

Comparison of clinical significance and allergenic cross-reactivity of storage mites *Blomia kulagini* and *Lepidoglyphus destructor* in Sweden and Brazil

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Comparison of the clinical significance and allergenic cross-reactivity of *Blomia kulagini* (*B. kulagini*) and *Lepidoglyphus destructor* (*L. destructor*) was made on sera from Sweden and Brazil using the radio-allergo-sorbent test (RAST) and the RAST inhibition technique. RAST-positive sera were obtained from 53 allergic Swedish farmers and 31 allergic subjects from Brazil who were positive to *B. kulagini* and/or *L. destructor*. *B. kulagini* was shown to be a common cause of sensitization especially in Brazil. There was a fairly high correlation between positive RAST results to *L. destructor* and *B. kulagini* based on sera from both Sweden and Brazil. The highest RAST scores were found against *L. destructor* in Swedish sera and against *B. kulagini* in Brazilian sera. The RAST inhibition studies showed that the *L. destructor* extract was able to inhibit the *B. kulagini* system (a positive RAST to *B. kulagini* allergen disc) in Swedish but not in Brazilian sera. In contrast, the *B. kulagini* extract was only able to inhibit the *L. destructor* system in sera from Brazil and not in sera from Sweden. This study shows that results obtained with RAST inhibition are not entirely dependent on the overall specificity of the IgE antibodies in the patient's sera, since the more subtle specificity of the primarily sensitizing allergen will dominate. Thus, conclusions drawn regarding allergenic cross-reactivity are dependent on the populations tested, and conclusions on the existence or absence of cross-reactivity, e.g. between two species of mites may be contradictory.

Key words: allergy; *Blomia kulagini*; Brazil; *Lepidoglyphus destructor*; Sweden.

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CLINICAL ASPECTS

Marked differences in allergenic cross-reactivity patterns are obtained when sera from different populations are examined.

The importance of storage mites as a cause of symptoms from airways and eyes in people living in farming environments was suggested a few years ago (6, 9, 27). These mite species are also indicated to be of importance for people living in damp houses where mould growth may encourage their development (21, 32). Allergic sensitization to storage mites in non-farming

populations has been reported from France (14), England (18, 32), the Netherlands (25), South East Asia (31), Hong Kong (7) and New Guinea and Australia (8). Several studies have shown that storage mites are common and may comprise up to 24% of the total mite count in house dust (7, 17, 18, 22, 24). The most common mite in homes is *Dermatophagoides pteronyssini*.

