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URTICARIA AND ANGIO-OEDEMA

A REVIEW OF 554 PATIENTS

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SUMMARY.—The records of 554 consecutive patients attending hospitals in the Cambridge region with urticaria have been analysed with the aid of a computer. These patients represent only a small minority of all patients with urticaria in the region. In 79% the aetiology was unknown although in many cases aggravating factors, for example, psychological stress, aspirin, or infection, were detected.

A past or family history of atopic disorders was not found more frequently in patients with urticaria than in controls and the course of the disease in patients with a background of atopy did not differ from the remainder, suggesting that an undetected allergy is not responsible for many of these undiagnosed cases. Allergy is relatively more important in acute urticaria and in patients who do not attend hospital.

The frequency of attacks and total duration of the disease are different in patients with urticaria alone, angio-oedema alone and both together but there was little difference in the aetiological factors, supporting the concept that urticaria and angio-oedema are fundamentally similar.

The prognosis is expressed in the form of life tables.

URTICARIA, including angio-oedema, is common, affecting perhaps some 15% of the population at some time in their lives (Sheldon *et al.*, 1954). Most of the medical profession still regard it as characteristically and almost invariably allergic in origin. Many acute cases are indeed demonstrably allergic reactions but in most chronic urticarias—70% of the Mayo Clinic series (Green *et al.*, 1965)—no causative factor, allergic or otherwise, can be reliably incriminated. The investigation of individual cases can be time consuming and fruitless.

The purposes of the present survey are:

1. To assess if allergy is important in patients attending hospital with urticaria by determining whether atopic disorders are more common in patients and their relations compared with a control group and whether urticaria patients with an atopic background differ in any other way from the remainder.
2. To assess whether urticaria and angio-oedema should be considered different manifestations of the same disease.
3. To assess the significance of certain other factors, especially aspirin and psychological stresses.
4. To determine the natural history and response to treatment.

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MATERIALS AND METHODS

The records of all 554 out-patients and in-patients with urticaria or angio-oedema attending hospitals in our region over the period 1956-67 were analysed. Data abstracted from the clinical records were supplemented by a questionnaire. In 22% of the patients the questionnaire was completed by interview and a further 48% of the patients returned the questionnaire through the post. Thirty per cent did not reply, or could not be traced. Papular urticaria (insect bites) and all cases which were considered to be drug eruptions, with the exception of those caused by aspirin, were excluded.

The following data were collected: sex; age of onset; past history of hay fever, asthma and atopic dermatitis; family history of urticaria, hay fever, asthma, atopic dermatitis; whether urticaria occurred alone, angio-oedema alone or both together and whether the lips, eyelids, tongue or other areas of skin were involved; the influence of psychological factors; the average duration of each attack and average interval between attacks; the total duration; whether the disease was still apparently active; the maximum severity; the response to aspirin; the response to treatment with antihistamines.

Information was available for each of these different variables in 84 to 99.5% of the cases except for the response to treatment and to aspirin, for which we had information on only 60% of patients. When analysing any particular item the unknowns were excluded.

The data were transferred to punched cards and analysed on the IBM 7090 computer at Imperial College, London, by means of the BMD computer programs (Dixon, 1965).

A similar questionnaire was also sent or handed to 200 patients of comparable age and sex attending the skin clinic with various skin lesions unlikely to be aetiologically associated with atopy, to assess the prevalence of urticaria and atopy. The incidence and course of urticaria in known atopic individuals was assessed by sending the same questionnaire to 50 patients who had attended hospital for seasonal hay fever and who have positive skin tests to grass pollens and to 50 patients aged over 15 attending with atopic dermatitis.

RESULTS

Using the generally accepted clinical classification of urticaria the cases fell into the groups shown in Table I. The following analysis relates to the 438 cases (79%) who were in the group of unknown aetiology. Included in this group are cases in which aspirin and psychological factors were of importance as we feel that the role of these factors is usually a contributory rather than the only cause. The age of onset of these cases is shown in Fig. 1, the incidence rate in the population being calculated from the 1961 census reports.

