THE ROLE OF DRUG METABOLISM IN THE DEVELOPMENT OF CLINICALLY SIGNIFICANT ADVERSE DRUG INTERACTIONS

Ivan Stockley

Department of Pharmacy
University of Nottingham,
University Park,
Nottingham.

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INTRODUCTION

For centuries it has been traditional for physicians to prescribe mixtures containing large numbers of ingredients, and there is little doubt that suggestible patients would be favourably impressed by the elegance of a carefully and well-written prescription, couched in abbreviated Latin, the meaning of which they could only guess at, but carrying all the power and mystery of a healing potion. And what did it matter if most of the ingredients were of little or no value if the intended placebo effects achieved the desired aims? Even if this type of traditional polypharmacy had derisory pharmacological value, the psychological benefits to be harvested were enormous, and moreover they were usually to be gained without the attendant risks of the drug toxicities only too familiar to us today.

Yet while we may be scornful of yesterday's materia medica, the pattern of modern prescribing is surprisingly traditional since polypharmacy seems to be just as rife today as ever. Investigations carried out by Cliff and Stewart /1/ on a hospital medical ward showed that the average patient received 14 drugs, while one received a total of 36. Wade /2/ has even described a patient in a hospital in the United States who had reached the incredible total of 64 drugs. In another study /3/ patients who were admitted to medical wards in Scotland were found to receive an average of 4 drugs, while 1 in every 5 had at least 10 drugs. This pattern of polypharmacy appears to be similar in the outpatient situation as well: Stewart and Cliff /4/ found that, on average, patients attending outpatient clinics at a teaching hospital had taken during the previous month 3 drugs prescribed for them, and 3 other drugs obtained elsewhere. These studies were all made in Britain and the USA, but there is no reason to believe that in other countries where virtually the same numbers of drugs are available the pattern of multiple-prescribing is any different.

It must have been because the old-fashioned remedies were for the most part almost inert which lead to a false sense of security about modern multiple drug administration, despite the known potency of the new synthetic drugs, and to the illogical conclusion that polypharmacy could still be indulged in without cost. With the benefit of hindsight one wonders how we could have been so incredibly shortsighted. Even though it was known as long ago as the end of the last century that one drug could interfere with the actions of others, it

was not until the early Nineteen-Sixties that a sufficiently serious adverse drug interaction - the sometimes fatal hypertensive crisis associated with the Monoamine Oxidase Inhibitors and sympathomimetic amines with indirect actions - brought the full significance of this phenomenon to the attention of pharmacologists, physicians and biochemists, and set the scene for the intense activity and interest in this field of modern pharmacological and biochemical knowledge.

It is now well recognized that the presence of some drugs can markedly affect the clinical response of patients to other drugs, and these drug interactions can have either beneficial or harmful effects. An example of the former type of interaction is seen in the use of two antihypertensive agents in combination (e.g. guanethidine with a thiazide diuretic) or two antitubercular drugs. The main problem, however, lies not with advantageous interactions like these but with those which are potentially harmful and which can result in either an increase in the efficacy of one drug, leading to the development of toxicity, or to decreased efficacy so that the patient is unwittingly unprotected from the disease condition for which he is receiving treatment.

A very large number of mechanisms of drug interaction are now known and have been investigated in detail, but in this review attention is particularly concentrated on those where some metabolic change leads to the alteration in the desired or expected pharmacological effect, and since the major impact of the phenomenon is in the clinical situation, it is the effect of these drug interactions on man on which attention will be focused. Biotransformation interactions fall into two main areas involving drug inhibition and drug induction, the former being dealt with first of all. A few examples will be set out in some detail to illustrate the main areas and the general principles involved, with passing reference to some other interactions which also have clinical significance.

INTERACTIONS DUE TO ENZYME INHIBITION

There is now a considerable corpus of knowledge derived from animal and *in vitro* experiments showing that the biotransformation of one drug can be inhibited by the presence of another. Cooke and Fellows /5/ were able to show that β-diethylamino-ethyl-diphenyl-propylacetate (SKF 525-A) extended the pharmacological effects of a number of drugs, and Brodie /6/ demonstrated that this was due to the

inhibitory effect of SKF 525-A on their metabolism. SKF 525-A is now a classic example of an enzyme inhibitor which has featured in countless studies, many of them designed to elucidate the precise nature of this inhibitory action. While SKF 525-A itself is a valuable research tool without direct therapeutic use, the clinical implications of drugs which also possess this same biochemical characteristic are considerable, a few examples of which will be discussed in detail.

Enzyme inhibition is a desirable property of some drugs and one which can be therapeutically exploited, but if the specificity of the enzyme-inhibitor is broad rather than narrow a number of unforeseen interactions may take place with other drugs because the liver microsomal enzymes involved may be responsible for the metabolism of a range of agents, or the enzyme inhibitory actions may spill over to affect enzyme activity elsewhere.

A. DISULFIRAM

Disulfiram or tetraethyliuram disulphide ('Antabuse') is a compound which has been widely used in the treatment of chronic alcoholism. The methyl congener was originally used as an accelerator substance in the rubber industry and the possibility of the application of this compound as a therapeutic agent was made by Williams /7/, who observed that workers in the chemical plant where it was being made became intolerant to alcohol. Williams /7/ described how as little as 6 ounces of beer caused a flushing of the hands and face, tachycardia, hypotension and vertigo, all of which were so unpleasant that the chemical plant workers involved were obliged to abstain from alcohol altogether. It was not until over a decade later that Danish workers /8, 9/ observed the same effect with the ethyl congener, disulfiram, which lead to experimental clinical studies on disulfiram and its application in the treatment of alcoholism.

