£25m—half the amount cut from the building programme. The question of paying for new hospitals is one of political priorities, and I cannot help feeling it is unfortunate that there is no political ideology which makes it imperative to rebuild the shack in which my grandfather died.

The Royal Commission could, perhaps, suggest that we devote more money to hospital building, or at least try to put it on the same time scale as other constructions of comparable complexity—Spaghetti Junction and the North Sea oil platforms didn't take decades to complete.

The Commission has also been asked to make recommendations about manpower. It might ask whether it is necessary for three-quarters of registrars to be in "dead-end" jobs. Those who fail to become senior registrars are all too often those with the best *clinical* training. Patient-orientated district hospitals and rat-race-orientated teaching hospitals would both benefit from an end to the distinction between them: there could be grouping into teaching areas, such as occurs to some extent in London. This would facilitate wider use of "rotational" schemes, which, if sensibly co-ordinated with further promotion, would be a legitimate way of filling unpopular jobs—just as house jobs and casualty posts are filled because of GMC and FRCS regulations.

Ultimately, however, doctors are going to be drawn into hospital training only by the rewards of becoming a consultant. The Commission should ask itself whether these rewards are adequate. The medical manpower market in the Western world is still free, and the NHS will get only what it pays for. Low pay differentials are accompanied in communist countries by restrictions on emigration: if Britain offers poor rewards to highly-trained men she should not be surprised if the more enterprising ones leave.

Five minutes as a witness

This unfortunate Commission will be bombarded with facts, figures, and indignation. If I had five minutes of their time, I should tell them first of all that most of the medicine I have seen practised in our tumbledown hospitals has been superb, in contrast to hair-raising hearsay evidence about standards in the plush private sector. Next I should point to the striking (if you'll pardon the phrase) lengthening of waiting lists in 1975 as evidence of the effect of staff morale on the service enjoyed by patients. Only by raising this morale, I would say (thumping the table), can this service be improved: we cannot be legislated into being punctual, sympathetic, or more industrious.

Then I might offer some impressions of misspending: the relentless increase in the numbers of administrators and high-ranking nurses; the creed that something disposable is cheaper than something we can use again (economic sense, but common-sense nonsense); the idea that building and patching up temporary premises is cheaper than proper permanent accommodation; or the fact that never once have I been asked to justify prescribing an expensive drug.

Lastly I should plead eloquently for some way of converting our suggestions and complaints into visible improvements; at present they seem merely to be adroitly fielded and thrown into a pigeon hole. Indeed (and I wouldn't dare say *this* to them), perhaps the whole idea of a Royal Commission is one huge governmental pigeonhole: "Ah, yes, well, we can't do anything here until the Royal Commission has reported." Does the Commission, already famous for its "experience, expertise, and wisdom," really believe that its cultured voice will influence an administration that has looked unmoved at the unthinkable sight of doctors going on strike? Or am I being too cynical?

Today's Treatment

Diseases of the alimentary system

Absorption, distribution, and metabolism of drugs; effects of disease of the gut

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Because the pharmacological and therapeutic effects of drugs are usually related to their free concentration in extracellular fluid a knowledge of the factors governing absorption, distribution, and elimination is essential to rational prescribing. Since most drugs are given by mouth, both for the convenience of the patient and because of the wide margin of safety that this route affords, the initial section of this article is confined to factors affecting absorption from the gut. It should, however, be remembered that advantages may result from a failure of drugs to be absorbed—for example, topical treatment with sulphonamides

and corticosteroids may reduce the systemic side effects of these drugs in inflammatory disorders of the bowel.

Drug absorption

The most important factors influencing absorption of drugs from the gastrointestinal tract are formulation, gastric and intestinal motility, physicochemical characteristics of the drug, and the surface area available for absorption.

FORMULATION

Drugs may be given by mouth in solution or suspension or as tablets, capsules, and slow-release preparations. Optimal absorption, however, cannot occur unless drugs are in solution by the time they reach the small intestine. Thus formulation is a major factor determining the rate and extent of absorption. An average tablet is a complex product with 20 or so constituents distributed between the core and its coating mass; typical ingredients include binding agents, diluents,

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disintegrating agents, dyes, and lubricants. Although various marketed brands of a single drug contain an identical amount, as dictated by the *British Pharmaceutical Codex*, and disintegrate in vitro within a specified time, they may differ in their rates of dissolution and particle size. Such variation between formulations may lead to major differences in the total amount of drug reaching the systemic circulation unchanged (bioavailability), as has been shown for digoxin, chloramphenicol, nitrofurantoin, phenindione, phenytoin, phenylbutazone, tolbutamide, and tetracyclines.¹

