SENSITIVITY REACTIONS TO DRUGS

A SYMPOSIUM

organized by

THE COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

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FOREWORD

The symposium on 'Sensitivity Reactions to Drugs' was held in Liège from July 9th to 12th, 1957, and is an example of the co-operation which exists between the C.I.O.M.S. and its member-organizations, in this instance the International Society of Clinical Pathology.

Indeed, the subject was suggested to the Council by the Society, which agreed to organize the meeting according to the Council's general principles.

It was also agreed that the chairman of the symposium, Professor M. L. Rosenheim, would report back to the Third International Congress of Clinical Pathology in order to give to the larger group an account of the discussions and conclusions of the smaller meeting.

It may be appropriate to mention at this point that the C.I.O.M.S. was founded in 1949, at Brussels, under the joint auspices of Unesco and of the World Health Organization. It groups fifty international organizations belonging to the basic sciences and to the clinical branches: it is, in fact, a confederation of associations of specialists. As such it is concerned, not with any one branch of medicine, but with all of them and with the relationship between them.

The Council has studied questions of general interest, questions which are of interest to all its member-organizations: it has dealt with problems of fundamental importance such as the support of medical research and with more practical ones such as the proper planning of international meetings.

The Council has a co-ordinating function and promotes international multidisciplinary symposia such as the present one.

Finally, the Council helps member-organizations to carry out their own programmes by offering them certain services, notably in the organization of their congresses.

A symposium on 'Sensitivity Reactions to Drugs' appeared very suitable for the Council to sponsor because the discussion of the mechanisms involved required the participation of investigators from many disciplines, and the practical conclusions of such a meeting cannot be ignored by physicians and surgeons alike.

The official languages were English and French but it soon

appeared that English allowed communication between all participants. It is pleasant to thank all those who willingly agreed to express themselves in a language which was not their own in order to help the meeting along.

The C.I.O.M.S. would like to put on record also its great indebtedness to Professor Rosenheim for steering the meeting with authority and for assuming such a large share of the editorial work, to Dr Moulton for transcribing the discussions, and to Professor Dallemagne who was the perfect host.

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INTRODUCTION

With a Note on Terminology

M. L. ROSENHEIM

When I was a student, I was brought up on a small thin book – *The Elements of Medical Treament*, written by Sir Robert Hutchison. In 1926, he wrote that:

> 'The number of drugs in the pharmacopoeia is very great, but by far the greatest number are superfluous. It is wise, therefore, to use only a few drugs, but to know them and their effects intimately, and to give them in sufficient doses.'
>
> 'Some of the discredit,' he goes on to say, 'into which drug treatment has fallen in this generation is no doubt due to the fact that we use medicines more timidly than our forefathers.'

Now, only some thirty years later, what a change. We have an ever-increasing array of really active drugs, mostly synthetic, used perhaps too widely and certainly in large and effective doses. The change in therapeutic outlook and practice is remarkable.

It is not surprising that the introduction of so many potent, and toxic, chemicals into clinical use has been accompanied by dangerous unwanted effects, and, today as never before, the clinician must not only know the drugs he uses and their pharmacological actions but must always be on the lookout for ill effects induced by his therapeutic efforts.

In 1955 D. P. Barr[1] reported that 'In a medical service in a great hospital, over a period when approximately 1000 patients were admitted, more than 50 major toxic reactions and accidents consequent to diagnostic and therapeutic measures were encountered'.

There is a tendency for the clinician, using new drugs, to depend upon routine investigations, such as the blood count, as a guide or warning of impending mishap. It is, therefore, important to try to define the value of such tests.

The present volume reports the proceedings of a symposium, held in Liège in July 1957, on the subject of Sensitivity Reactions to Drugs. This meeting was arranged, under the auspices of the Council for International Organizations of Medical Sciences (C.I.O.M.S.),

[1] *J. Amer. med. Ass.* (1955), **159**, 1452.

to precede the Third International Congress of Clinical Pathology, at which an account of its discussions was presented.

