION OF DRUG INTERACTION INFORMATION

Comprehensive reviews of drug interactions (Martin 1971; Hansten 1973; American Pharmaceutical Association 1973; Stockley 1974) suggested a group of nine drugs or drug categories whose documentation had stressed the importance or frequency of interactions when these agents were used in combination with other drugs (Table 12). The literature was therefore scrutinised for interactions with each of these nine drugs or drug categories, each interaction being classified in the manner referred to above.

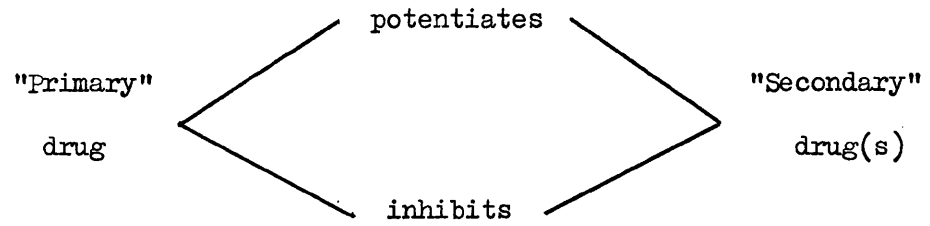
Nine sets of data resulted which had to be accommodated onto some form of warning device. Each set of data consisted of a "primary" drug interacting with a list of "secondary" drugs, thus:

| | |
|---|---|
| ALLOPURINOL | BETA ADRENERGIC BLOCKERS |
| ANTICOAGULANTS | MONOAMINE OXIDASE INHIBITORS |
| ANTICONVULSANTS | ORAL HYPOGLYCAEMICS |
| ANTIHYPERTENSIVES | TRICYCLIC ANTIDEPRESSANTS |
| ASPIRIN | |

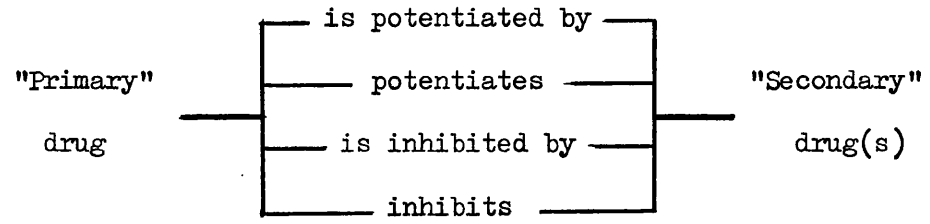
TABLE 12 Drugs frequently implicated in drug interactions.




It was also necessary to include "Secondary" drugs which were potentiated or inhibited by "Primary" drugs, thus:




The warning system, therefore, had to be capable of showing four possible interactions between pairs of drugs, thus:




and it had to highlight any interactions which were known to be harmful in man. Table 13 shows an example of each of these categories of interactions, accompanied by a representative list of references emphasising the volume of literature available on this subject.

The "Secondary" drugs comprised a list of 57 generic drugs or pharmacological categories in common use, shown in Table 14. One hundred and twenty four interactions between primary and secondary drugs were identified.

| Primary drug or drug category | Interaction | Secondary drug(s) | Reference |
|---|---|---|---|
| Anticoagulants notably Warfarin | are potentiated by | Phenylbutazone | A |
| Tricyclic Antidepressants | potentiate | Anticholinergics | B |
| Anticoagulants notably Warfarin | are inhibited by | Barbiturates | C |
| Tricyclic Antidepressants | inhibit | Guanethidine | D |
| Monoamine oxidase inhibitors | DANGEROUS COMBINATION | Sympathomimetic amines (indirect acting) e.g. ephedrine, phenylpropanolamine | E |

TABLE 13 Examples of categories of drug interactions included on the drug interaction warning system, with appropriate references.

| | |
|---|---|
| A. | Eisen, 1964; Fox, 1964; Aggeler et al, 1967; Hoffbrand and Kininmonth, 1967; Solomon and Schrogie, 1967a and b; O'Reilly and Aggeler, 1968; Udall, 1969; O'Reilly and Aggeler, 1970; O'Reilly and Levy, 1970; Koch-Weser and Sellers, 1971; Sellers and Koch-Weser, 1971; Lewis et al, 1974. |
| B. | Kessell et al, 1967; Rogers, 1967; Warnes, Lehman and Ban, 1967; Milner, 1969. |
| C. | Cucinell, Conney and Sansur, 1965; Goss and Dickhaus, 1965; Lewis, 1966; Robinson and MacDonald, 1966; MacDonald and Robinson, 1968; Aggeler and O'Reilly, 1969; MacDonald et al, 1969; Levy, 1970; O'Reilly and Aggeler, 1970; Breckenridge and Orme, 1971; Koch-Weser and Sellers, 1971. |
| D. | Leishman, Matthews and Smith, 1963; Mitchell, Arias and Oates, 1967; Mitchell et al, 1970; Iversen, 1971. |
| E. | Scherbel, 1961; Zeck, 1961; Dalby, 1962; Mason, 1962; Stark, 1962; Brownlee and Williams, 1963; Low-Beer and Tidmarsh,1963; MacDonald, 1963; Nymark and Nielsen, 1963; Tonks and Livingstone, 1963; Goldberg, 1964; Horowitz et al, 1964; Lewis, 1965; Lloyd and Walker, 1965; Sjöqvist, 1965; Tonks and Lloyd, 1965; Elis et al, 1967; Cuthbert, Greenberg and Morley, 1969; Humberstone, 1969; Krisko, Lewis and Johnson, 1969; Mason and Buckle, 1969; Lader, Sakalis and Tansella, 1970. |

TABLE 13 continued References.

| | |
|---|---|
| ALCOHOL | FRUSEMIDE |
| ANABOLIC STEROIDS | GLUTETHIMIDE |
| ANAESTHETICS (General) | GRISEOFULVIN |
| ANTICHOLINERGICS | GUANETHIDINE |
| ANTICOAGULANTS | HYPOGLYCAEMICS (Oral) |
| ANTICONVULSANTS | INDOMETHACIN |
| ANTIDEPRESSANTS (Tricyclic) | INSULIN |
| ANTIHISTAMINES | L-DOPA |
| ASPIRIN | MEFENAMIC ACID |
| AZATHIOPRINE | MEPROBAMATE |
| BARBITURATES | 6-MERCAPTOPURINE |
| BETA-ADRENERGIC BLOCKERS | METHAQUALONE |
| BENZODIAZEPINES | METHOTREXATE |
| BETHANIDINE | METHYLDOPA |
| BROAD SPECTRUM ANTIBIOTICS | MORPHINE |
| CARBAMAZEPINE | NALIDIXIC ACID |
| CHLORAL HYDRATE | NARCOTICS |
| CHOLESTYRAMINE | OXYPHENBUTAZONE |
| CLOFIBRATE | PARACETAMOL |
| CONTRACEPTIVES (Oral) | PHENOTHIAZINES |
| CORTICOSTEROIDS | PHENYLBUTAZONE |
| DIAZEPAM | PHENYTOIN |
| DICHLORALPHENAZONE | PRIMIDONE |
| DIGOXIN | PROBENECID |
| DIURETICS | SULPHONAMIDES |
| ETHACRYNIC ACID | SULPHONYLUREAS |
| FENFLURAMINE | SYMPATHOMIMETICS |
| FLUFENAMIC ACID | THYROXINE |
| | TOLBUTAMIDE |

TABLE 14 List of drugs in common use included on the drug interaction warning system.

## 5.3. PRESENTATION OF DRUG INTERACTION INFORMATION

### 5.3.1. Reference devices

Having assembled and classified all this information it was then necessary to present it in as compact a form as possible, with portability, clarity, and simplicity in use as the prime objectives. Two types of device appeared to satisfy these requirements - the slide rule and the circular reference disc. As the latter seemed to offer more in the way of design possibilities, this system was adopted in principle, and several examples of circular reference discs and calculators were studied to see how this format could be modified to accommodate drug interaction information. Two examples of such devices are illustrated in Figures 45 and 46. Both consisted of a reversible unit of two concentric superimposed discs which pivoted about a common centre. The BIS device (Figure 45) gave information on the quality and composition of sand appropriate for moulds and cores in the iron, alloy and steel industry, and the caterers' calculator (Figure 46) was designed to assist in stock control and pricing calculations. Other devices examined included gestation calculators, exposure calculators used in photography and circular reference systems used to assess central heating requirements.

### 5.3.2. Cardboard prototypes of the drug interaction warning system

The nature of the drug interaction information dictated that the nine primary drugs should be brought into opposition with the fifty seven secondary drugs to indicate whether or not an interaction would occur. This was achieved by arranging the secondary drugs along radii on the periphery of a large disc and the primary drugs on a series of arcs on a smaller disc. Each arc converged on a narrow window cut into the


FIGURE 45

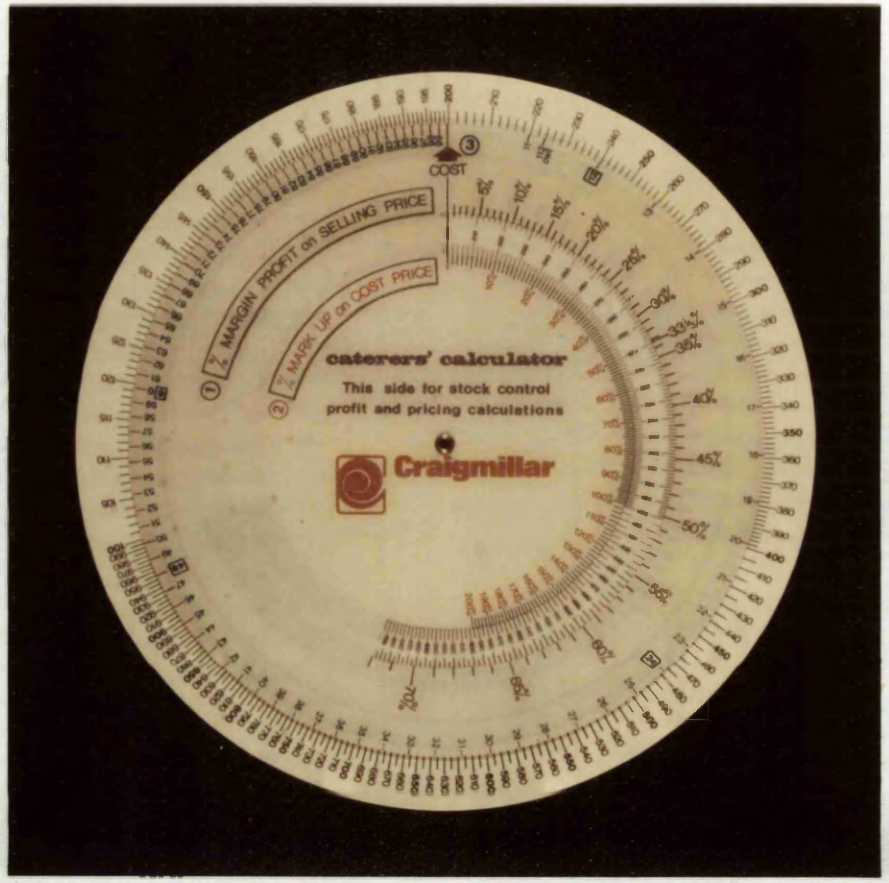
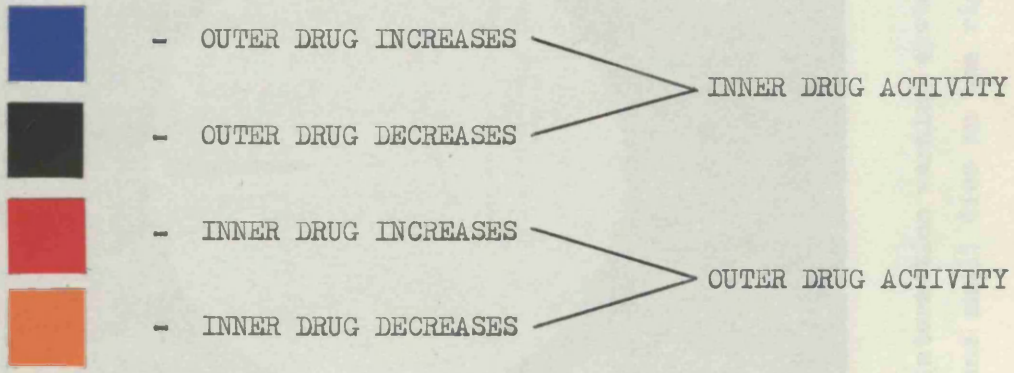



FIGURE 46

FIGURES 45 and 46 Examples of circular reference discs.

smaller disc and the two discs rotated freely about a common centre. Interactions between primary and secondary drugs were indicated by a series of colours which appeared in the window. Figure 47 shows the cardboard prototype disc which demonstrates all these features. The nine primary drugs were referred to as "inner drugs" and the secondary drugs as "outer drugs". Interactions between any two drug combinations were indicated thus:




This was in accordance with the inhibition-potentiation classification of drug interactions already decided on. A key to the colours appeared on the smaller disc.

A second prototype, shown in Figure 48, included the category of interaction which was known to result in harmful effects, i.e. a DANGEROUS COMBINATION, indicated by a distinct symbol - a white diagonal stripe on a black background, and a slightly different series of colours was used. These cardboard prototypes measured 21 cm. in diameter and established the design of the drug interaction warning system upon which all subsequent developments were based.

## 5.4. THE DRUG DISC

In the prevailing climate of anxiety engendered by multiple drug therapy and adverse drug interactions, it seemed pertinent to submit this warning system for publication, and the Methods and Devices Section of the Lancet seemed most appropriate. The second prototype was, therefore,

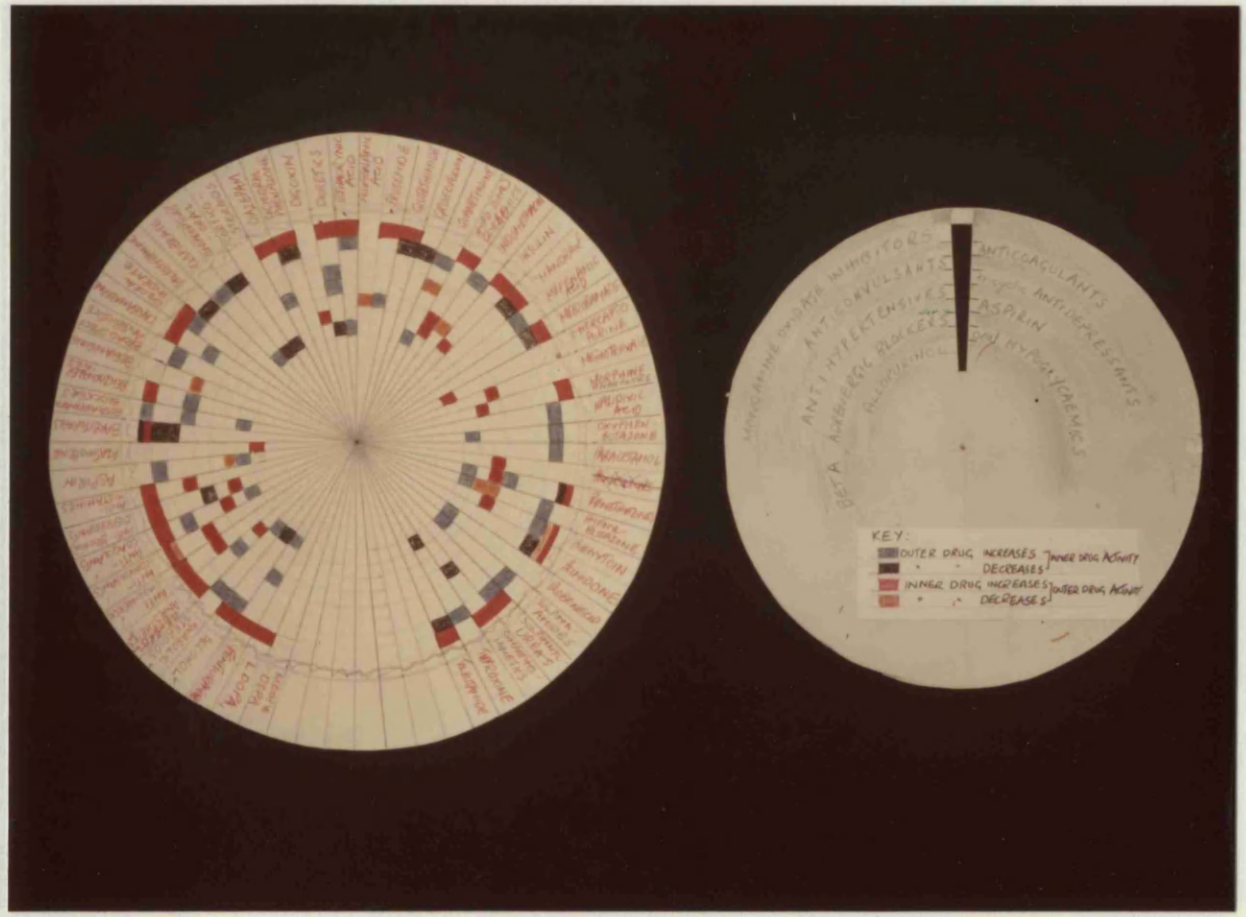



FIGURE 47 First cardboard prototype drug interaction warning system showing large disc on the left and small disc on the right.

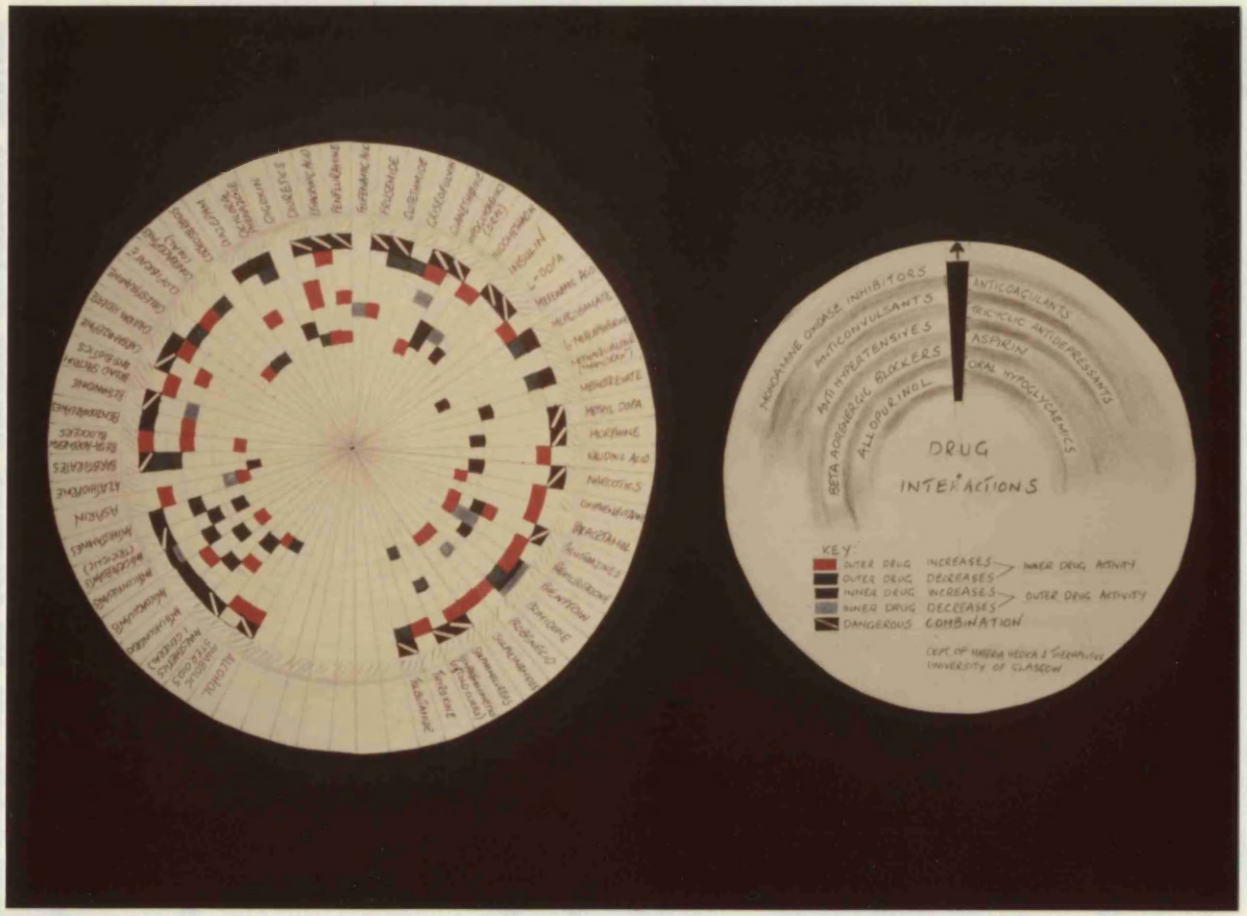
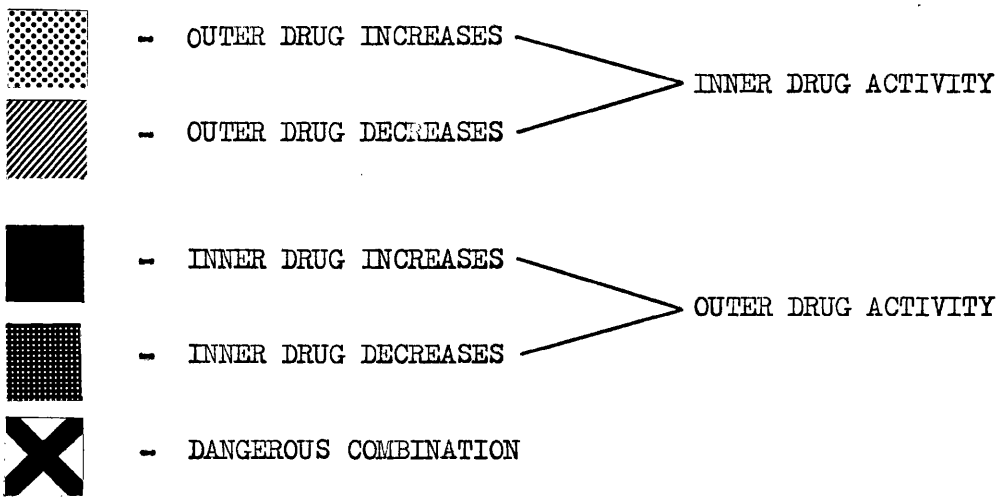



FIGURE 48 Second cardboard prototype drug interaction warning system showing large disc on the left and small disc on the right.

adapted for publication in association with Mr. P.S. Waldie, Head of the Department of Audio-Visual Services at Stobhill General Hospital, Glasgow. Because of the limitations imposed on printing in such a journal, the warning system had then to be conceived in black and white, and a series of black and white symbols replaced the prototype colours, thus:




This version of the warning system (Figure 49), subsequently referred to as the Drug Disc, measured 15 cm. in diameter and was published in the Lancet on May 12th, 1973 (Whiting, Goldberg and Waldie 1973).

