

ANGIO-OEDEMA

AP Kaplan, MD

National Allergy Asthma and Urticaria Centers of Charleston, Charleston, South Carolina, United States of America

MW Greaves, MD, PhD, FACP

National Skin Centre, Singapore, Singapore

ABSTRACT

Angio-oedema can occur in association with urticaria (acute or chronic) or can occur as swelling in the absence of hives. Causes that it shares with urticaria include food and drug allergies, anaphylaxis of any cause, insect stings, and reactions to radiocontrast agents or NSAIDs. Allergic causes of angio-oedema are IgE-mediated with mast-cell degranulation in the deep dermis and subcutaneous tissues so that swelling is the major manifestation. Chronic urticaria, whether autoimmune or idiopathic, is accompanied by angio-oedema in 40% of patients, with IgG anti Fc ϵ R1 α or IgG anti-IgE being pathogenic in the autoimmune subgroup.

Angio-oedema in the absence of urticaria can be caused by ACE inhibitors or C1 inhibitor deficiency with bradykinin as the key permeability factor. ACE inhibitors cause bradykinin accumulation because degradation is impaired, while bradykinin production is markedly enhanced by C1 inhibitor deficiency. C1 INH deficiency can be hereditary (autosomal dominant); type I is associated with decreased plasma protein levels while type II has normal plasma levels but protein function is markedly decreased. An acquired form of C1 INH deficiency can be due to lymphoma or connective tissue disease with C1 INH consumption (type I), or acquired C1 INH deficiency can be an autoimmune disorder with IgG anti-C1 INH (type II). A depressed C1Q level is seen with both. Idiopathic angio-oedema is defined as recurrent swelling in the absence of urticaria, with no apparent cause, and can be divided into a histaminergic group (i.e. responsive to antihistamines) and a relatively refractory, non-histaminergic group. Antihistamines can effectively treat most forms of angio-oedema and 1-3 days of high-dose corticosteroid can be used for acute episodes. An EpiPen can avert respiratory compromise; however intubation may be required particularly when stridor is present. Drugs used as prophylaxis for C1 INH deficiency are androgens (danazol, stanozolol, oxymethalone) or antifibrinolytic agents (tranexamic acid, *e*-amino caproic acid); acute episodes can be treated with fresh frozen plasma. Non-sedating antihistamines at double or triple the usual dose can be effective prophylaxis for frequent angio-oedema that is relatively mild. Treatment of idiopathic angio-oedema, when frequent and severe, requires high doses of first-generation antihistamines such as diphenhydramine at 50 mg q.i.d. and an H $_2$ receptor antagonist. Approaches to try in the non-histaminergic group include leukotriene synthesis inhibitors, tranexamic acid, low-dose corticosteroid and cyclosporine.

The term angio-oedema was originally used by Quinke in 1882 to describe swelling which we now know can affect the face, lips, tongue, pharynx, larynx, extremities and genitalia. The swelling lasts 1-3 days (typically) and is due to fluid leakage from small venules in the deep dermis and/or subcutaneous tissue. It can occur concomitantly with urticarial lesions or angio-oedema can be present in the absence of any hives. When present together, the cause (if known) is usually the same, as is the pathogenic mechanism, and the difference lies in the layer of the skin affected; urticaria is more superficial and involves the venular plexus in the superficial dermis. It is therefore useful to divide angio-oedema into these two broad categories, i.e. occurring with urticaria or in the absence of urticaria. In the latter group are two disorders mediated by bradykinin; namely, angio-oedema due to angiotension-converting enzyme inhibitors (ACE inhibitors) and C1 inhibitor deficiency (hereditary and acquired), while idiopathic angio-oedema is defined as recurrent episodes of swelling in the absence of urticaria when the cause is obscure. An extensive review of the pathogenesis and therapy of angio-oedema has been published recently.¹

ANGIO-OEDEMA WITH URTICARIA

Acute urticaria is frequently accompanied by angio-oedema. Some of the common causes are: food and drug reactions, insect stings, infection (particularly in children), anaphylaxis of any cause, and anaphylactoid reactions (e.g. radio-contrast agents, reactions to NSAIDs).

Angio-oedema is associated with chronic urticaria in about 40% of cases although the severity of the urticaria and prominence of angio-oedema is greater in the autoimmune subgroup (40-45%) when compared with the idiopathic subgroup (55-60%). The angio-oedema affects the lips and peri-orbital area, most commonly, but may also affect the tongue, pharynx, hands, feet and genitalia. Angio-oedema rarely, if ever, affects the larynx, and respiratory distress as a result of the angio-oedema is not a realistic concern. With pharyngeal oedema, one should expect indistinct speech, difficulty swallowing, a lump-in-the-throat feeling, but not stridor. Huge tongue swelling and/or pharyngeal swelling with inability to handle secretions with a risk of aspiration is more likely to occur with angio-oedema that is not associated with urticaria, such as that seen with ACE-inhibitor reactions or C1 inhibitor deficiency.

Angio-oedema can be due to 'physical' causes, some of which are typically considered to be urticarial reactions.^{2,3} Angio-oedema can accompany urticaria in entities such as cold urticaria, for example, submersion of one hand in cold water can cause the entire hand to swell in contrast to a hive that is seen when an ice-cube test is done. If a patient with cholinergic urticaria continues to exercise in spite of increasing urticaria, hives can become confluent and facial swelling may be seen. In vibratory angio-oedema, swelling is far more commonly seen than urticaria and in this instance vibration (e.g. rubbing a towel back and forth across the back) causes itch and swelling.

Contact urticaria, such as exposure to latex, can cause swelling as well.