It was felt that the symposium was well timed, for in the prevention and detection of such reactions, the clinical pathologist plays an important role. He is usually associated with the clinical trials of new drugs and must always be on the alert for evidence of toxic reactions.

Although the discussions were mainly limited to the fascinating immunological reactions of the blood and tissues to drugs, and while the gathering included pharmacologists, chemists, haematologists and immunologists, it was perhaps fitting that a clinician should take the chair, for it is he who is ultimately responsible for giving the drugs and thus provoking the reactions, and it is he who should be the first to diagnose them.

NOMENCLATURE

It soon became apparent that there was no general agreement concerning the nomenclature of the various types of reaction to therapeutic agents, and a session was devoted to a full discussion on terminology. As a result the following classification was generally accepted and it was felt that this might usefully be published. This classification follows, to a considerable extent, that suggested by E. A. Brown in 1955.[1] It was, of course, recognized that it was far from complete, but it was hoped that it might prove of value as a basis for a more complete classification and that a clear definition of the various terms might simplify future discussions.

UNWANTED EFFECTS OF DRUGS

1. *Overdosage*

With overdosage of a drug toxic effects occur in direct relation to the total amount of the drug in the body. These effects are likely to occur in any patient provided a threshold blood level is exceeded. Such overdosage may be *absolute* and may result from an excess given in error or as a result of *cumulation* of the drug in the body.

Under certain conditions *relative overdosage* may occur, the usual signs and symptoms of excess being produced by a normal or even reduced dose of the drug because of some underlying abnormality in the patient. Thus, in the presence of renal failure, drugs which are

[1] *J. Amer. med. Ass.* (1955), **157**, 814.

normally excreted in the urine, may produce a markedly raised blood level and toxic effects. Patients with renal tuberculosis associated with renal failure often tolerate only small doses of streptomycin, potassium may prove dangerous in uraemic patients and hexamethonium may produce severe and prolonged reactions in such patients. Another example of such relative overdosage is the sensitization of patients to the effect of digitalis by a low serum potassium. The characteristic symptoms and electrocardiographic changes of digitalis poisoning may appear in a digitalized patient if his serum potassium falls, and these may be relieved by the administration of potassium.

2. *Intolerance*

Intolerance to drugs may be defined as a lowered threshold to normal pharmacological action of a drug. Thus it is recognized that some patients develop symptoms of cinchonism on very small doses of quinine. Intolerance may result from the extremes of normal biological variation either in absorption, metabolism, excretion or in susceptibility to the drug.

3. *Side effects*

This term should be reserved for therapeutically undesirable, *but unavoidable*, effects of drugs. Many of these are *specific*, that is to say the undesired effect is a normal pharmacological effect of the drug, so that the dose has to be graduated to produce the maximal desired pharmacological action with the minimum undesired effect. Many examples can be given of such side effects. The parasympathetic blocking action of drugs such as hexamethonium limits their use as sympathetic blocking agents. The hypnotic effects of certain antihistamine drugs again limits their dosage. In other cases side effects may be produced because the drug acts as a histamine releasing agent, so that the desired action may be overshadowed by histamine effects. This problem is discussed by Lecomte (p. 188). Another side effect may be produced by the drug competing in some normal metabolic cycle. The interesting megaloblastic anaemia occurring in epileptic patients under treatment with phenytoin and primidone, discussed by Chalmers (p. 17), may result from these drugs inhibiting the action of folic acid. Other side effects, well recognized with many drugs, still lack specific pharmacological understanding and must, at present, be regarded as *non-specific*.

Even a thorough understanding of the pharmacology of a new drug may leave the clinician unprepared for some side effect. Thus the occurrence of goitre in patients treated with cobalt, of jaundice following the administration of chlorpromazine, and of myxoedema following the application of resorcin ointment were all unexpected side effects of therapy.