TABLE I

	Number of cases	% of urticaria patients
Ordinary urticaria and/or angio-oedema of unknown aetiology	438	79.1
Allergic urticaria	17	3.1
Cholinergic urticaria	28	5.1
Dermographism	47	8.5
Other physical urticarias	19	3.4
Cold	14	
Light	3	
Pressure	2	
Pregnancy urticaria	3	0.5
Hereditary angio-neurotic oedema	2	0.4
Totals	554	100.1

Atopic history.—The questionnaire used for the various groups of patients was essentially similar, reducing the hazards of relying on casual histories to assess the true prevalence of atopic disorders in the population.

A past history of seasonal hay fever, asthma or atopic dermatitis was found in 12.5 % of the 200 controls, and in 18.5 % of the urticaria patients. The difference is not statistically significant, $0.1 > P > 0.05$. The only significant difference in the prevalence of atopy in any of the different age or sex groups of the urticaria patients was a slightly higher prevalence in the 0–15 age group (22 %).

In 25 % of the 200 controls a history of seasonal hay fever, asthma or atopic dermatitis was found among parents, siblings or children, compared with 31 % of the urticaria patients. The difference is not statistically significant ($0.2 > P > 0.1$).

An atopic family history was found most frequently in the 0–15 age group of urticaria patients, but there was no statistically significant variation with either age or sex. A positive family history of atopy was found in 65 % of the patients with hay fever or atopic dermatitis. Altogether, 35 % of the controls and 40 % of the urticaria patients gave a personal or family history of atopy.

A family history of urticaria was found in 7 % of the controls and in 12 % of the urticaria patients.

Patients with atopic disorders of sufficient severity to attend hospital, frequently suffer from urticaria—23 % of

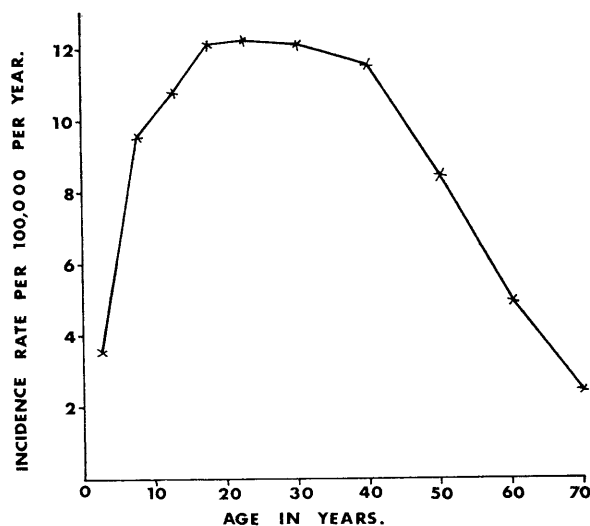


FIG. 1.—The incidence rate of ordinary urticaria referred to hospital, per 100,000 per year.

the patients with hay fever (hay urticaria is not included) and 36 % of the patients over 15 with atopic dermatitis. The urticaria ran a completely different course from that of patients primarily referred with urticaria. The attacks were of short duration, usually one to three days, and an allergic cause had been found by the patient in about 50 %.

Angio-oedema

Urticaria occurred alone in 40 % of the patients, urticaria and angio-oedema together in 49 % and angio-oedema alone in 11 %. None of these 3 groups differed significantly from the others in the association with atopy in the patient or the family, or psychological factors, or in the response to aspirin or to treatment. The only significant association with age and sex was that no males under the age of 15 had angio-oedema alone and comparatively few had angio-oedema and urticaria; there was a comparative excess of cases of urticaria in this age-sex group. In contrast there are more girls under 15 with angio-oedema with or

without urticaria and fewer with urticaria alone. These differences are statistically significant, $0.05 > P > 0.01$.