Correspondence: Dr AP Kaplan, National Allergy Asthma and Urticaria Centers of Charleston, Charleston, SC 29401, USA. Tel: +? 843-573-9373, fax + 843-573-9970, e-mail kaplana@musc.edu

Chronic autoimmune urticaria and angio-oedema

Urticaria and/or angio-oedema caused by allergen exposure is associated with degranulation of cutaneous mast cells and development of a cutaneous late-phase reaction. Nevertheless, when the process is chronic (defined as hives daily or close to daily for at least 6 weeks), the incidence of finding an exogenous allergen as cause is not greater than 1%. Our current understanding of this disorder includes the following observations:

1. There is a 25% incidence of antithyroid antibodies, either antimicrosomal antibody or antithyroglobulin antibody, or both.^{4,5}
2. 35-40% of patients demonstrate the presence of IgG anti-IgE receptor (high affinity) which is directed to the α subunit (IgE anti-Fc ϵ R1 α),^{6,7} while an additional 5-10% have functional IgG anti-IgE.^{8,9} This may be detected by the autologous skin test,^{6,10,11} by histamine release upon incubation of patient's serum with basophils^{7,12,13} or by basophil expression of activation markers such as CD63 assessed by flow cytometry.¹⁴
3. Augmentation of basophil (and presumably cutaneous mast cell) histamine release by activation of the classic complement pathway and release of C5a, an anaphylatoxin and chemotactic factor for neutrophils, eosinophils, and monocytes.¹⁵⁻¹⁷
4. Development of a non-necrotising perivascular infiltrate¹⁸⁻²⁰ consisting of neutrophils, eosinophils, monocytes, lymphocytes (exclusively T-lymphocytes most of which are CD4+ consisting of both T-helper 1 (Th1) and Th2 subtypes)²¹ and small numbers of basophils. This resembles the allergic late-phase response;²² however there is a greater percentage of neutrophils and monocytes,^{19,20} and the predominance of Th2 lymphocytes is not seen. Eosinophil presence can vary from relatively small numbers with clear mononuclear cell predominance to prominent eosinophilic infiltration. Yet major basic protein (MBP) may be seen even when eosinophils are not clearly identifiable, indicating eosinophil degranulation.²³

One recent publication presented evidence for the presence of antibody to the low-affinity IgE receptor and the authors propose a mechanism of direct eosinophil degranulation with mast-cell activation as a consequence of the release of eosinophil granular proteins (MBP, ECP, etc.).²⁴ This has not yet been confirmed nor has its presence been examined in patients with or without antibody to the high-affinity IgE receptor.

Chronic idiopathic urticaria and angio-oedema

By definition, this group has no autoimmune mechanism that we know of, and there are few studies that shed any light as to the cause of cutaneous mast-cell degranulation. Years ago the basophils of chronic urticaria patients were shown to be hyporesponsive to anti-IgE.²⁵ Although assumed to be in vivo desensitisation by circulating antireceptor antibody,²⁶ and to be associated with basopenia,²⁷ basophils of patients with chronic idiopathic urticaria were shown to share this abnormality.²⁸ Furthermore basophils derived from all chronic urticaria patients (both autoimmune and idiopathic) were found to be hyperresponsive to factors in serum.²⁸ An abnormality of signal transduction is suggested and at least one study described a defect in Ras-dependent signalling in chronic urticaria.²⁹ Most recently, a 95% incidence of a positive autologous skin

test has been found if autologous citrated plasma is employed³⁰ rather than serum, suggesting the presence of a permeability factor or mast-cell-activating factor even in 'idiopathic' patients, unless these observations reflect enhanced mast-cell responsiveness.³¹

ANGIO-OEDEMA IN THE ABSENCE OF URTICARIA

These disorders account for most patients: namely, angio-oedema due to ACE inhibitors, C1 inhibitor deficiency, and idiopathic angio-oedema.

ACE-inhibitor-induced angio-oedema

This is now the most common cause of angio-oedema seen in an emergency room setting, although cough is the more common side-effect. Angio-oedema can occur at any time, long after drug therapy was initiated; however it typically occurs within the first few weeks of treatment. The overall incidence is between 0.1% and 0.7%. Like C1 inhibitor deficiency, swelling can be very severe and has a predilection for the face. Swelling of lips, eyes, and tongue may be seen, and tongue swelling can be so extreme that secretions cannot be handled and the airway is obstructed. Pharyngeal oedema and/or laryngeal oedema can occur as well; the latter can cause stridor and asphyxiation (Fig. 1). Treatment is supportive therapy at whatever level indicated and stopping the drug immediately. Inhibitors of angiotension II can be a good alternative since they share with ACE inhibitors some of the prophylactic effects on cardiovascular disease and diabetes.



Fig. 1. Obstructing angio-oedema of the face, tongue, and pharynx in a patient taking an ACE inhibitor. This patient required intubation in the emergency room.

The cause of swelling is an accumulation of bradykinin.³² As shown in Fig. 2, bradykinin is cleaved in the circulation by kininase I (carboxypeptidase N) to des-Arg⁹-bradykinin by removal of the C-terminal Arg residue. Kininase II, which is synonymous with ACE, is also present in the circulation but in lower amounts. However most bradykinin is degraded with one or two circulations through the lungs and here ACE is the main inhibitor and is expressed at the surface of pulmonary vascular endothelial cells. ACE removes the dipeptide Phe-Arg and converts bradykinin to an inactive heptapeptide and a second cleavage removes Ser Pro so that a pentapeptide is the final product. When an ACE inhibitor is consumed, degradation of bradykinin is limited and blood and tissue levels will rise. It is not clear why only some patients manifest in this fashion;

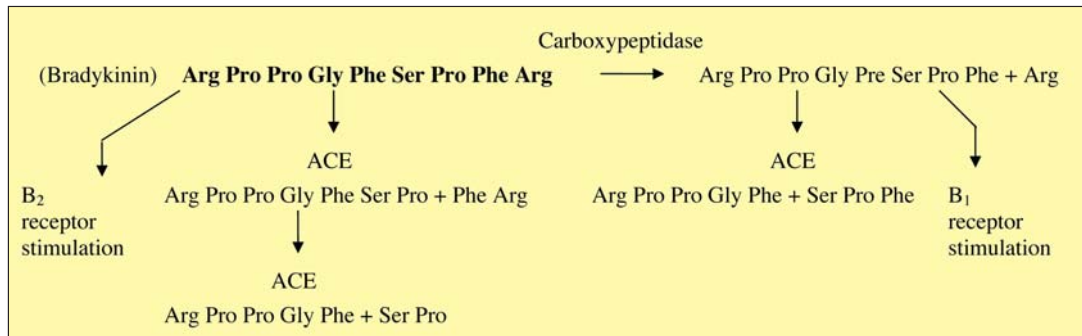


Fig. 2. Degradation of bradykinin by kininase I (plasma carboxypeptidase N) and kininase II (angiotensin-converting enzyme). Bradykinin can be generated either by the tissue kallikrein pathway (left) or the plasma/intrinsic coagulation pathway (right). Reproduced with permission from Kaplan and Greaves.¹

