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## **The role of dust mite allergens in atopic dermatitis**

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The term atopy was introduced to convey the observation that certain individuals and families were specially liable to develop 'supersensitivity' to foreign proteins in their environment (Coca & Cooke, 1923). Using prick or intradermal skin tests it was obvious that this type of sensitivity (now known as type I or immediate hypersensitivity) was very common, not only among patients with hay fever and asthma but also among patients with the form of chronic eczema known as Besnier's prurigo, neurodermatitis or infantile eczema. These positive wheal and flare skin tests which occur within 20 min were seen with a variety of extracts including foods, animal dander, pollens and house dust. The view that grass pollen sensitivity causes hay fever was established by Blackley (1873) and is obvious since most of the patients do not get symptoms during the months of the year when grass pollen is absent from the air. By contrast, proving that 'atopic allergens' are the major cause of asthma and eczema has proved much more difficult. It had long been known that patients with asthma improved when they went to Switzerland, but the reason for this was not known. In 1927 Storm van Leeuwen reported that similar improvement in asthma could be achieved with a special dust-free room in Holland. More recently it has been suggested that avoiding allergens can lead to an improvement not only in the symptoms of asthma but also in the underlying bronchial hyper-reactivity (Altounyan, 1970; Kerrebijn, 1970; Hargreave *et al.*, 1979; Platts-Mills *et al.*, 1981a). Thus, it now seems likely that allergens which cause immediate reactions in the skin can give rise to chronic changes in the lungs. Using an allergen-free room, Rost (1932) reported that many patients with eczema who were allergic to dust improved when they were taken away from their houses. Similarly, Sulzberger & Vaughan (1934) and Feinberg (1939) drew attention to the role of inhalant allergens (pollens, animal dander and house dust) in dermatitis. During the same period several authors reported patients who were improved by avoiding specific food to which the patients

appeared to be allergic (Hill, 1934; Schloss, 1915). Because of this range of evidence which suggested that these patients with chronic eczema were allergic to common allergens and that these allergens contributed to their disease, the disease became known as atopic dermatitis. The view that allergens and especially inhalant allergens were a major cause of atopic dermatitis was outlined very elegantly by Tuft in 1949. He reported a series of fifty-four patients, of whom forty-six were sensitive to extracts of floor dust made from their own houses ('autologous house dust'). He also reported two patients with atopic dermatitis who were 'cured' by cleaning their houses.

Over the few years after that report the theory that inhalant allergens were an important factor in atopic dermatitis became much less widely held. Today few dermatologists and a minority of allergists advise patients with atopic dermatitis to avoid house dust allergens. Indeed, most dermatology clinics do not consider diagnosis of inhalant allergy as part of the management of atopic dermatitis. It is worth going over briefly the observations that have been used as arguments against a role for inhalant allergens.

(1) Most patients (even adults) are not aware that inhalant allergens exacerbate their disease. In particular, it is unusual for patients to be aware that house dust is a cause of their skin irritation.

(2) Desensitization is not a consistently effective treatment for atopic dermatitis. At the time (i.e. the 1950s) this observation carried considerable weight with allergists.

(3) Simple injection of allergens into the skin of allergic individuals gives rise to wheal and flare reactions which resolve without leaving a mark on the skin. Thus, traditional techniques for skin testing do not indicate that allergens can cause eczema.

(4) Finally, Schnyder (1957) reported that all the patients who had positive skin tests to inhalant allergens also had inhalant allergy, i.e. rhinitis or asthma. He argued that the skin sensitivity was explained by their inhalant allergies.

These arguments were established before the discovery of IgE in 1967, and the demonstration that most of the patients with atopic dermatitis had raised total serum IgE (Ishizaka, Ishizaka & Hornbrook, 1967; Juhlin *et al.*, 1969; Johansson, Bennich & Berg, 1972; Johnson *et al.*, 1974). In severe atopic dermatitis total serum IgE is often very high, i.e. > 2000 International Units/ml (normal range 5–200 iu/ml; 1 iu = 2.4 ng). It also became clear that many of these patients had very high levels of IgE antibodies to allergens (Johansson *et al.*, 1972; Barnetson, Merrett & Ferguson, 1981; Chapman *et al.*, 1982a). However, again it has been argued that the IgE antibodies to dust allergens could be 'explained' by these patients' asthma. In many early publications the importance of sensitivity to house dust was stressed, although the nature of the allergen in floor dust was not clear. In 1969 Spieksma & Voorhoorst demonstrated that a large proportion of the allergen in house dust was produced by pyroglyphid mites, particularly *Dermatophagoides pteronyssinus*. In Europe dust mite extracts have largely replaced crude house dust for skin testing.

At present there is considerable nihilism about the role of allergens in atopic dermatitis (Norins, 1971; Dahl, 1981). Nonetheless it is clear that many of the patients are allergic to house dust and are also exposed to house dust; this raises several questions.

What is the protein in house dust/dust mite extracts to which these patients are allergic?

Can this allergen give rise to eczema?

Is exposure to house dust clinically relevant?

### Recent developments in dust mite scatology

Attempts to purify allergens from house dust were unsuccessful. Early attempts to purify allergens from dust mite cultures were also confusing because mites were grown on horse dander, fish meal or human skin scales. However, during the early 1970s Bencards Limited developed a technique for growing *D. pteronyssinus* on denatured non-ectodermal mammalian medium in large quantities. The availability of this culture made it possible to purify the major allergen, antigen P<sub>1</sub> (Chapman & Platts-Mills, 1978, 1980). Antigen P<sub>1</sub> is a glycoprotein of molecular weight 24,000 daltons which is very rapidly soluble in aqueous solution. It is unusual in that the allergen is found in a wide range of forms with different isoelectric points, pI 4·7–7·2. These isoallergens have a common protein structure but differ slightly in carbohydrate composition. This same protein has been independently identified as a major allergen and purified from *D. pteronyssinus* cultures grown on completely different media; thus, both antigen Dp. 42 purified by Lind & Lowenstein (Lind, 1981) and antigen Dpt. 12 purified by Stewart & Turner (1980) are the same protein as antigen P<sub>1</sub>. Most of our recent studies have been carried out using this protein which is the major allergen produced by the most prevalent dust mite in English houses. Using antigen P<sub>1</sub> we have carried out skin testing, lymphocyte proliferation *in vitro* and measurements of serum antibodies on a quantitative basis, using the same protein for each investigation. Using the purified protein it has also been possible to develop a sensitive radioimmunoassay to measure the quantities of this allergen both in patients' houses and in dust mite cultures.