Most of the signs and symptoms of this initially unintentional but now deliberately exploited interaction are generally agreed as being attributable to an increase in the systemic levels of acetaldehyde, the effects of which can be mimicked to some extent in untreated individuals by the intravenous injection of authentic acetaldehyde /10/. Only a small percentage of ingested alcohol is normally eliminated unchanged through the lungs, kidneys and sweat glands, while the majority, over 90%, is actively metabolized. During the first stage, alcohol is oxidised to acetaldehyde by alcohol dehydrogenase with DPN acting as the immediate hydrogen acceptor. This occurs almost

exclusively in the liver, although there is evidence of some small renal involvement as well. In the second stage, the acetaldehyde is oxidised to acetate, the reaction being so rapid that normally only very small traces of acetaldehyde actually appear in the blood. In the presence of disulfiram, this second stage is inhibited so that acetaldhydaemia occurs with levels reaching as much as 10 times those normally found. This is certainly not the whole explanation because excessively high levels of acetaldehyde have been recorded without the development of a typical antabuse reaction and there is evidence to suggest that catecholamines and histamine may have some part to play in the reactions. The hypotension observed is also inconsistent with the hypertension seen in animal experiments, so that the antabuse reaction in its totality can only be explained in terms which include the whole of the biochemical profile of disulfiram, which certainly extends beyond the inhibition of alcohol dehydrogenase.

A widening viewpoint of the biochemical spectrum of disulfiram was seen in 1966 when there was the report of another interaction, this time of a therapeutically undesirable nature. Three epileptic patients being treated with phenytoin began to show signs of phenytoin intoxication after receiving simultaneous treatment with disulfiram /11,12/. In each case the patients were taking dosages of phenytoin which had been well tolerated for several weeks prior to the first intake of disulfiram. Clinical experiments /13, 14/ subsequently undertaken to examine this reaction were carried out on 4 patients stabilized on long-term phenytoin treatment. When 400 mg of disulfiram daily was administered for 9 days, rises of between 100% and 500% in the serum phenytoin levels were seen with no sign of a levelling off until the disulfiram was withdrawn. Two of the patients in this study (see Fig. 1) showed signs of mild phenytoin intoxication.

A small amount of phenytoin is normally excreted unchanged in the urine while the majority undergoes hepatic biotransformation to parahydroxyphenyl-phenylhydantoin (HPPH). During treatment with disulfiram the rise in serum levels of phenytoin is accompanied by a fall in the urinary excretion of HPPH /14/. In a study on 5 patients, a 73% increase in the mean half-life of phenytoin (from 11.0 ± 1.2 to 19.0 ± 3.3 hours) was observed, coupled with a decrease in metabolic clearance of 34% (51.2 ± 17.2 to 33.9 ± 12.0 ml/min) when disulfiram was used concomitantly /15/. So the phenytoin intoxication which develops when serum phenytoin levels rise above about 20 μg/ml is

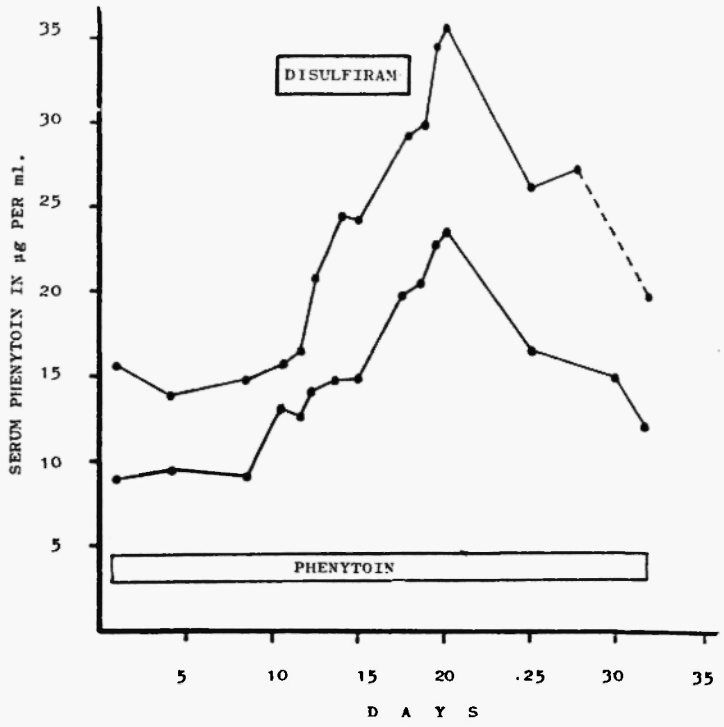

Fig. 1. The effects of disulfiram (400 mg daily for 4 days) on the phenytoin serum levels of two patients on long term phenytoin treatment. Both patients exhibited phenytoin intoxication and in one case (- - - - - -) the daily dose of phenytoin was withdrawn for a short time. (Modified and redrawn from Olesen, O.V., (1966) *Acta. Pharmacol. et Toxicol.* 24, 317 with permission)

the visible clinical manifestation of the inhibitory action of disulfiram on the hepatic biotransformation of the anticonvulsant agent.

Disulfiram is also implicated in two clinical cases in which the hypoprothrombinaemic effects of warfarin were enhanced by the concurrent administration of warfarin /16, 17/ and studies carried out in normal subjects suggest that this was due to inhibition of the metabolism of warfarin by the disulfiram /18/. This lack of specificity of disulfiram has been amply demonstrated by a number of other studies which have shown its inhibitory actions on ethylmorphine N-demethylase in rats /19/, in prolonging the hexobarbital sleeping times in animals /20/ and in inhibiting hepatic dopamine-β-hydroxylase /21/. So while disulfiram

exists in today's therapeutic armamentarium because of its known enzyme inhibitory actions on a particular system, the breadth of its general activity is responsible for other enzyme inhibitory effects and results in unsought-for or undesirable drug interactions in clinical practice.

B. MONOAMINE OXIDASE INHIBITORS

The development of antidepressant drugs of the Monoamine Oxidase Inhibitor (MAOI) type originally arose because of the initial observation that patients being treated with isoniazid and iproniazid for tuberculosis showed mood elevation. There has been a steady decline in their use over the last decade or so because of the introduction of other types of antidepressant and because of their potentially life-threatening interactions, which can take place with some drugs and certain food substances, but they are still in use for particular psychiatric and neurotic conditions.

