DRUG RESPONSES IN MAN

A Ciba Foundation Volume

Edited by
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J. & A. CHURCHILL LTD.
104 GLOUCESTER PLACE
LONDON, W. 1

1967
DRUG RESPONSES
IN MAN
First published 1967

Containing 23 illustrations

Standard Book Number 7000 1304 0

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Printed in Great Britain
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The Ciba Foundation

The Ciba Foundation was opened in 1949 to promote international co-operation in medical and chemical research among scientists from all parts of the world. Its house at 41 Portland Place, London, has become a meeting place well known to workers in many fields of science. Every year the Foundation organizes from six to ten three-day symposia and three or four one-day study groups, all of which are published in book form. Many other informal meetings also take place in the house, organized either by the Foundation or by other scientific groups needing a place to meet. In addition, bedrooms are available for visiting scientists, whether or not they are attending a meeting in the building.

The Ciba Foundation owes its existence to the generosity of CIBA Ltd, Basle, who, realizing the disruption of scientific communication caused by the war and by problems of distance, decided to set up a philanthropic institution whose aim would be to overcome such barriers. London was chosen as its site for reasons dictated by the special advantages of English charitable trust law, as well as those of language and geography.

The Foundation's many activities are controlled by a small group of distinguished trustees. Within the general framework of biological science, interpreted in its broadest sense, these activities are well summed up by the Ciba Foundation's motto, *Consocient Gentes*—let the nations come together.
Preface

The Ciba Foundation owes a very special debt of gratitude to Dr. Walter Modell in connexion with this symposium. It was his idea to use the technique of our kind of conference to discuss in depth the difficult and important subject of the predictability of adverse drug responses in man, how far such responses can be foreseen on the basis of animal experiments and, when animal tests are unavoidably inadequate, to what extent the risks of even the rarest reactions can become calculable. Dr. Modell gave us much good advice in the construction of the programme, making one visit to England for this purpose immediately after an operation, and crowned his helpfulness by taking the Chair throughout the symposium.

As with the Foundation’s other symposia, this meeting included people from different countries and different disciplines, and yet was severely restricted in size in the hope of giving every member a chance to take part effectively in the discussions. This is not an easy subject; the members were thoughtful and co-operative, and the editors have done their best, but the book will still require careful study. It is, however, the hope of all concerned with the meeting that these papers and discussions will contribute to a wiser understanding, both by scientists and the public, of the problems—arising from individual, genetic, sex, species, strain, statistical, metabolic, excretory, or even emotional differences—involving the introduction of new drugs.

From such understanding, valuable new remedies may be introduced in the future with the maximum of care, the minimum of risk, and under exhaustive long-term international observation.
CHAIRMAN'S OPENING REMARKS

W. Modell

It is a privilege and an honour to be chairman at this symposium. Meetings on toxic reactions to drugs are commonplace today, but they are not often productive, frequently because the conclusion reached is almost invariably the same: all drugs are toxic and their justifiable use in therapy is based on a calculable risk. This tired truism has been the conclusion not only of many small meetings, but also of large congresses such as the Second International Pharmacological Meeting in Prague in 1963. At this meeting it was put to the vote, and passed unanimously (as part of a democratic process rather than as the result of scientific deliberations) that all drugs are toxic. Such a statement is useless since it is part of the definition of a drug and gives no insight into what a drug does.

We must try, in the next three days, to formulate a different approach to the problem and this is the justification for bringing together this distinguished group of scientists. We need to consider the unexpected, unanticipated, unpredictable responses to drugs; responses that develop out of the blue after competent pharmacological examination in the laboratory, as well as testing in man, have defined the properties of the drug. If pharmacology is a scientific discipline, why does systematic and thorough pharmacological examination of a drug in man and other animals not always reveal all the responses that may occur when that drug is used clinically?

