

## Screening for IgE-Mediated Allergy

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Sera from 425 patients were analysed with Phadebas RAST reagents against a panel of 19 allergens and the most commonly positive results were to grass pollen, *Dermatophagoides pteronyssinus* and cat epithelium. Of the 275 sera RAST-positive to any allergen, 261 were positive by a RAST technique which used a mixture of the three most common U.K. allergens; the remainder were usually positive to a mould. We conclude that 1) when a positive result is obtained after screening by the mixed-allergen RAST and a representative mould RAST, then other positive RAST results are possible, but that the extent of the investigation can be guided by a knowledge of the total serum IgE level and a computer-based history analysis; 2) when the mixed-allergen RAST and a representative mould RAST is negative, then a more specified RAST including all 19 allergens used in this investigation will be negative; 3) a positive mixed-allergen RAST result is likely to be associated with a total serum IgE level over 40 U/ml and a positive symptom pattern score derived from the computer-based history analysis.

*Key words:* atopic allergy; cluster analysis; common U.K. allergens; immunoglobulin E; mini-computers in allergy diagnosis; questionnaire; radioallergosorbent test (RAST).

*Accepted for publication 12 January 1980*

Allergy may contribute to chronic obstructive airways disease, and limited skin-prick testing can provide a useful allergy screen (2, 3, 4, 7). However, it is rarely used in a general practice, and this is an area where an efficient and convenient screen has obvious advantages in reducing the unnecessary expenditure of time, and hence money, at the allergy clinic. We report on the combined use of three simple tests to select those patients likely to benefit from a detailed allergy investigation.

### METHODS

#### *Allergy screening tests*

*History symptom score.* Patients completed a detailed Allergy Questionnaire (Fig. 1) and their answers were recorded, analysed and 'scored' with the aid of an Olivetti P. 6060

mini-computer using programs written in Basic language (10). Symptoms scores over 30% were taken as positive, unless associated either with a 'Blank/Don't Know' score over 40% or with a 'contradiction score' above zero. An example of the computer print-out for one patient is shown in Fig. 2; it illustrates the summarizing of 'when' and 'where' symptoms can occur, and the allergens 'most likely' and 'less likely' to be related to symptoms.

*Total serum IgE.* Circulating levels were measured by a conventional radio-immunoassay, using a fast solid-phase double antibody separation technique (9). Briefly, an assay tube containing 100  $\mu$ l of test (or standard) serum diluted in a 1:1 mixture of horse serum, 50  $\mu$ l of  $^{125}$ I-labelled IgE (Phadebas RIST kit: Pharmacia GB Ltd., Hounslow, Middlesex), and 100  $\mu$ l of rabbit anti-IgE (Hoechst U.K. Ltd., Hounslow,

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ALLERGY QUESTIONNAIRE

This form is to be completed by you, the patient. Please read the instructions carefully, then put the correct symbol in the box, or boxes, by the question. (You may find it helpful to read the form straight through and underline the correct answers with a pencil before you start to answer the questions, and if so when you are in the morning.) Your answers will help to decide if you are likely to have an atopic allergy and if so when you are in the morning. It is important that you answer the questions truthfully so that we can benefit other sufferers in the future, so PLEASE ANSWER EVERY QUESTION and then send the completed form to the RAST Allergy Unit in the envelope provided.

(Example: 'Do you think the weather affects your symptoms?')

Yes = Y      No = N      Don't know = ?

If 'Yes'—put 'Y' in the box;      If 'No'—put 'N' in the box;

If in doubt—put '?'—symbol for 'Don't know.'

Please PRINT clearly:

Surname ..... Female = F

First Names ..... Male = M

Today's date .....  
.....  
.....

Address .....  
.....  
.....

Birth date .....  
.....  
.....

Example: 3 December 1968 =  
.....  
.....

Telephone.....

Country of Origin .....  
.....  
.....

**IMPORTANT**  
Have you ever had infectious hepatitis or jaundice?

Yes = Y      No = N      Don't know = ?

Are you a member of the Post office and Civil Service Sanatorium Society?

Yes = Y      No = N

Name and address of your Referring Doctor or Consultant: (please print)  
.....  
.....  
.....  
Telephone Number (if known) .....  
.....

SECTION ONE

It is important to define which part of you is **NOW** (that is, within the last year) periodically affected (that is, on at least 3 separate days), also if other parts of you were periodically affected in **PREVIOUS** years.

1. **NOW** : If you have had any of the symptoms in List One during the past year, put 'Y' in correct box or boxes (fill in every box):

Yes = Y      No = N      Don't know = ?