Part of the background to our understanding of the proposed mode of action of the MAOI rests on the observation that when reserpine was used as an antipsychotic or antihypertensive, some otherwise mentally stable patients developed depression which was indistinguishable from that which occurs spontaneously. Reserpine depletes stores of noradrenaline and serotonin at adrenergic neurones so that it is proposed that just as the resultant decreased availability of noradrenaline in the CNS causes depression, elevated amounts arising from MAO-inhibition would relieve depression. A dynamic equilibrium exists between the synthesis and catabolism by MAO and inhibition of the latter raises noradrenaline levels. The release of these elevated amounts of noradrenaline by nerve impulse stimulation increases the level of receptor stimulation and thereby relieves depression (see Fig. 2). The theory is consistent with much of the biochemical and pharmacological evidence available and also with some of the adverse interactions which can take place. Monoamine Oxidase is not a single entity, at least two types, MAO A and B having been distinguished, but for convenience it will be usually referred to here as MAO without qualification. The interactions seen with the MAOI occur because the MAO-inhibition is not confined the adrenergic neurones within the CNS, but also affects the MAO elsewhere in the body - in the intestinal wall, the liver and the peripheral adrenergic neurones associated with the cardiovascular system.

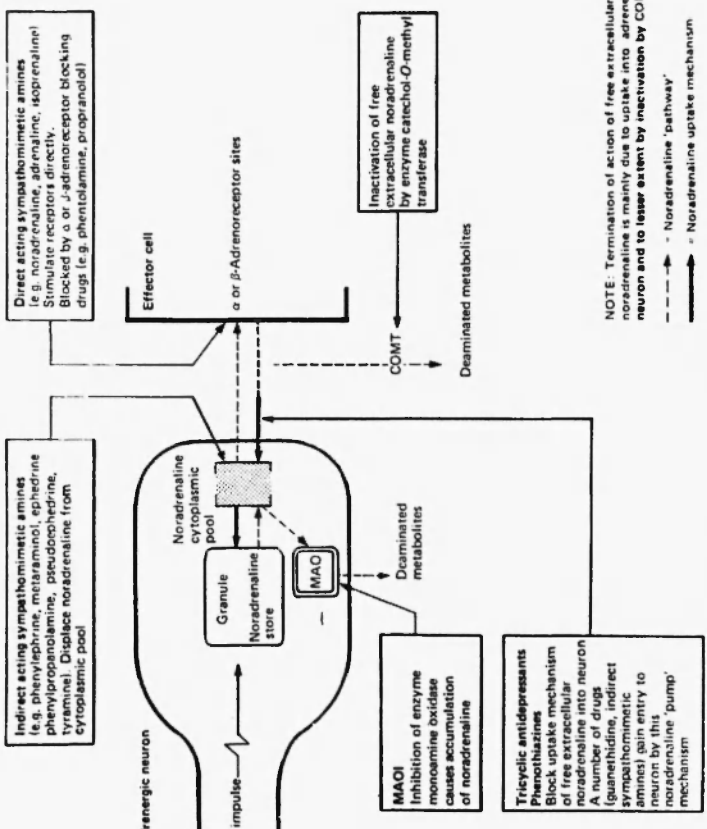

Fig. 2. A simplified schematic diagram of an adrenergic neurone to show the sites of action of drugs which modify neuronal activity.

One of the earliest interactions seen with the MAOI was the hypertensive crisis which can take place after the ingestion of cheese or yeast extracts which have undergone extensive bacterial degradation /22, 23/. Usually the individual experienced a severe headache, sometimes with nausea and vomiting, a grossly elevated blood pressure at rest (in excess of 200 mg.Hg.systolic) and changes in the cardiac rate and rhythm. Fig. 3 illustrates the blood pressure changes seen in a patient on tranylcypromine who was given 4 g yeast extract by mouth. Recovery from the accidental hypertensive episodes was usually uneventful but fatalities have occurred due to cardiac failure and intracranial haemorrhage. The substance almost certainly responsible for the reaction seen is tyramine produced by bacterial decarboxylation of tyrosine, although phenethylamine, another pressor amine, may also have some small part to play.

Ingested tyramine and phenethylamine are normally substrates for MAO within the intestinal wall /24, 25/ but during MAO inhibition tyramine and other pressor amines are absorbed unchanged and pass into the hepatic portal circulation. Again, normally, any of these amines which escape destruction by the intestinal MAO would be metabolized by hepatic MAO /26, 27/ but during MAO inhibition they pass largely unaltered through the liver into the general circulation and thence into contact with the peripheral sympathomimetic neurones concerned with the innervation of blood vessels. Tyramine is a sympathomimetic amine of the indirect type, so that it stimulates the contraction of blood vessels, not by a direct action on the receptors, but indirectly by releasing the noradrenaline held in store at adrenergic nerve endings. MAO-inhibition causes these stores to be particularly high, and the release of this accumulated noradrenaline causes a massive stimulation of the musculature of the blood vessels, resulting in a rapid rise in blood pressure. The response can be reversed by the intravenous administration of phentolamine which is an α-adrenoreceptor antagonist and which competes with noradrenaline for the receptors. This interaction has been seen with other foods and drinks where bacterial degradation has taken place and where tyramine has been produced: Chicken livers, pickled herrings, caviar, and some wines have all been implicated.

This particular interaction between the MAOI antidepressants and tyramine comes about because of the cumulative effects of the MAO inhibition at three sites (the intestinal wall, the liver and at peripheral nerve endings) but a similar interaction confined to MAO inhibition at the adrenergic nerve endings has been seen with the antihypertensive

