Hypersensitivity to Drugs Volume I

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Hypersensitivity to Drugs

VOLUME I

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PREFACE

"A bull who eats grass eats his health and his sickness. For grass can give strength or be poison, be a food or a drug. But a grass in itself is not a poison."

(THEOPHRASTUS PARACELSUS)

THAT drugs can be poisons and poisons drugs has been known since antiquity. It is a comparatively new experience that chemicals which are innocuous *per se* can be transformed by the host into compounds capable of inducing an immunological sequence that can lead to illness and death. Until the turn of the century, reactions caused by hypersensitivity to drugs were reported but not understood; and no serious attempts were made to differentiate between non-immunological and immunological reactions.

Clinical symptoms which are the result of hypersensitivity to drugs are the final step in a long and often complicated sequence. It is the objective of this volume to identify the conditions which must be met (1) by the drug and (2) by the host before immunological reactions can occur, and to illustrate the wide variety of responses which drugs can induce in organs and systems.

The design of the volume is the result of rewarding interactions between editors and authors. The editors have affectionate memories of the early development of individual chapters in a sunlit garden on the "Mainline" near Philadelphia, in the seclusion of a weekend at the Zieglerspital in Berne, on the sleek Trans-Europa Express between Lausanne and Paris, in the dining room of the Hôpital Broussais, during an evening walk at Hampton Court followed by a leisurely dinner at a country inn not far from London, on the way from and to airports, and in long-distance calls across the Continent and across the Atlantic Ocean.

Authors and editors share the responsibility for both content and form. The responsibility for content is mostly the authors'; the responsibility for form mostly the editors'. On occasion, however, content also raised serious editorial questions. It appeared justified, for instance, to assign a separate chapter to drug-induced reactions of the connective tissue, which represents a very active area of current investigation. Yet the published

evidence is spotty and does not add up to a pattern which makes sense. Dr. D. L. Gardner was kind enough to review our problem and to arbitrate. In the end he wrote: "The further I peer into the literature [on the reactions of connective tissue to drug hypersensitivity], the more convinced I am (as you were) that this field does not yet merit a separate item in your volume on hypersensitivity to drugs."

Other questions arose in regard to other chapters. In principle, the editors had insisted that—in order to qualify for inclusion—reactions must be mediated by clearly established or at the very least presumed antibodies. Yet it was not possible to apply this desire for editorial purity to every chapter of the volume, e.g. to the chapters which describe injuries to the liver and kidney. It is often uncertain whether hepatic or renal lesions are caused by a primary disease or by the toxic or sensitizing effect of drugs; moreover, there is good evidence that certain primary diseases might alter the responses to drugs with which they are treated. Schaffner and Raisfeld, in a recent review (*Adv. Int. Med.* **15**:221, 1969), conclude that none of the currently available tests can detect the sensitizing potential of a drug or, as it were, an individual at risk. The editors agree and, while the chapters on hepatic and renal changes include some non-immunological as well as immunological reactions, can only hope that future editions will clarify which is which.

It is not easy to prevent overlapping and occasional repetition in a volume which consists of contributions from authors who share a common interest in drug-induced immunology and rely on common sources of information. The authors have recognized the inherent difficulty of the task and have been generous in allowing us more editorial freedom than editors usually request or are given. Immunology is a young discipline: it has still semantic difficulties. Even so, the editors tried to adopt and enforce a uniform terminology: with very few exceptions—easily identified by annotations—this has been accomplished.

The translation of contributions which were submitted in languages other than English has been a major editorial challenge. In some instances it has been necessary to translate and re-translate critical passages in order to express the thoughts of the author accurately. James Howell, we think, has said: "Some hold translations not unlike to be the wrong side of a Turkey tapestry", but we are confident that our tapestry conveys the intended shades of color.

Our confidence is based on the advice and counsel of numerous consultants who have given freely of their time and contributed their efforts to make this a better book. We have already mentioned Dr. D. L. Gardner.

