CONFERENCE LECTURE

TOXIC HAZARDS FROM DRUGS

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Toxic hazards that might accompany the use of drugs have always been recognised by some, but it is probable that many of those who market and prescribe drugs largely discount the hazards and act on the assumption that existing practices and methods of control protect them and also those who receive the drugs.

In 1937 an enterprising chemist found that the problems presented by the insolubility of the new "wonder drug" sulphanilamide could be overcome by using diethylene glycol as a solvent. The resulting elixir, because of this solvent, killed at least 70 people (see Report of A.M.A. Chemical Laboratory, 1937). A tightening of the controls of the marketing of drugs by the U.S. Government soon followed (Anon., 1938).

Recent tragedies in the United Kingdom and Western Europe arising from the effects of a "safe" sedative have led to a renewed awareness of danger and consequently a demand for action to prevent risks of further injury from the toxic effects of drugs.

Similar situations arise in other fields of human activity. Farmers and growers all over the world had fought a long, hard battle against a variety of pests with a few dangerous and many rather ineffectual chemical agents when DDT and BHC arrived on the scene at the end of the last war and scored an immediate success. These insecticides were closely followed by parathion which, used with the same carefree techniques that were adequate for the safe application of DDT, promptly caused a number of deaths. These tragedies aroused a sudden interest in dangers from the use of chemicals on crops. In this country enquiries and control measures, which included some legislation for the protection of operators, followed and these controls, despite continued anxiety expressed in some quarters, have led to the safe use of pesticides in the United Kingdom.

Thirty years ago an industry might decide to use a new material in a chemical or manufacturing process without making any particular enquiries about its toxicity to mammals. When men or women exposed to the new material became ill or some even died, enquiries might then be made. Incidents in which more than a few people were involved led to an awakening to these new potential dangers. The whole position has now changed so that all responsible users of new industrial chemicals begin by seeking information about the possible hazards their use may present to those who may be exposed to them.

Except among a few enlightened people the atmosphere of many of our cities had been accepted as a natural accompaniment of urban life and the fogs of London were even a subject of humour or hallowed

tradition. A few catastrophies elsewhere failed to shake this complacency until 1952 when a concatenation of circumstances led to the publicising of the heavy mortality among those exposed to a prolonged London fog (Anon., 1953).

Life on this planet has always been surrounded with threats in one form or another to its continued existence. Human achievement in all fields has depended upon some individuals pushing out into the unknown and taking risks. Progress cannot be achieved without a simultaneous acceptance of some hazards. Even stagnation is not necessarily free from danger.

For many centuries the physician was called upon to deal with human ailments with no more than a handful of drugs which possessed any therapeutic value and a number that were probably harmful as well as being ineffective. Now, thanks to the advances in chemistry, physiology and allied sciences, the physician has a plethora. Not only can they be used for the treatment of serious disease but others may ameliorate the minor disorders and discomforts which are increasingly conspicuous in modern life.

The rising standards of public health have rid communities of much illness, but such standards also demand more from those who are concerned with possible hazards to health in places of work, the general environment and in the home. Every proposed additive to human food is closely scrutinised lest its consumption might prove to be injurious. For some curious reason far more attention is now paid to synthetic chemicals despite the well known fact that all the most toxic substances are of natural origin.

The industrial medical officer has the services of the engineer and technologist to rid the factory of whatever he believes to be a toxic contaminant. Thus he may be left free to deal with complaints arising from the discomforts produced by heat, noise or monotony.

In the same way, the doctor at home is called upon to ameliorate a host of minor complaints. He naturally turns to the armamentarium of drugs so temptingly put in his way by an enterprising pharmaceutical industry and freely provided by a benevolent health service.

Toxic hazards arising from the administration of drugs and their possible control should therefore be examined in the context of the situation in which they occur and useful comparisons can be made with toxic hazards met with under other circumstances. The object of this examination must be to make recommendations for actions that will effectively reduce the risks accompanying the proper use of drugs. It should be accepted at the outset that nothing will eliminate all risks, while allowing the effective use of drugs. The ineffective use of drugs may be a potent source of trouble but it cannot be considered here.

As in many other situations, it is probably too much to ask that the problem of the toxic hazards from the use of drugs should be viewed in perspective. The tremendous publicity and expensive advertising in all the media of communication aimed at reducing road deaths that have remained almost stationary at between 5,000 and 6,000 annually for 20

years may be compared to the efforts made to reduce cigarette smoking. This has caused deaths from lung cancer to rise fivefold from 5,000 to 25,000 per annum, in the same period. This disease kills more people in 1 year than motor traffic does in 4 years.

