DRUG INTERACTION IN ANAESTHESIA
A REVIEW

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RECENTLY, THE PROBLEMS and hazards associated with the interaction between drugs have received widespread attention. The potential for the interaction has certainly increased in recent years. It has been demonstrated that the average patient will receive eight different drugs during one hospitalization.[1] In many instances, one drug may profoundly modify the action of another. In such drug interactions the effect of one may be prevented, or its action may be intensified. Though sometimes beneficial, drug interactions are most often recognized when they increase mortality or morbidity. They form around 19–22 per cent of causes of adverse drug reactions.[2] There are a number of good general reviews on drug interactions,[3–6] but there are not many which are concerned primarily with the practice of anaesthesia.[7,8] The anaesthetist uses a wide variety of pharmacologically active drugs which may interact with one another or with other drugs the patient is receiving. The multitudes of possible interactions limit the possibility of reviewing each individual drug interaction. This also entails a lot of repetition and would not keep pace with the number of new drugs introduced into the market every month. Our aim is elucidation of the principles and mechanisms involved with examples which are of interest to the anaesthetist.

Several mechanisms of interaction are recognized.

1. *A direct physical or chemical interaction*

A familiar example is the neutralization of heparin with protamine. This is an example, also, of a useful drug interaction. The basic protamine combines with the strongly acidic heparin to form a stable salt with loss of anticoagulant activity. Heparin in high doses, 50–100 mg/kg can also antagonize d-tubocurarine due to the same mechanism.[9,10] The strongly acidic groups of heparin neutralize the basic curare molecule.

Tetracyclines are chelating agents and gastrointestinal absorption of these antibiotics is inhibited when given simultaneously with antacids which are multivalent cations (e.g. Ca^{++}, Mg^{++}, or Al^{+++}).[11]

Many drugs are incompatible physically or chemically and cannot be used together in intravenous solutions. Sometimes the incompatibility is perceptible visually as a precipitate, haze, etc., or it may pass unnoticed in spite of chemical decomposition or inactivation. Many drugs are supplied as systems in which environmental factors such as pH, gas content, solvent type, and moisture are carefully controlled. When they are diluted to a large volume by an aqueous solution having a different pH, which contains atmospheric oxygen and additional ingredients

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which may catalyze or initiate a reaction, decomposition probability increases. The pH of the admixture is probably the most dominating factor influencing chemical incompatibility.[12] Succinylcholine chloride is available in solution at a pH of 3.0–4.5. It is rapidly hydrolyzed if mixed with thiopentone sodium with a pH of 10.8. Meperidine (Demerol®) with pH adjusted between 3.5–6 forms a precipitate with thiopentone solution for the same reason. The buffer capacity of the intravenous fluid vehicle or additive is also important. In general, intravenous fluids containing organic anions, lactates, and acetates for example, have a relatively high buffer capacity. This is the reason why an acid-sensitive drug like thiopentone may precipitate in a fluid containing these anions at a pH of 5.5 and not precipitate in a plain dextrose solution at a pH of 4.5. In the latter case, the alkalinity of thiopentone is enough to raise the pH of the admixture beyond that of precipitation. Physical incompatibility may be manifested when mixing dextrose solutions and blood (the dextrose causes clumping of red cells which produces transfusion reactions), hypertonic solutions of mannitol and blood (the mannitol causes agglutination and irreversible crenation of red blood cells), and when administering insulin as an intravenous drip (part of the insulin adsorbs to the glass). The importance of these incompatibilities is obvious since the patient may not get the full therapeutic effect of the medication. In addition, by-products may be formed which could have an adverse effect. In view of the increasing trend toward mixing parenteral drugs, a knowledgeable pharmacist should be consulted before therapy with a drug mixture in intravenous solution is started.

2. *Interaction at the site of absorption*

Regarding intestinal absorption, many drugs are weak acids or weak bases and the proportion of ionized drug is dependent on the pH of its milieu. Un-ionized compounds generally are more soluble in lipid than they are when ionized. In an un-ionized form they readily cross cell membranes. Ionized drugs are generally polar or water soluble and transfer across cell membranes will be relatively slow. For this reason, weak bases are generally more rapidly absorbed from the intestines than weak acids. Absorption of weak acids in the small bowel is achieved, however, because of the large surface area.[13] Some drugs, such as iron salts, are absorbed best when the gastric content is highly acid; other drugs, such as penicillin G, are destroyed at low pH. Absorption may also be affected by the concomitant administration of other ions. We mentioned previously the fact that antacids containing Mg^{++} and aluminum interfere with the absorption of a variety of drugs from the intestinal tract, notably the tetracyclines. Neomycin, widely used for the preoperative sterilization of the alimentary tract, has been implicated in the production of a malabsorptive state in humans and animals.[14,15] Drugs like morphine, atropine, and other anticholinergic agents slow the absorption of other drugs from the small bowel by delaying the gastric emptying time. The anaesthetist is familiar with the latter action in relation to the hazards of pulmonary aspiration in patients with a full stomach.

The use of a mixture of a local anaesthetic and epinephrine is, as a general rule, beneficial in slowing the rate of absorption by producing vasoconstriction. This prevents the sudden flooding of the circulation with the local anaesthetic leading to systemic reactions with the additional benefits of prolonged anaesthesia and

decreased bleeding. However, the beneficial effect of epinephrine varies with the agent used. Thus the action of lidocaine is markedly prolonged, while that of prilocaine, mepivacaine, and bupivacaine are a good deal less or not at all affected. It has been suggested that lidocaine has a relatively low affinity for tissues and that epinephrine slows its rate of removal from the tissues. The other agents mentioned on the other hand have a higher tissue affinity. The effect of epinephrine also varies with the site of injection. It is thought that it does not prolong the duration of action of local anaesthetics on mucous membranes, nor does it hinder their rapid absorption therefrom.[16] On the other hand, the addition of hyaluronidase to a local anaesthetic hastens the onset of anaesthesia, tends to reduce the swelling caused by local infiltration, and prevents the onset of haematoma, due to the action of the "spreading factor". Unfortunately, the wider spread of the local anaesthetic solution increases its absorption, thus shortening the duration of anaesthesia and increasing the incidence of toxic reactions. When epinephrine is added, hyaluronidase does not affect the duration of analgesia nor does the epinephrine affect the diffusion facilitated by the hyaluronidase. However, the fact that it cannot compensate for an incorrectly placed needle, the increased incidence of toxic reactions and the introduction of new local anaesthetic drugs with marked penetrance, have limited the use of hyaluronidase.[17]

