Drug Interactions

C.T. DOLLERY, MB, FRCP, Professor, and
M.J. BRODIE, MD, MRCP, Lecturer,
Department of Clinical Pharmacology, Royal Postgraduate Medical School, London

Drug interactions are very common but, fortunately, often of more theoretical than practical importance. If a physician were to limit himself to the WHO list of 200 essential drugs and were to be extremely parsimonious in issuing prescriptions, he would still have some elderly patients with multi-system diseases who required as many as five different drugs at one time. This physician could, in theory, prescribe as many as \(3 \times 10^{11}\) different drug combinations. Even if only one in 100,000 of these was of sufficient magnitude to be potentially hazardous there would still be three million combinations to commit to memory. Clearly, such a task would be impossible, but the number of really important interactions is probably numbered in tens rather than millions. Even this small number is much easier to remember if the prescriber has some knowledge of the most important mechanisms of drug interaction. Drug interactions have attracted attention disproportionate to their significance largely because they give some fascinating insights into pharmacological and pharmacokinetic mechanisms. However, the important clinical examples are drawn almost entirely from a short list of groups of drugs with a narrow therapeutic ratio, i.e., whose dose must be adjusted within a narrow range and which have obvious adverse effects if too much or too little is administered. Thus, published examples of interactions often refer to coumarin anticoagulants, hypotensive or hypertensive agents, CNS depressants, anticonvulsants and the contraceptive pill.

Not all drug interactions have adverse consequences for the patient. There are many examples of combinations of drugs that are used deliberately to achieve a therapeutic effect or minimise an adverse effect in a way that could not be done with a single chemical entity. These include oestrogen-progesterone combinations for contraception, L-dopa and decarboxylase inhibitors for Parkinson's disease, diuretics and \(\beta\)-blockers for hypertension, iron and folic acid for prophylaxis of anaemia of pregnancy, and trimethoprim sulphonamide combinations for infection. Such combinations should also improve patient compliance. The major caveat is that the doses chosen be close to optimal for a substantial fraction of the patients for whom the product is designed.

Drug interactions can be classified in terms of mechanism, site, clinical importance, and predictability.

Mechanisms of Drug Interactions (Table 1)

Kinetic Considerations

Many of the most important drug interactions arise as a result of a change in activity of one of the main processes that terminate drug action and/or eliminate the drug from the body. The best known of these are inhibition or induction of the hepatic mixed function oxidases that metabolise a great many therapeutic drugs. Induction denotes an increase in the number of enzymic binding sites and, consequently, the \(V_{\text{max}}\) of the reaction. Inhibition usually arises from competition for the active site of the enzyme between the original drug and the interacting one. The situation is made more complex by the presence of multiple forms of these enzymes. There are six or more forms of cytochrome P-450, the terminal electron acceptor of the mixed function oxidase system, responsible for the metabolism of a wide variety of drugs. Many drugs are metabolised by more than one form of the enzyme and the same metabolic step can be catalysed by different forms[1]. Thus, inhibition of metabolism will occur only if both drugs can bind to the active site of the same form of the enzyme. A similar argument applies to enzyme induction. Known inducing agents such as phenobarbitone and polycyclic hydrocarbons produce a different profile of cytochromes P-450 in the liver, as they induce some forms of the enzyme to a greater extent than others[2].

Pharmacokinetic drug interactions are most likely to be important if a drug is eliminated by a single process.
made up of two equal components, one by metabolism and the other by renal excretion. Each of these has a rate constant of 0.05 h\(^{-1}\) (Fig. 2a). The interaction reduces the metabolic elimination to one quarter of the initial value, namely 0.0125 h\(^{-1}\). The overall rate of elimination (for rate constants can be summed) is 0.0625 h\(^{-1}\) giving a half-life of 11.2 hours (Fig. 2b). The degree of accumulation would be slight when comparing a 7 and an 11 hour half-life. The existence of an alternative pathway of elimination is a safeguard against this type of interaction, unless the second pathway is easily saturated or gives rise to a toxic product. This is an important reason why interactions due to induction or inhibition of metabolism are less prominent than might be expected. However, when there is only a single route, as with the hepatic oxidative metabolism of tolbutamide to its single major metabolite, inhibition of that route can cause considerable accumulation. Administration of sulphaphenazole caused a greater than threefold increase in the steady-state concentration of tolbutamide[3].

