Urticaria–Some Observations

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Urticaria has been known from antiquity. The disorder was known to the Arabs as *essera* and it has found a place in the writings of Cesius (circa 30 BC–45 AD). Although the condition was recognised as an entity, its cause was a mystery to the physicians of those times. It was initially thought to be a manifestation of idiosyncrasy and later believed to be a form of neuroses. However, now the pathophysiological basis of urticaria is well understood. The development of antihistamine group of drugs, paved the way for the management of urticaria.

Pathophysiology

The role of histamine. Initially, efforts to delineate the pathogenesis of urticaria focussed on a possible role for histamine. Intracutaneous injections, of histamine reproduce the pruritic wheal and flare reaction typical of urticaria. Although the capacity of antihistamines to inhibit urtication in many instances is suggestive, it does not firmly prove a role for histamine, since many of those drugs have additional pharmacological effects (anti-cholinergic, local anaesthetic, central nervous system effects etc.). That histamine is an important mediator of urticaria is best suggested by studies on physical urticarias. In cold urticaria, there is a transient elevation of histamine levels in venous plasma from the chilled extremity as it is warmed. Since the plasma half life of histamine is less than a minute, it is not surprising that the level of histamine in the opposite limb is normal. Further, as there is no such massive discharge of histamine in other forms of urticaria it follows that the levels

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of histamine in such conditions is essentially normal save the physical urticarias. Chilling of skin biopsies obtained from patients with cold urticaria results in basophil histamine release. Since the basophils also contain other mediators such evidence cannot be considered as sufficient proof that the cause of the urticarial lesions is histamine.

Paradoxically, in certain allergic urticarias decreased basophil counts and whole blood levels of histamine have been reported with normal levels of plasma histamine. This may be the result of basophil degranulation and rapid clearance of histamine from the plasma. Also of interest is the fact that the histamine content of vesicle fluid at sites of urticarial lesions is high. Normally the histamine levels in the uninvolved skin is higher than involved skin areas. It has been suggested that the basophils in such urticarial lesions are "leaky" but this has not been supported by *in vitro* studies which have actually demonstrated a decreased release of histamine by heterologous anti-IgE antibodies.

The initial enthusiasm that all urticarias could be explained as a consequence of histamine release faded with the demonstration over the years that the vast majority of urticarias are not IgE mediated–IgE being the chief trigger of basophil release. This led to the search for non IgE mediated immunological mechanism as well as non-immunological methods of histamine release. The current thinking, while acknowledging that histamine release is the final step in the process of the development of urticarial lesions recognises that stimuli other than IgE are capable of causing histamine release. For example, in cholinergic urticaria acetylcholine released from nerve endings may trigger basophil release while several drugs such as morphine and codeine can induce histamine release directly as can trauma.

Complement

Several components of the complement system such as C5a, C3a and C4a are powerful histamine releasers and it is conceivable that complement activation can lead to release of histamine. In fact, in a number of clinical situations where complement activation has been known to be a significant aspect of the disease, urticarial lesions have been identified commonly. These include the cryoglobulinaemias, SLE and

Sjogren's syndrome. In addition, a distinct entity known as hypocomplimentaemic urticarial vasculitis has also been reported.

Other Mediators

In view of the association between aspirin ingestion and the exacerbation of urticarial lesions it has been suggested that certain metabolites of arachidonic acid may play and important pathogenic role in urticaria. Leukotriene D_4, in fact, causes increased vascular permeability in human skin even at very low concentrations. Other mediators with a putative role in urticaria include kinins, serotonin and substance 'P'.

A number of factors can modulate the release of mediators and some of them are strikingly evident in certain cases. These include cutaneous vasodilators, drugs and hormones.

The Present Study

In order to study the clinical profile laboratory features and the role of mediators in urticaria the present study was conducted at the Allergy Clinic of the Govt. General Hospital, Madras, South India. This clinic serves as the referral centre not only for the city of Madras, but also other parts of the States of Tamil Nadu and neighbouring states.

A total of 615 patients with various forms of urticaria were studied over a 4 year period. The duration of the disease was six months or longer, to be considered as chronic urticaria and to be included in the study. In the present series 479 patients had urticaria alone (78%), 102 had urticaria and angioedema (17%) while 34 had angioedema alone (5%) (Table 1). This is in contrast to the study by Champion 1969[1], 49% of whose subjects had a combination of urticaria and angioedema, 40%

Table 1 Urticaria
(615 cases)

Urticaria alone	479 (78%)
Urticaria and angioedema	102 (17%)
Angioedema alone	34 (5%)
Dermographism was present in 105 cases	**(17%)**

urticaria alone and 11 % angioedema alone. This pattern appears to be common among adult population in the west. However, in paediatric populations in the west the pattern of lesions is similar to that obtaining in the present study; for example, Harris et al 1983[2] showed that 85 % children had urticaria alone, 9% had urticaria and angioedema, while only 6% had angioedema alone. (Table 2)

Table 2.