**LIST ONE**

Eyes irritation—itching—redness—swollen eyelids

Nose stuffiness—running—sneezing—sinusitis—recurrent colds—polyps

Chest wheeziness—tightness—cough—phlegm—shortness of breath

Skin and/or Ears itching—red patches—blisters—eczema

Gut nausea—sickness—diarrhoea

Mouth/Lips/Throat itching—soreness—swollen lip or tongue

2a **PREVIOUS** : Have you periodically had any other symptom/symptoms in List One apart from those you have now?

Yes = Y      No = N      Don't know = ?

2b **PREVIOUS** : IF the reply to 2a is 'Yes', then refer to List One and fill in the correct boxes below to indicate which part/parts of you used to be affected:

Yes = Y      No = N      Don't know = ?

Eyes      Skin and/or Ears

Nose      Gut

Chest      Mouth/Lips/Throat

3. At approximately what age did your present symptoms first occur ?

Examples:      two years old      0      2      19 years old      1      9

4. How many members of your immediate family (parents, grandparents, children, brothers, sisters—not including you, yet neither husband nor your in-laws) have suffered periodically from any of the symptoms in List One?

More than two = 3      Only one = 1      Don't know = ?

Only two = 2      None = 0

5. Do antihistamines (e.g. Dimotapp—Phenargan—Pirton) help to relieve some, or all, of your symptoms?

Yes = Y      No = N      Don't know OR have never tried = ?

Fig. 1. The layout of the Allergy Questionnaire used by the patients taking part in this study.

4. Do your symptoms usually occur or worsen:  
Indoors = 1      Outdoors = 2      No difference = 3

OR  
Have you two quite different sets of symptoms, one set worse indoors, the other outdoors? = 4.

5. Do your symptoms seem worse:  
After dark = 1      In daylight = 2      No difference = 3

OR  
Have you two quite different sets of symptoms, one set worse after dark, the other in daylight? = 4.

### SECTION THREE

1. Do some, or all, of your symptoms usually improve when you are away from home on holiday?

Yes = Y      No = N      Don't know = ?

2a Do some, or all, of your symptoms usually occur, or worsen, at work?

Yes = Y      No = N      Don't know = ?

2b If your answer to 2a, is 'Yes', please describe any suspected causes:

3. Do your symptoms wake you in the night?  
Yes = Y      No = N

4. Does dusting make your symptoms worse?  
Yes = Y      No = N      Don't know = ?

5. Does making beds make your symptoms worse?  
Yes = Y      No = N      Don't know = ?

6. In the box for each animal, put '1' if you think being near that animal causes you some, or all, of your symptoms. Otherwise put '2' if you consider in close contact with the animal several times a week, or '3' if you are only rarely in close contact with it.

If any other animal/s, bird/s or fish/es causes some, or all, of your symptoms, write the name/s here:

If you are in close contact with any other animal/s, bird/s or fish/es several times a week, write the names here:

7. Is the building or district where you live damp?  
Yes = Y      No = N      Don't know = ?

8. Are there mouldy patches in any part of your home?  
Yes = Y      No = N      Don't know = ?

6. Does a cromoglycate inhaler (e.g. Intal Spin-haler—Lomusal—Rynacrom) help to prevent some, or all, of your symptoms?  
Yes = Y      No = N      Don't know  
OR have never tried = ?

7. Does a corticosteroid inhaler (e.g. Becotide—Bextasol) help to relieve some, or all, of your symptoms?  
Yes = Y      No = N      Don't know  
OR have never tried = ?

### SECTION TWO

1. Do some, or all, of your symptoms usually occur continually all through the year?

Yes = Y      No = N      Don't know = ?

2. Do some, or all, of your symptoms occur haphazardly, at no particular time of year?

Yes = Y      No = N      Don't know = ?

(Note: If you filled in 'Yes' to questions 1 and/or 2 of this Section, it may still be correct to complete question 3 as well IF you have extra symptoms which only occur at specific times of year.)

3a Do some, or all, of your symptoms occur or worsen at certain specific seasons of the year?

Yes = Y      No = N      Don't know = ?