The significance of displacement of drugs from protein binding sites as a cause of drug interaction has been exaggerated. Some of the examples quoted are probably due to a different mechanism such as inhibition of metabolism. The well-known interaction between phenylbutazone and warfarin is due more to inhibition of the stereospecific metabolism of the S-isomer of warfarin than to protein binding displacement[4]. A quantitative example will illustrate the point. Suppose that a drug is 90 per cent bound to plasma proteins in a patient whose plasma volume is 3.5 litres and whose body water volume is 50 litres. If the free concentration of the drug in body water is 1 unit, the plasma concentration will be 10 units (9 bound and 1 free) (Fig. 3a). The plasma will contain 35,000 units of drug and the rest of the body 46,500 units. If another drug competes for the binding sites and reduces the binding to proteins to 30 per cent, the free concentration throughout the body water will rise to 1.58 units (Fig. 3b). Even this rise of less than a factor of two in the free concentration will probably be temporary, as elimination processes which work on the free level tend to restore the previous value. Much of the concern arose because redistribution of displaced drug throughout the body water was ignored. However, if a drug is very highly protein bound the effect may be greater in the uncommon event of a drug with an even higher affinity being administered. Thus, a patient on warfarin who is given chloral hydrate may show a slight potentiation of the anticoagulant effect due to displacement of warfarin by trichloroacetic acid[5]. Even in this case the effect is transient and of small magnitude.

The increase in drug concentration may take place outside the plasma and result in target organ toxicity. A possible example of this is the nephrotoxicity that occurs when potent loop diuretics such as frusemide are given to patients treated with cephaloridine[6].

**Dynamic Considerations**

The most common pharmacodynamic interaction concerns the additive tranquilising effects of centrally acting agents such as benzodiazepines, clonidine and methyl-
proteins, pharmacological effect, from of reduces the number in drugs containing dextropropoxyphene[7].

Small thiazines cal increase in the concentration, to.

Examples of competitive antagonism abound in clinical pharmacology. They include atropine and cholinergic drugs, morphine and naloxone, β-agonist and antagonists and are unlikely to arise by chance. Competitive antagonism may be therapeutically useful; for instance folinic acid rescue in methotrexate therapy and the use of vitamin K₁ in coumarin-related bleeding.

Interference with physiological or biochemical control loops at more than one point provides a series of interesting drug interactions. β-adrenergic blocking drugs are implicated in two examples of clinical relevance, one useful, the other unwanted. When vasodilators are used in the treatment of hypertension, the hypotensive response is blunted by a baroreflex-mediated rise in cardiac output which is prevented by concomitant β-blockade. The second example involves the prolongation by β-blockers of insulin-induced hypoglycaemia by inhibition of the physiological response of muscle glycogenolysis.

An interaction may modify an effector system and not the receptor itself. A useful example is the mutual potentiation of β-sympathomimetics, such as salbutamol, and xanthines in patients with asthma. Both increase bronchiolar cyclic AMP levels but by different mechanisms[8]. Another well-recognised problem is the potentiation of the arrhythmogenic effects of digoxin by the hypokalaemia produced by concomitant diuretic therapy.

Sites of Drug Interaction

Drugs can interact with one another at any point from their being mixed in a pharmaceutical formulation up to their final elimination from the body in urine or bile. The most important sites are listed in Table 2. Each of these sites deserves a brief discussion.

Table 2. Classification of drug interactions by site.

| Site                  |
|-----------------------|
| a. In the pharmaceutical formulation. |
| b. In the gut lumen.   |
| c. In the gut wall.    |
| d. In the liver at the first pass. |
| e. By displacement from protein binding. |
| f. At a cell transport system. |
| g. At a receptor or enzyme. |
| h. During metabolism in the liver. |
| i. During excretion into bile or urine. |

In the Formulation

Specialists in pharmaceutical formulation go to great trouble to ensure that ingredients of a drug mixture do not react chemically or adversely affect one another’s stability during storage. However, problems of this type occurred during the design of fixed-ratio drug combinations containing beta-adrenergic blocking drugs, thiazide diuretics and hydralazine.