How important is the unpredicted drug response in man? As Chairman of the Advisory Committee on New Investigational Drugs to the U.S. Food and Drug Administration, I examined the records of all drugs officially approved for clinical use by the Food and Drug Administration for the seven-year period 1958 to 1964. There were 251 such new drugs in this time. Eight of these—approximately 3 per cent—were more toxic than had been anticipated and gave rise to reactions so hazardous that the drugs had to be withdrawn from the market. There were occasional unanticipated favourable reactions—for example the unexpected finding that chlorothiazide was useful in the treatment of hypertension. Unexpected adverse reactions, but not so severe as to preclude continued
clinical use of the drug, also occurred—for example the diabetogenic action of chlorothiazide. Since thousands of drugs were also screened and discarded during this period, this suggests that the unanticipated drug response is uncommon. But, however small the incidence, these reactions are serious and occur with distressing regularity. The occurrence of any unanticipated responses suggests that our pharmacological screening is inadequate in some way.

The unpredicted response to two of the eight drugs removed from clinical use in the U.S.A. between 1958 and 1964 could have been anticipated. Critical laboratory data on triparanol (MER-29) were criminally suppressed. Pharmacological tests in the laboratories of the manufacturer of triparanol had shown that in rats and dogs cataract formation, loss of hair and gonadal changes occurred. Thus the effects that were subsequently seen in man—cataract, loss of hair, and impotence—were predicted by laboratory observations, but suppressed. The laboratory data on the second drug, bunamiodyl—a cholecystographic agent—were, in the opinion of consultants to the congressional investigative committee (and in my own opinion), sufficiently suggestive of renal toxicity to warrant further tests in animals. There remain six drugs in which laboratory and clinical investigation gave no indication at all that catastrophic reactions might develop. After general clinical use, three of these drugs gave rise to agranulocytosis and three to hepatitis.

I wish to place these problems before you: Is there a fundamental difference between drug responses that can and cannot be anticipated? Is there a method of investigation that we are not using which would help? Or is it inevitable that, in spite of thorough laboratory and pre-clinical investigation, some responses will appear only after drugs have been used extensively in man? If the discovery of such responses depends on using the drugs on very large human samples, how can this be done most efficiently, least dangerously, and with the smallest possible sample?

Just multiplying our present methods of drug testing will not solve these problems. We need new approaches and insights. These, I hope, will be provoked in the formal talks, and the discussions, at this meeting.

Carcinogenicity and teratogenicity have been purposely omitted from the programme. These are important subjects, both under intensive investigation, but to include them would reduce the time available for discussion of other vital problems.
PHARMACOLOGICAL DIFFERENCES, QUALITATIVE AND QUANTITATIVE, BETWEEN MAN AND OTHER SPECIES

ARNOLD D. WELCH

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It is about 150 years since the use of animals was begun as a means of obtaining information concerning the probable effects on man of various poisons (DuBois and Geiling, 1959) and, more recently, of potential drugs. During earlier centuries the methods employed often were more direct: the use of human slaves and prisoners to prove the efficacy of poisons, for example. In this more merciful age, however, man's innate inhumanity to man is exercised in other ways, and efforts are made to obtain information of benefit to man from studies of drugs in various animal species. But, in part because of possible major differences in the responses to drugs of animals and man, the knowledge gained from studies in animals is often not pertinent to human beings, will almost certainly be inadequate, and may even be misleading. Despite these considerations, present-day requirements for the gathering of data concerning the chronic toxicity of all new drugs have led to the establishment of routine procedures, while guarantees of extreme safety have been sought, although such considerations often give only illusory comfort to regulatory bodies. Even the most exhaustive studies in animals cannot provide assurances against some of the most important problems encountered in the use of drugs in man; furthermore, such studies may prolong inordinately, or even prevent, the desirable introduction of potentially valuable new agents. As well as the understandable desire to attain "absolute safety", one might consider the well-known cliché concerning the loss of the baby with the bath-water. In other words, in attempting to establish such excessive safeguards that man cannot be injured, the development of many potentially valuable new diagnostic or therapeutic agents can be greatly delayed, or even prevented. There is much evidence that this is now happening. It is ironical, as has
been pointed out by others (Koppanyi and Avery, 1966), that under present-day interpretations of regulations in the United States many invaluable non-proprietary drugs currently in common use probably would not be released if they were now to be introduced for the first time. Such valuable drugs as chloroform and ether, ipecac (emetine), cinchona (quinine and quinidine), and digitalis and allied cardiac glycosides, almost certainly would not be approved, while even penicillin could be excluded for years if its lethal effect on the guinea pig and golden hamster (*Meso-cricetus auratus*) were disclosed but not explained (Dack and Moloshok, 1947; Hamre et al., 1943; Schneierson and Perlman, 1956). How often, in new drug development, are such phenomena occurring today? Is it not now time for appropriate reassessments of what it is sensible to try to accomplish? Evidence will be presented later to suggest that these are not rhetorical questions.

