Allergic Drug Reactions

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EDWARD ARNOLD

First published 1976
by Edward Arnold (Publishers) Ltd.
25 Hill Street, London W1X 8LL

ISBN: 0 7131 4266 9

Printed in Great Britain
at the Alden Press, Oxford

General Preface to Series

The impact of immunological thought on medical practice has been increasing at a steady rate now for nearly twenty years. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumour therapy, particularly in the balanced use of surgery and radiotherapy. Moreover, immunological knowledge in other fields has allowed us to understand more readily the mechanisms whereby a single aetiological agent can produce a wide range of different clinical manifestations. Different disease patterns occur depending on the nature of the immunological reaction causing tissue damage. A completely different symptom complex from reactions involving soluble immune complexes reacting with the complement cascade will be found in those involving the reaction of specifically sensitized lymphocytes with antigen as part of a cell-mediated or delayed hypersensitivity reaction.

As a massive amount of new scientific material accumulates in this field, the clinician is frequently left behind and perplexed. Each year a new scientific journal is published specializing in fields as diverse as immunogenetics, immunochemistry or immunological techniques. We have journals emanating from continents as well as countries. The wealth of material is often bewildering. Simple textbooks of immunology are often too simple, whereas review articles may be too complicated for the specialist physician or surgeon who wants a treatise on those aspects of the subject particularly relevant to his own field of interest. It is hoped that this series will fulfil some of these needs by giving comparatively short reviews that will lay emphasis on immunological subjects which should appeal to both clinicians and those working in clinical laboratories. The aim is to provide the busy clinician in a particular field of medicine with a short volume relevant to his practice written by a specialist. It should introduce the reader to the immunological approach to his subject and indicate how modern immunological thought might influence his day-to-day work in the wards or clinical laboratory.

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Preface

Much has been written about drugs causing untoward clinical conditions and indeed many reported cases claim that the mechanism of drug-induced tissue damage is the result of an immunological reaction. An uncritical evaluation of the literature would suggest that these reports provide a wealth of material to form the basis of a book on allergic drug reactions but unfortunately many of the accounts do not give sufficient data to incriminate a drug either as an immunogen or as an elicitor of an immunological response; their value as models for drug-induced allergic disease is limited. An earnest attempt has therefore been made to resist the temptation of straying into the wider realms of adverse drug effects and to limit my remarks to examples in which there is some evidence of a drug acting as an antigen in association with clinical tissue damage.

The material chosen for inclusion in the monograph was highly selective and by no means comprehensive, the basis for inclusion was mainly on my own experience of investigating adverse drug reactions, consequently some of the views expressed are personal but I hope they may find a sympathetic ear of the reader.

Many of the *in vitro* procedures (Chapters 8, 9, 10, 11) have been given in some detail. This is not because I intended to write a methods section, but I felt it was necessary to give some indication to non-laboratory workers of the work entailed in carrying out the tests and the limitations in interpreting results.

The monograph has been written with the general physician very much in mind, but pathologists and sections of the pharmaceutical industry may find it a stimulus to a more in-depth enquiry.

London, 1976 H. E. A.

Acknowledgements

I should like to pay tribute to my colleague Dr Janet M. Jones for her invaluable help; she not only nursed the manuscript along but offered constructive criticism which has been noted. My secretary, Miss E. Craig, deserves my sincere thanks for typing the various drafts and for some excellent work chasing references.

H. E. A.

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The Problem of Adverse Drug Reactions

One successful approach to medical treatment is to administer chemicals which in some way alter the natural history of the disease to the benefit of the patient. Originally, most of these chemicals were obtained from natural flora and it was part of the pharmacist's or physician's skill to extract active ingredients in a form suitable for administration. This skill has now become the province of the pharmaceutical houses whieh in addition to synthesizing pharmacologically active molecules also undertake to test the compounds for toxicity and therapeutic efficiency.

Any substances or products that are used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient, can be called a drug. The key phrase in this World Health Organization definition of a drug (WHO, 1969) is 'for the benefit of the recipient'. If this is interpreted liberally, practically any substance can be used as a drug if a physician considers it of help to the recipient. Reference to old medical textbooks shows that the most noxious substances have been given to patients on the justification that the disease is being treated. It is now well recognized that even drugs which have been tested thoroughly can produce effects which are not beneficial to the patients although the compounds may ameliorate the disease process.

