Urticaria and Angioedema

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Preface

Urticaria is one of the most common diseases in dermatology and allergy. Unlike many other diseases, the fleeting nature of the wheals makes first diagnosis by both patients and physicians in many cases easy. However, this only refers to the ordinary wheals. The disease itself is highly complex in nature, with variety of clinical manifestations ranging from pinpoint-sized wheals to extensive angiodema. Complexity is also seen in the diversity of possible eliciting factors, the many different clinical subtypes and the therapeutic responsiveness.

Only in recent years has a better understanding of the diversity in the different subtypes led to new classifications and new evidence-based guidelines for diagnostics and management of the disease. While mast cells are in the center of most urticaria reactions, it is now clearly understood that the responsible mediators are not only limited to histamines.

The current book appears in a series of books by Springer. In 1986, the first monograph was edited by Professor Henz née Chanewsky. Since then, two updates of the book have appeared in the German language with Professor Henz as first editor and T. Zuberbier, J. Grabbe, and E. Monroe as the co-editors of the most recent English version, published in 1998. All these books have been written as a joint effort of Professor Henz together with her team at the Department of Dermatology at the Virchow Clinic, Humboldt University, Berlin.

With the retirement of Professor Henz from her chair as head of the department of dermatology and novel guidelines available, the current group of editors has taken up the task of developing a completely new setup for the book. A group of internationally known authors in the field of urticaria have been asked to write different chapters, focusing on practical guidelines regarding diagnosis and therapy.

This book is designed to be a useful reference for dermatologists, allergologists, pediatricians, and practitioners in general medicine, laying out clear-cut standard operating procedures on how to manage this disease efficiently.

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History of Urticaria

1

M Greaves

Core Messages

- The beginning of the twentieth century ushered in the era of molecular medicine, eventually leading to unravelling of the molecular and immunological basis of urticaria.
- The mast cell and its histamine content remain central to the pathophysiology of the pruritic wheal in most forms of urticaria, and the synthesis, storage, regulation of release of histamine as well as molecular characterisation of its receptors are becoming well understood.
- The challenge of the past 50 years has been to understand the causation of the promiscuous activation of dermal and mucosal mast cells in idiopathic chronic urticaria and angioedema.
- The discovery in the 1980s of autoreactivity in the serum of some patients with chronic urticaria (the autologous serum skin test) was a major step forward and prompted attempts to identify and characterise this activity.
- The subsequent finding in chronic urticaria of specific complement-dependent autoantibodies, which release histamine and other mediators from mast cells and basophils via dimerisation of their high affinity IgE receptors, has stimulated intense interest in the multifactorial modes of activation of mast cells and basophils in this disorder.
- Antihistamines, discovered in the 1940s, remain the cornerstone of treatment of most types of urticaria. Although recent derivative ("second-generation") compounds manifest greatly refined properties, they are often only moderately effective.
- New therapeutic approaches "round the corner" include bradykinin B2 antagonists (for angioedema) and the anti-IgE immunobiologic omalizumab.

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1.1 Introduction

The history of urticaria divides itself conveniently into the early, clinically descriptive, and later pathophysiological eras. Much has been written on the early history of urticaria as a clinical entity, from Hippocrates in the fourth century BC to Heberden and Willan at the end of the eighteenth century AD. For useful accounts of urticaria in early Western writings, the reader is referred to publications by Czarnetzki [1] and Humphreys [2] and the ESHDV Special Annual Lecture entitled "The History of Urticaria and Angioedema" delivered by the late Lennart Juhlin in 2000, a transcript of which is available online. However, in the last hundred years, a dramatic increase in the understanding of the cellular and molecular basis of some common forms of urticaria took place, the foundations for which were laid down by pioneers in the latter years of the nineteenth century and in the early and later twentieth century. This period is the focus of the present account, which attempts to reveal to the reader a historical perspective on "how we got to where we are" today in urticaria.

1.2 The Cellular and Molecular Basis of Urticaria: First Steps

Although the mast cell ("mastzellen") was discovered by Paul Ehrlich in 1877 [3], that it is the principal source and repository of tissue histamine (including the skin) was not appreciated until the seminal work of Riley and West was published in a series of papers in the 1950s. The correlation between histamine levels and mast cell content of skin of several species is well described in several publications summarised by Riley [4]. Histamine was discovered in 1906 by Dale in extracts of ergot [5] and he described all the important actions of histamine except for stimulation of gastric acid secretion. Dale also established the famous "Dale criteria," which should be fulfilled by a mediator deemed to be responsible for a given inflammatory response. Indeed, these criteria are only completely satisfied by histamine in the pruritic wheals of urticaria – hence we have previously designated histamine as the "quintessential mediator" [6].

