

a communication from the United Kingdom

CONTROLLED ACTIVITY MITE VACCINES FOR 'BARN ALLERGY'

O. D. CUTHBERT, MD*; W. D. BRIGHTON, PhD†; ROSA AYUSO, PhD‡; E. TRIVINIO, L.Biol‡; and J. CARREIRA PhD‡

Three species of mites, Tyrophagus longior, Glyciphagus destructor, and Acarus farris have been isolated from the dust of barns of farms in Orkney. The mites were cultured in amount sufficient for the production of bulk extracts. These were then tested by skin prick in a population of 30 inhabitants of Orkney and potency was assigned in units of biologic activity. The concentrations of the bulk extracts from the different species were adjusted to the same biologic potency and then used to make delayed-release vaccines for injection therapy and aqueous solutions for provocation tests and therapy by the nasal route.

The vaccines were then administered by injection to nine subjects at weekly intervals over a period of 2 months. Assessment by questionnaire suggested that there was a significant improvement in the symptoms of eight of the nine subjects. A course of nasal therapy with the aqueous solutions produced no improvement in four out of five subjects.

Introduction

AS A RECENT LEADING ARTICLE by Seaton¹ pointed out, 'occupational hazards lurk in the farming environment' and prominent amongst these is the condition that has been referred to as 'barn allergy.' This is best defined as conjunctivitis, rhinitis and/or asthma that affects farm workers and others on entering barn or byre and is caused by sensitivity to one or more of the mite species that commonly infect stored grain and hay.

It occurs both in atopics who are allergic to a number of other common allergens and in those who are allergic to the storage mites only and to no other common allergen, including *Dermatophagoides pteronyssinus*, the house dust mite. It was first noted by Cuthbert et al² amongst farming families and a more recent survey by Cuthbert et al³ of farm workers on the mainland of Scotland showed a prevalence of 21% of whom almost three-quarters experienced some symptoms of asthma, from tightness in the chest to pronounced wheeze and

breathlessness on contact with the hay dust. The principal species of mites found to be causing the condition amongst the Scottish farmers were *Glyciphagus destructor*, *Tyrophagus longior*, and *Acarus farris*, though the extent to which these or other species are present in hay may vary from area to area.

Although the wearing of protective respirators (especially those of the helmet-type, with a battery-powered unit to produce a forced air flow) is the most effective form of protection for these sufferers, it has often proved to be difficult to persuade farmers of the advisability of this precaution. It was therefore thought to be reasonable to investigate the possibility of immunotherapy, using vaccines specific for the mites to which each farmer was found to be allergic.

Materials and Methods

In order to test the effectiveness of such hyposensitization therapy in barn allergy, a small number of vaccines both for injection and for nasal therapy were prepared for individual patients in a pilot study of the treatment. Mites of the three species, *G. destructor*, *T. longior*, and *A. farris* were isolated from the hay dust from the barns of affected farmers. They were then grown on 75% yeast, 25% wheat germ medium, defatted, and bulk extracts made with 50 μ M ammonium

* From the General Practice, Evie, Orkney, United Kingdom.

† Allergy Technical Consultancy, Holland House, 33 Bedhampton Hill, Havant, Hampshire PO9 3JN, United Kingdom.

‡ Alergia e Inmunología Abello S.A., Julian Camarillo 8, Madrid 17, Spain.

bicarbonate solution. Potency of the three extracts was measured by skin test assays in a group of 30 sensitive individuals and the extracts were standardised in potency to the same biologic activity by the method of Carreira et al.⁵ Vaccines for injection therapy were prepared with aluminium hydroxide and sets contained only those components to which their skin tests had indicated the sensitivity of each patient. The vaccines were therefore personal preparations.

Patients selected for treatment were those whose history and skin tests indicated that they suffered from conjunctivitis, rhinitis and/or asthma as a result of contact with these mites at their place of work. Two patients with chronic or recurrent severe asthma were excluded because the treatment with extracts of these mites was novel. It was, therefore, not clear whether the strengths of solutions used were appropriate, or what was the likely rate of adverse reactions. Ethically, the risk was believed to be acceptable if the likely consequence was conjunctivitis, rhinitis or mild asthma, but not a severe asthmatic attack.

In addition, vaccines for nasal inhalation therapy were prepared with saline and lyophilised. Again, each treatment set contained only those components to which the individual patients were sensitised.

Initially, 17 patients were offered and accepted treatment; however, one moved away from the area. Two dropped out after the second injection, one on account of having developed rubella and the other because of a painful local reaction.

Of the remaining 14, nine were treated by injection and five by the nasal route. Thirteen were skin test positive to *G. destructor* and 13 to *T. longior*, but only ten to *A. farris*. Nine were skin test positive to all three of the mites.