On the farms of the United Kingdom, tractors and bulls kill more people in 6 months than all the so-called dangerous pesticides have done in the 15 years of their wide scale use. Yet compare the number of committees considering each of these hazards. Many dangerous chemicals are used in industry but deaths and injury are mainly caused by machinery.

No one doubts that lives have been saved or health and activity restored by the use of new drugs which may also have injured a few of those receiving them. Those who die from diseases no one can treat die "natural" deaths. Deaths following the use of drugs given in good faith are liable to lead to enquiries that would have been avoided had no drug been given. The toxic hazards from drugs or other chemical substances must be considered from two general standpoints.

The *toxicity* of a compound is its capacity to cause injury while the *hazards* represents the probability that it will do so. It is very important to separate these two aspects of the problem when considering ways of ensuring the safe use of drugs.

Toxicity

The toxic effect of a drug may be direct and obvious and due to an excessive pharmacological action caused by an overdose or by the undue sensitivity of the individual receiving the drug.

The toxic effect may be an unexpected side-effect such as liver necrosis following an anaesthetic or aplastic anaemia from one among the many antibiotics. It is perhaps important to beware of the toxic effect which is not due to the drug. For example the widespread incidence of hepatitis once believed to be due to the drug Salvarsan was later shown to be due to the virus of infective hepatitis transmitted from patient to patient in inadequately sterilised syringes (Bigger, 1943).

However, the genuine and completely unexpected side-effect of a drug is the problem in toxicity that rightly excites most attention. The main problem in controlling hazards from drugs centres on the satisfactory recognition of such side-effects at an early stage in their incidence.

Two special toxic effects must be briefly mentioned. The first arises from the sensitisation of a proportion of the individuals who receive a drug. Individual sensitisation can occur to almost anything whether naturally occurring or synthetic. It is therefore not a problem confined to the distribution and use of drugs and such is the range of individuality in this respect that the world cannot be made comfortable for everyone prone to show this reaction.

The other special toxic effect is addiction. While this has a strictly pharmacological aspect in that some drugs are particularly prone to produce addiction in any individual receiving repeated doses of them, there is also a strong human element in other cases where addiction to

some unusual drugs may occur. The subject is a complex one and may, in some cases, be related in unexpected ways to developments in modern civilisation (see below).

Hazards

The hazards from drugs will be related to the numbers who receive the drug and the dose administered. This last point has been well emphasised in accounts of agranulocytosis and aplastic anaemia in patients receiving chloramphenicol. In many of these cases the amounts prescribed greatly exceed those recommended (Hodgkinson, 1954). The toxic hazards may be enhanced because those who receive drugs are not healthy. But against the hazards which may be attributed directly to the drug must always be set those which would follow were the drug to be withheld, or alternative treatment applied. Thus a drug given to suppress thyroid function may carry some risk of inducing a serious or fatal agranulocytosis whereas an alternative treatment would be surgical removal of the gland or the injection of radioactive iodine which also carry a certain risk. However, in situations like this where the disease and its sequelae are well known and each form of treatment has been subject to many separate analyses by experts in different hospitals, the related hazards are well understood and can be accepted by all rational people. Where a drug is administered to produce an effect whose benefits are completely uncertain such as a drug to lower blood cholesterol and where administration is likely to be very prolonged and under very marginal medical supervision, the significance of any toxic side effect assumes very different proportions.

Finally, the real hazards will be appreciated only if any adverse effects of the drugs are detected and their significance recognised. The hazards will also be related directly to the nature of the toxic effect which may be either rapidly fatal, or rapidly reversible or leave the patient permanently injured. In this last respect the hazards from occupational and environmental poisons can be strictly compared with those from drugs. But considerations of hazards in relation to benefits is almost confined to the field of drugs. Thus an individual should not be expected to run a serious risk of poisoning when applying a pesticide that will mean others will benefit from the better crop resulting from the use of the pesticide. Nor should a factory worker be exposed to a greater risk because a commercial enterprise can be made more competitive by the use of a cheaper but more dangerous solvent.

It is worth bearing in mind that had the use of thalidomide saved pregnant women from a serious or fatal disease, the ultimate birth of deformed offspring would have been accepted as a price that had to be paid for the saving of the valuable lives of their mothers. Fortunately women in the early stages of pregnancy are usually in excellent health despite the discomfort of "morning sickness" and to attempt to alleviate this at the possible expense of the foetus seems inexcusable—in retrospect. It is perhaps salutory to consider the ways in which effects of the tragedy of thalidomide may be viewed. "The thalidomide tragedy did not

directly affect your Company but one of our most widely prescribed products . . . is for use in pregnancy sickness. Inevitably, since the discovery of the wholly unforeseen risks attendant on the use of thalidomide doctors have become hesitant about prescribing any drugs during the early stages of pregnancy" (Eley, 1963). It is to be hoped that commercial enterprises will follow the doctors by practising a similar hesitation in recommending drugs for this physiological condition.