GASTRIC AND INTESTINAL MOTILITY

A second major factor governing drug absorption is gastric emptying, which occurs exponentially at a rate that varies widely among individuals. For patients in whom gastric emptying is rapid, comparatively much of the dose is presented to the small intestine in a short time. If the formulation has ensured rapid dissolution in the stomach, drug absorption from the intestine can be both rapid and relatively complete. If, however, dissolution is slow but gastric emptying is rapid, undissolved drug will be presented to the small intestine and absorption may be incomplete—for example, certain brands of digoxin before September 1975. Gastric emptying may be modified by drug treatment and by surgery; metoclopramide improves the co-ordination of gastric muscular activity and thereby accelerates the rate of emptying, whereas anticholinergics (including many tricyclic antidepressants) have the opposite effect. The pattern and rate of gastric emptying may also be altered by partial gastrectomy or vagotomy and antrectomy. Drugs whose absorption has been shown to depend on gastric emptying include digoxin, levodopa, lithium carbonate, and paracetamol.

Intestinal motility is important in the absorption of water and electrolytes² but it also determines the surface area available for drug absorption.

PHYSICOCHEMICAL CHARACTERISTICS

Physicochemical characteristics that are important in determining the absorption of drugs include the size of the molecule, its ionisation constant, and the lipid partition coefficient.

Most drugs used in clinical practice are of relatively low molecular weight: cholestyramine is an exception and hence is unabsorbed. It can therefore be used to bind drugs within the gastrointestinal tract—for example, digitoxin—and will prevent enterohepatic recirculation of the latter. It also binds to warfarin and antibiotics³ and reduces their absorption.

Many drugs are either weak acids or bases; hence they exist in both ionised and non-ionised forms. The extent of ionisation is determined by the ionisation constant, or pKa, which is defined as the pH at which half of a drug is in the ionised state. The importance of this concept is that a non-ionised drug is lipid-soluble and diffuses freely across cell membranes, whereas the ionised (charged) moiety cannot cross cell membranes. Thus in the case of aspirin, which has a pKa of 3.5, most of the drug is non-ionised in the stomach (pH 1-2), and much of it is absorbed from this organ. The absorption of aspirin is, however, diminished in pernicious anaemia.

Most basic drugs are absorbed from the small intestine, but even here only a small proportion of quaternary ammonium compounds are in the non-ionised state, and their absorption is poor. Certain highly charged chemicals including the herbicide paraquat may be actively absorbed by a carrier-mediated transport system. Once dissolved, however, the most important factors determining the rate and amount absorbed are the drug's ionisation constant and the lipid partition coefficient of the non-ionised moiety.⁴

SURFACE AREA OF SMALL INTESTINE

Another factor determining drug absorption is the surface area of the small intestine. Normally this is about the size of two tennis courts (doubles size), but its absorptive capacity may be reduced in coeliac disease and some inflammatory bowel conditions. Impaired absorption of digoxin has been found in various malabsorption syndromes, especially coeliac disease. In contrast, most antibiotics are well absorbed in this condition (indeed, absorption may be slightly better than normal), but malabsorption of trimethoprim and clindamycin has been found in jejunal diverticulosis. The pattern of antibiotic absorption is often disturbed in Crohn's disease.⁵

Although local blood supply determines the rate of absorption of drugs given by subcutaneous and intramuscular injection, there is little evidence in man that blood flow to the gut limits absorption, except in patients with cardiogenic shock or gross heart failure.

Other factors reducing bioavailability

Several other factors may limit the amount of drug reaching the systemic circulation unchanged. Firstly, some drugs, including benzylpenicillin, are destroyed by gastric acid. Secondly, some metabolising enzymes are located in the brush border of the small intestine: these include sulphokinases, monoamine oxidase, non-specific esterases, and uridine diphosphate-glucuronyl transferase. The beta-adrenoceptor stimulant drug isoprenaline is extensively metabolised in the intestine, and normally only a small amount reaches the systemic circulation unchanged. The conjugation of isoprenaline may be reduced by salicylamide, and hence the effects of isoprenaline taken by mouth are increased. Similarly, levodopa is extensively metabolised in the intestine unless given with a decarboxylase inhibitor, and naturally occurring indirect sympathomimetics such as tyramine are normally inactivated in the intestine but may cause hypertensive crises in patients receiving monoamine oxidase inhibitors.