Dr. Hartmann Friederici reviewed the histopathology of immunological reactions caused by drugs and taught us how to standardize the variety of expressions and eponyms which had different shades of meaning in different chapters. We are indebted to Drs. Nicolas Costea, Herbert Goldschmidt, Paul Heller, E. W. Maynert, L. Meyler, R. C. Muehrcke, L. M. Solomon, and W. St. C. Symmers who guided us in the areas of their specific interest.

The staff of Pergamon Press assisted us in the handling of technical problems, and Dr. Georges Peters stood by, an experienced and fatherly guardian angel, with decisive answers to hesitant questions and with patience and understanding when progress was slow. Dr. C. Bernecker compared earlier and subsequent versions of several chapters, and Mrs. Joyce Young was in charge of the bibliographies, which had to be kept up to date: the more than 4 years which were needed to complete the manuscript were fast-moving years.

M.S./C.W.P.

CONTENTS

Subsection I

PRINCIPLES

CHAPTER 1

HYPERSENSITIVITY TO DRUGS: DEFINITION AND SCOPE

M. Samter
Chicago, Illinois

UP TO the recent past, hypersensitivity to drugs has been a vague and disturbing clinical entity which included a wide spectrum of unrelated symptoms. The terms "intolerance", "idiosyncrasy", "allergy", and even "toxicity" were applied almost interchangeably to side effects caused by drugs regardless of the mechanisms by which they occur. Alexander (1955) recognized clearly that many drug reactions, whatever their pathogenesis, are clinically similar and that, in many instances, either the responsible drugs or the reason why they cause untoward effects remain quite elusive. He felt that hypersensitivity to drugs connotes mechanisms (induced by therapeutic or subtherapeutic amounts of drugs) that are responsible for lesions which differ from those of pharmacological effects or those of overdosage, and which, he added, occur in only a small percentage of individuals. Step by step, definitions have become more precise: Peck and Lammers (1962), for instance, dissociate hypersensitivity from overdosage, toxicity caused by liberation of chemical mediators from "true" toxicity (Modell, 1965). Used in this section, hypersensitivity to drugs is a synonym for drug allergy: it requires the established or assumed presence of antibodies.

Antibodies form when appropriate cells of the lymphatic system are stimulated by antigens, i.e. substances which are "immunogenic"† and react specifically with the antibodies which they have induced. A hapten or, as it is now commonly called, an antigenic determinant is not immunogenic, but can react with specific antibodies once they exist.

† The term "immunogenic", now widely used, is not a fortunate term. It is applied with equal enthusiasm to sensitizing, i.e. potentially disease producing, as well as to immunizing, i.e. protective, antibodies, which should be clearly distinguished from each other.

Antigens are large, "foreign" substances. Some diagnostic and therapeutic agents are complete antigens (Chapter 3), but most drugs which induce hypersensitivity are comparatively small molecules. Small molecules cannot induce synthesis of antibodies unless they combine firmly with macromolecular components of one or several tissues of the host. The conjugate between the drug and macromolecular carrier is an antigen and stimulates the formation of antibodies. Hypersensitivity to drugs, in all its forms, depends on synthesis, distribution, tissue fixation of antibodies, and on subsequent antigen–antibody interaction.

It is the intention of Section 75 to clarify the conditions which must be met before a drug can become an antigen or an antigenic determinant, and to outline the sequence of events which are bound to occur when it does. While each chapter of the volume speaks for itself, a few introductory remarks might be in order.

As a rule, drugs are not antigenic determinants when they are taken: the formation of antigenic determinants is a byproduct of their biotransformation. Drugs are developed for optimal effectiveness—after absorption they are processed for optimal excretion. Lipid-soluble drugs, for instance, require transformation into water-soluble metabolites. Brodie (1964) has emphasized that biotransformation is frequently a two-step procedure: the first step catalyzes the formation of hydroxyl or amino groups which permit the second step, i.e. the conjugation of these newly formed groups to substances of low lipid solubility. "Polarized" metabolites might be either non-reactive or reactive; while they might be less lipid soluble, they are not necessarily less toxic.

