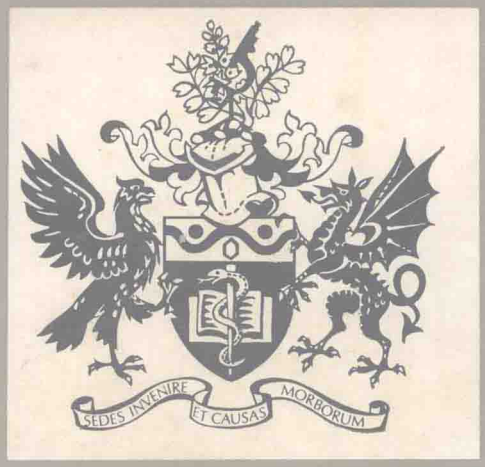

The Royal College of Pathologists

Drugs and Disease

EDITED BY SHEILA WORLLEDGE

Symposium organized by The Royal College of Pathologists and delivered in London in February 1975

Published for The Royal College of Pathologists by the *Journal of Clinical Pathology*, BMA House, Tavistock Square, London WC1H 9JR

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Preface

The large number of people who wished to attend this symposium on 'Drugs and disease' showed that there was a need for it, and the audience included not only pathologists, but also clinicians, pharmacologists and members of pharmaceutical firms. It is hoped that these published proceedings will prove of equal interest to those who came and also to a wider audience.

The explosion in the number of drugs and their complexity during the last 20 years has posed particular problems for pathologists even if they do not prescribe them. They may have to make the diagnosis of a drug-induced disorder or try to incriminate one drug out of a number of possibles. It is, therefore, of especial interest to read what clinicians and pathologists, expert in their various fields, have to say about the harmful effects of drugs upon different organs.

The proceedings open with a scholarly review by Professor Paton on the molecular basis of drug toxicity as illustrated by lipophilic substances, particularly anaesthetics. This is followed by a timely reminder by Professor Wade on the incidence of adverse reactions to drugs and the importance of reporting such reactions. The bulk of the proceedings contain papers on the metabolism and harmful effects of drugs on various organs—the kidney, blood, skin, liver and lung. These include, also, a paper by Professor Cameron on the wider problems of immunosuppressive agents and a paper by Professor Jacobs describing some ways in which drugs can be used *in vitro* to help to solve the problems of normal physiology. Finally, the proceedings close with a series of papers, many of which will be of interest to people not only as members of the medical profession but also as citizens.

I should like to thank the authors for their part in this symposium, and the College secretariat, and especially Mrs M. E. Halstead, for organizing what must be considered a most successful two days. Finally, I should like to thank Miss G. Liddle for her patience and help with the editorial work.

The College is also grateful to Messrs Pfizer, Searle Diagnostic and Leo Laboratories Limited for their support.

S. M. W.

Contents

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Mechanisms of drug action

The molecular basis of drug toxicity

W. D. M. PATON

From the University Department of Pharmacology, Oxford

This paper must necessarily be highly selective in an enormous field, and will represent my own attempts to come to grips with a particular group of pharmacological actions rather than to cover a wide field. Briefly, I would like to review the basis for the distinction of specific from non-specific pharmacological action, and, taking anaesthetics as the prototypes of non-specific action, use them as guides to the properties of fat-soluble (lipophilic) substances generally. Finally, I would like to consider ways in which unitary theories of anaesthesia fail or need adjustment and the types of mechanisms which may be involved. From this review a possible general pattern of lipophilic toxicity emerges.

The Distinction between Specific and Nonspecific Actions

The classic examples of specific action are found in drugs used in the autonomic field. The table lists some of the characteristics of these compounds which have generated the idea of the 'drug receptor', that is, an array of spatially organized sites interacting with details of the structure of the drug in the same way as a substrate does with its enzyme. These are by no means the only examples; the toxicity of fluoracetate, or of nitrosamines, the release of histamine by amines, the action of antibiotics, the reactions leading to sensitization to chemicals, and many others, all lead to pictures full of molecular detail.

General anaesthetics can be contrasted with all these. Thus, the chemical structures of active compounds lack specificity, ranging from the inert xenon through ether, chloroform, nitrous oxide, barbiturates, chloralose, to the steroid anaesthetics. Further, although there is a characteristic (though variable) progression of action with increasing dose from depression of higher centres downwards through the central nervous system and the body, yet almost every system or tissue is affected by concentrations of anaesthetic spanning only three- to five-fold differences. This differs considerably from the specificity of 1000-fold or more with, for example, some autonomic drugs, or penicillin. It is necessary to think differently and rather generally about anaesthetics, to accommodate both the extreme diversity of chemical structures and the unspecificity of effects. In fact, there are also other areas in pharmacology where a number of different compounds seem to produce the same general pattern of action: very many amines, for instance, will produce local anaesthesia and will act as anti-histamines, anti-adrenalines, or anti-acetylcholines in a modest way. Such observations underlie the remark that 'any drug will do anything' which is a rather lightweight saying comparable to 'any man is capable of any action'; doubtless true enough, yet we are in practice selective, and not many of us practise burglary! The important point is the inductive hint that there may be patterns of action which are not tightly coupled to detailed chemical structure.

Mechanisms of Anaesthesia

The best understood of these patterns is that of the general anaesthetics, and I think it is worth discussing this briefly. It is over 70 years since Overton and Meyer suggested that these were linked, not by chemical structure, but by the physical property of fat solubility; this produced the generalization that any

Existence of pairs of specific, and structurally related, agonists and antagonists (eg, propranolol/isoprenaline)
High potency (eg, acetylcholine/hyoscine) and high affinity when it is possible to determine it
Potency strongly dependent on small details of chemical structure (eg, noradrenaline)
Potency dependent on optical activity (eg, l-adrenaline vs d-adrenaline)
Activity strongly restricted to particular cells or parts of cells (eg, acetylcholine/tubocurarine)
Appropriate kinetic relationships between concentrations of agonist and antagonist producing a given effect (eg, mepyramine/histamine)
Evidence for specific binding to receptor sites (eg, atropine, bungarotoxin)