among the considerations are polymorphisms that might predispose to swelling involving ACE or other enzymes involved in bradykinin degradation (carboxypeptidase N, aminopeptidase M, neutral endopeptidase) or genetic variation in responsiveness to bradykinin via B₂ receptors (constitutively present) or even B₁ receptors (induced by inflammation and responsive primarily to des-Arg⁹-bradykinin). It is of interest that des-Arg⁹-bradykinin, the product of carboxypeptidase N digestion is not completely inactive but that removal of C-terminal Arg switches from binding to B₂ receptors to interaction with B₁ receptors, and that ACE can then act as a tripeptidase to degrade des-Arg⁹-bradykinin (8 amino acids) to the inactive pentapeptide.

C1 inhibitor deficiency (hereditary angio-oedema and 'acquired' syndromes)

C1 inhibitor deficiency presents as a genetic disorder with either decreased synthesis or production of an inactive protein or as an acquired deficiency syndrome caused by consumption of the protein. When functional blood levels are less than 25-30% of normal, angio-oedema is likely to occur. Hives are not present although episodes of swelling can be preceded by a subtle rash that resembles erythema marginatum. Swelling can affect virtually any part of the body including the larynx or gastrointestinal tract. Vocal cord oedema and swelling of the surrounding laryngeal tissues can cause asphyxiation and oedema of the bowel wall can cause severe cramps, nausea, vomiting, or diarrhoea. Attacks typically last 3 days.

Hereditary angio-oedema (HAE) has been reported in all races and there is no sex bias. The C1 INH gene has been mapped to chromosome 11 (11q12-q13-1). The disorder has been divided into types I and II, based on the particular mutation involved. Type I is present in 85% of patients and is associated with marked reduction in C1 inhibitor protein and a proportional decrease in function. Gene defects often seen include large deletions, insertions, stop codons, or frame-shift mutations.³³ Type II disease is more likely to have a point mutation (single amino acid substitution) with synthesis of a normal amount of C1 INH but with little or no function associated with the mutant gene protein. Since both types I and II disease have autosomal dominant inheritance, and the mutated gene product is either absent (type I) or functionless (type II), one would expect a C1 INH level of 50% which is usually sufficient to prevent episodes of angio-oedema. However there is also repression of synthesis of the normal gene product^{34,35} as well as accelerated consumption of the synthesised C1 INH (as a result of

binding to enzymes); thus the levels drop to between 5% and 40%. The C1 INH is the primary inhibitor of activated factor XII (factor XIIa), factor XII fragment (factor XII_f), kallikrein, as well as activated C1 (C1). Thus, with low C1 INH there is absence of the normal inhibition of the plasma bradykinin-forming cascade and markedly increased levels can result once activation is initiated. Although episodes of swelling occur seemingly spontaneously, they are certainly induced by trauma or infection; in women administration of oestrogen (which augments factor XII levels) is also detrimental. Additional precipitating factors can include vigorous exercise, alcohol consumption, and possibly emotional stress. The diagnosis is suspect if the C4 level is low (accurate about 90-95% of the time but in 5-10% it can be normal) because C4 is consumed even in the absence of swelling (implying continual activation of C1) and synthesis usually does not replenish it sufficiently.³⁶ During attacks of swelling C4 approaches zero, and C2 levels will decrease. Although C1 may autoactivate in the absence of C1 INH, there is a marked increase in enzymatic activation of C1_r and, to a lesser degree C1_s by factor XII_f (Fig. 3) with consumption of C4 and then C2.^{37,38} The possibility of a C2-derived kinin-like activity as mediator of the disease has been disproven,³⁹ and the major mediator of swelling is bradykinin.⁴⁰⁻⁴² As shown in Fig. 2, traces of any factor XIIa present leads to factor XII autoactivation, factor XIIa converts prekallikrein to kallikrein, and kallikrein digests high-molecular-weight kininogen to generate bradykinin.⁴³ There is also feedback activation of factor XII by kallikrein which is 50-fold faster than the factor XII autoactivation rate.⁴⁴ Kallikrein can initiate the fibrinolytic cascade by converting plasma prourokinase to urokinase (which is a potent plasminogen activator) and kallikrein can slowly digest plasminogen to directly convert it to plasmin. Fibrinolysis may be operative in this process because it can also convert factor XIIa to factor XII_f⁴⁵ and plasmin can also cleave C1 INH to inactivate it. Virtually all of these steps are inhibitable by C1 INH (Fig. 2).

Acquired C1 inhibitor deficiency

The acquired form of C1 INH deficiency disease has been described in patients with lymphoma who have circulating low-molecular-weight IgM and depressed C1 inhibitor levels. This entity has an unusual complement utilisation profile because C1q levels are low, which differentiates this condition from the hereditary disorder.⁴⁶⁻⁴⁸ The depressed C1 inhibitor level may be caused by depletion secondary to C1 activation by circulating immune complexes or C1 interaction with a tumour-cell surface antigen. For B-cell lymphoma, the

