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Recent Trends in
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Complement Research

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Drug Dosage
The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

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Introduction

Paul Kallós

This volume of ‘Progress in Allergy’ is devoted to recent advances in allergen- and complement-research, subjects of great importance. Ahlstedt and Kristofferson, in their review on the molecular mechanisms of the immune response to penicillin, stress that it is ‘remarkably nontoxic’. Fleming [9] emphasized this property of penicillin in his very first publication in 1929. He stated that the crude culture fluid, containing penicillin, was tolerated by animals ‘even in massive doses’ without adverse effects and did not interfere with the phagocytic activity of granulocytes. Chain et al. [3] succeeded in 1940 in the isolation of penicillin in pure form and after 1944 it was widely used therapeutically. In his ‘Linnacre Lecture’, Fleming [10] stated 1946 that ‘penicillin is the single chemotherapeutic or antibiotic agent which has no toxic properties - in the ordinary sense of word it is almost impossible to give an overdose - so there is no medical reason for underdosage’. This is undoubtedly right. However, already by then 17 reports had been published about adverse effects of penicillin therapy, such as fatal anaphylactic shock, severe asthma and hypotension, serum sickness-like syndrome, skin rashes (urticaria, bullous exanthema, contact dermatitis), agranulocytosis and melanoglossia (black tongue), all ascribed to penicillin allergy [2, 11, 12, 14, 15, 22, 23, 27-31, 33, 35-38]. Since then, penicillin has been regarded as one of the most frequent causes of drug allergy, especially anaphylaxis, in man. Ahlstedt and Kristofferson show that the penicillin molecule possesses reactive moieties which are able to bind to high molecular weight carriers present even in highly purified commercial preparations or released from the pathogenic bacteria under the influence of
There is no proof that immunogenic structures are produced through the binding of penicillin and/or its metabolites to protein carriers of the organism during therapy. Allergic sensitization resulting in immediate or delayed allergic reactivity is possible. The authors survey the factors important for the development of allergic reactivity or tolerance to penicillin and for the evaluation of the immune response of patients treated with the antibiotic. They conclude that IgE-, IgG- and IgM- or cell-mediated allergic reactions due to penicillin or high molecular weight immunogenic impurities and homopolymers in penicillin preparations are probably the most likely explanations of adverse reactions. Another possibility is polyclonal lymphocyte stimulation by the pathogen against which penicillin was given. Antibodies (IgG or IgM) against penicillin determinants, however, were found in the plasma of many individuals who tolerated the administration of penicillin without any adverse reaction. Antibody production in these cases must be regarded as an epiphenomenon, by no means uncommon in connection with drug therapy. The authors stress that it is often difficult to differentiate between pseudo-allergic reactions and those with allergic pathogenesis. This conclusion is in full accordance with the results of Dewdney [6] and with those concerning pseudo-allergic reactions to other drugs and chemicals [7,21]. Ahlstedt and Kristofferson outline some immunochemical and immunobiological pathways for future research in this clinically important field.