Table *Characteristics of specific drug action illustrated by agonists and antagonists in the autonomic, neuromuscular and histamine fields*

substance would cause anaesthesia if, when given in a suitable concentration, it dissolved in fat to a level of about 0·05M. A highly fat-soluble substance needs only a low inhaled concentration to yield the required level in fat and less soluble compounds are correspondingly less potent. This generalization for a long time remained just one of many. Indeed it was explicitly questioned by the clathrate theory of anaesthesia; this suggested that the intermolecular forces leading to solubility in fat would also lead to a characteristic structuring of water round the anaesthetic molecule and cause an interference with water-based biological processes. In this theory, there was a major difference of approach, the important events of anaesthesia taking place in a watery, not a fatty, environment. However, when fuller and better correlations were made of anaesthetic potency with water structuring on the one hand, and fat solubility on the other, particularly using modern (and conveniently anomalous) fluorine-containing compounds, it became clear that fat solubility was much the best candidate (fig 1). Furthermore, two other lines developed: it was possible to show that anaesthetics, dissolved in artificial or natural membranes, produced a 'fluidification' of the lipid of the membrane (Burgen and Metcalfe, 1970), together with evidence of a slight but definite expansion. Moreover, an old observation that very high pressure (around 100 atmospheres or 3000 ft of sea water) would reverse anaesthesia was re-examined and confirmed (Lever *et al*, 1971) (fig 2), with evidence that the compression so produced just about balanced quantitatively the expansion by the anaesthetic (Miller *et al*, 1973), and restored the normal mobility of the membrane (Trudell, Hubbell, and Cohen, 1973).

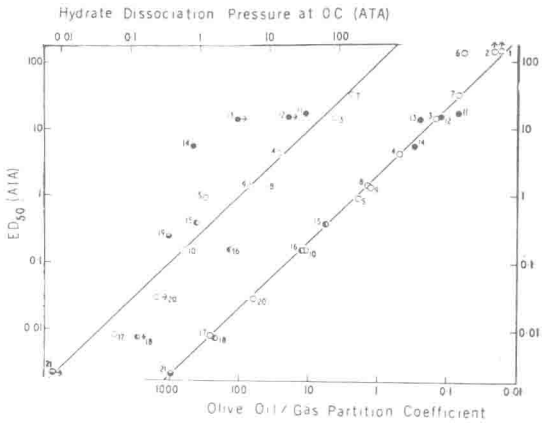

Fig 1 *The correlation of anaesthetic pressure (in atmospheres absolute, ATA) with hydrate dissociation pressure (ATA) at 0°C (left-hand graph) compared with the correlation of anaesthetic potency with the olive-oil partition coefficient at 37°C. Solid black dots are fully fluorinated molecules; partially black dots are partially fluorinated molecules (from Miller, Paton, Smith, and Smith, 1972,* Anesthiology, ***36,*** *339-351).*

It would be inappropriate to discuss further developments, but the success of fat solubility theories has enabled workers to focus more confidently on hydrophobic regions as the sites of action for such molecules. My own guess, at least so far as anaesthesia is concerned, is that the site of action of such substances is primarily the limiting membranes of nerve cells and these should be viewed in the light of modern

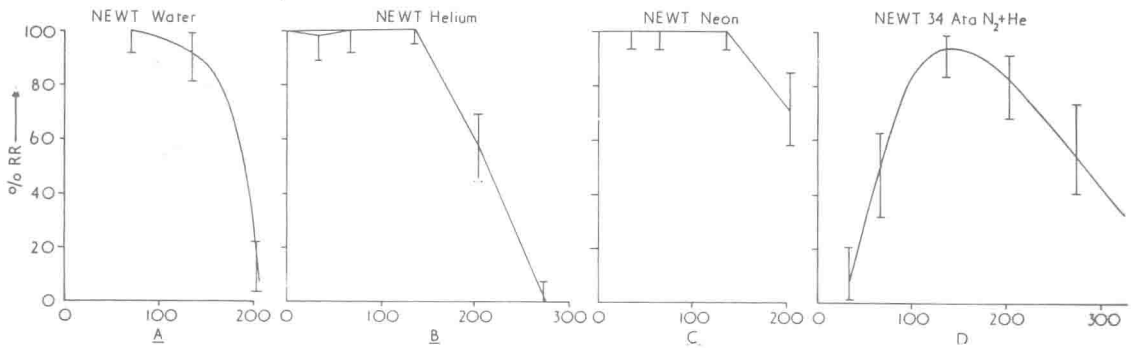

Fig 2 *Rolling response of newts (ordinate: % successful righting) under various conditions (abscissa: pressure of water or gas in atmospheres):* A, *exposed to hydrostatic pressure only;* B, *exposed to helium;* C, *exposed to neon;* D, *exposed to 34 ATA nitrogen to produce anaesthesia and then helium.*

Comparison of A, B *and* C *show that the effects of helium and neon are those of pressure* per se; *in* D *the application of high pressure by helium antagonizes the anaesthesia produced by nitrogen (from Lever, Miller, Paton, and Smith, 1971,* Nature (Lond.), ***231,*** *368-371).*

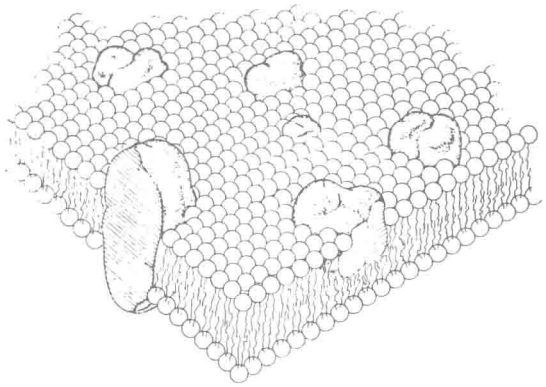

Fig 3 *The lipid-globular protein mosaic model with a lipid matrix (the fluid mosaic model); schematic three-dimensional and cross-sectional views. The solid bodies with stippled surfaces represent the globular integral proteins, which at long range are randomly distributed in the plane of the membrane. At short range, some may form specific aggregates, as shown (from Singer and Nicolson, 1972,* Science, ***175,*** *720-731. Copyright 1972 by the American Association for the Advancement of Science).*