Microsomes which have the task of preparing drugs for excretion have a certain freedom of choice: often alternate pathways exist for the biotransformation of drugs. Even so, the manner in which the drugs are handled might well depend on the pre-existing biochemical state of the host or on the demands made on microsomes by several drugs given simultaneously. Sulfa drugs, for instance, might be innocuous when they are transformed into N^4-acetylated or N^1-conjugated derivatives, but it seems likely that a comparatively small amount of an oxidized metabolite, e.g. 3-hydroxysulfanilamide, might become an antigenic determinant and combine with a willing macromolecular homologous carrier (Williams, 1959; Samter *et al.*, 1967; Samter, 1969). While comparatively few enzymatic reactions account for most of the metabolic changes, we are just beginning to understand their complexity, e.g. the role, of cytochrome-P-450 in the induction of enzyme activity (Staudinger *et al.*, 1969). Adaptation, pharmacokinetic drug interaction (Prescott, 1969), and genetic defects (Kalow, 1965;

Peters, 1968; Price Evans, 1969) might contribute to the development of unexpected or "faulty" metabolites.† Chapters 4 and 5 of the Section describe the formation of antigenic determinants and the conditions which must be met to permit their conjugation to tissue components.

The manner in which antigen induces elements of the lymphatic system to synthesize antibodies is not entirely clear. Several authors have presented suggestive evidence that macrophages participate as intermediaries in antibody formation, but *in vitro* studies indicate that simple contact between antigen and lymphocytes might be sufficient: we have no proof, so far, that the *in vitro* capacity reflects the *in vivo* behavior. It is certain, on the other hand, that exposure to the same antigen is not always followed by the formation of the same type of antibody in different hosts or even in the same host at different times. Meyler (1968), for instance, believes that patients with an allergic constitution are more prone to sensitization than are non-allergic patients: actually, there is some doubt whether this assumption is correct.‡

Different antigens might produce different antibodies; and the same antigen might produce a variety of antibodies in a single host. Antibodies of the "immediate" type might coexist with precipitating antibodies: in fact their ratio might determine the natural history of a drug-induced allergic reaction. Antigenic determinants conjugated to lipids might encourage the formation of sensitized lymphocytes; subsequently, contact with the "hapten" alone might cause "delayed" inflammation at the site of exposure. Chapter 6 identifies the type of antibodies which drugs might induce.

It is perhaps appropriate to emphasize that the presence of antibodies is a prerequisite for hypersensitivity to drugs, but does not, *per se*, imply that reactions *must* occur. Oort (1962) has emphasized that the recognition and interpretation of reactions caused by antibodies to drugs is not easy. In a discussion of reactions attributed to sensitization by drugs, he differentiates "central" reactions, i.e. reactions in the lympho-reticular-endothelial system (wherever it might be located) from "peripheral" reactions,

† "Genetically determined differences in metabolism are widespread and may be entirely innocuous for the individual unless a particular drug is prescribed. In this situation, however, the absence or deficiency of a particular enzyme or the abnormality of a receptor site may cause serious problems. Awareness of inherited variability in drug response is becoming more and more essential to the correct design of individual drug regimens." (La Due, Jr., 1971.)

‡ It is interesting that Meyler concluded previously that the nature of the reaction does not seem to depend on the nature of the drug. It appears that this is no longer as true as it was then; a pattern is beginning to emerge which will be apparent in the pages of this volume.

i.e. the eventual biochemical lesions produced by antigen–antibody interactions. Oort, who has studied passive cutaneous anaphylaxis, Arthus reactions, and tubercular reactions, arrives at the disturbing conclusion that the changes in the central system defy interpretation because we really do not know what to expect; and the changes in the peripheral lesions are complicated and often obscured by secondary and tertiary changes which might overlap even under precise experimental conditions. The morphology of drug reactions is described in Chapter 7.

