out, the results will also be affected by the natural history of this condition, particularly if the patient continues to drink. Indeed, the close supervision of our patients during the trial could have resulted in a significantly greater number abstaining from alcohol, but this applied to both the sclerotherapy and the control groups. We found no difference in the frequency of rebleeding between alcoholic patients who either continued to drink or stopped drinking and patients with non-alcoholic cirrhosis either in the sclerotherapy or control group.

The use of the flexible oesophageal sheath, developed at King's College Hospital by Williams and Dawson,[3] has certain advantages. Protrusion of the varices through a distal window with compression above and below provides easy access for injection: the gastro-oesophageal junction can be readily identified before injection of sclerosant. After injection the varix may be further compressed by rotation of the sheath, and immediately after the procedure none of our patients has required passage of a Sengstaken tube to control bleeding. The sheath used in conjunction with general anaesthesia lessens the risk of pulmonary aspiration during the procedure. However, injection of varices without a sheath and with simple sedation, as in routine endoscopy, is undertaken by other groups[13] (and by us in selected patients—usually those with limited residual varices after previous injection). Another variation of the technique is to use multiple submucosal injections between varices[14] rather than direct injection into the varices. In our experience accurate siting of the injections can be difficult, especially with local movement of the gastro-oesophageal junction even with the use of heavy sedation and antispasmodics. Several centres continue to recommend the rigid oesophagoscope,[15-17] particularly for emergency sclerotherapy, the advantage being that this instrument can be easily manoeuvred to compress actively bleeding varices during the stage of injection. However, the rigid oesophagoscope carried a much greater risk of oesophageal perforation.[16, 17] In general, we prefer to control haemorrhage with oesophageal tamponade before proceeding to injection sclerotherapy, since accurate positioning of injections is then easier.

Although studies of oesophageal function after injection sclerotherapy have shown diminished motility with reduction of lower-oesophageal sphincter pressures which may result in an increased susceptibility to oesophageal reflux,[18] symptoms of this condition have not so far been a practical problem in any of our long-term patients. Follow-up endoscopy has, however, shown acute inflammation of the distal oesophagus in several patients, and oesophageal ulceration and strictures do occur with repeated courses of injections in a significant number of our patients, although about half of these patients remain without symptoms. Ulceration and strictures may result from inadvertent reinjection of already sclerosed vessels, with consequent submucosal leakage of sclerosant. The oesophageal ulcers have invariably healed, and the main cause for concern has been the occurrence of bleeding from the site of ulceration or from remaining varices during delay before reinstitution of sclerotherapy.

We thank the many physicians and surgeons who have referred patients for their collaboration in the running of this trial, and the nursing staff for their willing help. We are grateful to Dr J. Saunders for the statistical analysis.

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BASOPHILS IN ALLERGEN-INDUCED PATCH TEST SITES IN ATOPIC DERMATITIS

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Summary Atopic dermatitis often occurs in patients who have high IgE levels and positive immediate skin tests to several common allergens. However, there is considerable doubt about the role played by allergens in this disease. Patch testing for 48 h at superficially abraded skin sites revealed that allergens could induce eczematous lesions in atopic dermatitis patients but only in those who also gave a positive immediate skin reaction to the same allergen. Lesions induced by the purified house dust mite antigen, antigen P_1 contained mononuclear cells, basophils, eosinophils, and neutrophils. These patients also had raised specific serum IgE against antigen P_1, and their leucocytes released histamine upon exposure to the same antigen. Thus an acute eczematous lesion can be induced by the application of inhalant allergens to the skin.

Introduction

ATOPIC dermatitis is a common debilitating skin condition occurring in all age-groups, though predominantly in the young. Most patients have high IgE levels and positive immediate skin tests to several inhalant allergens.[1,2] They also often have allergic rhinitis, asthma, and/or food allergy.

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Skin affected by eczema is infiltrated with mononuclear cells, which suggests that the condition may be a form of delayed hypersensitivity (DH). However, allergens that cause immediate responses do not usually give rise to DH skin lesions. This failure of allergens to produce delayed or eczematous lesions has often been given as a reason for not regarding allergens as an important cause of eczema.[3,4] However, the very small quantities of antigen used in skin testing atopic patients, or the local effects of vasoactive amines, may be why DH responses do not develop.[5] Another reason may be the reported impairment in these patients of cell-mediated immune responses to candida and tuberculin.[6]

Patients with atopic dermatitis often improve after admission to hospital, even though treatment is not changed.[7] Many of these patients are sensitive to allergens derived from the house dust mite *Dermatophagoides pteronyssinus* and are exposed to high levels of these allergens at home,[8,9] but not when they are in the relatively dust-free environment of a hospital. We therefore decided to re-investigate the effects of exposure of the skin to dust mite and other allergens.