3b If your answer to the last question, 3a, was 'Yes', please write in these squares the figures for the months when some, or all, of your symptoms occur or worsen:

|          |      |        |      |           |      |
|----------|------|--------|------|-----------|------|
| January  | = 01 | May    | = 05 | September | = 09 |
| February | = 02 | June   | = 06 | October   | = 10 |
| March    | = 03 | July   | = 07 | November  | = 11 |
| April    | = 04 | August | = 08 | December  | = 12 |

Example: If August, September, October, then fill in:

|   |   |
|---|---|
| 0 | 8 |
| 0 | 9 |
| 1 | 0 |

3c Also, if your answer to 3a was 'Yes', show in these squares in which months some, or all, of your symptoms are at their worst:

|   |   |
|---|---|
| 1 | 2 |
| 0 | 1 |
| 0 | 2 |

Example: if worst, in December, January and February, fill in:

SECTION FOUR

1. Does being near or cutting grass start or worsen some, or all, of your symptoms?  
Yes = Y      No = N      Don't know = ?      ☐
2. Does being near trees or hedges start or worsen some, or all, of your symptoms?  
Yes = Y      No = N      Don't know = ?      ☐
3. Does weeding start or worsen some, or all, of your symptoms?  
Yes = Y      No = N      Don't know = ?      ☐
4. Do you think the weather affects some, or all, of your symptoms?  
Yes = Y      No = N      Don't know = ?      ☐
5. If some, or all, of your symptoms occur in summer, are they better when it is:  
Wet = 1      Sunny = 2      No difference = 3      ☐  
OR No symptoms in summer = 4

6. If some, or all, of your symptoms occur in winter, are they better when it is:  
Frosty and snowy = 1      Damp = 2      No difference = 3      ☐  
OR No symptoms in winter = 4

SECTION FIVE

1. Have you had skin-tests for allergies?  
Yes = Y      No = N      ☐

2. If your answer to (1) is 'Yes,' to which of the following were your skin-tests positive?

|                                       |                              |                              |                              |
|---------------------------------------|------------------------------|------------------------------|------------------------------|
| (put 'Y' in the correct box or boxes) |                              |                              |                              |
| Animals                               | House Dust Mite              | Dust                         | Moulds                       |
| 1. <input type="checkbox"/>           | 2. <input type="checkbox"/>  | 3. <input type="checkbox"/>  | 4. <input type="checkbox"/>  |
| Grass                                 | Trees                        | Weeds                        | Foods                        |
| 5. <input type="checkbox"/>           | 6. <input type="checkbox"/>  | 7. <input type="checkbox"/>  | 8. <input type="checkbox"/>  |
| Drugs                                 | Insect Stings                | Other (*)                    | Nothing                      |
| 9. <input type="checkbox"/>           | 10. <input type="checkbox"/> | 11. <input type="checkbox"/> | 12. <input type="checkbox"/> |

(\*) If your skin-tests were positive for 'other' substances—please say which:

SECTION SIX

1. Do any of the following (OR any other food or drink) start or worsen some, or all, of your symptoms?

|                                                     |                              |            |                              |                    |                              |
|-----------------------------------------------------|------------------------------|------------|------------------------------|--------------------|------------------------------|
| Yes = Y                                             |                              | No = N     |                              | Don't know = ?     |                              |
| If 'Yes'—put 'Y' in the correct box or boxes below: |                              |            |                              |                    |                              |
| Whisky                                              | 1. <input type="checkbox"/>  | Wheat      | 14. <input type="checkbox"/> | Brazil Nut         | 27. <input type="checkbox"/> |
| Wine                                                | 2. <input type="checkbox"/>  | Rye        | 15. <input type="checkbox"/> | Coconut            | 28. <input type="checkbox"/> |
| Gin                                                 | 3. <input type="checkbox"/>  | Barley     | 16. <input type="checkbox"/> | Hazel Nut          | 29. <input type="checkbox"/> |
| Vodka                                               | 4. <input type="checkbox"/>  | Oats       | 17. <input type="checkbox"/> | Pecan Nut          | 30. <input type="checkbox"/> |
| Cider                                               | 5. <input type="checkbox"/>  | Rice       | 18. <input type="checkbox"/> | Walnut             | 31. <input type="checkbox"/> |
| Rum                                                 | 6. <input type="checkbox"/>  | Maize/Corn | 19. <input type="checkbox"/> | Flour (bread etc.) | 32. <input type="checkbox"/> |
| Beer                                                | 7. <input type="checkbox"/>  | Soya Flour | 20. <input type="checkbox"/> |                    |                              |
| Milk                                                | 8. <input type="checkbox"/>  | Meat       | 21. <input type="checkbox"/> |                    |                              |
| Cheese                                              | 9. <input type="checkbox"/>  | Chocolate  | 22. <input type="checkbox"/> | Other (*)          | 33. <input type="checkbox"/> |
| Egg                                                 | 10. <input type="checkbox"/> | Vegetables | 23. <input type="checkbox"/> | —                  | 34. <input type="checkbox"/> |
| Fish                                                | 11. <input type="checkbox"/> | Peanut     | 24. <input type="checkbox"/> | —                  | 35. <input type="checkbox"/> |
| Crab                                                | 12. <input type="checkbox"/> | Fruit      | 25. <input type="checkbox"/> |                    |                              |
| Shrimp                                              | 13. <input type="checkbox"/> | Almond Nut | 26. <input type="checkbox"/> |                    |                              |