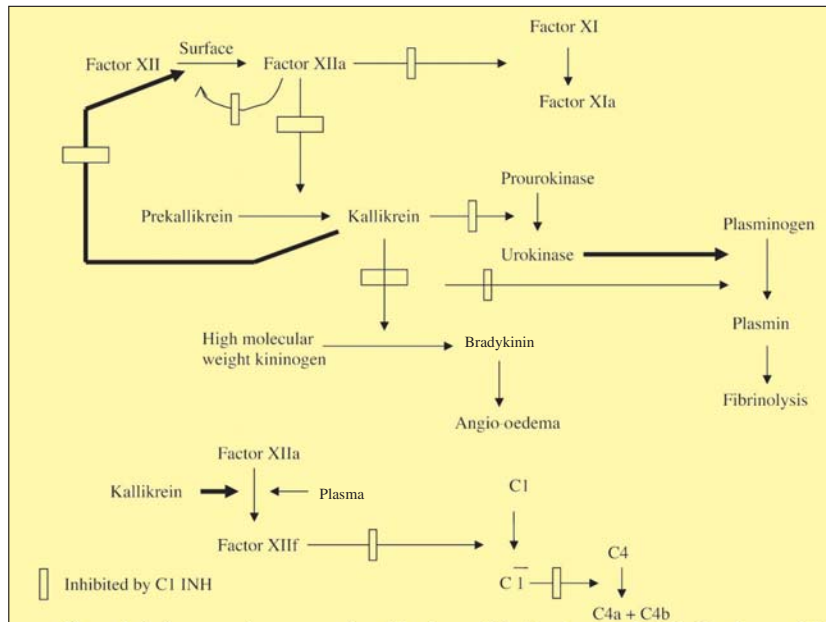


Fig. 3. Pathway for activation of the plasma bradykinin-forming pathway indicating the steps inhibitable by C1 inhibitor. HF (Hageman factor) is identical to coagulation factor XII. HFa = factor XIIa = activated Hageman factor HFf = factor XIIf = Hageman factor fragment. HFf is a major link of the kinin-forming pathway with complement. Reproduced with permission from Kaplan and Greaves.¹

most common associated malignancy, C1 fixation and C1 inhibitor depletion are caused by an anti-idiotypic antibody bound to immunoglobulin on the surface of the B-cell.⁴⁹

Patients with connective tissue disorders such as systemic lupus erythematosus or carcinoma^{50,51} can present with acquired C1 inhibitor deficiency, and like patients with the hereditary form, will respond to androgen therapy, which enhances C1 inhibitor synthesis. A second form of C1 inhibitor deficiency results from the synthesis of an autoantibody directed to C1 inhibitor itself.⁵²⁻⁵⁴ These patients also have low levels of C4, C1q, and C1 inhibitor protein and function, and no family history. This form of acquired C1 inhibitor deficiency appears to be increasingly recognised. Under normal circumstances, C1 inhibitor is a substrate for the enzymes it inactivates: the active enzyme cleaves C1 inhibitor, which exposes the active site in the inhibitor. The cleaved C1 inhibitor then binds stoichiometrically to the enzyme and inactivates it. When antibody to C1 inhibitor is present, the C1 inhibitor is cleaved and it is unable to inactivate the enzyme.⁵⁵⁻⁵⁷ Thus cleaved, functionless C1 inhibitor circulates and unopposed activation of the complement and kinin-forming cascade takes place. One circumstance in which the two forms of acquired C1 inhibitor deficiency merge is in an occasional patient with monoclonal gammopathy, in which the monoclonal immunoglobulin is in fact an antibody to C1 inhibitor.^{58,59}

The immune-complex-mediated depletion of C1 inhibitor and the autoantibody directed to C1 inhibitor represent types I and II acquired C1 inhibitor deficiency, respectively. The type II variety can be most readily determined by immunoblot with antibody to C1 inhibitor. The presence of a

C1 inhibitor cleavage product at 95 Kd differentiates the two forms of the acquired disorder, and it is not present in the hereditary disorder.

Table I is a summary of the laboratory tests that may be used to identify the different forms of C1 inhibitor deficiency. If there is a family history, one needs to differentiate the two types of HAE. Because the C4 level will be diminished in both, the distinction is usually made by comparing C1 inhibitor protein level and C1 inhibitor function. Both protein and function will be low in parallel in type I HAE, whereas the protein level will be normal or elevated in the type II form of this disorder with functional C1 inhibitor diminished. A low C1q level is seen in acquired C1 INH deficiency and a 95 Kd cleaved C1 inhibitor protein is seen in type II

disease. The absence of an acquired C1 INH abnormality or of any family history of swelling in patients with low C4 and abnormally low functional C1 inhibitor would define a patient with a probable new mutation. Such patients need to be evaluated carefully over time because there have been reports of angio-oedema of this sort preceding the diagnosis of the underlying disorder.

HAE with normal C1 INH activity in females (HAE type III)

In 2000 Bork *et al.*⁶⁰ reported 36 women from 10 families with HAE but with normal quantitative and functional C1 INH and C4 levels. The clinical picture including mucocutaneous swellings, respiratory obstruction and abdominal symptoms did not differ significantly from types I and II HAE. There was no urticaria and C1 inhibitor concentrate therapy was ineffective. Provoking factors included oestrogens and pregnancy. These and other authors propose an X-linked inheritance for this new entity.⁶¹

Idiopathic angio-oedema

This relatively common disorder is characterised by recurrent episodes of swelling in the absence of urticaria, without exogenous precipitant, and a normal C4 level and C1 INH protein and function. Episodes typ-

Table I. Assays for C1 inhibitor deficiency

	C1 INH protein	C1 function	C4	C1Q	95kD C1 INH
Hereditary type I	↓	↓	↓	N	No
Hereditary type II	N or ↑	↓	↓	N	No
Acquired type I	↓	↓	↓	↓	No
Acquired type II	↓	↓	↓	↓	Yes

ically affect lips, cheeks, eyes, tongue, pharynx, extremities and genitalia but laryngeal oedema is not seen. The presence of documented laryngeal oedema in the absence of HAE, acquired C1 INH deficiency, or an ACE inhibitor would suggest a diagnosis of idiopathic anaphylaxis. Although assumed to have the same pathogenesis of mechanisms as has been described for 'chronic urticaria and angio-oedema'; namely, division into idiopathic and autoimmune subgroups, there are three reasons why this may not be so. Firstly, some series (reported anecdotally, including these authors) have a male to female ratio of 60:40 whereas two-thirds of patients with chronic urticaria are female. Secondly, the incidence of antithyroid antibodies is less, and thirdly, the incidence of antibody to the IgE receptor is considerably less.

Idiopathic angio-oedema has also been divided into subtypes based on response to therapy:⁶² namely, a subgroup responsive to antihistaminics and a subgroup resistant to antihistaminics; a role for leukotrienes or bradykinin in these subgroups has been considered but not proven. However response of some of them to tranexamic acid (used to treat C1 INH deficiency in Europe) suggests a possible role for fibrinolysis and/or bradykinin.