Fig. 2 shows the average duration of attacks for patients with urticaria, angio-oedema and both conditions. Patients with angio-oedema had more short attacks with corresponding shorter intervals of freedom. This is partly because episodes of angio-oedema are more dramatic and can be more easily recognized as separate attacks. These differences are statistically highly significant, $0.001 > P$.

The average severity of angio-oedema cases is mild to moderate, that of the urticaria cases is a little worse than moderate while the average of cases of angio-oedema with urticaria is moderate to severe. These differences are very unlikely to be due to chance, $0.001 > P$. (Severity was assessed on a five point scale: trivial, mild, moderate, severe and very severe. The average severity was angio-oedema only 2.6 ± 0.12 , urticaria only 3.2 ± 0.07 , and urticaria with angio-oedema 3.5 ± 0.06 .)

In comparing these 3 groups of patients the various factors have been considered one at a time. Some of these factors, especially those describing the pattern of disease are inter-related. The 3 groups were therefore compared with multivariate discriminant analysis. This method of analysis selects the smallest numbers of variables which together comprise all the significant information for discriminating between the 3 groups of patients. Thus, although a variable may be significant when considered in isolation it will not be deemed significant in the multivariate analysis if it contains no discriminating information other than that already provided by more significant variables.

The analysis showed that only 5 of 12 variables were statistically significant (Table II). These 5 variables contain all the information available for separating out the 3 groups of patients. Their co-efficients with standard errors, in linear discriminant functions for separating the 3 groups of patients are shown in Table II. Fig. 3 shows the separation between the 3 groups achieved by these discriminant functions and the percentage of cases that are correctly classified when the midpoint between the means is chosen as the discriminant point. When all 3 groups of patients are considered together 58% can be correctly classified. This figure may be compared with 33% that would be achieved by random allocation.

Thus the analysis shows that the 3 groups of patients were very highly significantly different, $0.001 > P$. In particular the angio-oedema only cases were very different from those with urticaria with or without angio-oedema. The differences between the groups could be accounted for by 5 of the 12 factors considered. These were, in order of importance: 1, average interval of freedom

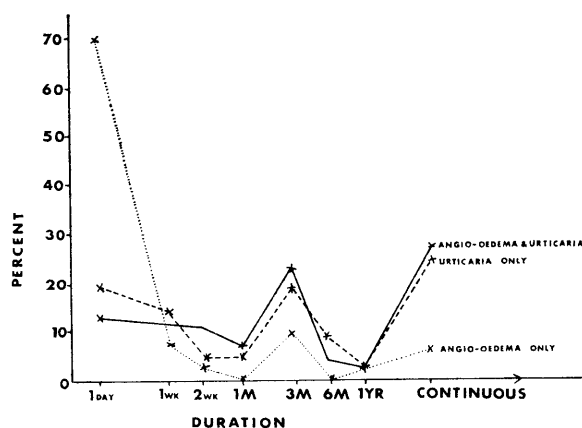


FIG. 2.—Frequency distributions of the duration of attacks of ordinary urticaria alone, angio-oedema, and urticaria with angio-oedema.

TABLE II.—*The Co-efficients, with Standard Errors, of the Significant Variables in Linear Discriminant Functions for Separating Patients with Urticaria Only, Angio-oedema Only and Angio-oedema with Urticaria.*

Variable	Angio-oedema v. Urticaria		Angio-oedema v. Urticaria with angio-oedema		Urticaria v. Urticaria with angio-oedema	
	Coeffs. of D1	s.e.	Coeffs. of D2	s.e.	Coeffs. of D3	s.e.
Duration of attack*	0.194	0.072	0.269	0.060	-0.265	0.108
Interval of freedom	0.437	0.114	0.415	0.095	-0.114	0.170
Severity†	0.521	0.165	0.805	0.137	-0.925	0.245
Multiple attacks‡	1.210	0.477	1.862	0.397	-2.129	0.709
Males < 15‡	1.347	0.412	0.465	0.343	1.718	0.613

* The points marked on the abscissa of Fig. 2 are taken as units of duration and of interval of freedom.