ideas of the structure of the cell membranes (fig 3). Intracellular membranes or the hydrophobic interior of protein macromolecules may well also be important. But although investigators now join in concentrating on hydrophobic regions, there is great uncertainty and a diversity of views on the more detailed molecular theory. The 'critical volume hypothesis' that our work at Oxford has supported and which says that anaesthesia occurs when insertion of a lipophilic molecule into the hydrophobic region critical for anaesthesia leads to a critical increase in its volume hardly provides a mechanism. The increased mobility of lipid chains, which would of course involve membrane expansion, could be envisaged as changing membrane permeability; but we also know that with lipophiles of higher molecular weight, order rather than disorder of the membrane occurs, although volume increases would still be expected. Consequently a considerable range of possibilities is being considered (see the symposium edited by Halsey *et al*, 1974): perturbation of the structure of the membrane (such that any deviation in either direction from normal ordering impairs function); perturbation at the site of insertion of macromolecules into the membrane, or propagation of disturdance from the lipid layers to the macromolecule; action within the macromolecule itself; interaction with intracellular membranes, eg, neurofilaments and tubules; interactions with mitochondrial membranes leading to metabolic changes, or to failure of Ca^{++} sequestration.

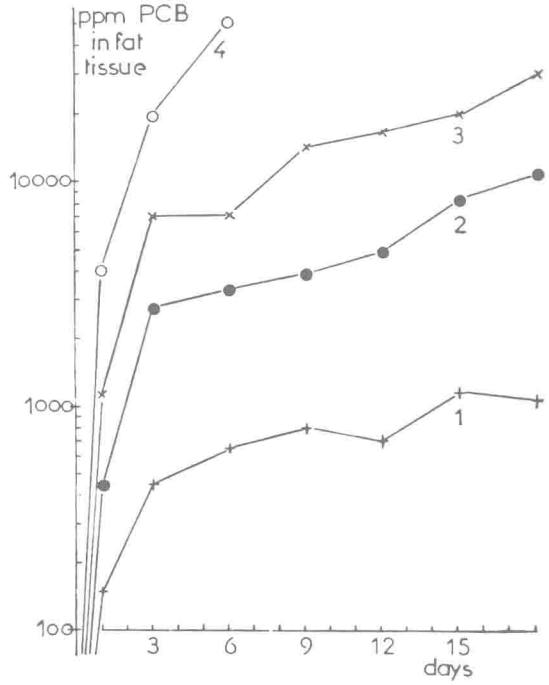

Fig 4 *Absorption of PCB by goldfish from different concentrations of PCB in water. Abscissa: Time in days. Ordinate: Concentration of PCB in fat tissue (ppm in log scale). Water concentration of PCB:*

1 +——+ *0·01 ppm*
2 ●——● *0·05 ppm*
3 ×——× *0·1 ppm*
4 ○——○ *0·5 ppm*

(from Hattula and Karlog, 1973, Acta pharmacol. toxicol., ***32,*** *237-245).*

Now all these are theories but there is evidence for each of them, and I think that they deserve attention, not just in connexion with clinical anaesthesia but in connexion with the action of any fat-soluble substance. Further, although anaesthesia is normally a short-term affair, chronic exposure may occur with other lipophiles and continued actions, of the types mentioned, even at a low-grade level, may present new features. Such possibilities must be taken seriously, because there is now something of a convergence of interest in lipophilic toxicity. For example, the toxicity of DDT, chlorinated biphenyls, hexachlorophane, industrial solvents, vinyl chloride, cannabis, the constituents of fuel oil in alcoholic drinks and the chronic effects of anaesthetics, are obvious cases. It is quite pretty to see, for instance, how polychlorinated biphenyls (PCB) are partitioned, as one would expect from simple physical principles,

into fat in fish (fig 4). I suspect, too, that a large range of other substances, such as amines, should also be included as they can exist in an uncharged lipid-soluble form. Although their ionizable groups must influence their actions and their distribution enormously, nevertheless a substantial hydrophobic component in the molecule could well bring about an anaesthetic-type action, at least at higher doses; one recalls that chlorpromazine can itself be used to produce anaesthesia and that poisoning with tricyclic antidepressants is a puzzling and refractory condition.

Possible Patterns of Lipophilic Toxicity

In attempting to map out the possible patterns of toxicity of a lipophile, one has to move from an inferred mechanism of action to possible patterns of effects. This is the reverse of the normal procedure and is made necessary by the lack of detailed toxicological study. It is probable that chronic toxicity will be more important than acute, simply because the elimination time is likely to be prolonged for a substance which segregates in fatty phases of the body, away from the water-based excretory system. There is one major qualification and that is in the liver. The microsomal system of this organ can be viewed as a mechanism for rendering fat-soluble chemicals more water-soluble (for instance by hydroxylation) and hence accelerating elimination (Parke, 1968). Consequently it is necessary to know the final balance between segregation and metabolism. If retention in fact occurs, then continued dosage would give much higher tissue levels than one would guess from single-dose studies and the latter would not be a reliable guide to toxic effects.

There is little guidance as to the likely pattern, either because many chemicals have never been studied chronically or (when they have) the question has usually been to determine a non-toxic level rather than to study the pattern of phenomena at a toxic level. However, there are a number of recurrent themes, if one draws on animal work with chronic exposure to anaesthetics, on some classical toxicology and on recent work with cannabis which is a highly lipophilic substance and is often administered chronically (see Mechoulam, 1973).

I shall start by being too 'unitary' and go on to a number of qualifications.

First, it has been known for some time that continued exposure to nitrous oxide can produce aplastic anaemia in animals (see Fink, 1968). This is one example of the ability of lipophiles to interfere with cell division. This may show itself directly, or as immunodepression, or as induction of reduction deformity in the fetus, or as interference with spermatogenesis.

Second, there is a range of biochemical effects, including the uncoupling of oxidative phosphorylation, interference with NADH reoxidation, and interference with protein and nucleic acid synthesis.