Unfortunately, drug reactions in man do not occur under precise experimental conditions. More often than not, the drug which has induced the reaction is not the only drug which has been taken. The interval between the administration of the drug and the appearance of clinical symptoms might be so long, e.g. in generalized periarteritis, that neither physician nor patient will correlate drug with disease. Drug reactions, on the other hand, might occur while the disease for which the drug was given is still present so that it might be impossible to dissociate symptoms produced by the drug from the symptoms produced by the disease. Experiments which sensitize experimental animals to drugs are usually carried out on a species which can be expected to produce predictable responses. Man, on the other hand, who takes drugs, is not predictable because, by and large, we have inadequate information about the complex sequence of the central as well as of the peripheral components which participate in the pathogenesis of reactions to drugs.

Of various forms of hypersensitivity to drugs, the immunological sequence which leads to reactions of the immediate type has been studied exhaustively for many years. Interaction of antigen and antibody initiate the explosive release of chemical mediator, e.g. of histamine (but other mediators as well—some known, some unknown), which act on capillaries, mucous glands, and smooth muscles. The response of these tissues (which are usually called "shock tissues" for want of a better term) does not only depend on the number of molecules of antigen and antibody but, equally, if not more so, on factors which are exclusively functions of the host, e.g. the number of mast cells which are present at the site of the antigen–antibody interaction, the structure and density of the tissue in which the interaction takes place, and the sensitivity of the appropriate receptors in the vascular bed, smooth muscles, and mucous glands. In fact, it is conceivable that interaction between impressive quantities of the antibody of the "immediate" type and corresponding antigens might occur without demonstrable clinical symptoms; and that even mild sensitization might produce exaggerated symptoms in patients who respond to minimal

amounts of chemical mediators with maximal reactions of an unusually sensitive vascular bed. It seems quite possible, for instance, that Meyler's observations that "allergic" patients are prone to develop hypersensitivity to drugs really means that the incidence of sensitization might be the same in the allergic and non-allergic groups, but that the allergic population tends to react more spectacularly once sensitization has occurred. Chapter 2 discusses individual variations in reactions to drugs as variations in interaction of antigen with antibody, of "mediator" with "receptor"—this, while only a beginning at this time, will eventually permit us to construct pharmacokinetic models and, perhaps, to forecast the response of the host in hypersensitivity to drugs.

In many instances the tissue in which the antigen–antibody interaction occurs is an innocent bystander: and *restitutio ad integrum* at the end of the reaction is the rule rather than the exception. If antigenic determinants, on the other hand, conjugate to non-circulating components of the tissue, the tissue might become part of the antigen and is no longer an innocent bystander: "cytotoxic" reactions of this type require the presence of complement but, as long as complement is available, tend to persist.

It is likely that drugs can induce under appropriate circumstances any conceivable immunological reaction in any conceivable tissue. Chapters 8, 9, 10, and 11 describe the reactions caused by drugs in the formed elements of the blood, in the skin, in kidney, and in liver. It is almost impossible to predict the type of reaction which a newly formed drug might produce, but we are beginning to learn that certain drugs tend to produce certain reactions preferentially and, moreover, tend to localize reactions at predictable sites: quinidine elicits purpura; phenolphthalein, a fixed exanthema; and chlorpromazine, cholestatic jaundice.

Chapter 12—the final chapter of the subsection—outlines the practical aspects of diagnosis and treatment of hypersensitivity to drugs. In the absence of clear understanding why hypersensitivity to drugs occurs, elimination of drugs which are known to sensitize might be the most feasible approach at the present time, but it is intriguing to speculate at which step of the sequence we might be able to abort reactions to drugs at some future date: at the level of the microsomes by the elimination of drugs which compete for enzyme and substrates; at the level of the macromolecular carrier, by a selective blockade of possible binding sites; at the level of the lymphocytes which might acquire a specific immunotolerance to certain drugs; at the level of complement which might be removed to prevent destructive changes in tissues; at the level of the chemical mediator; or at the level of the tissues which, like red blood cells or the vascular