Materials and Methods

Seventeen patients (aged 7–61) with severe atopic dermatitis were skin tested (by prick technique) with a variety of common inhalant allergens (Bencard Ltd., U.K.). These same allergens and extracts of floor dust were dialysed against saline before being used for patch testing. Antigen P_1 was purified from an extract of *D. pteronyssinus* culture by concentration over an 'Amicon PM_{10}' filter, fractionation on 'Sephadex G-100', and 'pevicon' block electrophoresis.[10] Controls consisted of ten non-allergic volunteers with negative prick tests and six volunteers who had a history of rhinitis or asthma and positive prick tests but no history of atopic eczema.

Patients were only patch-tested when their dermatitis was in remission, and tests were done on skin that was macroscopically normal. A 2 cm×2 cm area of skin was gently abraded by removing the upper layers of the epidermis but without causing capillary bleeding. 0·5 ml of aqueous allergen or normal saline was applied with a pad of sterile gauze, the area was occluded, and the dressing retained with hypoallergenic tape. Lesions were generally inspected at 48 h, when a biopsy specimen was also taken by the use of a 4 mm disposable biopsy punch (Stiefel Laboratories U.K. Ltd.). Care was taken to infiltrate local anaesthetic around the biopsy site but not into it. The biopsy specimens were immediately placed in Karnovsky's fixative.[11] After 24 h they were washed in four changes of 0·1 mol/l sodium cacodylate pH 7·4 (Sigma) at 4°C and dehydrated in varying concentrations of alcohol. Specimens were embedded in hydroxyethyl methacrylate and 1–2 μm sections were stained with Giemsa.[12] All sections were approximately 4 mm×2 mm, and the whole area was examined, the few cells in the epidermis and on the surface not being counted.

Total serum IgE levels were measured by double antibody inhibition radioimmunoassay, and specific antibodies to antigen P_1 of both IgE and IgG isotypes were assayed by the use of an antigen-binding radioimmunoassay technique.[13,10] Tests for in-vitro leucocyte histamine release in response to antigen P_1 were done for all subjects.[14] Dust samples were collected from the homes of the patients tested and assayed for antigen P_1 content.[9]

Results

Patch testing with allergens in seventeen atopic dermatitis patients produced a positive macroscopic response after 48 h in 38 out of 38 tests (table I). These lesions were evident at 24 h and progressed until 72 h. Most of the positive patches showed confluent papular erythema (++) while the stronger responses also showed oedema and exudation (+++). Scaling occurred in most lesions as they resolved over 4–10 days. Most patients were tested with more than one allergen, including extracts of house dust mite, grass pollen, guineapig dander, cat dander, and their own floor dust. Saline produced patchy erythema (+) on four occasions, and no reaction (0 or ±) in 19 patch tests on the same patients. These patients, who lived in England, had not been naturally exposed to ragweed pollen, and showed negative immediate skin tests with ragweed extract. In seven out of eight cases no striking response to patch tests with ragweed extract was demonstrable.

TABLE I—PATCH TESTS IN ATOPIC DERMATITIC PATIENTS AT 48 HOURS*

Macroscopic† appearance†	No. of responses with antigens giving positive prick tests‡	No. of responses with antigen giving negative prick tests§	No. of reactions with normal saline
+++	7	0	0
++	26	0	0
+	5	1	4
±	0	2	9
0	0	5	10

*Seventeen patients tested with a variety of common inhalant allergens Several of the patients were tested on more than one occasion.
†0 = no reaction; ± = erythema covering <10% of the patch area; + = patchy erythema with occasional papules; ++ = confluent papular erythema with or without a mild exudate; +++ = as ++ but with exudation, oedema, and extension beyond the patch area.
‡Allergens included grass pollen, cat dander, guineapig dander, floor dust, *D.pteronyssinus* extract, and antigen P_1.
§Ragweed extract (Greer Laboratories Inc., Lenoir, North Carolina).