Injection Therapy

The nine patients who received a full course of nine injections consisted of eight male farm workers aged from 22 to 59 years (mean 38) and one female office worker aged 36 years, who lived on a farm but was not employed there. She was found to be allergic to two of the storage mites but to no other common allergen, including the house dust mite, *D. pteronyssinus* (Table 1).

The treatment schedule for these patients is shown in Table 2. Starting with a dose of 0.05 biologic units (B.U.), each patient received a weekly injection of increasing strength up to a maximum of 10 B.U. over a period of 9 weeks. One man who developed mild asthmatic symptoms unrelated to his farm work was given a modified course, still of nine injections but only to a final dose of 5 B.U.

Three of the men and the woman chose to continue on a maintenance dose of 10 B.U., fortnightly, for 1 month and then monthly thereafter. One man continued for 1 month only, the other men for 5 months and the woman for 8 months.

Table 1. Storage Mite Species Giving Positive Skin Tests*

Patients	<i>Tyrophagus longior</i>	<i>Glyciphagus destructor</i>	<i>Acarus farris</i>
Patients treated by injection			
4	+	+	+
7	+	+	—
8	+	+	+
9	+	+	+
11	—	+	+
20	+	+	—
21	+	+	+
24	+	+	+
32	+	+	+
Patients treated nasally			
17	+	+	+
18	+	+	+
23	+	+	+
25	+	—	—
29	+	+	+

* Skin test results to storage mite extracts, showing that ten of the 14 patients treated were allergic to all three mites, with *A. farris* giving the least number of positive results. These results were used as an indication as to which mite species should be used in the make-up of the individual, personalised vaccines.

Table 2. Injection Schedule of Orkney Mites Given Subcutaneously at 3- to 7-day Intervals

Vial no.		Dose in	
		mL	ABU
1	0.1 ABU mL	0.5	0.05
		1.0	0.1
2	1.0 ABU mL	0.2	0.2
		0.5	0.5
		1.0	1.0
3	10.0 ABU mL	0.2	2.0
		0.4	4.0
		0.7	7.0
		1.0	10.0

Nasal Therapy

Of the five patients treated by nasal inhalation, four were male farm workers aged from 16 to 61 years (mean 35) and one farmer's wife aged 60 years. All suffered from allergic rhinitis and conjunctivitis in contact with hay. These patients were given nasal provocation tests in a clinic with three strengths of the mite extracts: 0.1 B.U./mL, 1.0 B.U./mL, and 10 B.U./mL. Three patients gave positive tests with the 1.0 B.U./mL and two with the 10 B.U./mL.

Standard schedules for nasal therapy have not been found in the literature and therefore the treatment was perforce arbitrary, although the schedule adopted by Mehta and Smith⁴ in a successful trial of nasal hypsensitization for hay fever was used as a basis. The patients were each given glass nasal sprays containing solutions of the mite extracts to which they were allergic and were instructed to spray the nose twice a week on ten occasions, over a 5-week period. In our treatment, the strength of solution used for each patient was that which had produced a positive nasal provocation test (nasal FEV₁ tests were found to be impractical in the circumstances) but a second strength was supplied for

them to use should the initial one fail to produce any symptoms of rhinitis during any one inhalation.

In the event, one patient found his initial dose of 10 B.U./mL to be too strong and was given one of 1.0 B.U./mL to use subsequently and he remained on this thereafter. Two others increased their doses from 1.0 to 10 B.U./mL during the 5 weeks, a fourth increased from 10 to 25 B.U./mL and one continued on his initial dose of 1.0 B.U./mL for the full course (Table 3).

Antibody Assays

Samples of sera were collected before and after the treatment and were analysed for the presence of IgE and IgG antibodies that were specific for the three mites. The IgE assays were done by a conventional RAST technique, using a specific solid phase of paper discs, activated with CNBr then sensitised with one of the specific mite extracts. The discs were treated with the

patient's sera and then a radiolabelled specific anti-human IgE monoclonal antibody, prepared in the laboratories of Abello S.A.

The IgG assays were done by a similar technique of radioimmunoassay, using the same solid substrates as the IgE assays, but the revealing antibody was a radio-labelled specific anti-human IgG monoclonal antibody (also prepared in the laboratories of Abello S.A.). Both assays were controlled with 'in house' standards of positive and negative sera in parallel titrations.