	Champion 1974	Harris 1983
Urticaria alone	40%	85%
Urticaria and angioedema	49%	6%
Angioedema alone	11%	9%

There have been conflicting reports regarding the association between urticaria and other atopic disorders. Several authors[3,4,5] found an increased incidence of urticaria among individuals with a previous history of eczema, hay fever and asthma. However, Champion and coworkers 1969[1] found no such increased incidence in chronic urticaria while they did demonstrate that acute urticaria was commoner in individuals with a past history of atopy. This prompted investigators to examine the issue of the extent to which a family history of atopy would influence the development of urticaria. It has been clearly shown that a family history of atopy was not a predisposing feature in chronic urticarias at least.[1,6] In the present study where the population studied consisted chiefly of individuals with chronic urticaria, no increased incidence of either family or personal history of atopic disorders was observed (Table 3).

Table 3. Urticaria and atopy–615 cases

Family history of atopy	132 cases (21 %)
Atopic disorders	174 cases (77 %)
Allergic rhinitis	72
Bronchial asthma	36
Eczema	61

Associated Disorders

Apart from the skin, wheals may develop at other sites especially the tongue, soft palate and pharynx. Various neurological complications have been reported. Cerebral edema may develop in association with urticaria and angioedema, Fowler 1962[7] reported a series of seven patients who developed changes possibly due to cerebral involvement and included *a* patient with headache. In the present series allergic headache was reported in as many as 34 cases.

Cardiac complications have been discussed by Kanof 1959[8] who gave a number of references to isolated cases with chest pain, ECG changes and urticaria. In the present series no ECG abnormalities were identified in 20 cases studied. However, hypertension was detected in 24 cases and this is probably unrelated to the urticaria.

Main and Paterson 1950[9] described a patient with pancreatitis clinically manifest 24 hours after the onset of acute urticaria. In the present series, diabetes (unrelated to the urticaria) was detected in 8 cases (Table 4). This is no different from the prevalence of diabetes in the general population.

Table 4. Associated disorders–615 cases

Hypertension	24 cases (4 %)
Allergic headache	34 cases (55%)
Pedal edema	23 cases (3.8%)
Hydrocele	11 cases (1.8%)
Anaemia	20 cases (3.25%)
Diabetes	8 cases (1.6 %)
Leprosy	3 cases (0.5%)

Fecal Sepsis

In the present series foci of sepsis were discovered in nearly a third of the cases (Table 5). However, eradication of the foci was beneficial in 12 out of 172 cases.

It must, however, be remembered that bacterial infection was often considered an important etiological feature of chronic urticaria especially in older literature. However this assumption was based on anecdotal evidence rather than on the basis

Table 5. Focal sepsis and urticaria (615 cases)

Dental caries	159 (20%)
Sinusitis	37 (6%)
Tonsillitis	13 (2%)

of controlled clinical studies. It has been suggested that some of the dramatic results reported in older literature were possibly due to the reaction of the operative trauma or to the natural history of the disease.[10] Currently, while recognising that every case of urticaria warrants a thorough clinical examination one must be wary of expending time and money on futile search for a presumed focus of sepsis in every such case.

Intestinal Parasites and Urticaria

In Western literature parasites do not figure prominently in the list of aetiological agents responsible for urticaria. However, in the present series a significant number of patients (60% harbored a variety of intestinal parasites and showed remission of their skin conditions with appropriate antihelminthic or antiprotozal therapy. The relationship between allergies and helminthic infection has been debated. One obvious possibility is that helminthic infection might cause allergic disease, first by inducing helminth–specific allergic symptoms or by exacerbating allergies to non helminth environmental antigens by potentiating heterologous IgE responses. Alternatively, helminthic infection might have an allergy-inhibiting effect by saturating mast cell Fc receptors with irrelevant IgE antibodies, stimulation of blocking antibodies or the desensitisation of mast celis by circulating parasites allergens.

Epidemiological studies have shown that, at any rate, there is not a greater prevalence of allergic disorders in helminth infected than non-infected people, a fact which in itself requires explanation. The idea that helminth induced IgE might actually decrease rather than promote allergic disorders developed from an experimental observation which showed that sensitization of human skin for the P.K. test with a specific IgE could be competitively inhibited with an IgE myeloma protein or its FC_e fragments.

A state of perpetual anaphylaxis would be expected to occur

with the Continuous presence of parasite specific IgE and parasitic allergen in the infected host. That this does not and could not occur since it would be incompatible with survival is indeed evidence for a regulatory mechanism ultimately affecting mast cell degranulation or mediator sensitivity. Many parasites do at one time or other cause severe allergic symptomatology. Allergic reactions to other antigens, although perhaps somewhat constrained, nevertheless do occur in helminth infected individuals. The picture we see probably reflects a balance of conflict between the allergy promoting and allergy inhibiting effects of helminth infection.