5.4.1. Response to the Drug Disc publication

This article immediately provoked a remarkable degree of interest throughout the world, as did a subsequent article in the American Journal, Drug Therapy (Whiting, Goldberg and Waldie 1974). A number of independent reviews appeared in various languages and the system was demonstrated on the B.B.C. Television programme "Tomorrow's World".

One thousand one hundred and fifty letters enquiring about the Drug Disc were received from doctors, pharmacists, students, pharmaceutical companies, drug regulatory bodies and various other official organisations.

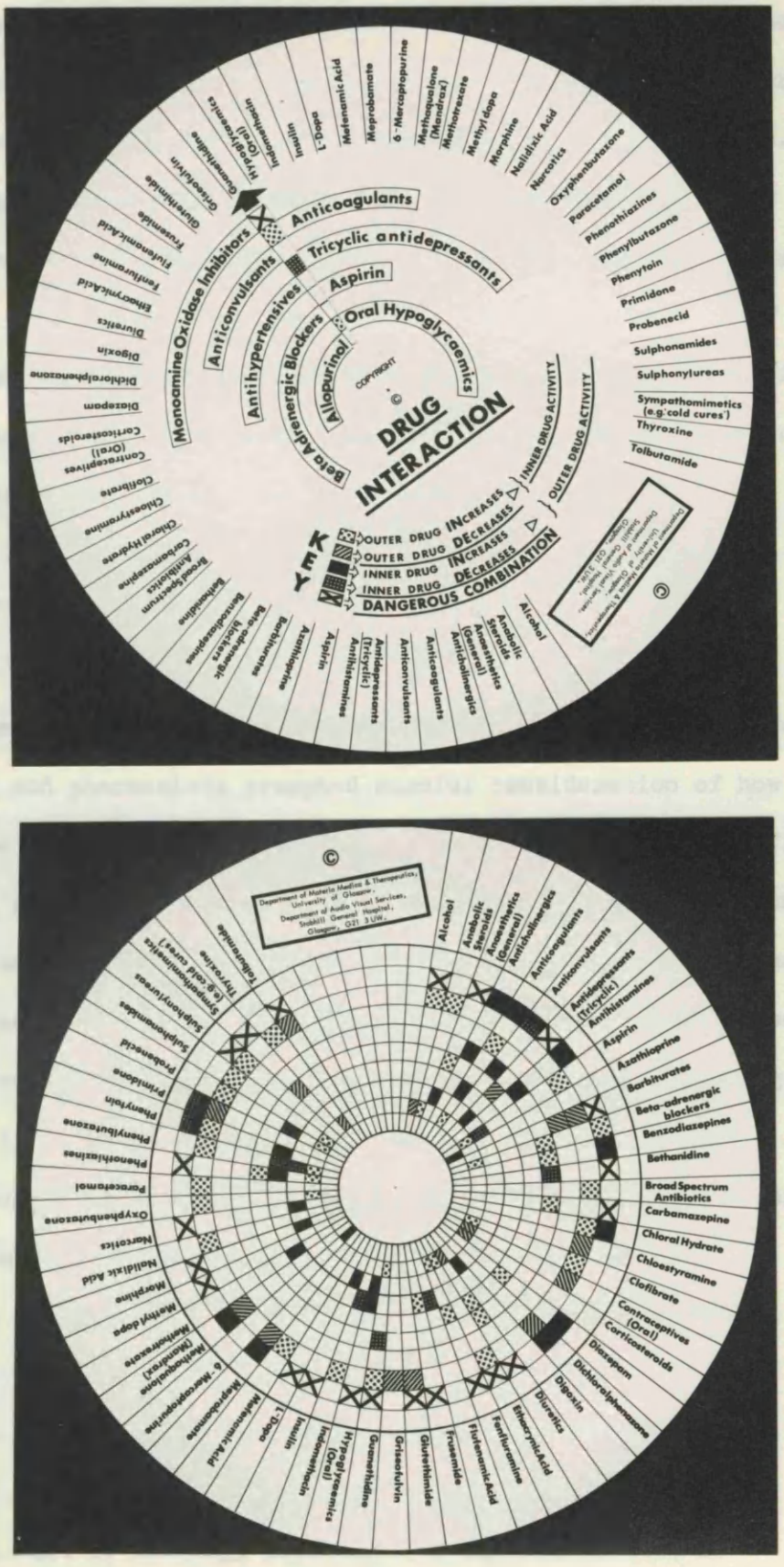



FIGURE 49 The Drug Disc as published in the Lancet, showing the complete system and detail of the large disc.

An analysis of this response appears in Tables 15-19. It was obvious that the Drug Disc had been well received and represented a growing need for this type of approach to the problem of drug interactions.

The response from pharmaceutical and commercial concerns had been anticipated, and a copyright protection of the disc had been applied for and obtained on 25th April, 1973. Direct association of the Disc with commercial interests, exemplified by the pharmaceutical industry, was thought to be inadvisable and requests for access to the copyright from such sources were therefore denied.

### 5.4.2. The Working Party

The extent of the response on the part of other groups such as doctors and pharmacists prompted careful consideration of how the Disc could be made generally available. It obviously required official support and approval and it seemed most appropriate to make an approach to the Scottish Home and Health Department. This approach was welcomed and subsequently led to the formation of a Working Party whose remit was to advise on further development of the drug interaction warning system, submit it to trial in the United Kingdom, and then to effect its free distribution to all doctors working in the National Health Service.

Members of the Working Party included:

1. Professor A. Goldberg, Department of Materia Medica, University of Glasgow.
2. Professor J. Crooks, Department of Pharmacology and Therapeutics, University of Dundee.
3. Dr. B. Whiting, Department of Materia Medica, University of Glasgow.
4. Mr. P.S. Waldie, Department of Audio-Visual Services, Stobhill General Hospital, Glasgow.

| D O C T O R S | | |
|---|---|---|
| Geographical area | Category | Number of letters |
| United Kingdom | Hospitals and Universities<br>General practitioners | 60<br>70 |
| U.S.A. | Hospitals and Universities | 450 |
| Canada | Hospitals mainly | 20 |
| Europe | Hospitals mainly | 80 |
| Other parts of the world, mainly from hospitals: Argentina, Australia, Czechoslovakia, Hong Kong, Hungary, India, Israel, Japan, Kenya, Mexico, New Zealand, Pacific Islands, Rhodesia, South Africa, Tunisia, Turkey. | | 60 |
| | Total | 740 |

TABLE 15 Worldwide response of doctors to articles and reviews about the Drug Disc.

| PHARMACISTS | |
|---|---|
| Geographical area | Number of letters |
| United Kingdom | 45 |
| Other countries - mainly U.S.A. | 70 |
| Total | 115 |

TABLE 16 Worldwide response of pharmacists to articles and reviews about the Drug Disc.

| STUDENTS and NURSES | |
|---|---|
| Geographical area | Number of letters |
| Students (medical, pharmacy and pharmaceutical technology), mainly United Kingdom, France and Germany. | 40 |
| Nurses, mainly United Kingdom. | 30 |
| Total | 70 |

TABLE 17 Worldwide response of students and nurses to articles and reviews about the Drug Disc.

| OFFICIAL ORGANISATIONS | |
|---|---|
| Geographical area and organisation | Number of letters |
| United Kingdom, including:<br>The Department of Health and Social Security.<br>The Ministry of Health and Social Services (Northern Ireland).<br>The British Industrial Biological Research Association.<br>The Ministry of Defence.<br>The Joint Pricing Committee for England.<br>The National Pharmaceutical Union.<br>The Association of the British Pharmaceutical Industry.<br>The Psychiatric Rehabilitation Association. | 10 |
| Other countries, including:<br>Switzerland<br>The World Health Organisation.<br>Czechoslovakia<br>State Institute for the Control of Drugs.<br>U.S.A.<br>United States Pharmacopoeia.<br>Poison and Drug Information Centres. | 35 |
| Total | 45 |

TABLE 18 Worldwide response of official organisations to articles and reviews about the Drug Disc.

PHARMACEUTICAL AND COMMERCIAL INTEREST

Enquiries and requests for acquisition of copyright, subsequent manufacture and distribution of the Drug Disc in its original or modified form came from companies in the following countries:

| | |
|---|---|
| ANGOLA | JAPAN |
| ARGENTINA | MEXICO |
| AUSTRALIA | NORWAY |
| BELGIUM | RHODESIA |
| CANADA | SOUTH AFRICA |
| COSTA RICA | SPAIN |
| DENMARK | SWEDEN |
| FRANCE | SWITZERLAND |
| GERMANY | UNITED KINGDOM |
| GREECE | UNITED STATES OF AMERICA |
| HOLLAND | VENEZUELA |
| ITALY | |

Total number of letters 180

TABLE 19 Worldwide response of pharmaceutical companies and other commercial companies to articles and reviews about the Drug Disc.

5. Members of the Scottish Home and Health Department including Dr. G.D. Forwell, Dr. I.S. McDonald, Dr. G.A. Scott and Dr. A.T.B. Moir.
6. Representatives from Her Majesty's Stationery Office.

## 5.5. LEGAL AND ETHICAL CONSIDERATIONS

Advice was sought on legal and ethical aspects of copyright and patenting in the medical field. This was the subject of a full enquiry by the Council of the British Medical Association (British Medical Association 1950, 1970) which approved of patenting in the medical field by members of the profession, provided that the patent, (in this case copyright of the Drug Interaction Warning System) was offered and assigned to the National Research Development Corporation (NRDC). This corporation was set up in 1949 under the Development of Inventions Act to give financial support to a variety of University and Polytechnic inventions which showed promise, although speculative, of having commercial value. Any assignation to the NRDC would ensure that the invention to which the patent related would be made available, developed and exploited in the best interests of the public. The present author, therefore, submitted the Drug Disc to the NRDC. After due consideration they came to the conclusion that they could offer no more assistance in Britain than was being given by the Scottish Home and Health Department and that their involvement would be superfluous. The important point was made that the "best interests of the public" would be served by the free distribution of the Disc to doctors throughout the United Kingdom. No further action on the part of the NRDC was therefore necessary.

As a large part of the response to the articles about the Drug Disc stemmed from abroad, it was important to bear in mind the possibility

of worldwide distribution. This would inevitably involve commercial considerations. Further advice on the ethical and professional aspects of this kind of involvement was therefore sought fromm Messrs. Hempsons of London, Solicitors to the British Medical Association and General Medical Council. They advised that nothing in the British Medical Association's ethical rulings would hinder plans for a worldwide distribution and strongly recommended an association with a reputable international publishing company specialising in medical literature.

## 5.6. SECOND VERSION OF THE DRUG DISC

### 5.6.1. Modifications

Having accepted the concept of the drug interaction warning system in principle, the Working Party examined the prototype (Lancet version) and agreed on three important modifications:

1. An increase in the capacity of the system by utilising both sides of the large disc, forming a reversible unit.
2. The introduction of colour, as printing of subsequent versions of the Disc would not be restricted to black and white.
3. The use of a durable material such as plastic rather than the grade four glossy bromide photographic paper used to construct several prototypes (Lancet version, Figure 49). Daily handling of these prototypes had soon demonstrated the need for stronger materials.

Two small discs, affixed to opposite sides of the large disc and rotating about a common centre effectively increased the capacity of the system and formed the basis for the second version of the Drug Disc. Sixteen primary drugs could now be accommodated on the small discs, eight on each side. The primary drugs were therefore increased to

include the original nine shown in Table 12 and seven others known to be implicated in drug interactions, including alcohol, shown in Table 20. As in the prototype, each drug was placed on an arc converging on an arrow-like window. Seven additional drugs were also added to those appearing on the large disc, which then contained an identical list of 64 drugs or drug categories printed in alphabetical order on each side.

### 5.6.2. Introduction of coloured symbols

The use of colour provided a means of introducing a more logical key system incorporating internationally recognised symbols for potentiation - a PLUS sign, and inhibition - a MINUS sign. Dangerous combinations would still be indicated by a diagonal cross. The new key system was realised by printing the drugs on the smaller discs in red and the drugs on both sides of the larger disc in black, subsequently referred to as "red" and "black" drugs respectively. The symbols used were chosen from those shown in Figure 50. Apart from the diagonal cross motif, the background colour of a symbol denoted the drug (red or black) whose action was modified, while the plus or minus symbol expressed the direction of the altered pharmacological activity in terms of potentiation or inhibition. Table 21 shows examples which will illustrate this system.

It was hoped that the use of these symbols would appeal to the user's sense of logic, thus avoiding the necessity for detailed instructions. Indeed, no problems in interpretation were encountered when the symbols were shown to twenty of the present author's medical colleagues.

## 5.7. UNITED KINGDOM TRIAL VERSION OF THE DRUG DISC

As the second version of the Disc would be submitted for trial in

| |
|---|
| ALCOHOL |
| AMINOGLYCOSIDE ANTIBIOTICS |
| ANTACIDS |
| BARBITURATES |
| CORTICOSTEROIDS |
| ORAL CONTRACEPTIVES |
| PHENOTHIAZINES |

TABLE 20 Additional drugs to be included on the small discs.

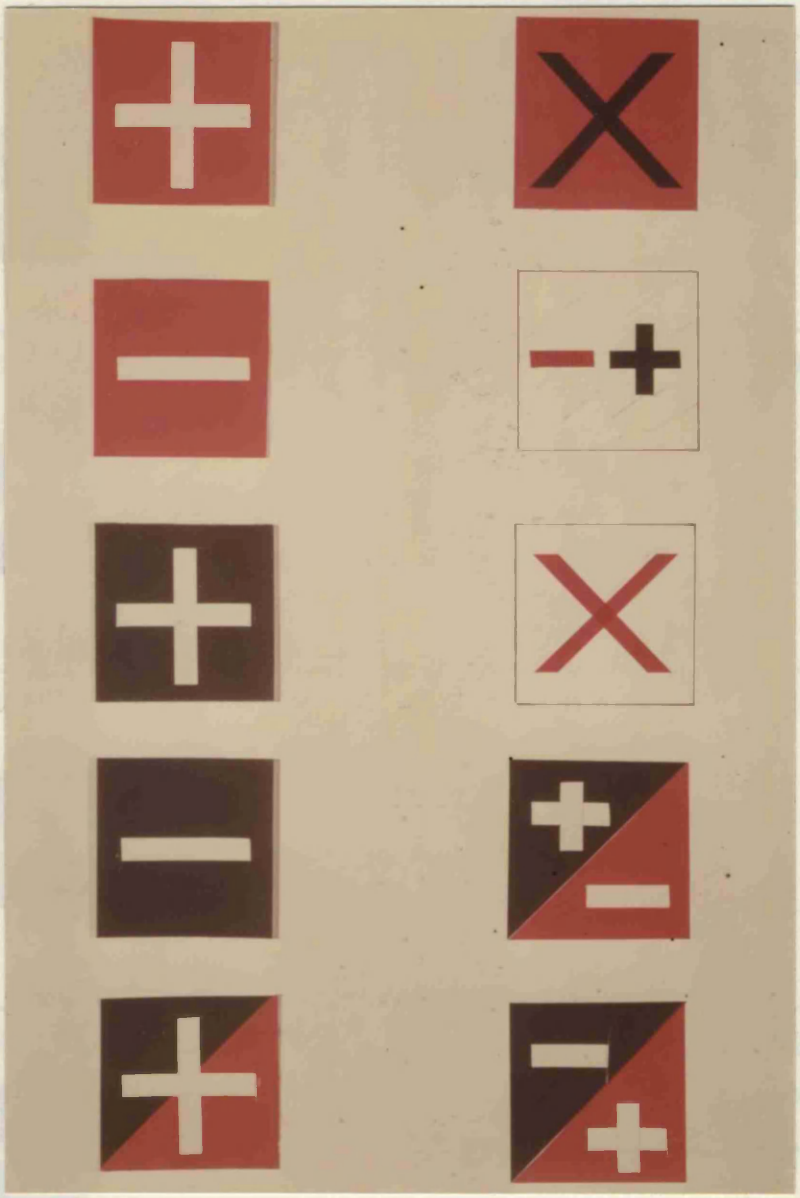


FIGURE 50 Series of coloured symbols considered for use on the Drug Disc.

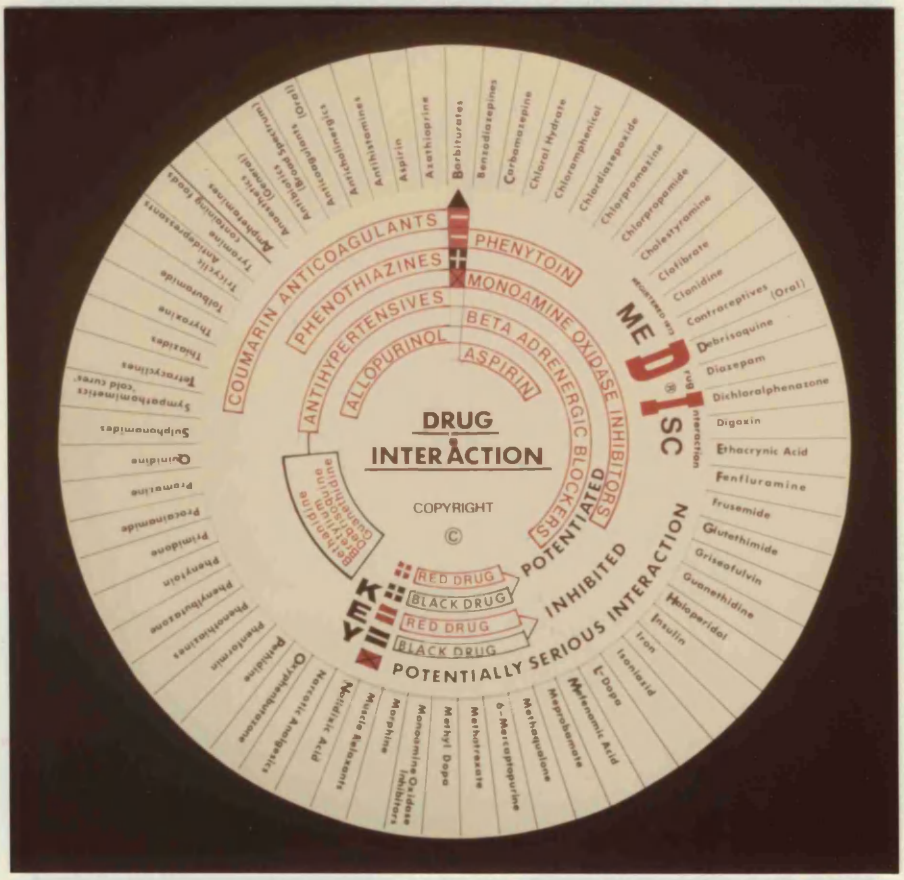
| | |
|---|---|
| COUMARIN ANTICOAGULANTS (Red Drug) and CLOFIBRATE (Black Drug) | |
|  | RED DRUG is potentiated, i.e. coumarin anticoagulants are potentiated by clofibrate. |
| AMINOGLYCOSIDE ANTIBIOTICS (Red Drug) and MUSCLE RELAXANTS (Black Drug) | |
|  | BLACK DRUG is potentiated, i.e. muscle relaxants are potentiated by aminoglycoside antibiotics. |
| COUMARIN ANTICOAGULANTS (Red Drug) and DICHLORALPHENAZONE (Black Drug) | |
|  | RED DRUG is inhibited, i.e. coumarin anticoagulants are inhibited by dichloralphenazone. |
| TRICYCLIC ANTIDEPRESSANTS (Red Drug) and CLONIDINE (Black Drug) | |
|  | BLACK DRUG is inhibited, i.e. Clonidine is inhibited by tricyclic antidepressants. |
| MONOAMINE OXIDASE INHIBITORS (Red Drug) and PETHIDINE (Black Drug) | |
|  | DANGEROUS COMBINATION or POTENTIALLY SERIOUS INTERACTION. |

TABLE 21 Examples of the use of coloured symbols on the second version of the Drug Disc.

the United Kingdom, arrangements were made for its production in plastic by Her Majesty's Stationery Office (H.M.S.O). A series of drafts prepared by the present author and Mr. P.S. Waldie were reviewed by the Working Party and the form shown in Figure 51 was finally accepted. Although copyright had been obtained in April 1973 by registration at Stationers Hall (Entry No.7822), Fitzpatricks, Chartered Patent Agents, advised further protection of the device by inclusion and registration of the trademark MEDISC. This can be seen in Figure 51.

The final draft of the second version was discussed with H.M.S.O., who agreed to produce about 500 Discs for the United Kingdom Trial. A plastic pocket for each Disc would also be provided, which would display the trademark and a cautionary note advising the user that the Disc was intended only as a guide, and that the appropriate pharmacological literature should be consulted for more detailed information.

Figures 52 and 53 show details of the trial version which was received from H.M.S.O., in December 1973. The only significant departure from the final draft (Figure 51) was a change in the "potentially serious interaction" motif - the black cross on a red background had been replaced by a red cross on a white background. The words "potentially serious interaction" had also been printed in red. The device measured 14 cm. in diameter and was made of a semi-rigid plastic material.