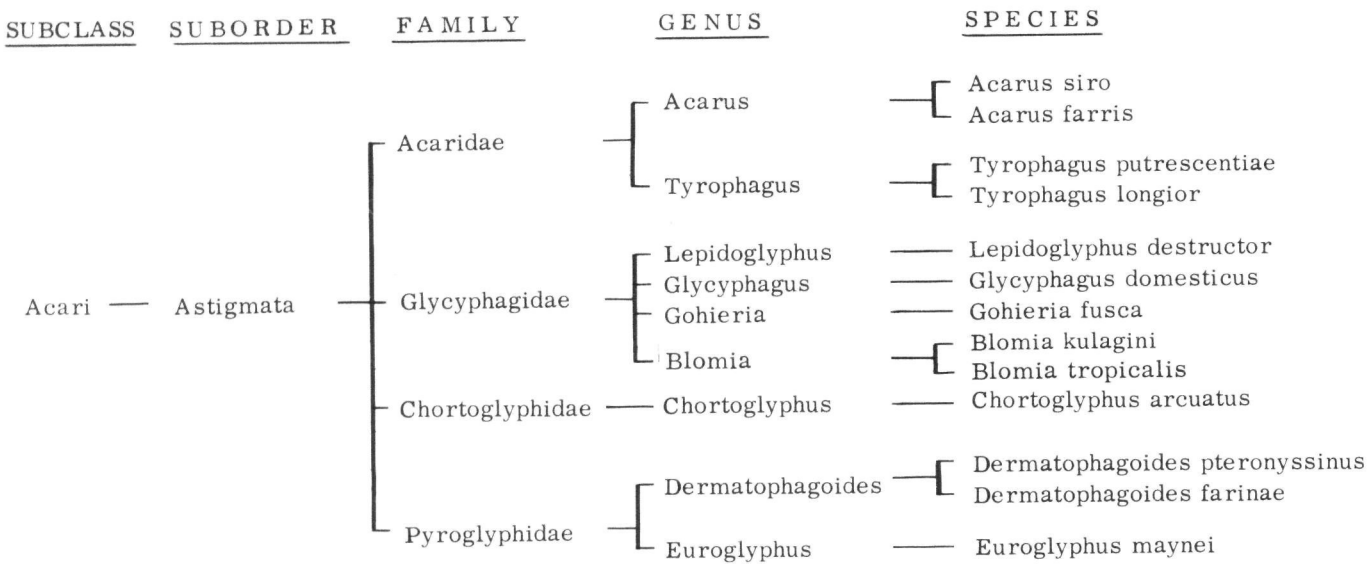


Fig. 1. The taxonomic position of the different storage and house dust mites.

nus (*D. pteronyssinus*) in northern Europe and *Dermatophagoides farinae* (*D. farinae*) North America.

Storage mites include a wide range of families and species, the most important and frequently reported of which are *Lepidoglyphus destructor* (*L. destructor*), *Glycyphagus domesticus* (*G. domesticus*), *Tyrophagus putrescentiae* (*T. putrescentiae*) and *Acarus siro* (*A. siro*). Hurtado & Parini have recently shown that non-pyroglyphid mites of the *Blomia* genus, which belong to the Glycyphagidae family (Fig. 1), more specifically the species *Blomia tropicalis*, next to *D. pteronyssinus* (15) are the dominating mites in homes in Caracas. In this study we present data concerning IgE-mediated sensitization to *Blomia kulagini* (*B. kulagini*), in people, from two different countries, Sweden and Brazil. Comparison of the allergenic cross-reactivity between *L. destructor* and *B. kulagini* as measured by IgE antibody levels and the RAST (30) inhibition technique on serum samples from the two populations illustrates the difficulties involved in using serum of allergic persons in studies of allergenicity.

SUBJECTS AND METHODS

Analyses of IgE antibodies to *B. kulagini* and/or *L. destructor* using RAST were performed on sera from 440 farmers from the Swedish island of Gotland ("Swedish farmers"). These farmers had previously participated in an epidemiolog-

ical investigation of allergic manifestations from airways and eyes. The first part of the investigation consisted of a self-administered questionnaire which was completed by a total of 2578 farmers representing more than 90 % of the studied farmers aged 15-65 years (9). Three hundred and sixty farmers with respiratory symptoms and 100 healthy farmers, of whom 440 attended, were selected for the second part of the study, which comprised a clinical examination and blood sampling for RAST analyses.

Sera from 34 atopic patients, aged 5-62 years, with asthma and/or rhinoconjunctivitis attending the Allergy Clinic at Hospital das Clinicas in Sao Paulo, Brazil ("Brazilian patients") were studied together with the Swedish sera. These patients had a history indicative of allergy to house dust and a positive skin prick test to *D. pteronyssinus* and *D. farinae* (Pharmalgen®, 100,000 BU, Pharmacia Diagnostics, Uppsala, Sweden).

Cross-reactivity between *L. destructor* and *B. kulagini* was first evaluated from the RAST results obtained in 53 Swedish farmers selected as being RAST-positive to at least one of the two storage mites and the 31 patients from Brazil. Sera from five Swedish farmers and seven patients from Brazil who were RAST-positive to both *L. destructor* and *B. kulagini* were inhibited with extracts prepared from these two mite species. Sera from four more farmers and two more subjects from Brazil were inhibited

with with one extract (homologous system) only and RAST were then performed against appropriate allergen discs. To demonstrate the presence of unique allergen/s in *B. kulagini* in comparison with *L. destructor*, four sera from Swedish farmers and one serum from Brazil which were either RAST positive to *B. kulagini* and negative to *L. destructor*, or the reverse, were inhibited with both *B. kulagini* and *L. destructor* extracts. All serum samples had been kept frozen at -20° until analysed.