† Using a five point scale.

‡ Scale: Yes = 1; No = 0.

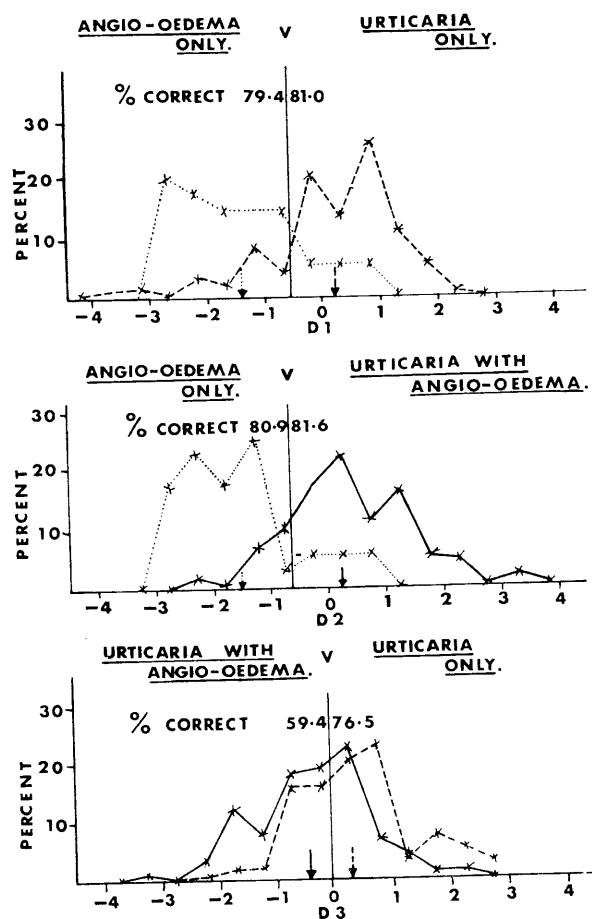


FIG. 3.—The performance of the 3 linear discriminant functions D1, D2, and D3 in separating patients with urticaria only, angio-oedema only, and urticaria with angio-oedema.

between attacks; 2, severity; 3, males under 15 as distinct from all other age-sex groups; 4, multiple in contrast to single attacks; 5, average duration of an attack.

The principal features distinguishing patients with angio-oedema, angio-oedema with urticaria and urticaria only are those describing the pattern of disease. Apart from the rarity of angio-oedema in boys under 15 there are no significant differences in the aetiological factors—age, sex, atopy, psychological stress. The lack of essential aetiological difference between these 3 groups is compatible with the view that angio-oedema is merely a different manifestation of the same disease.

In 90% of the 225 patients who had angio-oedema alone or with urticaria, the site of the angio-oedema was recorded. In 69.0% the eyelids were affected, 65.0% the lips, 21% the tongue, and 15% had other areas affected as well. We investigated whether, when the site was recorded, the chance of any one site

being affected was independent or whether the other sites were affected. The hypothesis of independence fitted the data well. The number of patients with single sites and all the various combinations of multiple sites affected was in close agreement with that predicted by the hypothesis. However, too much reliance cannot be placed on this finding, as under-recording of sites might invalidate the analysis.

Aspirin

Of the 268 patients for whom information was available 57 (21 %) were aware that they were made worse by aspirin, taken in conventional doses. In 10 the aspirin appeared to be the only cause, in the remainder only one factor. These cases occurred with similar frequency in all age and sex groups, whether or not there was a past or family history of atopy. The only statistically significant association found was with severity ($0.05 > P > 0.01$); the more severe cases tended to be aggravated.