A better known type of interaction may occur if drugs such as heparin and benzyl penicillin are mixed in an intravenous infusion bottle whose contents are delivered over many hours. Appreciable loss of activity can occur[9]. Adding drugs to intravenous infusions is, in any case, a skilled activity because of the numerous compatibilities and the possibility of errors in dose.

Table 3. Concentration of plasma proteins and the free fraction, which has a concentration of 1 unit per ml, is evenly distributed throughout the body water. Thirty-five per cent of the drug in the body is bound to plasma proteins. (b) A second drug which reduces the plasma protein binding suddenly from 90 per cent to 30 per cent is administered. The result is an increase in the free concentration, which exerts the pharmacological effect, from 0.1 to 0.5 units/ml. Such a small effect would probably pass unnoticed.

| Component                  | Concentration |
|----------------------------|---------------|
| Plasma volume 3 litres     |               |
| Free 1 U/ml bound 9 U/ml   |               |
| Total 30,000 U             |               |
| Body water 47 litres       |               |
| Free 1 U/ml                |               |
| Total 47,000 U             |               |
| Total in plasma            |               |
| + body = 77,000 U          |               |
| 90% Binding                |               |
| Plasma volume 3 litres     |               |
| Free 1.5 U/ml bound 0.6 U/ml|               |
| Total 6,300 U              |               |
| Body water 47 litres       |               |
| Free 1.5 U/ml              |               |
| Total 70,500 U             |               |
| Total in plasma            |               |
| + body = 76,800 U          |               |
| 30% Binding                |               |
In the Gut Lumen

Chemical reactions between drugs in the intestine before absorption are rare. The best established example is that between divalent and trivalent cations (Ca$^{2+}$, Mg$^{2+}$, Ca$^{2+}$, Al$^{3+}$) and tetracyclines to form a chelate[10]. This problem arises only if both drugs are physically present in the same part of the small intestine and can be avoided by separating the timing of doses. Cholestyramine is an anionic exchange resin that binds acidic drugs, interfering with their absorption[11]. A more common problem is the effect of drugs that alter gastrointestinal motility upon the bioavailability of drugs that are poorly soluble in the gut contents. Thus, probanthine has been shown to increase bioavailability of paracetamol, and metoclopramide to decrease it[12].

In the Gut Wall

The gut wall is an important physical barrier but it is also a vital chemical barrier for certain types of structure. Over 90 per cent of an oral dose of isoprenaline is metabolised to a sulphate conjugate during absorption from the gut, and simultaneous administration of salicylamide, which competes for the sulphate conjugating capacity, can greatly increase the amount that is absorbed unmetabolised[13]. Tyramine is another substance that is extensively metabolised during absorption through the gut wall. The enzyme responsible is monoamine oxidase[14]. Inhibition at this site is one component of the 'cheese reaction.'

First-pass Through the Liver

A number of drugs are extensively metabolised during their first pass through the liver after absorption from the gut into the portal blood. Some understanding of the kinetics of this situation is needed to explain the mechanism of drug interaction with it. The concentration of drugs such as propranolol and lignocaine in the hepatic venous blood is often only 10 per cent to 30 per cent of that in the portal blood. A convenient model to describe the situation is to consider the liver as a well-stirred volume to which drug is being added by the portal blood and from which drug is spilling over into the hepatic vein. If there is no metabolism these concentrations will be the same. If metabolism occurs, some of the blood in the stirred volume will be 'cleared' of the drug and the concentration in the hepatic vein will be less than that in the portal vein. This clearance, used in the same sense as renal clearance, is termed the 'intrinsic hepatic clearance'[15]. If it is very high, as it is for a drug like propranolol, the hepatic venous concentration may be very low. A relatively small proportion of the dose absorbed from the gut will reach the systemic plasma unmetabolised, because the 'first pass clearance' is so high. Once the drug is in the body it will continue to be cleared at a high rate by the liver but only from the blood passing through the liver. If the extraction ratio is high, the dominant factor in clearance of drug already in the body will be hepatic blood flow. An increase in intrinsic hepatic clearance which raised the liver extraction ratio from portal to hepatic venous blood from 90 to 99 per cent would reduce the proportion of the dose reaching the systemic plasma to one-tenth of what it had been. The same change would only alter the clearance and thus the half-life of drug that penetrated into the body by 10 per cent (the difference between hepatic blood flow multiplied by 0.90 and by 0.99). Thus drug interactions that diminish or increase the proportion of a drug that is metabolised at the first-pass can have a dramatic effect upon the apparent dose absorbed. An interesting example is provided by phenacetin whose first-pass metabolism in gut wall and liver can be induced by polycyclic hydrocarbons such as occur in charcoal broiled beef or hamburgers. The plasma concentration achieved by an oral dose of phenacetin was reduced by a factor of four when subjects ate charcoal broiled steaks and hamburgers compared with the same diet cooked in a different fashion[16].