The Study of Toxicity

It is now appropriate to consider in more detail what we can know about the toxicity of a compound. Toxicity is not a property capable of precise measurement like boiling point or molecular weight but the toxic effects of a drug will be related to the dose, frequency and route of administration and nature of the injury produced. Special toxic effects such as sensitisation may be brought out by topical applications of drugs like penicillin in doses far below those causing any general toxic effects.

The toxic side-effects of drugs are, or should be, the subject of special investigations on laboratory animals. Various recommendations for the type of investigation that should be made have been put forward (Lehman and others, 1959; Paget and Barnes, 1963), but their value depends far more on the quality of the man making the investigation than on the detail with which suggested procedures are laid down by experts or by committees.

The simplest early tests are made to discover the relation of the lethal dose to the supposed therapeutic dose and to decide whether death is due to the pharmacological action of the drug or to some side-effect perhaps superimposed upon the main action. Tests on different species will determine whether the effect is general or limited to a few species or highly varied in the different species making the necessary extrapolation of man correspondingly more difficult. What is not always realised is that the value of all subsequent investigations on the nature of such a suspected toxic action will depend upon the skill with which the investigator analyses the original observations so as to make his subsequent experiments add to his preliminary information. The extension of toxicity testing is not to make the world safe for rats or dogs but to extract information from the reactions of these species that will make the world safer for man.

Many drugs call for repeated administration and therefore toxicity tests must include animals similarly treated. Non-toxic doses will often be those showing no effect on the growth, food intake and general condition of young animals. Special tests of function related to the action of the drug may be included and the fate of the drug should be studied so that this may then be compared with its metabolism in the first patients to receive it. Very often the final arbiter in deciding that the repeated administration of a drug was innocuous to animals will be the pathologist called upon to look at the tissues of those killed at the end of the experiments. In order that the pathologist shall be able to recognise

small degrees of abnormality in the material which he is studying it is essential that his control animals be healthy. For this reason they should be comparatively young and senescent changes must be absent. They should also be, as far as possible, free from changes due to the common infections widespread in so many animal houses. This means that tests in which the drug is administered repeatedly should not run for more than a few months in small animals and should be carried out on specific pathogen-free stock. It seems to be the consensus of opinion (Dr. G. E. Paget, personal communication) that no new toxic effects will be discovered if a drug is administered for longer than 3–6 months provided that the short term studies have been adequately performed. Tests of much longer duration have to be carried out to determine whether a drug has a carcinogenic action on the test animals but the pathologists' problem is not so difficult when this involves the recognition of the existence of a tumour. Far too little attention has been paid to the importance of pathological work on laboratory animals and to the training of people for its performance. Whereas 50 years ago morbid anatomy and histology were often the end-point in pathology, today histology should more often be the starting point of further investigations because sensitive techniques have given evidence of slight tissue changes that may herald more significant ones if the administration of a drug is either increased or prolonged.

A comprehensive series of toxicity tests can be concluded with the following sort of information. The proposed drug produces liver necrosis or kidney damage or severe failure of growth or food intake in doses close to those likely to be prescribed. The compound is then rejected as a potential therapeutic agent unless it is likely to be valuable in an otherwise certainly lethal disease. Possibly it will be found that repeated doses produces a certain incidence of tumours in the animals used in the toxicity tests. It will then be necessary to consider whether the drug is to be used by the young or the old, for serious or mild conditions and whether it is unique in its therapeutic effects or only an alternative to a drug already shown not to have these properties. It cannot of course be fairly compared to a well established drug that has never been tested by the same procedures to determine whether or not it has such properties. It is quite possible that one or more drugs now widely used and long considered safe might, if subjected to some of the procedures recommended for testing substances for carcinogenicity, produce tumours in laboratory animals.

