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INHIBITION OF ALLERGIC REACTIONS DUE TO COMPETITION FOR MAST CELL SENSITIZATION SITES BY TWO REAGINS*

ELLEN E. E. JARRETT, T. S. C. ORR AND PATRICIA RILEY

Department of Bacteriology and Immunology, University of Glasgow and Fisons Pharmaceuticals Research Laboratories, Loughborough, Leicestershire

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SUMMARY

The ability of unrelated or incidental reagin to interfere competitively with mast cell sensitization by specific reagin has been examined using an experimental system whereby rats are induced to produce high levels of reaginic (IgE) antibody to two antigens. It is shown that passive sensitization by a reaginic antibody is inhibited (a) by simultaneous injection with a second reagin directed against another antigen, the degree of inhibition being related directly to the dose of the second serum or (b) if the test animal is actively producing unrelated reagin.

The skin test sensitivity of rats actively producing high levels of two reagins as opposed to only one is also discussed. The results are presented with particular reference to the interpretation of PCA and other skin tests and to the possible importance of interference effects in multiple allergies.

INTRODUCTION

The tests most commonly employed for the detection of titration of a reaginic antibody involve intradermal inoculation, either of antigen into putatively sensitive subjects, or of antibody into animals which are subsequently challenged with antigen in the Prausnitz-Küstner (PK) or passive cutaneous anaphylaxis (PCA) tests. Since the essential reaction occurs between antigen and antibody attached to the surface of mast cells (Mota, 1964; Movat, Lovet & Taichman, 1966), a question arises concerning the competitive role of other reagins adsorbed at the same mast cell surface.

To investigate the possibility that competition for mast cell receptors could influence the interpretation of intradermal tests we have made use of a method whereby rats can be induced to produce high circulating reaginic antibody levels to two unrelated antigens.

Production of egg-albumin reagins is potentiated in rats if at a critical time after inoculation of the antigen and *B. pertussis* suspension the animals are infected with the nematode *Nippostrongylus brasiliensis* (Orr & Blair, 1969). The parasite infection *per se* also stimulates the production of high levels of *N. brasiliensis* reagin (Ogilvie, 1966).

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Correspondence: Dr. Ellen E. E. Jarrett, Department of Bacteriology and Immunology, University of Glasgow, Glasgow.

The present paper describes experiments to determine the ability of each of these reagins to interfere with sensitization by the other for local or systemic anaphylaxis.

MATERIALS AND METHODS

Animals. Unless stated otherwise, female hooded Lister rats weighing 150–200 g were used.

Antisera. (a) Anti-*N. brasiliensis* serum (NbS) was obtained from rats which had been infected twice (at a 20-day interval) with 3000 and 5000 *N. brasiliensis* larvae. They were bled 6 days after the second infection. The pooled serum from these rats had an *N. brasiliensis* PCA titre of 2048. The method of maintaining the parasite in culture is described by Jennings, Mulligan & Urquhart (1963) and the preparation of the larval dose and infection techniques by Jarrett, Jarrett & Urquhart (1968).

(b) Potentiated anti-egg-albumin serum (EaS) was prepared after the method of Orr & Blair (1969). Fifty rats were injected intramuscularly with 1 mg egg-albumin (Sigma Grade V) and intraperitoneally with 0·5 ml *Bordetella pertussis* suspension (Burroughs Wellcome) containing 2×10^{10} organisms. Ten days later the rats were infected with 4000 *N. brasiliensis* larvae. Such rats are referred to as potentiated rats in the text. They were bled 12 days after infection. The pooled serum from these fifty animals had an egg-albumin PCA titre of 1600 and had no *N. brasiliensis* reagins, (the latter do not normally appear in the circulation until later in the infection). A further pool of EaS was prepared from twenty rats treated in a similar manner and this had an egg-albumin titre of 2048. The titration of these sera by PCA was carried out by intradermal injection of 0·1 ml of saline dilutions, each dilution being repeated in three rats. Seventy-two hours later the animals were injected intravenously with 2·5 mg egg-albumin in 0·25 ml saline or with 0·5 ml *N. brasiliensis* antigen (a saline extract of 1000 homogenized worms/ml) and 0·5 ml of a 1% Evans blue solution. The titre of the serum given is the reciprocal of the greatest dilution given a reaction size larger than 5 mm. There are no cross reactions between these two antigens and their reaginic antibodies.

RESULTS

Experiments were carried out to determine the ability of one reagin to interfere with the sensitizing efficiency of another, in three separate situations:

1. Passive-passive. Interference by a passively injected reagin with passive sensitization by another.
2. Active-passive. Interference by an actively produced reagin with passive sensitization by another.
3. Active-active. Interference effects between two actively produced reagins.