Extracts (1/10 w/v) were prepared from *B. kulagini* and *L. destructor*, in 0.15 M NaCl containing 0.02% NaN_3 using raw material obtained from Allergon AB (Ängelholm, Sweden).

The levels of circulating IgE antibodies were determined by RAST as described by Johansson et al. (16). Fifty microlitres of undiluted serum was incubated with an allergen disc for 3 h at room temperature. After repeated washings, ^{125}I -labelled, immunosorbent purified anti-IgE of mixed D ϵ 1 and D ϵ 2 specificity (1) corresponding to approximately 50 000 cpm was added for incubation at room temperature overnight. After washing, the count rates were measured in a gamma scintillation counter (Rackgamma, LKB-Wallac, Stockholm, Sweden). The cpm were related to those of the Phadebas[®] RAST reference system (Pharmacia Diagnostics AB, Uppsala, Sweden) and the results expressed in Phadebas RAST Units (PRU)/ml. Allergen discs with *L. destructor* (d71) were obtained from Pharmacia Diagnostics AB, Uppsala, Sweden. *B. kulagini* discs were prepared by coupling 0.5 ml of a 1/10 w/v extract to 100 cyanogen bromide (CNBr)-activated paper discs (4). The discs gave no non-specific uptake of labelled anti-IgE when tested against non-atopic serum samples with IgE levels of 20-4000 kU/ml. The discs did not contain significant amounts of wheat allergen, a potent inhalation allergen commonly used in mite growth media.

RAST inhibition studies were performed as previously described in detail (10). Mite allergen extracts were mixed in various dilutions with serum from persons with IgE antibodies against storage mites. The serum samples were first diluted 1/1-1/10 to give approximately 5000

cpm in RAST. The level of free IgE antibodies was then determined by RAST. The results were expressed as a percentage of the cpm value of the positive serum dilution after inhibition with allergen extract diluent, according to the following formula:

$$\% \text{ inhibition} = 100 - \frac{\text{cpm after inhibition with extract} \times 100}{\text{cpm after inhibition with diluent}}$$

A background value (buffer value) averaging 200 cpm was always subtracted from the actual count rate. The potency of the extracts was compared at 50% RAST inhibition. The inhibitory capacity was expressed in arbitrary units (U). The highest concentration of an extract used was assigned the value 1000 U/ml. The dilution of the 1000 U/ml solution of each extract was selected so that 50% RAST inhibition of the homologous system (e.g. the *B. kulagini* extract inhibiting the positive RAST to *B. kulagini* allergen discs) was obtained at an extract concentration in the order of 0.1-10 U/ml. For the *L. destructor* and *B. kulagini* extracts the concentration of 1000 U/ml represents 1/10 w/v. To establish the presence of unique allergens inherent in *B. kulagini* and *L. destructor*, we used monovalent sera, usually with low IgE antibody levels.

Therefore, a relationship between serum and extract concentration which differed from the one described above was necessary. Extract and serum were mixed in the ratio 19:1 giving a highest final allergen concentration of 50 U/ml compared with 500 U/ml obtained when equal amounts of serum and extract were used. In the latter case a final concentration of 500 U/ml corresponds to an extract concentration of 1000 U/ml.

Statistical analysis

To estimate the strength of the allergenic relationships between the different species of storage mites, Spearman rank correlation coefficients