In 1969 WHO considered it necessary to define an adverse reaction to a drug as 'an effect which is unintended and occurs at doses normally used in man for prophylaxis, diagnosis and therapy'.

Types of adverse drug reactions

Brown (1955) attempted to separate the undesirable effects of drugs into defined subgroups. Brown's classification is useful clinically but it is probably not complete. He maintains that drugs can cause adverse effects by overdosage, side effects, secondary effects, intolerance and idiosyncrasy. These are discussed below.

OVERDOSAGE

The deliberate intake of drugs in excess of the recommended dose does not fall within the WHO definition of an adverse effect but some drugs do have a cumulative action and it is possible to poison a patient by repeatedly giving the therapeutic dose. Overdosage can also occur if patients have any abnormality in the organs responsible for metabolizing or excreting the drug. Thus the toxic effects of overdosage are directly related to the total amount of drug in the circulation.

SIDE EFFECTS

The majority of drugs in current use have more than one action. It is the essence of chemotherapy to administer a drug in doses at which the major therapeutic effect is achieved with the minimum expression of other unavoidable pharmacological actions. The hypnotic effect of the antihistamines is an example of such a side effect and the individual variation in susceptibility is reflected by the number of antihistamine preparations on the market.

SECONDARY EFFECTS

Unlike side effects, a secondary effect of a drug is produced by the indirect but inevitable consequence of primary drug action. One of the most troublesome secondary effects which is often encountered is oral monilia in patients on tetracycline.

INTOLERANCE

Drug intolerance is difficult to define precisely. It occurs at the extreme ends of biological variation in absorption, excretion and metabolism and is manifest as an increased effectiveness of the drug. Intolerance is therefore a function of the recipient rather than the drug. The study of pharmacokinetics has revealed that many instances of drug intolerance are regulated genetically and are related to altered metabolism. The prolonged periods of apnoea occasionally experienced in some individuals on suxamethanium chloride have been shown to be due to abnormally low levels of pseudocholinesterase (Foldes *et al.*, 1963). The level of the enzyme is under genetic control, so an unfortunate individual homozygous for low levels is likely to react adversely to the drug. Many drugs are acetylated as part of the metabolic process, and Evans and White (1964) were able to show that acetylation rates fall into two groups, slow and fast, depending on the availability of hepatic acetyltransferase. Levels of this enzyme, like pseudocholinesterase, are determined genetically and drugs such as isoniazid and the sulphonamides,

which are affected by the enzyme, are present in high concentrations in the blood of slow acetylators.

IDIOSYNCRASY

The term 'idiosyncratic reactions' implies that there are true qualitatively abnormal responses to a drug. It is tempting to consider that all idiosyncratic reactions are due to immunological mechanisms but aberrant biochemical pathways can also be responsible for producing an idiosyncratic effect. Chloramphenicol, for example, produces fatal aplastic anaemia in about 1 in 20 000 patients and the seriousness of this complication constitutes a major hazard to the use of the drug. The incidence is low, however, and was not detected on the routine drug trials but only when the compound was widely used. Initially it was thought that the anaemia was due to a hypersensitivity reaction but the work of Krakoff, Karnofsky and Burchenal (1955) showing that the adverse effect was dose dependent is more suggestive of a biochemical abnormality.

Allergic drug reactions are dependent upon previous exposure to the inducing drug determinant. Drugs must combine with macromolecules before an immunological reaction can be induced and the formation of immunogenic complexes involving drug determinants may be a unique feature of metabolism in susceptible individuals. There is also the possibility that the genetic regulation of immune responsiveness may be important in controlling an individual's ability to react to a drug complex formed in the majority of patients taking the drug. Whatever mechanism is operative, the idiosyncratic nature of the response is evident.