2. If you put 'Y' in box 33 ('Other \*') please say which other food/s or drink/s start, or worsen, your symptoms:

3. If you say 'Yes' to Question 1 (i.e. food or drink does start, or worsen, your symptoms) please indicate which part or parts of your body is/are affected by food or drink:  
Yes = Y      No = N      Don't know = ?

|       |                             |                   |                             |
|-------|-----------------------------|-------------------|-----------------------------|
| Eyes  | 1. <input type="checkbox"/> | Skin and/or Ears  | 4. <input type="checkbox"/> |
| Nose  | 2. <input type="checkbox"/> | Gut               | 5. <input type="checkbox"/> |
| Chest | 3. <input type="checkbox"/> | Mouth/Lips/Throat | 6. <input type="checkbox"/> |

4. Do you personally know, or have you ever been told, that you are allergic to penicillin?  
Yes = Y      No = N      Don't know = ?      ☐
5. Are you allergic, or do you react violently, to wasp stings?  
Yes = Y      No = N      Don't know = ?      ☐
6. Are you allergic, or do you react violently, to bee stings?  
Yes = Y      No = N      Don't know = ?      ☐



PATIENT NO.: 4973

Perennial

Symptoms worst in 1st of fin/outdoorsf

Symptoms worst in 1st of frnight/dayf

Exposed to cats

Symptoms worse near grass-cuttings, Check with seasons

Believes foods affect (in code) 33 , Food screen: 3.1 , 3.2 , 6 , \*

Food pattern score= 33 %.

SYMPTOM PATTERN SCORE= 44 %

with BLANK & ? SCORE= 25 %

CONTRADICTION SCORE= 0 %.

If IgE level OVER 200 UIgE/ml, &/or SYMPTOM PATTERN SCORE >30%  
YOU should consider testing for \*less likely\* allergens

SEASONAL ALLERGENS (Seasonal symptom score= 18 %), especially:

grass,

\* Nothing more \*

less likely SEASONAL ALLERGENS

weed,

cladosporium,

alternaria,

tree,

\* Nothing more \*

PERENNIAL ALLERGENS (Perennial symptom score= 75 %), especially:

H.D.M. & dust,

\* Nothing more \*

less likely PERENNIAL ALLERGENS

cat,

indoor moulds,

dog,

\* Nothing more \*

(Perennial=H.D.M., dust, cat, dog, indoor moulds, candida, (food))

Also answers suggest: less likely \*

Fig. 2. A computer 'print-out' of the questionnaire analysis. The first section summarizes the answers given and calculates a food pattern score based on the patient's age, age of onset of symptoms, whether the symptoms include a combination of asthma and eczema, and a knowledge that some food or drink causes symptoms. In the middle section the symptom pattern score is printed and, as a check on the validity of this result, the 'Blank/Don't Know' score and 'Contradiction' score. Finally, the analysis weighs seasonal vs. perennial symptoms, and lists the allergens most likely and less likely to be implicated.

Middlesex), was incubated overnight at room temperature. 'Antibody-bound' was separated from the 'free'-tracer fraction by adding to the assay mixture 50  $\mu$ l of a suspension containing donkey anti-rabbit IgG covalently linked to polymaleic anhydride particles, shaking for 10 min and, finally, centrifuging for 2 min at 1,500 *g* before decanting the supernatant solution and counting radioactivity associated with the residual particles. Levels over 40 U IgE per ml were regarded as screen positive.