During his original studies on dust mites, Dr Spieksma observed that much of the allergen was present in the medium after live mites were removed (Spieksma & Vorhoorst, 1969). Mite debris includes cuticles, eggs and faecal particles. Since mites do not produce urine, their only important excretion is faecal. Assaying the quantities of antigen P<sub>1</sub> in different samples we found allergen in live mites, cuticles and faecal particles but not in the eggs. An assessment of the numbers of each produced suggested that mites produce fifty eggs, four cuticles and 2000 faecal particles (i.e. ~20/day) in a lifetime of 3 months. These calculations implied that >95% of the allergen accumulating in mite cultures would be in the form of faecal particles (Tovey, Chapman & Platts-Mills, 1981a). The presence of large numbers of mites in a culture at a time when food was becoming scarce, or if the mites were coprophagic, could alter these figures. However, the simple approach of removing live mites from a culture or directly examining the culture leaves little doubt that faecal particles represent a major form in which the allergen accumulates (see Table 1).

The properties of faecal particles are interesting; they have a mean diameter of 24 µm, similar to pollen grains, and their allergen content is very rapidly soluble. Their size is directly proportional to the length of the mites and none of the faecal particles are less than 10 µm in diameter (Chapman, Tovey & Platts-Mills, 1982b). The faecal particle has a peritrophic membrane which is probably made of chitin and appears to be strong. Certainly the particles do not break up when placed in saline for 16 h and our evidence from houses suggests that the

**Table 1.** Distribution of antigen P1 in dust mite culture

| Components                                                 | Number* | Antigen in each†<br>(ng) | Antigen P1<br>(ng) | %     |
|------------------------------------------------------------|---------|--------------------------|--------------------|-------|
| Mites                                                      |         |                          |                    |       |
| Adult                                                      | 214     | 3.4                      | 1493               | 11.9  |
| Young                                                      | 225     |                          |                    |       |
| Eggs                                                       | 191     | 0.01                     | 1.9                | 0.015 |
| Cuticles                                                   | 377     | 0.4                      | 151                | 1.2   |
| Total antigen P1 in components                             |         |                          | 1646               | 13.1  |
| Total antigen P1 in culture                                |         |                          | 12,509             | 100   |
| Apparent antigen P1 in faecal particles‡                   |         |                          | 10,863             | 86.8  |
| Estimated number of faecal particles<br>(0.15 ng/particle) |         |                          | 72,420             |       |

\* 50 mg of culture was examined on double-sided sellotape under incident light microscopy and the number of mites, eggs and cuticles were counted. Large numbers of faecal particles were present but identification was not sufficiently accurate for counting.

† The antigen content of each particle is based on three separate experiments in which 100 of each particle was isolated (*see* Tovey *et al.*, 1981a).

‡ This calculation assumes that all the remaining allergen is in faecal particles. We have not identified significant quantities of allergen in other particles, and the mites do not produce urine.

allergen in floor dust remains in the form of whole faecal particles. We have found very high levels of antigen P1 in dust from carpets, furniture, clothing, bedding and soft toys (Tovey *et al.*, 1981b) (Fig. 1). In air samples obtained in patients' houses the quantities of allergen are generally very low. Indeed, in undisturbed bedrooms we were unable to detect allergen, i.e. < 1.0 ng 'inhaled' in 8 h. However, during domestic activity some allergen appears in the air (~ 6–60 ng/m<sup>3</sup>) which remains airborne for a few minutes only and is largely associated with particles > 10 µm in diameter (Tovey *et al.*, 1981b). These properties of the airborne allergen are of considerable importance in considering approaches to cleaning a house. Air filtration cannot be effective if the allergen present in a room becomes airborne only during disturbance and falls rapidly afterwards. The most reasonable approach is to reduce the reservoirs of dust within the room or to prevent it becoming airborne. The properties and prevalence of dust mite faecal particles go a long way to explaining why this form of allergy is so common in England. In some houses dust samples have been estimated to contain > 500,000 faecal particles per gram. Thus, this particle is not only an appropriate size for carrying a rapidly soluble allergen to the nose but may well be the commonest protein-carrying particle in our houses. Just as grass pollen, the most common pollen grain in the air during the summer months, is the main cause of

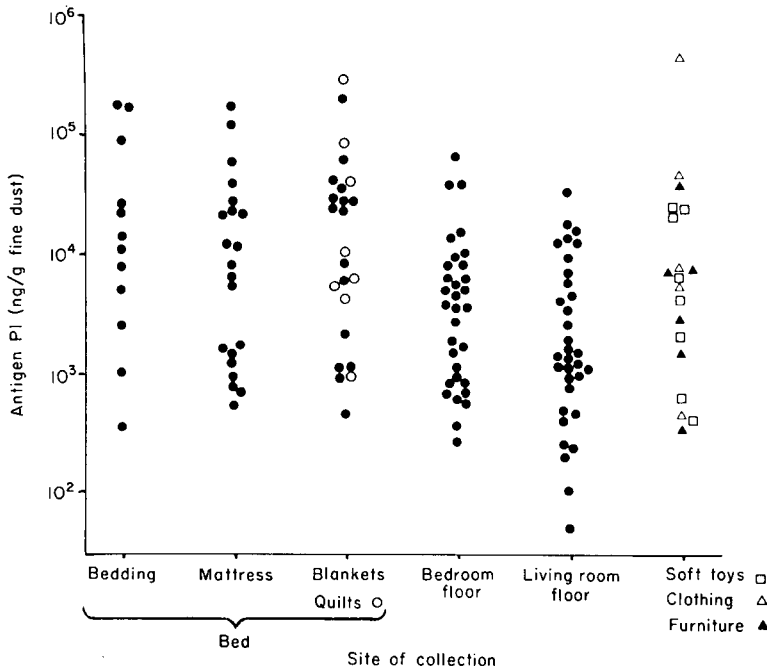


**Figure 1.** Dust mite allergen, antigen P<sub>1</sub>, in dust samples obtained with a hand-held vacuum cleaner from the houses of patients with atopic dermatitis. For details of collection and assay, see Tovey *et al.* (1981b).

seasonal hay fever, so dust mite faeces may be the commonest comparable particle in our houses year round.

