

## **Aspergillus hypersensitivity in asthmatics in Cape Town**

S. R. BENATAR, G. A. KEEN *and* W. DU TOIT NAUDE

*Departments of Medicine and Bacteriology, University of Cape Town,  
and Groote Schuur Hospital, Observatory, Cape, South Africa*

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### **Summary**

An analysis of skin prick reactions in 500 consecutive patients referred for investigation and management of asthma showed that 240 patients had multiple positive reactions. Of these patients 46% had positive reactions to *Aspergillus* and they differed from patients with multiple positive reactions excluding *Aspergillus* by having onset of asthma at a younger age and being more atopic. Precipitins to *Aspergillus* were present in the serum of twenty-six of seventy-one consecutive patients in whom these were looked for. Thirteen of the patients with positive precipitins had chest radiograph shadows compatible with allergic bronchopulmonary aspergillosis (ABPA) and in eight of these there was sufficient evidence to make a diagnosis of ABPA. These results were obtained in a region where ABPA had never been previously recognized and they highlight the importance of routine skin prick testing with *Aspergillus* antigen and of awareness of ABPA in making this diagnosis.

### **Introduction**

The *Aspergillus* fungus is found all over the world in soil and decaying vegetable matter. Its spores are widely distributed in the atmosphere with peak concentrations occurring in the wet cold months. The effect of inhalation of these spores is determined by the circumstances of exposure, the structural integrity of the respiratory tract and the immunological status of the host. The fungus may exist in the respiratory tract of normal man as a commensal, grow into a fungus ball in lungs damaged by tuberculosis or bronchiectasis, cause pneumonia or invasive *Aspergillus* infection in immunocompromised patients, result in allergic alveolitis if inhaled in very high concentrations, or give rise to allergic bronchopulmonary aspergillosis (ABPA) in asthmatics. Although ABPA has been most commonly recognized in the United Kingdom where it was first described (Hinson, Moon & Plummer, 1952) the condition has been identified in

Correspondence: Dr S. R. Benatar, Respiratory Clinic, Groote Schuur Hospital, Observatory, Cape, South Africa.

several other countries including South Africa (Hoene, Reed and Dickie 1973; Landri-gan, Wasty & Nigam, 1968; Benatar, 1977). The reasons for the apparent different frequency of ABPA in different countries are not clearly established and may be partly due to differences in awareness of the condition. There have been few studies of the incidence of positive skin prick reactions to *Aspergillus* or of ABPA in different populations of asthmatics so that true differences in the incidence of ABPA have not been established.

Cape Town is a coastal city with a Mediterranean climate, very similar to California. Prior to 1974 ABPA had never been diagnosed there or indeed anywhere in South Africa. In 1974 we began doing routine skin prick tests on all patients referred to our Respiratory Clinic with asthma or suspected asthma. It soon became apparent that many patients had positive prick reactions to *Aspergillus*. We then began looking for precipitins to *Aspergillus* in the serum of all patients with positive *Aspergillus* skin prick tests. A retrospective analysis of the first 500 prick-tested patients was made to determine the incidence of reactions to the various antigens used, in particular *Aspergillus*, to compare clinical features in patients with and without positive prick reactions to *Aspergillus*, and to compare clinical and radiographic features in patients with both positive prick tests and positive precipitins to *Aspergillus* with those patients having only a positive prick test to *Aspergillus*.

### Patients and methods

Skin tests were done using the modified skin prick method (Pepys, 1975). Eleven commercially available antigens (Bencard) and a control solution were used. The three *Aspergillus* strains included were *Aspergillus fumigatus*, *Aspergillus niger* and *Aspergillus terreus*. None of the patients had used antihistamines in the 24 h preceding testing. Weal diameters were measured with a mm rule 10 to 20 min after the prick test had been done. A positive reaction was defined as a weal equal to or greater than 2 mm in diameter in the absence of any reaction to the control solution, or a weal at least 2 mm larger than the control. *Aspergillus* precipitins were identified by double diffusion using locally prepared antigens of *Aspergillus fumigatus* and *A. niger* and Pasteur Institute antigens for *Aspergillus flavus*, *Aspergillus nidulans* and *Aspergillus terreus*. Serum was examined neat and after concentration three times using 'lyphogel'. Patient data and chest radiographs were reviewed retrospectively from our Respiratory Clinic records.