Protein Binding

This mechanism is less important than it seems, because of the kinetic situation already described. Naproxen is a highly protein bound non-steroidal anti-inflammatory agent with a low volume of distribution which has been well studied. Although concomitant administration of warfarin and naproxen has been shown to increase modestly the serum free fraction of warfarin after single or multiple doses in healthy subjects, there was no effect on steady-state concentrations of free warfarin or on the prothrombin time[17, 18]. One situation where this mechanism may be important is in the newborn infant with a poorly developed ability to conjugate bilirubin. Displacement of free bilirubin from serum albumin by drugs such as sulphamethizole may be important in the pathogenesis of kernicterus[19]. In general, if displacement has been shown and a clinically important event ensues, an additional mechanism must be invoked.

An increase in protein binding has recently been demonstrated for some basic drugs such as propranolol and chlorpromazine in patients with inflammatory bowel disease and infections in which plasma $\alpha_1$ acid glycoprotein is raised[20]. The clinical consequence of this effect remains to be demonstrated, but it can confuse interpretation of drug concentration in the plasma.

Transport Systems

Many physiological substances are poorly lipid soluble and are actively transported across cell membranes. The action of some drugs depends upon their ability to utilise transport systems. Adrenergic nerve blocking drugs such as guanethidine, bethanidine, debrisoquine and bretylium are concentrated over a thousandfold from plasma into the adrenergic nerve ending by the 'amine pump', otherwise known as Uptake-1. Inhibition of this pump by a tricyclic antidepressant such as imipramine, desipramine, amitriptyline or nortriptyline will antagonise the hypotensive effect of these drugs by inhibiting the transport system and preventing their concentration in the nerve ending[21].
**Receptor or Enzyme**

Drug interactions at a receptor or enzyme are more likely to arise by deliberate choice than by chance but where knowledge of drug action is incomplete they can be hazardous. The hypotensive effect of the \( \alpha \)-receptor agonist clonidine is antagonised by imipramine[22]. The most plausible explanation is that tricyclic compounds are weak \( \alpha \)-receptor antagonists and thus block the effect of clonidine upon a brain stem \( \alpha \)-receptor.

The uric acid lowering action of allopurinol was a chance discovery during its investigation as a potentiating agent for the antimetabolite 6-mercaptopurine in the treatment of leukaemia[23]. More recently it has been shown that the antihypertensive action of \( \beta \)-adrenergic blocking drugs and diuretics can be largely antagonised by concurrent treatment with indomethacin[24]. Our own study showed that the blood pressure of patients on propranolol rose by 14/5 mmHg when indomethacin 100 mg daily was added[25]. This is approximately the magnitude of the hypotensive effect of propranolol in patients with mild hypertension, suggesting an almost complete inhibition of its hypotensive action. The mechanism is unknown but it may be related to inhibition of formation of an endogenous prostaglandin such as prostacyclin which contributes to the late fall in the peripheral resistance after \( \beta \)-blockade.