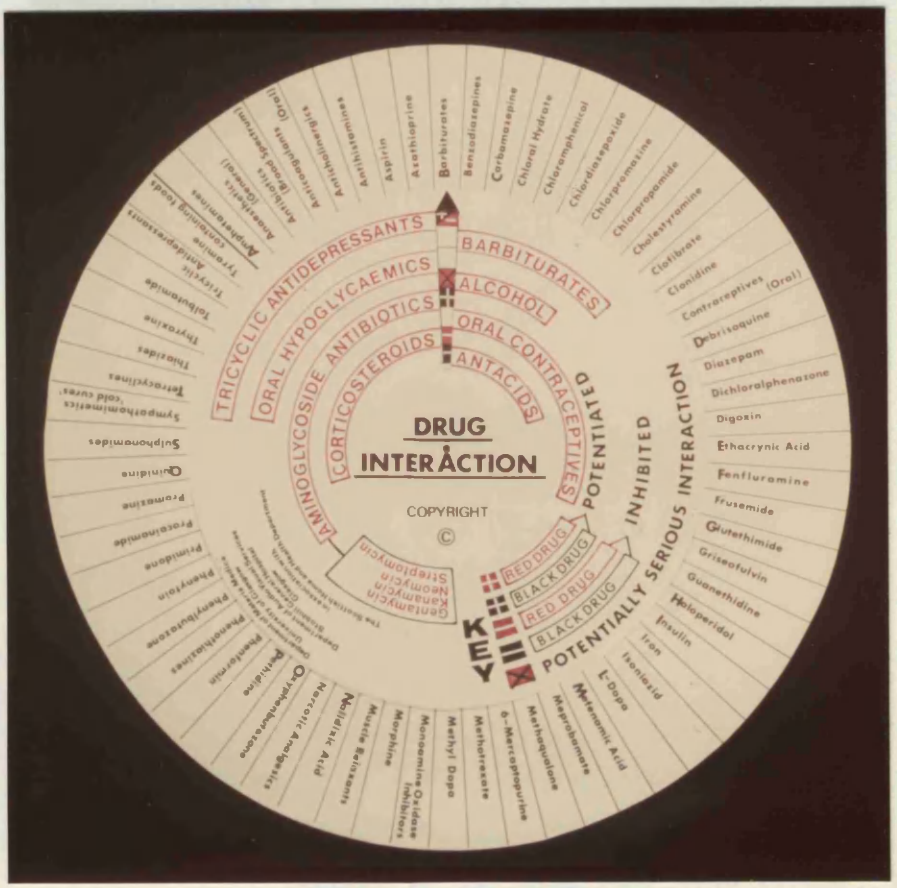




FIGURE 51 Draft of the United Kingdom Trial version of the Drug Disc, showing both sides.

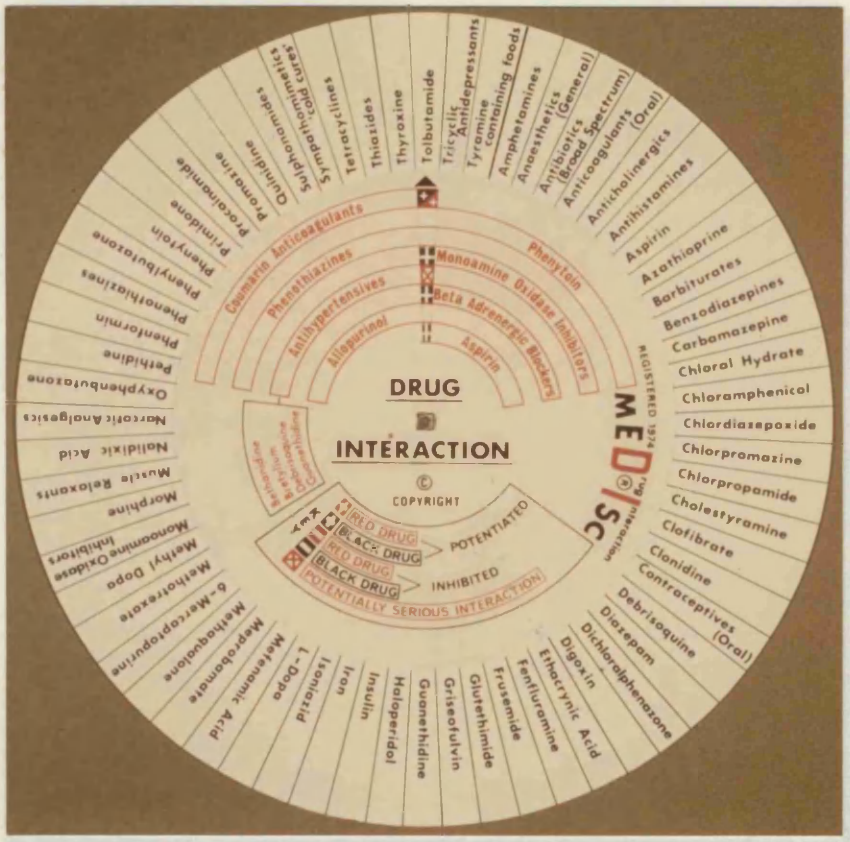



FIGURE 52 Side I of the United Kingdom Trial version of the Drug Disc with detail of the large disc.

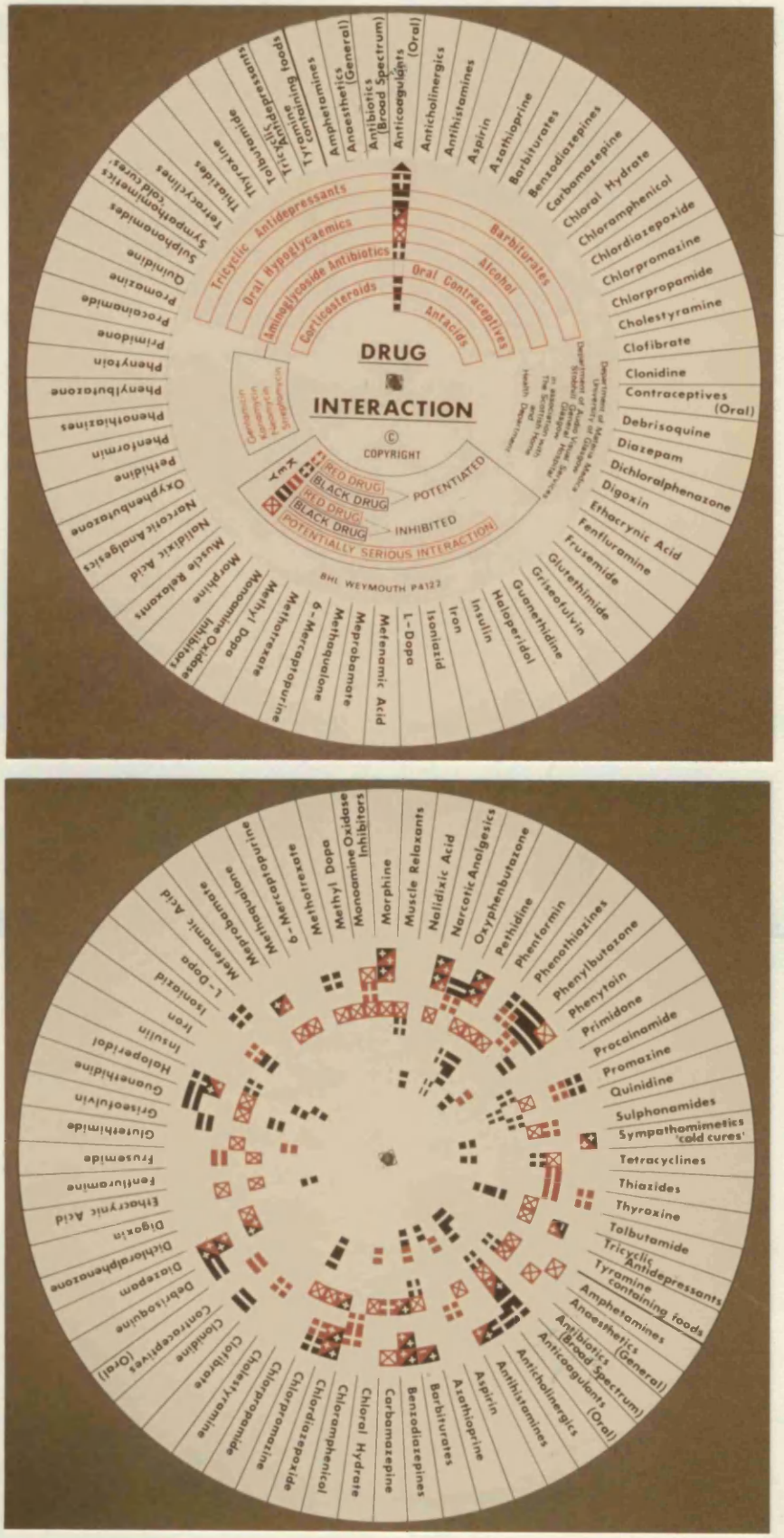



FIGURE 53 Side 2 of the United Kingdom Trial version of the Drug Disc with detail of the large disc.

# CHAPTER 6

## UNITED KINGDOM TRIAL OF THE DRUG INTERACTION WARNING SYSTEM

## 6. UNITED KINGDOM TRIAL OF THE DRUG INTERACTION WARNING SYSTEM

The aim of the trial was to assess the value of the drug interaction warning system in practice by exposing it to as many different clinical and scientifically relevant situations as possible. It was originally planned to conduct the trial in two phases, separated by one month, (Phases 1 and 2) but the lack of response on the part of some participants called for a third phase (Phase 3). Details of these phases are shown in Figure 54.

### 6.1. PHASE 1

Four hundred and fifty doctors and pharmacists, distributed as shown in Table 22 were invited to take part in the trial.

Each participant received:

1. A Drug Disc, contained in a plastic pocket (Figures 52 and 53).
2. An explanatory letter from the Department of Materia Medica, University of Glasgow, (Figure 55).
3. A questionnaire ("Initial Report", Figure 56) which was to be returned within one week to gain some impression of the immediate reaction to the Drug Disc.

The Initial Report sought answers to seven questions, which covered the design of the Disc, including the key system (Questions 1-4), the relevance of the information presented to clinical practice (Question 5), the usefulness of the system (Question 6) and Question 7 allowed for any further comments, including those of colleagues, to encourage an even wider distribution.

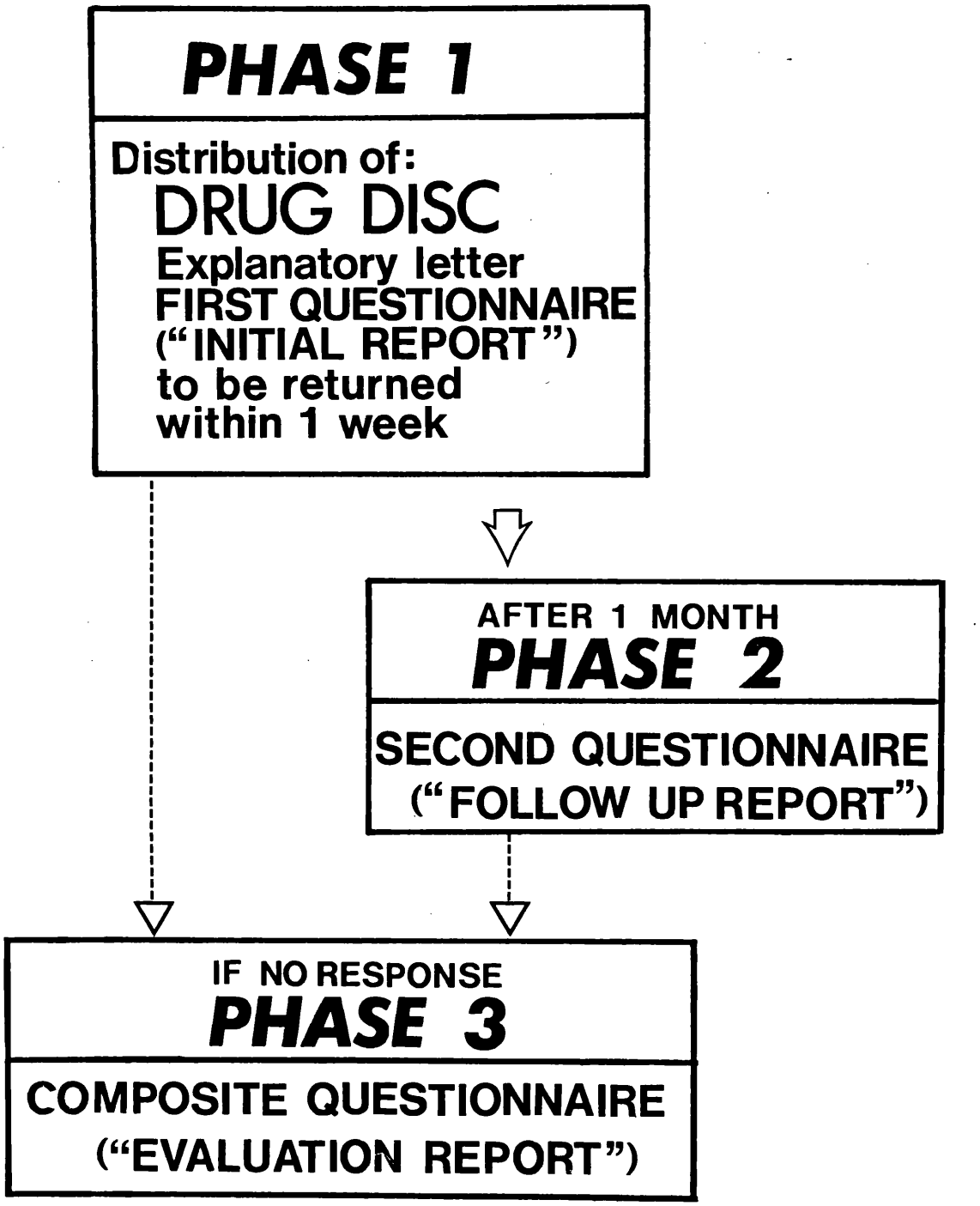



FIGURE 54 Details of the three phases of the United Kingdom Trial of the Drug Disc.

1. A group of EXPERTS, including Senior Lecturers and Professors of
   CLINICAL PHARMACOLOGY
   PHARMACOLOGY
   MEDICINE
   PHARMACY
   PHARMACEUTICAL CHEMISTRY

2. HOSPITAL DOCTORS in all grades and specialities in
   ABERDEEN
   DUNDEE
   EDINBURGH
   GLASGOW
   INVERNESS
   MANCHESTER

3. GENERAL PRACTITIONERS throughout the United Kingdom

4. HOSPITAL and AREA PHARMACISTS in Scotland

5. A miscellaneous group, including MEDICAL OFFICERS in the ROYAL AIR FORCE stationed in the United Kingdom, Germany and Cyprus, and various official organisations.

TABLE 22 United Kingdom Trial : distribution list.

THE UNIVERSITY OF GLASGOW

DEPARTMENT OF MATERIA MEDICA
STOBHILL GENERAL HOSPITAL
GLASGOW, G21 3UW
TELEPHONE: 041-558 5042
EXTENSION: 561

December 1973

Dear Colleague,

## THE DRUG DISC

On May 12 this year, Dr Brian Whiting, Mr Peter Waldie and I published a paper in the Lancet on the Drug Disc. This was intended to be a warning in the form of an *aide-mémoire* to doctors and pharmacists against adverse drug interactions. The publication aroused considerable interest. As a result, a Working Party was formed at the Scottish Home and Health Department at St Andrew's House, Edinburgh. This included members of the medical staff of the Scottish Home and Health Department and the Department of Health and Social Security in addition to Professor J Crooks of Dundee, Dr Whiting and myself. The aim of this group was to develop the disc for wide distribution to hospital doctors, general practitioners and pharmacists in this country.

We have improved the original disc and I enclose the latest version for your comments as I know this will be of interest to you. It would be helpful to have your initial reaction to the disc and your comments after you have used it for one month. To facilitate this, I am enclosing a questionnaire and in one month's time I will send you a second questionnaire. It would also be helpful if you could show it to any of your colleagues who might be interested and record their views under "any further comments".

On the basis of the completed questionnaires we will modify the present disc and produce a final one for general distribution.

I am most grateful for your anticipated collaboration.

Yours sincerely,

A. Goldberg.

A GOLDBERG, MD, DSc, FRCP, FRSE

FIGURE 55 Explanatory letter sent out at the beginning of the United Kingdom Trial.

THE DRUG DISC

Warning system for drug interactions

# EVALUATION

## INITIAL REPORT

We would like to gain some impression of your initial reaction to the Drug Disc. Would you please answer the following questions and return the top form within one week as an acknowledgement that you have received the disc. Retain the duplicate copy for your further reference.

Where you give a negative response to any of the first five questions, could you give your reasons and suggested changes under item 7.

1. Is the method of using the Disc readily understandable? _____ Yes/No*
2. Are the interaction symbols clear? _____ Yes/No*
3. Is the Key clear? _____ Yes/No*
4. Is the size convenient? _____ Yes/No*
5. Do you think the interactions shown are relevant to clinical practice? _____ Yes/No*
6. What is your initial overall impression of its usefulness?

   Very useful/useful/of limited use/of no use*.
7. Any further comments, including those of colleagues where appropriate

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Please return to:
Department of Materia Medica
Stobhill Hospital
Glasgow G21 3UW.

*Delete as applicable

Name _____

Date _____

Designation _____

Address _____

_____

_____

_____

FIGURE 56

## 6.2. PHASE 2

One month later, a second questionnaire ("Follow Up Report", Figure 57) was sent to each participant to find out whether use of the Disc during the trial period had altered the initial impression of its value (Questions 1 and 2). Its effect on drug administration (Question 3) and its value in teaching (Question 5) were also assessed. Suggestions for its improvement were invited (Question 4) and again, a space was provided for any other relevant comments, including those of colleagues (Question 6).

## 6.3. PHASE 3

Phase 3 was necessary because some participants failed to return one or both reports relating to Phases 1 and 2. A second approach was considered worthwhile and 160 modified questionnaires ("Evaluation Report", Figure 58) based on the Initial and Follow Up Reports, were distributed accordingly.

## 6.4. RESULTS

### 6.4.1. Response

The overall response to the three questionnaires is shown in Table 23, while the detailed response of the various groups involved is shown in Table 24. Two hundred and eighteen (48%) participants completed the trial satisfactorily before the institution of Phase 3. A further 95 then responded to the second approach, increasing the total number completing the trial to 313 (70%). These results are expressed graphically in Figure 59, and Figure 60 illustrates the different responses of the major groups at each stage of the trial.

THE DRUG DISC

Warning system for drug interactions

# EVALUATION

## FOLLOW UP REPORT

We would now like your comments after you have used the Drug Disc for one month.

1. What was your *initial* overall assessment?

   Very useful/useful/of limited use/of no use*.

2. Has using the disc for one month altered your initial assessment?_____Yes/No.

   If yes, what is your final assessment?

   Very useful/useful/of limited use/of no use.

3. Has it modified your drug administration at any time?_____Yes/No.

4. Do you have any suggestions for its improvement?_____

5. Do you think it may have value in teaching?_____Yes/No.

6. Any further comments, including those of colleagues where appropriate

Please return to
Department of Materia Medica
Stobhill General Hospital
Glasgow G21 3UW

Name _____

Date _____

Designation _____

Address _____

*Delete as applicable

FIGURE 57

THE DRUG DISC

Warning system for drug interactions.

EVALUATION REPORT.

We would like to gain some impression of your reaction to the Drug Disc. Would you please answer the following questions and return the form to me within one week.

Where you give a negative response to any of the first five questions, could you give your reasons and suggested changes under item 9.

1. Is the method of using the Disc readily understandable? ..... Yes/No.

2. Are the interaction symbols clear? ..... Yes/No.

3. Is the Key clear? ..... Yes/No.

4. Is the size convenient? ..... Yes/No.

5. Do you think the interactions shown are relevant to clinical practice? ..... Yes/No.

6. Has it modified your drug administration at any time? ..... Yes/No.

7. Do you think it may have value in teaching? ..... Yes/No.

8. What is your overall impression of its usefulness?

Very useful/useful/of limited use/of no use.

9. Any further comments, including those of colleagues where appropriate?

.....

.....

.....

.....

.....

.....

Name.....

Date.....

Address.....

.....

.....

Please return to:
Department of Materia Medica,
Stobhill General Hospital,
Glasgow, G21 3UW

FIGURE 58

| PHASE | QUESTIONNAIRES | |
|---|---|---|
| | Distributed | Returned |
| 1 | 450 | 285 (63%) |
| 2 | 450 | 218 (48%) |
| 3 | 160 | 95 (59%) |
| All phases | - | 313 (70%) |

TABLE 23 United Kingdom Trial : overall response to questionnaires.

| GROUP | Number of discs sent | Number of Questionnaires returned | | PHASE 3 | | Total number completed trial |
|---|---|---|---|---|---|---|
| | | PHASE 1 | PHASE 2 | Number of Questionnaires Sent | Returned | |
| GENERAL PRACTITIONERS | 100 | 87 | 74 | - | - | 74 (74%) |
| HOSPITAL DOCTORS: | 263 | 129 | 88 | 133 | 76 | 164 (62%) |
| ABERDEEN | 50 | 21 | 18 | 30 | 16 | 34 (68%) |
| DUNDEE | 50 | 15 | 8 | 30 | 24 | 32 (64%) |
| EDINBURGH | 30 | 27 | 10 | 10 | 8 | 18 (60%) |
| GLASGOW | 121 | 62 | 48 | 55 | 25 | 73 (60%) |
| INVERNESS | 6 | 2 | 2 | 4 | 2 | 4 (67%) |
| MANCHESTER | 6 | 2 | 2 | 4 | 1 | 3 (50%) |
| EXPERTS | 30 | 18 | 18 | 12 | 8 | 26 (87%) |
| AREA and HOSPITAL PHARMACISTS | 15 | 14 | 12 | 3 | 2 | 14 (93%) |
| ROYAL AIR FORCE | 8 | 6 | 6 | - | - | 6 (75%) |
| MISCELLANEOUS | 34 | 31 | 20 | 12 | 9 | 29 (85%) |
| TOTALS: | 450 | 285 (63%) | 218 (48%) | 160 | 95 (59%) | 313 (70%) |

TABLE 24 United Kingdom Trial : details of the response of the different groups participating in the trial.