A commentary may also be made concerning the probably rare instances when a new agent may have been investigated rather thoroughly in man before the extensive studies in animals that are now required. Is it justifiable, in such cases, for blockade to be maintained of the release of an agent already shown to be of value and apparently without significant hazard to man, while routine studies are carried out subsequently in various animals? These studies usually do not take into account plasma and tissue levels, appropriate measurements of metabolic alteration and other factors that could make such studies really useful for man. When the enormous costs of gathering these data and of the delays are considered—costs not only in terms of money, but also in other precious commodities such as the needs of sick human beings and the time of investigators—we may realize that the establishment of more-or-less routine procedures, without regard for special circumstances, is scarcely defensible.

A feature of chronic studies of toxicity, or predictive pharmacology (Burgen, 1963), that receives too little attention is that some of the most frequently occurring and important hazards to man cannot be assessed suitably by any of the techniques used in animal studies. Predictive pharmacology is essentially helpless in providing warnings about either the likelihood or severity of (a) allergic reactions (as for example with penicillin), (b) the potentiality for the production of toxic psychoses (as with lysergic acid diethylamide [LSD]), (c) the production of certain blood dyscrasias (as with chloramphenicol or methicillin [Modell, 1965]), or (d) the remarkable differences between individual responses of man, based on genetic or other factors (as with succinylcholine or isoniazid [Kalow, 1965]).
Animals have been and are of tremendous help in disclosing various types of biological activities and in elucidating certain aspects of the mechanisms of drug actions. Animal studies also provide some inadequate indications of possible types of toxicity, as well as of methods of absorption, distribution, metabolic alteration and excretion in man. But, in each of these areas, the behaviour of a chemical agent can be so remarkably different in different species that real assurances concerning what will occur in man cannot be obtained.

Brodie (Brodie, 1964a, b; Brodie, Cosmides and Rall, 1965) has been a leader in focusing attention not only on the varying mechanisms of drug metabolism in various species but, more importantly, he has emphasized that whatever factors cause differences in the plasma levels of an unbound drug (for example, rates of absorption versus elimination, rates and types of metabolic alteration, and binding on plasma proteins), valid comparisons of the reactions of animals to drugs usually cannot be made unless plasma levels, rather than dosage on any basis, are equated. Appropriate emphasis has rarely been given to this important reason for species differences as they affect the comparative study of new drugs.

A comment on the many factors that can influence the level of unbound drug in the plasma may be appropriate with respect to a sometimes neglected feature of the effects of drugs: the rates of excretion by all routes, often coupled with the rates of metabolic alterations, must equal or exceed the rates of utilization, or accumulation will occur. But even in this area, the interpretation of predictive studies in animals may be uncertain for man, and cannot be substituted for the assessment of potential cumulative hazards—or lack of them—in man himself.