THERAPY

Treatment of acute angio-oedema¹

If the respiratory tract is involved the first priority must be to secure the airway, which may require intubation or rarely a tracheostomy, and to administer oxygen. An intravenous line should be established. For these and other patients subcutaneous or intramuscular adrenaline may help reduce the oedema and should be given in dosage 0.3 mg repeated every 10 minutes (0.3 ml of 1:1 000 dilution). Diphenhydramine 50 mg administered intramuscularly or intravenously is helpful and hydrocortisone 200 mg or methylprednisolone 40 mg given intravenously may reduce the possibility of relapse. Patients with severe angio-oedema should be admitted for at least 24 hours' observation particularly where laryngeal oedema has occurred. Patients in whom a cause for the angio-oedema is proven or strongly suspected should be advised to wear a Medic Alert bracelet inscribed with this information.

Treatment of NSAID-induced angio-oedema

Emergency measures are as for acute allergic angio-oedema. Patients should be warned to avoid these drugs as a class. Intradermal injection of cysteinyl leukotrienes causes increased inflammatory responses in patients with chronic urticaria and leukotriene antagonists or lipoxygenase inhibitors might be assumed on theoretical grounds to be helpful in patients with NSAID-induced angio-oedema. Use of leukotriene antagonists to prevent exacerbations due to NSAIDs has been advocated but recent work sheds doubt on their efficacy. Furthermore, administration of leukotriene antagonists concurrently with aspirin has been reported to provoke anaphylaxis with urticaria and angio-oedema.⁶³ Patients with NSAID-induced angio-oedema can safely be given COX-2 inhibitors,^{64,65} but further data from controlled studies are required before unreservedly advising this measure.

Treatment of angio-oedema as a result of ACE-inhibitor therapy

Emergency treatment should take into account the risk of relapse after apparent recovery from the initial

episode, despite withdrawal of the offending drug.^{66,67} Therefore patients should be admitted for observation at least overnight. The severity of angio-oedema has occasionally necessitated admission to an intensive care department.⁶⁷ Other emergency procedures and drug administration are essentially as for treatment of acute allergic angio-oedema. Another ACE inhibitor should not subsequently be prescribed as the reaction is class- and not drug-specific, and the patient should be advised to wear a Medic Alert bracelet. It is also advisable to check the complement C4 level as patients with pre-existing angio-oedema, including HAE due to C1 esterase inhibitor deficiency, are predisposed to develop angio-oedema in response to ACE inhibitors.⁶⁸ In general, angiotensin II receptor antagonists are tolerated by patients who have reacted to ACE inhibitors.⁶⁹

Treatment of angio-oedema associated with chronic urticaria

Routine treatment for autoimmune and non-autoimmune chronic angio-oedema with or without urticaria is the same. Patients should be advised to avoid provoking factors (aspirin, overtiredness, overexcitement, over-vigorous exercise, excessive alcohol consumption).

Low-sedation antihistamines (loratadine 10 mg, cetirizine 10 mg, fexofenadine 180 mg, desloratadine 5 mg) are best prescribed for relief during the daytime and any of these can be employed in double or triple the usual dosage for treatment of resistant disease in severely affected patients. These newer compounds do not cause impairment of cognitive function, even in double or triple the dosage employed for allergic rhinitis. However sedative antihistamines such as hydroxyzine 10-50 mg can be added at night and patients refractory to non-sedating agents may respond to hydroxyzine, diphenhydramine, or doxepin in high dosage.⁷⁰ Diphenhydramine at 50 mg q.i.d. can be employed effectively to prevent frequent and/or severe episodes⁷ for patients with idiopathic angio-oedema (no urticaria) or for chronic urticaria (idiopathic or autoimmune) in association with angio-oedema.

Patients with autoimmune urticaria and angio-oedema are frequently treatment-resistant. After trying off-label dosage of fexofenadine or unsatisfactory control with sedating antihistaminics, patients can be offered cyclosporin⁷¹ or methotrexate⁷² to be taken concurrently with antihistamines. Cyclosporin, in dosage 2.5-4 mg/kg/day is given for up to 3 months in the first instance. Renal function (BUN, creatinine, urinalysis), lipid and cholesterol profile, and blood pressure need to be carefully monitored. Data⁷¹ from a controlled randomised study show that 80% of patients respond either completely or almost completely, and after withdrawing the treatment about two-thirds of cases either remain in remission or can be successfully controlled by routine antihistamines. The remainder may require a further course of cyclosporin or a trial of methotrexate.⁷² Additional immunomodulatory treatments that can be used include intravenous immunoglobulin infusions⁷³ and plasmapheresis.⁷⁴ Cyclosporin can also be effective for patients with chronic urticaria and angio-oedema who are in the idiopathic group without evidence of autoimmunity. Corticosteroid use on a daily basis is to be deplored for patients with any type or combination of urticaria/angio-oedema unless the dose is 10 mg/day or less. Every-other-day corticosteroid (20-25 mg q.o.d.) with a gradual tapering of 2.5-5.0 mg over 2-3 weeks is an effective alternative to use of cyclosporin, and one option can be employed when the other is ineffective or relatively contraindicated.

Addition of an H₂ antagonist adds protection of gastric hyperactivity with perhaps some minimal effect on any concomitant urticaria. Acute treatment for idiopathic angio-oedema or severe angio-oedema associated with chronic urticaria can employ 40-60 mg prednisone with a repeat for 1-2 days more if needed, and then discontinue without any taper.

Treatment of HAE

For acute emergency episodes antihistamines and corticosteroids are ineffective although subcutaneous adrenaline 0.3 mg every 10 minutes may be helpful. If the patient has serious respiratory obstruction intubation or tracheostomy should be carried out and may be life-saving. However most acute episodes are non-life-threatening and the mainstay of emergency medical treatment is intravenous fresh frozen plasma or C1 inhibitor concentrate.⁷⁵ The recent availability of lyophilised vapour-heated C1 inhibitor concentrate⁷⁶ has largely removed concerns about transmission of HIV, viral hepatitis and other infections. In this study the product used (Immuno; Aventis Behring, Vienna, Austria) after reconstitution with saline contained 550 plasma units in a 10 ml vial and was administered at a dose of 25 plasma units per kg body weight to a total of 1 000 plasma units repeated once if necessary. It is usually effective in diminishing swelling within 3-4 hours, and often within minutes.