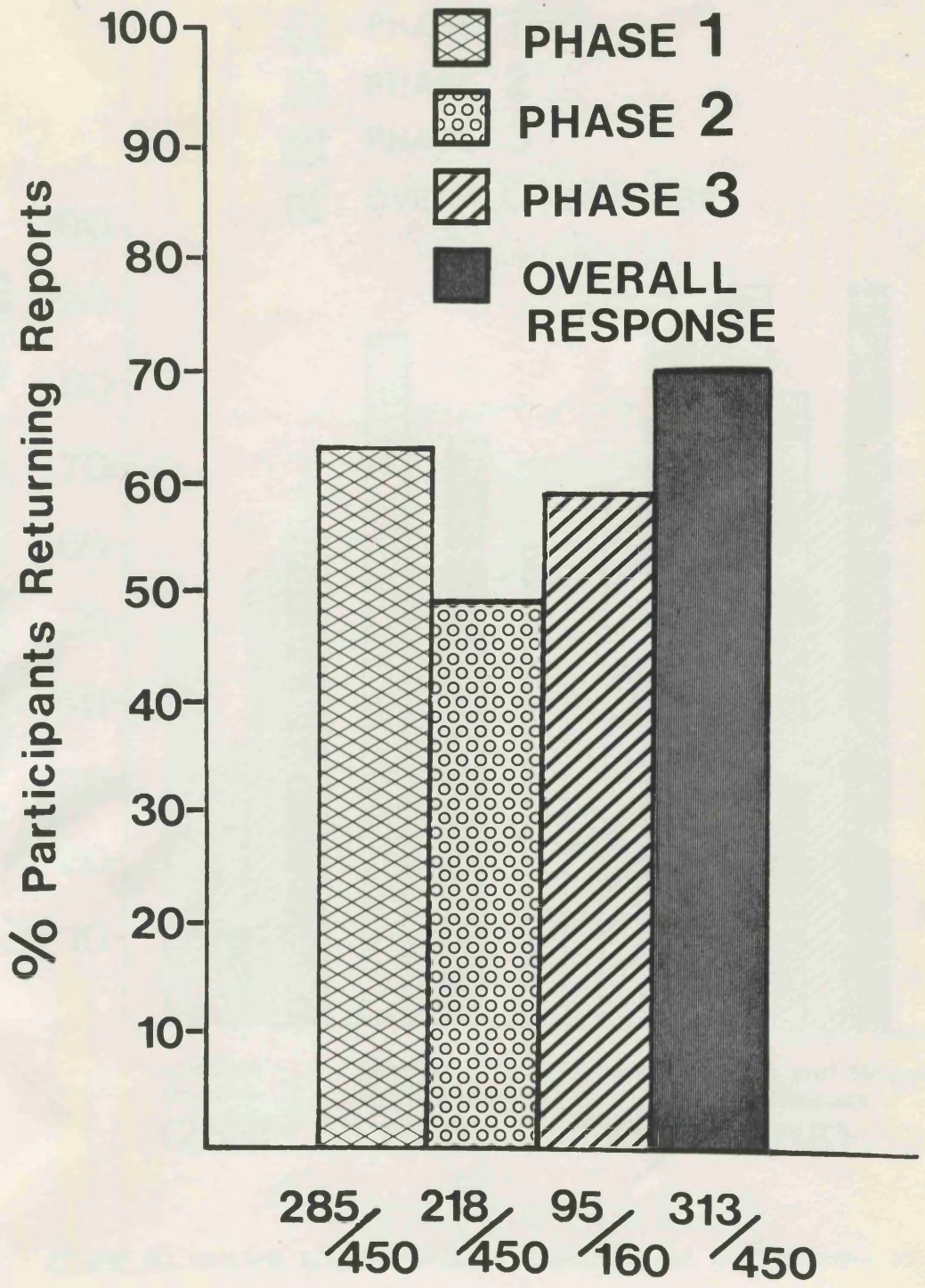



FIGURE 59 United Kingdom Trial : Graphical representation of the overall response.

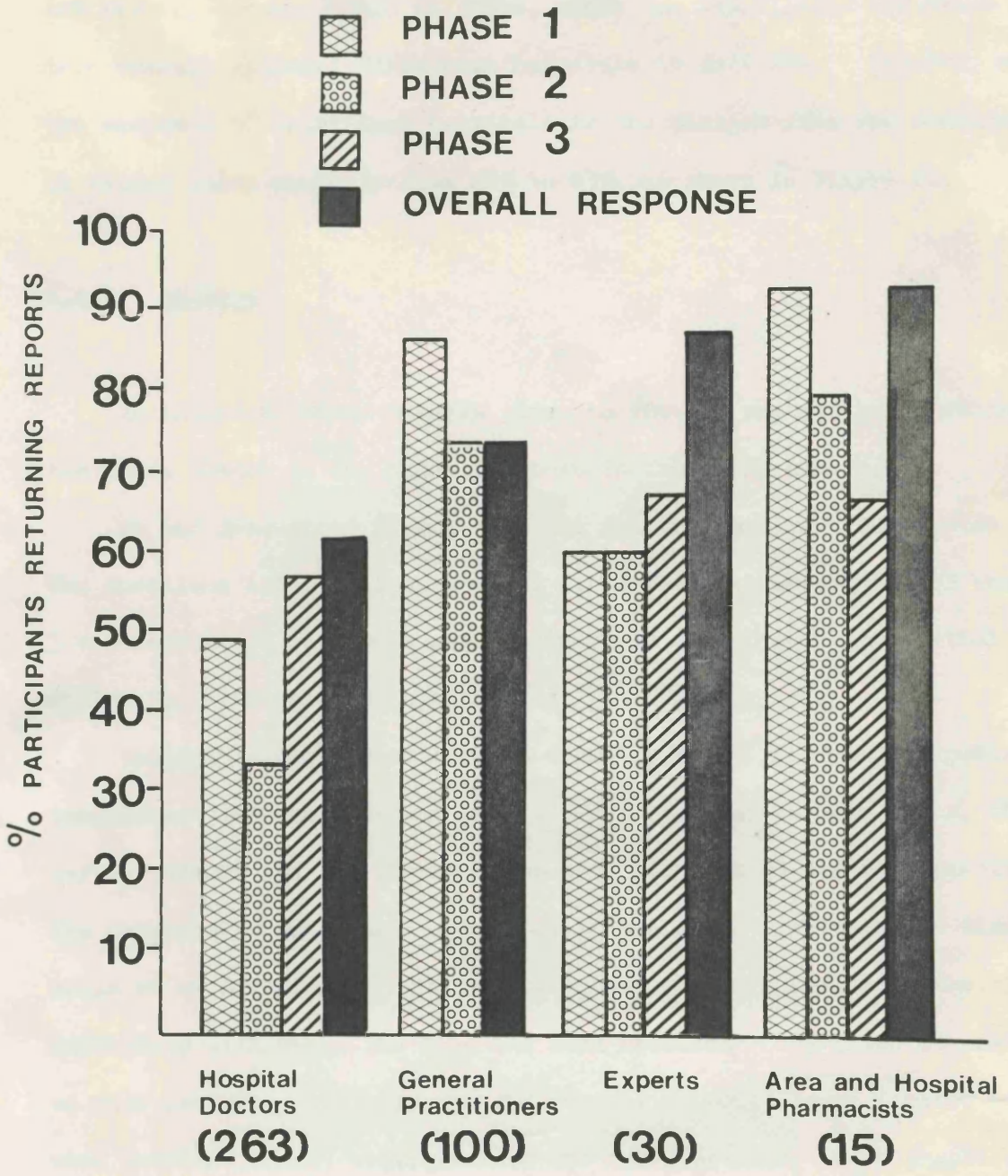



FIGURE 60 United Kingdom Trial : details of the response of the major groups participating in the trial.

The overall responses of hospital doctors was represented by a 62% return, and as Figure 61 shows, there was very little variation in this overall response throughout hospitals in Scotland. However, when the response of individual hospitals in the Glasgow Area was examined, it varied quite markedly from 45% to 83%, as shown in Figure 62.

6.4.2. Answers

An analysis of the answers given on the 598 reports returned in the three phases of the trial is shown in Tables 25 and 26.

As the Evaluation Report sent out in Phase 3 merely duplicated the questions asked in Phases 1 and 2, no separate assessment of Phase 3 was necessary. Answers were included in the appropriate Initial or Follow Up Report data as appropriate.

Table 25 clearly demonstrates that the majority of participants considered that the Disc was easy to use, the symbols were clear, the key was clear, and the interactions were relevant to clinical practice. The response to Question 4 suggested that a slight reduction in size would be an advantage. The response to Question 6 reflected the enthusiasm with which the Disc had been received - 85% rated it useful or very useful. The majority who thought it would be of limited use were paediatricians, obstetricians and anaesthetists, whose practice dictated the use of a relatively specialised range of drugs.

Table 26 shows that 85% of the participants completing the trial (313 reports) found no reason to change their initial assessment. This figure may be a little high as no opportunity for a revision of initial rating could be given in Phase 3. Thus if Evaluation Reports are excluded the figure falls to 79% (171 of 218 Follow Up Reports). The 21% (47 of 218 Follow Up Reports) who had changed their initial assessment were distributed as shown in Figure 63, and Table 27

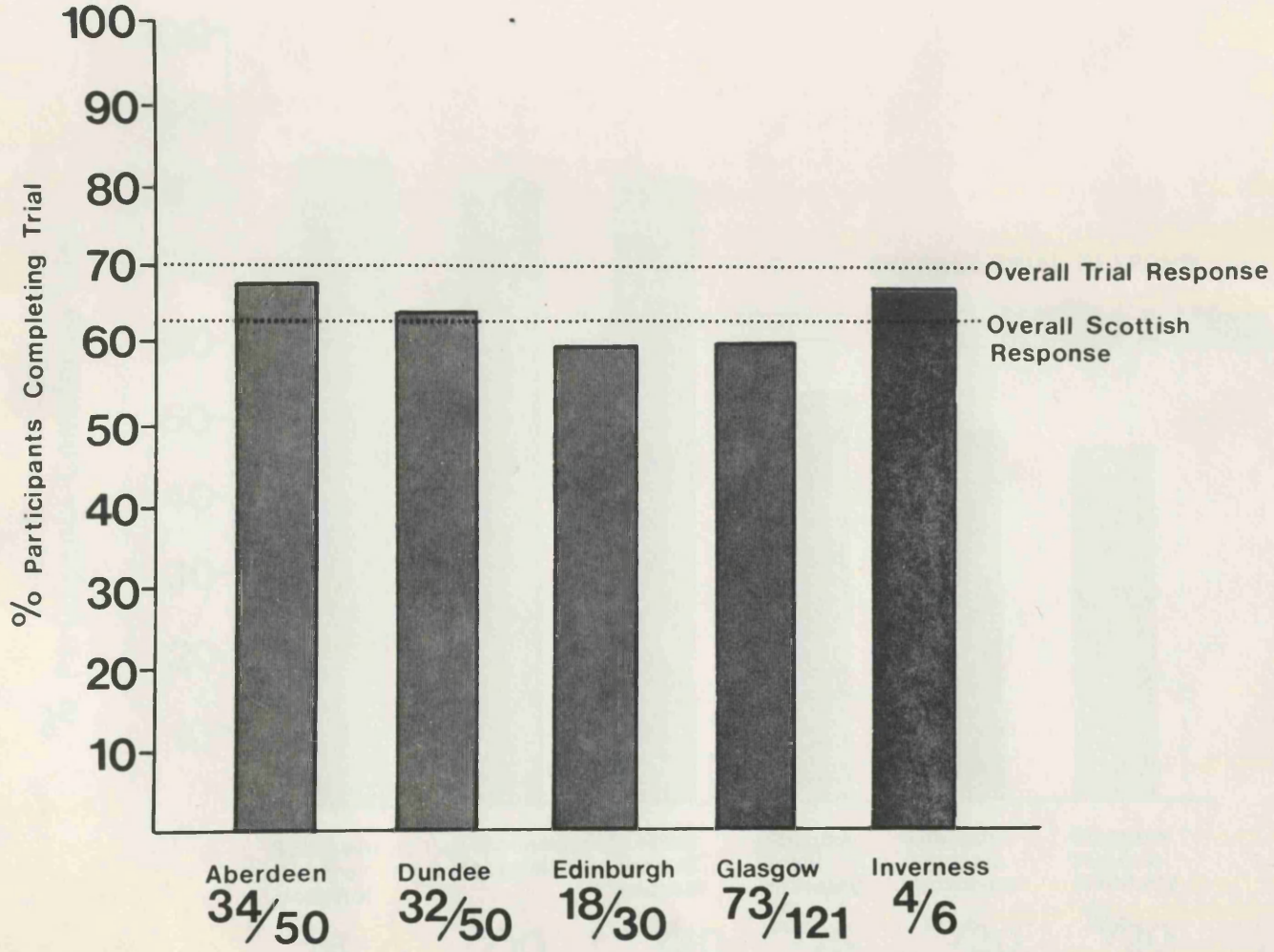



FIGURE 61 United Kingdom Trial : response of hospital doctors in Scotland.

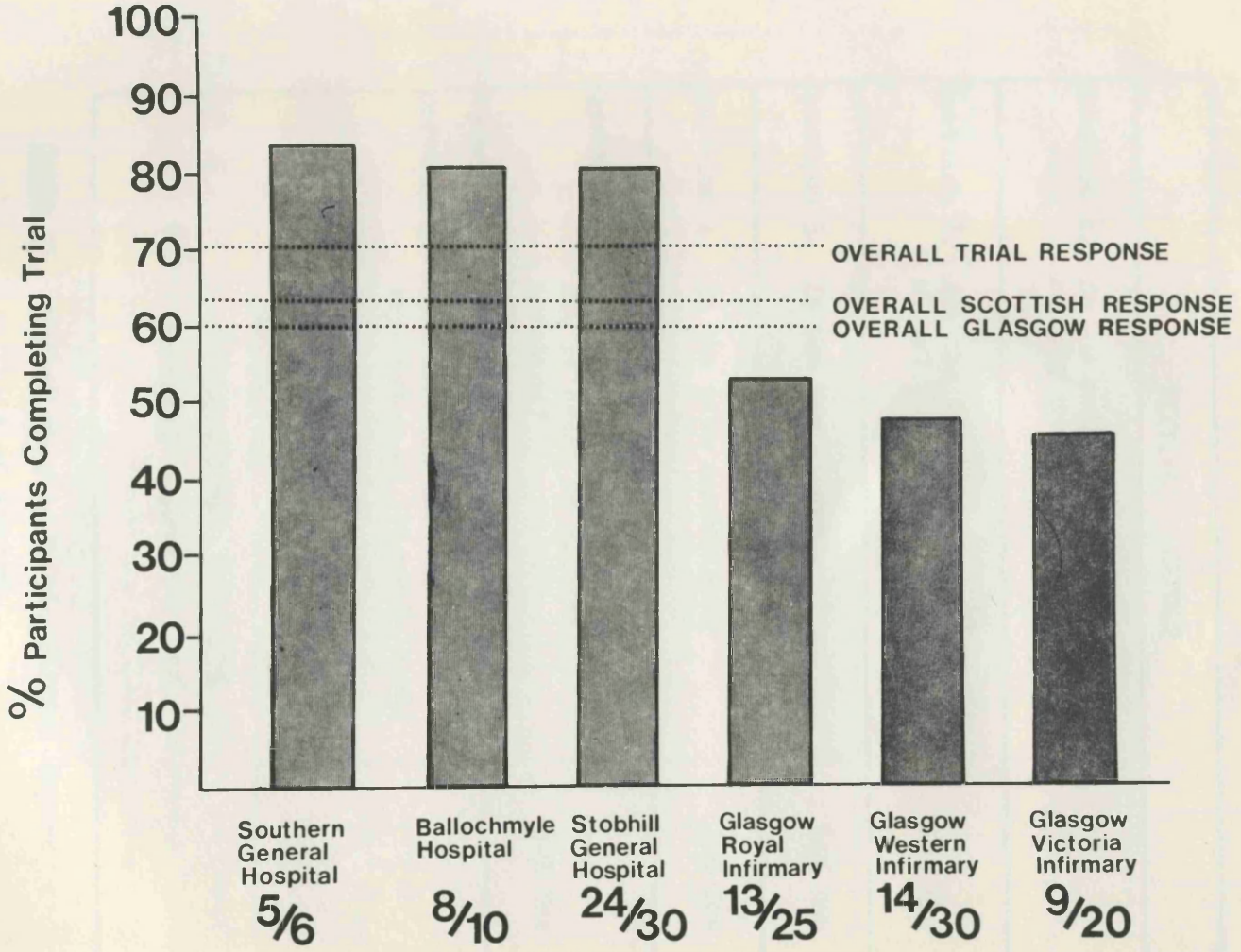



FIGURE 62 United Kingdom Trial : response of hospital doctors in the Glasgow area.

| INITIAL REPORT | | |
|---|---|---|
| Question 1. | Is the method of using the Disc readily understandable? | 95% Yes |
| Question 2. | Are the interaction symbols clear? | 95% Yes |
| Question 3. | Is the key clear? | 94% Yes |
| Question 4. | Is the size convenient? | 76% Yes |
| Question 5. | Do you think the interactions are relevant to clinical practice? | 90% Yes |
| Question 6. | What is your initial overall impression of its usefulness? | |
| | Very useful 40% > 85% | |
| | Useful 45% > 85% | |
| | Of limited use 13% | |
| | Reserved comment 2% | |

TABLE 25 United Kingdom Trial, Initial Report : analysis of answers.

| FOLLOW UP REPORT | |
|---|---|
| Question 2. Has using the Disc for one month altered your initial assessment? | 85% No |
| Question 3. Has it modified your drug administration at any time? | 43% Yes<br>51% No<br>(6% irrelevant) |
| Question 5. Do you think it may have value in teaching? | 80% Yes<br>15% No<br>(5% irrelevant) |

TABLE 26 United Kingdom Trial, Follow Up Report : analysis of answers. Participants who found Questions 3 and 5 irrelevant were those who neither administered drugs nor had the opportunity of teaching.

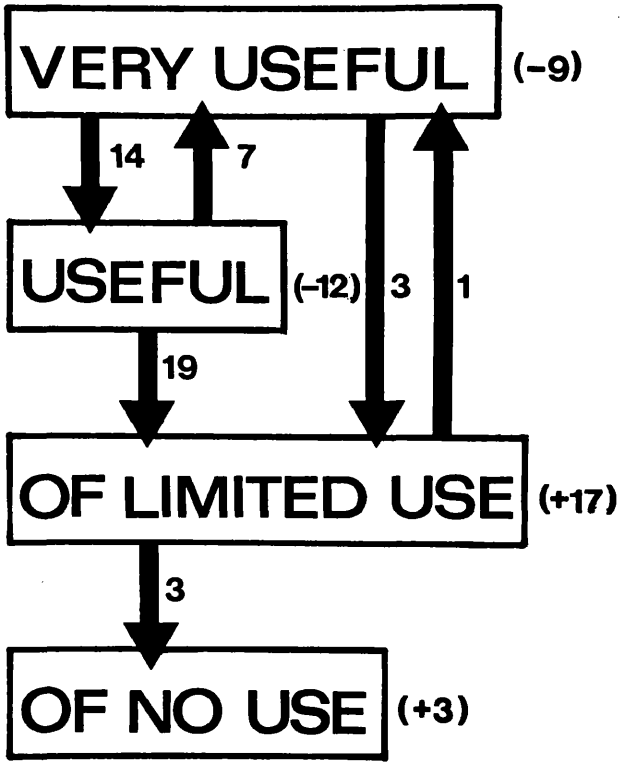



FIGURE 63 United Kingdom Trial : details of the participants revising their opinion of the Drug Disc during the course of the trial. Total number = 47 (21% of Follow Up Reports). Net changes are shown in parenthesis.

| Assessment | Total number of opinions expressed in PHASE 1 | Net change after one month | Revised opinion | Opinions expressed in PHASE 3 | Total number of opinions expressed in all phases |
|---|---|---|---|---|---|
| VERY USEFUL | 114 (40%) | -9 | 105 | 39 | 144 (39%) |
| USEFUL | 128 (45%) | -12 | 116 | 44 | 160 (43%) |
| OF LIMITED USE | 37 (13%) | +17 | 54 | 12 | 66 (17%) |
| OF NO USE | - | +3 | 3 | - | 3 ( 1%) |

TABLE 27 United Kingdom Trial : changes in assessment of the value of the Drug Disc throughout the trial period.

illustrates the effects of this change, and of the opinions expressed in Phase 3, on the final overall assessment of the value of the Disc.

These changes in rating could not take account of those participants who completed Phase 1 but failed to complete subsequent phases. However, the available data indicated that very little change in assessment occurred over the trial period, 82% completing all phases rating the Disc useful or very useful (Table 28).

Again, the group who thought that the Disc would be of limited use or of no use were largely represented by doctors using drugs in specialised circumstances, such as obstetrics, paediatrics and anaesthetics.

Some modification of drug administration attributable to the Disc during the trial period was reported by 43% of participants, and 80% considered that it would be of value in teaching (Table 26.)

### 6.4.3. Recommendations

It was obvious from the response that many of the participants had considered the Disc very carefully, and a number of valuable suggestions were made under "any further comments". These can be summarised as follows:

(a) Size The Disc would benefit from a slight reduction in diameter, which would enable it to fit into most pockets.

(b) Construction Mechanically linking the smaller discs so that they rotated together might simplify its use. Only one operation would then be required to look up interactions occurring with drugs on the periphery of the Disc.

(c) Key system Improvement in the meaning of the key system might be gained by some elaboration of the words "potentiated" and "inhibited". The logic of the key system appeared to be

| | ASSESSMENT | | | |
|---|---|---|---|---|
| | INITIAL | | FINAL | |
| VERY USEFUL | 40% | 85% | 39% | 82% |
| USEFUL | 45% | | 43% | |
| OF LIMITED USE | 13% | | 17% | |
| OF NO USE | - | | 1% | |
| RESERVED COMMENT | 2% | | - | |

TABLE 28 United Kingdom Trial : comparison of the initial and final assessments of the value of the Drug Disc.

satisfactory, but "potentially serious interactions" could be indicated by a more distinct symbol or colour.

(d) Content The information given on the Disc was in general thought to be relevant to clinical practice, but more guidance should be given as to whether an interaction was clinically significant or not. This suggested the introduction of another category to show interactions which were of "doubtful clinical significance", e.g. interactions based on animal data which cannot be extrapolated directly to man, interactions derived from in vitro data which may not be related to conditions in vivo, interactions demonstrated in single-dose experiments in healthy volunteers, the results of which may not be relevant for patients on chronic dosage schedules, and interactions based on relatively poor scientific evidence - small patient or volunteer samples and single "case reports".