It is equally important to remember the relationship between the alveolar ventilation and the rate of uptake of inhalation agents.[18] When an anaesthetic agent is introduced into the inspired air, the alveolar and the arterial concentrations of the agent gradually approach the inspired concentration. Alveolar ventilation is among the factors that determine the rate of equilibration. This is of the greatest importance for the more soluble anaesthetics such as diethyl ether and halothane. Thus overdosage with premedicant drugs, especially the narcotics, or too much intravenous barbiturate, or too early administration of a neuromuscular blocker, reduce ventilation and delay development of the alveolar concentration of the anaesthetic required to provide adequate anaesthesia. Conversely, carbon dioxide increases the speed of induction of inhalation anaesthesia by augmenting both the ventilation and the cerebral blood flow. In the past some anaesthetists have added 5 per cent of carbon dioxide to the inhalation mixture when inducing anaesthesia with a slow and highly soluble agent such as diethyl ether. In this way they would shorten the excitement stage with its potential for respiratory obstruction, cardiac arrythmias, and body injury. The technique of nitrous oxide, oxygen, diethyl ether sequence using carbon dioxide as a respiratory stimulant has been recommended by Inkster for the inexperienced anaesthetist when dealing with patients likely to vomit during the induction.[19] By speeding the induction, the patient does not remain too long in the phase of excitement, when central stimulation of the vomiting centre may occur. In addition, the drive to the respiratory centre overcomes any tendency to breath-holding, an essential preliminary to active vomiting. If in spite of this vomiting does occur, the protective reflexes should be still active. Unfortunately, the ill-advised use of carbon dioxide has dangers which have led many physicians to dispense with it entirely.

Another interaction at this site which is in daily use is based on the "second gas effect". Epstein and his colleagues demonstrated some years ago that when a constant concentration of halothane was inspired, the rise in alveolar concentration

was accelerated by concomitant administration of N_2O. This accelerated rise in alveolar halothane was called the "second gas effect" because it was postulated that it is due to a high initial uptake of the first gas, N_2O (being relatively insoluble), into the blood stream, creating a potential sub-atmospheric intrapulmonary pressure which leads to an increased tracheal inflow.[20] Stoelting and Eger have more recently advanced an additional explanation, called the "concentrating effect". As a result of the uptake of a large volume of N_2O, the alveolar gas volume is reduced, resulting in concentration of the second agent, for example, halothane.[21] This effect applies also to the other soluble anaesthetics such as diethyl ether and methoxyflurane.

3. *Interaction at the plasma protein binding sites*

Some drugs are highly bound to plasma proteins and in this state are usually pharmacologically inactive. It is thought that the unbound drug in the plasma is free to move into tissues to combine with postulated possible receptor sites. The binding is often to the albumin fraction and is reversible. The mechanism of the binding may be complex and depends on the molecular structure of the drug and its binding site. Since the binding is reversible, simple mass laws can often describe the relationship between bound and unbound drug at equilibrium.[22,23]

In a simple analysis the extent of plasma protein binding of a drug depends on two factors: (1) The number of binding sites available, and (2) The affinity of the drug for those sites. There are usually a limited number of binding sites for any drug having an affinity for plasma protein. At low plasma concentrations of drug, when only a small fraction of available sites are occupied, a specific proportion of the drug will be bound depending on the affinity of the drug for the binding site. When the available sites become nearly saturated, however, increasing concentrations of drug will result in a higher ratio of unbound to bound drug. To be clinically relevant the extent of protein binding for any drug should be studied at therapeutic plasma concentrations. Evaluation of binding at concentrations above the therapeutic range may, however, be of some value in explaining toxic reactions due to overdose.

Competition between drugs for the same binding sites on plasma proteins may cause unexpected results.[24] When displaced from binding sites by another drug, a drug becomes available in the unbound and pharmacologically active form, and its action may be intensified. For example, the oral hypoglycaemic tolbutamide binds to plasma proteins. Bishydroxycoumarin (Dicumarol®) displaces tolbutamide from its binding site, making more tolbutamide available in the free form. As a consequence, diabetic patients taking tolbutamide may have a sudden and dangerous hypoglycaemia if they take bishydroxycoumarin simultaneously. These interactions are particularly significant with highly bound drugs, since a small shift in their complex with protein will result in a relatively large increase in the unbound, active component. The order of administration of the interacting drugs may also be of importance. Tolbutamide displaces bishydroxycoumarin in patients maintained on that anticoagulant, leading to increased anticoagulant activity. However, the latter does not seem to be altered in patients who receive bishydroxycoumarin while on tolbutamide therapy.[25] This agrees with a later observation made by Sellers and Koch-Weser while studying the displacement of warfarin

from its binding sites on albumin by chloral hydrate.[26] They found that if only a single dose of warfarin was given to their volunteers who were maintained on chloral hydrate therapy, no potentiation of warfarin action was observed. This is in contrast to the reaction of subjects maintained on both warfarin and chloral hydrate. If only a single dose is given, the consequences of the increased rate of elimination of the drug may overcome the effect of the initial higher free warfarin concentration. It is apparent that to study the clinical effects of the interaction of these anticoagulants with respect to their hypothrombinemic effect, the subjects should be maintained on the anticoagulant.

Both d-tubocurarine and succinyldicholine are bound to plasma proteins.[27,28] Usubiaga, *et al.*, attributed the prolongation of succinylcholine apnea by some local anaesthetics to competition at the plasma protein sites.[29] Although this example has been much quoted, we doubt the validity of the explanation. During the first 45 minutes subsequent to administration, the binding of succinylcholine to plasma is negligible, and it is unlikely that the local anaesthetic concentration in the blood would reach a level high enough to be of displacing value. Also for a rapidly metabolized drug like succinylcholine, displacement will reduce its biological half life by providing more substrate for enzymatic hydrolysis. Nevertheless, since binding of the myoneural blocking agents is reasonably high, other highly bound drugs may interact, increasing the concentration of the non-depolarizing relaxants at the myoneural junction. This remains a theoretical possibility. Barbiturates are bound to a varying extent by the albumin fraction of proteins. The chemical structure of the barbiturates is important since compounds having longer side chains are bound more strongly than those with short ones. The sulphur analogues are more strongly bound than the oxygen congeners. As a rule short acting barbiturates are more strongly bound than the long acting. In the case of thiopentone, 60–70 per cent of the drug in the blood may be protein bound.[30] Lasser, *et al.*, have shown that several opaque media used in clinical radiology extend the duration of pentobarbital anaesthesia in rats. This confirms a previous clinical impression and was shown to be due to competitive protein binding.[31]

Anaesthetic gases and vapors interact with proteins. Changing the plasma protein concentration affects the solubility of anaesthetic drugs.[32] It is theoretically possible that competition by another drug for the plasma protein sites could decrease the solubility of the anaesthetic. This in turn may affect its uptake and distribution.[33] However, since the association of anaesthetics with proteins is not particularly high, it is unlikely that this is of clinical significance.