EXAMPLES OF SPECIES DIFFERENCES IN RESPONSE TO DRUGS

6-Azauracil and 6-azauridine. The discovery of the reversible toxic effects of 6-azauracil (azauracil)—the precursor of 6-azauridine (azauridine)—on the central nervous system in man (Welch, Handschumacher and Jaffe, 1960; Shneider et al., 1960; Wells et al., 1957) was particularly interesting. Azauridine, the ribonucleoside of azauracil, is a remarkably non-toxic chemotherapeutic agent. It effectively controls both psoriasis (Calabresi and Turner, 1966; Turner and Calabresi, 1964) and mycosis fungoides, a malignant disease of the skin (Calabresi and Turner, 1966; Záruba, Kúta and Elis, 1963). Azauridine is also used to treat choriocarcinoma, polycythæmia vera (DeConti, Turner and Calabresi, 1965) and for the termination of early human pregnancy (Vojta and Jirásek, 1966). The absence of toxic effects on the central nervous system of various animals, including the
mouse, rat, dog, and even the monkey, with azauracil (Welch, Handschumacher and Jaffe, 1960) was in striking contrast to the presence of such effects in man. Massive doses of azauracil caused no apparent toxic effects of any kind in the monkey, and no changes in electrical potentials in various areas of the brain, or on thresholds to electrical stimulation (Welch, Handschumacher and Jaffe, 1960). In man, on the other hand, albeit with considerable variation in relation to size of dose and time, azauracil produced bizarre electroencephalographic distortions, together with unpleasant clinical features that obviated its continued use (Welch, Handschumacher and Jaffe, 1960; Shnider et al., 1960; Wells et al., 1957). The cause of this striking difference between the responses of the central nervous systems of man and monkey to azauracil has not been discovered, but the observations may permit us to take comfort in the idea that the monkey may not be as closely related to man as some have assumed, and often cannot be regarded as a "junior human being" of sure value in predictive pharmacological studies.

In contrast to azauracil, azauridine (administered either intravenously or, as its catabolic precursor 2',3',5'-triacetyl-6-azauridine, orally) (Handschumacher et al., 1962a, b) rarely causes signs of central nervous system disturbance, apparently because of the limited transport of this stable nucleoside across the blood-brain barrier. Nevertheless, azauridine offers another striking example of the difference between man and an animal, in this case the dog. The canine bone marrow is so susceptible to the 5'-phosphate ester (formed intracellularly) of azauridine that a dog dies from leucopenia within 7 to 10 days of a total daily dosage of 27 mg. azauridine/kg., given three times daily either orally or parenterally (Welch, 1965; Welch et al., 1961). All clinical applications for azauridine might have been proscribed as a result of these findings; yet, in man, relatively fantastically large amounts of the drug—60 mg./kg. three times daily intravenously for many weeks, or up to a total daily dose of 600 mg./kg./24 hr. for shorter periods of time (Welch et al., 1961; Handschumacher et al., 1962a)—have had no significant effect on the leucocyte count in a large number of individuals. The long-continued administration of 2',3',5'-triacetyl-6-azauridine in massive oral doses (for example 270 mg./kg./24 hr.) inhibits the formation of haemoglobin and erythrocytes in man, but anaemia develops slowly and disappears promptly on temporary withdrawal of the drug and thus is not important clinically (Calabresi and Turner, 1966; Turner and Calabresi, 1964).

These very striking species differences in response to azauridine have been at least partially explained. Thus, the formation of leucocytes in the dog is
more dependent on the biosynthesis of pyrimidines de novo (in which pathway, azauridine, as the 5'-phosphate, inhibits the formation of uridylic acid from orotidylic acid) (Handschumacher, 1960b; Handschumacher and Pasternak, 1957; Pasternak and Handschumacher, 1959; Škoda, Hess and Sorm, 1957; Welch, 1965) than is the case in man. In man, the preformed or salvage pathway (uracil → uridine → uridylic acid) can provide essential pyrimidines despite blockade of the pathway by which pyrimidines are synthesised de novo. Significant amounts of azauridine are not converted by mammalian cells into the 5'-tri-phosphate derivative, and thus the drug does not serve appreciably as a precursor of the ribonucleic acids or of a deoxy-form that could affect the formation of DNA (Handschumacher, 1960a; Handschumacher and Welch, 1960; Wells, Gaines and Koenig, 1963). Because of this, and in view of the rapid renal excretion of azauridine, it is not surprising that the effects of the drug in man are evanescent and can be perpetuated only by continued maintenance dosage.

