
Preface

With its roots in immunology and pharmacology, advancement in the science of drug allergy and its application to clinical medicine has ultimately always been heavily reliant on application of a broad range of investigative methodologies in humans rather than laboratory animal models. The variety of chemically diverse pharmacological agents administered to patients is large and continues to expand and with every new drug released, there is always potential for adverse reactions, some of them allergic. This diversity in chemical structure and pharmacological action together with the range of observed adverse clinical responses; the need to access sufficient numbers of adequately phenotyped patients to study; the necessity of collaborative inputs from laboratory and clinic; and the variety of chemical, cellular, and clinical methodologies needed ensured that progress in the field has generally fallen short of the hoped-for insights. In fact, post the penicillin era when drug allergy was given a much-needed structural perspective, at both the research level and in terms of patient benefits this specialized section of allergic diseases could not be said to have made great advances. There are a number of reasons for this. In the first place, the seemingly perpetual confusion over what constitutes an allergic reaction is something that affects many clinicians as well as the public and the mass media. The term “allergy” continues to be used inappropriately to refer to all sorts of nonimmune-based reactions to a drug and, for many in the medical profession, this reflects a state of mind that is not conducive to reporting/recording, diagnosing, and seeking to understand the true nature of many drug-induced reactions. To reinforce this point, attention is drawn to the 1970s and 1980s when the value of skin testing—prick, intradermal, and patch—although widely advocated and promoted by a few practitioners and aficionados, was not widely understood, appreciated, and applied. Examples were the neglect of the skin test in the diagnosis of drug allergies to anesthetic agents, drugs used in surgery, antibiotics, and other antimicrobial drugs where attitudes to the test sometimes ranged from the uninformed to cynicism of its scientific and clinical relevance. One only needs to talk to anesthesiologists from that period who were aware of anaphylaxis to neuromuscular blocking drugs to learn of the skepticism of skin testing by many of their professional colleagues. To help overcome this problem, research findings and leadership and instruction, for example, in the form of issued practice parameters and standard operating procedures by the relevant professional bodies, were needed. In anesthesia, this is, in fact, now being

undertaken by Societe Francaises d'Anesthesie et de Reanimation, the Association of Anaesthetists of Great Britain and Ireland, the British Society of Allergy and Clinical Immunology, and the Scandinavian Society of Anaesthesiology and Intensive Care Medicine, all of whom have issued clinical practice guidelines. Over the whole broad area of drug allergy, the European Network for Drug Allergy under the aegis of the European Academy of Allergology and Clinical Immunology has published numerous position papers on allergy practice over the last decade with emphasis, for example, on standardization of methods for the diagnosis of drug allergies.

While acknowledging the sometimes under-appreciation of the problem of drug allergy and the inadequacy of its diagnosis, a third inhibitory factor to progress was probably inevitable. This relates to research directed at identifying underlying mechanisms and improving patient outcomes for cell-mediated drug-induced hypersensitivities such as the various cutaneous reactions ranging from mild exanthemas to severe bullous eruptions. Knowledge of the intricate cellular immune processes involved in antigen recognition, lymphocyte receptor repertoires, and the adaptive immune response as well as recognition of the value and application of a pharmacogenetic approach needed to progress to somewhere near their present levels of understanding before significant inroads could begin to occur. In particular, understanding the role of MHC restriction, drug-specific T cells, and the availability of improved genotyping technologies should significantly increase the chances of advancing knowledge of the cellular hypersensitivity mechanisms and developing new diagnostic and predictive tests. As advantage is increasingly being taken of the results obtained from the extraordinary investigative activity directed at defining cellular and molecular mechanisms of immune processes, chemical approaches, used so effectively in the studies on penicillin and neuromuscular blocking drugs, are being less often utilized as biological and clinical emphases dominate research efforts. The results of this neglect can be seen in the dearth of detail available on the structures recognized by the cellular immune system in delayed hypersensitivity responses. With increasing employment of mass spectrometric characterizations, carefully selected synthetic drug conjugates, and the realization that drugs may be recognized or participate in immune processes in their free state, we can expect that this situation may soon be remedied as investigators seek to expand their current cellular preoccupation, much of it often speculative in nature, with a deeper understanding of the fine structural features that determine allergenic recognition in cell-mediated drug reactions.

With this background and perspective in mind, we set out here to identify the most important culprit drugs implicated in immediate and delayed drug hypersensitivities and to collate up-to-date information on classifications, clinical features, diagnoses, underlying mechanisms, and structure–activity relationships. Chapters dealing with the molecular and cellular mechanisms of drug hypersensitivities, nonimmune-mediated sensitivities, and diagnostic methods are presented as introductory material for in-depth treatises on the β -lactam antibiotics, other antibiotics and antimicrobials, drugs used in anesthesia and surgery, opioid analgesics, corticosteroids, monoclonal antibodies and other biologics, drugs used in chemotherapy, proton pump inhibitors,

iodinated and gadolinium-based contrast media, and nonsteroidal anti-inflammatory drugs. For the latter two groups of drugs where only some of the adverse reactions are truly allergic in nature, discussions have been extended to cover the more dominant and more often seen drug-induced sensitivities or intolerances.