Psychological Factors

Psychological factors were considered to be the main cause of 11.5 % and a significant contributory cause in a further 24 % of the cases. Their frequency varied significantly with age and sex; they were less frequent in children and in men over 45 and more frequent in women 15 and over, in 44.5 % of whom such factors were incriminated. When psychological factors were involved the total duration of the disease was on average significantly longer by approximately a year. Psychological factors were however only considered to be involved in 1 out of 25 (4.0 %) of the very severe cases of urticaria.

Natural History and Treatment Response

The expected total duration of urticaria is shown in the form of Life tables Figs. 4a, b and c. These figures are based on all the cases and the life table method of construction makes allowance for those in whom the disease was still active. Three tables were constructed for patients with urticaria, angio-oedema, and urticaria with angio-oedema, because the total duration of the three forms of the disease differs significantly. Figs. 4a, b and c may be used to assess the prognosis in individual cases. For example, from Fig. 4a we would expect that after 6 months from onset 50 % of hospital patients with ordinary urticaria only would still have active disease, and after 10 years 20 %. Thus of patients with active urticaria, after 6 months $20\%/50\% = 40\%$ are expected to have active disease after 10 years.

Response to antihistamine therapy was considered good in 31 %, moderate in 46 %, slight in 17 % and none in 6 %. Treatment response was not associated with a history of atopy, nor does it appear to be associated with age, sex, psychological factors, the occurrence of angio-oedema, the severity, the duration of an individual attack or the number of attacks. The interval between attacks is on average significantly shorter for those making a good response (9 months compared with $2\frac{1}{2}$ years, $0.05 > P > 0.01$) and the total duration of the disease is also associated with response to treatment, $0.01 > P > 0.001$. The average total duration is 9 months in those with a good response to antihistamine therapy, 18 months in those with a moderate response, and 28 months in those with a slight or no response.