Another species difference that has influenced the development of azauridine for therapeutic use in man is the excellent absorption after oral administration to such species as the mouse and dog, compared with an absorption of only about 30 per cent in man (Handschumacher et al., 1962a, b). This relatively poor absorption afforded an unexpected hazard to man, which also could not have been predicted from animal studies. In the lower bowel in man unabsorbed azauridine, which is not catabolized by mammalian cells, nevertheless is cleaved to azauracil by certain microorganisms. In these circumstances, the free base can be absorbed, with resultant unpleasant effects on the function of the central nervous system in man. This additional problem of species difference was circumvented by preparing 2',3',5'-triacetyl-6-azauridine (Handschumacher et al., 1962a, b), a new compound that is lipid-soluble and rapidly absorbed from the upper bowel with concomitant enzymic removal of its acetyl groups. The blood levels of azauridine provided by oral administration of this triacetyl derivative at 8-hour intervals are higher than those attained by any other method, except the continuous intravenous infusion of azauridine.

The clinical pharmacology of azauridine has now been studied extensively and large numbers of patients with psoriasis and various types of malignant disease have received long-term treatment with massive oral doses (270 or 135 mg./kg./24 hr.) of the triacetyl derivative of the drug. In spite of all this, and the knowledge that this derivative serves only as a source of azauridine (except for a small amount of the monoacetyl form) (Calabresi and Turner, 1966; Handschumacher et al., 1962a, b; Turner and Calabresi, 1964), the present regulations in the United States
will probably demand prolonged and costly administrations of the triacetyl derivative to both large and small animals before it can be used in man. In view of the knowledge already available, and the number of people with severe forms of psoriasis, often coupled with arthritis, one must ask what degree of zeal for "safety" can be truly justified, if in the meantime the release of this compound is prohibited. And if exhaustive studies of chronic toxicity must be done, in view of the inordinate sensitivity of the dog to azauridine, what large animal is appropriate for these studies. Should it be the monkey, whose central nervous system is so remarkably insensitive to azauracil, or perhaps the pig? A ruminant does not appear to be suitable. And is the information to be gained from such studies, together with long-term administration of the drug to rats (which could easily lead to a two-year delay in the release of the drug) even remotely likely to yield information that could not be obtained in man with a reasonable degree of safety?

It is difficult to protest effectively against these requirements, when it is clearly impossible to guarantee absolutely that the long-term administration of this clinically non-toxic drug for one or two years to rats, and monkeys or pigs, could not cause damage, which might be disclosed only at post-mortem, to any organ. This difficulty cannot be easily overcome, nor can one cope easily with such a question as: "You surely do not want to take any chance of deleteriously affecting a human being, do you?" The answer to this question is a qualified yes when the drug is to be used for the treatment of a disease with suffering of such degree that suicide may occur, even if the disease is not neoplastic. In the aura of present-day regulatory zeal and congressional investigating committees, however, the expressor of such a view might be made to appear as a callous monster! Such a question resembles the classical "Have you stopped beating your wife?" More appropriate to our theme is the evasion of the issue of the relative merits of permitting perhaps thousands of patients from being treated effectively, while currently unobtainable guarantees of absolute safety are sought.

The problems of mutagenicity and carcinogenicity also need to be elucidated, for the present state of our knowledge in these areas is quite unsatisfactory. We need better and more practicable methods of testing for the mutagenicity of drugs in mammals (Bateman, 1960; Bateman, 1966; Lüning, 1966; Partington and Jackson, 1963; Partington and Bateman, 1964). We also need clarification of the uncertain relationship between the induction of tumours in rodents by a great variety of chemical agents and the possible carcinogenicity of such agents in man. Until these exceedingly complex problems have been solved, are we to postpone indefinitely.
the release of new drugs as valuable as the drugs developed in a period before these concerns were raised?