These and many other bits of information may be learnt from well conducted toxicity trials on laboratory animals but however innocuous the drug may appear to be in the dose ranges that are to be recommended there is still no guarantee that (*a*) a certain number of people who receive the drug will not develop agranulocytosis; (*b*) no one will become very sensitive to the drug; (*c*) that if given to pregnant women the foetus may not be injured; (*d*) that some quite new effect will not first be seen in some human beings who receive the drug. A detailed analysis of the findings in rats, dogs and man has been made by Litchfield (1962) who

compared the reactions of 6 drugs of different pharmacological activity which had been tested for toxicity in dogs and rats and then given to at least 500 patients. From the animal tests it was possible to predict that certain toxic effects might be seen in man and 26 such predictions out of a possible 38 were correct. It was also possible to suggest what effects should not occur and out of 48 such possible instances 38 predictions were correct. This seems to be the only instance where an attempt has been made to find out how valuable tests on animals may be as a guide as to what may and what may not occur when a drug is given to man. Clearly the conclusions from this investigation are that tests on animals must continue to be the basis upon which first decisions about the safety or otherwise of a drug are based. Toxicity testing can reasonably ensure that the drug is unlikely to produce some well recognised toxic effect either generalised or confined to one organ in all the patients who receive the first doses to treat their ailments.

Assessing Hazards

If toxicity testing can give such a limited warranty of absolute safety it is then necessary to consider the hazards in more detail always remembering that there are other hazards that could arise if the drug was not given. Thus a new drug may relieve a serious disease but cause a certain number of casualties. Such an occasional effect is likely to be recognised early because the treated patients, suffering from a serious disease, will be under close medical surveillance. Similarly if a completely new compound is introduced into industry the medical officer responsible for the health of the exposed population will be on the alert for any new reports of illness. When a new pesticide is introduced into agriculture which by evidence of studies on animals appears likely to present a hazard then its introduction will be limited or the inspectors of the Ministry of Agriculture as well as the medical adviser of the manufacturer will be on the alert for reports of poisoning.

A drug, whether old or newly developed, may be found to relieve the symptoms of some common and harassing disease that is neither dangerous nor lethal. If the drug causes toxic side-effects then the speed with which these come to be recognised will depend very much on their nature. Thus a drug that relieved dyspepsia or the pain of peptic ulceration but caused peripheral neuritis in a significant number of those receiving it might soon be recognised as the probable cause of the new complaints. A drug that was found to give immediate relief to anxiety or neurosis might have to produce outstanding neurological or psychiatric side-effects before it became recognised as the cause of a new disease. For homely remedies the delay in recognising toxic effects from their administration may be very long indeed. In 1914 a disease of infants called acrodynia or "Pink Disease" was first described and it has been reported in Europe, America and Australia. Its aetiology remained a mystery until 34 years later when its possible association with mercury poisoning was put forward (Warkany and Hubbard, 1948). The mercury was in most cases undoubtedly that present in many infant teething

powders. A plea to make it illegal to add calomel to such preparations was still being made in 1954 (Dathan, 1954).

The problem of recognising toxic effects may face an industrial medical officer where a new process was introduced and within a short time a number of operatives applied for a transfer or left their employment. If the new chemical to which they were being exposed only caused rather general effects such as headache, fatigue, sleeplessness or anxiety, the operatives might not associate these disturbances with the introduction of a new solvent but attribute their complaints to some quite extraneous cause. Thus the hazards presented by a new toxic material may only be recognised early if the toxic effects are outstanding in their incidence or their manifestations. A new drug might induce severe sensitisation in 1 in 1,000 people who received it in the recommended doses. This might hardly impress itself on a practitioner with a total of 3,000 registered patients of whom he is unlikely to give one particular drug to more than a small fraction. The physician in an out-patient department of a large hospital might see several such cases but find it difficult to pin-point the cause of the illness to the use of a new drug of the use of which the patient might not be aware.

Other hazards may, of course, arise as the result of new techniques of promotion. Carbromal and bromvaletone had for many years been known to relatively few people as safe sedatives and they were present in a number of proprietary preparations available over the counter. A few years ago increased advertising including the use of television led to a greater number of people being introduced to these drugs and a few became addicted to them, sometimes with disastrous results.

Thus safe and useful drugs may prove to be a hazard for a few who discover them through popular advertising and do not take them under medical supervision (Seager and Foster, 1958; Copas, Kay and Longman, 1959). The question of the control of such drugs raises the problem as to whether this should be done solely in the interests of the unstable minority of the population (Glatt, 1959).

The fear that the widespread advertising on radio and television of the so-called safe sedatives containing phenacetin might lead to an increased incidence of renal damage has recently been published (Friend, 1963). So serious has the problem of renal damage due to phenacetin poisoning become in some countries that the drug is no longer available for purchase over the counter. The dependence which some acquire for the pharmacological action of ethanol is well known as a social problem but the hazards from other solvents such as trichloroethylene as drugs of addiction are not widely recognised and may prove fatal (James, 1963). That new uses may introduce new hazards was illustrated about 15 years ago when a drug discarded as dangerous found a new use as a weed killer in agriculture. Used without any particular care for long hours in hot weather to spray young corn, dinitro-*ortho*-cresol was responsible for a few cases of serious and even fatal poisoning among agricultural workers in the early years after its introduction (Hunter, 1950). Subsequently it proved possible to devise techniques by which it could be safely applied.