Third, there is an interesting interaction with red cells and lysosomes: low doses of lipophiles appear to stabilize these and high doses to disrupt them. The work of Burgen and Metcalfe with a model anaesthetic, benzyl alcohol, detectable by nuclear magnetic resonance, shows that the lipophile first interacts with and 'fluidifies' lipid of red cell membrane, and later, with increasing concentrations, disrupts the lipoprotein complex. We think we have encountered this in our high pressure experiments at Oxford. Mr Steve Daniels found that pulmonary oedema occurred in mice decompressed from exposure to the fat-soluble compound SF_6. Furthermore, we have found that a range of anaesthetics, dissolved in saline and instilled intratracheally in guinea-pigs' excised lungs, produces 'solidification' of the lung, failure to recover instilled fluid (fig 5) and a release of a substance with the properties of a pulmonary surfactant. This suggests that the anaesthetic breaks the lipoprotein link binding the lipid of surfactant in the alveoli.

Fourth, there is some evidence that anaesthetics can interfere with intracellular calcium sequestration, allowing its concentration to rise in the cytoplasm.

Finally, one must take account of the results of interaction with microsomes. Here, two responses

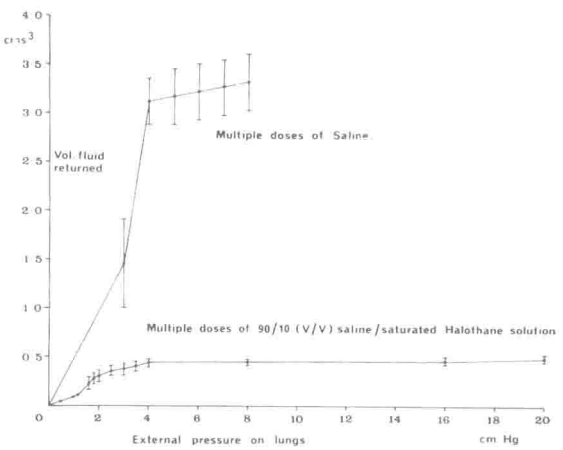

Fig 5 *Effect of halothane on the recovery of saline instilled into the guinea pig isolated lungs. Abscissa, extrapleural pressure applied to lungs; ordinate, volume of fluid returned. Upper curve, saline control; lower curve, after using saline 10% saturated with halothane.*

can occur, either inhibition, for instance by cannabidiol (Paton and Pertwee, 1972), or induction of activity, for instance by phenobarbitone. In either case a considerable range of secondary effects might be seen, for example, altered metabolism of endogenous steroid hormones, as well as alterations of the response to some external drug.

Modulation of Specificity in the Action of a Lipophile

So far, of course, it is implied that all lipophiles should be alike. It is obvious that they are not: even within the field of practical anaesthesia, the effects of ether and halothane are very different. Should a general approach be abandoned, or can other general factors be found to account for these differences? There are a number of these.

The first is the kinetics of a drug. A highly fat-soluble drug would not be expected to behave in quite the same way as one less so. Fat solubility goes hand in hand with water insolubility and protein binding, so that with a strong lipophile the concentration free in the plasma will be very low and tissue uptake will be both slow and blood flow limited. This alone could focus uptake on particular systems and hence bring out particular initial effects.

Second, metabolism sometimes changes the whole picture and converts a drug with seemingly non-specific actions into one capable of specific chemical reaction; in particular, hydroxylation can give rise to the formation of highly reactive epoxides (these have been found with barbiturates and with tetrahydrocannabinol), which could react covalently with tissue constituents in still unknown ways. Another example is the observation that carbon tetrachloride can give rise to metabolites binding covalently with phospholipids (particularly phosphatidyl serine) in rat liver microsomes (Reynolds and Moslen, 1974). This seems to be a process with an important potential; a very small proportion of the drug so converted and bound (too small to be detected by clearance studies) could well accumulate to form a substantial amount of altered lipid.

It is interesting that the lipophilicity of the parent compound could direct where this takes place.

Third, it is too simple to suppose that the insertion of a lipophile into a hydrophobic site will be entirely independent of molecular shape and size. There was some justification for the idea since it has been found that the optical isomers of halothane are equiactive. But, with larger molecules it is already known from biophysical studies that their location in the membrane depends on molecular size and other features. Corresponding to this, for instance, the optical isomers of tetrahydrocannabinol are known to differ in potency in mice by a factor of 13 (Jones *et al*, 1974).

Lastly a rather special point should be mentioned. The forces between the molecules of a substance give it a self cohesiveness, and Hildebrand has shown how this may be characterized by what he termed δ, the solubility parameter, a function of the energy of evaporation and the molar volume (see Hildeband *et al*, 1970). When intermolecular forces are low (as in fluorinated hydrocarbons), evaporation is easy and δ is low. With strongly associated liquids, eg, ethanol, linked by hydrogen bonds, more energy is needed, and δ rises. The interesting point emerges that if δ differs too much between two compounds, they become immiscible; this is to say that if one is very much more self-cohesive than the other, it will prefer to associate with itself rather than with the molecules of the other compound and the latter will be extruded to form a separate phase. Therefore, there is another source of specificity, the physicochemical 'match' between the lipophilic solute and the lipid of membrane. In anaesthesia, for instance, there are reasons for believing that the properties of the membranes critical for acute effects and presumably synaptic, differ from those involved in chronic toxicity.

The argument may be summarized thus:

(*a*) A general distinction exists in pharmacology between 'specific' and 'nonspecific' action.

(*b*) This must be expected to apply in toxicology, and toxicity may not be related only to specific chemical groups with specific actions but also to more general physicochemical properties such as fat solubility with general actions.

(*c*) Taking anaesthetics and other lipophiles as a guide, one can tentatively suggest types of chronic toxicity that may occur. They include effects on cell division, on cell metabolism, on lipoprotein integrity, on calcium sequestration and on microsomal activity.

(*d*) Characteristically, chronic toxicity will be more important than acute toxicity.

(*e*) Although general patterns may be discernible, there are several mechanisms (kinetic, metabolic or physical) where differentiation between lipophiles will occur.

There are two final comments. The first is to reject false antitheses. It will have been noticed that even under 'nonspecific' action, specificity rears its head. It is also normal industrial practice to try to increase the potency of highly specific compounds by lipophilic loading, and extensive studies exist correlating potency of specific action with fat solubility. The issue is essentially operational and not of logical principle: sometimes it is better to consider specific factors and supplement them with nonspecific additions; sometimes it is more useful to begin with

general physicochemical effects and introduce specific corrections. There is no need to waste time on semantics.