Table 6 shows the incidence of various intestinal parasites in the present series. In many cases there was a gratifying remission of urticarial lesions with treatment of the underlying helminthiasis. The results of such therapy are shown in Table 7.

Parasites other than intestinal have also been known to be associated with urticaria. The occurence of urticarial lesions

Table 6. Intestinal parasites and urticaria (615 cases)

Ascaris	168 (27.3%)
E. Histolytica	158 (25.6%)
Ascaris + E. Histolytica	88 (14.3%)
Giardia - Lamblia	44 (7.15%)
Others	30 (4. 87%)

Table 7. Intestinal parasites and urticaria response to treatment

	No. **treated**	**Favourable response**
Ascaris + EH	39	36 (92%)
Ascaris	40	15 (37.5%)
EH	30	10 (33%)
GL	9	1 (11%)
Ascaris + GL	10	6 (60%)
Anky	7	1 (14.2%)
Total	135	69 (50%)

in association with malaria has been reported by some workers.[11] In the present series one patient had urticarial lesions synchronous with the appearance of a spite in temperature and demonstration of the parasite in the peripheral smear.

The role of filarial infection was also investigated in the present study. 24 individuals with urticaria had clinical filarial disease. Of these 2 had circulating microfilaria and remission was achieved with Diethyl carbamazine therapy (DEC)– Table 8. However, the role of DEC in urticaria in such situations needs to be viewed in the context of its antifilarial as well as its antiallergic effects.

Table 8. Parasites and urticaria (615 cases)

Filariasis	24 cases
(2 patients with circulating mF) Malaria	5 cases

Drugs and Urticaria

Drug induced urticaria may be the result of several mechanisms operating in the same individual. Further, the same drug may produce urticaria through different immunological mechanisms. (Penicillin producing urticarial lesions both by type I and type III reactions in addition to a non-specific mechanisms). The situation is complicated further when an individual receives more than one drug or develops urticaria to additives commonly found in drugs.

Table 9 illustrates the incidence of associations seen between drug ingestion and the development of urticaria in the present series. Commonly implicated drugs include penicillin, sulpha group of compounds and aspirin.

Table 9. Drugs and urticaria–615 cases

Aspirin	9 (1.5%)
Paracetamol	8 (1.4%)
Analgin	15 (2.4%)
Sulpha	15 (2.4%)
Penicillin	11 (1.8%)
B. Complex	6 (1.0%)

Immunological Investigations

Estimation of serum IgG, IgA and IgM levels in various types of urticaria showed no significant alteration of these antibody levels as compared with those obtaining in a control local population. (Table 10).

Table 10. Immunoglobulins in urticaria

	Mean values IU		
	IgA	IgG	IgM
Idiopathic (12)	176	1975	187
Parasites (17)	194	2088	238
Infection (6)	224	1800	222
Atopy (9)	204	2186	187
Drugs (4)	104	2440	164
Hormonal (4)	269	2115	240
Controls : IgA –(172 ± 72)			
IgG –(1295 ± 414)			
IgM –(192 ± 95)			

However, serum IgE levels were elevated in virtually all forms of urticarias (Table 11). The highest levels were seen in individuals with a personal history of atopy. C_3 and C_4 levels in various forms of urticaria were within normal limits when compared with local controls.

Table 11. Serum IgE levels in urticaria

Idiopathic	(11)	2568 ± 1565
Helminthiasis	(17)	3169 ± 1999
Atopy	(8)	5093 ± 2556
Infection	(4)	3250 ± 2320
Hormonal	(3)	2716 ± 579
Drugs	(3)	4600 ± 999
Controls	(6)	954 ± 236

Management of Urticaria

The mainstay of therapy has been the antihistamine group of drugs which have been successful in the vast majority of cases. Corticosteroids have also been useful especially in life threatening situations such as angioedema. Recently several drugs have been tried with varying results in urticaria. These include the H_2 blockers such as Cimetidene; Danazol, a modified androgen and the trycyclic antidepressents. Traditionally

physicians have also used I.V. calcium in the management of urticaris.

An useful adjunct to the therapy of urticaria has been the employment of DEC–a drug already found to be useful in allergic diseases such as bronchial asthma[13] and allergic rhinitis[14] Several cases in this study showed significant improvement on treatment with this drug when administered in an open trial. The drug is being assessed for its efficacy in urticaria in a double blind trial currently.

Table 12. Complement levels in urticaria

		C3 g/lit	C4 g/lit
Parasites	(6)	1.168	0.489
Idiopathic	(5)	1.130	0.409
Infection	(4)	1.076	0.623
Atopy	(4)	1.190	0.538
Controls		0.55–1.20	0.2–0.5

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