4. *Secondary effects*

Secondary effects may be defined as the indirect consequence of a primary drug action. They are not the pharmacological result of drug administration, but occur because of some effect the drug has produced. They have assumed great importance recently, following the introduction of antibiotics. The occurrence of moniliasis or evidence of vitamin deficiency in patients given antibiotics orally are examples of such secondary effects. It is possible that reactions due to released products from killed micro-organisms should also be classified under this heading.

5. *Idiosyncrasy*

True idiosyncrasy implies an inherent qualitatively abnormal reaction to a drug, and the best example of this is the occurrence of a haemolytic anaemia in American negroes given primaquine as an antimalarial (see Discombe, p. 6). One out of every ten such negroes develops evidence of haemolysis within a few days, and the red cells of such reactors have been shown to be deficient in a specific enzyme, glucose 6-phosphate dehydrogenase. This is a true – probably inborn – idiosyncrasy to the drug.

6. *Hypersensitivity-allergic reactions*

These reactions may be defined as those reactions to drugs in which clinical symptoms are conditioned by previous exposure to and sensitization to the drug. They are mediated by an antigen-antibody reaction. These reactions were grouped together under the term 'Sensitivity Reactions to Drugs' as a title for the present symposium.

This classification is clearly tentative. There is unavoidable overlap between the groups and it is difficult to place every known drug reaction under one of these six headings. Nevertheless, some such classification is necessary and may help to clarify a complex subject. The classification may be summarized as follows:

UNWANTED EFFECTS OF DRUGS

1. *Overdosage*	*a.* Absolute	Immediate Cumulative
	b. Relative	
2. *Intolerance*		
3. *Side Effects*	*a.* Specific	
	b. Non-specific	
4. *Secondary Effects*		
5. *Idiosyncrasy*		
6. *Hypersensitivity-Allergic Reactions*		

The symposium was primarily devoted to the last group, hypersensitivity-allergic reactions to drugs, but certain related topics were discussed. Although few new facts emerged during the meeting the publication of the proceedings provides a review of the present situation. In order to make this volume of value as a work of reference, a special attempt has been made to provide a full bibliography. A symposium such as this will have fulfilled its purpose if it defines how far knowledge extends today and if it points the way along which further investigation may extend that knowledge.

HAEMOLYTIC REACTIONS TO DRUGS

A General Review

G. DISCOMBE

Almost every drug, and many foods have, at one time or another, been accused of causing some more or less dangerous unwanted effect (for references to food, see Discombe and Mestitz (21)). In many cases the association is probably a chance one; but so firmly has the maxim 'post hoc, ergo propter hoc' been implanted in the Western mind, that it is very difficult to persuade even trained minds to abandon it: and as for minds untrained, they insist that every event has a 'cause' and that the cause is usually simple. In fact, many therapeutic mishaps attributed to the use of drugs are co-incidental: but there are a number in which the mechanism has been elucidated, and the mechanisms by which red cells, leucocytes and platelets are destroyed as a response to the administration of drugs appear to be remarkably similar. This paper is a review of haemolytic processes which develop in patients to whom drugs have been administered.

Even though a haemolytic process develops during administration of some drug, it is a grave error to attribute the haemolysis to the drug alone. The recipient must also be considered, for it is his red cells which are attacked and it is only common sense to suppose that one individual may have erythrocytes much more susceptible to haemolysis than another, or that the metabolism of a drug may differ from individual to individual. The range of susceptibility may be wide or narrow, and deficiencies of enzymes may be complete or partial. One should not, therefore, necessarily expect to be able to test for susceptibility to every drug in every patient, but it may be possible, in the case of some of the commoner and more useful drugs, to detect those individuals who are particularly susceptible. This hope develops from the work of Dern, Beutler, Alving and their associates (11-19).