*Mixed-allergen radioallergosorbent test (RAST).* IgE antibodies directed against a mixture

of three common U.K. allergens were measured simultaneously by a sandwich radioimmunoassay—the performance and standardization of which has previously been described in detail (8). Briefly, an assay tube containing 100  $\mu$ l of test (standard) serum and 50  $\mu$ l of a suspension with an excess of meadow fescue pollen, *Dermatophagoides pteronyssinus* and cat epithelial allergens (Bencard Ltd., Brentford, Middlesex) linked to cellulose particles was incubated for 3h at room temperature. The reaction was stopped by adding 2ml of decanting aid (Pharmacia GB

Table 1

Cluster analysis of 19 allergens

267 patients RAST positive to at least one allergen

- 
1. GRASS
  2. *Alternaria*, *Aspergillus*, *Penicillium*, *Cladosporium*
  3. MITE, egg, milk
  4. Plantain, GRASS, MITE, plane
  5. Codfish, CAT, dog, horse, MITE
  6. Horse, dog, *Penicillium*, CAT, *Cladosporium*, *Aspergillus*, EGG, MITE, GRASS, birch
  7. Peanut, wheat, mugwort, plane, hazel nut, plantain, birch, GRASS, milk, egg, *Penicillium*, horse
  8. CAT, mugwort, GRASS, *Alternaria*
  9. All 19 allergens
- 

Ltd.), centrifuging the assay tube at 1,500 *g* for 2 min and decanting the supernatant solution; after an overnight incubation with 100  $\mu$ l of  $^{125}$ I-labelled anti-IgE (Pharmacia GB Ltd.) the particles were washed and counted. When the amount of IgE associated with the allergen-particles was equivalent to at least 1 U IgE/ml the test was regarded as screen positive. The mixed-allergen RAST values were determined by referring to a total serum IgE calibration curve derived by sandwich RIA. This total IgE RIA was performed similarly to a mixed-allergen RAST, except that anti-IgE antibodies replaced allergens as the solid phase; the lower detection limit for this assay was 0.1 U IgE/ml, and this value was also the background level for mixed-allergen RAST.

#### *Specific IgE tests*

Tests for 13 different inhalant and six ingestant allergens used Phadebas RAST reagents (Pharmacia GB Ltd.) and a modification of the manufacturer's procedure, to allow for a more economical use of the radiolabelled anti-IgE (6). Briefly, in this altered procedure 50  $\mu$ l of test (or standard) serum was diluted to 150  $\mu$ l with RAST buffer and incubated overnight at room temperature with an allergen-paper disc, the disc was washed with 0.9% saline and again incubated overnight with  $^{125}$ I-labelled anti-IgE before washing and counting the radioactivity associated with the disc. Results were classified on the Phadebas scale of 0–4, with scores of 2 or more being regarded as

positive for all allergens—except moulds, for which a score of 1 was accepted as positive.

#### *Patients*

The study extended over 12 months, and comprised 512 patients whose symptoms were possibly related to IgE-mediated allergy. However, after results of the allergy-screening tests were evaluated, we reduced the number of sera submitted for the detailed RAST analysis so as to include a) all those patients who were likely to have at least one positive RAST result—this for frequency and cluster analyses of allergen-specific IgE—and b) a representative sample of the patients unlikely to have any positive RAST result—this, when combined with patients in category (a), to test the hypothesis that “a detailed RAST investigation is warranted only when two or more of the three tests in the allergy-screen are positive”. The first category, (a), included all 330 patients with at least two positive screening tests and all eight patients who were positive only to the mixed-allergen RAST; the second category, (b), included half of all the 126 patients with a single positive screen result to either the total IgE or the history tests (i.e. 63 patients), and half of all the 48 patients with negative results to all three allergy-screening tests (i.e. 24 patients). Thus, this report is restricted to 425 patients, whose ages ranged from 6 months to 77 years, with an average age of 35.7 years, and included 207 males and 218 females.

## COMMON IgE ANTIBODIES IN G.B.

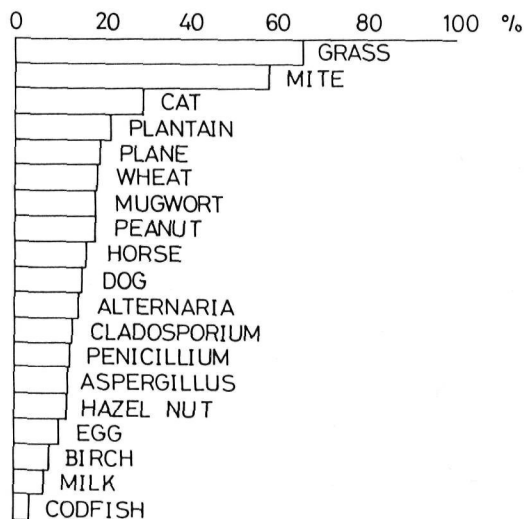


Fig. 3. The relative frequencies of positive RAST results to 19 common UK allergens.

The cluster analysis was carried out using Ward's method and the University of London's computer program.