Allopurinol. Another new drug of great value and no serious toxic hazard to man is allopurinol \((4\text{-}\text{hydroxipyrazolo}(3,4\text{d})\text{pyrimidine})\). This agent, which was developed rationally on the basis of fundamental knowledge of metabolic processes, is a selective inhibitor of xanthine oxidase, an enzyme essential to the formation of uric acid (Elion \textit{et al.}, 1963\textit{a, b}). Although this drug has few ancillary biological effects, and exhibits any species differences in toxicity primarily because of the different degrees of dependence of animal species on the oxidation of purines to the level of xanthine and uric acid, the release of allopurinol for other than investigational use—at least in the United States—has been much too long delayed. Allopurinol is of tremendous value in preventing hyperuricaemia, with its complications of urolithiasis and renal insufficiency, not only in gout (Elion \textit{et al.}, 1963\textit{b}; Klinenberg, Goldfinger and Seegmiller, 1965; Rundles \textit{et al.}, 1963), but also in certain neoplastic disorders (Firmat \textit{et al.}, 1960; Frei \textit{et al.}, 1963; Kritzler, 1958; Weisberger and Persky, 1953). In view of the number of premature deaths that are certainly occurring because of the present unavailability of this remarkably non-toxic new drug, how can the delays in its release be justified?*

Pyrexal, cyanine dyes and sulphonamides. There are many examples of the effect of the undue severity of present restrictions in the United States on the development of new drugs. I cannot refrain from emphasizing that potentially valuable, minor agents are being lost to medicine because their producers think that the possible economic rewards do not justify the very costly efforts needed to carry such substances through the present morass of regulatory obstacles. One example was encountered at Yale during clinical studies of a potent and useful bacterial product that causes discharge of mature granulocytes from the bone marrow. This agent (pyrexal) enables the chemotherapist repeatedly to assess the functional capacity of the bone marrow during treatment with antineoplastic drugs (Fink and Calabresi, 1962). There has been a great demand for this valuable substance but, for the reasons just described, it is now unlikely that it will ever be made generally available.

A penultimate example—of a different type of species difference in response to drugs—involves the observation of a great difference in the response of closely related parasites to a very active nematocide. We had found that this agent, a new cyanine dye, was both active and sufficiently

* Since the presentation of this paper (June 1966) allopurinol, already available in Great Britain, has been approved for sale in the United States.
safe to cure wild cotton rats (*Sigmodon rattus*) infected with a naturally occurring filarial worm, *Litomosoides carinii*. This worm is closely related to *Wuchereria bancrofti*, the commonest cause of filariasis in man (Peters et al., 1949; Peters, Welch and Higashi, 1949; Welch et al., 1947). After elaborate toxicity studies of the compound in animals, and in patients with neoplastic disease, and with the expectation that a cure for human filariasis had at last been found, clinical trials were carried out in patients with filariasis in Puerto Rico. Although in the cotton rat the drug killed the adult worm but had no effect on the microfilaria, in man the situation was reversed: a clinically useless temporary disappearance of microfilaria occurred in man but the adult worms were not killed. These results were the reward of naivety; however, it was quite impossible to carry out the initial study of this relatively toxic drug in man. This example illustrates, rather painfully for those concerned, another problem of species differences in the response to drugs.

There are also many instances in which species differences between animals and man have been invaluable, as illustrated by my final example. The peripheral nervous system of the chick is inordinately sensitive to some of the sulphonamides (Bieter et al., 1941). This observation was used too late, unfortunately, to prevent the neuropathies caused by sulphamethylthiazole (Little, 1942) but in time to be of value in testing other sulphonamides (Welch et al., 1943). Unfortunately, man is often the most sensitive species, a phenomenon that was illustrated dramatically by the thalidomide disaster.

**CONCLUSIONS**

To conclude this brief introduction to a vast subject—recently reviewed by Koppanyi and Avery (1966)—we need to explore in depth the inconsistencies in the design, execution and interpretation of present-day predictive pharmacological studies in animals. Important differences in both qualitative and quantitative responses of man and other species to drugs offer great difficulties, but also great opportunities for obtaining information of greater relevancy to man than any rigid sequence of studies in animals can possibly provide. Above all, we need enlightened policies concerning the earliest possible examination, consistent with a reasonable degree of safety, of the action of new drugs in man. Sir George Pickering (1964) and Sir Derrick Dunlop (1965) have spoken and written wisely and forcefully on this subject.