Control of Hazards

Hazards from all sorts of toxic chemicals depend upon how they are used. This could apply to solvents, pesticides or drugs. What are their physical and biological properties? How many people are exposed to them? What quantities do they receive? The industrial medical officer will examine the use of a new substance in the factory for which he is responsible. A new pesticide will not be used until the proposals for its application to seeds, crops or stored food have been scrutinised by expert committees. A similar screening procedure is promised for drugs. What might an enlightened Society do to protect its members from the introduction of drugs that could thereby put some or all of the members of that Society at some risk? Control could aim at four targets.

1. *Fewer new drugs.*

2. *The promulgation of new laws.* These would be designed to control the introduction of new drugs with the implication that only those of recognised value and with little or no associated hazard would be offered for sale or prescription.

3. *Better education.* This would be aimed at those people responsible for the administration and distribution of drugs so that only people in real need received drugs which were of recognised value and of proven safety.

4. *More research.* Support for research might make it possible to distinguish safe and dangerous drugs before they are given to large numbers of human beings.

No one would probably dispute that if all these steps were implemented in a general and enlightened way Society might be a safer place as far as risks from drugs were concerned but it is necessary to look a little more closely at each type of control as some favour one or more in preference to others. To each, serious drawbacks can be seen if they were to become the dominating means of control.

Fewer drugs. This may appear to be the simplest way of limiting hazards but if the emergence of new and more specific remedies is impeded this will mean that some patients will continue to receive larger doses of a less effective and possibly a more dangerous drug. Furthermore the full value of a new drug can never be assessed until it has been given to sick people and its effects observed. The reason that there are perhaps too many drugs available at present is that it is difficult to make out a case for discontinuing a drug that is not obviously better as a therapeutic weapon than another which has been long in use and shown to have a fairly well recognised margin of safety and incidence of side-effects. There is no case to be made out for restricting the number of drugs entering proper clinical trials, always provided that some satisfactory preclinical tests on animals have been carried out and adequately recorded. The clinical trial will tell the observers whether or not the new drug was superior to existing methods of treatment which in some cases will be the use of other drugs. Very few clinical trials reveal the full toxic potential of a new drug.

Even when the possibility of a toxic effect upon the bone marrow had been considered probable because of its chemical structure a very full trial of chloramphenicol "failed to disclose any evidence of this" (Smadel, 1949). Yet the wider use of this antibiotic has led to many cases of marrow damage being reported.

That there may be more drugs available than are really necessary to treat the diseases and illness encountered today is partly due to the difficulties of deciding whether significant differences do or do not exist between a number of different substances recommended for treatment of the same condition.

Some drugs linger on because they are believed to be valuable by those who use them. However such "clinical impressions" are notoriously difficult to measure or to assail. Perhaps it might be true to say that drugs are as reliable as those who prescribe them. No physician is perfect and neither is any drug. A careless or a non-observant physician is the equivalent of a potentially injurious drug. No label, "safe" or "dangerous", can be applied to a drug any more than it can be applied to a chemical used in industry. Safety depends in the ways in which substances are applied or prescribed. No case can therefore be made for restricting the numbers of new drugs *per se* but everything is to be said for the provision of better means to follow the use of new drugs and for the continued education of the users.

New Laws

Leglisation to control the introduction of new drugs has a good deal to be said for it but it must be remembered that the Law itself is poor protection against injury. It may exact penalties from those who are caught infringing its provisions but it is usually singularly ineffective in providing remedies for those who are injured. Laws may give the appearance of a safeguard but their existence does not deter the criminally minded. To some extent the existence of a law and the penal sanctions that accompany it may deter those who wish to indulge in doubtful practices. The section of the Pharmacy and Poisons Act which enables the Poisons Board to put certain drugs into Schedule IV (that is available on doctors' prescription only) has undoubtedly prevented much drug addiction and misuse of valuable therapeutic agents. So many new drugs are now pharmacologically active agents that it is questionable whether any new or worthwhile remedies should be available for the public to try for themselves. However some people clearly hope that new legislation will make it possible to prevent the introduction of drugs which subsequently prove so injurious that they have to be withdrawn. Unfortunately it is impossible to devise a set of tests to which a new drug must be submitted and the results of which will make it possible to say unequivocally that the drug is safe or dangerous. It is certain that a law could make it necessary that any new drug should be registered before it becomes available, particularly for prescription within the Health Service. Under such a law it could be stated that a Statutory Body would have to scrutinise evidence and state whether the drug had