The second is the concept of a 'lipophilic' burden. It is important to ask whether toxicity of nonspecific type matters. I do not think we know. However, from experiments with anaesthetics and the amateur and industrial use of organic solvents, we can show that these substances interfere with cell turnover and with cell division. Moreover, if the huge mass of prescriptions of psychoactive drugs (some known to be unexpectedly prolonged in action) is considered, we may feel uneasy, particularly about effects on maturation of developing organisms. Since anaesthetics as a class are additive in their effects, we may need to think of a toxic 'lipophilic burden' made up of perhaps some petrol fumes, some household cleaning fluid, a little anaesthetic in hospital, a tranquillizer or two, a few sleeping tablets and some recreational lipophiles. It is, I think, largely speculation, but perhaps worth some attention, partly in trying to understand existing toxicity but also for instance, in the pharmaceutical field, where there may be a still unrecognized price to be paid for obtaining high potency by lipophilic loading.

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The incidence of adverse reactions to drugs

O. L. WADE

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Concern about adverse reactions to drugs is not new. In 1887 at a meeting in Manchester the British Medical Association set up a small committee to examine the sudden and unexpected deaths which sometimes occurred during chloroform anaesthesia. This was the first collaborative investigation of an adverse reaction of a drug in human subjects. Professor McKendrick, Professor of Physiology in Glasgow, and Dr Coats, pathologist, and Dr Newman, pathological chemist, at the Western Infirmary, Glasgow (1880) reported that chloroform was hazardous in man not only because excessive doses depressed respiration but because small doses had a deleterious effect on the heart and might cause cardiac arrest. This report was contrary to the experience of many who had used chloroform extensively. Its findings were repudiated by Surgeon Major Lawrie, Residency Surgeon at Hyderabad in the Deccan, with such heat that it is surprising that the now yellowing pages of the *Lancet* of 1889 and 1890 are not a little charred. Major Lawrie appointed two Hyderabad Chloroform Commissions, on both of which he sat as President. Following the extensive administration of chloroform to dogs that Commission in its final report stated, in the words of a contemporary Anglo-Indian, that chloroform given in doses which did not cause respiratory depression was 'as safe as whisky and water' (Lawrie, Brunton, Bomford, and Hakin, 1890). But the report received little attention in Britain for here it was already indisputable that in human beings sudden death did sometimes occur in the early stages of chloroform anaesthesia.

This ancient controversy is worth recalling. It not only showed for the first time the enormous emotion that may be aroused in doctors when a drug which they value is found to cause serious adverse reactions, but it also demonstrated, although the lesson has yet to be fully appreciated, that the administration of a drug to animals may fail to reveal its hazards in man.

Towards the end of the first World War another collaborative investigation concerning an adverse reaction to a drug was instituted. The Medical Research Committee, later to become the present Medical Research Council, appointed a 'Special Committee on the Manufacture, Biological Testing and Clinical Administration of Salvarsan and its Substitutes'. Its enquiries followed an outbreak of acute yellow atrophy due to neoarsphenamine benzoate at Cherry Hinton Hospital near Cambridge in 1917 and 1918. The Committee reported (Medical Research Council, 1922) that the most probable cause of the outbreak was the toxicity of organo-arsenical compounds. But Professor Stuart McDonald, Professor of Pathology at Newcastle, suspected that there was an additional factor causing the epidemic of jaundice which was probably microbial infection (McDonald, 1918). The aetiology of this jaundice was in retrospect probably serum hepatitis. By a strange coincidence the Committee also made a report of a peculiar outbreak of malaria among patients treated with neoarsphenamine '606' at Portobello Hospital, Dublin. Eight soldiers had died, and Professor A. C. O'Sullivan, Professor of Pathology at Trinity, found their organs full of malaria parasites, although only one of them was known to have served in a tropical country. The Committee found no reason to dissent from Professor O'Sullivan's opinion that the infection had been conveyed from one or more carriers of the disease to others through the apparatus for injecting '606', the blood of the carrier regurgitating into the last segment of the rubber tubing remaining in the crevices there and being washed into the veins of the next patient. If the hazard of crossinfection had been considered as a cause of the epidemic of jaundice at Cherry Hinton Hospital identification of an infectious cause of jaundice might have been made 20 years earlier than was the case.

The introduction of the sulphonamides in the late 1930s brought familiarity with adverse reactions to all physicians. But these drugs, and later penicillin, streptomycin, and the adrenocorticosteroids, led to such advances in medical treatment that adverse reactions, although recognized, caused no great anxiety. This complacency was shattered in 1961. At a congress of gynaecologists at Kiel on 19-20 October 1961, von Massenbach from Lubeck, Lenz from Hamburg, and Wiedemann from Kiel drew

attention to the large number of children who had recently been born in Germany with hypoplastic or aplastic limb deformities. A month later, at a paediatrics meeting in Dusseldorf, Lenz first suggested that the hypnotic drug thalidomide might be the responsible agent (Taussig, 1962). Thalidomide was marketed in Germany under a number of proprietary names and often was compounded with analgesics for the treatment of pain, cough, and insomnia. Not only were these preparations widely prescribed by doctors but they were purchased over the counter by the public. The profusion of preparations and names made retrospective inquiries about the medicines women had used in pregnancy difficult but Lenz's suspicions were soon confirmed. It is now believed that more than 6000 deformed babies were born in West Germany and some 500 in Britain as a result of the use of thalidomide. Many of these children still live, and remain a grim reminder of a tragedy that shocked the world.

One result of the public outcry after the thalidomide tragedy was that governments in many countries established organizations to ensure that adequate and appropriate toxicity tests were carried out before new drugs were used in human beings. However, as it became recognized that the results of tests in animals cannot be directly extrapolated to man, an urgent need developed for monitoring the use of drugs, especially newly introduced drugs, to identify adverse reactions as soon as possible. In Britain a report on the assessment of drug toxicity which was prepared for the Medical Research Council (1963) not only gave advice about the way in which a system of notification of adverse reactions by doctors using drugs should be established but stated: 'Early recognition alone is not always enough. The purpose of determining the toxic effects (of a drug) in man will usually be to obtain intelligent restriction of its further use. To make such a decision possible it is necessary not only to recognize the toxic effect but also to estimate its incidence and to compare that with the danger of the diseases for which the drug is being used.'