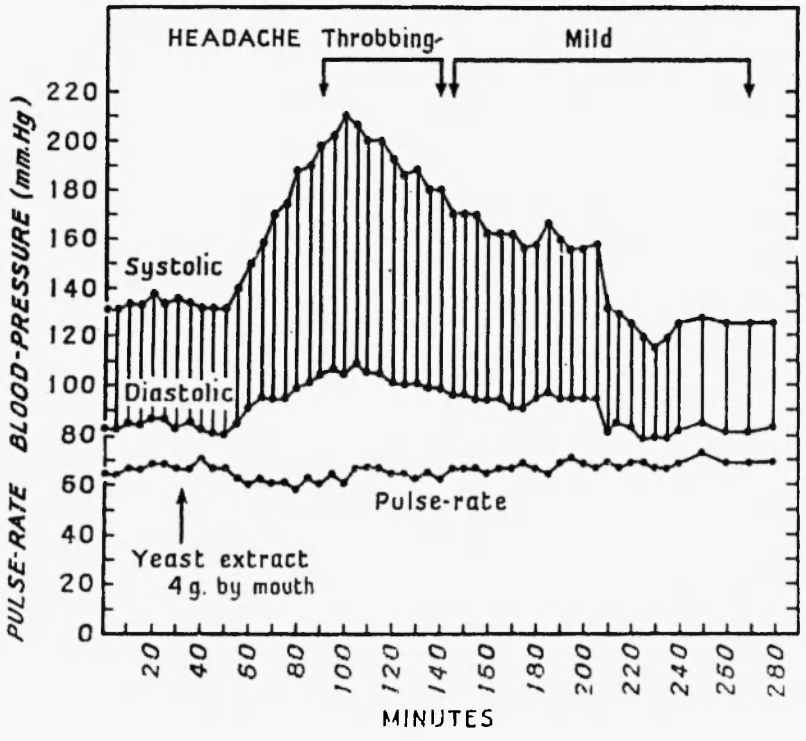

Fig. 3. Blood pressure and pulse rate changes of a woman treated for two years with tranylcypromine after takin 4G yeast extract orally preceded by 20 mg tranylcypromine. (reproduced with permission from Blackwell, B., Marley, E., and Mabbitt L.A., (1965), Lancet 1, 940)

agent debrisoquine which selectively inhibits MAO at this one site /28/ and leaves the MAO in the intestinal wall and the liver unaffected. A single clinical case of this interaction has been reported /29/ (see Fig. 4).

The interaction with MAOI and sympathomimetic amines of therapeutic importance which possess indirect actions such as phenylpropanolamine, ephedrine, the amphetamines and L-DOPA (after metabolism to dopamine) closely resembles the interaction seen with tyramine for obvious reasons /30, 31, 32/. Phenylephrine, on the other hand, is a directly-acting sympathomimetic amine which acts, like noradrenaline, directly on the receptors and not by the release of

Fig. 4. Hypertensive response of a patient to 50 G Gruyere cheese receiving 70 mg debrisoquine daily. (reproduced with permission from Amery, A., and DeLoof W., (1970), Lancet 2, 613)

noradrenaline, so it might be expected to be unaffected by the presence of an MAOI, but this is not the case. There is a considerable difference between the intravenous and oral doses of phenylephrine because most of the latter is metabolized after absorption by intestinal and hepatic MAO and normally only a fraction of the dose actually reaches its intended sites of action. During MAO inhibition, this normal oral dose represents a massive overdose because it is absorbed almost completely unchanged, so that the same precautions apply to phenylephrine given orally as to sympathomimetic amines of the indirect type /33/.

Pethidine given to patients receiving MAOI therapy can induce serious reactions including excitation, tremor, muscular twitching and rigidity, increased tendon and plantar reflexes, severe hyperpyrexia, sometimes Cheyne-Stokes respiration and shock. A considerable amount of experimental work has been undertaken to elucidate this interaction, much of which has centred around changes in brain 5-HT levels postulated as arising from MAO-inhibition /34, 35/ but there is still no satisfactory explanation of the detailed mechanism of this interaction which embraces all the pharmacological and biochemical observations made.

C. ALLOPURINOL

Allopurinol (4-hydroxypyrazolopyrimidine) is a compound intended as a specific inhibitor of xanthine oxidase for the treatment of gout and other hyperuricaemias. By inhibiting xanthine oxidase (see Fig. 5) it prevents the production of uric acid so that the serum and urinary levels of uric acid fall. Because of this diminished uric acid formation, both hypoxanthine and xanthine accumulate and their urinary excretion increases. Both of them are more soluble than uric acid and do not precipitate out to the same extent, so that they are rapidly cleared and this is accompanied by the relief of the symptoms of gout.

Apart from this direct clinical use in the treatment of gout, allopurinol finds application in the control of the high blood concentration of uric acid seen in leukaemic patients. An interaction can however occur in patients treated with either azathioprine, or 6-mercaptopurine to which it is metabolized, because 6-mercaptopurine is detoxified to 6-thiouric acid by xanthine oxidase. In the presence of allopurinol, this pathway is blocked and the excretion of 6-thiouric acid is reduced /36/. Although there is evidence for the existence of an alternative metabolic pathway capable of carrying out some of the detoxification

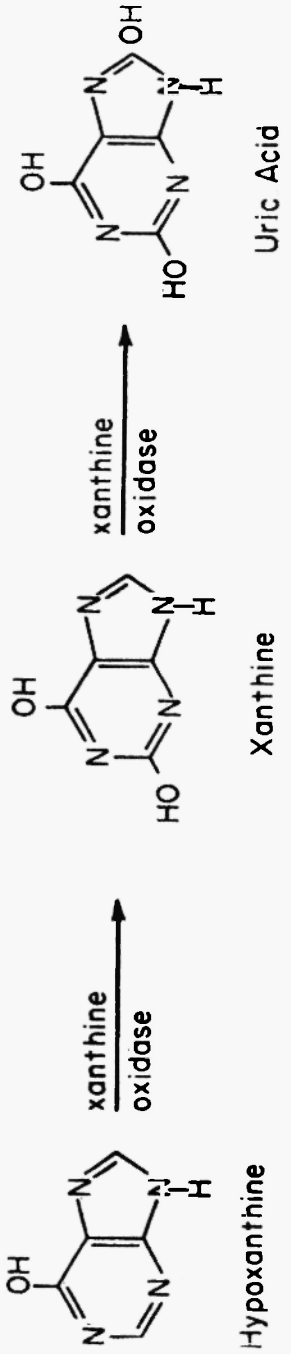

Fig. 5. Enzymic transformation of hypoxanthine to uric acid by xanthine oxidase.