### Measurement of specific antibodies to inhalant and other allergens in serum from patients with atopic dermatitis

IgE antibodies in serum can be measured by the radioallergosorbent technique (RAST) (Wide, Bennich & Johansson, 1967). In this technique the allergen is bound covalently to a particle, usually a cellulose disc, and incubated with serum. Subsequently the presence of IgE bound to the disc is detected with radiolabelled antibodies to IgE (anti-IgE). RAST is convenient because a very wide range of different allergens can be linked to the discs, but it has some problems which are of particular relevance to atopic dermatitis. Most important is the non-specific background which depends on the quantity of non-antibody IgE that binds to the discs. Non-specific binding is directly related to the total IgE and can vary considerably with different allergens on the particles. In particular some food allergens can give anomalous high background (Aas, 1978; Aalberse, 1982). The effect of total IgE is such that in any serum with > 2,000 iu of IgE/ml, a 'one plus' RAST result is probably unreliable, while with total IgE > 10,000 iu/ml, a 'two plus' RAST result may be unreliable. Levels of total IgE as high as 10,000 iu/ml are not unusual in patients with atopic dermatitis. Therefore, as a minimum all RAST results on sera from patients

with atopic dermatitis have to be related to the total serum IgE and the relevant background for each allergen-coated disc (*see* Barnetson *et al.*, 1981; Platts-Mills, Chapman & Tovey, 1981b).

An alternative approach to measuring IgE antibodies is the double antibody-antigen binding technique. In this technique serum antibodies are allowed to bind soluble radiolabelled allergen and then different classes of immunoglobulin are precipitated with specific antisera to that immunoglobulin. This type of assay has been used for measuring IgG and IgA antibodies for some years (Newcombe, Ishikawa & de Yald, 1969; Lichtenstein *et al.*, 1973; Platts-Mills *et al.*, 1976), and can be modified to measure IgE antibodies. This has proved particularly useful for studying antibodies in secretions (Platts-Mills *et al.*, 1978; Platts-Mills, 1979). The technique of this assay requires the addition of myeloma IgE to make the IgE anti-IgE precipitate, and the relatively small quantity of IgE in the patient's serum makes no effect on the background. By contrast the assay depends on direct competitive binding of IgG and IgE antibodies so that if there is a large excess of IgG antibodies to an allergen this will interfere with measurement of IgE antibodies. Using an antigen binding assay to measure IgG and IgE antibodies to antigen Pr in sera from patients with atopic dermatitis, we have reached several conclusions (Chapman *et al.*, 1982a; Mitchell *et al.*, 1982a).

- (1) The levels of both IgE and IgG antibodies to antigen Pr are high in a large proportion of these patients.
- (2) In some cases the IgE antibodies against dust mite and grass pollen allergens together make a significant contribution to the total IgE.
- (3) Skin tests on these patients often have little flare relative to the size of the wheal and should only be carried out on skin that is not involved or is in remission. Nonetheless, there is a good correlation between positive skin tests and the presence of IgE antibodies in serum.
- (4) There is a proportion of patients with atopic dermatitis who have never had asthma and they too can have very high levels of IgE antibodies to antigen Pr. Thus, the levels of IgE antibody to inhalant allergens cannot be explained by concomitant asthma.
- (5) Finally, we have *not* found IgE antibodies against diphtheria toxoid or against allergens to which these antigens have not been exposed. This suggests that they do not universally make IgE responses. Indeed, the IgE antibody responses appear to be predominantly against well-recognized allergens.

Thus, the studies on antibodies and skin tests show unequivocally that many patients with atopic dermatitis are allergic to allergens produced by the house dust mite. In many cases it appears that they are quantitatively more allergic to these proteins than to any others. Also many of these patients are exposed to these allergens both in the air of their houses ( $\text{ng/m}^3$ ) and in the dust in beds ( $5\text{--}100\ \mu\text{g/gram}$ ).

These observations led to the question: what is the effect of large quantities of allergen applied directly to the skin? The quantity of allergen that can be injected intradermally is very limited because of the risks of anaphylaxis. By contrast, large quantities can be applied on a patch test. Most known contact-sensitizing agents are low molecular weight, lipid-soluble substances and are not impeded by the normal epidermis. Because most allergens have a molecular weight  $> 10,000$  daltons and are water soluble, we decided to mildly abrade the skin to remove the keratinized layers, before applying allergen on a pad of gauze for 48 h.

### Eczematous reactions to patch tests with inhalant allergens

The application of allergen for 48 h to the mildly abraded skin of a patient with atopic dermatitis causes a marked reaction which includes erythema, papules, exudation and scaling (Mitchell *et al.*, 1982a). In contrast, saline generally causes minimal reactions. The evidence that this is an immunologically specific reaction is two-fold; first, subjects who are not allergic do not react to allergens in this way, and second, the patients do not react to proteins to which they are not allergic (e.g. extract of ragweed pollen which is an important allergen in the U.S.A.). The time course of these reactions suggests that they are a form of delayed hypersensitivity response. It is emphasized that this form of patch testing is only performed when patients are in remission, either naturally or because of hospital admission, as the application of damp gauze to the skin of a patient with severe or moderately inflamed eczema can give rise to a non-specific irritant response. Although it was clear that the same allergen extract could produce an immediate wheal and flare response or a delayed patch response in the same patient, it remained possible that the two responses were produced by different proteins in the extract. Using the purified dust mite allergen, antigen P<sub>I</sub>, it was clear that the delayed patch response could be induced with the same protein which gave immediate responses. These patch tests were performed with 5 µg antigen P<sub>I</sub>, which was at least 100,000 times greater than the quantity necessary to give an immediate wheal and flare response.