Androgens were first demonstrated to be effective for prevention of episodes of HAE by Spaulding in 1960⁷⁷ and antifibrinolytic agents^{78,79} have also been used. These are now superseded by oral attenuated 17 α -alkylated androgens including danazol and stanozolol.⁸⁰⁻⁸² These anabolic steroids increase the circulating levels of normal functional C1 INH in both type I and type II HAE. Since they are known rarely to cause hepatotoxicity and liver tumours,⁸³ danazol and stanozolol should be prescribed in the lowest effective dosage⁸⁴ (stanozolol 2-4 mg/day; danazol 50-300 mg/day). There is no need to bring about complete normalisation of C4 and C1 INH levels.⁸⁵ Other reversible side-effects in women include deepening of voice, menstrual irregularities, acne and hirsutism. For patients in whom attacks are infrequent and not life-threatening, it may be sufficient to restrict treatment to avoidance of known provoking factors including oestrogens and ACE inhibitors together with administration of C1 inhibitor concentrate or fresh frozen plasma prophylactically before dental treatment or other minor surgical procedures.

Treatment of acquired C1 inhibitor deficiency

Treatment of the underlying disease, if one has been identified, is essential plus treatment with the aforementioned drugs, essentially the same treatment as for the hereditary disorder. Treatment of type II acquired C1 inhibitor deficiency with an autoantibody directed to C1 inhibitor is indeed more difficult because the ability to replenish C1 inhibitor is significantly compromised. Plasmapheresis and use of a cytotoxic agent in addition to the use of prophylactic androgenic compounds or ϵ -aminocaproic acid may be necessary for chronic treatment, and infusion of plasma or C1 inhibitor concentrate employed for acute emergency treatment. The latter is clearly preferable to prevent volume overload and to be able to give enough C1 inhibitor to bind the autoantibody so as to raise the C1 inhibitor level significantly. In a practical sense, this is often not feasible. Tranexamic acid has also been successfully employed in the treatment of type II acquired C1 inhibitor deficiency in which activation of the

bradykinin-forming cascade and fibrinolysis (the latter determined by elevated levels of plasmin- α 2 antiplasmin complexes) was observed.⁸⁶

Treatment of idiopathic angio-oedema⁷⁰

If episodes are infrequent, diphenhydramine 50 mg b.i.d. to q.i.d. can be used with or without corticosteroid. Steroids should be used for more severe episodes, particularly facial, tongue, and pharyngeal angio-oedema, and can consist of prednisone 60 mg in a single dose followed by 40-60 mg the following day. This is usually sufficient and steroids can be stopped without any taper. Epinephrine can be employed for rapidly accelerating angio-oedema. If episodes are frequent but mild, a double-dose of a non-sedating antihistamine given daily may suffice. For severe frequent episodes, these authors recommend a regular administration of diphenhydramine at 50 mg q.i.d. If successful, taper to lowest effective dose. This would define the 'antihistamine-responsive' subgroup. For the refractory group, one might consider alternate-day corticosteroid 15-20 mg prednisone q.o.d., tranexamic acid (not available in the USA), or zileuton as a leukotriene synthesis inhibitor.

Declaration of conflict of interest

Dr Kaplan is a consultant on ACE-induced angio-oedema for Pfizer Inc., a consultant on drug-induced angio-oedema for Sanofi-Aventis, and a consultant on purified C1 inhibitor for treatment of hereditary angio-oedema (HAE) for Lev Pharmaceuticals. He has received a grant for research on pathogenesis of swelling in HAE from Lev Pharmaceuticals.

Dr Greaves declares no conflict of interest.

REFERENCES

- 1 Kaplan A, Greaves M. Angioedema. *J Am Acad Dermatol* 2005; **53**: 373-388.
- 2 Gorevic P, Kaplan A. The physical urticarias. *Int J Dermatol* 1980; **19**: 417-435.
- 3 Black A. Physical urticaria and cholinergic urticaria. In: Greaves M, Kaplan A, eds. *Urticaria and Angioedema*. New York: Marcel Dekker, 2004: 171-214.
- 4 Leznoff A, Josse R, Denburg J, et al. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983; **119**: 636-640.
- 5 Leznoff A, Sussman G. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66-71.
- 6 Hide M, Francis D, Grattan C, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993; **328**: 1599-1604.
- 7 Ferrer M, Kinet J, Kaplan A. Comparative studies of functional and binding assays for IgG anti-Fc(epsilon)RIalpha (alpha-subunit) in chronic urticaria. *J Allergy Clin Immunol* 1998; **101**: 672-676.
- 8 Gruber B, Baeza M, Marchese M, et al. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988; **90**: 213-217.
- 9 Grattan C, Francis D, Hide M, et al. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1992; **21**: 695-704.
- 10 Grattan C, Wallington T, Warin R, et al. A serological mediator in chronic idiopathic urticaria - a clinical, immunological and histological evaluation. *Br J Dermatol* 1986; **114**: 583-590.
- 11 Sabroe R, Grattan C, Francis D, et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**: 446-452.
- 12 Tong L, Balakrishnan G, Kochan J, et al. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997; **99**: 461-465.
- 13 Kikuchi Y, Kaplan A. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001; **107**: 1056-1062.
- 14 Wedi B, Novacovic V, Koerner M, et al. Chronic urticaria serum induces histamine release, leukotriene production, and basophil CD63 surface expression-inhibitory effects of anti-inflammatory drugs. *J Allergy Clin Immunol* 2000; **105**: 552-560.
- 15 Ferrer M, Nakazawa K, Kaplan A. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 1999; **104**: 169-172.