Experiment 1(*a*). *Skin test reaction sizes induced by injection of antigen into rats passively sensitized with a single or with a mixture of two reaginic antibodies*

Five groups of three rats were injected intraperitoneally with 1 ml EaS and simultaneously with 0, 1, 2, 4 or 8 ml of the NbS. Twenty-four hours later each rat received into the shaved skin of the back, six intradermal injections with decreasing doses of egg albumin (as shown in Table 1) in 0·1 ml saline. Evans blue (0·5 ml of a 1% solution) was injected intravenously. They were killed after 20 min and the diameters of the resulting blued areas were measured on the inner surface of the skin. Table 1 shows the mean reaction sizes, and the

degree of inhibition produced by the interfering serum. Reactions of 5 mm or less are regarded as negative since this size of reaction was elicited in unsensitized control animals receiving similar egg-albumin injections.

It is evident that the injection of *N. brasiliensis* reagins interferes with sensitization by simultaneously injected egg-albumin reagins. Fig. 1 also shows that the degree of interference is related directly to the dose of NbS. Reactions in the groups of rats receiving both

TABLE 1. Inhibition of passive sensitization with reagins by simultaneous injection with a second reaginic antibody. All rats were injected with 1 ml of egg-albumin reaginic serum (titre 1600) plus 0, 1, 2, 4 or 8 ml of *N. brasiliensis* reaginic serum (titre 2048). All rats were challenged 24 hr later with ID egg albumin and IV Evans blue

ID dose of egg albumin	Mean reaction size* and (% inhibition)									
	Dose of *N. brasiliensis* serum									
	(0)	(1 ml)		(2 ml)		(4 ml)		(8 ml)		
100 μg	21	18	(14)	14	(34)	10·6	(50)	7	(67)	
10 μg	18	16·6	(8)	11	(39)	8·3	(54)	9	(50)	
1 μg	20·6	16·6	(19)	13	(37)	7·6	(63)	7·6	(63)	
100 ng	15·6	14	(10)	10	(36)	7·3	(53)	7	(55)	
10 ng	15·3	12	(22)	9·3	(39)	6·6	(57)	4	(100)	
1 ng	14	11·6	(17)	7·3	(48)	6	(58)	4	(100)	

* Three rats

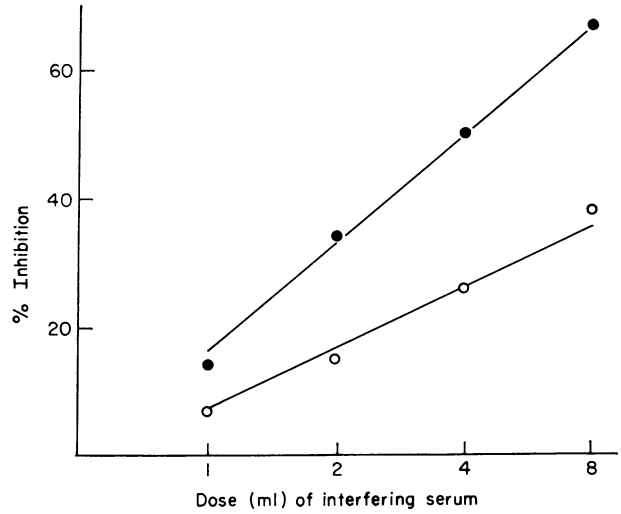

FIG. 1. Inhibition of skin test reaction sizes in rats passively sensitized by IP injection of two reaginic sera (Exp. 1a). ●, interference by *N. brasiliensis* reagin with sensitization by egg-albumin reagin; skin tests with 100 μg egg albumin; ○, interference by egg-albumin reagin with sensitization by *N. brasiliensis* reagin: skin tests with twenty-five worm equivalents.

TABLE 2. PCA blocking effect by admixture of two reaginic antibodies. Egg albumin (EaS) and *N. brasiliensis* (NbS) reaginic sera, both of titres 512, were mixed in varying concentrations before ID injection in the PCA test

A. Effect of NbS on EaS PCA

Mean EaS reaction size at 1/128 dilution	Dilution of NbS added	Mean reaction size of mixture	% inhibition
20	2	0	100
19	4	0	100
21	8	0	100
22	16	0	100
20	32	0	100
23	64	13	43·5
21	128	21	0
20	256	21	0

B. Effect of EaS on NbS PCA

Mean NbS reaction size at 1/128 dilution	Dilution of EaS added	Mean reaction size of mixture	% inhibition
19	2	0	100
19	4	0	100
20	8	0	100
17	16	0	100
21	32	13	38·1
20	64	18	10
17	128	16	0
19	256	19	0

sera were markedly less intense in colour and less oedematous than those of the animals sensitized with EaS alone.

Heat inactivation at 56°C for 3 hr destroyed almost entirely the sensitizing ability of EaS without reducing its titre in a passive haemagglutination test. Heat inactivation of NbS for 3 hr totally destroyed both its PCA titre and its ability to interfere. Normal rat serum was not found to have any interfering effect in this system.