Monitoring adverse effects

There can be no valid objection to the principle of establishing national or international centres to collate information on the untoward effects produced by drugs. The first real attempt to form a registry of adverse drug effects was inaugurated in the USA in 1955. It was designed in the first instance to record the number of induced blood dyscrasias arising from drug administration but it was later enlarged to include other undesirable effects. This registry existed for about eight years but dealt with only approximately 1000 reports, an extremely low figure and in retrospect one which does not reflect the true incidence of the drug-induced tissue damage. Perhaps the reluctance of physicians to co-operate with a central registry could be attributed to a number of factors. One of the most prominent at the time was the concern that confidentiality between physician and patient would suffer if detailed records were kept by a central organization. Lack of publicity of the registry and the tedious procedure for recording the circumstances of iatrogenic disease were probably also to blame.

It was not until the thalidomide tragedy in 1962 that public opinion and the conscience of the medical profession were aroused sufficiently to take

seriously the recording of adverse drug effects. In Britain a subcommittee of the Standing Advisory Committee to the Minister of Health was set up to consider and report on the problem. Under the chairmanship of Lord Cohen it recommended that a full committee should be formed, a Committee for the Safety of Drugs. It would be responsible for analysing all reports of untoward effects in association with drug administration and for informing the medical profession of the general implications of the analysis. Another important function ascribed to the Committee would be that of receiving submissions from the many pharmaceutical houses on products which were intended for the British market. The Committee was to satisfy itself that all possible toxicity studies had been carried out and that the product was safe to be used for initial control trials in man. The Committee began work in 1963 under the direction of Sir Derrick Dunlop.

Similar committees have been set up in other countries, notably in the USA. These watchdog committees are doing valuable service in ensuring that all possible care is taken in the testing of new products but unfortunately they are political rather than scientific. Undoubtedly they can consult expert scientific advisers but a recommendation on a product reputed to produce adverse effects must take into account public opinion, often moulded by emotional reporting in the press. In view of the delicate position of these watchdog committees and the lack of their own facilities to finance basic research into a product, it is important that physicians reporting on adverse reactions should be fully aware of their responsibilities. All too often, a deviation from the natural history of a disease is attributed to drug administration on the most circumstantial of evidence and seized upon as the means to a quick publication. Clinicians who use drugs are in the best position to observe untoward effects but it is irresponsible to publish reports in the scientific literature before an adequate investigation has been carried out or reference made to the Safety of Medicines Committee.

The pharmaceutical companies, like all commercial organizations, are governed in part by the profit motive yet modern medicine is based on the use and exploitation of the products which they produce. Thus the contribution of the pharmaceutical industry to medicine is equally as important as the physicians who use the drugs on individual patients. It is unthinkable that there should ever be another thalidomide disaster and it is right that the unfortunate recipients of this particular drug should be compensated. The compensation met by the company marketing the drug is an illustration of the part played by the company in patient treatment. Clinicians who prescribe drugs should therefore no longer consider themselves totally responsible for their patients. There must be mutual respect and closer co-operation between the bodies who make drugs and those who prescribe them. The pharmaceutical companies have intimate knowledge of their products and this must be imparted to the medical profession. On the other hand, the medical profession should not be too anxious to accept new products without being fully satisfied that the drugs are safe as well as therapeutically effective, although this places considerable responsibility on the clinicians electing to do drug trials.

Genesis of a drug

The work involved in the creation of a new drug is often not appreciated by most clinicians. Figure 1.1 shows schematically the steps which have to be considered before a drug is finally launched. It can be seen that in the first instance market research, medical needs, research ideas, financial considerations and division policy are all given equal weight. A commercial organization has to justify the enormous expense of producing a drug by first ensuring that there is a market for the preparation which will yield a profitable financial return. Under these circumstances it is difficult to persuade a company to produce a drug which has a limited market but for which there is a significant medical need. Penicillamine, for example, was used by Walsh (1956) to treat Wilson's disease but it was difficult to interest a company to produce the compound for such a small market. When penicillamine was found to benefit rheumatoid arthritis patients, the potential of a wider market became apparent and the pharmaceutical houses began large-scale production of the drug.