/37/ 6-mercaptopurine can still accumulate causing the development of acute toxicity if the intake of 6-mercaptopurine is not reduced. A clinical study /38/ demonstrated that with daily doses of allopurinol in the 200-300 mg range, the dosage of 6-mercaptopurine should be reduced to about 25% to obtain the therapeutic response required without the development of mercaptopurine toxicity.

The enzyme-inhibitory effects of allopurinol are not limited to its effects on xanthine oxidase. There is evidence that it also has inhibitory effects on liver microsomal enzymes concerned with the metabolism of antipyrine and *bis*hydroxycoumarin /39/, and the effects on the latter may possibly have clinical significance.

D. OTHER ENZYME INHIBITORY AGENTS

Apart from drugs which were originally selected for their primary enzyme inhibitory actions but which have other far-reaching enzyme inhibitory effects, there are a number of other drugs which can initiate clinically significant interactions by enzyme inhibition but whose primary effects are not mediated in this way. In the great majority of cases, the effect of the inhibitory agent is to cause the accumulation of the second drug leading firstly to an increase in its intended pharmacological effect and, if the extent of the inhibition is sufficiently large, to the development of toxicity. Table 1 lists some of the drugs which interact with phenytoin and parallel the interaction with disulfiram which has already been described. Exaggerated therapeutic responses to tolbutamide have also been reported to have been caused by the use of chloramphenicol /40/ and sulphaphenazole /41/ all due to enzyme inhibition, and similarly with chlorpropamide and phenylbutazone /42/.

TABLE 1. *Some drugs reported to elevate the serum levels of phenytoin by inhibiting its hepatic biotransformation in man*

Bishydroxycoumarin	Hansen, Kristensen, Skovsted and Christensen (1966)
Chloramphenicol	Christensen and Skovsted (1969)
Isoniazid	Kutt, Brennan, Dehejia and Verebeley (1970)
Methylphenidate	Garrettson, Perel and Dayton (1969)
Phenyramidol	Solomon and Schregie (1967)
Sulthiame	Hansen, Kristensen and Skovsted (1968)

INTERACTIONS DUE TO ENZYME INDUCTION

The converse of enzyme inhibition is the phenomenon of enzyme induction which can be broadly defined as an increase in drug-metabolizing capacity induced by drugs or other chemical agents. A very large number of lipid-soluble drugs exhibit enzyme-inducing activity and this has been demonstrated in man with barbiturates, carbamazepine, ethchlorvynol, glutethimide, griseofulvin, meprobamate, phenazone, phenytoin, primidone, rifampicin, the tricylic antidepressants, and the chlorinated insecticides, a list which can by no means be regarded as exhaustive. The whole phenomenon has been very thoroughly investigated in a large number of experiments in both man and animals /43, 44/.

One of the consequences of induction is that the half-life of the inducing agent is shortened because its rate of metabolism is increased and, in the context of drug interactions, the half-lives of other drugs which are present in the body at the same time and which are substrates for microsomal enzymes are similarly reduced. Table 2 lists the effects of some enzyme-inducing agents on the half-lives of other drugs when administered together. Enzyme induction is not an instantaneous response but, depending on the dose, develops over a period of time and similarly persists for days or weeks after withdrawal of the inducing agent. The usual consequence of enzyme induction is a reduction in the therapeutic response of the patient to one or both drugs because drug metabolites do not usually have significant pharmacological activity of their own.

A. ORAL ANTICOAGULANTS

Among the drugs on which enzyme-induction interactions can have considerable clinically significant effects are the oral anticoagulants. The introduction of these agents in the treatment of the thromboembolic diseases came about as a result of studies into the cause of a haemorrhagic disease of cattle which, investigation showed, had been fed on spoiled sweet clover. The active pharmacological principle proved to be a coumarin derivative, from which the coumarin and later the indanedione oral anticoagulant drugs in current use were developed. The traditional and orthodox explanation of their mode of action is substrate competition with dietary derived vitamin K for the synthetic processes within the liver by which the blood clotting factors II, VII, IX and X are produced, although recent evidence suggests that this conventional explanation is too simplistic. Nevertheless, the

TABLE 2. *Some drugs which reduce the half-life of other drugs in man*

Drug	*Enzyme-inducing drug*	*Drug ½-life before treatment with inducer*	*Drug ½-life after treatment with inducer*	*References*
Ethylbiscou-	Phenobarbitone 150 mg daily for 10 days	60 hours	25 hours	Van Dam and Gribnau-Overkamp, 1967
Phenytoin	Carbamazepine 600 mg daily for 9 days	10.6 hours	6.4 hours	Hansen, Siersboek-Nielsen, Skovsted, 1971
Warfarin	Carbamazepine 200-600 mg daily for 21 days	74 hours	44 hours	Hansen, Siersboek-Nielsen, Skovsted, 1971
Warfarin	Glutethimide 1 g daily for 21 days	52 hours	29 hours	MacDonald, Robinson, Sylwester and Jaffe, 1969

prolongation of the one-stage prothrombin time which results from the administration of these oral anticoagulants is dose-dependent and reversible by the administration of vitamin K. There is a continual metabolic turnover of the factors concerned in the blood clotting cascade process, and similarly the anticoagulants are metabolized by hepatic microsomal enzymes, so that it is necessary to maintain a dynamic and balanced equilibrium between the intake of the anticoagulant and dietary vitamin K if the desired extension of the prothrombin time is to be achieved.