Biopsy of these allergen-induced patch test responses revealed a cellular infiltrate most prominent in the dermis. Epidermal changes of spongiosis and microvesiculation were sometimes present, particularly in patch responses maintained for more than 2 days. Appropriate tissue fixation and embedding procedures revealed that the cellular infiltrate included mononuclear cells, eosinophils, neutrophils and basophils. The cellular infiltrate in these patch lesions is that of cutaneous basophil hypersensitivity (CBH) which is a form of delayed hypersensitivity (Dvorak, Mihm & Dvorak, 1976; Askenase, 1979). A similar response has been reported to *Staphylococcus aureus* antigen in these patients (Henocq & Gaillard, 1981). It is therefore clear that these lesions should be interpreted in terms of our current knowledge of the prolonged effects of immediate hypersensitivity, as well as our present understanding of delayed hypersensitivity.

#### *Cutaneous basophil hypersensitivity (CBH)*

In 1970 Dvorak and his colleagues reported a form of delayed skin reaction in experimental animals that was infiltrated with basophils (Dvorak *et al.*, 1970). The animals had been immunized with protein without using mycobacterial adjuvants (i.e. without Freund's complete adjuvant). The term cutaneous basophil hypersensitivity (CBH) was used to describe these responses in order to distinguish them from classical delayed hypersensitivity (DH) lesions which contain very few basophils. Delayed hypersensitivity is normally observed after animals have been immunized using antigen together with mycobacterial adjuvants. CBH lesions are less indurated than classical DH responses and resolve more rapidly, i.e. within 48 h. In 1934 Jones & Mote described a human skin reaction that could be elicited following repeated intradermal injections of rabbit serum proteins. These reactions are now considered to be a

human example of cutaneous basophil hypersensitivity (Dvorak *et al.*, 1970). Experimental immunization of animals with worms, ticks, fungi and tumours commonly gives rise to lesions of this type which generally include eosinophils and neutrophils as well as mononuclear cells and basophils (Askenase, 1977). Using routine techniques for fixation and staining of specimens, tissue mast cells can be demonstrated but basophils are usually completely degranulated and cannot be identified. By contrast when skin specimens are fixed rapidly in Karnovsky's fixative, embedded in methacrylate and examined in 1  $\mu$ m sections, the metachromatic granules of polymorphonuclear basophils are easily demonstrable (Dvorak *et al.*, 1970; Godfrey *et al.*, 1981).

The expression of cutaneous basophil hypersensitivity is under complex control (Askenase, 1979). There seems little doubt that basophil infiltration requires sensitized T cells, and that transfer of sensitized T cells to a non-immune animal can transfer sensitivity (Dvorak *et al.*, 1976). However, there appear to be other controls which can prevent basophil infiltration as well as other mechanisms by which basophils can be recruited. Surprisingly, T cells from an animal immunized to give classical delayed hypersensitivity will transfer CBH, which suggests that the ability to express CBH responses is suppressed in the donor animal (Askenase, 1977). In keeping with this possibility, if both serum and cells from donor animals are transferred together, the recipients will show delayed hypersensitivity with very few basophils (Mitchell & Askenase, 1982). Thus, the serum of immunized animals contains substances which can regulate the morphology of delayed hypersensitivity responses. If similar regulatory responses occur in humans they could well play a role in controlling the site and form of reactions to allergens.

Cutaneous basophil hypersensitivity can also be transferred from one guinea-pig to another using IgG1 antibodies (Haynes, Rosenstein & Askenase, 1978). This transfer is not a parallel of the Prausnitz-Kustner reaction since it can only be achieved by systemic injections and not by local injection into the skin. Other evidence suggests that this transfer of CBH by antibody is dependent on T cells and may involve a role for cytophilic antibodies in T cells. Most CBH lesions contain eosinophils as well as basophils, and the lesions transferred with IgG1 antibody contain abundant eosinophils. It is important to note that all these experimental skin lesions are induced with between 10 and 100  $\mu$ g of protein injected into the skin. This quantity is far greater than can be used for immediate skin tests in humans but is comparable to the quantities used in the modified patch tests.

#### *Late reactions in the skin*

Most immediate positive skin tests resolve in about 2–3 h; however, some of the stronger reactions may persist and then show increased induration and erythema between 6 and 12 h after the test. This late reaction following an immediate response has also been observed in the lungs and the nose and has often been taken as a model of the way in which allergens cause delayed symptoms (Dolovitch *et al.*, 1973; Pepys & Hutchcroft, 1975; Pelikan, 1978). Following immediate skin tests a cellular infiltrate occurs in the dermis with the same time course as the late reactions. This infiltrate includes mononuclear cells, eosinophils and basophils and would appear to be cutaneous basophil hypersensitivity (CBH). In addition, late reactions can be transferred with IgE antibody, and the transferred lesions also have a cellular infiltrate (Solley *et*

*al.*, 1976). However, the simple view that late reactions are CBH and can be transferred does not hold up. First, it is not clear that the cellular infiltrate of the passively transferred lesion includes basophils; our own experience with passive transfer suggests that basophils are not a feature of passively transferred lesions. Second, it has been shown that a cellular infiltrate follows late reactions even in the absence of a macroscopic late reaction (Richerson *et al.*, 1979). Thus, at present, it appears that there are two separate events following an immediate skin test; a cellular infiltrate including basophils which is usually not visible macroscopically, and a swelling of the skin site (which may be tender) which appears to be a direct consequence of IgE mediated mediator release. We would also support the view that eosinophil infiltrates can be induced by IgE antibody on mast cells or repeated non-specific mast cell triggering but that basophil infiltration depends on sensitized T cells (Dvorak *et al.*, 1976; James, Kennedy & Eady, 1982). *In vitro* studies on chemotactic factors support this conclusion; it is well established that production of eosinophil chemotactic factor and neutrophil chemotactic factor can be triggered by anaphylactic degranulation of mast cells and/or basophils. By contrast, basophil chemotactic factor has only been demonstrated as a product of sensitized T lymphocytes (Ward *et al.*, 1975; Lett-Brown, Boetcher & Leonard, 1976).