The validity of certain interactions was questioned and the inclusion of others suggested.

Doctors engaged in certain specialities, notably obstetrics, paediatrics and anaesthetics, considered that the Disc was too general in its application and suggested the development of similar Discs which would relate solely to their own clinical situation. As interactions with general anaesthetics was a major subject in itself, it was suggested that "general anaesthetics" was too broad a category to be included and should, therefore, be removed from the Disc.

(e) Proprietary names Many general practitioners made a plea for the inclusion of proprietary names, particularly where drug categories such as tricyclic antidepressants and anticholinergics were indicated. A separate "G.P. version" of the Disc was also suggested.

(f) Companion text Many participants suggested that a small booklet containing explanatory notes and reference sources could accompany the Disc. It was also suggested that a more comprehensive survey of drug interactions with appropriate references could be linked to the Disc.

## 6.5. DISCUSSION

It was very gratifying to obtain an overall trial response of 70%, as this yielded a great deal of useful information and comment which could then be incorporated into a final version of the Disc. Bearing in mind that the different groups involved in the Trial were of unequal size, the experts, pharmacists and general practitioners proved the most responsive, complementing the interest displayed in the Disc subsequent to its first publication. The response of the miscellaneous group (85%) was high because most of this group had expressed a particular interest in the Disc and had offered to participate in the Trial. There was little variation in the response of hospital doctors throughout Scotland (overall 62%) and the variation of 45% to 83% in individual hospitals in the Glasgow area could be partly attributable to the different numbers involved.

A market research survey of this kind with results based on a voluntary return can often fail to elicit a satisfactory response, but in general, this was not the case in this Trial. Phase 3 increased the response from 48% to 70% and was therefore an important component.

A review of answers to specific questions, comments, suggestions and criticisms indicated that the Disc had been received with obvious enthusiasm and would be of considerable value in practice. Certain modifications, however, were necessary, and would be incorporated into the final design, with the agreement of the Working Party. The Trial

had demonstrated the acceptance of the warning system in principle and its basic format. The most important modification would involve a reclassification of the interactions to distinguish clearly between those of clinical and those of doubtful clinical significance. Every interaction would be scrutinised and re-evaluated in the light of this new "doubtful clinical significance" category, which would be awarded a distinctive colour. Reference to clinically significant interactions shown in the key would be expanded to convey the concept of alteration in the therapeutic and/or toxic effect of one or other of the interacting drugs.

Having accepted that the amount of space on the small discs limited the number of primary ("red") drugs to sixteen (eight on each side), consideration would be given to suggestions about changes in these drugs which would stress the importance of certain interactions not shown on the Trial version.

The introduction of proprietary names would seriously compromise space and no further consideration would be given to this suggestion.

As the Disc was designed to be a convenient and rapid source of information, any booklet giving details of drug interaction mechanisms and associated references would be somewhat superfluous and would defeat the basic objective of the system. But a small explanatory booklet outlining the rationale and operation of the Disc, with selected reference sources would undoubtedly enhance its use. The booklet could also stress that the Disc was not intended to be a complete compilation of drug interactions or a definitive authority for clinical use. An interaction revealed by a symbol or the presentation of information which might question the therapeutic value of a proposed regimen should induce confirmation of such facts before proceeding further with the medication. In this context, it would be appropriate to associate it with a national publication such as the British National Formulary.

The Trial had exposed the rather stark quality of the words used to describe the outcome of an interaction - drug "potentiated" or "inhibited" - and it had also been suggested that these words carried a somewhat strict pharmacological connotation, not ideally suited to a wide clinical setting. As these categories would be reserved for interactions of "clinical significance" on the final version of the Disc, the words "potentiated" and "inhibited" could well be re-appraised and replaced by terms which would be more clinically meaningful.

The concept of linking the smaller discs so that they would act as a single unit was an attractive one. It would, however, lead to some complications in construction and might eventually result in erroneous information if any disturbance in alignment occurred. But this idea did stress the importance of rapid identification of the position of the same "black" drug on each side of the large disc and moreover, emphasised that the Disc's acceptability would be enhanced by any measure which simplified its use.

The results of the Trial testified to the value of a drug interaction warning system, and, subject to the modifications discussed, confirmed that the Drug Disc would fulfil the necessary requirements.

# CHAPTER 7

## FINAL DEVELOPMENT OF THE DRUG INTERACTION WARNING SYSTEM

# 7. FINAL DEVELOPMENT OF THE DRUG INTERACTION WARNING SYSTEM

## 7.1. ADOPTION OF MODIFICATIONS

As the trial had produced such encouraging results, the Working Party had no hesitation in sanctioning further work on the project and recommended the formulation of a final version of the Disc with appropriate modifications.

The following were agreed on in principle:

1. Slight reduction in diameter.
2. Linkage of the small discs.
3. Re-evaluation of all interactions and introduction of a "doubtful clinical significance" category, signified by a distinctive colour.
4. Improvement of the reference in the key to the results of an interaction.
5. No change in the symbol for "potentially serious interactions".
6. Substitution of some primary ("red") drugs with alternatives which were of greater clinical significance than those shown on the Trial Disc. This would also involve readjustment of drugs on the large disc.

## 7.2. RE-EVALUATION OF DRUG INTERACTIONS

All interactions were re-evaluated and assigned to one of three categories according to the following broad considerations:

1. CLINICALLY SIGNIFICANT INTERACTIONS

   Interactions which were known to alter the pharmacological activity of one or both drugs in a combination, either enhancing or diminishing the therapeutic and/or toxic effects of the

drugs concerned. Once recognised and understood, many such interactions could be allowed for by intelligent adjustment of dosage or dosing interval.

2. INTERACTIONS OF DOUBTFUL CLINICAL SIGNIFICANCE

Interactions which had not, apparently, caused any significant harm in man. Many such interactions had been demonstrated in vitro or in animal experiments but seemed to have little relevance to the clinical situation.

3. POTENTIALLY SERIOUS INTERACTIONS

Interactions which were well documented as having harmful effects in man. This would serve to indicate that such combinations should be used with extreme caution, if at all.

## 7.3. FINAL VERSION OF THE DRUG INTERACTION WARNING SYSTEM

The final version, drafted by the present author and printed by Mr. P.S. Waldie, is illustrated in Figures 64 and 65. It measured 12.8 cm. in diameter and was constructed of thin but strong glossy cardboard. The smaller discs were linked at the centre and rotated together. The windows pointed in opposite directions when viewed from one side, (Figure 66) but when the disc was turned over in a horizontal direction (see arrows, Figure 66) the windows assumed identical positions and pointed at identical ("black") drugs. This necessitated printing the "black" drugs clockwise on one side and anticlockwise on the other side, (Figure 67) so that the windows would "track" the same drug simultaneously.

Details of the large disc, shown in Figures 64 and 65 reveal that a considerable number of interactions were "down graded" to a new category of "doubtful clinical significance", indicated by a green colour. Several changes in the "red" drugs were effected to highlight a number of

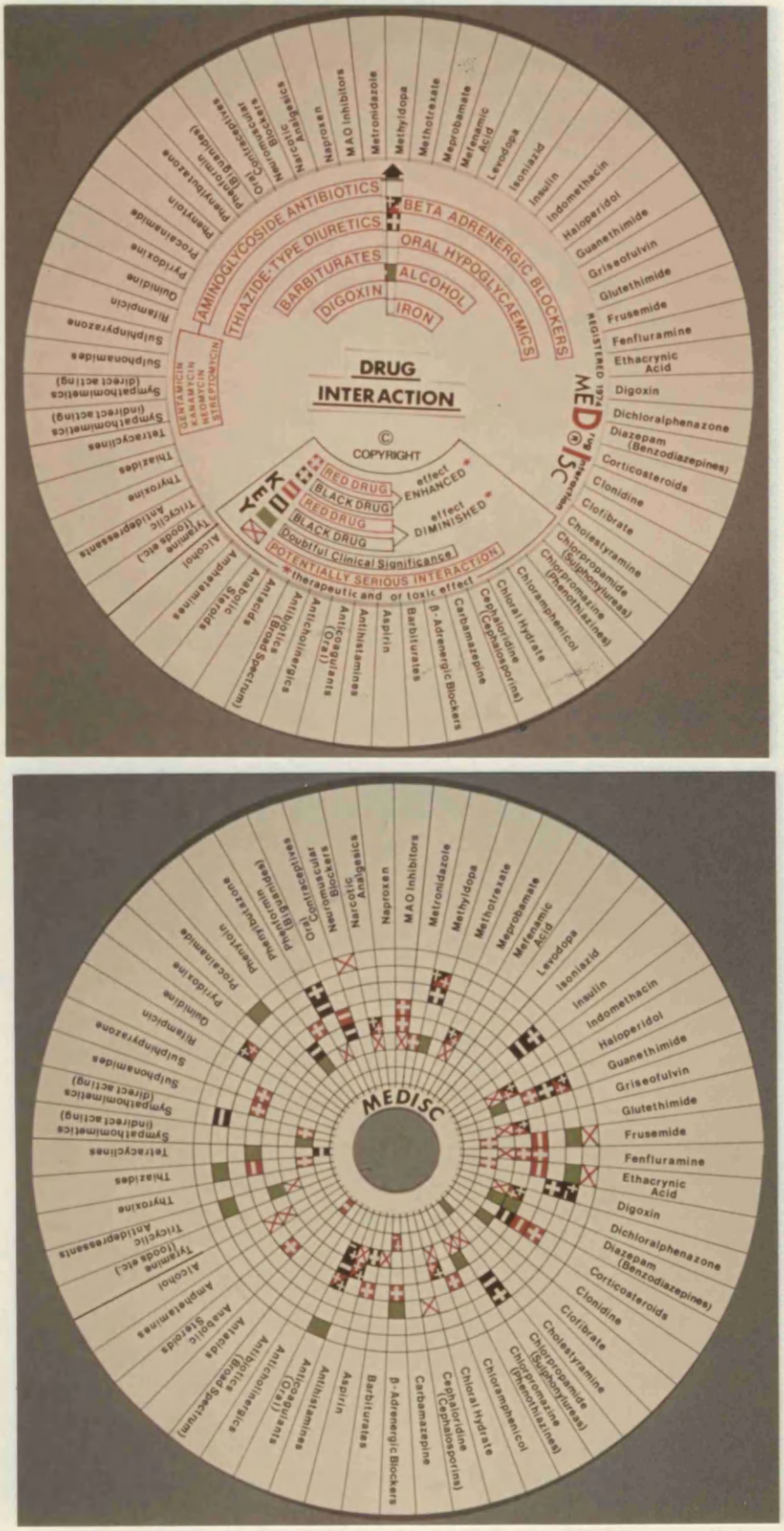



FIGURE 64 Draft of the final version of the Drug Disc : Side I, with detail of the large disc.

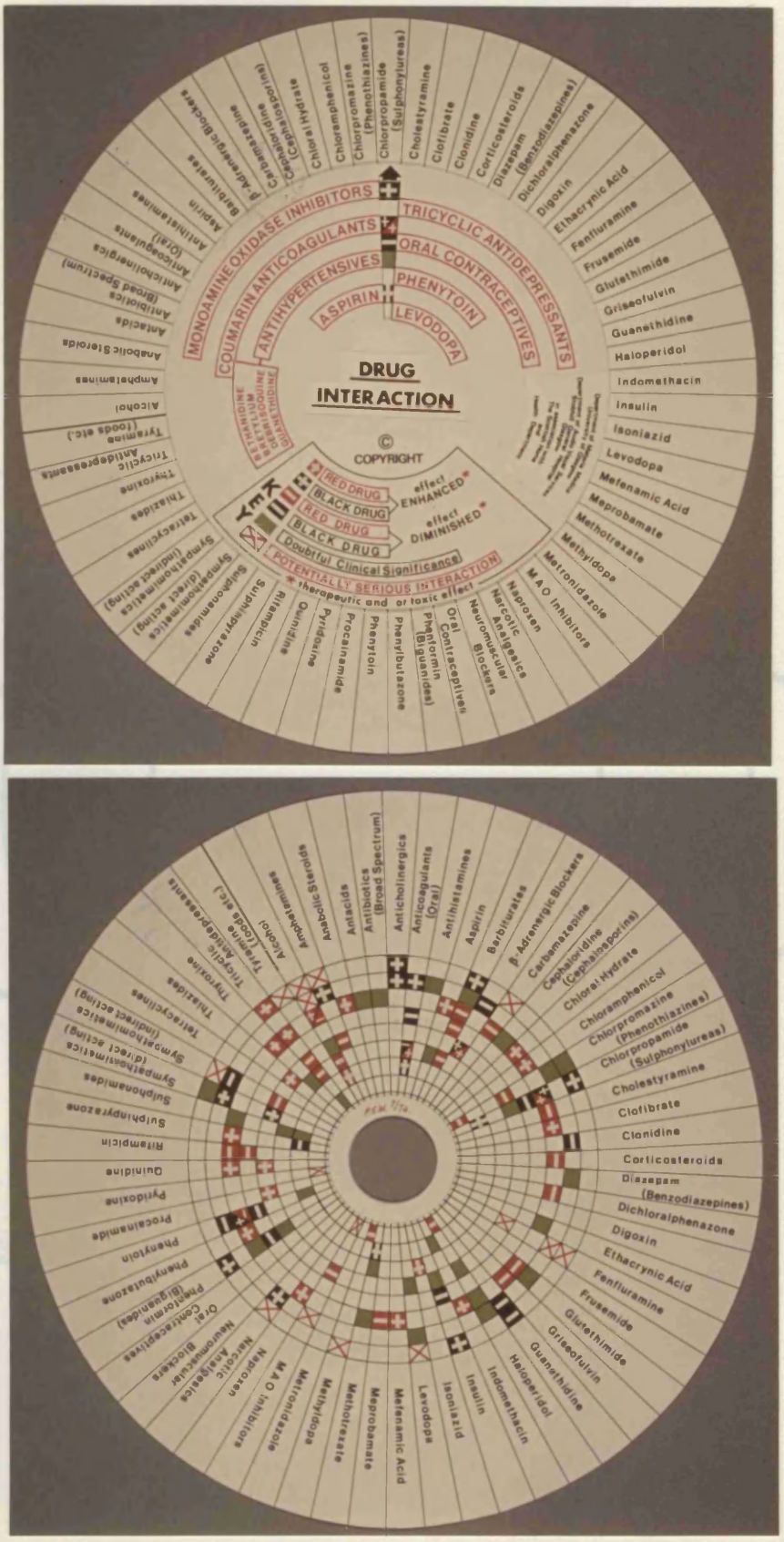



FIGURE 65 Draft of the final version of the Drug Disc : Side 2, with detail of the large disc.

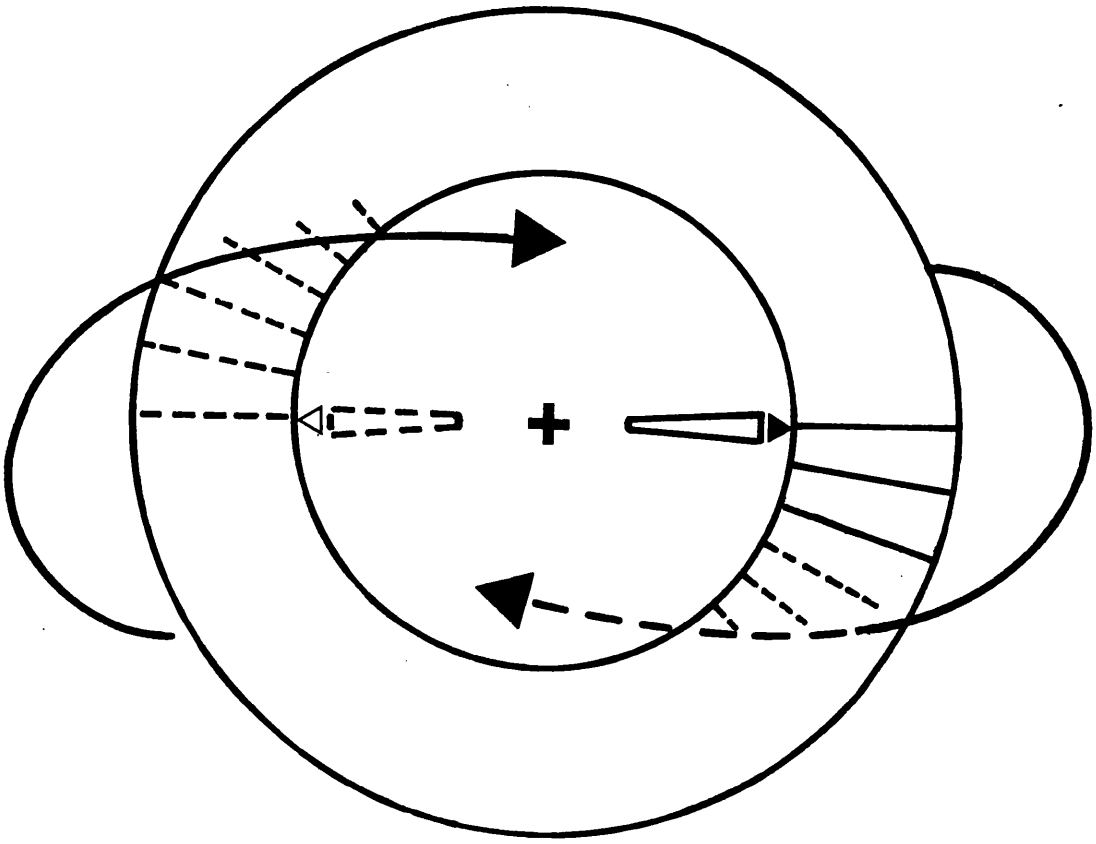


FIGURE 66 Details of the design of the final version of the Drug Disc, showing the relative position of the windows on each side.
Turned horizontally, as indicated by the arrows, the window and/or the peripheral drug at which it points, assume the same position.

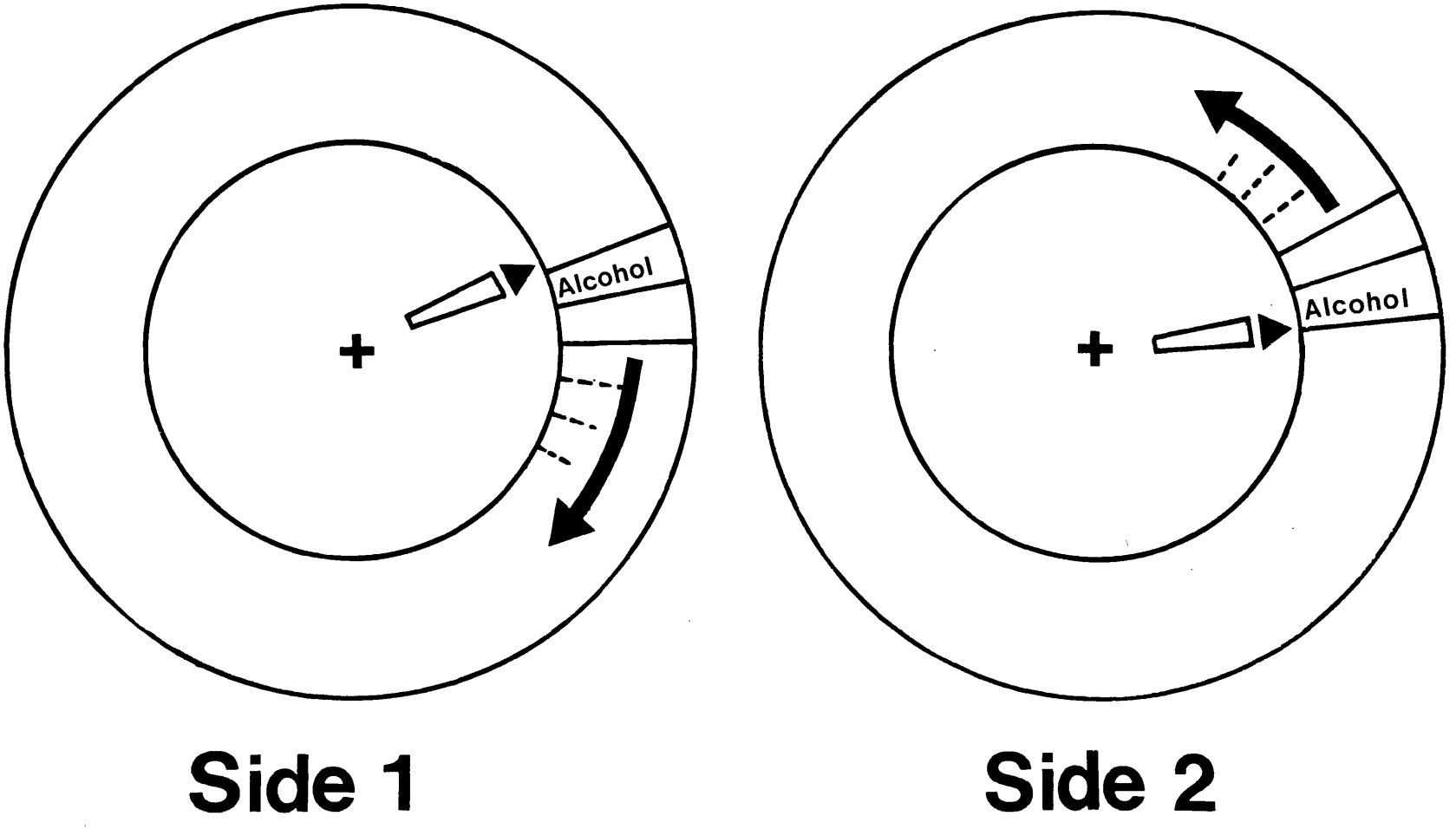



FIGURE 67 Details of the design of the final version of the Drug Disc, showing the order of printing of drugs on each side of the large disc. This is meant to illustrate the principle used; "Side 1" and "Side 2" do not necessarily refer to the final production version.

interactions which deserved this prominent position. Thus, digoxin, iron, levodopa, and thiazide-type diuretics displaced allopurinol, antacids, corticosteroids and phenothiazines. Table 29 shows the final list of "red"drugs. No significance was attached to the order in which these drugs appeared. It was dictated by the space available in the arcs, which diminished towards the centre of the small discs.