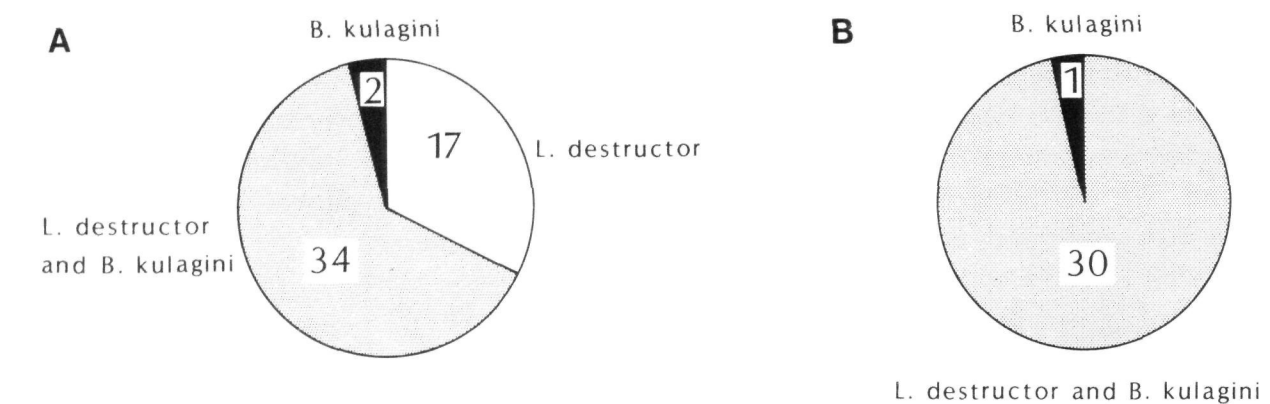


Fig. 2. The distribution of positive (≥ 0.35 PRU/ml) tests against *L. destructor* and *B. kulagini* among the studied (A) Swedish farmers and (B) patients from Brazil.

between positive RAST scores (positive to at least one of the two species) were calculated. Estimates of correlation coefficients were tested for a significant departure from zero. For all tests $P < 0.05$ was considered significant.

RESULTS

Distribution of positive RAST

To allow calculations of prevalence, samples from adequately designed epidemiological investigations should be available for analyses. The Swedish farmers represented such a samp-

le. Thus, it was possible to establish that *B. kulagini* showed a prevalence of 4.5 %. Among farmers with possibly IgE-mediated symptoms the corresponding figure was as high as 27.2 %. Farmers with asthma alone or asthma in combination with rhinoconjunctivitis were more often sensitized to these mite species than farmers with rhinoconjunctivitis alone.

When only subjects with a positive RAST to at least one of the two mites were considered (53/440), a total of 51/53 (96.2 %) of the Swedish farmers had IgE antibodies to *L. destructor* and 36/53 (67.9 %) to *B. kulagini*. A positive RAST to both mite species was found in 34