#### *Significance of the eczematous response to allergen patch tests*

When 'large' quantities of allergen are applied to a mildly abraded skin test site it is probable that several different events are occurring. First, there is an immediate positive reaction which may be apparent as oedema and itching after one hour. Second, there are the known consequences of repeated immediate reactions, i.e. an eosinophil infiltrate with or without induration. Finally, there is a further cellular infiltrate including T cells and basophils. Since these basophils are sensitized with IgE antibody they may also react to antigen in the skin site and add further to the local inflammation. In guinea-pigs it has been clearly demonstrated that basophils infiltrating the skin can be triggered by local allergen. Furthermore, it has been shown that basophils recruited by one antigen and sensitized with IgG<sub>1</sub> antibody to a second antigen can be triggered by the second antigen (Mitchell, Brown & Askenase, 1982b). This last phenomenon is potentially of great importance in considering human atopic dermatitis, because many of the patients appear to be sensitive to multiple allergens and also to a range of contact sensitizing agents. It is possible that basophils recruited to a skin site by a contact sensitizing agent, e.g. detergent or perfume, could be triggered by an allergen, e.g. house dust mite allergen on the skin. The skin reaction produced by traditional patch tests for contact sensitivity is known to include a basophil infiltrate.

The published histology of chronic lichenified atopic dermatitis does not include a basophil or eosinophil infiltrate but has been shown to have increased numbers of mast cells (Mihm *et al.*, 1976). The lesions we are looking at have only been present for 2 days and it is very difficult to find comparable naturally occurring lesions. Furthermore, it has been shown that continued stimulation of experimental basophil-containing lesions may lead to progressive 'replacement' of basophils by mast cells (Dvorak *et al.*, 1976). It is interesting that chronic contact sensitivity lesions similarly are not the same as acute lesions induced with a patch test (Dvorak *et al.*, 1974; Mihm *et al.*, 1976).

The modified patch test is not envisaged as a diagnostic test. The quantity of allergen used is potentially hazardous so that the patients should always remain under supervision for at least 1 hour after application of the test. It is necessary to have patients in remission or with relatively quiet disease at the time of the test. Even with patients in remission some of the biopsy sites become locally infected with *S. aureus*. None of our patients have required more than local dressing of the biopsy sites, and none of the patients have shown any evidence of systemic effects from allergen. We feel that the modified patch test is an interesting experimental model of the way in which allergens might give rise to eczema in allergic patients. We hope that further studies of these patches will elucidate the immunological mechanisms involved.

### **Allergen-specific treatment in the management of atopic dermatitis**

While there is considerable theoretical interest in the mechanisms by which allergens might cause eczema, the real interest lies in the implications for management. Historically the demonstration of a role for a given allergen has led to two separate approaches, either avoidance of the offending allergen or desensitization.

#### *Desensitization treatment*

The mechanisms involved in the reduction of pollen-induced seasonal hay fever symptoms by desensitization injections are not understood. The improvement cannot be attributed simply to reduced IgE antibody or increased IgG 'blocking' antibody (Platts-Mills, 1981). In general, desensitization either with house dust or dust mite extracts has not been very successful in treating either perennial rhinitis or asthma. Some years ago Herxheimer & Prior (1952) suggested that the problem with desensitization using house dust extracts was due to the intermittent large doses of dust that patients were exposed to in their own homes. They thought that these large doses interfered with the gradual process of desensitization.

The general experience with desensitization treatment for atopic dermatitis has been unsuccessful. Perhaps this is not surprising since the major allergen for many of these patients appears to be house dust, and exposure in their beds is often very high (see Fig. 1). It might be thought that desensitization would not work in atopic dermatitis if the skin inflammation was mediated by T cells as well as IgE antibodies. However, it is perfectly possible that similar mechanisms are involved in allergic rhinitis and asthma, and that the role of desensitization in these diseases is to alter the response of sensitized T cells. Certainly the failure of specific desensitization in the treatment of atopic dermatitis cannot be taken as evidence against a role for allergens in the immunopathogenesis of atopic dermatitis. At present, we feel that this treatment has no place in the management of atopic dermatitis.

#### *Allergen avoidance*

*House dust mite.* There have been occasional reports for some years that dust avoidance can help atopic dermatitis (Tuft, 1949). The main problems with assessing this mode of treatment are the practical difficulties in cleaning houses. The advice normally given to dust allergic

**Table 2.** Patients whose atopic dermatitis has shown prolonged improvement on allergen avoidance at home

| Patient | Age | Sex | Dust avoidance | Diet               |
|---------|-----|-----|----------------|--------------------|
| C.H.    | 16  | M   | †              | none               |
| S.C.    | 31  | F   | *              | Egg-free           |
| N.S.    | 26  | M   | †              | none               |
| S.W.    | 17  | F   | †              | none               |
| P.P.    | 9   | M   | †              | none               |
| J.S.    | 37  | M   | *              | none               |
| C.E.    | 14  | F   | †              | none               |
| R.L.    | 2   | M   | none           | Milk-free          |
| S.M.    | 22  | F   | none           | Egg-free           |
| M.M.    | 35  | F   | none           | Egg- and milk-free |

\* Mattress vacuumed regularly and bedding washed regularly.