**Induction or Inhibition of Hepatic Metabolism**

Some of the most important drug interactions occur because of a change in the activity of the hepatic drug metabolising enzymes. Provided the drug does not have a high first pass clearance, this type of interaction chiefly affects the rate of elimination from the body and thus the duration of action and the steady-state concentration during prolonged treatment. The time course of changes due to inhibition and to induction is quite different. Inhibition is immediate as it depends only upon the presence of the drug. The time to peak effect will depend upon the half-life of the target drug after its metabolism has been partially inhibited. Induction of drug metabolism involves the synthesis of increased amounts of the enzyme and, in man, may take two to three weeks to reach its maximal effect or to decline again when the inducing agent is stopped. Thus, inhibition of drug metabolism is more likely to be of immediate clinical relevance. A number of drugs that can inhibit hepatic metabolism are in common use, including oral contraceptives, dextropropoxyphene, allopurinol, sulphonamides, isoniazid, cimetidine[9] and ethyl alcohol which has acute inhibitory and chronic inducing effects[26]. Of particular interest is the inhibition of phenytoin metabolism in patients taking isoniazid for the treatment of tuberculosis. All patients found to be slow acetylators of isoniazid had raised phenytoin levels, whereas fast acetylators of the drug showed no increase in phenytoin concentration[27].

The use of phenobarbitone has declined and its place as the foremost enzyme inducer has been taken by the antibiotic rifampicin. This drug is a powerful inducing agent of the metabolism of natural substrates and other drugs. Treatment with rifampicin 600 mg for 14 days reduced the plasma concentration of 25-hydroxycholecalciferol by 70 per cent, reduced the half-life of antipyrene from 14.8 to 7.8 hours and caused a five-fold increase in urinary ratio of 6-beta-hydroxycortisol to 17-hydroxycorticosteroids[28]. Rifampicin therapy may reduce the effectiveness of corticosteroid therapy[29] or precipitate narcotic withdrawal in drug addicts[30]. Other drugs with inducing properties are phenytoin, spironolactone, griseofulvin, glutethimide and carbamazepine[9]. Dietary factors may also be important contributors to rates of hepatic drug metabolism. A high protein/low carbohydrate diet increases metabolism, as may cigarette smoking, environmental chemicals such as DDT, caffeine, and cabbage and other members of the brassica family[31,32].

**Excretion into Bile and Urine**

These interactions are not of great importance as a source of unexpected adverse effects but they are made use of in therapy, especially with uricosurics and potassium conserving diuretics. A recent example of this is the use of probenecid to delay renal elimination of methotrexate in patients with malignant disease[33]. On the other hand, unwanted effects can arise from the reduction in the renal clearance of lithium by indomethacin[34] and of digoxin clearance by quindine[35]. In addition, quinidine appears to displace digoxin from tissue binding sites. The net result is a substantial rise in circulating digoxin concentration. Interference with the enterohepatic circulation of drugs with a high biliary excretion can have clinical consequences. Cholestyramine administration can shorten the half-life of the cardiac glycoside digitoxin by 47 per cent[36].

**Clinically Important Interactions** (Table 3)

| Table 3. Classification of drug action by clinical importance. |
| --- |
| 1. The drug has a major effect upon a vital process, e.g. blood pressure, blood coagulation, control of breathing. |
| 2. The drug has a steep dose response curve, i.e. doubling the drug dose produces a clinically obvious increase in effect. |

Any interaction that disturbs treatment of a serious disease may under some circumstances lead to important adverse effects. Poor blood pressure control in a patient given guanethidine and a tricyclic antidepressant might lead to a stroke. Inhibition of phenytoin metabolism and consequent ataxia might lead to a patient falling and breaking a bone. Loss of potassium caused by a thiazide diuretic might precipitate a life-threatening cardiac arrhythmia. These combinations of events would not be expected to occur with any great frequency and only a few drug interactions are likely to have serious consequences in a high proportion of cases. Three of these are worth special mention.

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Haemorrhage on Warfarin

Warfarin antagonises the action of vitamin K in the liver and so reduces the synthesis of some of the proteins in the coagulation cascade. Warfarin is metabolised in the liver by oxidation. A number of drugs induce the mixed function oxidase system which metabolises warfarin in human liver endoplasmic reticulum. These include several barbiturates, rifampicin, carbamazepine, glutethimide and griseofulvin[9]. The time taken for maximal increase in the rate of warfarin metabolism is two to three weeks. By itself this effect is not particularly dangerous. The gradual loss of anticoagulant control can be restored by an increase in warfarin dosage although the dose might need to be doubled or tripled. A serious problem is likely to arise only if the physician in charge of the patient fails to realise what has happened and stops the inducing agent while maintaining the adjusted warfarin dose. Reversal of the inducing effect also takes several weeks and after this interval the patient might be exposed to the risk of a serious haemorrhage due to the now excessive dose of warfarin.