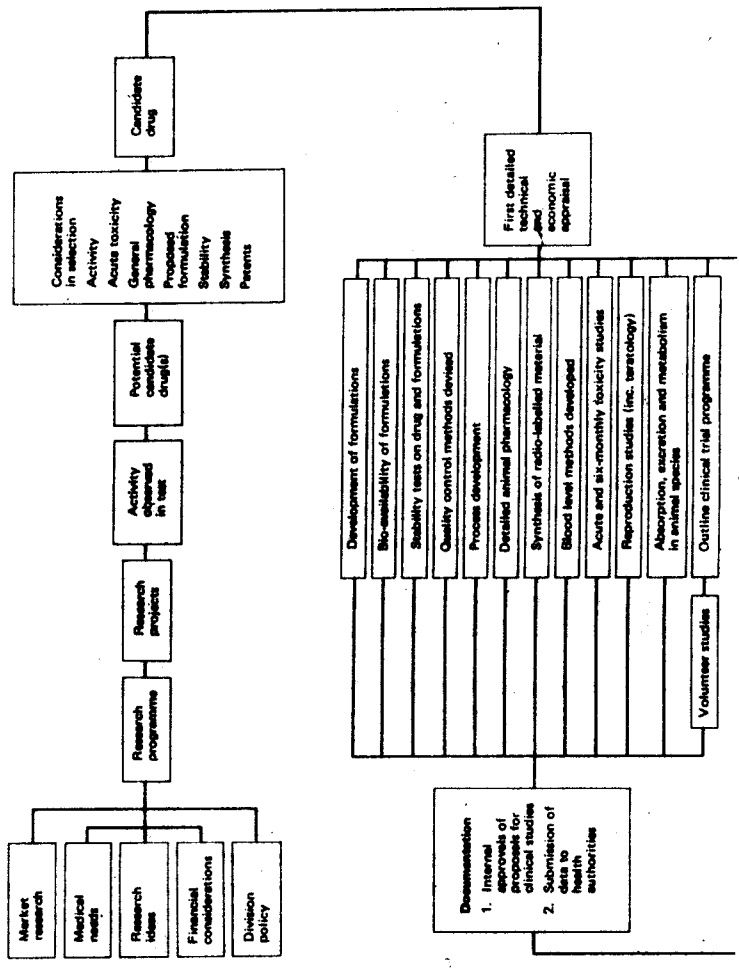
The selection of a drug from many potential drug candidates is based on laboratory experiments and the result of acute toxicity studies. The chosen compound is then subjected to a detailed appraisal which includes acute and six-monthly toxicity studies in at least two animal species. Although animal studies are carried out, it is accepted that the data obtained cannot be extrapolated directly to man. Metabolites generated in animals may not be formed in humans; this makes it essential to go into man as early as possible. It is certainly interesting to speculate on the number of potentially valuable compounds that have been rejected by finding an adverse effect in one species alone.

There is a school of thought which advocates that studies on volunteers should be initiated at a much earlier stage than they are at present. This is a rational approach and under controlled conditions the risks could be minimal but the information gained invaluable. It is possible that by going into man early and by studying the effect of the drug on tissue cells, some of the biochemical idiosyncratic reactions might be detected.

Hypersensitivity reactions, however, are more difficult to predict from the safety evaluation procedures carried out routinely. They form a unique type of adverse effect which can be serious and difficult to detect with certainty. The following chapter is designed to put hypersensitivity drug reactions into perspective and to outline procedures which may be of use in investigating this difficult problem.

Conclusion

Adverse effects due to drug administration are an increasing problem, especially as the tendency of the pharmaceutical houses at present is to produce large numbers of drugs some of which differ from existing products only with respect to their formulation. There are indications, however, that


Market research
Medical needs
Research ideas
Financial considerations
Division policy
Research programme
Research projects
Activity observed in test
Potential candidate drug(s)
Considerations in selection
Activity
Acute toxicity
General pharmacology
Proposed formulation
Stability
Synthesis
Patents
Candidate drug
First detailed technical and economic appraisal
Development of formulations
Bio-availability of formulations
Stability tests on drug and formulations
Quality control methods devised
Process development
Detailed animal pharmacology
Synthesis of radio-labelled material
Blood level methods developed
Acute and six-monthly toxicity studies
Reproduction studies (inc. teratology)
Absorption, excretion and metabolism in animal species
Outline clinical trial programme
Volunteer studies
Documentation
1. Internal approvals of proposals for clinical studies
2. Submission of data to health authorities