Dunlop (1965, p. 439), in discussing the elaborate procedures for examining the toxicity of drugs in animals, emphasized, as I have tried to do, that:
"Man is a distinct species, and it is not always true that a drug which appears safe to animals will be safe for man, or, conversely, that a drug which shows alarming toxicity in animals will necessarily represent the same hazard for man. Though it is manifestly essential for animal tests to precede those on human beings, we must realize that as the result of the requirements which are now insisted upon some effective and safe drugs may never see the light of day, and if we take a retrospective view some useful drugs would never in the present atmosphere have reached clinical trial."

In referring to the very effective unofficial work in Great Britain of the Safety of Drugs Committee, Dunlop commented (p. 440): "It is so much better to do things by persuasion and mutual agreement, so far as is possible, than by legal sanctions."

Finally, speaking of drug legislation, Dunlop wisely concluded (pp. 440-441):

"The problems and responsibilities of government in assuring the safe use of drugs are indeed formidable. It is so important to see that a law... is executed so as to achieve its high purpose without imposing any non-essential restraint on the pharmaceutical industry or the physician. . . . future legislation concerning the safety of drugs is bound to be more difficult, because no drug is ever entirely safe and its safety must be related to the purpose for which it is to be used. . . . a high degree of toxicity might be tolerated if a drug cured or stayed the progress of an otherwise fatal disease, but no significant toxicity would be permissible in a drug used for a trivial condition or if it was shown to be worthless. This brings up the whole question of efficacy and of relative efficacy; and who is going to dogmatize on this? Again, who is going to say that the occasional fatal toxic reactions which may result, for instance, from the use of psychotrophic drugs in depressive illnesses are or are not greater than the danger of an increased incidence of suicide if such drugs are forbidden?

"Doubtless a committee of experts will advise the appropriate Ministers, and if experts are occasionally wrong they are less often wrong than non-experts... we interfere with the prescribing doctor's final freedom of decision at our peril... It is easy to set up a sort of pontifical therapeutic Establishment; but Establishments—Aristotle and Galen, for instance—have not always been in the van of progress."

Osler once shrewdly described what is probably the greatest problem of all in the study of pharmacological differences between man and other species, namely, that the insatiable desire to take medicine is the chief thing
which differentiates man from the lower animals. In view of this great need of the highest form of life, let us hope that this symposium will provide a new impetus for the design of fundamental investigations, the results of which could hasten greatly, rather than impede disastrously, the introduction of new and valuable drugs into the armamentarium of the physician.

REFERENCES


DISCUSSION

Brodie: Would you elaborate on your statement that drugs could safely be screened in man at an earlier stage than they are at present?

Welch: As well as the 251 drugs which reached the Food and Drug Administration (FDA) between 1958 and 1964, as described by Dr. Modell in his opening remarks, there must have been many other compounds that were bypassed, perhaps prematurel, before they were tried in man. This worries me. The ultimate test-animal for the efficacy of a drug is not the rat or mouse, or even the dog or monkey, but man. In our trials of azauridine we could have decided that the compound is so ruinous to the bone marrow of the dog that clinical trials in man would be unwarrantably dangerous. In fact, we took more than a year to work up from our original dose—a fraction of the lethal dose in the dog—to the vastly higher dose at which there was such a dramatic effect on
human bone marrow. This high dose is effective in man in a type of leukaemia in which the biochemical lesion is such that abnormal leucocytes only are susceptible to azauridine. The use of these high doses in leukaemia led to increased information about the safety of this drug in man, and, ultimately, to R. W. Turner and P. Calabresi's (1964. *J. invest. Derm.,* 43, 551–7) trials of azauridine in psoriasis. If we had used only the dog, and had not carefully (although some might say dangerously) begun to study azauridine in man, we would not have discovered its therapeutic effect in psoriasis.

Laurence: I am familiar with the testing of new drugs in the United Kingdom, since I am a member of the subcommittee on Clinical Trials and Therapeutic Efficacy of the Committee on Safety of Drugs (the Dunlop Committee). It is a common dictum today that digitalis and penicillin are so toxic in animals that they would not pass the modern drug-controlling organizations. But I have a higher opinion of the energy and insight of the developers of drugs, and of the foresight of the drug-controlling organizations, than is implied by this remark. I believe that provided the therapeutic potentiality of a drug is realized, as it was for penicillin, knowledge of serious toxicity in one animal species would not have led to the abandonment of such a drug even in 1940, and certainly not now. Similarly, a drug like digitalis with powerful effects on the myocardium would not now be dismissed for the treatment of a serious and common condition such as heart failure unless other effective cardiac stimulants were available. Acceptance of a drug must depend on what it is going to be used for.