Results

Assessment of the results was done by questionnaire during the month of November, when the farmers were once again working inside barns and feeding hay to their cattle. This process constituted a unique natural challenge, the benefit to which was easily recognised by the farmers and was therefore probably the most realistic way of assessing the efficiency of the treatment. The form of questionnaire is shown in Table 4. It indicates whether they considered that the treatment had been generally successful and which specific symptoms had been 'much improved,' 'improved,' 'unchanged,' or 'made worse.' It also asked if they had altered their medication or the use of their respirator.

Of the nine who received injection treatment, eight claimed that they had received benefit. Four reported that one or more symptoms were 'much improved' and four reported that one or more symptoms were 'improved.' None claimed to have been made worse and only one found that his condition was 'unchanged.'

With regard to medication, two of the injected patients said that they now took 'less' and one, 'much less.' The others either had not been taking medication, or only occasionally using an inhaler or nose or eye drops and had noticed no change. The use of respirators was misleading, since four claimed to make use of them before the treatment was commenced and four after-

Table 3. Schedule of Nasal Doses

Patient	Number and strength of nasal inhalations taken twice weekly over 5 wk	Effect on symptoms of rhinitis and conjunctivitis
17	4 doses of 1 B.U./mL rising to 6 doses of 10 B.U./mL	Improved
18	2 doses of 1 B.U./mL rising to 8 doses of 10 B.U./mL	No change
23	2 doses of 1 B.U./mL rising to 8 doses of 10 B.U./mL	No change
25	5 doses of 1 B.U./mL rising to 5 doses of 10 B.U./mL	No change
29	2 doses of 10 B.U./mL rising to 8 doses of 25 B.U./mL	No change

Nasal inhalations of storage mite extracts given to each of five patients, according to the strength of solution, to produce a positive nasal provocation test. The strengths were increased if no symptoms of rhinitis resulted from a single inhalation, although in one instance the dose had to be reduced. The results of treatment show that only one patient noticed improvement in his condition when again in contact with hay dust.

Table 4. Hyposensitization to Mite Allergens

You will now have completed your initial course of injections or inhalation treatment, although one or two of you may be continuing with a maintenance course of injections. I should like therefore to assess the benefits, if any, that have been obtained by this treatment so far.

Please would you help by answering the following questions, putting a tick where appropriate?

1. Do you think that, on the whole, the treatment has benefited you?

YES/NO

2. What has been the effect on the following symptoms when working with hay?

- (a) Nose
(Sneezing, itching, blocked or runny nose)
(b) Eyes
(Itchy, sore or runny eyes)
(c) Chest
(Wheeze or tightness in chest)

Much improved	Improved	No change	Worse

3. What has been the effect on the amount of tablets, inhalant etc. that you use? Do you use:

Much less	Less	Same	More

4. Did you use a respirator whilst working with hay previously?

YES/NO

Do you use one now? YES/NO

Name:

Number:

wards, though it is doubtful if any used them consistently. One patient found that he could give up use of his respirator whilst another was persuaded during the course of treatment of the wisdom of wearing one!

Of the five patients who received nasal therapy, only one claimed to have experienced any improvement on his return to working inside, though none found that they were made worse (Table 3).

Skin Tests

Skin tests after treatment showed no significant differences in respect of weal size to those before treatment.

IgG

In the majority of patients following injection therapy there was an increase in specific IgG to the mites (Fig 1), but there was no obvious correlation between the variations in specific IgG and symptomatic improvement (Table 5).

IgE

Only two patients, Nos 4 and 32 of those treated by injection showed significantly high levels of IgE by RAST before treatment (Fig 2). In both these patients, the level of IgE to the mites fell following the course of treatment, though still remaining above the 'normal' level. The remaining seven patients all had specific IgE titres within normal limits both before and after treatment. Although two patients with high IgE titres both showed some improvement of symptoms with treatment, their improvement seemed to be less than that of the other six (Table 5).

Side Effects

All the patients who received injections experienced some local reaction that lasted from a single day to the whole week between treatments. Only one patient abandoned the treatment because of this, after the second dose. No patient experienced any general reaction from