Readers with a historical perspective may be able to detect in this book the influence of two past investigators who made important contributions to hypersensitivity research. Each had widely different professional training, research backgrounds, and clinical involvement, but both were well known for their infectious, unrelenting enthusiasm and the pleasure they derived from pursuing, over many years, original ideas and observations that were very much their own. Time spent by the author in the 1970s in both laboratories left a career-long imprint. In so many ways, the difficult Elvin Kabat in the Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital, and the urbane Jack Pepys at the Brompton Hospital, London, could not have been more different but both were undoubtedly exceptional investigators, one in the laboratory relentlessly applying his quantitative approaches and the other in the world of patients, exploiting the diagnostic potential of, and promoting, one of the simplest technical procedures ever employed in clinical work. The quantitative immunochemical methodologies introduced and developed by the Landsteiner-Heidelberger school of immunochemistry and so expertly applied and propagated by Kabat in his classic text *Kabat and Mayer's Experimental Immunochemistry* (C. C. Thomas, Springfield, IL) influenced a generation of immunologists and maintained a direct line back to Landsteiner and the origins of immunochemistry. By the early 1950s in studies backed by the Office of the Surgeon General, U.S. Army, Kabat had demonstrated a relationship between dextran structures and molecular weight and the propensity of the polysaccharides to provoke systemic allergic reactions. This work ultimately led to a dramatic 90-fold reduction in dextran-induced anaphylactic reactions by pre-dosing with a dextran monovalent hapten. Application of this competitive hapten inhibition strategy, straight out of the Landsteiner-Heidelberger-Kabat quantitative immunochemical protocols, made dextrans easily the safest of all the plasma volume expanders in use. Likewise, Pepys' championing and application of the specificity, sensitivity, and wide applicability of skin prick and provocation testing, despite their apparent simplicity, aided understanding of some important fungal-induced hypersensitivity diseases of the chest, increased appreciation of the clinical value of the procedures, and emphasized their utility for research, diagnosis, and studies of mechanisms in clinical immunology and allergology. Together with his original contributions over many years in the field of occupational allergic diseases studying hypersensitivity pneumonitis (extrinsic allergic alveolitis), his early contributions to our understanding of the late reaction and the training of a constant stream of visiting clinicians from all over the world, Pepys was also fascinated by what often appeared to be hypersensitive responses to "small" molecules including drugs and in his later years he began studies in this area. This was after his earlier pioneering investigations into the sensitizing and allergenic properties of platinum in refinery workers. This work, including the detection

of IgE antibodies to platinum salts, was to prove a forerunner of later interest in patient reactions to the important and heavily used platinum chemotherapeutic drugs. The legacies of Elvin Kabat and Jack Pepys remain apparent today in the originality of their scientific research and value of their clinical contributions. To that can be added the many practitioners in laboratories and clinics who pass on what they themselves learned from the enthusiastic tutelage of these too-often forgotten important early contributors to our knowledge of hypersensitivity states.

In pursuing the authors' own interests and research in drug allergies, some of it recounted in this volume, we would like to acknowledge our enduring collaboration with Dr Malcolm M. Fisher who introduced one of us to the then mechanistically poorly understood problem of perioperative anaphylaxis to what, at the time, were called muscle relaxants. The long-standing clinical interest by Dr Fisher provided all the necessary clinical background and patient material for successful investigations of underlying mechanisms, led on to the study of a range of other drug allergies, and ultimately the development of a useful battery of routine in vitro drug allergy tests. In what was a remarkably small manpower input over many years, we are indebted to Gail Knowland in particular for her long-standing, versatile, and always reliable input into all of the projects, to Dr David Harle for his sustained careful investigations and technical expertise, and, in later years, to Dr. Zhenjun Zhao who, like all his fellow investigators, assiduously pursued the laboratory's quantitative approaches to mechanistic and diagnostic studies on a wide range of poorly understood adverse drug reactions. Dr. John Redmond, Dr. Mary Smal, Dr. Sue Cooney, and Dr. Alistair McCaskill had key roles in the laboratory's research on PAF mentioned here and the development of a sensitive, high-throughput immunoassay for the mediator.

The inclusion in this book of some important photographs and figures was greatly assisted by the generosity and cooperation of Professor S. R. Durham, Dr. D. G. Ebo, Dr. J. S. Fok, Dr. D. Gin, Dr. F. Hasdenteufel, Professor R. J. Heddle, Dr. A. Mar, Dr. P. A. J. Russo, Dr. R. Spiewak, Dr. F. C. K. Thien, and Dr. S. Van Nunen.

Our intention has been to provide a scientifically based textbook with the relevant chemical, immunological, pharmacological, biochemical, and, where appropriate, pharmacogenomic information without losing the clinical perspective that is, in any case, the stimulus and the need for studying drug allergies in the first place. In addition to clinicians, other healthcare professionals, and researchers, the book has been aimed at undergraduate and graduate courses in the biomedical sciences and to serve as a text for students of medicine, pharmacy, nursing, and dentistry.

Finally, as with any subject still beset by many questions, alternative interpretations and different priorities, some analyses, arguments, or conclusions expressed here may not find universal acceptance. In such cases, we remain open and ready to consider all comments in an ongoing effort to improve the book and correct any errors.

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Drug Allergy

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