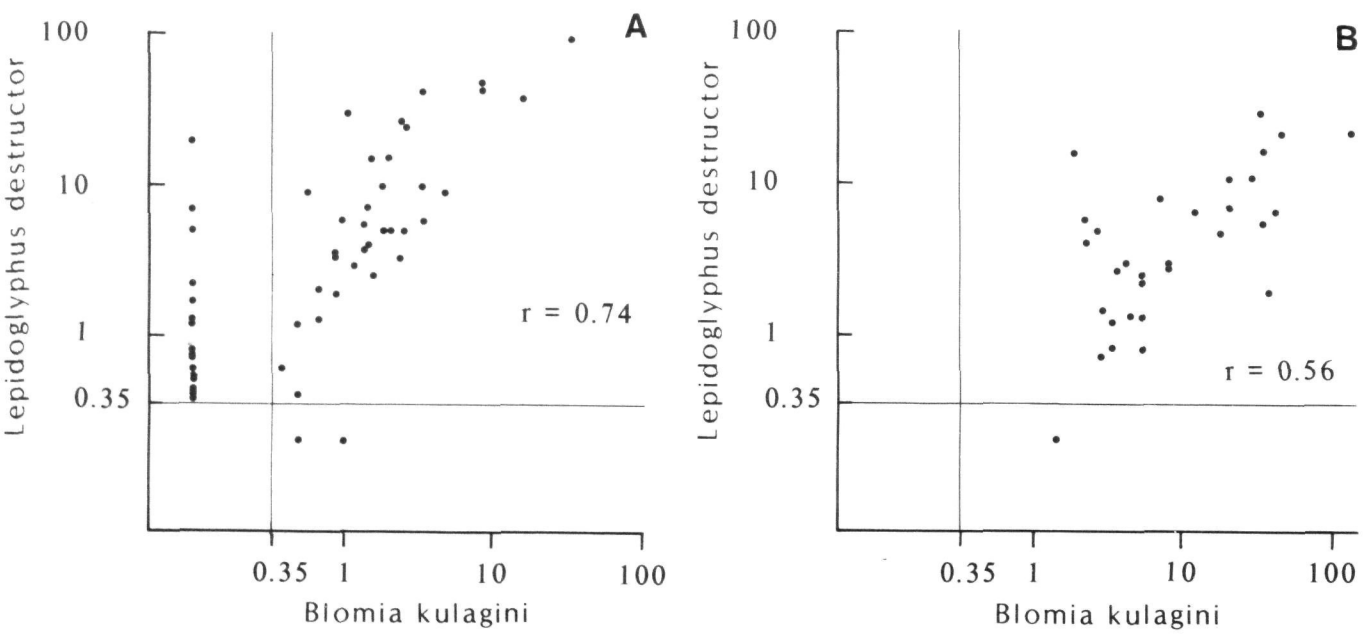


Fig. 3. RAST scores to *L. destructor* and *B. kulagini*. The correlation coefficient was calculated among (A) all Swedish farmers ($r = 0.74$) and (B) the patients from Brazil ($r = 0.56$) with a positive RAST (≥ 0.35 PRU/ml) to at least one of the two mites.

(64.2%) of these farmers, whereas 17 had positive RAST scores to *L. destructor* only and two to *B. kulagini* only (Fig. 2A).

Nearly all patients from Brazil (31/34), were positive to *B. kulagini* and 30/34 had IgE antibodies to *L. destructor* (Fig. 2B). Since the Brazilian study group was rather small no calculation of prevalence figures could be made.

RAST correlation studies

The correlation coefficient between RAST values against *L. destructor* and *B. kulagini* among the Swedish farmers was fairly high 0.74 ($P < 0.001$) (Fig. 3A). The corresponding correlation coefficient among the patients from Brazil was 0.56 ($P < 0.01$) (Fig. 3B). However, in general, the Swedish farmers had higher IgE antibody levels against *L. destructor* than *B. kulagini*, whereas the reverse was found in the group of patients from Brazil.

The existence of subjects with IgE antibodies exclusively to *L. destructor* or *B. kulagini* indicates that these two species possess their own unique allergen/s as well as allergens in common.

RAST inhibition

The inhibitory capacity of the *L. destructor* and *B. kulagini* extracts is shown in Fig. 4. In Swed-

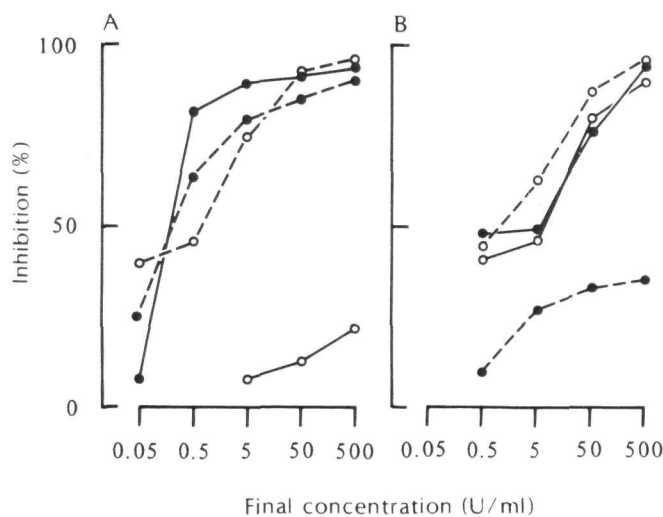


Fig. 4. The inhibiting effect of *L. destructor* extract on a positive RAST to discs coated with *L. destructor* ●—● and *B. kulagini* ●—●—● and the inhibiting effect of *B. kulagini* extract on a positive RAST to discs coated with *L. destructor* ○—○ and *B. kulagini* ○—○—○ on sera from (A) Sweden and (B) Brazil.