- 16 Kikuchi Y, Kaplan A. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. *J Allergy Clin Immunol* 2002; **109**: 114-118.
- 17 Niimi N, Francis D, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; **106**: 1001-1006.
- 18 Natbony S, Phillips M, Elias J, et al. Histologic studies of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1983; **71**: 177-183.
- 19 Elias J, Boss E, Kaplan A. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes, and mast cells. *J Allergy Clin Immunol* 1986; **78**: 914-918.
- 20 Sabroe R, Poon E, Orchard G, et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-FcepsilonRI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999; **103**: 484-493.
- 21 Ying S, Robinson D, Meng Q, et al. C-C chemokines in allergen-induced late-phase cutaneous responses in atopic subjects: association of eotaxin with early 6-hour eosinophils, and of eotaxin-2 and monocyte chemoattractant protein-4 with the later 24-hour tissue eosinophilia, and relationship to basophils and other C-C chemokines (monocyte chemoattractant protein-3 and RANTES). *J Immunol* 1999; **163**: 3976-3984.
- 22 Grattan C, Boon A, Eady R, et al. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. *Int Arch Allergy Immunol* 1990; **93**: 198-204.
- 23 Peters M, Schroeter A, Kephart G, et al. Localization of eosinophil granule major basic protein in chronic urticaria. *J Invest Dermatol* 1983; **81**: 39-43.
- 24 Puccetti A, Bason C, Simeoni S, et al. In chronic idiopathic urticaria autoantibodies against Fc epsilonRII/CD23 induce histamine release via eosinophil activation. *Clin Exp Allergy* 2005; **35**: 1599-1607.
- 25 Kern F, Lichtenstein L. Defective histamine release in chronic urticaria. *J Clin Invest* 1976; **57**: 1369-1377.
- 26 Sabroe R, Francis D, Barr R, et al. Anti-Fc(epsilon)RI auto antibodies and basophil histamine releasability in chronic idiopathic urticaria. *J Allergy Clin Immunol* 1998; **102**: 651-658.
- 27 Grattan C, Walpole D, Francis D, et al. Flow cytometric analysis of basophil numbers in chronic urticaria: basopenia is related to serum histamine releasing activity. *Clin Exp Allergy* 1997; **27**: 1417-1424.
- 28 Luquin E, Kaplan A, Ferrer M. Increased responsiveness of basophils of patients with chronic urticaria to sera but hypo-responsiveness to other stimuli. *Clin Exp Allergy* 2005; **35**: 456-460.
- 29 Confino-Cohen R, Aharoni D, Goldberg A, et al. Evidence for aberrant regulation of the p21Ras pathway in PBMCs of patients with chronic idiopathic urticaria. *J Allergy Clin Immunol* 2002; **109**: 349-356.
- 30 Asero R, Tedeschi A, Riboldi P, et al. Plasma of patients with chronic urticaria shows signs of thrombin generation, and its intradermal injection causes wheal-and-flare reactions much more frequently than autologous serum. *J Allergy Clin Immunol* 2006; **117**: 1113-1117.
- 31 Kaplan A, Horakova Z, Katz S. Assessment of tissue fluid histamine levels in patients with urticaria. *J Allergy Clin Immunol* 1978; **61**: 350-354.
- 32 Nussberger J, Cugno M, Amstutz C, et al. Plasma bradykinin in angioedema. *Lancet* 1998; **351**: 1693-1697.
- 33 Tosi M. Molecular genetics of C1 inhibitor. *Immunobiology* 1998; **119**: 358-365.
- 34 Kramer J, Katz Y, Rosen F, et al. Synthesis of C1 inhibitor in fibroblasts from patients with type I and type II hereditary angioneurotic edema. *J Clin Invest* 1991; **87**: 1614-1620.
- 35 Kramer J, Rosen F, Colten H, et al. Transinhibition of C1 inhibitor synthesis in type I hereditary angioneurotic edema. *J Clin Immunol* 1993; **91**: 1258-1262.
- 36 Zuraw B, Sugimoto S, Curd J. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. *J Allergy Clin Immunol* 1986; **78**: 1115-1120.
- 37 Ghebrehiwet B, Randazzo B, Dunn J, et al. Mechanisms of activation of the classical pathway of complement by Hageman factor fragment. *J Clin Invest* 1983; **71**: 1450-1456.
- 38 Ghebrehiwet B, Silverberg M, Kaplan AP. Activation of the classical pathway of complement by Hageman factor fragment. *J Exp Med* 1981; **153**: 665-676.
- 39 Kaplan A, Ghebrehiwet B. Does C-2 kinin exist? *J Allergy Clin Immunol* 2005; **115**: 876.
- 40 Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of 'spontaneous' formation of bradykinin. *J Allergy Clin Immunol* 1983; **72**: 54-60.
- 41 Zahedi R, Bissler J, Davis AR, et al. Unique C1 inhibitor dysfunction in a kindred without angioedema. II. Identification of an Ala443->Val substitution and functional analysis of the recombinant mutant protein. *J Clin Invest* 1995; **95**: 1299-1305.
- 42 Nussberger J, Cugno M, Cicardi M, et al. Local bradykinin generation in hereditary angioedema. *J Allergy Clin Immunol* 1999; **104**: 1321-1322.
- 43 Kaplan AP, Joseph K, Silverberg M. Pathways for bradykinin formation and inflammatory disease. *J Allergy Clin Immunol* 2002; **109**: 195-209.
- 44 Dunn JT, Silverberg M, Kaplan AP. The cleavage and formation of activated human Hageman factor by autodigestion and by kallikrein. *J Biol Chem* 1982; **257**: 1779-1784.
- 45 Kaplan AP, Austen KF. A prealbumin activator of prekallikrein. II. Derivation of activators of prekallikrein from active Hageman factor by digestion with plasmin. *J Exp Med* 1971; **133**: 696-712.
- 46 Caldwell J, Ruddy S, Schur P, et al. Acquired C1 inhibitor deficiency in lymphosarcoma. *Clin Immunol Immunopathol* 1972; **1**: 39-52.
- 47 Hauptmann G, Lang J, North M, et al. Acquired C1-inhibitor deficiencies in lymphoproliferative diseases with serum immunoglobulin abnormalities. A study of three cases. *Blut* 1976; **32**: 195-206.
- 48 Schreiber A, Zweiman B, Atkins P, et al. Acquired angioedema with lymphoproliferative disorder: association of C1 inhibitor deficiency with cellular abnormality. *Blood* 1976; **48**: 567-580.
- 49 Geha R, Quinti I, Austen K, et al. Acquired C1-inhibitor deficiency associated with antidiotype antibody to monoclonal immunoglobulins. *N Engl J Med* 1985; **312**: 534-540.
- 50 Donaldson V, Hess E, McAdams A. Lupus-erythematosus-like disease in three unrelated women with hereditary angioneurotic edema. *Ann Intern Med* 1977; **86**: 312-313.
- 51 Cohen S, Koethe S, Kozin F, et al. Acquired angioedema associated with rectal carcinoma and its response to danazol therapy. Acquired angioedema treated with danazol. *J Allergy Clin Immunol* 1978; **62**: 217-221.
- 52 Jackson J, Sim R, Whelan A, et al. An IgG autoantibody which inactivates C1-inhibitor. *Nature* 1986; **323**: 722-724.
- 53 Alsenz J, Bork K, Loos M. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 1987; **316**: 1360-1366.
- 54 Colman RW. Inhibition of angiogenesis by a monoclonal antibody to kininogen as well as by kininostatin which block proangiogenic high molecular weight kininogen. *Int Immunopharmacol* 2002; **2**: 1887-1894.
- 55 Malbran A, Hammer C, Frank M, et al. Acquired angioedema: observations on the mechanism of action of autoantibodies directed against C1 esterase inhibitor. *J Allergy Clin Immunol* 1988; **81**: 1199-1204.
- 56 Jackson J, Sim R, Whaley K, et al. Autoantibody facilitated cleavage of C1-inhibitor in autoimmune angioedema. *J Clin Invest* 1989; **83**: 698-707.
- 57 He S, Sim R, Whaley K. Mechanism of action of anti-C1-inhibitor autoantibodies: prevention of the formation of stable C1s-C1-inh complexes. *Mol Med* 1998; **4**: 119-128.
- 58 Cicardi M, Beretta A, Colombo M, et al. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angioedema. *Clin Exp Immunol* 1996; **106**: 475-480.
- 59 Chevallier A, Arlaud G, Ponard D, et al. C-1-inhibitor binding monoclonal immunoglobulins in three patients with acquired angioneurotic edema. *J Allergy Clin Immunol* 1996; **97**: 998-1008.
- 60 Bork K, Barnstedt S, Koch P, et al. Hereditary angio-oedema with normal C1-inhibitor activity in women. *Lancet* 2000; **356**: 213-217.
- 61 Binkley K, Davis Ar. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000; **106**: 546-550.
- 62 Cicardi M, Bergamaschini L, Zingale L, et al. Idiopathic nonhistaminergic angioedema. *Am J Med* 1999; **106**: 650-654.
- 63 Ohnishi-Inoue Y, Mitsuya K, Horio T. Aspirin-sensitive urticaria: provocation with a leukotriene receptor antagonist. *Br J Dermatol* 1998; **138**: 483-485.
- 64 Sanchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, et al. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001; **87**: 201-204.
- 65 Mastalerz L, Setkowicz M, Sanak M, et al. Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol* 2004; **113**: 771-775.
- 66 Oike Y, Ogata Y, Higashi D, et al. Fatal angioedema associated with enalapril. *Int Med* 1993; **32**: 308-310.
- 67 Thompson T, Frible M. Drug-induced, life-threatening angioedema revisited. *Laryngoscope* 1993; **103**: 10-12.
- 68 Orfan N, Patterson R, Dykewicz M. Severe angioedema related to ACE inhibitors in patients with a history of idiopathic angioedema. *JAMA* 1990; **264**: 1287-1289.