As can be seen in Figures 64 and 65 the words "potentiated" and "inhibited" were replaced by "effect enhanced" and "effect diminished", with a subscript reference to therapeutic and/or toxic effect, which carried a much more meaningful clinical connotation than "potentiated" and "inhibited".

Assignation of interactions to one of the three categories depended on the considerations already discussed, supported by opinions expressed by members of the Working Party and by doctors and pharmacists participating in the trial.

The importance of keeping an open mind on the category in which an interaction was placed must be stressed. It would be wrong to allow consideration of an interaction per se to obscure the other factors which determine the overall response of a patient to a drug or combination of drugs. Even when specific interactions can be predicted, the clinical consequences will be the result of the interplay of all these factors, as discussed in Chapter 3 of this thesis. The inclusion of interactions of "doubtful clinical significance" also underlines the impossibility of providing a complete and authoritative guide and stresses the need for regular review and revision of the system whenever necessary.

## 7.4. PRODUCTION AND WORLDWIDE DISTRIBUTION

Her Majesty's Stationery Office had been invited to participate in the project from the outset and had subsequently undertaken to print and

| | |
|---|---|
| AMINOGLYCOSIDE ANTIBIOTICS | MONOAMINE OXIDASE INHIBITORS |
| BETA ADRENERGIC BLOCKERS | TRICYCLIC ANTIDEPRESSANTS |
| THIAZIDE-TYPE DIURETICS | COUMARIN ANTICOAGULANTS |
| ORAL HYPOGLYCAEMICS | ORAL CONTRACEPTIVES |
| BARBITURATES | ANTIHYPERTENSIVES |
| ALCOHOL | PHENYTOIN |
| DIGOXIN | ASPIRIN |
| IRON | LEVODOPA |

TABLE 29 Final list of drugs shown on the small discs.

manufacture the Trial version of the Disc. It had been intended that H.M.S.O. should thereafter maintain a continuing interest in the project and arrange for the printing, manufacture and distribution of the final version throughout the United Kingdom. Unfortunately, a number of problems, including a printers' strike, precluded this, and alternative arrangements had to be made.

Many international pharmaceutical and advertising companies had offered to distribute the Disc throughout the world, but the professional and ethical considerations already presented obviated any direct association of this kind. However, an association with a reputable international publishing company specialising in medical literature had been recommended, and this encouraged further exploration of an approach made by the Excerpta Medica Foundation. This approach had initially taken the form of a request to obtain exclusive distribution rights for the Drug Disc in the United States and it was subsequently established that Excerpta Medica was prepared to promote the Drug Disc on a worldwide scale, not only in English, but also in Spanish, German, French, Italian, etc. A promotion plan drawn up by Excerpta Medica, based on private market research, indicated that other groups in addition to doctors and pharmacists, such as dentists, nurses and other paramedical health personnel had expressed interest in the Disc. The plan included distribution via third parties and it was suggested that the following organisations should be considered:

1. The World Medical Association and all national medical associations.
2. National and international specialist associations.
3. National and international pharmaceutical associations.
4. The international Hospital Federation and its national affiliates.
5. National Ministries of Public Health and National Health Services (e.g. the Department of Health and Social Security in

England and the Scottish Home and Health Department).

6. The World Health Organisation.

7. The International Red Cross Scoiety (I.R.C.S), national members in Western Countries and equivalents of the I.R.C.S. in the Middle East and Far East.

8. National and International Dental Associations.

If this pattern of dissemination was not feasible in certain areas, consideration should then be given to distribution via local pharmaceutical industries, provided that the Disc was not used as a vehicle for advertising material.

The plan also pointed out that there were approximately two million potential users of the Disc throughout the world, as detailed in Table 30, but no meaningful indication of the eventual response could be given.

An initial meeting with representatives from Excerpta Medica (Mr. James Cauverien, Director, and Mr. Jaap van Manen, then Deputy Director, now Director,) established that any agreement with the publishing company would include the supply of a large number of Discs free of charge to the Scottish Home and Health Department. This would satisfy the principle aim of the Working Party - to effect a free distribution of the Disc to all doctors working in the National Health Service.

Subsequent negotiations resulted in an agreement whereby Excerpta Medica will produce and publish the Disc throughout the world under licence for an initial period of ten years and will provide 60,000 free copies for distribution throughout the National Health Service.

On completion of the agreement, the draft shown in Figures 64 and 65 was transferred to the American division of Excerpta Medica. Its format and content were scrutinised and approved by a number of American medical and pharmaceutical experts, but it was felt that the two smaller discs should be allowed to rotate independently. This would make the user responsible for alignment of the discs and would circumvent the

| | DOCTORS | PHARMACISTS |
|---|---|---|
| Africa | 52,000 | 14,000 |
| Canada | 35,000 | 11,500 |
| U.S.A. | 326,000 | 138,000 |
| South America | 140,000 | 23,000 |
| Central America | 48,000 | 2,700 |
| Japan | 125,000 | 65,000 |
| Asia (excluding Communist China and the U.S.S.R.) | 237,000 | 52,000 |
| Europe | 749,000 | 154,000 |
| Australasia | 20,000 | 1,000 |
| Oceania | 1,000 | 100 |
| Total | 1,733,000 | 461,300 |

TABLE 30 Geographical distribution of potential users of the Drug Disc (compiled by Excerpta Medica from the W.H.O. Statistics Annual, 1970 (published 1974), extrapolated to 1974 on the basis of the increase in the number of doctors and pharmacists between 1960 and 1970).

risk of faulty information arising from misalignment due to any mechanical failure in the linkage.

The final version produced by Excerpta Medica is shown in Figures 68 and 69. Each side is identified by the Roman numerals I and II, contained in an arrow, which serves to indicate the direction of the alphabetical order of the drugs on each side of the large disc. American spelling is used because this particular Disc is intended primarily for use in the U.S.A. Appropriate adjustments in spelling will be made for other English speaking countries such as Australia, New Zealand, South Africa and the United Kingdom. The latest example is presented with this thesis.

Each Disc will be accompanied by a guide to its use in the form of a small descriptive booklet, which will also indicate useful reference sources and the criteria which determined selection of the information presented on the Disc. Distribution within the United Kingdom, planned for early 1976, will be followed by worldwide distribution.

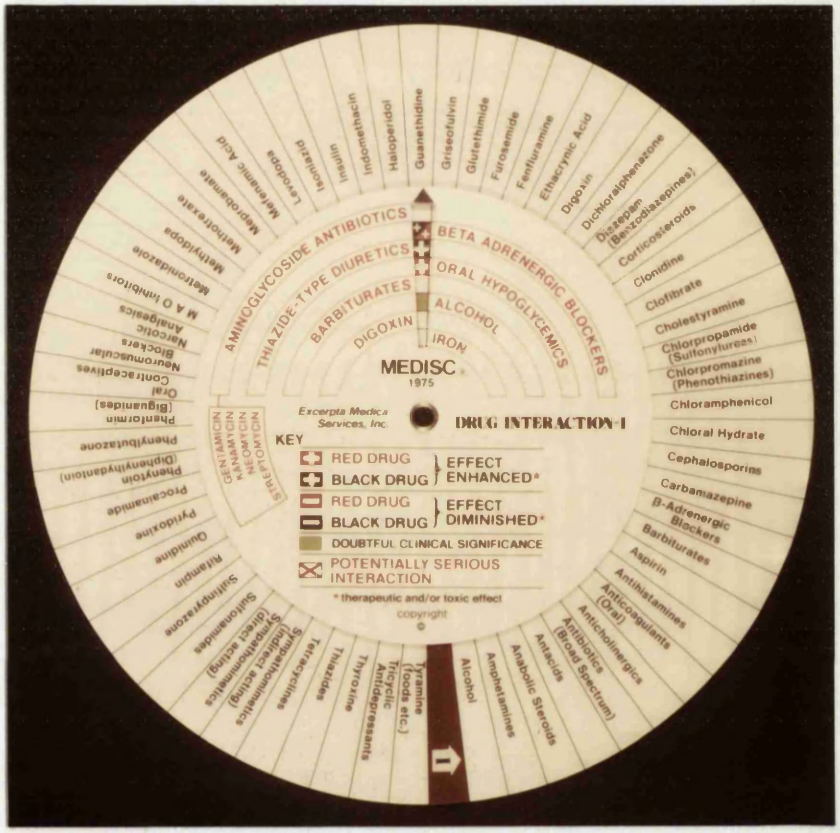



FIGURE 68 Final version of the Drug Disc, Side I.

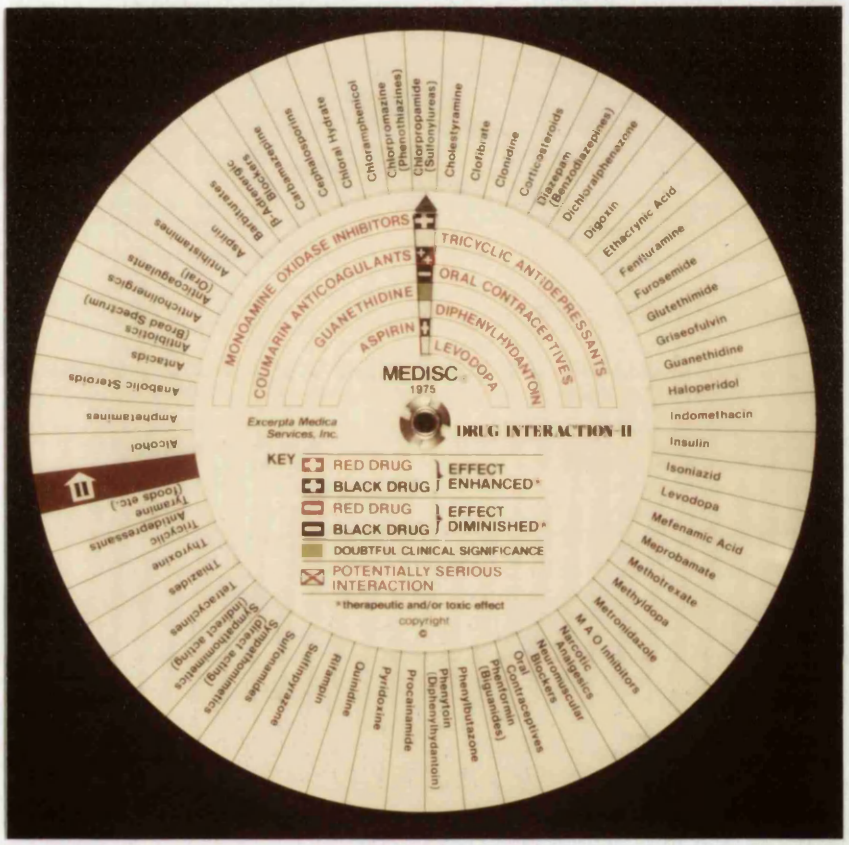



FIGURE 69 Final version of the Drug Disc, Side 2.

# CHAPTER 8

# CONCLUSIONS

CONCLUSIONS.

1. The increasing number of drugs prescribed for individual patients complicates modern therapeutics by presenting the opportunity for drug interactions to develop.

2. Drug interactions are one of the important factors which determine drug response in man. Unlike genetic and pathophysiological factors, which also make important contributions to this response, drug interactions are often the consequence of therapeutic decisions made by the doctor and sometimes by the patient. Many interactions, therefore, are avoidable.

3. An increased awareness of the problems associated with multiple drug therapy is desirable and can be effected by the presentation of clinically relevant drug interaction information which should be available whenever therapy is prescribed.

4. A drug interaction warning system - the Drug Disc - has been developed to provide this kind of information in as concise and convenient a form as possible.

5. A trial of the warning system in the United Kingdom and subsequent consumer research in other countries have confirmed the value of this system, both as a practical aid in prescribing and in teaching.

6. The degree of interest and enthusiasm stimulated by the Drug Disc reflects the problems implicit in modern multiple drug therapy and suggests that its worldwide distribution is warranted. It is hoped that it will contribute to safer, more rational prescribing.

# REFERENCES

REFERENCES

Abramson, E.A., Arky, R.A. and Woeber, K.A. (1966) Effects of propranolol on the hormonal and metabolic responses to insulin-induced hypoglycaemia. Lancet, 2, 1386-1388.

Abramson, E.A. and Arky, R.A. (1968) Role of beta-adrenergic receptors in counterregulation to insulin-induced hypoglycaemia. Diabetes, 17, 141-146.

Adjepon-Yamoah, K.K., Scott, D.B. and Prescott, L.F. (1973) Impaired absorption and metabolism of oral lignocaine in patients undergoing laparoscopy. British Journal of Anaesthesia, 45, 143-147.

Affrime, M. and Reidenberg, M.M. (1973) The binding of drugs to plasma from patients with cirrhosis. Pharmacologist, 15, 207.

Affrime, M. and Reidenberg, M.M. (1975) The protein binding of some drugs in plasma from patients with alcoholic liver disease. European Journal of Clinical Pharmacology, 8, 267-269.

Aggeler, P.M., O'Reilly, R.A., Leong, L. and Kowitz, P.E. (1967) Potentiation of anticoagulant effect of warfarin by phenylbutazone. New England Journal of Medicine, 276, 496-501.

Aggeler, P.M. and O'Reilly, R.A. (1969) Effect of heptabarbital on the response to bishydroxycoumarin in man. Journal of Laboratory and Clinical Medicine, 74, 229-238.

Alexanderson, B., Sjöqvist, F. and Price Evans, D.A. (1969) Steady-state plasma levels of nortriptyline in twins : Influence of genetic factors and drug therapy. British Medical Journal, 4, 764-768.

American Pharmaceutical Association. (1973a) In Evaluations of Drug Interactions - 1973, 1st ed., p.172. Washington : American Pharmaceutical Association.

American Pharmaceutical Association (1973b) In Evaluations of Drug Interactions - 1973, 1st ed., pp. 38-40. Washington : American Pharmaceutical Association.

Annotations (1967) Propranolol. Lancet, 1, 939-940.

Anton, A.H. and Corey, W.T. (1971) Interindividual differences in the protein binding of sulphonamides : the effect of disease and drugs. Acta Pharmacologica et Toxicologica, 29, 134-151.

Åsberg, M., Cronholm, B., Sjöqvist, F. and Tuck, D. (1970) The correlation of subjective side effects with plasma concentrations of nortriptyline. British Medical Journal, 4, 18-21.

Åsberg, M., Cronholm, B., Sjöqvist, F. and Tuck, D. (1971) Relationship between plasma level and therapeutic effect of nortriptyline. British Medical Journal, 3, 331-334.

Beckett, A.H. and Cowan, D.A. (1972) Digoxin problems. Pharmaceutical Journal, 209, 174.

Berman, M. and Weiss, M.F. (1968) Users Manual for SAAM. National Institute for Arthritis and Metabolic Diseases, Bethesda, Maryland.

Binnion, P.F. and McDermott, M. (1972) Bioavailability of digoxin. Lancet, 2, 592.

BMD Biomedical Computer Programs, (1968) ed. Dixon, W.J., Berkeley and Los Angeles : University of California Press.

Block, L.H. and Lamy, P.P. (1968) Therapeutic incompatibilities of legend drugs with o-t-c drugs. Journal of the American Pharmaceutical Association, NS 8, 66-84.

Block, L.H. and Lamy, P.P. (1969) Drug interactions with emphasis on o-t-c drugs. Journal of the American Pharmaceutical Association, NS 9, 202-207.

Bloom, P.M. and Nelp, W.B. (1966) Relationship of the excretion of tritiated digoxin to renal function. American Journal of Medical Sciences, 251, 133-144.

Bolt, H.M., Kappus, H. and Bolt, M. (1975) Effect of rifampicin treatment on the metabolism of oestradiol and 17 α-ethinyloestradiol by human liver microsomes. European Journal of Clinical Pharmacology, 8, 301-307.

Boston Collaborative Drug Surveillance Program (1972) Adverse drug interactions. Journal of the American Medical Association, 220, 1238-1239.

Breckenridge, A. and Orme, M.L'E. (1971) Clinical implications of enzyme induction. Annals of the New York Academy of Sciences, 179, 421-431.

Breckenridge, A. Orme, M.L'E., Thorgeirsson, S., Davies, D.S. and Brooks, R.V. (1971) Drug interactions with warfarin : studies with dichloralphenazone, chloral hydrate and phenazone (antipyrine). Clinical Science, 40, 351-364.

Breckenridge, A. and Orme, M. L'E. (1972) The plasma half-lives and the pharmacological effect of the enantiomers of warfarin in rats. Life Sciences, 11, (Part 2), 337-345.

Briant, R.H., Reid, J.L. and Dollery, C.T. (1973) Interaction between clonidine and desipramine in man. British Medical Journal, 1, 522-523.

British Medical Association (1950) Patenting in its relation to the medical profession. British Medical Journal, Suppl., 1, 276.

British Medical Association (1970) The doctor and commercial undertakings. In Medical Ethics, pp 26-29. London : British Medical Association.

Brodie, B.B., Axelrod, J., Soberman, R. and Levy, B.B. (1949) The estimation of antipyrine in biological materials. Journal of Biological Chemistry, 179, 25-29.

Brodie, B.B. and Axelrod, J. (1950) The fate of antipyrine in man. Journal of Pharmacology and Therapeutics, 98, 97-104.

Brodie, B.B., Gillette, J.R. and La Du, B.N. (1958) Enzymatic metabolism of drugs and other foreign compounds. Annual Review of Biochemistry, 27, 427-454.

Brooks, P.M., Bell, M.A., Sturrock, R.D., Famaey, J.P. and Dick, W.C. (1974) The clinical significance of indomethacin-probenecid interaction. British Journal of Clinical Pharmacology, 1, 287-290.

Brownlee G. and Williams, G.W. (1963) Potentiation of amphetamine and pethidine by monoamine oxidase inhibitors. Lancet, 1, 669.

Cascorbi, H.F., Vessell, E.S., Blake, D.A. and Helrich, M. (1971) Genetic and environmental influence on halothane metabolism in twins. Clinical Pharmacology and Therapeutics, 12, 50-55.

Christensen, L.K., Hansen, J.M. and Kristensen, M. (1963) Sulphaphenazole-induced hypoglycaemic attacks in tolbutamide-treated diabetics. Lancet, 2, 1298-1301.

Clinite, J.C. and Kabat, H.F. (1969) Errors during self-administration. Journal of the American Pharmaceutical Association, NS 9, 450-452.

Committee on Safety of Drugs (1965) Annual Report of the Committee on Safety of Drugs, p.14.

Conney, A.H. (1967) Pharmacological implications of microsomal enzyme induction. Pharmacological Reviews, 19, 317-366.

Conney, A.H. (1969) Drug metabolism and therapeutics. New England Journal of Medicine, 280, 653-660.

Conney, A.H. and Burns, J.J. (1962) Factors influencing drug metabolism. Advances in Pharmacology, 1, 31-58.

Conney, A.H., Welch, R.M., Kuntzman, R. and Burns, J.J. (1967) Effects of pesticides on drug and steroid metabolism. Clinical Pharmacology and Therapeutics, 8, 2-10.

Consolo, S., Morselli, P.L., Zaccala, M. and Garattini, S. (1970) Delayed absorption of phenylbutazone caused by desmethylimipramine in humans. European Journal of Pharmacology, 10, 239-242.

Crooks, J., Clark, C.G., Caie, H.B. and Mawson, W.B. (1965) Prescribing and administration of drugs in hospital. Lancet, 1, 373-378.

Crooks, J., Weir, R.D., Coull, D.C., McNab, J.W., Calder, G., Barrett, J.W. and Caie, H.B. (1967) Evaluation of a method of prescribing drugs in hospital, and a new method of recording their administration. Lancet, 1, 668-671.

Cucinell, S.A., Conney, A.H. and Sansur, M. (1965) Drug interactions in man. 1. Lowering effect of phenobarbitone on plasma levels of bishydroxycoumarin (Dicoumarol) and diphenylhydantoin (Dilantin). Clinical Pharmacology and Therapeutics, 6, 420-429.

Cuthbert, M.F., Greenberg, M.P. and Morley, S.W. (1969) Cough and cold remedies : Potential danger to patients on monoamine oxidase inhibitors. British Medical Journal, 1, 404-406.

Dally, P.J. (1962) Fatal reaction associated with tranylcypromine and methylamphetamine. Lancet, 1, 1235-1236.

Davidson, C. and Gibson, D. (1973) Clinical significance of positive inotropic action of digoxin in patients with left ventricular disease. British Heart Journal, 35, 970-976.

Davison, W. (1972) Unwanted drug effects in the elderly. In Drug Induced Diseases, ed. Meyler, L. and Peck, H.M. Vol.4 Ch. 28. Amsterdam : Excerpta Medica.

Dettli, L. (1970a) Multiple dose elimination kinetics and drug accumulation in patients with normal and with impaired kidney function. In Advances in the biosciences, 5, 39-54. ed. Raspé, G. Oxford, New York and Braunschweig : Pergamon Press and Vieweg.

Dettli, L. (1970b) Drug dosage in patients with impaired kidney function. Postgraduate Medical Journal, 46, Suppl. 32-35.

Dettli, L., Spring, P. and Ryter, S. (1971) Multiple dose kinetics and drug dosage in patients with kidney disease. Acta Pharmacologica et Toxicologica, 29, Suppl. 3, 211-224.

Diamond, L.K., Naiman, J.L., Allen, D.M. and Oski, F.A. (1963) The treatment of iron-deficiency anaemia - palatable but ineffective iron medication. Pediatrics, 31, 1041-1044.

Doherty, J.E. and Flanigan, W.J. (1967) Studies with tritiated digoxin in anephric human subjects. Circulation, 35, 298-303.

Dollery, C.T. (1973) In Clinical Pharmacology, 4th edition, ed. Laurence, D.R. p.6. 23. Edinburgh and London : Churchill Livingstone.

Doluisio, J.T. (1972) Panel discussion on case histories in bioavailability of drugs. Pharmacology, 8, 153-198.

Dunlop, D. (1970) Abuse of drugs by the public and by doctors. British Medical Bulletin, 26, 236-239.

Eales, L. and Linder, G.C. (1962) Porphyria - the acute attack. An analysis of 80 cases. South African Medical Journal, 36, 284-292.

Eisen, M.J. (1964) Combined effect of sodium warfarin and phenylbutazone. Journal of the American Medical Association, 189, 64-65.