Professor Welch, and many others, have referred to the rigid requirements for animal testing of the drug-controlling organizations in the United States. In Great Britain the Committee on Safety of Drugs has no such rigid requirements. I doubt if any drugs have been held up for an unreasonably long time here although this may have occurred in the USA. Allopurinol for example, a valuable drug brilliantly developed in the United States, has gone through the complete official system of drug control here and is now marketed in Great Britain; but it is not yet marketed in its country of origin.* It is an anomaly, if not a tragedy, that a useful drug may not be generally available in the country in which it was scientifically developed but is freely available in other countries.

Modell: Professor Gross, can you comment on the differences in the timing of acceptance of drugs in different countries?

Gross: There is often an enormous delay in releasing a drug in the United States. Some of the toxicity studies required by the FDA and comparable institutions in other countries, in the hope that safety may be more certain, are unrealistically severe. The duration of treatment in man is often not sufficiently considered by drug-controlling organizations. Drugs given once or twice only—antidotes for acute poisoning or drug overdosage for example—need less rigorous chronic toxicity studies than, say, antidiabetic or antihypertensive drugs that will be given for many years. If a drug will only be given for a limited period,

* Allopurinol has now been approved for sale in the United States.
toxicity studies are only needed for a correspondingly limited period. One of the causes of the enormous delay in the release of drugs in the United States is the requirement of the FDA for long-term (a year or more) toxicity studies. If toxic effects occur during this time, even with doses far in excess of therapeutic ones, repeated studies to confirm these effects may be demanded. This is exceedingly time-consuming. But even greater delays result from the demand for additional, extensive, clinical studies; these requirements may be difficult or impossible to satisfy.

Kalow: Have any adverse reactions been discovered in animals after the administration of a drug for two months that have not been detected during the first two months in which the drug was given?

Paget: In 1963, as a member of a Study Group of the European Society in the Study of Drug Toxicity, I asked all the toxicologists in the pharmaceutical industry who were members of that society (this, in practice, included all the European and most of the American industrial toxicologists) exactly that question except that the time I selected was three months. We found no convincing examples of new adverse reactions developing after three months' continuous treatment with a drug, excluding carcinogenesis and the appearance of mutations.

Brodie: I doubt if a carcinogenic reaction has been detected after three months on a drug which had not revealed itself before this time. Can more be learned by increasing the duration of chronic toxicity studies? It may be actually self-defeating to test some drugs for prolonged periods, since drugs that stimulate their own metabolism will become less and less toxic with time, thus giving a false sense of security. In screening for teratogenic effects, for example, a drug may stimulate its own metabolism to such an extent that by the time the sensitive stage of pregnancy is reached the plasma level of the drug may be virtually zero. Thus a potential teratogenic effect may be overlooked (King, C. T. [1966]. In Environmental Variables in Oral Disease, pp. 241-58. eds. Kreshover, S. J., and McClure, F. J. Washington, D.C.: AAAS).

Paget: Another reason for the delay in the introduction of drugs in the United States is the enormous backlog of compounds waiting to be assessed by the FDA. We in the United Kingdom, with its committees for assessing drug safety, are more fortunate than our colleagues in the United States in this. But an element of inexpertness exists in the FDA's long-term testing of drugs. It is much simpler to ask for additional investigations on a drug than to take a decision. No investigation of a drug is ever so complete that one could not think of yet another experiment. One hears alarming stories that the FDA are enrolling donkeys, apes and pigs as experimental animals. Studies in relatively unusual animal species should be encouraged as a means of advancing scientific knowledge, but not as a retreat from making decisions. There could be no end to this use of more and more esoteric animals. But the medical profession in the United States, not the FDA, holds the remedy for these delays. Physicians should ask