- 69 Johnsen S, Jacobsen J, Monster T, *et al.* Risk of first-time hospitalization for angioedema among users of ACE inhibitors and angiotensin receptor antagonists. *Am J Med* 2005; **118**: 1428-1429.
- 70 Kaplan A. Clinical practice. Chronic urticaria and angioedema. *N Engl J Med* 2002; **346**: 175-179.
- 71 Grattan C, O'Donnell B, Francis D, *et al.* Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000; **143**: 365-372.
- 72 Gach J, Sabroe R, Greaves M, *et al.* Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol* 2001; **145**: 340-343.
- 73 O'Donnell B, Barr R, Black A, *et al.* Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138**: 101-106.
- 74 Grattan C, Francis D, Slater N, *et al.* Plasmapheresis for severe, unremitting, chronic urticaria. *Lancet* 1992; **339**: 1078-1080.
- 75 Judge M, Watson K, Greaves M. C1 esterase inhibitor concentrate in the management of hereditary angioedema. *J Dermatol Treat* 1993; **4**: 95-97.
- 76 Waytes A, Rosen F, Frank M. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med* 1996; **334**: 1630-1634.
- 77 Spaulding W. Methyl testosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). *Ann Intern Med* 1960; **53**: 739-744.
- 78 Frank M, Sergeant J, Kane M, *et al.* Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. *N Engl J Med* 1972; **286**: 808-812.
- 79 Sheffer A, Austen K, Rosen F. Tranexamic acid therapy in hereditary angioneurotic edema. *N Engl J Med* 1972; **287**: 452-454.
- 80 Gelfand J, Sherins R, Alling D, *et al.* Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976; **295**: 1444-1448.
- 81 Sheffer A, Fearon D, Austen K. Clinical and biochemical effects of stanozolol therapy for hereditary angio-oedema. *J Allergy Clin Immunol* 1981; **68**: 181-187.
- 82 Sheffer A, Fearon D, Austen K. Hereditary angio-oedema: a decade of management with stanozolol. *J Allergy Clin Immunol* 1987; **80**: 855-860.
- 83 Cicardi M, Bergamaschini L, Tucci A, *et al.* Morphologic evaluation of the liver in hereditary angio-oedema patients on long-term treatment with androgen derivatives. *J Allergy Clin Immunol* 1983; **72**: 294-298.
- 84 Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine* 1992; **71**: 206-215.
- 85 Warin A, Greaves M, Gatecliff M, *et al.* Treatment of hereditary angio-oedema by low dose attenuated androgens: disassociation of clinical response from levels of C1 esterase inhibitor and C4. *Br J Dermatol* 1980; **103**: 405-409.
- 86 Cugno M, Cicardi M, Agostoni A. Activation of the contact system and fibrinolysis in autoimmune acquired angio-oedema: a rationale for prophylactic use of tranexamic acid. *J Allergy Clin. Immunol* 1994; **93**: 870-876.

BOOK FILLER – ATLAS OF ALLERGIES