If patients must be given more than one drug at a time, and if some among these are ordinarily highly bound, one should remain alert to the possibility of interaction and its consequences.

4. *Interaction at the receptor site*

For many drugs, a specific chemical reaction seems to take place between the drug and some specialized site in the tissue called a receptor. This is in contrast to drugs like the general anaesthetic agents which act at relatively high concentrations and which would appear to interact with tissues more by physicochemical than by specific chemical reactions. The reaction between a drug and its receptor is assumed to follow the law of mass action. It may take place in the cell membrane

and may involve changes in membrane permeability. Although the structure of the receptors is unknown, it seems likely that they are compounds of high molecular weight, probably protein, and rather similar to enzymes or antibodies. For a comprehensive review of the theories of drug action and the interaction of drugs with receptors, the reader is referred to reviews by Waud, Furchgott, and Ariëns.[34–36]

Two drugs may interact with one receptor. The result depends on their affinities for the receptors as well as their intrinsic activities or efficacies relative to each other. D-tubocurarine occupies the same receptors as acetylcholine at the myoneural junction, but the complex with the receptor is biologically inert (intrinsic activity is 0) and is unable to trigger the depolarization mechanism. This is called "competitive antagonism". Acetylcholine will have less effect when added in the presence of curare, because of the limited accessibility to the full receptor pool. In classical competitive antagonism the receptor-antagonist complex, like the receptor-agonist complex, can dissociate, i.e., the antagonism is reversible. Theoretical application of mass action equations to equilibrium conditions show that the log concentration-effect of the agonist will be shifted to the right in the presence of the antagonist, but remains parallel, i.e., the slope and the maximum response remain unchanged. This may be achieved with the two drugs occupying the same or different sites on the same receptor. In the latter case, the combination of one drug with the receptor may induce a conformational change that alters the binding energy of the combination with another drug. One drug may inactivate the receptor so that the effective complex with the agonist cannot be formed regardless of its concentration. This is called "noncompetitive antagonism". The antagonist may combine with the receptor at the same site as the agonist, but so firmly that it cannot be displaced. Alternatively, it combines with a different site, in such a manner as to prevent a configurational change in the receptor that is essential to its proper combination with the agonist or that is requisite to producing the characteristic biologic response. In contrast to competitive antagonism, the agonist curve, though also shifted to the right, has a slope which is not so steep and the maximum response will diminish in relation to the degree of noncompetitive blockade established. The antagonism exerted by certain β-haloalkylamines like dibenamine against norepinephrine fits into this category. (Furchgott regards these agents as producing irreversible competitive antagonism.[35]) If two agonists act on the same receptor, and one of them produces a smaller maximal effect than the other (i.e. its intrinsic activity is less than 1 but greater than 0), the latter is termed a "partial agonist". The effects of a partial agonist and those of a full agonist acting on the same receptor may be additive or the partial agonist may antagonize the full agonist, depending upon their relative concentrations. This explains the term "dualistic action" which was first proposed by Ariëns and his colleagues to describe this kind of event.[36] An example for the anaesthetist is the interaction between the opiates and opiate antagonist nalorphine (Nalline®) and levallorphan (Lorfan®) which seem to be partial agonists. The antagonists produce respiratory depression, but this reaches a plateau at a certain dosage. Used with small doses of morphine or meperidine, they add to the respiratory depression. It is only when respiratory depression is profound due to larger doses of the opiate that they exert "reversal", reducing the depression to their own intrinsic level.[37,38]

Finally, if the two drugs acting on the same receptors have equal intrinsic activity, their combined action may be expected to be additive. Drugs may also interact at different receptors. In such a case it is possible that the effect of the combination may be greater than the effect of the sum of the drugs (1 + 1 = 3). Magnesium ion potentiates the action of d-tubocurarine at the myoneural junction. The main action of magnesium is on receptors at the motor nerve terminal interfering with the release of acetylcholine while curare acts on receptors at the postjunctional membrane.[39]

So far we have considered the combination of drugs with active receptor sites, whose interaction induces an effect. However, drugs may also interact with receptors in the transport and metabolism systems, storage receptors, silent receptors, etc. (The storage receptors differ from the silent receptors. The release from the storage is regulated. The silent receptors are inert sites of absorption where the drug is absorbed in a physical equilibrium with the free drug.) These receptors have been called "sites of loss" by Veldstra because, though the interaction is not essential for the induction of the effect, it does influence the relation between dosage and effect.[40] The interaction of drugs with plasma proteins fall into this category. The potentiation of curariform drugs by various quaternary ammonium bases and other strong bases which are devoid of curare-like activity by themselves has been attributed to a displacement of the former by these bases from nonspecific sites of binding, e.g. the sulfate groups in the acidic mucopolysaccharides of the tissues.[41] Veldstra in a review of synergism and potentiation concludes that in a large proportion of cases synergism can be explained on the basis of a competition between an active compound and a synergist at various sites of loss for the former.

There is fairly general agreement on the theoretical explanations for the drug interactions discussed in the above paragraphs. However, in the absence of chemical identification of receptor substances, other theoretical concepts are being advanced to explain experimental data which remain unsolved or to replace some of the old views. Discussion of these fall beyond the scope of this review. The interested reader should refer to the various current publications covering molecular pharmacology.

Interactions at the receptor level are usually studied in isolated tissue preparations to obtain valid dose-response curves. In this way the many variables that modify the action of drugs in the whole body such as absorption, distribution, protein-binding, biotransformation, excretion, and others mentioned in this paper can be eliminated. Nevertheless the effect of drugs might vary from organ to organ and from species to species. Nalorphine is an analgesic in man, but it is nearly devoid of this activity in animals presumably because of species difference in intrinsic activity. These considerations must be taken into account when applied to human pharmacology.

5. *Interaction through alteration of drug excretion*

Interaction at this level may be due to:

(a) Changes of urinary pH:

If the urine is at a pH at which the drug is present primarily in the ionized form, the possibility of passive reabsorption of the drug in the distal tubule may be con-

siderably reduced, with resulting diminution of drug levels and lowered therapeutic effectiveness. If the urine is at a pH at which the drug is un-ionized, passive reabsorption is enhanced, resulting in higher plasma levels with prolongation of action and increased likelihood of side effects.