The effect of drugs on erythrocytes can be conveniently classified as:

1. Direct action on some part of the cell:
   (*a*) on cell membrane or stroma,
   (*b*) on haemoglobin of cell,
   (*c*) on enzyme systems of cell.
2. Combination with the cell to form an antigen to which an antibody is developed, i.e. the drug functions as a pro-antigen.
3. The drug can activate some haemolytic process which thereafter continues without need of any more drug. One personal case, so far unpublished, is referred to below.

In the first two groups one must consider, very carefully, the susceptibility of the subject. To some drug all subjects may be susceptible but will vary somewhat in degree of susceptibility; to another the susceptibility may depend on age, sex, or even on physiological activity such as pregnancy, while genetic factors have already been shown to be important.

DIRECT ACTION ON SOME PART OF THE CELL

No drugs in common use effect haemolysis by directly damaging the cell membrane, though in naphthalene poisoning (32) and in Promanide (Promin) (29) and sulphonamide (30, 31) haemolysis there seems to be some alteration of the cell surface. However, several drugs may affect the globin, an effect possibly demonstrated by the appearance of Heinz bodies within the red cell. Of these the best known are potassium chlorate (28), Promanide (29) and phenylsemicarbazide (Cryogénine) (1-3).

Potassium chlorate (28) produces a rapid destruction of cells. It is absorbed fairly completely, destroyed only slowly by the body, and slowly excreted in the urine. There are variations in susceptibility which depend on the balance between absorption of the salt from the gut and its excretion in the urine, as well as on the intrinsic susceptibility of the red cell to damage. In some patients quite small doses, of about 10 g., produce acute intravascular haemolysis with consequent anuria, while in others the toxic dose is three or four times as great. This range of susceptibility is narrow compared with that found with some other drugs. Haemolytic anaemia resulting from the therapeutic use of potassium chlorate is thus a manifestation of intolerance (p. 3), and occurs only in those at one extreme of the distribution curve of sensitivity.

Phenylsemicarbazide (Cryogénine) (1-3) is one of the most powerful antipyretic drugs known, and may be the only one capable of controlling the exhausting remittent fever once so common in tuberculosis. For some years it has been, in France, a popular component of household remedies, and has even been specially recommended for children – for example, the preparation Défébryl-enfants was a suppository containing phenylsemicarbazide. Unfortunately in about 2 per cent of all adults it produces Heinz bodies and a significant increase in red cell destruction: more serious, however, is the effect on infants, of whom a much higher proportion are susceptible. Here we have a drug which has a very narrow range of indications, known to be particularly toxic to infants, which has been advertised widely to parents for use on their young children suffering from the minor exanthemata. The problem here is not so much that of discovering the susceptible among recipients but of controlling the distribution of the drug.

Promanide (Promin), a sulphone, regularly produces a haemolytic anaemia, apparently by affecting the cell surface, but possibly haem or enzyme systems are involved since methaemoglobin is also formed: this will be referred to again when discussing haemolysis due to primaquine.

Primaquine Sensitivity (11-19). The work of Dern, Beutler, Alving and their colleagues has elucidated the pathogenesis of the haemolytic anaemia which occurs after the administration of primaquine, and their results are of extreme theoretical as well as practical importance. This antimalarial drug is harmless to nearly all Americans of Caucasian origin. Nine American negroes out of ten can take the drug without any ill effects, but the tenth will develop, in the course of a few days, a moderate haemolytic anaemia in which the haemoglobin falls by 40-50 per cent, the reticulocyte count rises to 2-3 per cent, and the excretion of urobilinogen increases. When the drug is withheld, the blood is rapidly restored to normal.

By experiments in which cells from a susceptible individual were tagged and transfused into a normal subject, and vice versa, prior to challenge with the drug, it was found that the susceptibility resided in the cells of the susceptible individual, and that it was only those cells aged more than 50-60 days which were destroyed by primaquine. Further, these elderly cells were destroyed because primaquine inhibits an enzyme, glucose 6-phosphate dehydrogenase,