Elbe, J.N., West, B.D. and Link, K.P. (1966) A comparison of the isomers of warfarin. Biochemical Pharmacology, 15, 1003-1004.

Elis, J., Laurence, D.R., Mattie, H. and Prichard, B.N.C. (1967) Modification by monoamine oxidase inhibitors of the effect of some sympathomimetics on blood pressure. British Medical Journal, 2, 75-78.

Field, J.B., Ohta, M., Boyle, C. and Remer, A. (1967) Potentiation of acetohexamide hypoglycaemia by phenylbutazone. New England Journal of Medicine, 277, 889-894.

Forney, R.B. and Harger, R.N. (1969) Toxicology of ethanol. Annual Review of Pharmacology, 9, 379-392.

Fotherby, K. (1973) Pharmacokinetics of contraceptive steroids in humans. In Pharmacology and the future of man, Proceedings of the 5th International Congress of Pharmacology, Vol. 1, pp. 230-239. Basel : Karger.

Fox, S.L. (1964) Potentiation of anticoagulants caused by pyrazole compounds. Journal of the American Medical Association, 188, 320-321.

Fraser, E.J., Leach, R.H. and Poston, J.W. (1972) Bioavailability of digoxin. Lancet, 2, 541.

Fraser, E.J., Leach, R.H., Poston, J.W., Bold, A.M., Culank, L.S. and Lipede, A.B. (1973) Dissolution and bioavailability of digoxin tablets. Journal of Pharmacy and Pharmacology, 25, 968-973.

Freyschuss, U., Sjöqvist, F. and Tuck, D. (1970) Tyramine pressor effects in man before and during treatment with nortriptyline or ECT : Correlation between plasma level and effect of nortriptyline. Pharmacologia Clinica, 2, 72-78.

Gessner, P.K., (1974) The isobolographic method applied to drug interactions. In Drug Interactions, ed. Morselli, P.L., Garattini, S. and Cohen, S.N. pp. 349-362. New York : Raven Press.

Gessner, P.K. and Cabana, B.E. (1970) A study of the interaction of the hypnotic effects and of the toxic effects of chloral hydrate and ethanol. Journal of Pharmacology and Experimental Therapeutics, 174, 247-259.

Glende, E.A. (1972) Carbon tetrachloride induced protection against carbon tetrachloride toxicity. The role of the liver microsomal drug - metabolising system. Biochemical Pharmacology, 21, 1697-1702.

Goldberg, L.I. (1964) Monoamine oxidase inhibitors. Adverse reactions and possible mechanisms. Journal of the American Medical Association, 190, 456-462.

Goldner, M.G., Zarowitz, H. and Akgun, S. (1960) Hyperglycaemia and glycosuria due to thiazide derivatives administered in diabetes mellitus. New England Journal of Medicine, 262, 403-405.

Goldstein, A., Aronow, L. and Kalman, S.M. (1969) In Principles of Drug Action. Ch. 2. pp.194-205. New York, Evanston and London : Harper and Row.

Goodman, L.S. and Gilman, A. (1970) In The Pharmacological Basis of Therapeutics, 4th ed., pp. 677-708. London, New York : Macmillan.

Gordon, N. (1964) The use of Ospolot in the treatment of epilepsy. Epilepsia, 5, 68-73.

Goss, J.E. and Dickhaus, D.W. (1965) Increased bishydroxycoumarin requirements in patients receiving phenobarbital. New England Journal of Medicine, 273, 1094-1095.

Gothoni, G. Pentikäinen, P., Vapaatalo, H.I., Hackman, R. and Björksten, K.A. (1972) Absorption of antibiotics : Influence of metoclopramide and atropine on serum levels of pivampicillin and tetracycline. Annals of Clinical Research, 4, 228-370.

Greenberger, N.J., Ruppert, R.D. and Cuppage, F.E. (1967) Inhibition of intestinal iron transport induced by tetracycline. Gastroenterology, 53, 590-599.

Gulati, O.D., Dave, B.T. Gokhale, S.D. and Shah, K.M. (1966) Antagonism of adrenergic neuron blockade in hypertensive subjects. Clinical Pharmacology and Therapeutics, 7, 510-514.

Halkin, H., Sheiner, L.B., Peck, G.C. and Melmon, K.L. (1975) Determinants of the renal clearance of digoxin. Clinical Pharmacology and Therapeutics, 17, 385-394.

Hammer, W. and Sjöqvist, F. (1967) Plasma levels of monomethylated tricyclic antidepressants during treatment with imipramine-like compounds. Life Sciences, 6, 1895-1903.

Hansen, J.M., Kristensen, M. and Skovsted, L. (1968) Sulthiame (Ospolot) as inhibitor of diphenylhydantoin metabolism. Epilepsia, 9, 17-22.

Hansten, P.D. (1973) Drug Interactions. Philadelphia : Lea and Febiger.

Hart, L.G. and Fouts, J.R. (1963) Effects of acute and chronic DDT administration on hepatic microsomal drug metabolism in the rat. Proceedings of the Society for Experimental Biology and Medicine. 114, 388-392.

Hasselblatt, A. (1972) Interactions of drugs at plasma protein binding sites. Proceedings of the European Society for the Study of Drug Toxicity, 13, 89-97.

Hay, G. (1962) Severe reaction to monoamine oxidase inhibitor in a dexamphetamine addict. Lancet, 2, 665.

Hayes, M.J., Langman, M.J.S. and Short, A.H. (1975a) Changes in drug metabolism with increasing age : 1. Warfarin binding and plasma proteins. British Journal of Clinical Pharmacology, 2, 69-72.

Hayes, M.J., Langman, M.J.S. and Short, A.H. (1975b) Changes in drug metabolism with increasing age : 2. Phenytoin clearance and protein binding. British Journal of Clinical Pharmacology, 2, 73-79.

Heading, R.C., Nimmo, J., Prescott, L.F. and Tothill, P. (1973) The dependence of paracetamol absorption on the rate of gastric emptying. British Journal of Pharmacology, 47, 415-421.

Hicks, B.H., Ward, J.D., Jarrett, R.J., Keen, H. and Wise, P. (1970) A controlled study of clopamide, clorexolone and hydrochlorothiazide in diabetes. European Journal of Clinical Investigation, 1, 134.

Hoddinott, B.C., Gowdey, C.W., Coulter, W.K. and Parker, J.M. (1967) Drug reactions and errors in administration on a medical ward. Canadian Medical Association Journal, 97, 1001-1006.

Hoffbrand, B.I. and Kininmonth, D.A. (1967) Potentiation of anticoagulants. British Medical Journal, 2, 838-839.

Hooper, W.D., Bochner, F., Eadie, M.J. and Tyrer, J.H. (1974) Plasma protein binding of diphenylhydantoin. Effect of sex hormones, renal and hepatic disease. Clinical Pharmacology and Therapeutics, 15, 276-282.

Horler, A.R. and Wynne, N.A. (1965) Hypertensive crisis due to pargyline and metaraminol. British Medical Journal, 2, 460-461.

Horowitz, D., Lovenberg, W., Engelman, K. and Sjoerdsma, A. (1964) Monoamine oxidase inhibitors, tyramine, and cheese. Journal of the American Medical Association, 188, 1108-1110.

Houghton, G.W. and Richens, A. (1973) Inhibition of phenytoin metabolism by sulthiame. British Journal of Pharmacology, 49, 157P - 158P.

Houghton, G.W. and Richens, A. (1974a) Inhibition of phenytoin metabolism by sulthiame in epileptic patients. British Journal of Clinical Pharmacology, 1, 59-66.

Houghton, G.W. and Richens, A. (1974b) Phenytoin intoxication induced by sulthiame in epileptic patients. Journal of Neurology, Neurosurgery and Psychiatry, 37, 275-281.

Humberstone, P.M. (1969) Hypertension from cold remedies. British Medical Journal, 1, 846.

Hurwitz, N. (1969) Predisposing factors in adverse reactions to drugs. British Medical Journal, 1, 536-539.

Hvidberg, E.F., Andreasen, P.B. and Ranek, L. (1974) Plasma half-life of phenylbutazone in patients with impaired liver function. Clinical Pharmacology and Therapeutics, 15, 171-177.

Ingram, T.T.S. and Ratcliffe, S.G. (1963) Clinical trial of Ospolot in epilepsy. Developmental Medicine and Child Neurology, 5, 313-316.

Iversen, L.L. (1971) Role of transmitter uptake mechanisms in synaptic neurotransmission. British Journal of Pharmacology, 41, 571-591.

Jefferys, M., Brotherston, J.H.F. and Cartwright, A. (1960) Consumption of medicines on a working-class housing estate. British Journal of Preventive and Social Medicine, 14, 64-76.

Jick, H. and Chalmers, T.C. (1964) Drug combinations - uses, dangers and fallacies. Clinical Pharmacology and Therapeutics, 5, 673-676.

Jick, H., Miettinen, O.S., Shapiro, S., Lewis, G.P., Siskind, V. and Slone, D. (1970) Comprehensive drug surveillance. Journal of the American Medical Association, 213, 1455-1460.

Johnson, B.F., Greer, H., McCrerie, J.A., Bye, C. and Fowle, A.S.E. (1973) Rate of dissolution of digoxin tablets as a predictor of absorption. Lancet, 1, 1473-1475.

Jounela, A.J. and Sothmann, A. (1973) Bioavailability of digoxin. Lancet, 1, 202-203.

Jounela, A.J., Pentikäinen, P.J. and Sothmann, A. (1975) Effect of particle size on the bioavailability of digoxin. European Journal of Clinical Pharmacology, 8, 365-370.

Kale, A.K. and Satoskar, R.S. (1970) Modification of the central hypotensive effect of alpha-methyldopa by reserpine, imipramine and tranylcypromine. European Journal of Pharmacology, 9, 120-123.

Kalow, W. (1962) Pharmacogenetics - Heredity and the Response to Drugs. Philadelphia, London : W.B. Saunders Co.

Kaplan, S.A., Lewis, M., Schwartz, M.A., Postma, E., Cotler, S. Abruzzo, C.W., Lee, T.L. and Weinfeld, R.E. (1970) Pharmacokinetic model for chlordiazepoxide HCL in the dog. Journal of Pharmaceutical Sciences, 59, 1569-1574.

Kater, R.M.H., Carulli, N. and Iber, F.L. (1969) Differences in the rate of ethanol metabolism in recently drinking alcoholic and nondrinking subjects. American Journal of Clinical Nutrition, 22, 1608-1617.

Kater, R.M.H., Roggin, G., Tobon, F., Zieve, P.D. and Iber, F.L. (1969) Increased rate of clearance of drugs from the circulation of alcoholics. American Journal of Medical Sciences, 258, 35-39.

Kessell, A., Williams, A.G., Young, T.D.C. and Jensen, G.R. (1967) Side effects with a new hypnotic : drug potentiation. Medical Journal of Australia, 2, 1194-1195.

Koch-Weser, J. (1974) Bioavailability of drugs. New England Journal of Medicine, 291, 233-237.

Koch-Weser, J. and Sellers, E.M. (1971) Drug interactions with coumarin anticoagulants. New England Journal of Medicine, part 1, 285, 487-498 and part 2, 285, 547-558.

Koechlin, B.A. and D'Arconte, L. (1963) Determination of chlordiazepoxide (Librium) and of a metabolite of lactam character in plasma of humans, dogs and rats by a specific spectrofluorometric micro method. Analytical Biochemistry 5, 195-207.

Koechlin, B.A., Schwartz, M.A., Krol, G. and Oberhaensli, W. (1965) The metabolic fate of $^{14}$C-labelled chlordiazepoxide in man, in the dog and in the rat. Journal of Pharmacology and Experimental Therapeutics, 148, 399-411.

Kolmodin, B. Azarnoff, D.L. and Sjöqvist, F. (1969) Effect of environmental factors on drug metabolism : Decreased plasma half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides. Clinical Pharmacology and Therapeutics, 10, 638-642.

Kolmodin-Hedman, B., Alexanderson, B. and Sjöqvist, F. (1971) Effect of exposure to lindane on drug metabolism. Decreased hexobarbital sleeping-times and increased antipyrine disappearance rates in rats. Toxicology and Applied Pharmacology, 20, 299-307.

Kotler, M.N., Berman, L. and Rubenstein, A.H. (1966) Hypoglycaemia precipitated by propranolol. Lancet, 2, 1389-1390.

Krisko, I., Lewis, E. and Johnson, J.E. (1969) Severe hyperpyrexia due to tranylcypromine-amphetamine toxicity. Annals of Internal Medicine, 70, 559-564.

Kunin, C.M. and Finland, M. (1961) Clinical pharmacology of the tetracycline antibiotics. Clinical Pharmacology and Therapeutics. 2, 51-69.

Kutt, H. and McDowell, F. (1968) Management of epilepsy with diphenylhydantoin sodium. Journal of the American Medical Association, 203, 969-972.

Lader, M.H., Sakalis, G. and Tansella, M. (1970) Interactions between sympathomimetic amines and a new monoamine oxidase inhibitor. Psychopharmacologia, 18, 118-123.

Lasagna, L. (1963-1964) The diseases drugs cause. Perspectives in Biology and Medicine, 7, 457.

Lassen, N.A. (1960) Treatment of severe acute barbiturate poisoning by forced diuresis and alkalinisation of the urine. Lancet, 2, 338-342.

La Veck, G.D., de la Cruz, F. and Thomas, D.B. (1962) Clinical evaluation of a new anticonvulsant, sulthiame. Neurology, 12, 923-928.

Lawson, D.H. (1974) Personal communication.

Leewy, C.M., Hove, W.T., Opper, A. and Popovie, S. (1970) Influence of ethanol and microsomal drugs on hepatic haemodynamics. Annals of the New York Academy of Sciences 170, 315-331.

Leishman, A.W.D., Matthews, H.L. and Smith, A.J. (1963) Antagonism of Guanethidine by Imipramine. Lancet, 1, 112.

Levine, R. (1970) Mechanisms of insulin secretion. New England Journal of Medicine, 283, 522-526.

Levy, G. (1970) Effect of protein binding on the distribution and metabolism of a highly protein bound drug (bishydroxycoumarin). In Proceedings, Fourth International Congress of Pharmacology, ed. Eigenmann, R. Vol. IV. p. 150. Basel, Stuttgart : Schwabe.

Levy, G. and Hollister, L.E. (1964) Inter- and intrasubject variations in drug absorption kinetics. Journal of Pharmaceutical Sciences, 53, 1446-1452.

Levy, G., O'Reilly, R.A., Aggeler, P.M. and Keech, G.M. (1970) Pharmacokinetic analysis of the effect of barbiturate on the anticoagulant action of warfarin in man. Clinical Pharmacology and Therapeutics, 11, 372-377.

Levy, G., Gibaldi, M. and Procknal, J.A. (1972) Effect of an anticholinergic agent on riboflavin absorption in man. Journal of Pharmaceutical Sciences, 61, 798-799.

Lewis, E. (1965) Hyperpyrexia with antidepressant drugs. British Medical Journal, 1, 1671-1672.

Lewis, R.J. (1966) Effect of barbiturates on anticoagulant therapy. New England Journal of Medicine, 274, 110.

Lewis, R.J. and Trager, W.F. (1971) The metabolic fate of warfarin : studies on the metabolites in plasma. Annals of the New York Academy of Sciences, 179, 205-212.

Lewis, R.J., Trager, W.F., Chan, K.K., Breckenridge, A., Orme, M.L'E., Roland, M. and Schary, W. (1974) Warfarin, stereochemical aspects of its metabolism and the interaction with phenylbutazone. The Journal of Clinical Investigation, 53, 1607-1617.

Liegler, D.G., Henderson, E.S., Hahn, M.A. and Oliverio, V.T. (1969) The effect of organic acids on renal clearance of methotrexate in man. Clinical Pharmacology and Therapeutics, 10, 849-857.

Lindenbaum, J., Mellow, M.H., Blackstone, M.O. and Butler, V.P. (1971) Variation in biologic availability of digoxin from four preparations. New England Journal of Medicine, 285, 1344-1347.

Lindenbaum, J., Butler, V.P., Murphy, J.E. and Cresswell, R.M. (1973) Correlation of digoxin-tablet dissolution rate with biological availability. Lancet, 1, 1215-1217.

Linnoila, M., Saario, I., Seppala, T., Olkoniemi, J. and Liljeqvist, R. (1974) Methods used for evaluation of the combined effects of alcohol and drugs on humans. In Drug Interactions, ed. Morselli, P.L., Garattini, S. and Cohen, S.N. pp. 319-325. New York : Raven Press.

Lloyd, J.T.A. and Walker, D.R.H. (1965) Death after combined dexamphetamine and phenelzine. British Medical Journal, 2, 168-169.

Low-Beer, G.A. and Tidmarsh, D. (1963) Collapse after "Parstelin". British Medical Journal, 2, 683-684.

Lown, B., Marcus, F. and Levine, H.D. (1959) Digitalis and atrial tachycardia with block. New England Journal of Medicine, 260, 301-309.

Manninen, V., Melin, J. and Hartel, G. (1971) Serum digoxin concentrations during treatment with different preparations. Lancet, 2, 934-935.

Manninen, V., Apajalahti, A., Melin, J. and Karesoja, M. (1973) Altered absorption of digoxin in patients given propantheline and metoclopramide. Lancet, 1. 398-401.

Marchand, C., McLean, S. and Plaa, G.L. (1970) The effect of SKF 525A on the distribution of carbon tetrachloride in rats. Journal of Pharmacology and Experimental Therapeutics, 174, 232-238.

Martin, A.N., Swarbrick, J. and Cammarata, A. (1969) In Physical Pharmacy, 2nd ed. chapter 13. Philadelphia : Lea and Febiger.

Martin, E.W. (1971) Hazards of Medication. Philadelphia and Toronto : J.B. Lippincott Company.

Mason, A. (1962) Fatal reaction associated with tranylcypromine and methylamphetamine. Lancet, 1. 1073.

Mason, A.M.S. and Buckle, R.M. (1969) "Cold" cures and monoamine oxidase inhibitors. British Medical Journal, 1, 845-846.

Mattila, M.J., Neuvonen, P.J., Gothoni, G. and Hackman, C.R. (1972) Interference of iron preparations and milk with the absorption of tetracyclines. Proceedings of the European Society for the Study of Drug Toxicity, 13, 128-133.

Mawer, G.E., Ahmad, R., Dobbs, S.M., McGough, J.G., Lucas, S.M. and Tooth, J.A. (1974) Prescribing aids for gentamicin. British Journal of Clinical Pharmacology, 1, 45-50.

Mawer, G.E., Ahmad, R., Dobbs, S.M. and Tooth, J.A. (1974) Experience with a gentamicin nomogram. Postgraduate Medical Journal, 50, Suppl. 7, 31-32.

Milne, M.D. (1965) Influence of acid-base balance on efficiency and toxicity of drugs. Proceedings of the Royal Society of Medicine, 58, 961-963.

Milner, G. (1969) Gastro-intestinal side effects and psychotropic drugs. Medical Journal of Australia, 2, 153-155.

Mitchell, J.R., Arias, L. and Oates, J.A. (1967) Antagonism of the antihypertensive action of guanethidine sulphate by desipramine hydrochloride. Journal of the American Medical Association, 202, 973-976.

Mitchell, J.R., Cavanaugh, J.H., Arias, L. and Oates, J.A. (1970) Guanethidine and related agents. 111. Antagonism by drugs which inhibit the norepinephrine pump in man. Journal of Clinical Investigation, 49, 1596-1604.

Moir, D.C. and Hedley, E.A. (1971) Re-evaluation of a method of prescribing drugs in hospital. Health Bulletin, 3, 131-136.

Morselli, P.L., Rizzo, L. and Garattini, S. (1971) Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. Annals of the New York Academy of Sciences, 179, 88-107.

MacDonald, R. (1963) Tranylcypromine. Lancet, 1, 269.

MacDonald, M.G. and Robinson, D.S. (1968) Clinical observations of possible barbiturate interference with anticoagulation. Journal of the American Medical Association, 204, 97-100.

MacDonald, M.G., Robinson, D.S., Sylwester, D. and Jaffe, J.J. (1969) The effects of phenobarbital, chloral betaine and glutethimide administration on warfarin plasma levels and hypoprothrombinemic responses in man. Clinical Pharmacology and Therapeutics, 10, 80-84.

Neuvonen, P.J., Gothoni, G., Hackman, R. and Björkstein, K.A. (1970) Interference of iron with the absorption of tetracycline in man. British Medical Journal, 4, 532-534.

Nies, A.S. (1974) Drug interactions. The Medical Clinics of North America, 58, No.5, 965-975.

Nimmo, J., Heading, R.C., Tothill, P. and Prescott, L.F. (1973) Pharmacological modification of gastric emptying : Effects of propantheline and metoclopramide on paracetamol absorption. British Medical Journal, 1, 587-589.

Nocke-Finck, L., Brewer, H. and Reimers, D. (1973) Wirkung von Rifampicin auf den Menstruationszyklus und die Ostrogenanescheirdung bei Einnahme oraler Kontrazeptiva. Deutsche Medizinische Wochenschrift, 98, 1521-1523.

Nymark, M. and Nielsen, I.M. (1963) Reactions due to the combination of monoamine oxidase inhibitors with thymoleptics, pethidine, or methylamphetamine. Lancet, 2, 524-525.

Odar-Cederlof, I., Lunde, P.K.M. and Sjöqvist, F. (1970) Abnormal pharmacokinetics of diphenylhydantoin in a patient with uraemia. Lancet, 2, 831-832.

Ogilvie, R.I. and Ruedy, J. (1967) Adverse drug reactions during hospitalisation. Canadian Medical Association Journal, 97, 1450-1457.

O'Malley, K., Crooks, J., Duke, E. and Stevenson, I.H. (1971) Effects of age and sex on human drug metabolism. British Medical Journal, 3, 607-609.

O'Malley, K., Velasco, M., Pruitt, A. and McNay, J.L. (1975) Decreased plasma protein binding of diazoxide in uraemia. Clinical Pharmacology and Therapeutics, 18, 53-58.

O'Reilly, R.A. and Aggeler, P.M. (1968) Phenylbutazone potentiation of anticoagulant effect : fluorometric assay of warfarin. Proceedings of the Society for Experimental Biology and Medicine, 128, 1080-1081.