Ten patients were tested with the purified dust mite allergen, antigen P_1. All ten showed positive patch responses to the 5 μg dose (in preliminary experiments we found that 0·05 μg would elicit a mild reaction), while nine out of ten non-allergic controls showed no reaction (table II). The ten patients had marked immediate hypersensitivity to antigen P_1 as judged by the intradermal skin test and in-vitro leucocyte histamine release (table II); they also had high levels of serum IgE and IgG antibodies against antigen P_1 (table III). Total serum IgE levels were very high in the patients with atopic dermatitis (geometric mean 5460 IU/ml), which was in keeping with the fact that most of these patients had had extensive skin involvement within the previous 6 months (table III). Six dust-mite-allergic individuals who did not have dermatitis were also patch-tested with antigen P_1 and four of them showed positive responses (table II).

Histologically the positive patches induced with antigen P_1 showed a moderate to severe dermal inflammatory cell infiltrate most prominent around blood vessels. This contrasted with the scarcity of inflammatory cells in the responses to saline in nine out of ten of these patients and in the responses to the allergen in nine out of ten of the non-allergic controls. In biopsy specimens of positive lesions taken at 48 h the epidermis contained occasional inflammatory cells. At 72 h epidermal changes, including focal spongiosis and microvesiculation, were more evident. Differential cell counts done blind showed highly significant increases in the number of basophils in positive lesions (table IV)—e.g., the dermatitic patients showed a mean of 41 basophils in response to antigen P_1, while non-allergic controls had 1 (table IV). No differences in absolute mast cell counts were noted in the different groups. Eosinophils were a predominant infiltrating cell in the positive biopsies; they

TABLE II—RESULTS OF PATCH TESTS, INTRADERMAL SKIN TESTS, AND TESTS FOR LEUCOCYTE HISTAMINE RELEASE

Subjects	Patch test at 48 h: Antigen P_1 (5μg)	Patch test at 48 h: Saline	Intradermal skin test* (15 min) antigen P_1 (μg/ml)	AgP_1 leucocyte histamine release† (%)
Atopic dermatitic (n=10)	++	−	10^{-5}	32
	++	−	10^{-4}	27
	++	±	10^{-5}	56
	+++	+	10^{-4}	0
	++	+	+‡	47
	+++	−	10^{-5}	20
	++	±	10^{-6}	55
	++	−	10^{-5}	34
	+++	±	+‡	34
	++	−	10^{-6}	45
Atopic non-dermatitic (n=6)	−	−	10^{-5}	45
	++	±	10^{-3}	0
	+	−	10^{-4}	16
	+	+	10^{-5}	20
	±	±	10^{-4}	31
	+	±	10^{1}	0
Non-atopic controls (n=10)	−§	N.D.	$<10^{1}$¶	>10//

*Done with 0·02 ml of serial 10-fold dilutions of antigen P_1. A wheal of >6×6 mm was regarded as the endpoint. Skin tests negative at 10 μg/ml are recorded as $>10^{1}$.

†Nine out of ten patients showed histamine release (>10% above background) with dilutions of antigen P_1 from 1 μg/ml to 10^{-6} μg/ml. Values shown are % release above background using 10^{-4} μg/ml).

‡Positive by prick test.

§One subject gave a (+) reaction and one gave a (±) reaction.

¶One subject positive at 1 μg/ml.

//One control showed 15·5% histamine release at 10^{-4} μg/ml. The other 9 controls had <10% release at concentrations up to 1 μg/ml.

were more numerous than basophils (table IV). Biopsy specimens of the positive lesions also showed mononuclear cell and neutrophil infiltration. For each cell type the number of infiltrating cells in reactions to antigen P_1 in atopic non-dermatitic controls was midway between that in the positive patient reactions and that in negative control reactions. Their characteristic ultrastructural features[15] seen on electron microscopy confirmed the presence of basophils, mast cells, eosinophils, and neutrophils. A typical basophil in the skin is shown in the accompanying figure.