Accordingly, weak acids are often reabsorbed poorly from an alkaline urine and weak bases from an acidic urine. The favorable pKa for pH-dependent excretion is within a range of 7.5–10.5 for weak bases and 3.0–7.5 for weak acids. Changes in the urinary pH may be produced by drugs like ammonium chloride, sodium bicarbonate, thiazides, or acetazolamide (Diamox®). Sodium bicarbonate, by increasing the urinary pH, increases the excretion of barbiturates (particularly phenobarbital) and salicylates thus diminishing their toxicity in case of overdosage.[42] On the other hand, ammonium chloride, by acidifying the urine, hastens the elimination of basic drugs such as amphetamine and ephedrine.[43] Beckett and his colleagues recently demonstrated that amphetamine was cleared from blood more rapidly than could be accounted for by glomerular filtration when the urine was acidic. Probably as urine flowed down the tubules, the drug passes from the blood to the urine because of the high concentration gradient of the un-ionized drug across the lipid membrane.[44]

(b) Blocking of renal tubular transport:

The best known example is the inhibition of penicillin excretion by the competitive inhibitor of tubular transport, probenecid, which leads to elevated blood levels of the antibiotic in the blood. This is another example of a potentially useful interaction.

(c) Effect on renal blood flow and/or the glomerular filtration rate:

General anaesthetic drugs decrease the renal blood flow and depress the glomerular filtration rate.[45] The magnitude is proportional to the depth of anaesthesia and the mean blood pressure level. One may speculate that this may prolong the action of a drug which is excreted unchanged. On the other hand, forced diuresis by mannitol has been used to hasten the elimination of such drugs, for example in barbiturate poisoning.

6. *Interaction through alteration of the acid base balance*

Many drugs are bases or acids which are capable of ionization within the physiological pH range. The degree of ionization can be calculated if the pKa of the drug and the pH of the medium in which it is dissolved are known.

$$\text{For a base, per cent ionization} = \frac{100}{1 + \text{anti log}\,(\text{pH} - \text{pKa})}$$

$$\text{For an acid, per cent ionization} = \frac{100}{1 + \text{anti log}\,(\text{pKa} - \text{pH})}$$

The relationship between ionization and pH is not linear, but sigmoid as shown in Figure 1. It is evident that a small change in pH can make a large change in the percentage ionized, particularly if the values of pKa and pH lie close together. For example, if pilocarpine (pKa = 7.3) is used at a pH 7.6, it is only 33 per cent

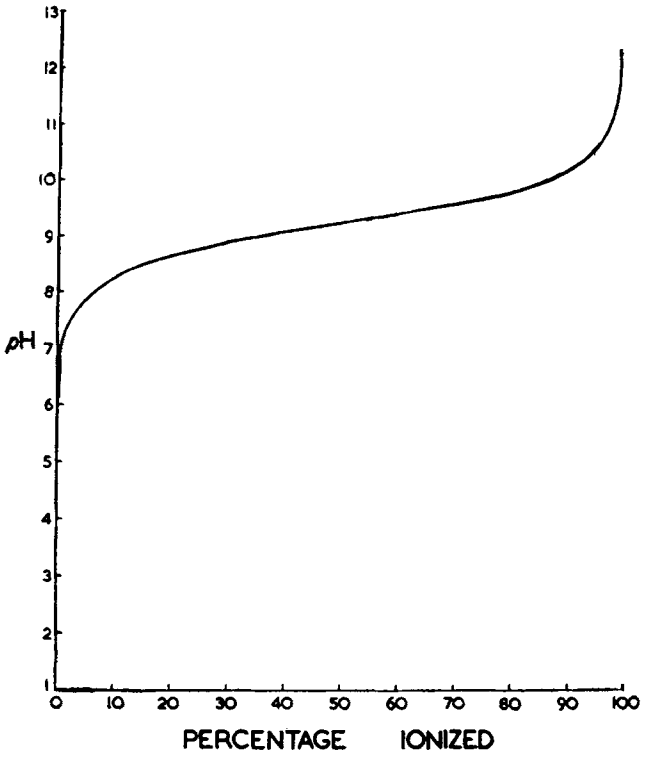

FIGURE 1. Typical curve obtained in the potentiometric titration of an acid (boric acid [pK = 9.2] at 20°). (From ALBERT A. Ionization, pH, and biological activity. Pharmac. Rev., *4*: 136, 1952.)

ionized, but if used at pH 7.0, it is 67 per cent ionized. Thus, a variation of 0.6 unit in the pH doubles the concentration of ions. An acid or base when half ionized has a pH equal to its pKa. When an acid is 10 per cent ionized (or a base is 90 per cent ionized), the pH is 1 unit below the pKa. When an acid is 90 per cent ionized (or a base is 10 per cent ionized), the pH is 1 unit above the pKa. Drugs with high pKa values are 100 per cent dissociated over the whole physiological pH range while those with low pKa are 100 per cent non-ionized.[46] A change in the biological response to a drug often accompanies a change in its degree of ionization or of its receptor or of both. This may be due to:

(a) Alteration in the drug distribution across lipid membranes:

The lipid rich cell membranes allow the ready penetration of the lipid-soluble un-ionized form of the drug, but resist the penetration of lipid-insoluble ionized form. Thus Waddel and Butler showed that inhalation of carbon dioxide increased the tissue-to-plasma ratio of the weak acid phenobarbital, while hyperventilation or administration of sodium bicarbonate decreased the tissue-to-plasma ratio with decreased anaesthetic effect.[47] Roth, Barlow, and Goldberg, using autoradiographic techniques demonstrated that penetration of the brain by phenobarbital, acetazolamide, and salicylic acid was increased with hypercapnia and decreased with hypo-

capnia. Each of the three ionizable drugs showed proportionately higher concentrations in white matter than in gray which may be due to the multiplicity of myelin lamellae in the former. Hyperventilation produced the opposite effect.[48,49] Most local anaesthetics in common usé are secondary or tertiary amines with pKa values between 8 and 9. When applied to intact tissue, they are usually more effective in alkaline solution (in which the uncharged form predominates), than in neutral solution (in which the cationic form predominates). It is now known that this is not due to local anaesthetic activity residing only (or mainly) in the uncharged form of the molecule but rather that the latter penetrates the nerve more readily.[50] That the cation is the major active form at the receptor sites in the nerve membrane has been demonstrated by Ritchie and Greengard who could block or unblock conduction in nonmyelinated fibres by lowering or raising respectively, the pH of the bathing medium.[51] When the pH is low and conduction is blocked, most of the anaesthetic must be in its cationic form. Solutions of local anaesthetic agents at present available have a pH which is lower than the pKa of the drug. This is due to their water solubility characteristics and the addition of epinephrine and stabilizing agents. The anaesthetic solution injected must be buffered in the tissues if a higher pH is to be attained, and the amount of free base required for nerve penetration released. Thus,