### Results

One hundred and eighty-eight patients had no positive skin prick reactions, 312 had positive reactions and of these, seventy-two had only a single positive reaction. The incidence of positive reactions to various allergens in the 240 patients with multiple reactions is shown in Table 1 (reactions of 3 mm or greater in size are also shown in this Table). The distribution of weal sizes for nine allergens is shown in detail in Fig. 1. Comparison of clinical features in patients with multiple positive skin prick reactions to allergens including *Aspergillus* and with patients having multiple positive skin prick reactions but not to *Aspergillus* are shown in Table 2. There was no significant difference in the age of the patients, in male to female ratio, ethnic distribution, or the number who were steroid dependent. Significantly more patients with positive *Aspergillus* prick tests, however, had had onset of asthma under the age of 10 and a positive

**Table 1.** Incidence of positive prick reactions to individual allergens in 240 patients with multiple +ve reactions

| Allergen           | Weal size   |             |
|--------------------|-------------|-------------|
|                    | 2 mm<br>(%) | 3 mm<br>(%) |
| House dust         | 90          | 79          |
| House dust mite    | 79          | 67          |
| Feathers           | 68          | 54          |
| Pollens            | 66          | 50          |
| <i>Aspergillus</i> | 44          | 26          |
| Dog hair           | 35          | 25          |
| Mixed moulds       | 27          |             |

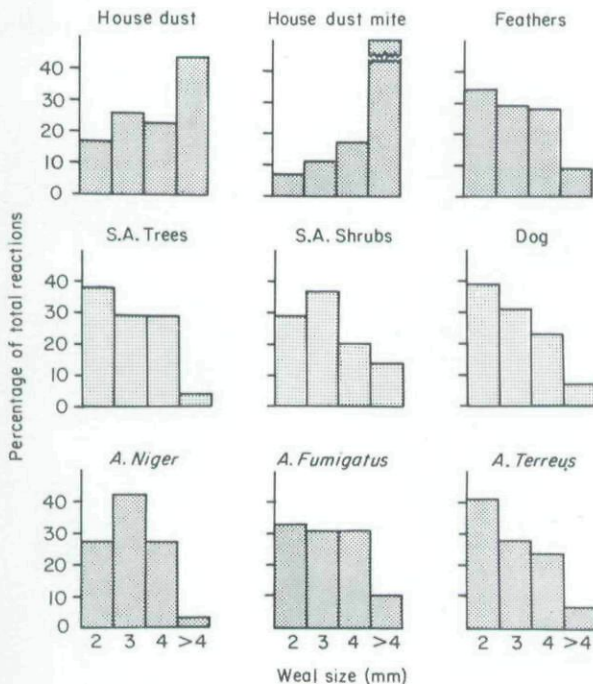


**Fig. 1.** Distribution of weal sizes to nine allergens expressed as percentages of total reactions to each allergen.

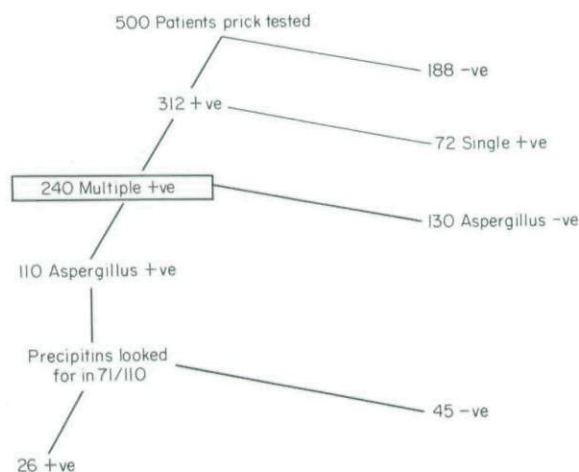
family history of atopy. They were also significantly more atopic as assessed by the number of positive prick reactions and other atopic symptoms (rhinitis and urticaria).