These wise words bear repetition for hasty and unnecessary decisions to ban the use of a drug have been a feature of recent years and are often the result of undue, unbalanced, and sometimes premature publicity by the press which lead to overreaction of the public or politicians. It is, however, now widely recognized that there is a need not only to identify the adverse reactions to a drug but to determine their incidence in relation to the use of the drug. The data available to answer such questions have come from sources each of which has had its limitations.

Medical Literature

Although there was increasing awareness of the serious nature of adverse reactions to certain drugs following the introduction of the sulphonamides in 1935, it was considered sufficient throughout the 1950s to leave the duty of reporting the toxic effects of drugs to individual physicians or pharmacologists who usually reported them in articles or letters in medical journals. It is, however, usually difficult for a physician to establish the relationship between an unexpected toxic effect and a drug. The patient may be receiving many drugs and a single physician may seldom see the same adverse reaction to a drug more than once or twice in his professional life. Nevertheless since 1957 Dr L. Meyler and his colleagues have published a number of most valuable surveys of reports of adverse reactions to drugs occurring in the world literature (Meyler, 1957; Meyler and Herxheimer, 1968). These surveys are of great value as works of reference, for the reader can rapidly ascertain what reactions have been reported with any given drug. However, they seldom provide reliable information about the incidence of reactions and indeed may give a false impression of the incidence, for many reports may appear about certain reactions of special interest to physicians or pharmacologists.

The Registries Reports of Adverse Reactions

In 1951 two American haematologists, Wintrobe and Sturgeon, found by accident that each had seen two or three cases of aplastic anaemia in patients who had been treated with chloramphenicol. It was Dr Wintrobe's idea to establish a Registry of Blood Dyscrasias and between 1955 and 1962 reports of 1195 patients with blood dyscrasias suspected as due to drugs were received. The number of reports received was small: this was due to poor publicity, the novelty of the scheme, and the dauntingly detailed form which had to be filled in. There was also anxiety, which persists in the United States, that by reporting an illness as due to a drug he has prescribed, a physician might expose himself to a charge of negligence by his patient. The establishment of this registry by Dr Wintrobe marks the beginning of systemic monitoring of adverse reactions to drugs (Erslev and Wintrobe, 1962).

After the thalidomide catastrophe registries of adverse reactions were established in a number of countries. Their main purpose is to provide an early warning that a drug causes an adverse reaction. It is clear, however, that only a small proportion of adverse reactions that occur are reported. In the United Kingdom in 1966 when the relationship

between the oral contraceptive pill and thrombosis was of wide public interest, it was found that in a sample of 53 women who had died of thrombotic illnesses and who were known by their family doctor to be on oral contraceptives only eight had been reported to the Committee on Safety of Drugs (Inman and Vessey, 1968). It is known, too, that many deaths of asthmatic patients using isoprenaline aerosols were never reported, but this was because the relationship between these aerosols and sudden death was unsuspected (Inman and Adelstein, 1969).

Yet despite serious defects these registries still constitute one of our most valuable sources of information about adverse reactions. The Committee on Safety of Medicines (the name was changed when the Medicines Act was passed in 1968) receives about 350 reports a month. It is now possible to characterize a profile of the reactions of a given drug or group of drugs. When a new but related drug is marketed suspicions may be aroused if reports of an unexpected reaction such as jaundice begin to arrive (Wade, 1970).

The Committee's policy has always been to ask for a simple report from doctors and a supply of prepaid yellow postcards is sent to every medical practitioner. They are asked to report all unexpected and all serious adverse reactions to drugs, especially those suspected to be due to new drugs. It has been a disappointment that so few reports of adverse reactions to drugs have come to the Committee from hospitals. Reporting from a hospital can be greatly increased if a physician on the staff takes a major interest in the problem and if junior doctors, nurses, or pharmacists can be employed as 'drug safety officers'. In the West Midlands Region a Midlands Adverse Reactions Study Group has been formed and reporting from a number of the hospitals has increased greatly. It may be possible to stimulate the interest of family doctors working in the community, and this is desirable because the use of drugs by them is very different from the use in hospitals.

Intensive Monitoring

The seriousness of an adverse reaction depends not only on its nature but also on its frequency in relation to the use of a drug. In the US Army Custer (1946) determined the incidence of aplastic anaemia due to the antimalarial drug mepacrine with a precision which will seldom be equalled. He showed that the incidence was 2·84 per 100 000 men taking mepacrine compared with 0·1 per 100 000 men not taking mepacrine. In spite of this low incidence, Custer's evidence that mepacrine can cause aplastic anaemia is accepted because he surveyed millions of troops with excellent medical records.

Intensive monitoring has been developed in hospitals. Patients are kept under surveillance, all drugs administered are recorded, and any event which might be an adverse reaction to a drug is noted. In a survey carried out at the Belfast City Hospital, Hurwitz and Wade (1969) showed that about 10% of patients in our wards had adverse reactions to drugs (table I), that these tended to be commoner in women than men (table II), and were more frequent in the aged than in the young (table III). It was interesting to find that patients who on admission had a history of previous drug reactions or of allergic illness were at greater risk than those who had no such history (table IV) and it was possible to identify certain drugs (table V) which caused a high incidence of reactions and certain combinations of drugs (table VI). Similar findings have been reported by others.