This equilibrium can be disturbed by the concurrent use of drugs which increase the hepatic biotransformation of oral anticoagulants, amongst which are a number of drugs used as hypnotics including the barbiturates /45/, glutethimide /46/, and dichloralphenazone /47, 48/. Each of these hypnotics can induce the hepatic microsomal enzymes concerned with the metabolism of the oral anticoagulants so that the serum levels are lower than in the absence of the enzyme inducer, and the rate of synthesis of the blood clotting factors in the liver increases. The net result is that the particular blood clotting index being measured swings towards pretreatment values, and the patient is in effect exposed

to the further possibility of spontaneous thromboses. A considerable number of reports and experimental studies of this interaction in man have been made, with different combinations of oral anticoagulants and barbiturates /45, 49, 50/. Fig. 6 is an early and now classic illustration of this interaction with the effect of phenobarbitone on the hepatic metabolism of *bis*hydroxycoumarin in the rat /51/ and Fig. 7 is the comparable situation in man with the same barbiturate and oral anti-

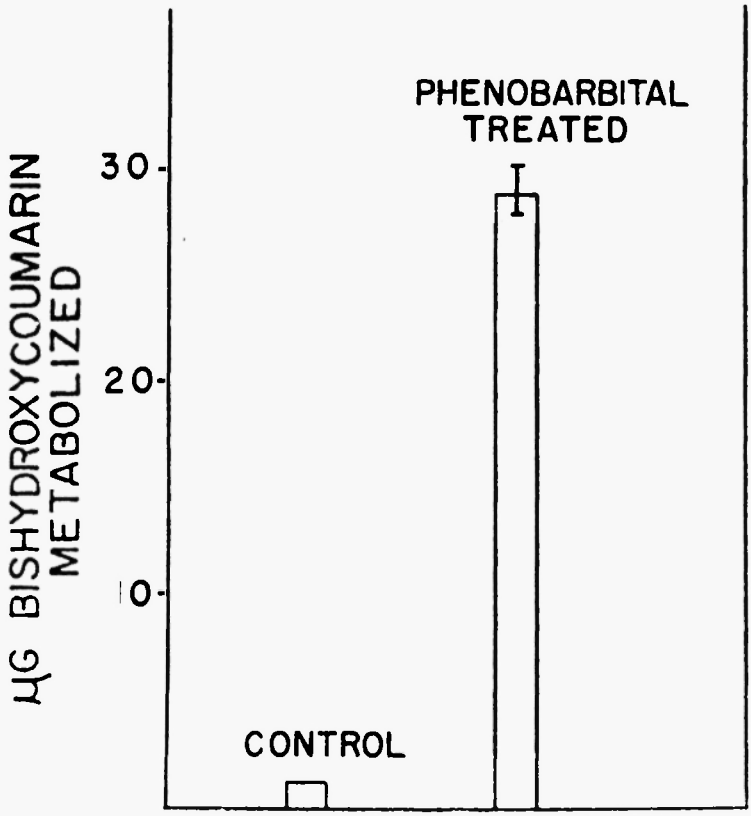

Fig. 6. The effect of phenobarbitone treatment on the metabolism of bishydroxycoumarin in the rat. (reproduced with permission from Cucinell, S.A., Conney, A.H., Sansur, M., and Burns, J.J., Drug Interactions in man I Lower-effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin), *Clin. Pharmacol. Ther.* 6, 420-429, 1965)

coagulant to show not only the changes in serum anticoagulant levels but also the associated alteration in the one-stage prothrombin times. Fig. 8 illustrates a similar situation in a woman taking warfarin and dichloralphenazone, the phenazone or antipyrine component being the enzyme-inducing agent /47/ and Fig. 9 shows the response of a patient to warfarin before, during and after treatment with carbamazepine /52/.

Just as the presence of the enzyme-inducer reduces the effects of the anticoagulant, so the equilibrium can swing in the opposite direction if the inducing agent is withdrawn without an appropriate reduction in the dosage of anticoagulant. This has happened with patients stabilized on a dosage of anticoagulant in the presence of an enzyme-inducing drug who were subsequently discharged without the enzyme-inducer but readmitted within a few days because of spontaneous haemorrhage. Thus an enzyme-induction interaction of this kind can be doubly hazardous if the appropriate precautions are not taken.

B. ORAL CONTRACEPTIVES

The mode of action of the oral contraceptives is a complex summation of a number of drug-induced reactions on the body which results in the failure of the male and female gametes to unite and the resulting zygote to implant successfully. The inhibition of ovulation induced by the oestrogen-progestrogen contraceptives is accompanied by a reduced endogenous progesterone secretion, with changes in the development of the endometrial layer which are inimical to the successful blastocyst implantation if the unlikely event of conception were to take place. The free movement of sperm is also reduced by changes in the viscosity of the cervical mucous. These contraceptives are extremely reliable when used correctly and because of this are widely used by those who choose to avoid conception for social reasons, and by women whose disease conditions make pregnancy undesirable. Interactions with drugs used to treat these diseases and which can make the oral contraceptives unreliable are therefore of considerable importance.

Rifampicin used in the treatment of tuberculosis has been implicated as the cause of oral contraceptive failure and in an increase in the incidence of menstrual cycle disorders /53, 54, 55, 56/. The latter workers reported that out of a total of 88 tuberculous women on oral contraceptives of the oestrogen-progestrogen type, 5 pregnancies had occurred and 68 had experienced breakthrough bleeding and spotting. In vitro studies carried out by Bolt *et al* /57/ on hepatic tissue from