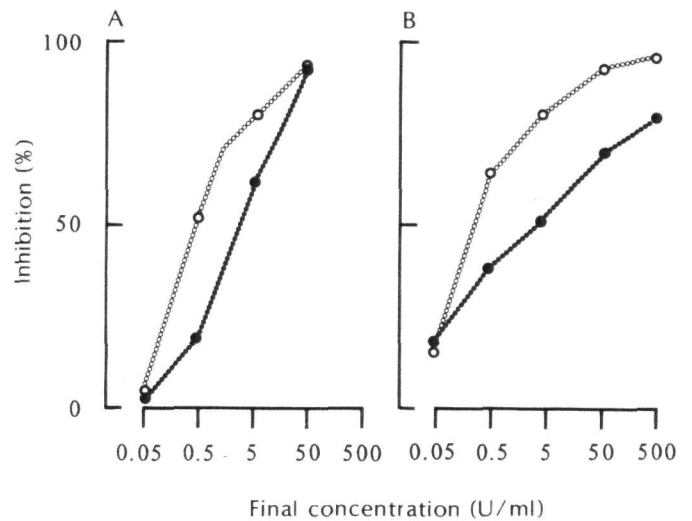


Fig. 5. The inhibiting effect of extracts of *L. destructor* ●—● and *B. kulagini* ○—○ on sera from (A) Sweden and (B) Brazil which are RAST positive to *B. kulagini* and negative to *L. destructor*. Discs were coated with *B. kulagini*.

ish sera a similar amount of *L. destructor* extract was needed to inhibit the homologous system (a positive RAST to *L. destructor*) as in the *B. kulagini* system, (a positive RAST to *B. kulagini*).

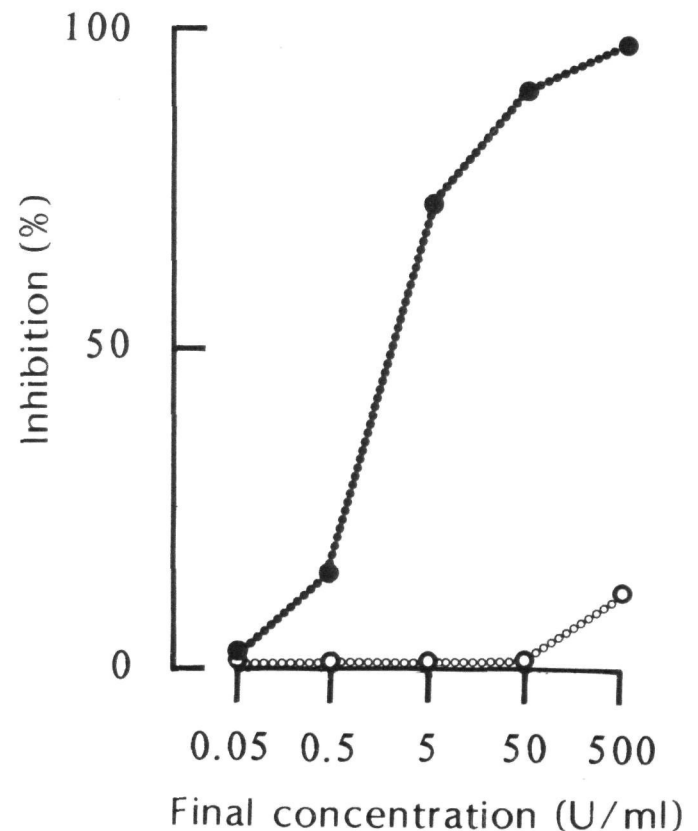


Fig. 6. The inhibiting effect of extracts of *L. destructor* ●—● and *B. kulagini* ○—○ on a serum from Sweden which is RAST positive to *L. destructor* and negative to *B. kulagini*. Discs were coated with *L. destructor*.

However, the *B. kulagini* extract could not achieve a 50% inhibition of the *L. destructor* system (Fig. 4A) in two tested sera, but when over 100–1000 times more *B. kulagini* extract was used in three other tested sera, a 50% inhibition of the *L. destructor* system was produced compared with the amount required in the *B. kulagini* system. In contrast, in sera from Brazil the *L. destructor* extract could not inhibit the *B. kulagini* system, but, about the same amount of *B. kulagini* extract could inhibit both the homologous and the *L. destructor* system (Fig. 4B). Similar results were found in a total of seven tested sera.