† Whole bedroom altered as well, including replacement of carpet and removal of soft furniture.

patients with asthma is not carefully observed and in most cases does not achieve a significant reduction in dust mites or dust mite allergens (Burr *et al.*, 1980; Korsgaard, 1982). Although dust mite allergens may be present all over the house, bedrooms and particularly beds represent a major source and probably justify the greatest efforts. It is perfectly possible to design a bedroom that is effectively dust mite-free but this requires replacing carpets with washable flooring, regular hot washing of all bedding, curtains and clothes and awareness that mattresses are exceptionally good reservoirs for mites. Regular vacuuming of the mattress and covering is required. It is well recognized that patients with atopic dermatitis improve when they are admitted to hospital (Rost, 1932; Tuft, 1949). The hospital rooms that we have studied have very low levels of dust mite allergens, are dry, have easily washable bedding and no carpets. Our own experience is that 20 out of 23 dust-allergic patients admitted to hospital without changing their medical treatment have shown dramatic improvement within 10 days. Obviously hospital admission has many effects in addition to avoiding house dust allergens. However, we are already aware of a group of patients who have shown long term improvement after cleaning their bedrooms (Table 2).

*Food.* There is extensive literature on the use of diets in atopic dermatitis which varies from totally enthusiastic to completely unimpressed (*see* Hill, 1934; Atherton *et al.*, 1978). The difficulties in adhering to a strict diet are a major problem in food allergen avoidance. Egg-free diets are relatively easy, but milk-free or colouring- and preservative-free diets are difficult to maintain because of the wide use of colouring, preservatives and milk proteins in prepared foods. Certainly any diet requires supervision by a dietetic department in order to prevent nutritional or vitamin deficiencies. This risk is greatest among young children and has led many paediatricians to oppose any form of diet in the management of eczema.

Some patients are aware that certain foods (e.g. fish or eggs) or skin preparations (e.g. perfumes or lanolin) will exacerbate their skin and have avoided these foods and ointments for years. When patients are admitted to dust-free conditions in hospital it often becomes clear that other dietary or contact sensitizing agents are also playing a role. If multiple factors are involved in exacerbating a disease it is not surprising that attempts to control the dermatitis by dietary measures at home are often confusing. At present, we feel that all cases of severe eczema which are unresponsive to local steroids, or require continuous local steroid treatment, should be assessed in dust-free conditions. We attempt to diagnose dust allergy, by skin tests and serum antibody measurements, in all our patients and give advice on creating a 'dust mite-free' bedroom to most of them. On the dietary front it is often not possible to diagnose food 'allergy' by skin tests or *in vitro* assays so that many changes in diet have to be empirical. In most patients we attempt to simplify the diet by removing colouring and preservatives. Only where other measures are failing do we proceed to a full milk- and egg-free diet. From our experience there seems little doubt that a combination of dust avoidance, dietary control, avoidance of sensitizing agents, and control of skin infection can dramatically reduce the symptoms of atopic dermatitis. However, it remains to be proven that a practicable policy of cleaning houses with or without dietary control has an important role to play in the management of severe eczema at home.

## Conclusions

Curiously, we seem to be in the same state of knowledge today as we were in 1947. The evidence that allergens are important in atopic dermatitis, although strong, is largely circumstantial and the evidence that allergen avoidance is helpful is not controlled. On the other hand, all the arguments used against a role for dust in the pathogenesis of atopic dermatitis now appear to be either wrong or irrelevant. In particular, we have shown that allergens applied to the skin can give rise to lesions which have both the macroscopic appearances of eczema and a dermal cellular infiltrate. Further, the fact that patients are often unaware that allergens exacerbate their eczema is not surprising if the response is a delayed response and the allergens, e.g. house dust, are present every day. Finally, the fact that there are no controlled trials to establish that cleaning houses is helpful in the management of this disease may simply reflect the difficulty of carrying out such a trial.

## References

- AALBERSE, R.C. (1982) Personal communication.
- AAS, K. (1978) The diagnosis of hypersensitivity to ingested foods: Reliability of the skin prick testing and the radioallergosorbent test with different materials. *Clinical Allergy*, **8**, 39-50.
- ALTOUNYAN, R.E.C. (1970) *Disodium Chromoglycate in Allergic Airways Disease* (Ed. by J.Pepys and A.W.Frankland), pp. 47-53. Butterworths, London.
- ASKENASE, P. (1977) Role of basophils, mast cells and vasoamines in hypersensitivity reactions with a delayed time course. *Progress in Allergy*, **23**, 199-320.
- ASKENASE, P.W. (1979) Basophil arrival and function in tissue hypersensitivity reactions. *Journal of Allergy and Clinical Immunology*, **64**, 79-89.
- ATHERTON, D.J., SEWELL, M., SOOTHILL, J.F., WELLS, R.S. & CHILVERS, C.E.D. (1978) A double-blind controlled crossover trial of an antigen-avoidance diet in atopic eczema. *Lancet*, **i**, 401-403.