$$R.NCl + NaHCO_3 \rightleftharpoons R.N + NaCl + H_2CO_3$$

It has been speculated, therefore, that previous alkalinization of the anaesthetic solution will increase its clinical efficacy. This has not been substantiated, probably because the tissues possess considerable buffering powers and can readily adjust injected solutions to the pH of the extracellular fluid. Alkaline preparations in addition have the disadvantage of being relatively unstable. However, tissues vary in their buffering ability; inflamed tissue has a low pH and this interferes with anaesthetic action.[52] Manufactured mixtures of local anaesthetics containing epinephrine usually have a low pH to maintain stability of the latter (the pH of the mixture of lidocaine and epinephrine is 3.3–5.5 compared to 6–7 of that without epinephrine). It has been suggested that when using an epinephrine mixture, greater penetrance and better results are more likely to follow if the appropriate amount of epinephrine is added immediately before use to the plain solution of local anaesthetic at relatively high pH.[53]

(b) Alteration of the drug-receptor interaction:

The ionized or non-ionized molecules of the drug are expected to interact with the complementary groups in the receptors, in the ionized or non-ionized form, respectively. This implies that not only the degree of ionization of the drug but also that of the complementary group on the receptor has to be taken into account. For bases, for example amines, the complementary group on the receptor may be a carboxyl group, a phosphate group, or some other. For acidic drugs the complementary group on the receptor may be a pyridine group, histidine, or some other. These groups will exist in the ionized or in the non-ionized form depending on the pH in their vicinity. From the changes in the activity of drugs, together with changes in pH, information can sometimes be obtained concerning the pKa value

of the cationic or anionic site of the receptor. These pKa values in their turn may allow conclusions to be drawn about the character of these parts of the receptor. Thus, Rocha e Silva and Ariëns, *et al.*, studying the pH-dependent spasmogenic action of histamine were able to suggest that the anionic site of the histamine receptor consists of an imidazole ring.[54,55] Information may also be obtained about the active form of the drug. Beckett suggested that analgesics of the morphine type, like the local anaesthetics, need to be ionized before becoming effective.[56] The same was suggested for analgesics related to meperidine.[57]

There are various examples of changes in the affinity between a drug and its receptor under the influence of changes in the pH. Acidosis potentiates the neuromuscular block produced by d-tubocurarine while alkalosis produces the opposite effect.[58] This has been explained by the change in ionization of the two hydroxyl groups in the d-tubocurarine molecule, coinciding with the fluctuations in the pH. This would vary the magnitude of attachment to the end-plate receptor. Bromage, *et al.*, have tested the local anaesthetic salt of carbonic acid on the assumption that carbon dioxide would diffuse intracellularly very rapidly, lowering the pH there and thus favoring the active cationic moiety formation at the receptor site. They did demonstrate a more rapid induction and more profound anaesthesia with the use of such solutions in epidural anaesthesia compared to the hydrochloride counterpart.[59]

(c) Changes of absorption of the drug from the gut

(d) Changes of excretion of the drug in the urine:

These have been discussed before and follow the basic principle in (a). It behooves the anaesthetist who not uncommonly induces changes in the acid-base status of his patients to consider the effect of such alterations on the pharmacological response to other drugs.

7. *Interaction due to acceleration of drug metabolism*

The duration of drug action often depends on the rate at which it is activated or inactivated (metabolized). Many drugs are metabolized by enzymes in the liver which alter them by a variety of chemical transformations. The majority of these enzymes are located in the microsomal fraction. Certain drugs and other foreign chemicals have been found to alter the rate of drug metabolism, some stimulating, others inhibiting. The stimulation of the drug metabolizing enzymes in the hepatic microsomes has been called "enzyme induction". It usually results in enhanced formation of inactive metabolites, and consequently a decrease in pharmacologic action. However, enhanced toxicity may also result; for example organophosphate insecticides, such as parathion and tremorine, are converted to more toxic compounds. Some drugs such as chlorpromazine, codeine, and ephedrine are N-demethylated to form metabolites having pharmacologic properties similar to those of the parent compounds. Enzyme induction has been demonstrated in animals after the repeated administration of barbiturates (especially phenobarbital), certain analgesics (aminopyrine), tranquilizers such as chlorpromazine and meprobamate, antihistamines, oral antidiabetic agents, anti-inflammatory drugs such as phenylbutazone, probenecid, anticonvulsants, sex hormones, ... etc.[60] Other than

drugs, certain insecticides and herbicides stimulate drug metabolism. It was also demonstrated in cigarette smokers[61] and after ingestion of alcohol.[62] Coffee or tea drinking by rats, equivalent to about eight cups of coffee per day for a 70-Kg man also produced enzyme induction.[63] Food additives, like butylhydroxytoluene (BHT) also stimulate drug metabolism.[64] These observations all seem to indicate that the phenomenon is a commonly occurring one. Evidence indicates that the stimulation of activity of microsomal enzymes may involve new protein synthesis. The stimulating agents are without effect in vitro; animals have to be pretreated, and a period of time has to elapse that corresponds to known rates of protein synthesis. Electron microscopy shows that after phenobarbital treatment there is an increase in the amount of smooth endoplasmic reticulum in liver cells.[65] These are associated with the microsomal drug-metabolizing enzymes. Other stimulators may not increase protein synthesis but alter the enzyme protein to make it more active. This increased activity may be partly explained by a higher concentration of the oxygen activating cytochrome P_{450}. Probably, other factors that influence the activity of the cytochrome system are involved.

Drugs may also stimulate their own metabolism which may produce a state of tolerance. Thus rabbits pretreated with pentobarbital for three days slept a much shorter time after an intravenous test dose than did controls. Apart from the experimental animal, there are several instances in which enzyme induction has been demonstrated in patients. Thus bishydroxycoumarin is more rapidly metabolized when given with phenobarbital. As a result, larger than usual amounts of the anticoagulant are required to produce a therapeutic effect. If the sedative is discontinued without reducing the dose of the anticoagulant a bleeding catastrophe may occur.[66] Other instances include acceleration of the metabolism of diphenylhydantoin (Dilantin®) by phenobarbital, the acceleration of the metabolism of hydrocortisone by diphenylhydantoin, and stimulation of the metabolism of aminopyrine by the anti-inflammatory drug phenylbutazone.[67,68] It should be noted that apart from the reports of the interaction between bishydroxycoumarin and phenobarbital, enzyme induction has not been incriminated as the cause of any documented clinical drug reaction. Probably other instances of drug interaction occur in man but pass unrecognized necessitating nothing more than increasing the dosage of a therapeutic regimen.