	No.	*Adverse Reaction to Drugs*	*Rate (%)*
Patients admitted	1268	118	9·3
No. given drugs	1160	118	10·2

Table I *Adverse reactions to drugs in hospitals*

Sex	*No. of Patients*		*Rate (%)*
	Given Drugs	*With Reactions*	
Males	682	50	7·3
Females	478	68	14·2
Total	1160	118	10·2

Table II *Sex and drug reaction*

$0{\cdot}01 > P > 0{\cdot}001$

Age of Patients (years)	*No. Given Drugs*	*No. with Reactions*	*Rate (%)*
10–19	64	2	3·1
20–29	100	3	3·0
30–39	122	7	5·7
40–49	159	12	7·5
50–59	222	18	8·1
60–69	252	27	10·7
70–79	178	38	21·3
80–89	59	11	18·6
90–99	4	0	0
Total	1160	118	10·2

Table III *Age and drug reactions*

Rank correlation coefficient = + 0·86

	Previous Reactions	*Allergic Disease*	*Jaundice*
1042 patients with no drug reactions	70 (6·7%)	48 (4·6%)	46 (4·4%)
118 patients with drug reactions	27 (22·9%)	19 (16·1%)	4 (3·4%)
P	<0·001	<0·001	0·70 > P > 0·50

Table IV *Adverse reactions and a history of previous reactions, allergic disease, and jaundice*

Drug	*No. of Patients*		*Rate (%)*
	Given Drugs	*With Reactions*	
Ampicillin	103	8	7·8
Other penicillins	167	0	0
Orciprenaline	74	6	8·1
Choline theophyllinate	100	5	5·0
Methoxyphenamine	133	1	0·8
Morphine	90	5	5·6
Methadone	78	2	2·6
Opium	57	1	1·8
Pethidine	200	1	0·5
Dihydrocodeine	76	0	0
Paracetamol	128	0	0

Table V *Drugs and adverse reactions*

	Patients Given Drugs	*Reactions to Digitalis*	*Reaction Rate (%)*
Digitalis alone	53	5	9
Digitalis and frusemide	79	16	20
Digitalis and hydroflumethazide	23	8	35
Digitalis, frusemide and hydroflumethazide	18	6	33
Digitalis and other diuretics	24	4	17
Digitalis and all diuretics	144	34	24

Table VI *Reactions to digitalis and diuretics*

The Therapeutic Audit

The thoughtful doctor will realize that it is not enough to establish and improve the monitoring of adverse reactions to drugs. If sensible decisions are to be made much needs to be known about the use of the drug. How widely is it used? Who prescribes it? Which patients receive it? For what illnesses? What good does it do? What other drugs are available?

Studies on the use of drugs in the community are very much in their infancy. Dr Helen Hood and I had the fortunate opportunity to have access to details of all prescriptions written by family doctors in Northern Ireland from 1966 onwards (Wade, 1970). All the data are recorded on computer tape to allow payments to be made to pharmacists and we have been able to follow the change of prescribing of individual drugs over time. Figure 1 shows the changes in the prescribing of hypnotic drugs between 1966 and 1970 (Wade and Hood, 1972a). The great increase in the prescribing of Mandrax was probably related to intense and skilful advertising of this preparation; its use decreased after 1969 and nitrazepam (Mogodon) is now the group leader. Of special interest, in view of the deaths caused by

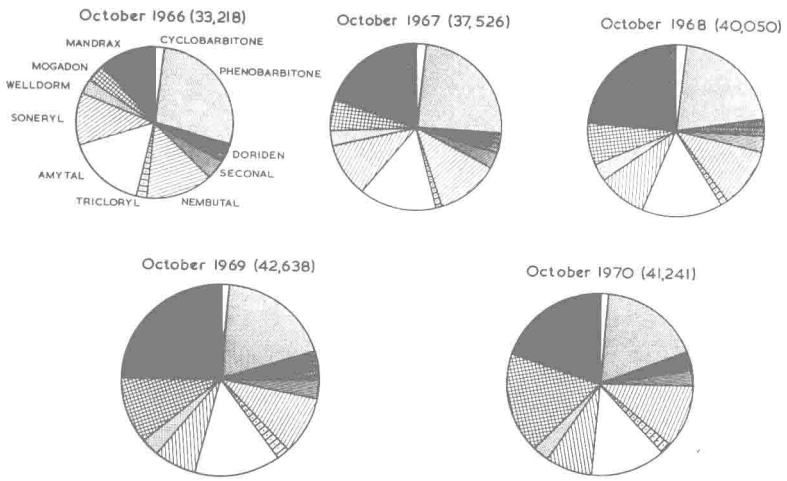

Fig 1 *The prescribing of hypnotic drugs in Northern Ireland 1966-1970.*

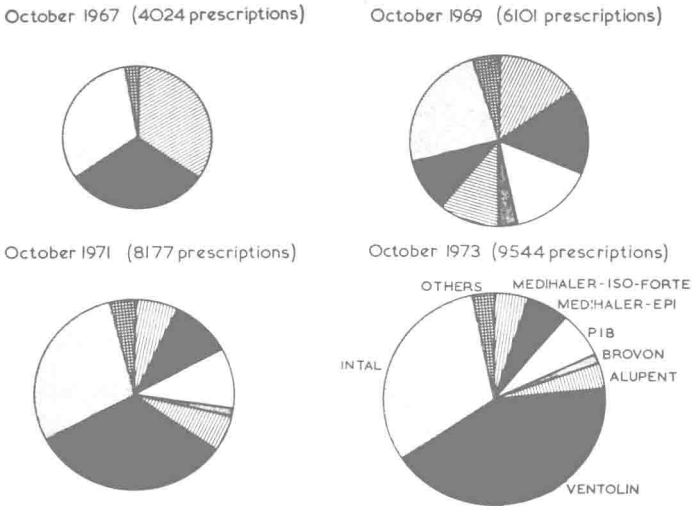

Fig 2 *The prescribing of bronchodilator aerosols in Northern Ireland 1967-1973.*

excessive use of isoprenaline aerosols, is a study of the use of bronchodilator aerosols. This shows (fig 2) a considerable increase in the use of chromoglycate (Intal) and salbutamol (Ventolin) while the use of the isoprenaline aerosols decreased (Wade and Hood, 1972b).

It has also been possible to study the geography of drug use. One of our first studies was of the use of insulin and oral hypoglycaemic drugs (Wade, Hadden, and Hood, 1972). The prescribing of insulin was remarkably evenly distributed throughout the province. But there were great variations in the prescribing of oral hypoglycaemic drugs (fig 3). At the time of the survey (1966) the drugs being mainly used were tolbutamide and chlorpropamide. A detailed survey was made of the use of these drugs in Londonderry and Newry, low- and high-use areas respectively (table VII). It was found that in each city almost exactly the same proportion of persons were receiving oral hypoglycaemic drugs. The difference in overall use was due to the low daily doses prescribed for each patient in Londonderry and the high doses in Newry. I suspect that the main reason for this difference was that in Londonderry the diabetic clinic had a dietician who gave advice and detailed supervision of patients. In Newry there was no dietician. These observations may be important in relation to the anxiety raised by the University Diabetic Group Project (1970) in the USA. The incidence of cardiovascular complications found in that survey was higher in patients on the oral antidiabetic drugs than in those on insulin. This might be investigated in areas where the use of the oral drugs differs greatly.