Hay fever poses no similar problems, as the allergic, IgE-mediated nature of this disorder has been amply confirmed by the results of direct skin- and passive transfer-tests, RAST, ELISA, histamine release from basophil leucocytes and of specific hyposensitization with pollen extracts. Pollinosis is a model of allergic disorders of the immediate type. The review by Baldo, Sutton and Wrigley, entitled ‘Grass allergens with particular reference to cereals’ shows this to be so since 1873 [1], although this most thoroughly investigated subject is still open to new approaches. The botanical data provided by the authors widen our views and will be helpful in clinical situations, e.g. in cases in which cross-reactivity between grain and pollen plays a role. The authors emphasize that grain and straw dust contain allergenic contaminants, such as products of fungi, mites, insects and rodents, and these are often involved in allergic respiratory diseases. Different methods for identification of individual proteins and allergens of pollen and grain extracts are critically discussed. RAST, RAST-inhibition and the immunoelectrophoretic techniques, reviewed in 1978 in this series by Lowenstein [24] are the most suitable for these purposes. Lowenstein
et al. [25] and Lowenstein and Marsh [26] have recently successfully used quantitative immunoelectrophoretic methods for identification and isolation of antigens of Ambrosia elatior (short ragweed) pollen. They found in a crude extract 52 antigens, which reacted with a high-titer rabbit-antiserum. Thus, there is an enormous heterogeneity. Baldo et al. stress that plant tissues, such as endosperm, bran and straw, contribute to the wide spectrum of antigens found in such allergen extracts. They devised several modifications of RAST and a new membrane-transfer technique which permit allergen identification following fractionation of crude extracts by gelelectrophoresis and gel-isoelectric-focusing. It should be mentioned in this connection that Einarsson and Karlsson [8] showed recently that isotachophoresis is a sensitive and practical method for identification of individual pollen allergens. Baldo et al. have also used allergen-specific monoclonal antibodies, produced by mouse hybridomas, for identification and isolation of pollen- and flour-allergens. It is to be hoped that the results of these investigations will add considerably to the understanding of the molecular basis of allergenicity.

The molecular mechanism of complement activation is the subject of the reviews by Loos and Kazatchkine and Nydegger. Loos highlights the first steps of complement activation via the classical pathway. Kazatchkine and Nydegger treat in depth the complicated molecular interactions leading to complement activation via the alternative pathway. In both reviews the interplay of activated components and regulatory proteins is emphasized. The clinical importance of unimpaired complement function for natural resistance and certain pathological processes is stressed in both reviews. I may perhaps add that clinical interest in complement function increased considerably during the past few years, since it has been shown that therapeutic doses of some drugs, X-ray contrast media (tri-iodinated benzoic compounds) and plasma-volume expanders, such as dextran, and physical influences on plasma, e.g. contact with a hemodialysis membrane, are all able to activate complement either via the classical or the alternative pathway [5, 13, 18, 19, 21, 34]. Complement activation results in the generation of peptides with powerful smooth muscle contracting (spasmogenic) and mast cell stimulating activity. These active peptides, the anaphylatoxins C3a and C5a, are short-lived, their activity under normal conditions being abolished within a few minutes through the regulatory plasma enzyme, carboxypeptidase N, which is able to split off their carboxy-terminal arginine-moiety that is essential for the spasmogenic and mast cell stimulating activity. Despite their transient nature, anaphylatoxins play perhaps a role in the initial phase
of some inflammatory processes [16, 17, 21]. When the amount or activity of carboxypeptidase N is reduced or when the enzyme is absent, anaphylatoxins play a causative role in severe shock syndromes, such as hemorrhagic shock in the course of dengue fever, dextran shock [4, 16] and possibly also pseudo-allergic reactions to certain drugs [20, 21, 32]. Desarginized C5a, lacking spasmogenic and mast cell stimulating activity, retains a powerful granulocyte aggregating and stimulating activity. C5adesArg has been shown to be the causative factor of the shock syndrome observed in patients during hemodialysis [18, 19]. Leucocytes adhere to lung capillaries (leucostasis, leucoemboli) and damage the endothelium through releasing toxic oxygen radicals leading to shock lung. C5adesArg plays possibly a pathogenetic role in several other disease states too [for review: 5, 18, 19, 21] and in some pseudo-allergic reactions to drugs and chemicals [21].

The situation of research reminds me of a saying by Alice in that wise and charming book of Lewis Carroll entitled ‘Through the Looking Glass’. There Alice said to herself ‘I should see the garden far better if I could get to the top of that hill: and here’s a path that leads straight to it - at least, no, it doesn’t do that, but I suppose it will at last. But how curiously it twists! It is more like a cork-screw than a path!’ No path of research is straight and we are never able to see the whole garden, no matter which path we follow, so we continue to climb the hills forever, hoping to be able to pluck on the way some hidden flower. It seems to me that the contributors to the present volume collected a colorful bouquet. I would like to extend the sincerest thanks of the editors to them and to the publisher, Dr. Thomas Karger, for their splendid cooperation.

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