O'Reilly, R.A. and Aggeler, P.M. (1970) Determinants of the response to oral anticoagulant drugs in man. Pharmacological Reviews, 22, 35-96.

O'Reilly, R.A. and Levy, G. (1970) Pharmacokinetic analysis of potentiating effect of phenylbutazone on anticoagulant action of warfarin in man. Journal of Pharmaceutical Sciences, 59, 1258-1261.

O'Reilly, R.A. (1971) Interaction of several coumarin compounds with human and canine plasma albumin. Molecular Pharmacology, 7, 209-215.

Osler, W. (1891) Recent advances in medicine. Science, 17, 170-171.

Parker, W.J. (1970) Clinically significant alcohol drug interactions. Journal of the American Pharmaceutical Association, NS10, 664-673.

Pettinger, W.A., Soyangco, F.G. and Oates, J.A. (1968) Inhibition of monoamine oxidase in man by furazolidone. Clinical Pharmacology and Therapeutics, 9, 442-447.

Pittinger, C.B., Eryasa, Y. and Adamson, R. (1970) Antibiotic-induced paralysis. Anesthesia and Analgesia, 49, 487-501.

Polacsek, E., Barnes, T., Turner, N., Hall, R. and Weise, C. (1972) Interaction of Alcohol and Other Drugs, 2nd edition. Toronto, Ontario, Canada : Addiction Research Foundation.

Powell, L.W. and Axelsen, E. (1972) Corticosteroids in liver disease : Studies on the biological conversion of prednisone to prednisolone and plasma protein binding. Gut, 13, 690-696.

Prescott, L.F. (1970) The absorption, metabolism, excretion and C.N.S. effects of phenacetin. In Renal Infection and Renal Scanning, ed. Kincaid-Smith, P. and Fairley, K.F. p. 359. Melbourne : Mercedes.

Prescott, L.F. (1973) Pharmacokinetic drug interactions - Mechanisms of toxicity. Proceedings of the European Society for the Study of Drug Toxicity, 14, 49-58.

Prescott, L.F. (1974) Drug absorption interactions - Gastric emptying. In Drug Interactions, Ed. Morselli, P.L., Garattini, S. and Cohen, S.N. pp. 11-20. New York : Raven Press.

Prescott, L.F. and Nimmo, J. (1971) Generic inequivalence - clinical observations. Acta Pharmacologica et Toxicologica, 29, Suppl. 3, 288-303.

Price Evans, D.A. (1969) Genetic factors in drug therapy. The Scientific Basis of Medicine Annual Reviews, Chapter 10, 166-182.

Price, K.E., Zolli, Z. Jr., Atkinson, J.C. and Luther, H.G. (1957) Antibiotic inhibitors. Antibiotics and Chemotherapy, 7, 672-701.

Reed, M.J., Fotherby, K. and Steele, S.J. (1972) Metabolism of ethinyloestradiol in man. Journal of Endocrinology, 55(2), 351-361.

Reidenberg, M.M. (1971) Impaired renal function and drug sensitivity. In Renal Function and Drug Action, ch. 4. Philadelphia, London, Toronto : Saunders.

Reidenberg, M.M. (1974a) Effect of excretion changes on drug action and drug interactions. In Drug Interactions, ed. Morselli, P. L., Garattini, S. and Cohen, S.N. pp.41-49. New York : Raven Press.

Reidenberg, M.M. (1974b) Effect of disease states on plasma protein binding of drugs. Medical Clinics of North America, 58, 1103-1109.

Reidenberg, M.M., Odar-Cederlof, I., von Bahr, C., Borga, O. and Sjöqvist, F. (1971) Protein binding of diphenylhydantoin and desmethylimipramine in plasma from patients with poor renal function. New England Journal of Medicine, 285, 264-267.

Reidenberg, M.M., James, M. and Dring, L.G. (1972) The rate of procaine hydrolysis in serum of normal subjects and diseased patients. Clinical Pharmacology and Therapeutics, 13, 279-284.

Reidenberg, M.M. and Affrime, M. (1973) Influence of disease on binding of drugs to plasma proteins. Annals of the New York Academy of Sciences, 226, 115-126.

Reidenberg, M.M. and Katz, M. (1973) Slow extra-renal excretion of digoxin. New England Journal of Medicine, 289, 1148.

Reimers, D. and Jezek, A. (1971) Rifampicin un andere Antituberkulotika bei gleichzeitiger oraler Kontrazeption. Praxis der Pneumologie, 25, 255-262.

Remmer, H. (1964) Drug-induced formation of smooth endoplasmic reticulum and of drug metabolising enzymes. Proceedings of the European Society for the Study of Drug Toxicity, 4, 57-77.

Remmer, H. (1967) Die Induktion arzneimittelabbauender Enzyme im endoplasmatischen Retikulum der Leberzelle durch Pharmaka. Deutsche Medizinische Wochenschrift, 92, 2001-2008.

Remmer, H. (1972) The induction of the microsomal oxidase (CYT. P-450). Proceedings of the European Society for the Study of Drug Toxicity. 13, 10-20.

Remmer, H., Schoene, B. and Fleischmann, R.A. (1973) Induction of the unspecific microsomal hydroxylase in the human liver. Drug Metabolism and Disposition, 1, 224-230.

Reuning, R.H., Sams, R.A. and Notari, R.E. (1973) Role of pharmacokinetics in drug dosage adjustment. 1. Pharmacologic effect kinetics and apparent volume of distribution of digoxin. Journal of Clinical Pharmacology, 13, 127-141.

Robinson, D.S. and MacDonald, M.G. (1966) The effect of phenobarbital administration on the control of coagulation achieved during warfarin therapy in man. Journal of Pharmacology and Experimental Therapeutics, 153, 250-253.

Rogers, S.G. (1967) Imipramine and Benzhexol. British Medical Journal, 1, 500.

Rosinga, W.M. (1968) Interaction of drugs and alcohol in relation to traffic safety. In Drug Induced Diseases, ed. Meyler, L., Peck, H.M. Vol. 111, pp. 295-306. Amsterdam : Excerpta Medica.

Rubin, E., Gang, H., Misra, P.S. and Lieber, C.S. (1970) Inhibition of drug metabolism by acute ethanol intoxication. A hepatic microsomal mechanism. American Journal of Medicine, 49, 801-806.

Samaan, N., Dollery, C.T. and Fraser, R. (1963) Diabetogenic action of benzothiadiazines. Lancet, 2, 1244-1246.

Scherbel, A.L., (1961) Current drug therapy. Amine oxidase inhibitors. Clinical Pharmacology and Therapeutics, 2, 559-566.

Schoene, B., Fleichmann, R.A., Remmer, H. and Olderhausen, H.F. (1972) Determination of drug metabolising enzymes in needle biopsies of human liver. European Journal of Clinical Pharmacology, 4, 65-73.

Schrogie, J.J. and Solomon, H.M. (1967) The anticoagulant response to bishydroxycoumarin. 11. The effect of D-Thyroxine, clofibrate and norethandrolone. Clinical Pharmacology and Therapeutics, 8, 70-77.

Seidl, L.G., Thornton, G.F., Smith, J.W. and Cluff, L.E. (1966) Studies on the epidemiology of adverse reactions. 111. Reactions in patients on a general medical service. John Hopkins Hospital Bulletin, 119, 299-315.

Seller, R.H., Cangiano, J., Kim, K.E., Mendelssohn, S., Brest, A.N. and Swartz, C. (1970) Digitalis toxicity and hypomagnesemia. American Heart Journal, 79, 57-68.

Sellers, E.M. and Koch-Weser, J. (1970) Potentiation of warfarin-induced hypoprothrombinaemia by chloral hydrate. New England Journal of Medicine, 283, 827-831.

Sellers, E.M. and Koch-Weser, J. (1971) Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. Annals of the New York Academy of Sciences, 179, 213-225.

Sellers, E.M., Lang, M., Koch-Weser, J., LeBlanc, E. and Kalant, H. (1972a) Interaction of chloral hydrate and ethanol in man. 1. Metabolism. Clinical Pharmacology and Therapeutics, 13, 37-49.

Sellers, E.M., Carr, G., Bernstein, J.G., Sellers, S. and Koch-Weser, J. (1972b) Interaction of chloral hydrate and ethanol in man. 11. Haemodynamics and performance. Clinical Pharmacology and Therapeutics, 13, 50-58.

Shaw, T.R.D., Carless, J.E., Howard, M.R. and Raymond, K. (1973) Particle size and absorption of digoxin. Lancet, 2, 209-210.

Shaw, T.R.D., Raymond, K., Howard, M.R. and Hamer, J. (1973) Therapeutic non-equivalence of digoxin tablets in the United Kingdom : Correlation with tablet dissolution rate. British Medical Journal, 4, 763-766.

Sjöqvist, F. (1965) Psychotropic drugs (2). Interaction between monoamine oxidase (MAO) inhibitors and other substances. Proceedings of the Royal Society of Medicine, 58, 967-978.

Sjöqvist, F. and Alexanderson, B. (1972) Drug interactions. A critical look at their documentation and clinical importance. Proceedings of the European Society for the study of Drug Toxicity, 13, 167-179.

Skeith, M.D., Simkin, P.A. and Healey, L.A. (1968) The renal excretion of indomethacin and its inhibition by probenecid. Clinical Pharmacology and Therapeutics, 9, 89-93.

Skellern, G.G., Meier, J. and Whiting, B. (1976) The application of high-pressure liquid chromatography to the determination of some 1,4 benzodiazepines and their metabolites in plasma. Il Farmaco, in press.

Smith, J.W., Seidl, L.G. and Cluff, L.E. (1966) Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. Annals of Internal Medicine, 65, 629-640.

Soberman, R., Brodie, B.B., Levy, B.B., Axelrod, J., Hollander, V.

and Steele, J.M. (1949) The use of antipyrine in the measurement of total body water in man. Journal of Biological Chemistry, 179, 31-42.

Solomon, H.M. and Schrogie, J.J. (1967a) The effect of various drugs on the binding of Warfarin-$^{14}C$ to human albumin. Biochemical Pharmacology, 16, 1219-1226.

Solomon, H.M. and Schrogie, J.J. (1967b) Change in receptor site affinity : A proposed explanation for the potentiating effect of D-Thyroxine on the anticoagulant response to warfarin. Clinical Pharmacology and Therapeutics, 8, 797-799.

Solomon, H.M. and Abrams, W.B. (1972) Interactions between digitoxin and other drugs in man. American Heart Journal, 83, 277-280.

Sotaniemi, E. and Palva, I.P. (1972) The use of polypharmaceutical drug therapy in a medical ward. Annals of Clinical Research, 4, 158-164.

Stark, D.C.D. (1962) Effects of giving vasopressors to patients on monoamine oxidase inhibitors. Lancet, 1, 1405-1406.

Stern, I.J., Hollifield, R.D., Wilk, S. and Buzard, J.A. (1967) The anti-monoamine oxidase effects of furazolidone. Journal of Pharmacology and Experimental Therapeutics, 156, 492-499.

Stewart, M.J. and Simpson, E. (1972) New formulation of lanoxin : expected plasma levels of digoxin. Lancet, 2, 541.

Stockley, I. (1974) In Drug Interactions and their mechanisms pp. 11-13. London : The Pharmaceutical Press.

Sumner, D.J., Russell, A.J. and Whiting, B. (1975) Digoxin kinetics : Multicompartmental analysis and its clinical implications. British Journal of Clinical Pharmacology. In press.

Tonks, C.M. and Livingstone, D. (1963) Monoamine oxidase inhibitors. Lancet, 1, 1323-1324.

Tonks, C.M. and Lloyd, A.T. (1965) Hazards with monoamine oxidase inhibitors. British Medical Journal, 1, 589.

Tygstrup, N. (1964) The galactose elimination capacity in control subjects and in patients with cirrhosis of the liver. Acta Medica Scandinavica, 175, 281-289.

Udall, J.A. (1969) Drug interference with warfarin therapy. Clinical Research, 17, 104.

Varney, J.M. (1974) Multiple Prescribing. British Medical Journal, 2, 727.

Vessell, E.S. and Page, J.G. (1968a) Genetic control of blood levels in man : phenylbutazone. Science, 159, 1479-1480.

Vessell, E.S. and Page, J.G. (1968b) Genetic control of blood levels in man : antipyrine. Science, 161, 72-73.

Vessell, E.S. and Page, J.G. (1968c) Genetic control of dicoumarol levels in man. Journal of Clinical Investigation, 47, 2657-2663.

Vessell, E.S. and Page, J.G. (1969) Genetic control of the phenobarbital-induced shortening of plasma antipyrine half-lives in man. Journal of Clinical Investigation, 48, 2202-2209.

Vessell, E.S., Page, J.G. and Passananti, G.T. (1971) Genetic and environmental factors affecting ethanol metabolism in twins. Clinical Pharmacology and Therapeutics, 12, 192-201.

Vessell, E.S., Passananti, G.T., Greene, F.E. and Page, J.G. (1971) Genetic control of drug levels and of the induction of drug - metabolising enzymes in man : Individual variability in the extent of allopurinol and nortriptyline inhibition of drug metabolism. Annals of the New York Academy of Sciences, 179, 752-773.

Waddell, W.J. and Butler, T.C. (1957) The distribution and excretion of phenobarbital. Journal of Clinical Investigation. 36, 1217-1226.

Wagner, J.G. (1966) Design and data analysis of biopharmaceutical studies in man. Canadian Journal of Pharmaceutical Sciences, 1, 55-68.

Wagner, J.G. (1971) In Biopharmaceutics and relevant pharmacokinetics, p. 257. Hamilton, Illinois : Drug Intelligence Publications.

Wallace, S. and Whiting, B. (1974) Some clinical implications of the protein binding of digoxin. British Journal of Clinical Pharmacology, 1, 325-328.

Wallace, S. and Brodie, M.J. (1976) Decreased drug binding in serum from patients with chronic hepatic disease. European Journal of Clinical Pharmacology, In press.

Wallace, S., Whiting, B. and Runcie, J. (1976) Factors affecting drug binding in plasma of elderly patients. British Journal of Clinical Pharmacology. In press.

Wallace S.P. and Lawson, D.H. (1974) Personal communication.

Waller, J.A. (1971) Drugs and highway crashes. Journal of the American Medical Association, 215, 1477-1482.

Wardell, W.M. (1974) Redistributional drug interactions : A critical examination of putative clinical examples. In Drug Interactions, ed. Morselli, P.L., Garattini, S. and Cohen, S.N. pp. 123-134. New York : Raven Press.

Warnes, H., Lehmann, H.E. and Ban, T.A. (1967) Adynamic ileus during psychoactive medication : a report of three fatal and five severe cases. Canadian Medical Association Journal, 96, 1112-1113.

Weissler, A.M., Lewis, R.P., Leighton, R.F. and Bush, C.A. (1972) Comparative responses to the digitalis glycosides in man. In Basic and Clinical Pharmacology of digitalis, ed. Marks, B.H. and Weissler, A.M. pp. 260-280. Springfield, Illinois : Charles Thomas.

Welling, P.G., Craig, W.A. and Kunin, C.M. (1975) Prediction of drug dosage in patients with renal failure using data derived from normal subjects. Clinical Pharmacology and Therapeutics, 18, 45-52.

White, A.G. (1965) Methyldopa and amitriptyline. Lancet, 2, 441.

Whiting, B., Rodger, J.C. and Sumner, D.J. (1972) New formulation of digoxin. Lancet, 2, 922.

Whiting, B., Goldberg, A. and Waldie, P.S. (1973) The Drug Disc : Warning system for drug interactions. Lancet, 1, 1037-1038.

Whiting, B., Goldberg, A. and Waldie, P.S. (1974) The Drug Disc. A warning system for drug interactions. Drug Therapy, Feb. 1974, 79-82.

Woodford-Williams, E., Alvarez, A.S., Webster, D., Landless, B. and Dixon, M.P. (1964) Serum protein patterns in "normal" and pathological ageing. Gerontologia, 10, 86-99.

Zeck, P. (1961) The dangers of some antidepressant drugs. Medical Journal of Australia, 2, 607-608.

# PUBLICATIONS AND COMMUNICATIONS

List of Publications and Communications of work included in the Thesis

Publications

Skellern, G.G., Meier, J. and Whiting, B. (1976) The application of high-pressure liquid chromatography to the determination of some 1,4 benzodiazepines and their metabolites in plasma. Il Farmaco, in press.

Sumner, D.J., Russell, A.J. and Whiting, B. (1975) Digoxin kinetics : Multicompartmental analysis and its clinical implications. British Journal of Clinical Pharmacology, in press.

Wallace, S. and Whiting, B. (1974) Some clinical implications of the protein binding of digoxin. British Journal of Clinical Pharmacology, 1, 325-328.

Wallace, S., Whiting, B. and Runcie, J. (1976) Factors affecting drug binding in plasma of elderly patients. British Journal of Clinical Pharmacology, in press.

Whiting, B., Rodger, J.C. and Sumner, D.J. (1972) New formulation of digoxin. Lancet, 2, 922.

Whiting, B., Goldberg, A. and Waldie, P.S. (1973) The Drug Disc : Warning system for drug interactions. Lancet, 1, 1037-1038.

Whiting, B., Goldberg, A. and Waldie, P.S. (1974) The Drug Disc. A warning system for drug interactions. Drug Therapy, Feb.1974, 79-82.

Communications

Whiting, B., Goldberg, A. and Waldie, P.S. (1975) The Drug Disc : Drug Interaction Warning System. In Frontiers of Internal Medicine, 1974. 12th International Congress of Internal Medicine, Tel Aviv,

1974. pp. 395-399. Basel : Karger.

Whiting, B. and Goldberg, A. (1976) The use of Medisc in drug interactions. Proceedings of the Symposium on Drug Interactions, London, March, 1975. ed. Grahame-Smith, D.G. London : Macmillan, in press.

# STUDIES ON THE SAFE ADMINISTRATION OF DRUGS : EVALUATION AND PREVENTION of DRUG INTERACTIONS

by

Brian Whiting, MB. Ch.B.(Glasg) MRCP (U.K.)

## S U M M A R Y

of

Thesis presented to the University of Glasgow
for the degree of Doctor of Medicine

from the

Department of Materia Medica,
University of Glasgow,
Stobhill General Hospital,
Glasgow

submitted

February 1976

SUMMARY.

The history of drug therapy, from the earliest herbal remedies to the impressive range of drugs available today, has proved the accuracy of the observation made by Sir William Osler in 1891 that "a desire to take medicine is, perhaps, the great feature which distinguishes man from other animals". Modern therapeutics has brought undoubted benefit to the patient, but not without risk. Unwanted effects and adverse reactions have now become an integral part of drug therapy. A small but significant proportion of these adverse reactions can be attributed to drug interactions, the phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another. Drugs may interact in ways not readily foreseeable from the action of either agent alone and may result in increased or reduced therapeutic efficacy, or sometimes toxic or even fatal reactions.

Numerous surveys have proved that in hospital medicine, multiple drug therapy is now common practice and such interactions as have come to light are merely a small indication of an ever increasing problem. The number of over-the-counter drugs which can be purchased indiscriminately by the public complicates matters further because of the difficulty in ascertaining their composition and strength, the dosages employed, and the combinations in which they are taken with prescribed drugs. Alcohol consumption also adds to the therapeutic problems which face the doctor. If safe and effective therapy is to be attained, he must be aware of all the drugs that a patient is taking and carefully review all drug combinations.

Other factors may play an important part in determining the overall response of a patient to a drug, and drug interactions must be seen in this perspective. Genetic, environmental and pathophysiological factors, particularly renal and hepatic disease, together with allergy and idiosyncrasy may all make important contributions to this response.

In addition, variations in the biological availability of drugs due to pharmaceutical factors may assume importance. Assessment of the contribution of these various factors in individual patients is necessary for rational prescribing. Renal impairment, for example, reduces the clearance of drugs such as digoxin which depend on glomerular filtration for their excretion. Pharmacokinetic studies can derive mathematical models which define these changes accurately and predict appropriate dosage adjustments to maintain optimum therapeutic effect. Simulation of the changes can be usefully achieved by analogue computation.

A number of basic mechanisms are responsible for many drug interactions and an appreciation of these mechanisms can greatly facilitate their interpretation, prevention and treatment. Interactions can be viewed in terms of the three phases of drug action, the pharmaceutical phase, the pharmacokinetic phase and the pharmacodynamic phase. Quantitative changes, reflected as alterations in plasma and tissue concentrations, occur during pharmaceutical and pharmacokinetic interactions while qualitative changes at receptor sites modifying onset, intensity or duration of action, or interference with homeostatic mechanisms occur as a result of interactions in the pharmacodynamic phase.

It is virtually impossible for the practising doctor to sustain the mass of detailed information which is now available on drug interactions. To overcome this problem, a simple, portable drug interaction warning system, the Drug Disc, has been developed. It consists of a reversible unit of two concentric superimposed discs which pivot freely about their common centre. Interactions are indicated by symbols which appear in a window cut into the upper disc when individual drugs or drug categories shown on the two discs are brought into alignment. The information presented embraces the majority of drug interactions which have a bearing on therapeutics and different symbols are used to grade interactions

according to their degree of clinical significance. This grading was based on the nature and severity of the interaction, the adequacy of published information, and opinions expressed by the developers of the Disc, including a Working Party established by the Scottish Home and Health Department, and 450 doctors and pharmacists who participated in a trial of the Disc in the United Kingdom. This survey of attitudes about the warning system indicated that the majority of participants found the information provided to be both clinically useful and informative. Subsequent consumer research in other countries has confirmed that the system would be of value both as a practical aid in prescribing and in teaching. The degree of interest and enthusiasm stimulated by the Drug Disc showed that drug interactions are an aspect of modern medicine that cannot be ignored, and suggested that this kind of aid to prescribing was warranted. It is planned to effect a free distribution of the Disc to Health Service Doctors in the United Kingdom and the Excerpta Medica Foundation has accepted responsibility for its worldwide distribution.

Further experience with drug combinations and the introduction of new drugs will largely dictate much of the relevance of drug interactions in the future. The Drug Disc will be subjected to constant review and appropriate changes made whenever necessary. It is hoped that a system of this kind will foster a more critical approach to multiple drug therapy and help to reduce many of the hazards implicit in drug combinations.