Inhibition of warfarin metabolism by enzyme inhibitors such as cimetidine, phenylbutazone, allopurinol, chloramphenicol, sulphonamides[9] and the contraceptive pill[37] potentiate the anticoagulant effect but do so on a much shorter time scale than induction. Treatment with cimetidine of a patient on coumarin anticoagulants doubles the plasma concentration of the anticoagulant and causes a substantial increase in the prothrombin time[38]. The maximum effect was reached within four days of starting treatment with cimetidine in patients taking warfarin but in a shorter time in those taking nicoumalone and phenindione. The main factor determining the time to peak effect is probably the half-life of the particular anticoagulant.

Unwanted Pregnancy on the Pill

Following the discovery that the incidence of thrombo-embolism was related to the oestrogen dose, the oestrogen content of oral contraceptives was reduced. Pregnancies have been reported in women on the pill taking enzyme inducing drugs such as rifampicin and phenobarbitone[39]. Rifampicin has been shown to increase the metabolism of both the oestrogen and progestogen components of the pill[40, 41]. Indeed, there have been reports of amenorrhea and increased cycle length in women taking rifampicin alone, presumably due to induction of the metabolism of endogenous steroids. A patient on glucocorticoids who relapsed during treatment with rifampicin has been reported[42]. It therefore seems advisable for patients treated with known enzyme inducing drugs to take two 'pills' each day or use alternative methods of contraception.

Hypertensive Crisis on Monoamine Oxidase Inhibitors

During the early 1960s there were dramatic reports of severe hypertension occurring in depressed patients being treated with monoamine oxidase inhibitors (MAOI) when they ate matured cheeses, Marmite and other food-stuffs[43]. The common factor was the high content of tyramine and certain other monoamines such as histamine in the foodstuffs responsible. Later it was recognised that cough and cold cures containing phenylpropanolamine could also cause severe hypertension in patients taking MAOI drugs. The hypertension was severe enough to cause a subarachnoid haemorrhage in some patients[44].

The outline of the mechanism was elucidated soon after the problem presented itself. Tyramine is normally extensively metabolised in the gut wall during absorption and in the liver at the first pass. Very little penetrates to the systemic arterial plasma. In a patient treated with MAOI drugs substantial amounts of tyramine reach the systemic circulation. Tyramine is an indirectly acting sympathomimetic amine that releases noradrenaline from storage granules in sympathetic nerve endings. Intravenous injection of 2 to 5 mg in an adult human causes a sharp but transient rise in blood pressure. However, the amount of tyramine absorbed from food-stuffs that cause the 'cheese reaction' may be little greater than this, so there must be another component of the reaction. In our opinion this is the inhibition of intraneuronal monoamine oxidase. Noradrenaline, released by tyramine, does not escape from the nerve by normal exocytotic process via vesicles but diffuses out. Under these circumstances, the intra-axoplasmic concentration of noradrenaline must be extremely high and if the A type intraneuronal monoamine oxidase is inhibited, it will be released as noradrenaline rather than as deaminated metabolites. This would also explain the observation that huge amounts of tyramine failed to raise the blood pressure in men pre-treated with deprenyl, a selective type B MAOI drug[45]. At present this is largely of theoretical interest but the development of new selective inhibitors will rekindle interest in the problem.

Prediction of Drug Interactions (Table 4)

Table 4. Classification by predictability.

|   |   |
|---|---|
| 1. | Predictable from existing knowledge of pharmacological effect. |
| 2. | Predictable from existing knowledge of pharmacokinetic properties. |
| 3. | Unpredictable from present knowledge. |
| 4. | Predictable but not predicted. |
| 5. | Overlooked or forgotten. |

Avoidance of unwanted drug interactions requires some knowledge of both the pharmacological action and pharmacokinetic properties of the drug. Most physicians know more about the former than the latter. There is need for more understanding of the fate of commonly used drugs even if this is at a very simple level. It does not usually matter whether the prescriber knows the precise chemical reaction that a drug undergoes but it is helpful to know if it is excreted unchanged in urine, if it is metabolised primarily by oxidation or conjugation, if it is an enzyme inducer or inhibitor, if it has a long or short half-life, and if it is highly protein bound. Some simple examples of
predictability may help to establish this point.