been examined sufficiently comprehensively for both therapeutic value and adverse side-effects. However if a drug is passed by such a Body it must inevitably gain some hallmark of apparent safety. Those who press for legislation on this matter might well pause to consider whether more would not be achieved by enlisting voluntary co-operation. At least no drug need be made available under purely domestic rules of the Ministry of Health until the tests on animals to which it had been submitted had also been scrutinised by a committee appointed by the Ministry. If this Committee made an error in rejecting a drug of undoubted value, the drug might still find a place on the open market of private practice where the doctors and manufacturers shared the responsibility for any damage it might do to the patient. If it then proved to be unexpectedly safe or effective its further use could be reconsidered. Under a purely legal sanction errors of judgement might lead to the permanent exclusion of a potentially valuable material. It is necessary to face squarely the issue that tests on animals may lead to a safe drug being excluded or a dangerous drug accepted. It is therefore illogical to press for the rigorous application of toxicity tests on animals as a basis for the exclusion or acceptability of a new substance as a drug. No tests on animals can show that a drug is safe. These tests on animals may show that a drug has toxic properties which may either lead to its exclusion from further use or to its introduction with due care and watchfulness for such side-effects as have been observed in animals. It is still possible to buy ragwort from a herbalist although there is published work showing the poisonous action of this plant on livestock and the alkaloid present in ragwort will not only kill rats as a result of an acute liver necrosis within a few days but in smaller doses lead to their death from liver cancer 18 months later (Schoental and Magee, 1959). How can we logically accept tests on rats as a basis for accepting or rejecting drugs fresh from the synthetic chemists bench when we allow free sale, not even under medical control, of preparations which on the basis of studies on laboratory or domestic animals would never have been considered for sale as drugs? In this illogical Society must all the controls be placed on those who attempt to meet requirements by providing information while those who rely on ignorance and folk lore are allowed to distribute without any control whatsoever materials that are dangerous? If the recipients become ill and are finally obliged to seek real medical aid they rarely, if ever, admit their previous folly in consulting unqualified distributors of herbal remedies. If care is not exercised at this stage much effort will be spent in protecting the few from an occasional mishap occurring in the cause of a *bona fide* attempt to provide what is believed to be scientific treatment while others are exposed to the unscrupulous uncontrolled distribution of Nature's so-called remedies.

Education in the Use of Drugs

Patients receive drugs either because their medical attendants believe that the drugs will alleviate their illnesses or because the patients demand them. In this country it is unusual, though not unknown, for patients

to demand a specific drug. In some countries where popular journalism presents medicine and therapeutics in a way that all and sundry can recognise and remember the names of remedies, doctors may be put in a more difficult position. Sometimes the puzzled doctor may prescribe a simple and probably harmless drug for a week or two so that when he sees the patient again he can judge whether or not the signs and symptoms he first observed and whose significance to him appeared doubtful now point less ambiguously to the diagnosis. It is essential that a drug used in this way shall at least be completely harmless whatever be its therapeutic attributes. If the patient demands no more than a "bottle" as indeed they did 25 years ago, at least a harmless mixture could be prescribed. But if the patient demands specific treatment for his or her symptoms and even names the drug or type of drug required there is no reason why they should not accept part at least of the responsibility for any adverse effect which the drugs produced. It is easy to criticise the doctor who believes the claims made in the latest glossy circular or presented by a most personable representative. It is perhaps surprising how often doctors may accept advice on treatment from people who have never had the responsibility for the health of a single patient. On the other hand if pressed by his patient for "medicine" why blame the doctor for acceding to the importuning from someone who would not be sitting before him were he or she not the victim of some ill be it physical, mental or purely emotional. The actual nature of some drugs is probably of little importance compared with the confidence with which they are offered and the faith with which they are received. While cheap and inactive materials were distributed in this way relatively little harm was done to those who took the medicine or those who poured them away. Those who were really ill soon came back unrelieved and were sent on for a more careful scrutiny in hospital. Nowadays the wider distribution of powerful drugs with effects upon the sensorium may well cause untold harm not by their toxic side effects as much as by their pharmacological actions in masking symptoms. Indeed the doctor has been given powerful new weapons with which to modify bodily functions. While the main anxiety may at present be directed to the toxic side-effects which some drugs may produce in a few of those who receive them, the possible action of drugs in disguising signs and symptoms of serious disease seems to have excited little, if any, public discussion. It may be unwise to put powerful active drugs in the hands of those who cannot fully appreciate what such drugs could be capable of doing even in therapeutic doses. The world is becoming increasingly full of dangerous materials whether used in industry, on the roads, in the air, fields and homes. To reduce or prevent accidents the most essential step is the education of the user into the potentialities of what he is using. Drugs are no exception and the user here may be the doctor distributing them or the patient demanding or buying them.