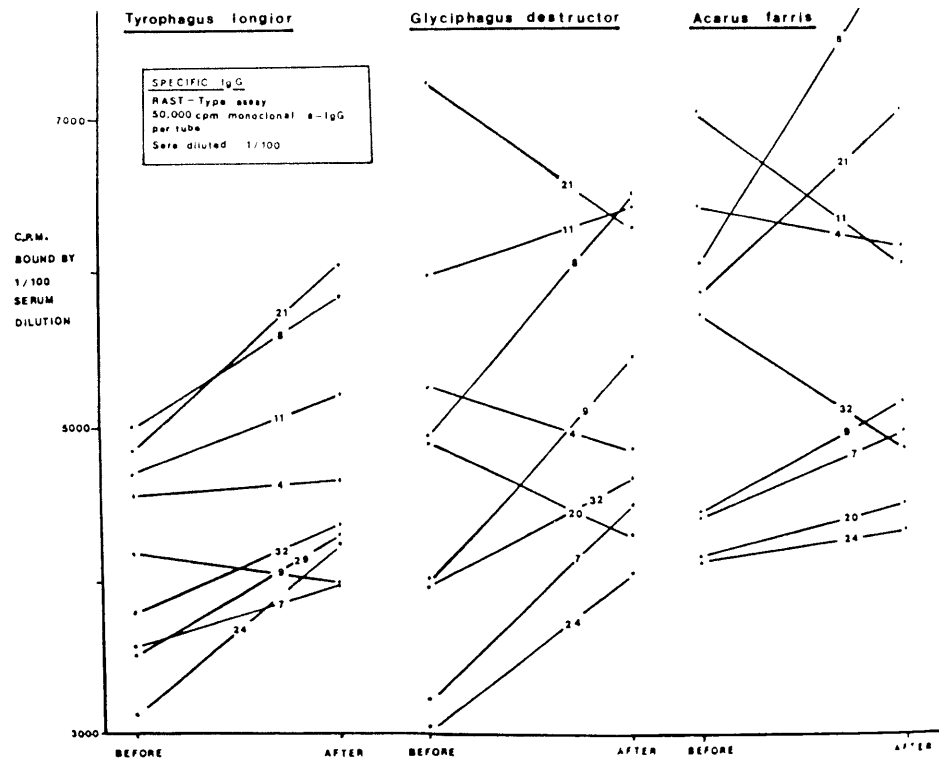


Figure 1. IgG titres for each of the injected patients before and after hyposensitization treatment.

MITE VACCINES — CUTHBERT ET AL

Table 5. Movement of IgG Titres and Symptom Changes after Hyposensitization by Injection

Patient no.	IgG Titres*			Symptoms		
	<i>T. longior</i>	<i>G. destructor</i>	<i>A. farris</i>	Nose	Eyes	Chest
4	same	down	down	No change	Improved	None
7	up	up	up	Improved	None	Improved
8	up	up	up	Much improved	Much improved	Improved
9	down	up	up	Much improved	(Improved)†	Much improved
11	up	up	down	None	None	Much improved
20	up	down	up	Improved	Improved	(No change)†
21	up	down	up	No change	None	None
24	up	up	up	Much improved	Much improved	Improved
32	up	up	down	Improved	No change	None

* Alteration in specific IgG titres bears no relationship to alteration in symptoms following hypersensitization, but the results of treatment indicate improvement in the condition of eight of the nine patients treated.

† The brackets around symptoms indicate that originally there was no complaint of the symptom but the questionnaires contained these answers!

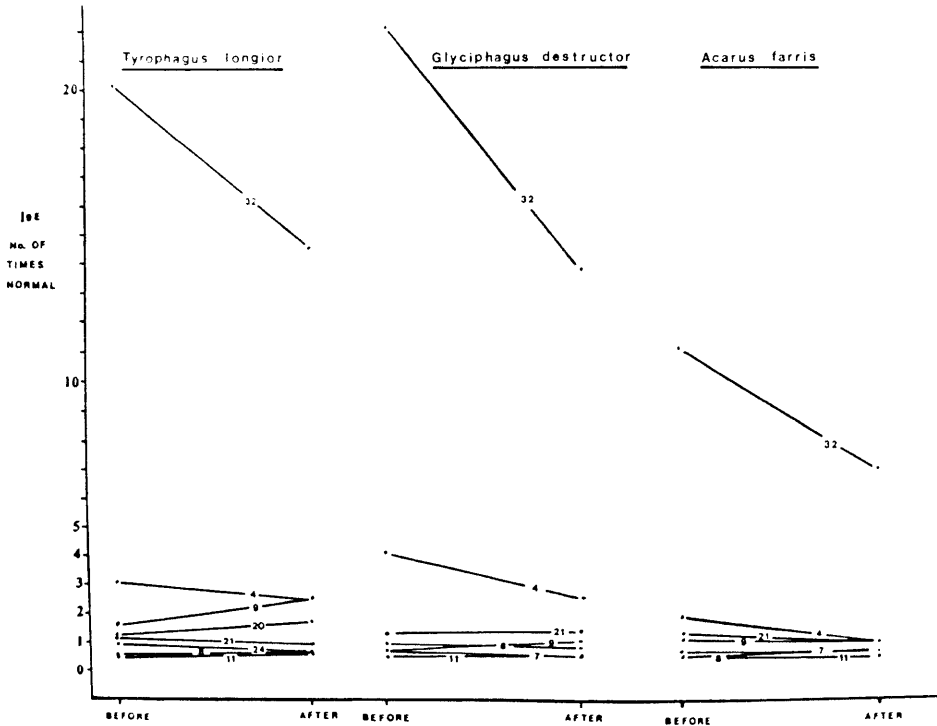


Figure 2. IgE titres for each of the injected patients before and after hypsensitization treatment.

the injections. One patient experienced severe symptoms of rhinitis with the initial dose from his nasal spray and the strength of the dose was reduced (Table 3).