The possibility of utilizing enzyme induction as specific therapy has been explored in a few instances. For instance, phenobarbital has been used for the treatment of neonatal hyperbilirubinaemia and was given to mothers in the last weeks of pregnancy to lower the bilirubin levels in the infant after birth.[69] Diphenylhydantoin and DDE (a metabolite of DDT) also have been used in patients with Cushing's syndrome, because of their ability to stimulate steroid metabolism.[70]

The drugs which would be affected by the liver microsomal enzymes and influenced by their induction are those which are metabolized at least in part in the liver. This includes most of the drugs used by the anaesthetist. Indeed few are excreted unchanged because central nervous system depressants are generally highly soluble in lipids and lipid solubility favors tubular reabsorption. For example, pretreatment of rats with phenobarbital, twice daily for four consecutive days,

shortened the sleeping time produced by pentobarbital, thiopentone, hexobarbital, diazepam, and others.[71]

Recently, attention has been focused on the inhalation anaesthetics. Phenobarbital, 50 mg/kg daily for two days, induced the methoxyflurane ether cleaving system as well as the dechlorination of halothane and methoxyflurane. Exposure of the animals to the vapours of methoxyflurane in subanaesthetic concentrations for 7 hours a day for 10 days resulted in induction of the dechlorinating system, an example of "self-induction".[72] Berman, *et al.*, recently demonstrated that methoxyflurane is also a nonspecific stimulator of drug metabolism.[73] This had been shown earlier for nitrous oxide and diethyl ether.[74] Cohen recently reported that repeated injection of halothane $-2\ C^{14}$ intravenously in the mouse at weekly intervals, resulted in a markedly increased level of the nonvolatile metabolites in the liver.[75] Most of the importance of these exciting observations rests in toxicity studies. For example, the possibility exists that repeated administrations of halothane may lead to self-induction of enzymes producing a toxic accumulation of some intermediary metabolites. However this still has to be thoroughly evaluated as a cause of occasional "halothane liver damage".[76] It is also possible that repeated administration of an inhalation anaesthetic or exposure to subanaesthetic concentrations as occurs in anaesthetists may influence the metabolism of a concomitantly administered drug. This has not yet been studied clinically.

The liver certainly plays the principal role in the metabolism of foreign compounds. However, other organs also take part in drug metabolism. Dorfman and Goldbaum first observed the decreasing thiopentone concentration during incubation with rat kidney slices[77] and later Cooper and Brodie demonstrated that in rabbits thiopentone is metabolized in the liver, kidney, and brain.[78] The microsomal enzyme systems in the extra-hepatic organs can also be stimulated. Gilman and Conney induced demethylation of dimethyl aminoazobenzene in isolated microsomal fractions of the liver, lung, and kidney of rats by pretreatment with 3-methylcholanthrene.[79] Remmer reported that barbiturate metabolism in homogenates of rabbit liver and kidney is strongly stimulated by phenobarbital.[80] The formation of toxic or reactive metabolites within the cells of nonhepatic tissues seems to be of some importance in producing general or local toxicity and allergic phenomena and is especially important in chemical carcinogenesis.[81]

The anaesthetist is also interested in individual variations in response to the drugs he administers. Marked individual differences in the rate of drug metabolism have been reported recently for a number of compounds like chlorpromazine. Levi and his associates showed that the plasma half life of phenylbutazone was shorter in patients taking various drugs thought to induce the liver microsomal enzymes. In fact, a history of previous ingestion of certain drugs was more important in determining the half life of phenylbutazone than was severe liver disease.[82] Kolmodin and his colleagues have shown that the half life of antipyrine was shorter in workers exposed to various insecticides than it was in control subjects.[83] These observations illustrate the relative importance of environmental factors as explanations of individual differences in the response to drugs. Genetic factors have been claimed to be of major importance. Based on studies in twins, Vesell and his asso-

ciates recently suggested that the individual differences in the half life of antipyrine, phenylbutazone, and dicoumarol are largely genetically determined.[84] It is hoped that this exciting debate will lead to a better understanding of the mechanisms underlying sensitivities to drugs.

It is now apparent that enzyme induction tests should be incorporated in the design of safety evaluation studies of drugs. Measurement of the disappearance of a test dose of phenylbutazone and the rate of antipyrine metabolism before and after chronic administration of a drug have been evaluated in the dog.[85] However, species variation must be considered since stimulation of the metabolism of phenylbutazone and tolbutamide follows their repeated administration to dogs, but a similar effect has not been observed in man. The dose response relationship should also be considered in evaluating animal studies, since many drugs can cause enzyme induction at high dosage in animals but appear to exert little or no effect at the usual clinical dose level in man. The importance of exposure to other environmental agents such as pesticides or chemicals is difficult to evaluate. Information is also needed on the length of treatment necessary to produce induction and its duration. In the meantime, the clinician must be alert to other possible interactions of this type which may be verified in the laboratory.

8. *Interaction by inhibition of drug metabolism*

This may occur by:

(a) Inhibition of the liver microsomal enzymes:

This is the opposite of enzyme induction. In animals, several drugs have been shown to be capable of inhibiting the metabolism of other agents. These inhibitors include several narcotic analgesics like meperidine and morphine, some inhalational anaesthetic agents like diethyl ether and chloroform, the antibiotic chloramphenicol and several antidepressant drugs.[60] The following are some examples: an injection of morphine into rats decreases to less than half the activity of the microsomal enzyme system responsible for the N-demethylation of meperidine.[86] Diethyl ether added to liver homogenates inhibits the metabolism of pentobarbital.[87] Hepatic tissue removed from dogs anaesthetized with diethyl ether or chloroform was unable to metabolize procaine at normal rates, whereas tissues of animals anaesthetized with thiopentone showed no such impairment.[88] This correlated well with the observation that the blood levels of procaine in the intact dog were higher when anaesthesia was carried out with ether or chloroform than with thiopentone, using the same dosage of procaine. Concurrent intramuscular or intravenous administration of therapeutic doses of chloramphenicol prolongs the duration of pentobarbital anaesthesia in dogs and cats.[89] Definite instances of inhibition of hepatic enzymes have been demonstrated in man. For example, bishydroxycoumarin slows the inactivation of diphenylhydantoin (Dilantin®), thereby potentiating both its anticonvulsant and toxic effects.[90] The same drug potentiates the hypoglycaemic effects of tolbutamide while it in turn prolongs the action of sulfonamides. Chloramphenicol inhibits the biotransformation of tolbutamide, diphenylhydantoin, and bishydroxycoumarin.[91] As in enzyme induction, species differences and the dose-response relationship should always be considered. The latter would be critical if the inhibition is produced by competition of the drugs for the

metabolizing enzymes. Some drugs, like certain monoamine oxidase inhibitors have a biphasic action, first inhibiting and then stimulating the microsomal enzymes. While more research is still needed in this important field, the anaesthetist's interest is more than justified. Experiments in animals suggest that some of the drugs used in anaesthesia may exhibit this phenomenon after only one administration. As Greene points out, it cannot be assumed that the rates of metabolism and durations of action of drugs administered parenterally, e.g. narcotics and hypnotics, are the same when an inhalation anaesthetic is given and when it is not.[92]