## RESULTS

### RAST analyses

The frequency of positive Phadebas RAST results to the 19 allergens tested is summarized in Fig 3. The most commonly positive allergens were those comprising the mixed-allergen RAST screen, i.e. grass pollen (meadow *fescue*), the dust mite (*D. pteronyssinus*) and cat epithelium: 94.9% of the patients with any positive Phadebas RAST result were positive to at least one of these allergens.

The remaining 5.1% of patients were likely to be Phadebas RAST-positive to moulds only, and it can be seen after cluster analysis (Table 1) that they represented a small but highly significant group, second only to that comprising persons with a single positive result

## 275 RAST POSITIVE PATIENTS

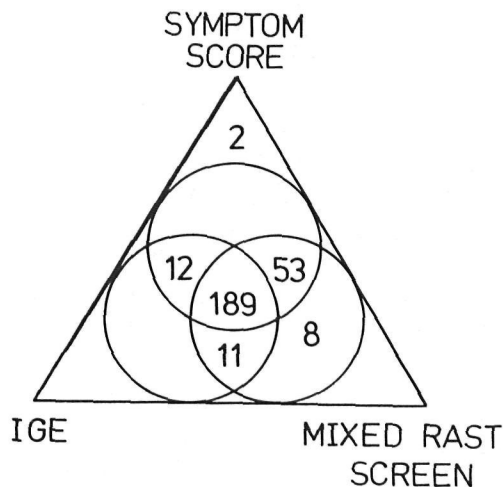


Fig. 4. Allergy screen results plotted as a Venn Diagram for the 275 patients who were positive to at least one allergen in the Phadebas RAST panel. 265 patients would have been referred as likely to benefit from further allergy investigations.

for grass pollen. The fifth cluster comprised patients with positive results to animals, including dust mite and cod-fish, but thereafter the clusters were less significant until, finally, the 10 patients who apparently had IgE antibodies to all 19 allergens were encountered.

### Allergy test screen

Two hundred and seventy-five patients had circulating IgE antibodies to one or more of the 19 allergens in the Phadebas RAST panel, and the results of their three allergy-screening tests are summarized by the Venn Diagram in Fig. 4. When using the criterion that at least two screening tests should be positive before a detailed RAST investigation was warranted, 265 of the 275 patients would have been candidates for further study. Of the 10 remaining patients, eight were positive only to the mixed-allergen RAST screen (all were

## 150 RAST NEGATIVE PATIENTS

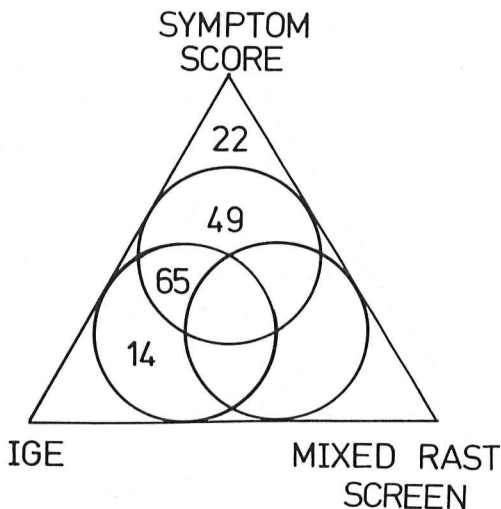


Fig. 5. Allergy screen results plotted as a Venn Diagram for the 150 patients who were negative to all the 19 allergens in the Phadebas RAST panel. 65 patients (all mixed RAST screen negative) would have been referred for further allergy investigations.

Phadebas RAST-positive to one of the allergens comprising the screen) and two were negative to all three screening tests (one patient was Phadebas RAST-positive to *Alternaria*, the other to peanut and hazel-nut).

One hundred and fifty patients had negative results to the Phadebas RAST panel, but it can be seen (Fig. 5) that 65 of them, if studied prospectively, would have been candidates for a detailed RAST analysis because two of their allergy-screening tests were positive. However, it was noted that none of these patients was positive to the mixed-allergen RAST screen.

### *Computer prediction of allergens to be tested for by RAST*

From answers given to the questionnaire, 3,455 RAST determinations were suggested as being useful in evaluating the symptoms of the 330 patients with positive results to at least two of the three allergy-screening tests. When the list of these predictions was compared to the

results obtained using the 19-allergen RAST panel, it was found to include 814 of the 1,023 positive test results—a “catch” of 80%.

## DISCUSSION

A careful allergy investigation takes time, and the object of this study was to see if a laboratory could provide sufficiently useful information to assist the general practitioner in selecting patients for referral to an allergy clinic. The three allergy-screening tests took little of the clinician's time, since the same blood sample was used for measuring total and specific IgE antibodies, and the patient filled in the questionnaire—certainly taking less time overall than it would have taken to perform and evaluate skin tests.