Discussion

Our study has shown that a modification of the usual method of presenting immediate hypersensitivity allergens can consistently induce an eczematous delayed skin response. The dose of allergen used was larger than that necessary to produce an urticarial wheal in the same patients, but it is similar to that used to elicit delayed hypersensitivity responses. Furthermore, we found that dust from the beds of eight of our patients contained high levels of antigen P_1 (50 ± 10·5, [SE] μg/g). Abrasion and prolonged exposure, both features of the technique used, simulate naturally occurring conditions, since scratching is an important feature of the disease and exposure to house dust allergens is likely to be prolonged and repeated.

The basophil infiltrate reported here is similar to that which occurs in induced contact dermatitis and in the late cutaneous response.[16-18] Furthermore, electron microscope evidence of basophil degranulation, as has been reported in contact dermatitis,[19] was present in some of the patch responses. The presence of basophils is interesting because these patients' leucocytes released histamine in response to the same antigen, and it is probable that the infiltrating basophils were sensitised to antigen P_1. The presence of basophils may also imply that sensitised T cells are involved in the skin response, since human T cells can release a basophil chemotactic factor.[20] Unlike induced contact dermatitis, the patch responses always showed a marked eosinophil infiltration.[16] Recruitment of eosinophils into allergen-induced patch sites probably depends on the release of eosinophil chemotactic factor(s) from either mast cells or basophils. Neither basophils nor eosinophils have been reported to be increased in naturally occurring lesions of atopic dermatitis; however, it has been suggested that eosinophils may participate in the development of the lesions.[21] The differences in histological findings between

TABLE III—TOTAL SERUM IgE AND SPECIFIC ANTIBODIES TO ANTIGEN P_1

Subjects	Total IgE* (units/ml)	IgE anti P_1 (binding activity)†	IgG anti P_1 (binding activity)†
Atopic dermatitic (n=10)	5460 (2 065–14 435) p<0·001	206 (44–978) p<0·001	811 (321–1998) p<0·001
Atopic non-dermatitic (n=6)	293 (137–625) p<0·001	9 (1–52) p<0·01	19 (2–164) NS
Non-atopic (n=10)	25 (13–50)	<3 (0)	5 (3–9)

*1 unit IgE was assumed to be equivalent to 2·4 ng.

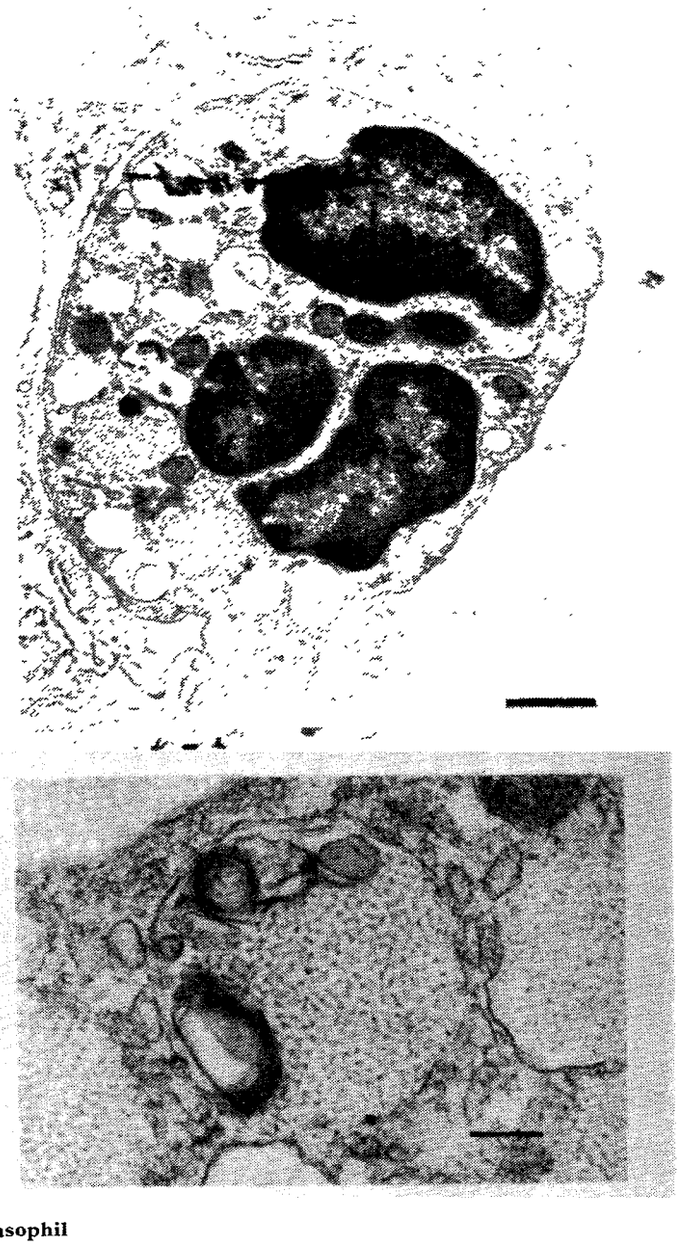
†Results obtained from a control curve and expressed in arbitrary units of binding activity (1 BA unit ≙ 1ng).[9] Results are expressed as geometric mean values. Figures in parentheses represent one standard deviation range above and below the geometric mean. An unpaired *t* test was used to compare the results of both the patient group and the atopic non-dermatitic group with the non-atopic control group. All results were converted to log values before statistical analysis.