It was Lewis who first delineated the potency of histamine as a mediator of whealing in human skin [7]. Lewis showed that, in low dosage, histamine could produce central whealing (vasopermeability) redness (vasodilation) and a surrounding bright red axon reflex flare (Lewis's triple response) characteristic of the urticarial wheal. Curiously, in all his intensive studies of actions of histamine in skin, he never once mentions itching! We now know that, in addition to itching (and pain), intracutaneous injection of histamine can also cause alloknesis (perception of itching in response to local nonpruritic stimuli such as fine touch or even temperature change) [8]. These vascular effects are receptor-mediated and involve two subclasses of histamine receptors, H1 and H2, both of which were cloned and sequenced in the early 1990s [9, 10]. Histamine-induced itching is served by H1 receptors. First evidence of the effectiveness of H1 antagonists in the treatment of urticaria emerged in the late 1940s [11, 12]. Recently described and characterised H4 receptors and their

antagonists [13] are currently under scrutiny regarding possible relevance to urticaria and its management. That histamine is released in lesional skin of chronic urticaria has been demonstrated repeatedly in skin tissue fluid, and more recently by skin microdialysis technology [14, 15]. However, histamine, although playing a significant role, is clearly not the only mediator, especially in chronic urticaria and this supposition is supported by kinetic studies [16].

1.3 The Enigma of Chronic "Idiopathic" Urticaria

The problem of how, in urticaria, the dermal mast cell is prompted to relieve itself of its burden of histamine and other mediators has puzzled investigators in the post Second World War era. The discovery and characterisation of the "reaginic" IgE immunoglobulin by Ishizaka [17] enabled elucidation of the relatively uncomplicated acute allergic urticaria, which could be explained by a straightforward immediate (Gell and Coombs type I reaction) [18] between dermal mast cell-bound IgE and specific allergen leading to release of histamine and other mast cell-derived mediators. However, the aetiology and pathogenesis of chronic "idiopathic" urticaria (CIU) remained obscure and even in the twenty-first century there remain numerous unanswered questions. Why do the dermal mast cells degranulate explosively in a seemingly random way with no evident triggering factor?

In the 1960s and 1970s, attempts were made, mainly in Europe, to popularise the role of common food additives, colouring agents and preservatives such as tartrazine, sodium benzoate, and antioxidants as aetiological agents in CIU. Protagonists of this theory included Juhlin, Doeglas and Warner [19–21]. Complex exclusion diets were devised and successes were claimed. Some of these regimes did include challenge tests, but were not adequately controlled and the reproducibility of apparent positive reactions was not investigated. Latterly, this approach has been revived and refined, food additives now being described as "pseudoallergens" [22], further successes being claimed following use of pseudoallergen-free diets in CIU, but this issue, which was reviewed in more detail recently [23], remains controversial.

Foci of infections are always liable to be invoked to explain otherwise inexplicable relapses in any chronic diseases, and chronic urticaria is no exception. The literature contains numerous usually anecdotal accounts of patients with severe chronic and recalcitrant urticaria who made a dramatic recovery following removal of an infected gallbladder/tooth, or treatment of an infected sinus or urinary tract. The 1980s saw the emergence of a new putative microbial culprit – Helicobacter pylori. Because of its ubiquity, especially in European populations, it was frequently found in patients with CIU. When patients with Helicobacter were treated, some got better both from the infection and from the urticaria. Although carefully controlled studies have not substantiated an aetiological relationship between H pylori and urticaria despite its frequency in these patients [24], a more indirect role in the pathogenesis has been proposed [25].

The notion that antibodies may be causative in CIU is an old one. As long ago as 1962, Rorsman, a Swedish dermatologist, reported the striking basopenia in chronic urticaria and

remarked on its absence in physical urticarias. He also pointed out that "In cases where the basopenia is marked it appears probable that antigen–antibody reactions … bring about degranulation of basophil leukocytes" [26]. Over 20 years later [27], we noted the impaired histamine release evoked by anti-IgE in basophils from patients with CIU. In 1988, Gruber et al. found that more than 50% of patients with cold urticaria, CIU and urticarial vasculitis had IgG autoantibodies directed against IgE [28]. There was also indirect evidence arising from the strong association between autoimmune thyroid disease and CIU [29]. The HLA class 11 DRB1*04 alleles were increased in frequency in CIU consistent with a possible role for autoimmunity in CIU [30]. However, at this juncture there was no convincing evidence that any autoantibodies found in CIU were anything more than passive bystanders in the pathogenesis of this disorder.

Against this background, an important observation was made in 1986 by Grattan [31]. He demonstrated that the serum of some but not all patients with CIU would cause whealing when reinjected intracutaneously in an autologous fashion into the same patient's clinically uninvolved skin. This finding greatly encouraged attempts to identify circulating vasoactive factors in the blood of CIU patients [32, 33]. As had previously been suspected by earlier writers [26, 28], the culprit turned out to be a functional, histamine-releasing autoantibody – at least in some patients. Hide et al. in 1993 and subsequently Fiebiger et al. and Tong et al. found that in 30–50% of patients with CIU, a circulating histamine-releasing factor with the characteristics of an IgG anti-FcεR1 autoantibody was demonstrable in serum [34–37]. Indirect evidence as well as successful passive transfer [38] supported the view that these autoantibodies are the cause of the whealing in those patients that have them. Although "autoimmune urticaria" has yet to justify, in a strict sense, its designation as an autoimmune disease (there is no animal model), these advances have for the first time put the investigation and treatment of chronic urticaria on a sound scientific basis. Lack of a convenient specific and sensitive screening test for autoimmune urticaria remains the main drawback to further progress.