To check the efficiency of these tests, it was assumed that atopic persons have circulating IgE antibodies directed against at least one from a panel of 19 allergens in the Phadebas RAST. We justify the use of the Phadebas RAST panel as a standard partly because of the association of immunoglobulin E (IgE) with atopic allergy (1, 5), and partly because, as a result, atopic persons have been defined immunologically as those who readily synthesize IgE antibodies upon natural exposure to common environmental allergens (11, 12). This immunological definition of atopy is likely to be at least as good as the various clinical definitions, and less likely to be open to different interpretations.

As a result of this definition, it would be expected that the mixed-allergen RAST technique would be the most discriminating screening test for atopy. However, it may be dangerous to assume that all major allergens are detectable by Phadebas RAST—either because some may be unsuitable for linking to cyanogen bromide activated solid supports (e.g. carbohydrates, colouring agents) or because antibodies other than IgE might yet prove to be important in some atopic allergies (e.g. short-term sensitizing IgG). For these reasons, analysis of the answers given to the

detailed questionnaire, and determination of total serum IgE, are given equal weight in the allergy screen: in future, it may be important to recognize those patients with negative mixed-allergen RAST but with positive symptom pattern scores, and with total IgE levels of over 40 U IgE/ml. However, for the present, history and total IgE tests can be used a) to predict 'which' and 'how many' allergens should be tested at the allergy clinic, and b) to assess the relevance of these results. This aspect will be referred to after the screening tests have been discussed.

### *Mixed-allergen RAST*

The most common U.K. allergens were shown by skin-prick test to be *D. pteronyssinus*, grass pollen and animal danders (4); similarly, as a part of this study, we found that the most common circulating IgE antibodies were specific for *D. pteronyssinus*, grass pollen and cat epithelium (Fig. 3). Cluster analysis of the results from 275 RAST-positive sera showed that all but one cluster—the moulds—included at least one of these three allergens. In addition, 94.9% of the patients with any positive Phadebas RAST result were RAST-positive to one or more of these three allergens. Therefore, it is reasonable that these three allergens should form the basis of the mixed-allergen RAST.

The technique, as expected, proved to be more discriminating than either the history-score or the total serum IgE in deciding if a more detailed RAST investigation was required (Figs. 4 & 5). However, it must be remembered that a mixed-allergen test might prove positive as a result of the additive effect of two, or three, borderline results. Such an explanation could account for the positive mixed-allergen RAST results found in 13 cases with negative, but borderline, Phadebas RAST results to the same three allergens: in the follow-up, all these patients' sera proved RAST-positive to other Phadebas allergens—seven cases were positive to moulds and six to

foods. Another explanation might be the difference in the allergens used in these tests, since they came from different commercial companies; however, the overall agreement between the mixed-allergen RAST and the Phadebas RAST for the three common U.K. allergens was good, and so it is unlikely that we have failed to couple any major allergens to the particles used in the mixed-allergen RAST, unless the same allergens were also missing from Phadebas RAST discs.

In future, it might be useful to include a mould in the mixed-allergen RAST; however, the twin disadvantages of increasing the possible cumulative effect of borderline results, and the "high background" which we find associated with commercially available moulds in this type of test, outweigh the theoretical advantage of increasing the atopic "catch" beyond 94.9%. At present, it would be safe to say that if the mixed-allergen RAST, together with either Phadebas RAST for *Aspergillus fumigatus* (if the total IgE is elevated) or *Alternaria tenuis* (if the total IgE is below 100 U/ml), were negative, then an extended RAST investigation would be very unlikely to produce a positive result.

### *History symptoms scores*

The simple system adopted for 'scoring' histories (10) confirmed its early promise, because 92.4% (254/275) of the patients with positive Phadebas RAST results gave positive history symptom scores (Fig. 4). However, it was less discriminating than the mixed-allergen RAST screen because 76% (114/150) of the patients with negative Phadebas RAST results gave positive histories (Fig. 5). The main difficulty lay in deciding if allergy played a significant role in those patients whose perennial symptoms were exacerbated during the winter months. Nevertheless, during a preliminary investigation, the questionnaire offers the definite advantage of taking all histories in a standardized way and of being a valuable time-saver when used in conjunction with computer assessment. In future, the

questionnaire might be replaced by direct patient-interaction with a micro-computer, since this would offer the advantage of being able to rephrase in several different ways any question not fully understood by the patient.