The relationship between the inhibitory capacity of *B. kulagini* and *L. destructor* appeared slightly different when sera positive to only one of the two mites were used. Figs. 5 and 6 show the inhibitory capacity of the two extracts on a positive RAST to discs coated with *B. kulagini* (Fig. 5) and *L. destructor* (Fig. 6). Sera from two Swedish farmers who were RAST positive to *B. kulagini* and negative to *L. destructor* were studied. In comparison with the homologous system, a similar amount of *L. destructor* extract could produce a 50% inhibition of the *B. kulagini* system (Fig. 5A). When the one serum from Brazil which was solely RAST positive to *B. kulagini* was tested (Fig. 5B), over 10 times more *L. destructor* extract was needed to inhibit the *B. kulagini* system compared with the amount required in the homologous system, despite the fact that it was RAST negative to *L. destructor*.

In the *L. destructor* system, two Swedish sera which were only RAST positive to *L. destructor* were inhibited by the *L. destructor* extract but not by the *B. kulagini* extract (Fig. 6).

In four Swedish and two Brazilian sera one concentration only of the two extracts was added to achieve a 50% inhibition of the homologous system. The results supported the findings of our detailed dose-related RAST inhibition study.

DISCUSSION

The interest in house dust mites as possible causes of allergic disorders has been confined to the past three decades. It was not until 1964

that mites belonging to the genus *Dermatophagoides* were shown to be the major source of allergen in house dust by Voorhorst et al. (28). Since then several studies using skin prick tests and nasal and bronchial challenge tests have clearly established that pyroglyphid mites are of great importance for house dust allergy (19, 23, 26, 28, 29, 32).

As earlier suggested by us, storage mites may be the major cause of sensitization in agricultural environments (9). Our epidemiological study of respiratory symptoms among Swedish farmers has shown that the prevalence of storage mite allergy, defined as a typical case history with immediate onset symptoms and a positive RAST to storage mites, was as high as 6.2%. In contrast, a positive RAST to common respiratory allergens, such as pollens, animal danders and moulds was low (0.1–1.7%) (11). The dominant species of storage mites provoking IgE formation was *L. destructor* (96.2%).

When considering hyposensitization with mite extracts, knowledge of possible allergenic cross-reactivity between various mite species is needed. However, as yet, the cross-antigenic and allergenic properties of the clinically relevant mite species are poorly known. We studied the allergenic cross-reactivity between four storage mites (*G. domesticus*, *T. putrescentiae*, *A. siro* and *L. destructor*) and the house dust mite *D. pteronyssinus* with RAST and a RAST inhibition technique. The latter technique is a valuable tool for assessing overall allergenic cross-reactivity. The results supported our hypothesis that each of the examined storage mite species as well as *D. pteronyssinus* possess their own unique allergen or allergens. There existed no cross-reactivity between *L. destructor* and *D. pteronyssinus*. Further, *L. destructor*, *G. domesticus* and *T. putrescentiae* seem, allergenically, to be more closely related to one another than to *A. siro* (10). We have also studied cross-reactivity between *L. destructor* and *D. pteronyssinus* *in vivo*. Bronchial challenges with *D. pteronyssinus* extract were performed on asthmatic farmers who were RAST positive to *L. destructor* and negative to *D. pteronyssinus*, and with *L. destructor* extract on subjects with asthma and a positive RAST to *D. pteronyssinus* and negative to *L. destructor*, neither

of whom developed a fall in forced expiratory volume in 1 s (FEV₁) of 20 % or more (12).