Research into the Action of Drugs

Our idea of national priorities is indicated by the fact that the slice of the National Income put at the disposal of the University Grants

Committee does not equal that distributed as a subsidy to egg producers. Since it may be optimistic to expect too much from the better education of the prescribers and users of drugs it is necessary to see what can be done to ensure that new drugs are more effectively tested in order that those with undesirable toxic side-effects shall be excluded from general use. This may have the superficial attraction of diverting the responsibility for the safety of drugs from the user to the provider. In other words the manufacturers will be made responsible for the expensive work of testing their new materials more comprehensively for evidence of their possible harmful effects. However, no maunfacturer has the monopoly of wisdom in devising tests on animals that will provide evidence of the safety of his drug to man. He and his fellow manufacturers will therefore demand that those who wish to use the drugs or approve their distribution will tell them what tests and other research they should initiate in order to provide evidence of safety.

The first proposals are likely to be for the extended use of laboratory tests on animals. Many pharmacologists, both in industry and outside, are interested in the action of drugs and in studying the pharmacological activity of related compounds in order to provide evidence for or against current theories of modes of action. This will eventually provide a better understanding of physiological processes. Unfortunately few, if any, departments of pharmacology take any active interest in the study of the toxic side-effects of drugs. These, when they are detected, may result in a lessened interest in the study of a compound; indeed it is unlikely that a manufacturer would continue to produce such a material even for laboratory work. One result of this lack of interest in research in toxicology is that more and more reliance tends to be placed upon the performance of some patterns of tests on a few species of laboratory animals in order to see whether any unusual effect shows up. Certainly in the context of existing information there is sometimes little more that anyone can recommend as a method for examining a new compound for unsuspected side-effects. However unless more research into means of detecting toxic side-effects is undertaken this method of approach is likely to remain unimproved or even become less realistic. For example the recent outburst resulting mainly from the publication of "Silent Spring" has led The Scientific Advisory Committee to the President (1963) to recommend further laboratory tests of the toxicity towards mammals of new pesticides despite the fact that these are tested at least as thoroughly as many drugs. Furthermore people are exposed only to pesticides in minute fractions of the doses of which they receive drugs. It is recommended that tests on pesticides be continued for 2 generations of laboratory animals but there is no evidence whatever that these tests will reveal anything relevant to the possible hazards run by people exposed to such pesticides.

It is not difficult to make it appear that more is being done to make drugs safer by insisting that more animals are given doses for longer periods. All this work takes time, effort and expense and with the limited facilities available fewer can be spared for research. Since the

thalidomide disaster recommendations have been made for carrying out tests for a possible teratogenic effect on animals of new drugs (Somers, 1963). A great number of such tests have been, or are in the process of being, carried out. What is really needed, however, is an intense and diversified investigation of the biochemical and other mechanisms whereby thalidomide produces its teratogenic effects so that when more was known about this, some more rational tests might be devised to look for similar reactions from other compounds. Few will probably share the view that "teratogenicity—should not again be a danger to man; the test on rabbits should be applied as part of the routine pharmacological testing of all new drugs" (Macgregor and Perry, 1962). The danger will undoubtedly be least if the advice "to bar absolutely the use of new drugs by women who are believed to be in the early stages of pregnancy" (Woollam, 1962) is followed. An absolute faith in the predictive value of tests on animals will be misplaced; a failure to take some risks may not be the way to make progress.

Most toxic effects come as unpleasant surprises but each as it arises can offer an opportunity for research which may throw a great deal of light on the body processes in general. An excellent example of this was described in the last Conference Lecture when the story of the haemolysis produced in some patients receiving primaquine was described (Clark, 1962). This particular toxic side-effect has been thoroughly investigated and shown to be due to a heredity defect in the level of an enzyme in the red blood cells of certain members of the population (Beutler, 1960).

These studies explain the haemolytic reaction that may occur after exposure not only to the drug primaquine but also to a number of other drugs, substances used in industry or occurring naturally in plants (Larizza and others, 1960). Furthermore the observation that only a proportion of the exposed population is unduly sensitive to these substances is also explained. No progress whatever would have been made if the only result of the original observations had been that a dozen more tests should have been recommended to be carried out on laboratory animals in order to see whether a new drug produced haemolysis.