### *Total serum IgE*

Total serum IgE was also less discriminating than the mixed-allergen RAST—in the Phadebas RAST-positive group 77.1% (212/275) patients had levels over 40 U/ml, compared with 52.7% (79/150) of the patients in the Phadebas RAST-negative group. However, the test has much value in helping to determine the extent of the search for allergen-specific IgE antibodies—i.e. if the total IgE is less than 200 U/ml only those allergens strongly suggested by the history need be considered, whereas cases with higher levels will require that the less likely allergens also be taken into account.

### *Allergy screen and computer assessment as a guide to further investigation*

More detailed IgE investigations for allergen-specific antibodies were most likely to provide positive results when applied to those patients who were positive to at least two of the three screening-tests—of 275 patients with identifiable specific IgE antibodies, 265 were in this category, and a further eight were positive to the mixed-allergen RAST and so defined as atopics.

When the computer predictions derived by analysis of the questionnaires filled in by these 265 patients were analysed, we found that 80% (814/1,023) of all the positive RAST results were predicted. The history synopsis was useful both for guiding the laboratory investigations and also for interpreting the results—e.g. a diagnosis of grass-pollen atopy will be unhelpful in treating an asthmatic whose symptoms are worse during the winter months (unless cereal-flours could be the problem).

## CONCLUSIONS

It is usual to consider that the RAST technique be used by allergists as a follow-up to skin testing. This study suggests a new view: that the technique can be useful to the general practitioner prior to referring the patient to an allergy clinic because it takes less time than skin testing, can be applied even when the patient is taking antihistamines or has a severe skin complaint, and—above all—is absolutely safe. Moreover, when the mixed-allergen RAST is combined with the computer-based history analysis and a total IgE estimation, a considerable amount of practical information is made available. This concept of the practitioner referring a single blood sample and a completed questionnaire has now been applied to over 1,000 members of the Post Office And Civil Service Sanatorium Society, and we have found that in many cases the information so derived has influenced the choice of treatment.

## ACKNOWLEDGEMENTS

We thank the Post Office And Civil Service Sanatorium Society for supporting this work, Edward Beckett for advice in devising questionnaires, Pharmacia GB Limited for helping to defray the questionnaire printing costs and Misses H. Coltman-Rogers and E. Standen for technical excellence.

## REFERENCES

1. Bennich, H. & Johansson, S.G.O.: Studies on a new class of human immunoglobulins. In Killander, J. (ed.): Nobel Symposium III, p. 199. Almqvist & Wiksell, Stockholm, 1967
2. Du Bois, R. M., Poulton, C. A., Smithers, Y. & Hughes, D. T. D.: Skin testing in hospital. *Br. Med. J.* **1**, 839, 1977.
3. D'Souza, M. F. & Davies, R. J.: Positive immediate skin tests in the community. *Lancet*, **ii**, 325, 1973.
4. Hendrick, D. J., Davies, R. J., D'Souza, M. F. & Pepys, J.: An analysis of skin prick test reactions in 656 asthmatic patients. *Thorax* **30**, 2-8, 1975.

5. Ishizaka, K., Ishizaka, T. & Hornbrook, M. H.: Physicochemical properties of reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J. Immunol.* 97, 75-85, 1966.
6. John, A. C. & Merrett, T. G.: The radio-allergosorbent test (RAST) in nasal polyposis. *J. Laryngol. Otol* 93, 889-898, 1979.
7. McCarthy, O. R.: Selection of skin tests in asthma. *Br. J. Dis. Chest*, 67, 238-240, 1973.
8. Merrett, J. & Merrett, T. G.: RAST atopy screen. *Clin. Allergy*, 8, 235-240, 1978.
9. Merrett, T. G. & Merrett, J.: Methods of quantifying circulating IgE. *Clin. Allergy* 8, 543, 1978.
10. Pantin, C. F. A., Merrett, J., Leighton, M., Colman Rogers, H. & Merrett, T. G.: Computer analysis of allergic histories taken by questionnaire. *Clin. Allergy* 8, 227-233, 1978.
11. Pepys, J.: Atopy. In Gell, P. G. H., Coombs R. R. A. & Lachmann P. J. (eds.) *Clinical aspects of immunology*, p. 877. Blackwell Scientific Publications Ltd., Oxford, p. 877, 1975.
12. Pruzansky, J. J.: Immunologic and cellular aspects of immediate hypersensitivity. In Patterson, J. (ed.): *Allergic diseases—diagnoses and management*, p. 56. J. B. Lippincott Company, Philadelphia, 1972.

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