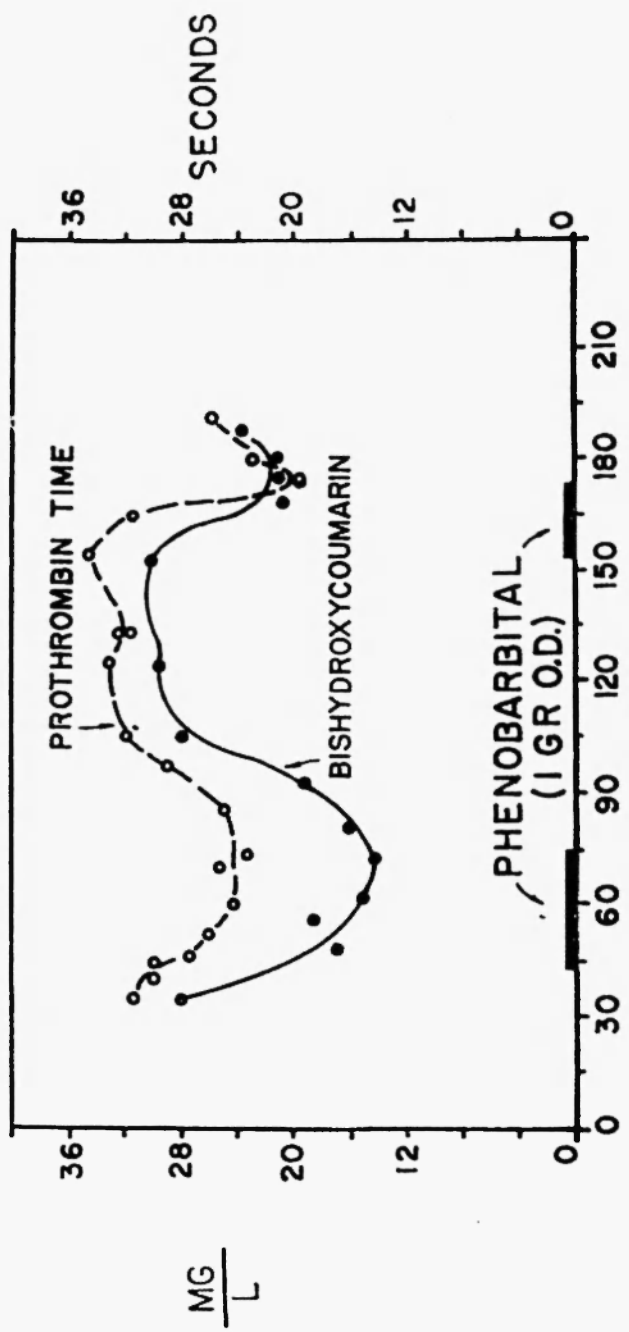

Fig. 7. Effect of phenobarbitone treatment on the plasma levels of bishydroxycoumarin (75 mg daily) and the prothrombin response of a human subject. (Reproduced with permission from Cucinell, S.A., Conney, A.H., Sansur, M., and Burns, J.J.: Drug Interactions in man. I Lowering effect of phenobarbital on plasma levels of bishydroxycoumarin (Dicumarol) and diphenylhydantoin (Dilantin), *Clin. Pharmacol. Ther.* 6, 420-429, 1965)

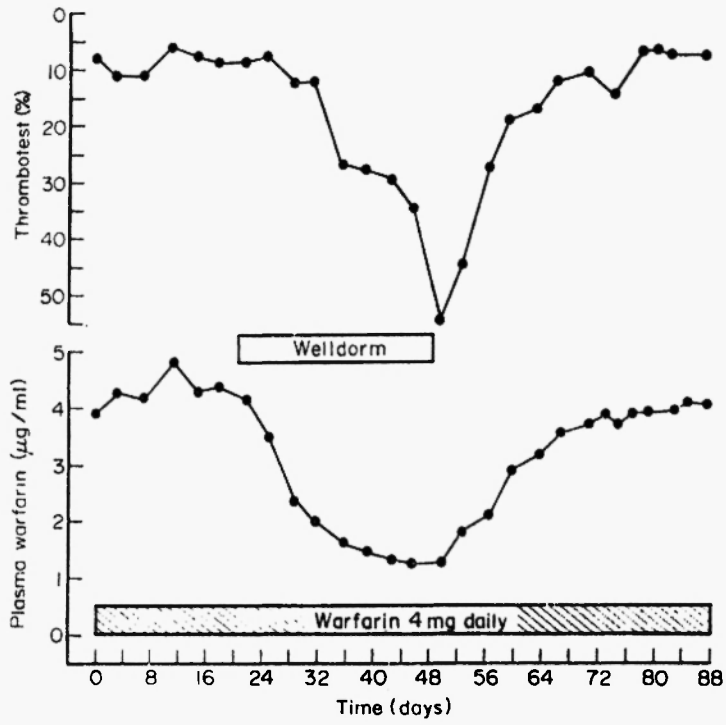

Fig.8. Effect of dichloralphenazone (1300 mg nightly) on the plasma levels of warfarin and the thrombotest percentage in a human subject.

patients and undertaken to elucidate the reason for this interaction showed that the hydroxylation rates of oestradiol and 17 α-ethinyloestradiol by the microsomal enzymes was increased fourfold by pretreatment with rifampicin, and that the increased aromatic hydroxylation lead to an enhancement of the irreversible binding to microsomal protein. Since the effectiveness of oral ethinyloestradiol as a contraceptive is due to its relatively slow rate of metabolism compared with oestradiol, the administration of rifampicin moves the half-life of the former in the direction of oestradiol thereby diminishing its effectiveness as a contraceptive and would seem to explain the contraceptive failures observed. The same situation would seem to apply equally to those combined oral contraceptives which contain mestranol as an alternative to ethinyloestradiol because it must be demethylated in vivo before it acts as an effective oestrogen /58/.