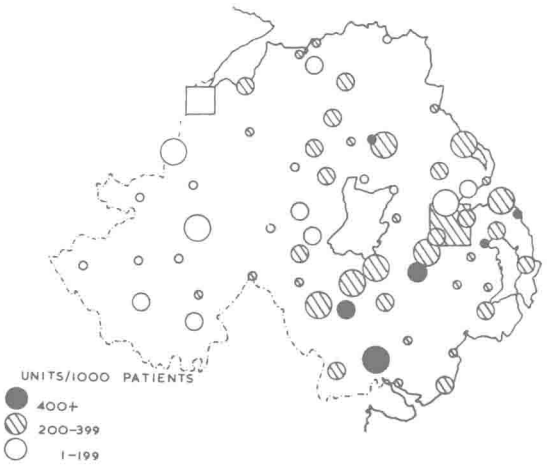

Fig 3 *The prescribing of oral hypoglycaemic drugs in Northern Ireland 1966.*

The circles indicate the population in different towns and rural areas. The prescribing density is represented by the shading and hatching.

	Newry	*Derry*
Diabetic patients	39	101
Diabetics per 1000 patients	1·21	1·33
Units of antidiabetic drugs/1000 patients/month	411	132
Units of antidiabetic drugs/month/per doctor	837	263

Table VII *Prescribing of oral antidiabetic drugs in two towns*

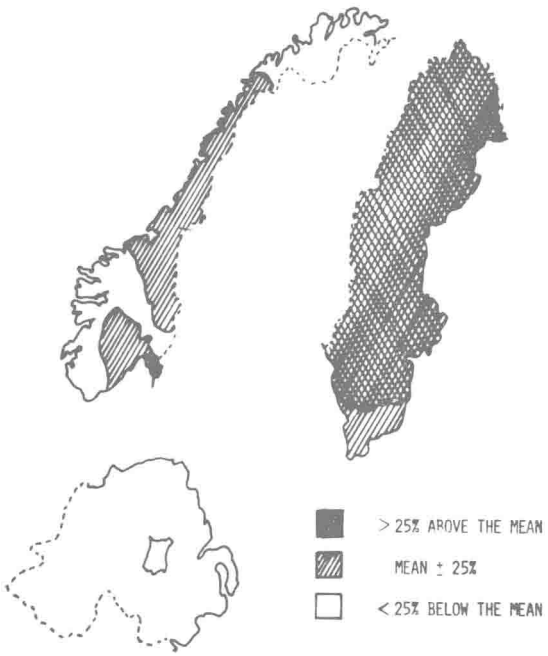

Fig 4 *The prescribing of oral hypoglycaemic drugs in Norway (top left), Sweden (top right) and Northern Ireland (bottom left) in 1972.*

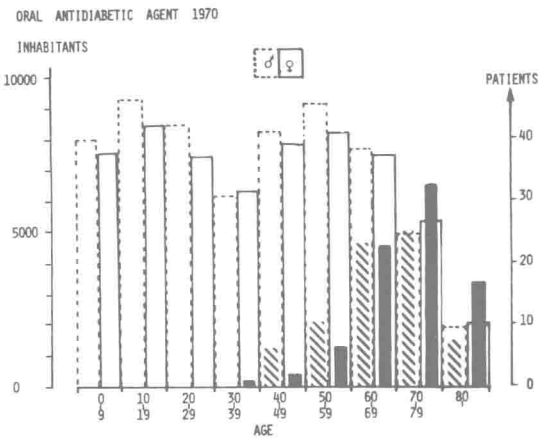

Fig 5 *Prescribing of oral antidiabetic drugs in Jamtland, 1970.*

The age and sex of the community is shown in open histograms and superimposed is the hatched and shaded histogram of patients receiving oral antidiabetic drugs.

Recently it has been possible to carry out a study of the prescribing of the oral hypoglycaemic drugs in Northern Ireland, Norway, and Sweden (Crooks, Elmes, Friebel, Halse *et al*, 1974). The analysis is not yet complete but it is clear that the differences in prescribing found within Northern Ireland are very much smaller than the differences which exist between these three countries (fig 4). It seems to me that if large differences in the prescribing of drugs are occurring it may be possible not only to learn more about the incidence of adverse reactions to the drug but also to assess what value its use is, by comparing the morbidity, span of life, and mortality of communities in which the drug is used with those where it is not used. It has been particularly interesting to find that in one area of Sweden, the county of Jamtland, it is possible not only to enumerate all the citizens by age and sex but also to identify who in the community gets a particular drug. Cardiac glycosides, antihypertensive drugs, and oral hypoglycaemic drugs are found to be prescribed predominantly to the over 60s (fig 5).

It is likely that studies in other countries would show other important differences in the use of drugs. Some eight years ago a study of the sales of antibiotics in six European countries showed that at that time a quarter of all antibiotics used in Germany was chloramphenicol (table VIII) (Engels and Siderius, 1968).

Death and Drugs

It has always seemed to me that the most important adverse reactions of drugs are those which cause or contribute to death. With Dr Tesh and with the cooperation of Professor Curran and his colleagues, I have recently arranged an investigation of the part that drugs may have played in the death of 100 patients coming to necropsy at the Queen

	France	*UK*	*West Germany*	*Belgium*	*Sweden*	*Holland*
Penicillins	20	35	45	11	55	30
Ampicillins	1	15	5	13	15	30
Tetracyclines	40	35	20	20	25	30
Macrolides	8	5	1	30	2	2
Combined tetracyclines and macrolides	8	2	1	15	0	1
Chloramphenicol	5	1	25	1	1	1
Others	18	7	3	10	2	6

Table VIII *Sales of antibiotics in Europe. As percentage of total sales within each country*