- BARNETSON, R.St C., MERRETT, T.G. & FERGUSON, A. (1981) Hyperimmunoglobulinaemia E in atopy. *Clinical and Experimental Immunology*, **46**, 54–60.
- BLACKLEY, C.H. (1873) *Experiments and Researches on the Causes and Nature of Catarrhus Aestivus*. Balliere, London.
- BURR, M.L., DEAN, B.V., MERRETT, T.G., NEALE, E., ST LEGER, A.S. & VERRIER-JONES, J. (1980) Effects of anti-mite measures on children with mite-sensitive asthma: a controlled trial. *Thorax*, **35**, 506–512.
- CHAPMAN, M.D. & PLATTS-MILLS, T.A.E. (1978) Measurement of IgG, IgA and IgE antibodies to *Dermatophagoides pteronyssinus* by antigen-binding assay, using a partially purified fraction of mite extract (F4P1). *Clinical and Experimental Immunology*, **34**, 126–136.
- CHAPMAN, M.D. & PLATTS-MILLS, T.A.E. (1980) Purification and characterization of the major allergen from *Dermatophagoides pteronyssinus* antigen P1. *Journal of Immunology*, **125**, 587–592.
- CHAPMAN, M.D., ROWNTREE, S.R., MITCHELL, E.B., FUENMAJOR, M.C. & PLATTS-MILLS, T.A.E. (1982a) Quantitative assessments of IgG and IgE antibodies to inhalant allergens in patients with atopic dermatitis. *Journal of Allergy and Clinical Immunology*, in press.
- CHAPMAN, M.D., TOVEY, E.R. & PLATTS-MILLS, T.A.E. (1982b) Physical properties and origin of house dust mite allergen. *Folia Allergologica*, **29**, 25–35.
- COCA, A.F. & COOK, R.A. (1923) On the classification of the phenomena of hypersensitiveness. *Journal of Immunology*, **8**, 163–170.
- DAHL, M.G.C. (1981) Allergy and the skin. In: *Immunological and Clinical Aspects of Allergy* (Ed. by M.H.Lessof), pp. 179–215. MTP Press.
- DOLOVITCH, J., HARGREAVE, F.E., CHALMERS, R., SHIER, K.J., GAULDIE, J. & BIENENSTOCK, J. (1973) Late cutaneous allergic responses in isolated IgE dependent reactions. *Journal of Allergy and Clinical Immunology*, **52**, 38–46.
- DVORAK, H.F., DVORAK, A.M., SIMPSON, B.A., RICHERSON, H.B., LESKOWITZ, S. & KARNOVSKY, M.J. (1970) Cutaneous basophil hypersensitivity. II. A light and electron microscopic description. *Journal of Experimental Medicine*, **132**, 558–582.
- DVORAK, H.F., MIHM, M.C., DVORAK, A.M., JOHNSON, R.A., MANSEAU, E.J., MORGAN, E. & COLVIN, R.B. (1974) Morphology of delayed type hypersensitivity reactions in man. I. Quantitative description of the inflammatory response. *Laboratory Investigation*, **31**, 111–130.
- DVORAK, A.M., MIHM, M.C. & DVORAK, H.F. (1976) Degranulation of basophilic leucocytes in allergic contact dermatitis reactions in man. *Journal of Immunology*, **116**, 687–695.
- FEINBERG, S.M. (1939) Seasonal atopic dermatitis. *Archives of Dermatology and Syphilis (Chicago)*, **40**, 200.
- GODFREY, H.P., PASTORE, M.S. & ASKENASE, P.W. (1981) A modified giemsa stain for demonstrating basophils in glycol methacrylate embedded tissues sections. *Journal of Histotechnology*, **4**, 80–82.
- HARGREAVE, F.E., RUFFIN, R.E., JUNIPER, E.F., FRITH, P.A. & DOLOVITCH, J. (1979) Changes in bronchial response to allergen after allergen inhalation tests. *Journal of Allergy and Clinical Immunology (abstract)*, **63**, 150–154.
- HAYNES, J.D., ROSENSTEIN, R.W. & ASKENASE, P.W. (1978) A newly described activity of guinea pig IgG1 antibodies. Transfer of cutaneous basophil reactions. *Journal of Immunology*, **120**, 886–894.
- HENOCQ, E. & GAILLARD, J. (1981) Cutaneous basophil hypersensitivity in atopic dermatitis. *Clinical Allergy*, **11**, 13–20.
- HERXHEIMER, H. & PRIOR, F.N. (1952) Further observations on induced asthma and bronchial hyposensitization. *International Archives of Allergy*, **3**, 189–207.
- HILL, L.W. (1934) Chronic atopic eczema (Neurodermatitis) in childhood. *Journal of the American Medical Association*, **103**, 1430.
- ISHIZAKA, K., ISHIZAKA, T. & HORN BROOK, M.M. (1967) Allergen binding activity of IgE, IgG and IgA, antibodies in sera from atopic patients: *in vitro* measurement of reaginic antibody. *Journal of Immunology*, **98**, 490–501.
- JAMES, M.P., KENNEDY, A.R. & EADY, R.A.J. (1982) A microscopic study of inflammatory reactions in human skin induced by histamine and compound 48/80. *Journal of Investigative Dermatology*, **78**, 406–413.