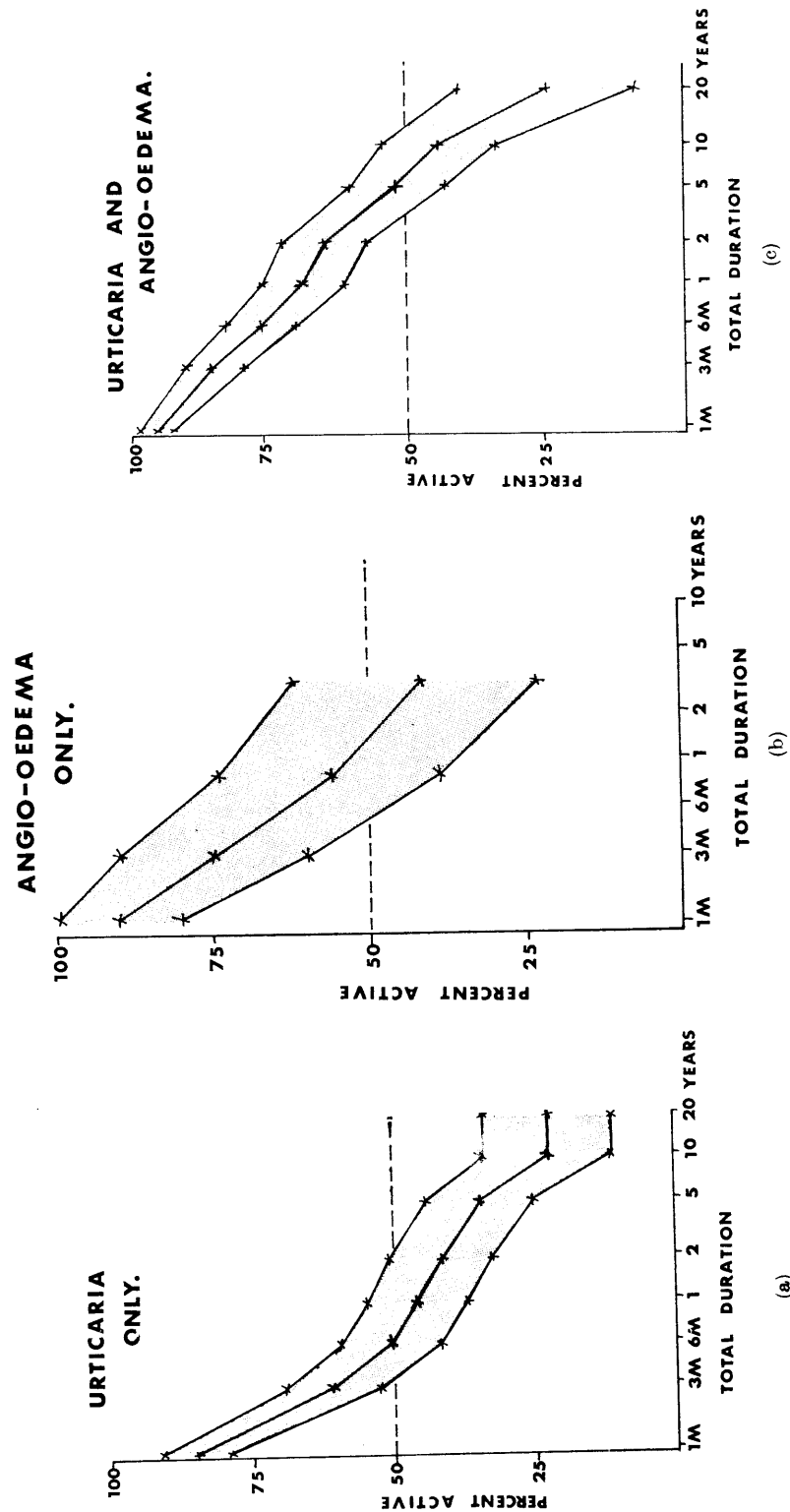


FIG. 4.—The expected percentage of patients active, with 95% confidence limits, by the total duration of disease (log scale).

The response to skin testing with pharmacological agents will be considered elsewhere.

Other Types of Urticaria

The age at onset of cholinergic urticaria is shown in Table III. Over half the cases began between 15 and 19 and 64% were male. There was no increased incidence of past or family history of atopy and no patients had angio-oedema. None knew they were made worse by aspirin. The condition was very persistent and our limited data suggests that nearly 90% may expect to have some symptoms after 7 years.

TABLE III.—*Age of Onset of Cholinergic Urticaria and Dermographism*

Age of onset	Cholinergic urticaria %	Dermographism %
<15	7.1	17.0
15—	67.8	21.3
25—	7.1	17.0
35—	10.7	17.0
45—	3.6	14.9
55+	3.6	12.8
Total	100.0	100.0
No. of cases	28	47

The age of onset of symptoms of dermatographism severe enough to bring patients to hospital is also shown in Table III. No age group seems especially at risk; 34% were male. There was no increased past or family history of atopy. Two patients were made worse by aspirin. Nearly 90% of patients with dermatographism may expect to have symptoms after 7 years. Six of the patients with dermatographism also had ordinary spontaneous urticaria. We agree with Moore-Robinson and Warin (1968) that combinations of the various types of urticaria, especially the physical urticarias, are frequent.

DISCUSSION

The problems of mechanism, diagnosis and management of urticaria will not be discussed in detail (see Beall, 1964, Champion, 1968). We believe that histamine release from mast cells may be only one of the mechanisms involved and that the fundamental pharmacological changes which lead to urticaria have yet to be elucidated. These fundamental changes may be influenced by many factors, including allergy, psychological stresses, aspirin and systemic disease which should be sought and eliminated but not necessarily blamed for the whole of the patient's disease. Often the change in one factor (not necessarily the most important) may be sufficient to stop the patient's symptoms, but when credit is being given the self-limiting natural history of urticaria should also be recalled.

Our results are essentially similar to those from the Mayo Clinic (Green *et al.*, 1965). We also were unable to make an aetiological diagnosis in the majority of cases. This contrasts strongly with other series where a cause has been found in the majority, sometimes approaching 100%. This discrepancy is no doubt partly due to selection of cases and partly to the enthusiasm with which different investigators interpret such findings as positive skin tests and focal sepsis.