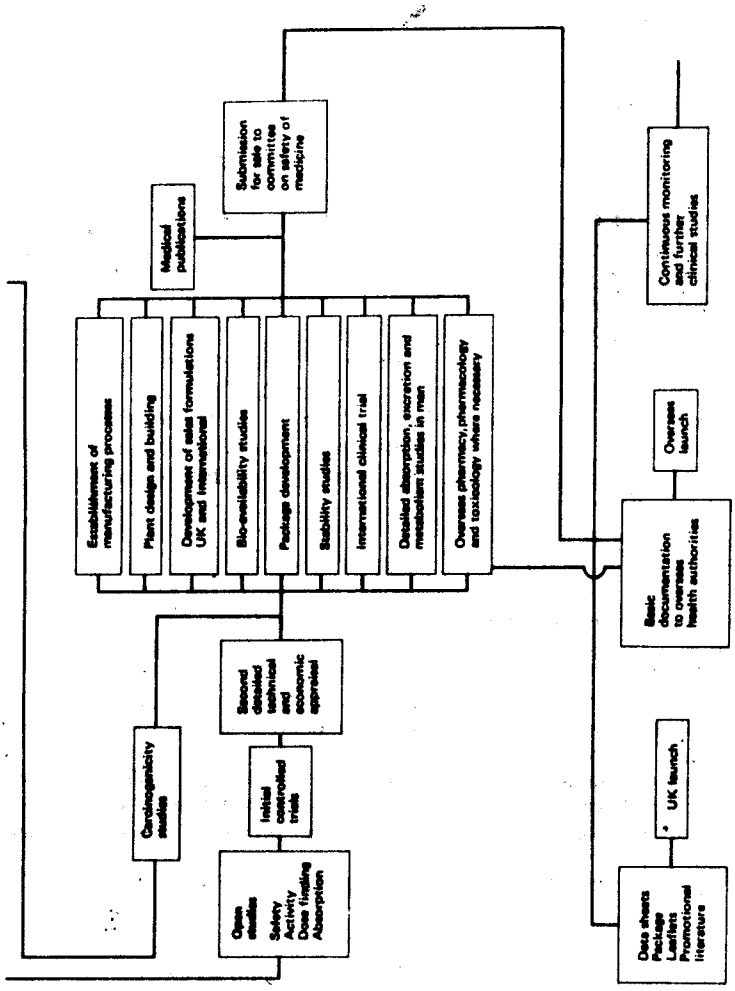


Fig. 1.1 Genesis of a drug. (Reproduced by courtesy of I.C.I. Ltd.)

more selectivity is beginning to appear in the design of drugs. This has resulted from the progress made in recent years in understanding the pathogenesis of many diseases. It is now becoming possible to select the stages in certain diseases at which therapeutic attack should be directed in order to arrest ongoing processes and reduce the need for symptomatic treatment. However, the cost of producing drugs is now so high that fewer drugs with greater specificity of action are likely to be the rule for the future.

The assessment of toxicity studies in relation to drug safety should also be equated with cost. It would be a pity if the expense incurred in preparing a submission to the various committees on drug safety becomes so prohibitive that the industry steers away from the production of ethical preparations towards other more lucrative fields. By testing in volunteers early in the evaluation it might be possible to reduce production costs by obtaining a speedy and more reliable assessment.

The types of adverse reaction caused by drugs have been well publicized and many of them can be eliminated by adhering rigidly to the recommended dose and by careful clinical monitoring. Idiosyncratic reactions, however, will continue to be a problem. The production of tissue damage by immunological means is a fundamental challenge in basic biology and will be solved only when the nature of the immune response is elucidated completely.

References

BROWN, E. A. (1955). Problems in drug allergy. *J. Amer. med. Ass.*, **157**, 814.

EVANS, D. A. P. and WHITE, T. A. (1964). Human acetylation polymorphism. *J. Lab. Clin. Med.* **63**, 387.

FOLDES, F. F., FOLDES, V. M., CRISPIN SMITH, J. and ZSIGNOMD, E. K. (1963). The relation between plasma cholinesterase and prolonged apnoea caused by succinylcholine. *Anesthesiology* **24**, 208.