1.4 Treatment of Urticaria: Antihistamines

Fortunately, most patients with chronic urticaria, whatever the cause, can be effectively managed by H1 antihistamines. These were first characterised by Bovet and Staub [39], a discovery which was, in part, responsible for conferment of the Nobel Prize on Bovet in 1957. Their use in treatment of chronic urticaria was explored intensively after the end of the First World War [11, 12]. O'Leary and Farber, referring in 1947 to diphenhydramine [11] stated that it is effective in chronic urticaria and also pointed out that it "is not a potent antipruritic drug" – a view that present-day clinicians will echo in respect of its present-day successors. These early "first-generation" antihistamines, though carrying a baggage of annoying rather than serious side effects, are still very much in use today by urticaria sufferers. Although initially believed to be competitive antagonists of histamine at the H1 receptor, all currently available H1 antihistamines are now considered to behave

as inverse agonists – that is, they downregulate and stabilise the constitutively activated state of the H1 receptor [40]. H2 histamine receptors are also expressed by human skin blood vessels [41] and the possibility was entertained that combination of H2 receptor antagonists (e.g. cimetidine) with first-generation H1 antihistamines would have a "sparing" effect on the latter, thus mitigating the unwanted effects of H1 antihistamines. Although some benefits were established for use of this combination [42], they were small and in any case their use was largely superseded by the advent of second-generation antihistamines.

Second-generation H1 antihistamines, as defined by Simons [43], are essentially H1 antihistamines with low or non-sedating properties at therapeutic dosages. Many of these are active metabolites or enantiomers of first-generation compounds. Their usage over the past 15 years in chronic urticaria, especially as daytime treatment, has greatly improved the quality of life of otherwise severely handicapped sufferers [44–47]. However, they are less effective in relieving wheeling than itching in urticaria and sedative first-generation antihistamines still have a place in the management of nocturnal pruritus in urticaria sufferers. Combination of montelukast, a leucotriene inhibitor, with an H1 antihistamine has been advocated, but results have been variable [48]. The cloning and sequencing of the H1 receptor in 1991 [9, 49] has laid the foundation for emergence of a truly new "third generation" of anthistamines for clinicians and patients alike to look forward to.

Future developments in the diagnosis and management of urticaria have also been greatly encouraged by the recent establishment of European Guidelines for definition, classification, diagnosis and management of urticaria [50, 51]. These should also give much needed help to clinicians faced with investigation and treatment of urticaria.

1.5 Take Home Pearls

- The autologous serum skin test established that in patients with chronic "idiopathic" urticaria, the causation was endogenous rather than due to external factors such as food allergy or pseudoallergy, and "focal infection."
- In some patients, this endogenous activity turned out to be attributable to specific autoantibodies (autoimmune urticaria), which promiscuously activate dermal mast cells and basophils and this has led to advent of immunotherapy (e.g. cyclosporine) in selected patients.
- The "cause" of chronic urticaria is, however, multifactorial and other factors such as dysregulation of intracellular signal transduction in dermal mast cells and basophils are likely to be important in other patients.
- However, H1 antihistamines remain the mainstay of treatment and recent refinements have greatly improved the effectiveness and tolerability of these compounds.
- As knowledge of the pathomechanisms of urticaria advances, novel treatments are appearing, including the anti-IgE monoclonal omalizumab and anti-cytokines such as anti-TNF-α.

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Aetiopathogenesis of Urticaria

2

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Core Messages

- Urticaria is a disease with diverse clinical presentations and aetiologies
- The cutaneous mast cell is the primary effector cell in most patterns of urticaria
- Histamine is the most important preformed mediator in mast cells. It mediates itch, weal and flare
- Leukotrienes may also be important in pseudoallergic reactions
- Bradykinin is responsible for angio-oedema in patients with C1 esterase inhibitor deficiency and in patients on angiotensin converting enzyme inhibitors
- Mast cell degranulation may be due to immunological stimuli activating the high affinity IgE receptor (FcεRI) or non-immunological stimuli, such as opiates
- Activation of FcεRI may be through allergen cross-linking of specific IgE bound to the receptor (Type I hypersensitivity) or IgE autoantibodies binding the receptor directly or IgE itself
- Type I reactions may be the cause of acute urticaria but not chronic disease. Functional autoantibodies can be demonstrated in about 50% of patients with ordinary spontaneous chronic urticaria
- The role for inflammatory cells in urticarial lesions needs further investigation

Urticaria is defined clinically by swellings of the integument that resolve completely within hours or days. Superficial skin swellings, known as weals, usually begin as sharply defined pale plaques of variable size with a surrounding red flare. They nearly always itch intensely before changing from pale to pink, spreading outwards and becoming more diffuse before fading. The deeper swellings of angio-oedema are predominantly located in the loose connective tissue below the skin and the mucosa. They tend to be pale and painful and last longer than weals. Within this basic clinical definition of urticaria exists a wide spectrum of presentations that can usually be grouped into patterns on the strength of

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