If a patient treated with propranolol develops an attack of wheezing he will not respond to any readily attainable dose of inhaled salbutamol or terbutaline. The shift of the dose-response curve to these agonists may be anything from ten to 300-fold depending upon the dose of propranolol. The interaction is easily predicted from a knowledge of pharmacology. If a patient with epilepsy, who is on phenytoin, develops tuberculosis and is treated with isoniazid he may develop phenytoin toxicity [27]. This is not so easily predicted unless one knows that phenytoin is metabolised by hydroxylation and that isoniazid is an inhibitor of hepatic drug oxidation. Cimetidine is also an important inhibitor of drug oxidation [38], so one might predict a need for caution if an epileptic patient on phenytoin required treatment for a peptic ulcer. The problem here is that the multiple forms of cytochrome P-450 make accurate prediction difficult. We can say that an interaction may occur but we cannot be certain that it will.

However, a more common source of drug interactions is the failure to predict events that are easily predictable or the overlooking of ones that are already known. We have seen patients whose death from haemorrhage while on warfarin was almost certainly due to unthinking addition of an inhibitor of microsomal oxidation (phenylbutazone) or withdrawal of inducing agents upon discharge from hospital. Aides-mémoire in the form of charts, discs and even textbooks can identify well-recognised interactions. However, the number of potential interactions with old and new agents are limitless and constant vigilance is required, especially in patients receiving multiple drug therapy. Think before adding or withdrawing other therapy to patients one of whose existing medicines has to be adjusted within a very narrow range. If that medicine is an anticoagulant, an antihypertensive, an anticonvulsant or a CNS depressant, think twice.