(b) Inhibition of specific enzymes:

The anaesthetist is familiar with several examples in this category. Neostigmine inhibits cholinesterase, an interaction which is useful in terminating the action of non-depolarizing muscle relaxants at the end of operations. However, the same type of interaction may lead to unwanted effects when succinylcholine is given to a patient who is receiving potent anticholinesterase eye drops such as echothiophate iodide,[93] the action of which may persist for months after cessation of the treatment and may lead to undue prolongation of the neuromuscular blocking action of succinylcholine.

The monamine oxidase inhibitors (e.g. hydrazine derivatives, pargyline, tranylcyrpomine, modaline) interact with many drugs of interest to the anaesthetist, such as sympathomimetics, narcotics, anaesthetics, barbiturates, to mention a few.[94] The interaction may take the form of potentiation of the normal action of a drug, like potentiation of the increase of blood pressure produced by a vasopressor or atypical manifestations may occur in response to a normal dose of meperidine such as hyperpyrexia, hypotension, and/or convulsions.

The term "monoamine oxidase" (MAO) is used to designate a group of enzymes catalyzing the oxidative deamination of tyramine, tryptamine, serotonin, norepinephrine, dopamine, and other monoamines.[95] In vitro, the inhibitors and the substrates generally compete for the enzyme as long as the inhibition is not complete. Once this has become complete, however, it is uncompetitive and almost irreversible. The drugs, with the exception of tranylcypromine have to be metabolized to form the actual inhibitors. There is no absolute parallel between MAO inhibition and monoamine increase. Thus, the enzyme has to be inhibited at least to 85 per cent before the monoamine content of brain and possibly other tissues rises.[96] Some MAO inhibitors of the hydrazine type interfere with a variety of enzymes other than MAO, e.g. diamine oxidase, choline oxidase, cholinesterase, etc.

A good deal of research has been done in the last few years to elucidate the mechanisms involved in the interaction between the monamine oxidase inhibitors and other drugs. The potentiation of sympathomimetics may be explained by the increased norepinephrine stores in the sympathetic nerve endings, since monoamine oxidase is the principal enzyme responsible for its inactivation at that site. This results in an increased release of the transmitter by indirectly acting agents. Directly acting drug may also be potentiated. Monoamine oxidase inhibitors may block the release of catecholamines during nerve stimulation after prolonged treatment and thus cause the receptors to become unusually sensitive to sympathomimetic amines. This is referred to as denervation supersensitivity.[97] Hypotension and

hypotensive collapse may be due to ganglionic blockade, an action which is probably unrelated to monoamine oxidase inhibition.[98] Another explanation is that not only norepinephrine, but also other amines like dopamine or octopamine may accumulate in the adrenergic nerve fibres when monoamine oxidase is inhibited. These weak pressor amines may then compete with norepinephrine at the alpha receptors (i.e. amines may function as false transmitters).[99] A more recent hypothesis postulates impairment of histamine metabolism, allowing its accumulation in the tissues.[100]

Recently Rogers and Thornton studying the interaction between monoamine oxidase inhibitors and narcotic analgesics in mice suggested that the toxicity is related to an increased concentration of the monoamine 5-hydroxytryptamine inside the brain.[101] They also demonstrated that a critical level of cerebral serotonin may be necessary before the drug interaction takes place. The acute toxicity of meperidine was not potentiated until the 5-HT content of the brain was some 60 per cent above control values. This may explain the case report of Taylor in which a patient receiving a monoamine oxidase inhibitor reacted normally on one occasion, but reacted abnormally on another when the dose of the inhibitor was increased.[102] Another important result of this study is the fact that pretreatment of mice with monoamine oxidase inhibitors increased the mortality not only from meperidine, but also from the three other narcotic analgesics used; morphine, pentazocine (Talwin®), and phenazocine. The previous clinical reports and animal experiments deal almost exclusively with meperidine. To confirm the role of 5-HT, Gessner and Soble demonstrated that pretreatment of mice with p-chlorophenylalanine, an inhibitor of 5-HT synthesis or chlorpromazine, a 5-HT antagonist lowered the mortality caused by tranylcypromine-meperidine interaction.[103]

Summers has shown recently that inhalation of halothane by cats leads to hyperthermia and occasionally skeletal muscle stiffness when they have received beforehand an intraperitoneal injection of a monoamine oxidase inhibitor.[104] Feldberg and Lotti demonstrated the hyperthermic action with pentobarbital sodium and chloralose as well.[105] They postulated that anaesthetics ordinarily cause hypothermia by releasing norepinephrine in the anterior hypothalamus which overcomes the temperature raising effect of 5-HT released as well. It appears that in cats, only 5-HT, not norepinephrine, is the substrate of the brain MAOI. Its inhibition would therefore prevent the destruction of the released 5-HT, which could then overcome the temperature lowering effect of norepinephrine. More recently Feldberg and Lang suggested that the monoamine oxidase inhibitors may not act only through monoamine oxidase inhibition and that an amphetamine-like effect may also be involved with inhibitors having strong amphetamine-like actions.[106] Amphetamine itself produces the same temperature raising response. Based on these findings, Horsey recently suggested that malignant hyperthermia during anaesthesia might be secondary to acceleration of 5-HT release in the hypothalamus.[107] However, while the aetiology of this syndrome still remains obscure, clinical and experimental evidence available to date indicate that the site of the defect is peripheral rather than central.[108]

The intensity, onset, and duration of action of the monoamine oxidase inhibitors depend on the species, the tissue, the amine, the mode of administration, and the

chemistry of the drug. The inhibition of the enzyme in the brain generally lasts longer than in the other organs. Because of the long lasting effect (days to weeks), repeated therapeutic doses of MAOI such as hydrazine derivatives and pargyline may lead to almost complete inactivation of the enzyme in man. A minimum of two weeks of abstinence from these drugs should be allowed before anaesthetizing patients for elective operations.