KRAKOFF, I. H., KARNOFSKY, D. A. and BURCHENAL, J. H. (1955). Effects of large doses of chloramphenicol on human subjects. *New. Engl. J. Med.* **253**, 7.

WALSH, J. M. (1956). Penicillamine: a new oral therapy for Wilson's disease. *Amer. J. Med.* **21**, 487.

WHO (1969). International drug monitoring. *Wld Hlth Org. techn. Rep. Ser.* No. 425.

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Hypersensitivity Mechanisms Responsible for Tissue Damage

The immunological system is one of the body's basic defence mechanisms against foreign substances. Immunological responses should therefore be beneficial to the body and in many cases they are, but for reasons which are not entirely understood some reactions do produce tissue damage. These damaging reactions are termed collectively 'hypersensitivities' to indicate that the body has overreacted to the offending substance. In an attempt to understand how hypersensitivity reactions damage tissue, Coombs and Gell (1953) analysed the clinical manifestations and proposed four possible mechanisms: types I–IV.

TYPE I

This first type corresponds to immediate hypersensitivity and is brought about the the antigen-antibody reaction at the surface of mast cells and basophils, resulting in the release of pharmacologically active mediators. Clinically, type I hypersensitivity is expressed as systemic anaphylaxis or as a local weal and flare reaction.

TYPE II

The damage associated with type II is mainly complement-mediated cytolysis, brought about by antibody reacting with antigens on the surface of cells and fixing complement. The antigenic determinants can be part of the cell surface such as blood group antigens, or may become fixed to the cell surface so that the cell is damaged indirectly. The latter is the mechanism for antigen formation in haemolytic anaemia induced by penicillin.

TYPE III

Type III damage results from the deposition of antigen-antibody complexes. The clinical signs and symptoms produced depend on the target organ in which the complexes are deposited but the organs which are most

often affected are the kidneys and the skin. Serum sickness is also included in this category of hypersensitivity.

TYPE IV

Type IV reactions correspond to reactions termed originally 'delayed hypersensitivities'. No serum antibodies are involved in this type: the tissue damage is brought about by the direct interaction of antigen with specifically sensitized (allergized) lymphocytes.

Each of these types of tissue damage has been induced by drug antigens. It is not known why one type should predominate at a clinical level for it is likely that a hypersensitivity reaction involves elements from all types. The Coombs and Gell classification is used in this monograph as a basis for determining mechanisms of allergic drug reactions. Further details of this system for rationalizing the mechanisms of allergic tissue damage are given on the following pages.

Type I reactions

An acute anaphylactic response following drug administration is the reaction most feared by clinicians. Prompt medical treatment, which may include prolonged periods of intensive care, is necessary to prevent death from asphyxia or circulatory collapse.

The mechanism of anaphylaxis is still not entirely understood but the signs and symptoms are compatible with the widespread release of mediators acting on smooth muscle and blood vessels. In man the mediators which have been implicated in anaphylaxis are histamine (H) slow reacting substance A (SRS-A), eosinophil chemotactic factor (ECF-A) and the prostaglandins E_1 and E_2. These mediators are released from mast cells and basophils. Prostaglandins are also probably freshly synthesized by tissues as a consequence of primary damage. The sequence of events which leads ultimately to the release of these pharmacologically active substances is complex and the subject of much research.

A fundamental requirement for producing anaphylaxis is the production of a specialized class of antibody, IgE. This antibody class has a normal serum concentration of about 0·1–0·7 μg/ml. In certain allergic states, however, IgE levels have been shown to rise considerably, presumably due to the production of specific IgE antibody directed against the inducing antigen. For example, Wide and Juhlein (1971) showed that patients with type I skin responses to penicillin have markedly raised total serum IgE levels with detectable IgE antibodies of penicilloyl specificity.

IgE will bind to target tissue, mast cells and basophils in a reversible manner by means of its Fc piece (Stanworth, Humphrey and Bennich, 1967). The Fc piece of the molecule is the end which is not involved in combination with the antigen. When antigen cross-links two adjacent IgE molecules, an