TABLE IV—DIFFERENTIAL CELL COUNT OF INFILTRATING CELLS IN 1–2 μm SECTIONS OF SKIN BIOPSY SPECIMENS

Subjects	Patch test	Basophils	Mast cells	Eosinophils	Mononuclear	Neutrophils	Total
Atopic dermatitic (n=10)	Antigen P_1	41 (17–96)	60 (29–94)	190 (67–541)	698 (461–1059)	53 (21–138)	1,149 (710–1858)
	Saline	2‡ (0–6)	52 (30–92)	11‡ (4–31)	366† (236–569)	17* (7–38)	462‡ (301–711)
Atopic non-dermatitic (n=6)	Antigen P_1	12 (2–90)	65 (38–112)	24 (0–506)	455 (278–746)	24 (4–169)	787 (443–1400)
Non-atopic controls (n=10)	Antigen P_1	1‡ (0–4)	53 (31–92)	1‡ (0–2)	279‡ (166–468)	5‡ (1–16)	350‡ (212–577)

Histological sections examined were of similar size (4 mm width), and all cells infiltrating the dermis down to the level of the panniculus adiposus were counted. Results are expressed as geometric mean values. The figures in parentheses represent 1SD range above and below the geometric mean.

Results for antigen P_1 and saline patch sites in atopic dermatitic patients were compared by paired *t* test. Results for antigen P_1 lesions in atopic dermatitic patients and those in non-atopic controls were compared by an unpaired *t* test. Figures were converted to log values prior to statistical analysis.* $p<0·02$; †$p<0·01$; ‡$p<0·001$.



Basophil

Under the electron microscope basophil leucocytes (magnif. × 12 285; bar = 1 μm) had multilobed nuclei, large variable granules (diam. 860 nm ±226), and knob-like surface protrusions. The granules (below) (magnif. × 48 940; bar = 0·2 μm) were particulate and had a variable number of myelinoid membranous figures.

atopic dermatitis and the patch test lesions may reflect three features of these patches. Firstly, they are of a known duration (48 h); secondly, they probably represent a fairly intensive local stimulation; and thirdly, they have not undergone the regular scratching which occurs with naturally occurring eczema and which may influence both dermal and epidermal histology.

The pathogenesis of atopic dermatitis is certainly multifactorial since in many patients stress, skin infection, contact sensitivity, and foods can cause exacerbations. Genetic factors, itch threshold, and abnormalities of autonomic responses may also be important.[4,22] Although many recent workers have discounted the role of inhalant allergens, several early investigators considered that house dust, pollen, and animal dander allergens were an important cause of dermatitis.[7,23] Our results support the view that inhalant allergens should be considered as a factor in the disease in those patients who are sensitive to these allergens. Proof that any factor is important in atopic dermatitis can only be established by controlled avoidance and exposure experiments. However, the delayed nature of the response reported here might explain why patients are often unaware that a particular allergen exacerbates their eczema.

The patch test reponse to allergens has obvious parallels with cutaneous basophil hypersensitivity (CBH) in guineapigs[24]—they both contain basophils and eosinophils, they have a similar time course, and they are elicited by similar doses of antigen. The basophils infiltrating guineapig lesions are known to be sensitive to the eliciting antigen and can release mediators locally.[25] It seems likely that as in guineapig CBH the response to allergens in our patients involves both T cells and anaphylactic antibodies, and that both lesions represent an overlap between immediate and delayed hypersensitivity.

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