*Aspergillus* precipitins were looked for in the serum of seventy-one patients with positive *Aspergillus* skin prick tests. Precipitins were present in twenty-six and absent in forty-five (Fig. 2). All patients with positive precipitins had these to either *Aspergillus fumigatus* or *Aspergillus niger* (Table 3). A comparison of clinical features in

**Table 2.** Comparison of patients with and without positive prick reactions to *Aspergillus*

|                              | Multiple +ve<br>prick reactions<br><i>Aspergillus</i> +ve<br>(n=110) | Multiple +ve<br>prick reactions<br><i>Aspergillus</i> -ve<br>(n=130) |
|------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| <40 years old                | 58%                                                                  | 52%                                                                  |
| Male : female                | 0.8:1                                                                | 0.8:1                                                                |
| *B:C:W                       | 1:9:9                                                                | 1:9:9                                                                |
| Steroid dependent            | 59%                                                                  | 50%                                                                  |
| Onset of asthma < 10 yrs old | 52%†                                                                 | 29%                                                                  |
| Mean no. of +ve reactions    | 6.2                                                                  | 4.2                                                                  |
| > 5 +ve reactions            | 56%†                                                                 | 13%                                                                  |
| Other atopy                  | 48%‡                                                                 | 32%                                                                  |
| Family history               | 57%‡                                                                 | 42%                                                                  |

\* B = black; C = coloured (mixed race); w = white.

†  $P < 0.001$ .‡  $P < 0.05$ .**Fig. 2.** Skin prick tests in 500 consecutive patients referred for investigation and treatment of asthma.

patients with both positive *Aspergillus* prick tests and positive precipitins and patients having only positive *Aspergillus* prick tests showed no significant differences in the age of the patients, male to female ratio, ethnic distribution, family history of atopy, number of positive prick reactions, number of patients who were steroid dependent or age of onset of asthma (Table 4). Chest radiograph shadows compatible with ABPA were present in 50% of the patients with precipitins as compared with 9% of those without. This difference was highly significant. Of the thirteen patients who were prick and precipitin positive and showed shadows on the chest radiograph, a diagnosis of

**Table 3.** Aspergillus precipitins in patients with +ve Aspergillus prick tests

|                                       |            |
|---------------------------------------|------------|
| Precipitin -ve                        | 45 (63.4%) |
| Precipitin +ve                        | 26 (36.6%) |
| <i>A. fumigatus</i>                   | 18         |
| <i>A. niger</i>                       | 13         |
| <i>A. fumigatus</i> + <i>A. niger</i> | 5          |
| <i>A. flavus</i>                      | 5*         |
| <i>A. nidulans</i>                    | 5*         |
| <i>A. terreus</i>                     | 4*         |

\* Always with *A. fumigatus* or *A. niger*.

**Table 4.** Comparison of patients with and without positive Aspergillus precipitins

|                                  | Prick +ve<br>Precipitin +ve<br>(n=26) | Prick +ve<br>Precipitin -ve<br>(n=45) |
|----------------------------------|---------------------------------------|---------------------------------------|
| <40 years old                    | 62%                                   | 55%                                   |
| male:female                      | 1:1                                   | 1:1                                   |
| *B:C:W                           | 1:4:6                                 | 1:9:9                                 |
| Family history                   | 55%                                   | 55%                                   |
| Mean no. of +ve pricks           | 6                                     | 6                                     |
| Steroid dependent                | 67%                                   | 52%                                   |
| Onset of asthma <30 yrs          | 88%                                   | 67%                                   |
| CXR shadows compatible with ABPA | 50%†                                  | 9%                                    |

\* B=black; C=coloured (mixed race); W=white.

†  $p < 0.001$ .

ABPA was unequivocal in eight and probably in five (Table 5). The distribution of weal sizes to Aspergillus antigens in relation to precipitins and chest radiograph shadows is shown in Table 6.