Discussion

Farmers do not often complain and those who suffer from barn allergy are frequently prepared to endure it, since the symptoms are often limited to the time that

they spend storing hay or feeding stock, which may only occupy them for 10 or 15 minutes twice a day during the winter months. Further, they can neither afford time off work nor are they in a position to seek alternative employment. Nevertheless, the condition is a considerable nuisance as most of them admit, and over the years permanent lung damage may result, especially if in addition they also suffer from 'farmer's lung,' as many of them do. Most respirators available to farmers are either inadequate, uncomfortable to wear, or expensive.

Hyposensitization therefore, if successful, offers a means of treating the sufferers without recourse to drugs such as antihistamines and steroids, whose side-effects may be undesirable.

The numbers involved in the present study are too small for any authoritative conclusions to be drawn, but the improvement shown by eight of the nine patients treated by injection indicated that further studies would be worth undertaking and that this form of treatment may have a place in the care of those farmers who find the condition a handicap and the treatment acceptable. It is worth recording that all patients who derived benefit thought the exercise to be worth-while and would welcome further courses of treatment if they became necessary.

Those patients who were treated with the 'nasal' regimen, with one exception, found no benefit from it and it is doubtful whether this form of treatment is worth pursuing. For practitioners who believe this approach to be of value, investigation of other treatment schedules may prove to be more rewarding. In the present study, the nasally treated patients may be regarded as forming a control group that helps to validate the positive results of injection therapy.

Although one patient who received injections had to have his course modified because of his asthma, none had any general reaction and the local reactions, with one exception, were well-tolerated. It may be that we should consider giving higher doses of vaccine and it is interesting to speculate as to whether the two patients whose high levels of IgE had begun to fall would have achieved an even greater fall and more effective protection if this had been done. It has been shown by Cuthbert et al.⁶ however, that IgE levels tended to fall from October to November even when no treatment is

applied, so these two variations are probably not significant.

Whether or not practitioners subscribe to the use of hyposensitization in the treatment of allergic conditions, there seems to be little doubt that the storage mites commonly found in stored animal feedstuffs should be considered to be a possible cause when farm workers present with symptoms of allergic disease. In this respect, therefore, it would seem to be essential that extracts of these mites for skin testing be made available commercially. Whether commercially prepared vaccines for the treatment of the affected farmer should also be available may have to depend on the results of future studies amongst larger cohorts of patients, bearing in mind that there may be species variations from country to country and from one part of a country to another. The vaccine may therefore always have to be individual, rather than stock mixed vaccines.

Acknowledgments

The initial culture of the mites was done by Mr. I. G. Jeffery of the Agricultural Scientific Services of the Department of Agriculture and Fisheries for Scotland, and thereafter by Abello S.A. of Madrid who also prepared the extracts for skin testing and the treatment sets for individual patients. IgG and IgE estimations were also made at the laboratories of Abello S.A.

References

1. Seaton, Anthony: Leading article: the breathless farm worker. *Br Med J* 1984;288:1940-1941.
2. Cuthbert OD, Brostoff J, Wraith DG, et al: 'Barn allergy'. Asthma and rhinitis due to storage mites. *Clin Allergy* 1979;9:229-236.
3. Cuthbert OD, Jeffery IG, McNeil HB, et al: Barn allergy among Scottish farmers. *Clin Allergy* 1984;14:197-206.
4. Mehta SB, Smith JM: Nasal hyposensitization and hay fever. *Clin Allergy* 1975;5:279-284.
5. Carreira J, Rubio M, Herrero T, et al: Collaborative clinical assay of the biological potency of allergen skin test extracts. *Clin Allergy* 1984;14:503-507.
6. Cuthbert OD, Brighton WD, Jeffery IG, et al: Serial IgE levels in allergic farmers related to the mite content of their hay. *Clin Allergy* 1980;10:601-607.

Requests for reprints should be addressed to:
Dr. W. D. Brighton
Allergy Technical Consultancy
Holland House, 33 Bedhampton Hill
Bavant, Hampshire
United Kingdom PO9 3JN