It is perhaps not unreasonable to believe that some of the other toxic side-effects of drugs that are seen only in man could be investigated more closely and yield as interesting a harvest of information as did the study of primaquine sensitivity. In the case of toxicity from drugs it seems that in almost all cases research will have to start with some study of man. Those substances with obvious side-effects in animals which are shown up in the preliminary toxicity tests will never be introduced. Thus it is to be hoped that committees set up to investigate the alleged incidence of toxic side-effects of drugs will also have the interest and be provided with the facilities to look into the mechanisms of toxic side-effects as well as just being responsible for recording their incidence and treating the victims.

It is not appropriate here to go into details as to how more research in toxicology should be promulgated. Each toxic substance is itself a

research tool and it may be particularly important to use a compound as a basis for such a piece of research if it seems to be a drug with great promise as a remedy yet apparently possessing some serious but limited side-effects. For example a candidate drug may produce an unusual incidence of one particular type of tumour in only one of several species of laboratory animal. It would be perfectly reasonable to reject such a material as a colour or flavouring agent in human food because its use would not benefit the consumer. However, if the use of such a drug held out hope of the relief of distressing symptoms or the eradication of a chronic infection for which no cure yet existed then it would be ridiculous to condemn it outright as a carcinogen unsuitable for use as a drug. Instead this would be an opportunity for intense research to understand why the sensitive species reacted in the way it did and on the basis of this to decide whether man might or might not be expected to react likewise.

The situation might be generally improved if the place of toxicology and the experimental toxicologist was reconsidered. At present there is a tendency for the man responsible for the toxicology to be at the end of the line saying "yes" and "no" to the onward passage of a new drug into the development of which his colleagues may have put much effort and on to which they and others have pinned great hopes. If research into toxicology was considered a vital part of research in pharmacology a much more productive arrangement might eventually emerge. If such a combined approach became common practice in departments of pharmacology as well as among those promoting new drugs then it would probably be needless and undesirable for Authority to insist that every new drug must be put through some programme of tests the significance of which in relation to the hazard to man was often very doubtful.

Conclusions

All human activity involves the incurring of some risks and the only ways in which these, if they are serious, should be reduced is by better education of those who run the risks or whose actions inflict such risks on others.

The further study of physiology, biochemistry and all the ancilliary medical sciences will eventually lead to better drugs and better means of using drugs. Prescribing doctors and patients have their share of responsibility in seeing that they find out about the drugs they give or those they request. Manufacturers and distributors have a big share of responsibility as soon as they make use of modern methods of sale persuasion. Every new drug that is made freely available for prescribers introduces an added risk of the production of side-effects. When these side-effects occur it may be argued that the proper reaction of Authority should be to make it more difficult to distribute so many different drugs, and that the most effective way will be by instituting time consuming and expensive toxicity testing and other scrutiny. The more widespread and large are the sales of a drug then so must the hazards from it increase.

A drug that has undoubted value for a relatively small number of people with a dangerous disorder may appear to be undesirable and dangerous for a significant number of those receiving it when it is prescribed to relieve a common condition of minor discomfort.

The Law has little or no place in protecting patients from dangerous drugs made available by *bona fide* manufacturers. It offers no more and no less of a safeguard against the wilful and criminal as it does in other walks of life.

Toxic hazards from chemicals used in industry, compounds used as pesticides, substances used as food additives and the toxic hazards from drugs have something in common but each have important distinctions. The toxicity of all the compounds used for these different purposes is often difficult to assess and to understand in strictly scientific terms. There is a serious danger that, by insisting on schemes of testing often prolonged and expensive but lacking a real scientific basis in their design and execution a better understanding of the toxic side-effects produced by drugs will never be obtained. While some general safeguards such as a minimum general testing of new drugs will long remain essential, this type of investigation should not be needlessly multiplied. Research in toxicology which is closely linked with pharmacology will be the only way in which safer drugs or drugs whose actions are more fully understood will eventually become available. The final word in any discussion on this subject can appropriately go to the Minister of Health (Mr. Enoch Powell) who in a recent debate included these words:

"I do not want to pass from this subject without saying emphatically that when we use the word 'safety' in this context we should not be understood to mean 'absolute safety'. Safety in this sphere is relative whatever may be the arrangements, whatever may be the law, it is relative to the illness and in the sense that there is no system that can be devised which will make doctors or scientists aware of what medicine and science have not yet suspected".

The Welfare State with all its benefits particularly in the field of the Health Service does possibly lead to a diminution of individual responsibility and a cry for protection against all possible risks or disturbances to comfort. The introduction and use of drugs involves many individual decisions. A form of blanket cover to guard against all risks will be either frustrating or deceptive. Increasing individual awareness is the only way of progress in this as in all fields of human activity.

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