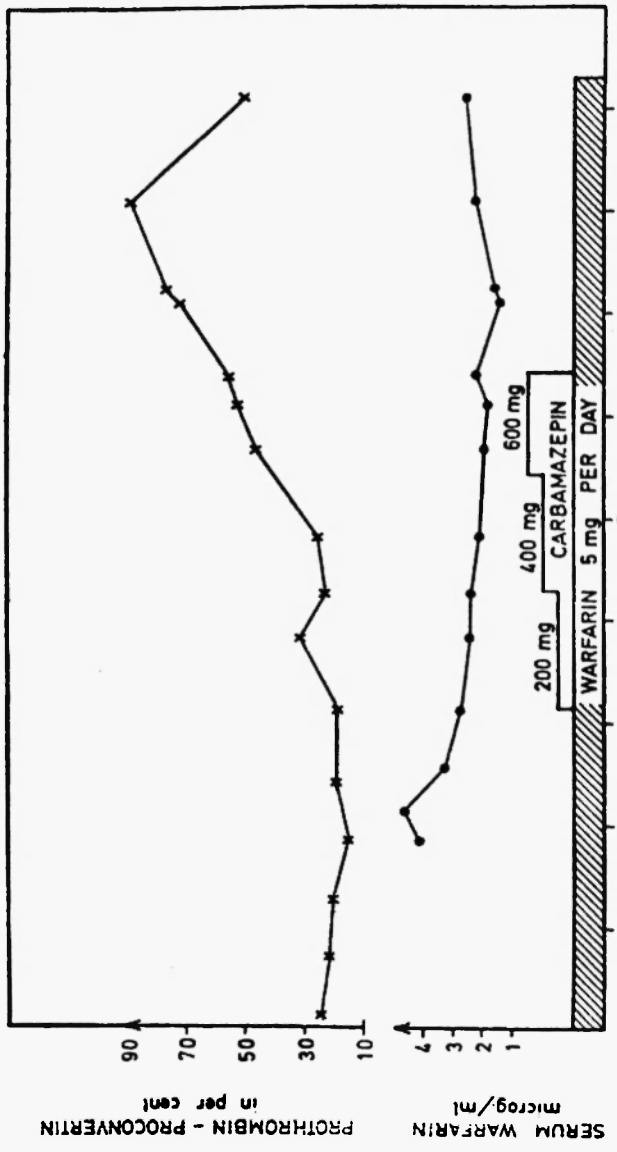

Fig. 9. Effect of carbamazepine treatment on the plasma levels of warfarin and the prothrombin-proconvertin percentage in a human subject. (Reproduced with permission from Hansen, J., Molholm, Siersboek-Nielsen, K., and Skovsted, L., Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man, *Clin. Pharmacol. Ther.* 12, 539-543, 1971)

There is evidence that enzyme induction leading to an increase in the metabolism of the oestrogenic component was also responsible for the break-through bleeding and complete failure of oral contraceptives with antiepileptic agents including phenytoin, phenobarbitone, methylphenobarbitone and primidone /59, 60, 61/ and proprietary analgesics containing amidopyrine /60/.

STUDIES ON BIOTRANSFORMATION INTERACTIONS

With a full and detailed knowledge of the characteristics of drugs, most 'accidental' interactions could have been avoided, and in a more alert and better informed atmosphere they would have been. Now there is considerable legislative pressure through official bodies like the CSM and FDA for those concerned with drugs to forsee and check for potential interactions between newly developed compounds and those drugs which are in common use. A number of studies have therefore centred around a range of experimental methods for examining the metabolic effects of one drug on another.

These investigatory methods have included the measurement of plasma antipyrine half-lives; urinary ascorbic acid excretion studies in rats; changes in phenylbutazone metabolism in dogs; *in vitro* studies of enzymic activity using different substrates such as antipyrine, hexobarbital and zoxazolamine; alterations in the pharmacological effects of hexobarbitone and zoxazolamine in rats, as well as direct clinical studies in man using drugs which in clinical practice are often, or likely to be, used together. It is clearly recognized that animal studies are not directly applicable to man because species variation is considerable and the ultimate test must be in man himself, but valuable information can be gleaned from preclinical and toxicological testing undertaken *in vitro* and in animals.

Studies of drug interactions in man may not necessarily be an absolutely reliable guide to the situation which occurs when the drug is finally released for general use. Moreover the permutations and combinations of drugs which can and will occur is astronomical, so that predictive investigations can only take place with small selected areas of drugs, alterations in whose pharmacological responses are potentially serious. Even with those drugs which are thoroughly investigated in man misleading conclusions may be drawn because some drugs which might be expected to reduce half-lives and act as some form of predictor for the likely inductive effects of other drugs do not

necessarily affect every individual equally. Tremendous variations can occur between individuals because human biochemical profiles are essentially individual and genetically controlled. Some subjects show no changes in response even to phenobarbitone, generally regarded as a potent enzyme inducer, so that clinical experiments undertaken with a group of individuals who fall into the relatively 'non-reactor' end of the spectrum would provide an unwary investigator with very unreliable data on which to base general conclusions.

Changes in the half-lives of drugs administered intravenously have been used as a method of observing alterations in the rate of drug metabolism, but the results of such experiments are open to considerable misinterpretation because the half-life is a function of several factors and not simply of the rate of hepatic metabolism. The hepatic extraction ratio is a function of how much free (that is to say, non-protein bound) drug is available for hepatic enzyme metabolism, and this can be influenced by another drug which acts as a protein-binding displacing agent and affects the half-life in this way. Similarly, alterations in the binding of drugs affect the apparent volume of distribution and this too has an influence on the half-life. Half-life change data obtained from single intravenous dose experiments must be handled with circumspection because they cannot be uncritially used to predict the response to drugs administered orally. More predictively reliable measurements would be obtained by direct observations of steady-state plasma levels. The total pharmacokinetic profile of any drug is complex, to which must be added the uniqueness of the response of the subjects on whom the studies are being made, so that any observations made and the conclusions built upon them, must be made with a full recognition of all the pharmacological and biochemical factors which are likely to have an influence. The predicting of drug interactions arising from changes in the rate of biotransformation is beset with pitfalls for those who concentrate their attentions on too few of the factors which influence the final outcome of a patients response to drugs.
This is regrettably one of the reasons why the literature on drug interactions has more than its fair share of myths relating to the probable outcome of the use of one drug with another.

CONCLUSION

The drug interactions mentioned in the paragraphs under the headings of "Introduction" and "Interactions Due to Enzyme Inhibition" have been described in some detail to emphasise the significance and clinical outcome of interactions which arise from changes in enzyme activity, and to underline the wide spectrum of biochemical and physiological systems involved. They are only illustrations. The sheer volume of knowledge available can only be adequately appreciated by reference to the literature. The tabular compilation of information by Sher /62/ which covers the 1957-1970 period is an indication of the amount of work which had been undertaken in this field up to that time.

The problem of interactions is not one which will vanish overnight merely because we are now cognisant of their existence and aware of some of the means by which they occur. Although we are now much more alert than we were a decade ago to the potential for interactions with drugs possessing certain characteristics, it is doubtful if we shall ever be in a position to foresee and prevent the occurence of every possible new interaction because novel compounds are likely to be continually synthesised and exploited. Interactions will continue to cause undesirable and unsought-for reactions in patients, and their avoidance should certainly occupy attention. At the same time, it can be said that their existence is not an entirely ill-wind because there is no doubt that as a by-product they have given us new insights into the way drugs behave, and it seems likely that their investigation will remain one of the important ways in which our knowledge of drug action and activity will continue to grow.

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