The final obstacle that a drug must traverse before reaching the systemic circulation is the liver. Many lipid-soluble drugs, including beta-adrenoceptor antagonists—such as propranolol and oxprenolol—the analgesics paracetamol and pentazocine, tricyclic antidepressants, and some tranquilisers undergo extensive extraction and biotransformation in this organ. This may lead to major individual differences in the peak levels attained after administration by mouth. This phenomenon is often referred to as a "first-pass effect"; together with variation in the rate of gastric emptying it may lead to major individual differences in response to drugs given by mouth.

Distribution

The major factors governing drug distribution are physicochemical, the route of administration, regional blood flow, binding to proteins, and the existence of transport systems; these are, however, interdependent.

Drugs enter the extracellular space by passive diffusion through gaps between the capillary endothelial cells. Thus unless they are too large to diffuse through the pores—in the case of heparin, for example—most drugs will be distributed throughout extracellular fluid. Access to the brain and cerebrospinal fluid (CSF) is, however, limited by the existence of tight junctions between the endothelial cells, which, together with a continuous turnover of CSF and active carrier-mediated outward transport (for instance, penicillin), constitute the blood-brain barrier.⁶ Drugs that are extensively un-ionised at physiological pH are freely diffusible across lipoprotein cell membranes and can enter the brain, CSF, and cells throughout the body. Their apparent volume of distribution may therefore be several times that of body water. Lipid-soluble basic drugs, including lignocaine, propranolol, and the tricyclic antidepressants, are widely distributed and concentrate in the tissues, especially brain, liver, and lung. This pattern of distribution may have important consequences in terms of both efficacy and side effects.

Drug distribution is also influenced by the route of administration. Drugs injected intravenously are preferentially distributed to organs and tissues with a high regional blood flow—for example, heart, brain, and kidneys. Thus anaesthesia occurs within seconds of a single intravenous injection of thiopentone because the drug rapidly achieves a high concentration in the brain. But its action is short-lived because subsequent redistribution into other tissues occurs and the concentration in the brain falls below the minimum needed to induce sleep. Similarly, the cardiac effects of drugs start within a minute or less of intravenous injection, and reversion of cardiac arrhythmias often occurs during this time. Fatal arrhythmias, however, may occur when potassium salts are given too rapidly by this route.

Many drugs are carried in blood bound to non-specific sites on plasma proteins, usually albumin. Drug bound to protein is in equilibrium with that free in the plasma water, but only the latter exerts a pharmacological effect. The amount of drug bound to protein is determined by the number of binding sites available (which varies for different drugs), their affinity for the drug, and its concentration. Plasma protein binding is important in drug distribution (and elimination) since only the unbound fraction is available for distribution. Thus the higher the binding of sulphonamides to albumin the

greater the proportion that remains in the blood and the lower the concentration in CSF.⁷ In the case of diazoxide, 96-98% of which is normally bound to plasma proteins, it is possible to saturate the binding sites by rapid intravenous injection of the drug. This allows the drug to be distributed to sites on vascular smooth muscle and enhances its therapeutic effect. The distribution and efficacy of drugs that are heavily bound to plasma proteins may be influenced by disease, including hypoalbuminaemia caused by cirrhosis of the liver⁸ or the nephrotic syndrome. In addition, binding may be abnormal in patients who are uraemic.⁹

Some drugs become highly concentrated in the tissues because their chemical structure allows them to be taken up by selective transport systems. For example, the adrenergic neurone blocking drugs bethanidine, debrisoquine, and guanethidine become concentrated in the adrenergic nerve terminal because they are transported by a system known as uptake.¹⁰ In contrast the concentration of penicillin in CSF is reduced by a carrier-mediated outward transport that can be blocked by the uricosuric probenecid.¹¹

Elimination (including inactivation)

The action of many drugs ends with their excretion; possible routes of elimination include pulmonary, renal, biliary, and intestinal. Almost all volatile anaesthetics are excreted, largely unchanged, by the lungs. In addition, the anticonvulsant paraldehyde is partially eliminated by this route. Factors that influence the rate of elimination, therefore, include the effective tidal volume, frequency of ventilation, the solubility of the drug, and ventilation-perfusion relationships in the lung.

Drugs may be handled at three sites in the nephron: they may be filtered at the glomerulus or either secreted by the proximal convoluted tubule or passively reabsorbed from the distal convoluted tubule, or both. Glomerular filtration is determined largely by cardiac output, which in turn relates to plasma volume, but may be reduced by renal disease and in old age. Drugs that undergo active tubular secretion include penicillins, cephalosporins, and probenecid. Most lipid-soluble drugs are almost entirely reabsorbed in the distal nephron by passive diffusion; the latter is pH-dependent and alkalisation promotes the excretion of phenobarbitone and aspirin, whereas acidification increases the clearance of amphetamine.