As mentioned before, monoamine oxidase inhibitors also inhibit the liver microsomal enzymes. This seems to explain the prolonged but essentially normal pharmacological action of some drugs like pentobarbital and phenothiazines when given to patients treated with monoamine oxidase inhibitors.

Disulfiram (Antabuse®), the drug used in aversive therapy for chronic alcoholics blocks the enzymatic biosynthesis of norepinephrine from dopamine. This may lead to impairment of compensatory sympathoadrenal responses under anaesthesia.[109,110] Acetazolamide (Diamox) inhibits carbonic anhydrase which catalyzes the reversible reaction of hydration of CO_2. The action of a central nervous system depressant such as an anaesthetic or narcotic may be altered.

9. *Interaction due to general physiologic alteration*

A drug may induce some changes in the patient which makes him react differently to another drug. For example, a patient on diuretic therapy may react in an enhanced way to the non-depolarizing myoneural blocking agents, due to the potassium depleting effect of the diuretic. Cyclopropane anaesthesia usually is associated with a well maintained blood pressure level and increased myocardial contractility and stroke volume. These effects are due to catecholamine release. Administration of a beta-blocker like propranolol while the subject is under that anaesthetic leads to a sharp decline in the parameters mentioned by blocking the cardiac action of catecholamines.[111] Simpson and his colleagues recently made the interesting observation that sodium pentobarbital protects mice against the toxicity of d-tubocurarine. Fully anaesthetized animals could survive ten times the usual lethal dose of curare.[112] They propose that the barbiturate through peripheral vasodilation induces hypothermia which antagonizes the competitive neuromuscular blocker. A similar mechanism has been suggested for 5-HT antagonism to d-tubocurarine, although our own studies are not in agreement with this particular interaction. It is apparent that to understand the effect of a combination of drugs, the action of the individual components must be thoroughly understood.

One pharmacological response may be the result of different drugs working through different mechanisms. Respiratory depression may be produced by drugs acting centrally, like narcotics, or peripherally at the nerve root level like a high epidural or subarachnoid anaesthetic or at the myoneural junction level like the muscle relaxants. A combination produces an additive respiratory depression.

CONCLUSIONS

One of the important reasons for a preoperative visit by the anaesthetist is to interrogate the patient about present and past drug intake. Hospitalized patients often receive multiple medications to which the anaesthetist will add more. This

polypharmacy not only increases the risk of hazardous interaction but may also complicate the problem of determining which drugs are responsible. Thus, in this regard, the fewer drugs used the better. A sound rationale for combining two or more drugs is usually based upon physiological or biochemical considerations. There has been recent advocacy of the use of fixed-dose combinations of drugs. With a few exceptions, there are probably no valid reasons for such combinations.[113] The claims for therapeutic superiority over the single agent are not usually adequately substantiated. Thus the patient is exposed to more potential poisons when only one exposure might have been necessary. In addition, it is impossible to adjust the individual dosage of each drug to the needs of a particular patient. Proper timing of administration of each component may be sacrificed with the use of fixed-dose mixtures. It has been stated frequently that a single mixture will entail less cost and more convenience to the patient than separately prescribed components. This argument would be valid if the use of two or more agents has proved to be more effective than a single ingredient in a particular situation and where the ratio and dosage of the combination are the result of well controlled studies. An example is the combination of a local anaesthetic and epinephrine. The components are always given at the same time and, usually, in the same ratio. It has also been stated that the experience and thought behind many fixed combinations can be an important source of information and reassurance in the wise use of combined therapy.[114] Unfortunately the extensive commercial advertising of such combinations and their indiscriminate use fosters careless diagnosis and irrational therapy.

Adverse reactions to drugs are collected and evaluated through different agencies. The American Medical Association employs a reporting system which is intended primarily to alert the medical profession to the potential for haematotoxicity of drugs. The information obtained is essentially "raw data" obtained from many sources with no attempt at follow-up investigation. The Federal Drug Administration in the United States has a program in which hospitals are participating. This program also has the basic and inherent disadvantage that it does not have the facilities to follow up on the incomplete reaction reports. In the majority of cases it is necessary to follow up the reports by studying the hospital charts or the physician's office notes, interviewing the physician and/or the patient and obtaining complete information on various laboratory tests performed. It is revealing that neither of these programs have detected a single new adverse drug reaction of significance.[115] The pharmaceutical industry has the incentive and the material facilities for the follow up of adverse reaction reports concerning their products. This applies also to the private investigator who reports his findings with adequate critical evaluation in the medical literature. All the methods mentioned so far are "spontaneous" reporting schemes, since they are dependent on clinical judgment in establishing a connection between a drug and an adverse event. However, with adverse reactions or interactions previously not reported, the physician usually attributes reactions to the patient's disease or other factors in his environment, rather than the drugs themselves. In a recent report, even though 26 per cent of patients receiving intravenous ethacrynic acid developed gastrointestinal bleeding (as opposed to 4.5 per cent of other patients), no

association between the bleeding and the drug was suspected by the attending physicians till it was disclosed by the appropriate program.[116] An ideal program records all drug exposures and all adverse events, regardless of whether or not these events are attributed to a drug. Such a one is the Boston Collaborative Drug Surveillance Program.[1] Its originators claim that in addition to the detection of unsuspected side effects and drug interactions, a comprehensive drug surveillance program permits the quantitation of known effects, the evaluation of the role of influencing factors and the conduction of therapeutic trials without interfering with the ward routine. The program essentially monitors all drug exposures in several hospital wards and requires the collaborative efforts of clinical pharmacologists, statisticians, computer personnel, and monitors of the drug therapy (usually nurses). The advantages would seem to justify the expense of initiating similar sophisticated programs in several centers.

There are problems in information relating to drug interaction. Searching the biological science literature for papers dealing with the subject may not be easy because the papers are usually not properly indexed. We need a comprehensive bibliography of papers published on drug interaction, organized by categories and a documented extraction of data which will permit evaluation of the validity of a report and which can be used as a guide for the researcher and for application by the clinician.[117]

To predict drug interactions before they lead to a mishap or to use some of them for the therapeutic advantage of the patient, knowledge is needed about the chemical and pharmacologic properties of the agents concerned. Unfortunately, in many instances this is incomplete. More research is needed on absorption, distribution, bindings, metabolism, and excretion of drugs as they relate to drug interactions. Because of species variation, studies in man will ultimately provide the most meaningful clinical information. Until these basic mechanisms are thoroughly investigated, physicians have to be always on the alert when using drug combinations for the possible hazards involved.

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