## Discussion

In this study the incidence of positive prick reactions to common allergens in Cape Town is similar to that found in the United Kingdom, with house dust and house dust mite being the most frequently positive (Hendrick *et al.*, 1975). The incidence of positive Aspergillus reactions in our patients is, however, higher than in the United Kingdom where such reactions are found in 10–20% of unselected extrinsic asthmatics. There could be several reasons for this difference. Firstly, the patients attending our Clinic represent a highly selected group in that they are usually referred because they have asthma of long duration which is difficult to control. This is evidenced by the fact that 50% of our patients were steroid dependent. Secondly, it is possible that our patients had been exposed to higher concentrations of Aspergillus spores. The peak atmospheric Aspergillus spore count in Cape Town is 20–25/m<sup>3</sup> air (Hirst Spore Trap Method). This is similar to the levels reported in Cardiff (Mullins, Harvey & Seaton, 1976) and Cambridge (Hudson, 1973), but the counts cannot strictly be compared as

**Table 5.** Clinical features in support of a diagnosis of allergic bronchopulmonary aspergillosis in thirteen patients

|                                    | Undoubted<br>ABPA (n=8) | Possible<br>ABPA (n=5) |
|------------------------------------|-------------------------|------------------------|
| Asthma                             | 8                       | 5                      |
| +ve <i>Aspergillus</i> skin test   | 8                       | 5                      |
| +ve <i>Aspergillus</i> precipitins | 8                       | 5                      |
| Eosinophilia                       | 7                       | 1                      |
| Chest radiograph shadows           |                         |                        |
| Transient                          | 7                       | 0                      |
| Fixed                              | 4                       | 5                      |
| Contracted upper lobes             | 1                       | 2                      |
| Tramlines                          | 0                       | 2                      |
| Central bronchiectasis             | 3                       | 1                      |
| On steroids at time of evaluation  | 1                       | 4                      |

**Table 6.** Relationship between size of *Aspergillus* skin prick reactions, *Aspergillus* precipitins and radiographic shadows

| Size of weal on<br>prick test (mm) | +ve Precipitins<br>+ve CXR<br>(n=13) | +ve Precipitins<br>-ve CXR<br>(n=13) | -ve Precipitins<br>-ve CXR<br>(n=45) |
|------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
| 2                                  | 4 (31%)                              | 6 (46%)                              | 17 (38%)                             |
| 3                                  | 3 (23%)                              | 5 (38%)                              | 12 (27%)                             |
| > 3                                | 6 (46%)                              | 2 (16%)                              | 16 (35%)                             |

different methods of spore collection were used. It would seem that if anything spore counts in Cape Town are lower rather than higher than those in the United Kingdom. Spore count studies in the homes of asthmatics in Cape Town have, however, shown that although *Aspergillus* spores are one of the less common spores in the general atmosphere they are the fifth most common indoors, and very high counts have been detected in some homes (E. Weinberg, personal communication). This aspect needs more careful study. High counts have been previously reported in hospital wards in the United Kingdom (Nobel & Clayton, 1963). Another possibility we considered was whether we were over-interpreting the skin tests. The incidence of positive reactions to *Aspergillus* using 3 mm weals as the cut-off point (Table 1) is 26% and this is, perhaps, a more realistic figure. An analysis of precipitin reactions in relation to weal sizes and radiographic shadows (Table 6) showed that while 46% of patients with positive precipitins and chest radiograph shadows have reactions greater than 3 mm in diameter, two patients with undoubted ABPA had weal reactions of 2 mm. Investigators using the house dust mite antigen have shown that there is a good correlation between skin prick tests as small as 1–2 mm in diameter, specific IgE and nasal challenges (Stenius *et al.*, 1971). We thus felt that we could reasonably accept a 2 mm reaction as positive. Reactions smaller than this are difficult to read accurately.

The importance of recognizing ABPA lies in the fact that although its natural

history is variable and, as yet, not fully documented in its entire spectrum, it can undoubtedly result in irreversible lung damage (McCarthy & Pepys, 1971). With early diagnosis and early corticosteroid therapy it is possible to prevent recurrent episodes, and to some extent reduce long-term damaging effects (Safirstein *et al.*, 1973). The importance of this study in our community is that it has shown that with the routine use of simple skin prick testing with commercially available *Aspergillus* antigen in asthmatics, and careful further investigation of patients with positive reactions it is possible to identify patients with ABPA at least as frequently as in the United Kingdom, despite the fact that until routine prick tests had been done the existence of ABPA was denied locally. We believe that these findings may be relevant in other parts of the world and suggest that skin prick testing with *Aspergillus* antigen (the simplest screening procedure for ABPA) should be a routine part of the investigation of all asthmatic patients.

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