Five hundred and fifty four hospital cases in 12 years from an estimated population of 417,000 gives no idea of the proportion of the population affected by urticaria. A figure of 15-20 % is often quoted and 12.5 % of our control group had had urticaria. From these figures it can be deduced that the patients who attend hospital represent a very selected group of all cases of urticaria in our region. Logan and Custon (1958) found that 1.4% of the population attend a general practitioner's surgery with urticaria each year.

This study provides little evidence to suggest that allergy is an important and often missed factor in the causation of chronic urticaria in patients attending hospital, although an allergic cause must always be considered. Allergy is much more important in acute urticaria. It seems probable that allergic urticaria is mainly due to reagins (IgE) and therefore more likely to occur in patients with an atopic background, although it is well known that almost anybody can form reagins under suitable conditions. Other types of antibody can give rise to urticaria, for example IgG in serum sickness but here the clinical picture is different. We have not found the eosinophil level in the blood or in the weals of any help in differentiating the allergic cases, although the exceptional finding of a definite eosinophilia would warrant a thorough search for an allergic cause, e.g. worm infestation.

The attacks of urticaria to which atopics are especially prone tend to be of shorter duration and very often the patient is able to make the correct diagnosis and therefore does not attend hospital. Our evidence suggests that atopy may play a part in some of the severe short-lived attacks in childhood and that an appreciable number of such cases were placed in the group of unknown aetiology. More persistent urticaria in patients with an atopic background does not appear to differ from that in the non-atopic.

Of the 17 patients with allergic urticaria, 8 were sensitive to foods (cheese, fish, shellfish, grapes, nuts, plums), 4 were known to be penicillin sensitive and their chronic urticaria could have been attributed to ingestion of traces of penicillin, although we have no proof of this. One patient was allergic to horses, and in one patient severe urticaria and angio-oedema were the presenting symptoms of scabies. Even in these patients not all the attacks could readily be attributed to their allergies.

We have found little to encourage us to do routine skin testing in all patients with chronic urticaria although many tests have been done. Perhaps the rare surprise picked up in this way may be sufficient justification but so far we have had no such cases. We are currently trying to confirm Holti's work (1966) on the importance of candida infection in some patients with chronic urticaria. It may play a part in a small minority of patients.

This investigation confirms that with the important exception of hereditary angio-oedema whose pharmacology is now better understood, angio-oedema with or without urticaria is fundamentally similar to urticaria alone.

Exacerbation by aspirin occurred in 21 % of our patients confirming the views of Warin (1960) that this drug is an important and a common factor in chronic urticaria and that all patients should be warned of the hazard. As with aspirin asthma (Samter and Beers, 1967, 1968) it is considered that this is more likely to be produced by a pharmacological than an immunological mechanism.

The role of psychological factors is extremely difficult to assess and we made no special efforts to do this thoroughly. In 11.6 % of the cases it was felt that emo-

tional disturbances were the main factor and in a further 23.8% a contributory one. Russell Davis who examined some of our cases very thoroughly was able to find some psychological factor in a very large proportion but considers that in many of these the ordinary stresses and strains of life are contributing to a disease in which multiple factors are important (Kennard and Davis, 1964). The fact that we could not find a significant correlation between psychological factors and any other variable fits in very well with this concept.

This series confirms that in the majority of cases, urticaria is a benign, self-limiting disease and that antihistamines provide useful symptomatic relief in the majority.

We are indebted to our patients for their co-operation, to Dr C. H. Whittle and Dr A. J. Rook for permission to include patients under their care, to Miss Helen Lloyd and Mr R. Thurston of the Department of Human Ecology for punching the cards for us, and also to Mr Thurston for drawing the diagrams. We are also grateful to Imperial College for permission to use their 7090 computer for the analysis.

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