Biliary excretion is relatively unimportant for most drugs, because in man the threshold for elimination by this route lies at a molecular weight of about 500 (in contrast to rats, in which the threshold occurs at a molecular weight of 325). None the less, a few drugs do undergo biliary elimination in man, but some—for example, digitoxin and practolol—are reabsorbed from the small intestine, a process referred to as enterohepatic recirculation.

Recently several drugs have been shown to undergo direct elimination across the intestine; they include the beta-adrenoceptor antagonist acebutolol, the antibacterial-antiprotozoal drug metronidazole, and the short-acting cardiac glycoside ouabain. The precise mechanism of this form of excretion is unknown. Small amounts of drugs may be excreted in other fluids, such as breast milk, tears, saliva, and sweat. These routes, however, are quantitatively relatively unimportant and are not considered further.

Drug metabolism

Drugs may be metabolised at many sites but the liver is the most important one. Most drugs are biotransformed by a group of enzymes of relatively low specificity that are also responsible for the degradation of endogenous materials such as bilirubin and hormones. These drug-metabolising enzymes, which are associated with the endoplasmic reticulum, are most active in the liver but exist also in the intestine, kidney, lung, and skin. Pathways of drug metabolism in the microsomal system can broadly be categorised into two main types—firstly, pre-conjugation or phase I reactions, which serve to append or reveal suitable chemical groupings such as OH, NH₂, and COOH within the drug; and, secondly, conjugation or phase II reactions, in which groupings revealed by phase I reactions are coupled to endogenous compounds such as glucuronic acid and sulphate. The end products are more water soluble and can be eliminated in bile or urine. Phase II reactions may occur without prior oxidation, reduction, or hydrolysis if suitable groupings already exist.

Most phase I metabolites are generated by a common hydroxylating enzyme system known as cytochrome P450. The activity of the system is in part genetically determined but is also under the influence of

environmental factors including substances present in the diet and various medicines. Drugs may affect the activity of the P450 cytochrome system in one of two ways. Firstly, the amount and activity of the enzyme may be increased by drugs that are referred to as inducers of microsomal oxidation. These include barbiturates, glutethimide, dichloralphenazone (the phenazone fraction), haloperidol, alcohol (in some people), and the antifungal agent griseofulvin. When one of these drugs is introduced into the treatment of a patient stabilised on another that is metabolised by hepatic microsomal enzymes, the effect is to increase gradually the rate of inactivation of the latter. Thus to maintain the previous pharmacological and therapeutic effects it may be necessary to increase the dose twofold or threefold (sometimes tenfold). Other drugs may inhibit the action of hepatic microsomal enzymes and include methylphenidate, chloramphenicol, disulfiram, allopurinol, alcohol (some people), and dextropropoxyphene (in Distalgesic).

Generally phase I reactions lead to a diminution of pharmacological activity, but there are important exceptions to this rule. These include the red dye Prontosil and imipramine, which are converted to the active metabolites sulphanilamide and desipramine respectively. Toxic metabolites of phenacetin and paracetamol may also be generated by this system.

Some phase II reactions take place in the cell sap; among the enzymes located therein, N-acetyltransferase is responsible for the acetylation of isoniazid, hydrallazine, sulphonamides, and procainamide. The activity of this enzyme is genetically determined (probably in an autosomal recessive manner), and patients are either fast or slow acetylators. The proportion of the two genotypes varies among ethnic groups; some 95% of Eskimos are fast acetylators, whereas among Caucasians the proportion is less than half.

Hydrolysis of some drugs takes place in the blood; non-specific esterases exist in plasma, and these are responsible for the hydrolysis of succinylcholine, procaine, and procainamide. The activity of plasma esterase (pseudocholinesterase) is also genetically determined, but the trimodal distribution in activity suggests an autosomal, autonomous inheritance. Both the heterozygotes and homozygotes for normal enzyme activity hydrolyse succinylcholine rapidly, whereas the homozygotes for the atypical enzyme may suffer from prolonged apnoea after the use of this neuromuscular blocking drug.

Consequences of differences in bioavailability and rates of elimination

Despite the convenience of taking drugs by mouth individual differences in the amount of drug reaching the systemic circulation and in the rate of elimination of drug from the body may lead to major differences in response to treatment. Thus average doses quoted in textbooks and the *British National Formulary* should be regarded as optimal for only a proportion of patients. Standard doses may be totally inadequate for some patients, because of either reduced bioavailability or rapid elimination, while in others the same dose may be excessive and cause toxicity.

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