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References
1. Boobis, A. R., Brodie, M. J., Kahn, G. C. and Davies, D. S. (1980) In Microsomes, drug oxidations and chemical carcinogenesis, in press.
2. Lu, A. Y. H., Kuntzman, R. and Conney, A. H. (1976) Frontiers in Gastrointestinal Research, 2, 1.
3. Christensen, L. K., Hansen, J. M. and Kristensen, M. (1963) Lancet, 2, 1298.
4. Lewis, R. J., Trager, W. F., Chan, K. K., Breckenridge, A., Orme, M., Rowland, M. and Schary, W. (1974) Journal of Clinical Investigation, 53, 1607.
5. Sellers, E. M. and Koch-Weser, J. (1970) New England Journal of Medicine, 283, 827.
6. Anon (1979) Lancet, 1, 962.
7. Miller, R. R. (1977) American Journal of Hospital Pharmacy, 34, 415.
8. Goldberg, A. and Singer, J. J. (1979) Proceedings of the National Academy of Sciences, USA, 64, 134.
9. Griffin, J. P. and D’Arcy, P. F. (1979) A Manual of Drug Interactions, Bristol: John Wright.
10. Prescott, L. (1969) Lancet, 2, 1239.
11. Gallo, D. G., Bailey, K. R. and Sheffner, A. L. (1965) Proceedings of the Society of Experimental Biology & Medicine (N. Y.), 120, 60.
12. Nimmo, J., Heading, R. C., Tothill, P. and Prescott, L. F. (1973) British Medical Journal, 1, 587.
13. George, C. F., Blackwell, E. W. and Davies, D. S. (1974) Journal of Pharmacy and Pharmacology, 26, 265.
14. Marley, E. (1977) In Drug Interactions, p. 171. (ed. D. G. Grahame-Smith), London: Macmillan.
15. Wilkinson, G. R. and Shand, D. G. (1977) Clinical Pharmacology and Therapeutics, 18, 377.
16. Pautuck, E. J., Hsiia, K.-C., Conney, A. H., Garland, W. A., Kappas, A., Anderson, K. E. and Alveares, A. P. (1976) Science, 194, 1055.
17. Slattery, J. T., Levy, F., Jain, A. and McMahan, F. G. (1979) Clinical Pharmacology and Therapeutics, 25, 51.
18. Jain, A., McMahan, F. G., Slattery, J. T. and Levy, G. (1979) Clinical Pharmacology and Therapeutics, 25, 61.
19. Silverman, W. A., Anderson, D. H., Blanc, W. A. and Crozier, D. N. (1956) Paediatrics, 18, 614.
20. Piafsky, K. M., Borgia, O., Oder-Cederlof, I., Johansson, C. and Spoqest, F. (1978) New England Journal of Medicine, 299, 1455.
21. Bouillin, D. J. (1977) In Drug Interactions, p. 57. (ed D. G. Grahame-Smith). London: Macmillan.
22. Reid, J. L. and Briant, R. H. (1977) In Drug Interactions, p. 231. (ed D. G. Grahame-Smith). London: Macmillan.
23. Muggia, F. M., Ball, T. J. and Ulltman, J. (1967) Archives of Internal Medicine, 120, 183.
24. Durao, V., Prata, M. M. and Goncalves, L. M. P. (1977) Lancet, 2, 1005.
25. Watkins, J., Abbott, E. C., Hensby, C. N. and Dollery, C. T., in preparation.
26. Linnoila, M., Mattila, M. J. and Kitchell, B. S. (1979) Drugs, 18, 299.
27. Brennan, R. W., Deheja, H., Kutt, H., Verebelyi, K. and McDowell, F. (1970) Neurology, 20, 687.
28. Brodie, M. J., Boobis, A. R., Dollery, C. T., Hillyard, C. J., Brown, D. J., MacIntyre, I. and Park, B. K. (1980) Clinical Pharmacology and Therapeutics, in press.
29. Hendricks, W., McKiernan, J., Pickup, M. and Lowe, J. (1979) British Medical Journal, 1, 306.
30. Bending, M. R. and Skacel, P. O. (1977) Lancet, 1, 1211.
31. Vessel, E. S. (1978) Clinical Pharmacology and Therapeutics, 22, 659.
32. Conney, A. H., Pautuck, E. J., Kuntzman, R., Kappas, A., Anderson, K. E. and Alveares, A. P. (1979) Clinical Pharmacology and Therapeutics, 27, 707.
33. Aherne, G. W., Piall, E., Marks, V., Mould, G. and White, W. F. (1978) British Medical Journal, 1, 1097.
34. Frolich, J. C., Leftwich, R., Ragheb, M., Oates, J. A., Reimann, I. and Buchanan, D. (1979) British Medical Journal, 1, 1115.
35. Hager, W. D., Fenster, P., Mayersohn, M., Perrier, D., Graves, P., Marcus, F. I. and Goldman, S. (1979) New England Journal of Medicine, 300, 1538.
36. Rollins, D. and Klaassen, C. D. (1979) Clinical Pharmacokinetics, 4, 368.
37. Teresa, E., Vera, A., Ortigosa, J., Alonso Pulpon, L., Puente Arus, A. and Artaza, M. (1979) British Medical Journal, 2, 1260.
38. Serlin, M. J., Sibone, R. G., Mossman, S., Breckenridge, A. M., Williams, J. R. B., Atwood, J. L. and Willoughby, J. M. T. (1979) Lancet, 2, 317.
39. Burley, D. M. (1977) In Drug Interactions, p. 295. (ed D. G. Grahame-Smith). London: Macmillan.
40. Bolt, H. M., Kappus, H. and Bolt, M. (1975) European Journal of Clinical Pharmacology, 8, 301.
41. Back, D. J., Breckenridge, A. M., Crawford, F., MacIver, M., Orme, M., Park, B. K., Rowe, P. H. and Smith, E. (1979) European Journal of Clinical Pharmacology, 15, 193.
42. Edwards, O. M., Courtenay-Evans, R. J., Galley, J. M., Hunter, J. and Tait, A. D. D. (1974) Lancet, 2, 549.
43. Blackwell, B. (1963) Lancet, 1, 849.
44. Blackwell, B., Marley, E., Price, J. and Taylor, D. (1967) British Journal of Psychiatry, 113, 349.
45. Ekstedt, B., Magyar, K. and Knoll, J. (1979) Biochemical Pharmacology, 28, 919.