- JOHANSSON, S.G.O., BENNICH, H. & BERG, T. (1972) The clinical significance of IgE. In: *Progress in Clinical Immunology* (Ed. by R.S.Schwartz), pp. 157-181. Grune & Stratton, New York.
- JOHNSON, E.E., IRONS, J.S., PATTERSON, R. & ROBERTS, M. (1974) Serum IgE concentration in atopic dermatitis. *Journal of Allergy and Clinical Immunology*, **54**, 94-99.
- JONES, T.D. & MOTE, J.R. (1934) The phases of foreign protein sensitization in human beings. *New England Journal of Medicine*, **210**, 120-122.
- JUHLIN, L., JOHANSSON, S.G.O., BENNICH, H., HOGMAN, C. & THYRESSON, N. (1969) Immunoglobulin E in dermatoses. *American Medical Association Archives of Dermatology*, **100**, 12-23.
- KERREBIJN, K.F. (1970) Endogenous factors in childhood CNSLD. Methodological aspects in population studies. In: *Bronchitis III* (Ed. by N.G.M.Orie and R. van der Lende), pp. 38-48. Royal Vangorcum, Assen, The Netherlands.
- KORSGAARD, J. (1982) Preventive measures in house-dust allergy. *American Review of Respiratory Diseases*, **125**, 80-84.
- LETT-BROWN, M.A., BOETCHER, D.A. & LEONARD, E.J. (1976) Chemotactic responses of normal human basophils to C5a and to lymphocyte derived chemotactic factor. *Journal of Immunology*, **117**, 246-252.
- LICHTENSTEIN, L.M., ISHIZAKA, K., NORMAN, P.S., SOBOTKA, A.K. & HILL, B.M. (1973) IgE measurements in ragweed hay fever. Relationship to clinical severity and the results of immunotherapy. *Journal of Clinical Investigation*, **52**, 472-482.
- LIND, P. (1981) Characterization of a partially purified allergen preparation of dermatophagoides pteronyssinus and of two isolated major-allergens. *Proceedings of the Scandinavian Allergological Congress, Gothenberg*, June 1981.
- MIHM, M.C., SOTER, N.A., DVORAK, K.F. & AUSTEN, K.F. (1976) The structure of normal skin and the morphology of atopic eczema. *Journal of Investigative Dermatology*, **67**, 305-312.
- MITCHELL, E.B. & ASKENASE, P.W. (1982) Suppression of T cell mediated cutaneous basophil hypersensitivity by serum from guinea pigs immunized with mycobacterial adjuvant. *Journal of Experimental Medicine*, **156**, 159-172.
- MITCHELL, E.B., CROW, J., CHAPMAN, M.D., JOUHAL, S.S., POPE, F.M. & PLATTS-MILLS, T.A.E. (1982a) Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet*, **i**, 127-130.
- MITCHELL, E.B., BROWN, S.J. & ASKENASE, P.W. (1982b) Antibody dependent mediator release at CBH reactions. *Journal of Immunology*, **129**, 1663-1669.
- NEWCOMB, R.W., ISHIZAKA, K. & DE VALD, B.L. (1969) Human IgG and IgA diphtheria antitoxins in serum, nasal fluids and saliva. *Journal of Immunology*, **103**, 215-224.
- NORINS, A.L. (1971) Atopic dermatitis. *The Paediatric Clinics of North America*, **18**, 801-838.
- PELIKAN, J. (1978) Late and delayed responses of the nasal mucosa to allergen challenge. *Annals of Allergy*, **41**, 37-56.
- PEPYS, J. & HUTCHCROFT, B.J. (1975) Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *American Reviews of Respiratory Diseases*, **112**, 829-859.
- PLATTS-MILLS, T.A.E., VON MAUR, R.K., ISHIZAKA, K., NORMAN, P.S. & LICHTENSTEIN, L.M. (1976) IgA and IgG anti-ragweed antibodies in nasal secretions. Quantitative measurements of antibodies and correlation with inhibition of histamine release. *Journal of Clinical Investigation*, **57**, 1041-1050.
- PLATTS-MILLS, T.A.E., SNAJDR, M.J., ISHIZAKA, K. & FRANKLAND, A.W. (1978) Measurement of IgE antibody by an antigen binding assay: correlation with PK activity and IgG and IgA antibodies to allergens. *Journal of Immunology*, **120**, 1201-1210.
- PLATTS-MILLS, T.A.E. (1979) Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *Journal of Immunology*, **122**, 2218-2225.
- PLATTS-MILLS, T.A.E. (1981) Desensitization treatment for hay fever. *Immunology Today*, **2**, 35-37.
- PLATTS-MILLS, T.A.E., CHAPMAN, M.D. & TOVEY, E.R. (1981b) Radioimmunoassays in Allergy. In: *Immunoassays for the 80s* (Ed. by A.Voller and D.Bartlett-Bidwell), pp. 289-311. MTP Press, Lancaster.
- PLATTS-MILLS, T.A.E., TOVEY, E.R., MITCHELL, E.B., MOZARRO, H., NOCK, P. & WILKINS, S.R. (1982) Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet*, **ii**, 675-678.

- RICHERSON, H.B., RAJTORA, D.W., PENICK, G.D., DICK, F.R., YOO, T.J., KAMMERMEYER, J.K. & ANURAS, J.S. (1979) Cutaneous and nasal allergic responses in ragweed hay fever: Lack of clinical and histopathologic correlations with late phase reactions. *Journal of Allergy and Clinical Immunology*, **64**, 67-77.
- ROST, G.A. (1932) Ueber Erfahrungen mit der allergenfreien Kammer nach Storm van Leeuwen: insbesondere in der Spatperiode der exsudativen Diathese. *Archives of Dermatology and Syphilis (Berlin)*, **155**, 297.
- SCHLOSS, O.M. (1915). Allergy to common foods. *Transactions of the American Paediatric Society*, **27**, 62-68.
- SCHNYDER, U.W. (1957) The importance of intracutaneous tests in various types of constitutional neurodermatitis. *International Archives of Allergy*, **11**, 64-72.
- SOLLEY, G.O., GLEICH, G.J., JORDAN, R.E. & SCHROETER, A.L. (1976) The late phase of the immediate wheal and flare skin reaction—its dependence on IgE antibodies. *Journal of Clinical Investigation*, **58**, 408-420.
- SPIEKSMAN, F. TH M. & VOORHORST, R. (1969) Comparison of skin reactions to extracts of house dust, mites and human skin scales. *Acta Allergologica*, **24**, 124-135.
- STEWART, G.A. & TURNER, K.J. (1980) Isolation and characterisations of allergens from *Dermatophagoides pteronyssinus*. In: *Advances in Allergology and Applied Immunology* (Ed. by A.Oehling, E.Mathov, I.Glazer and C.Arbesman), pp. 703. Pergamon Press, Oxford.
- STORM VAN LEEUWEN, W. (1927) Asthma and tuberculosis in relation to 'climate allergens'. *British Medical Journal*, **ii**, 344-347.
- SULZBERGER, M.B. & VAUGHAN, W.T. (1934) Experiments in silk hypersensitivity and the inhalation of allergen in atopic dermatitis. *Journal of Allergy*, **5**, 544-548.
- TOVEY, E.R., CHAPMAN, M.D. & PLATTS-MILLS, T.A.E. (1981a) Mite faeces are a major source of house dust allergens. *Nature*, **289**, 592-593.
- TOVEY, E.R., CHAPMAN, M.D., WELLS, C.W. & PLATTS-MILLS, T.A.E. (1981b) The distribution of dust mite allergen in the houses of patients with asthma. *American Review of Respiratory Diseases*, **124**, 630-635.
- TUFT, L.A. (1949) Importance of inhalant allergens in atopic dermatitis. *Journal of Investigative Dermatology*, **12**, 211-219.
- WARD, P.A., DVORAK, H.F., COHEN, S., YOSHIDA, T., DATA, R. & SELVAGGIO, S.S. (1975) Chemotaxis of basophils by lymphocyte dependent and lymphocyte independent mechanisms. *Journal of Immunology*, **114**, 1523-1531.
- WIDE, L., BENNICHT, H. & JOHANSSON, S.G.O. (1967) Diagnosis of allergy by an *in vitro* test for allergen antibodies. *Lancet*, **ii**, 1105-1107.

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