The non-pyroglyphid mite *Blomia* is essentially a stored food feeder, but it is also found in house dust (3). Summarising existing information on *Blomia* genus Bronswijk, et al. (2) stated that *B. tropicalis* is a regular and sometimes abundant inhabitant of houses in tropical and subtropical regions. This means that many people are exposed to *Blomia* making it a potentially important house dust allergen. Gabriel & Cunnington (7) reported large infestations of *Blomia* in house dust from Hong Kong. This mite was the predominant species and produced the highest number of positive skin tests among six tested storage mite species. Furthermore, the results of a preliminary survey of the house dust mite fauna in Tampa Bay, Florida, USA, have shown that *Blomia* is found in 30 % of the dust samples analysed (E. Fernandez-Caldas personal communication). In addition, Miyamoto et al. (20) have found *Blomia* species in house dust in Japan. They showed that some degree of allergenic cross-reactivity existed between *Blomia* species and *T. putrescentiae*. Hurtado & Parini (15) recently showed that the storage mite *B. tropicalis* was present in 96 % of bedding dust samples examined, and contributed an average of 15 % of total mite species in Caracas, Venezuela.

The RAST correlation between *L. destructor* and *B. kulagini* based on Swedish sera showed that the highest PRU values were found against *L. destructor*, whereas sera from Brazil had the highest IgE antibody levels against *B. kulagini*. These results primarily indicate that *L. destructor* is the main sensitizer in Sweden and *B. kulagini* in Brazil. Accordingly, a mite inventory of Swedish barn dust has shown that *L. destructor* is the dominating mite species (van Hage-Hamsten et al. in preparation), whereas a similar investigation of homes in the surroundings of Sao Paulo revealed that *Blomia* species are found in about 30 % of house dust samples (J. Croce personal communication). However, the existence of subjects with positive RAST exclusively to either *L. destructor* or *B. kulagini* strongly supports the presence of a unique allergen or allergens in the two species.

The results from the RAST inhibition suggest that *L. destructor* and *B. kulagini* share some allergenic components, but they also seem to lack some allergenic determinants in relation to each other. However, this apparent deficiency of allergen/s is dependent on where the subject has been sensitized. If we had only investigated the Swedish farmers with respect to allergenic cross-reactivity between *L. destructor* and *B. kulagini*, our conclusions would have been that *L. destructor* is the important mite having all the major allergens and that *B. kulagini* is not important since it seems to lack the major allergenic determinants of *L. destructor* and has no major allergens of its own. In contrast, if only the subjects from Brazil had been studied the conclusion would have been the reverse: *B. kulagini* is the important mite and *L. destructor* is just cross-reacting.

Our findings demonstrate the difficulties inherent in studying allergenic cross-reactivity in human systems. For definition and detailed mapping of allergenic epitopes the use of monoclonal antibodies is probably a useful (5) but laborious approach. Although there may be as many as 20 major mite species it is essential to establish which is the main provoker of IgE-mediated sensitization in each region. Thus, further epidemiological and immunological studies of mite allergy are needed in various parts of the world.

As *B. kulagini* and *L. destructor* belong to the same family, Glycyphagidae, they should be closely related. The results of the RAST inhibition study are in good agreement with our previous findings of allergenic cross-reactivity between *T. putrescentiae* and *A. siro*. These two mite species also belong to the same family, Acaridae, but like *B. kulagini* and *L. destructor* they appeared to share fewer allergen/s than the less related *T. putrescentiae* and *L. destructor*. Why the *L. destructor* extract inhibited the *B. kulagini* system in sera from both Brazil and Sweden which were solely positive to *B. kulagini* is not altogether clear. It might be due to inadequate concentration of the inhibiting allergenic component on the *B. kulagini* disc. Further studies are to be made on similar sera from South

America. However, we recently found the same results when studying allergenic cross-reactivity between *D. pteronyssinus* and the less known house dust mite *Euroglyphus maynei*. In some sera the *E. maynei* extract could partially inhibit the *D. pteronyssinus* system (13).

There is no doubt that many people become allergic to storage mites. The finding that all Brazilian study subjects had a positive RAST to *Blomia* indicates that this species may be an important cause of allergy in tropical climates, and should be considered when hyposensitization treatment is planned. In Sweden, however, where the climate is much cooler, the farmers primarily respond to *L. destructor*. When allergenic cross-reactivity between different mite species is considered, it is essential to know which mite species is the main sensitizer in the population studied. Our data clearly show that marked differences in allergenic cross-reactivity patterns are obtained when sera from different populations are used.

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