A similar experiment was done in which the roles of the two reaginic sera were reversed. Groups of three rats were injected with 1 ml NbS and 0, 1, 2, 4 or 8 ml EaS of the second pool having a titre of 2048. Twenty-four hours later they were injected with *N. brasiliensis* antigen intradermally and Evans blue intravenously. As can be seen from Fig. 1 egg-albumin reagins interfered with sensitization by *N. brasiliensis* reagins far less efficiently than vice versa.

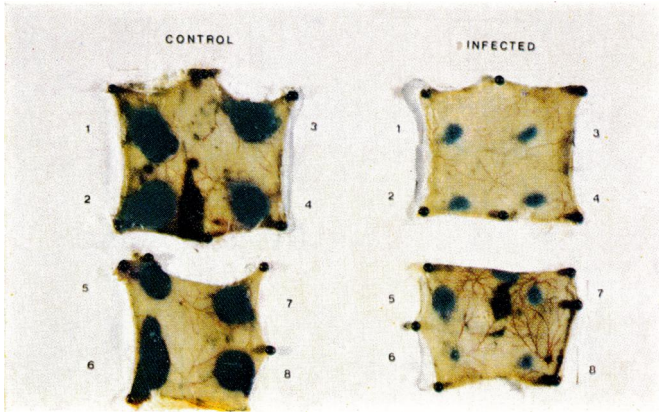

FIG. 2. Inhibition of passive sensitization with reaginic antibody by actively produced reagins to another antigen. Normal rats and infected rats having a circulating *N. brasiliensis* reagin titre of 2048 were passively sensitized with 1 ml egg albumin reaginic serum of titre 1600. Both groups were challenged 24 hr later with ID injections of egg albumin and IV injections of Evans blue. Nos 1–8 represent ID doses of egg albumin as listed from top to bottom in Table 3.

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Experiment 1(*b*). *PCA reactions with single or with mixed reaginic sera*

In this experiment the EaS and NbS were both adjusted to have a titre of 512. In this instance female Sprague Dawley CSD strain rats were used. Groups of five 100 g rats were used for the PCA tests. Intradermal injections of 0·1 ml of serum were made, the animals being challenged 24 hr later by an intravenous injection of 2·5 mg egg albumin or 0·25 ml *N. brasiliensis* antigen (about 1 mg/ml total protein). A dilution of 1/128 of each of the above sera gave areas of blueing with a mean diameter of 20 mm.

By maintaining this dilution of one serum and adding various concentrations of the other the effect on a 20 mm PCA reaction of increasing amounts of the second reagin could be found.

The results given in Table 2 show that either reagin could inhibit PCA induced by the other. Where the reagins were injected in equal effective concentrations no measurable inhibition of the PCA reaction diameter of either resulted. Where the blockading reagin was injected in higher proportion the PCA reaction of the other reagin was reduced in dye intensity and size or completely abolished. In repeated experiments NbS was found to have a stronger interfering effect on the egg-albumin PCA results than vice versa, i.e. a similar effect to that observed in Experiment 1(a).

Experiment 2(*a*). *The ability of reagins actively produced as a result of parasitic infection to interfere with passive sensitization with egg-albumin reagins for systemic anaphylaxis and skin test reactions*

A group of rats which had been infected 23 days previously with 3000 *N. brasiliensis* larvae and a group of uninfected control rats were used in this experiment. The rats of both groups were sensitized by intraperitoneal injection of 1 ml EaS titre 1600. Twenty-four hours later the animals were challenged with intravenous or intradermal injections of egg albumin.

For the induction of systemic anaphylaxis 1 mg, 0·1 mg or 0·01 mg of egg albumin was injected intravenously into each of two infected and two control rats. There was a very striking difference in the reactions between the infected and control animals. Both control rats injected with 1 mg of egg albumin died within a few seconds. The remaining four rats injected with 0·1 mg or 0·01 mg were severely shocked, with severe dyspnoea and complete prostration for 15 min after which they were killed. In the infected rats on the other hand, all three doses of egg albumin induced only mild and short-lived signs of shock and the rats appeared little affected at 15 min after challenge.

Another six rats of each groups were injected intradermally on four sites of the shaved back with decreasing amounts of egg albumin in 0·1 ml saline as shown in Table 3 and with 0·5 ml 1% Evans blue intravenously. Each dose of egg albumin was thus repeated in three rats. The rats were killed after 20 min and the reactions were measured on the inner surface of the skin. As in Exp. 1(a) reactions of 5 mm or less were considered negative, since these could not be distinguished from similar small reactions induced in unsensitized control animals. As can be seen from figures in Table 3 and the photograph Fig. 2, the reactions in the infected rats were much smaller, or negative. They were also less intensely blue and in contrast to the control rats there was no wheal. It was also noted that the higher dose intradermal injections were inducing mild signs of systemic shock in the control but not in the infected rats. The pooled serum from the infected rats used in the skin tests was found to have an *N. brasiliensis* PCA titre of 2048.

TABLE 3. Inhibition of passive sensitization with reaginic antibody by actively produced reagins to another antigen. Normal rats and infected rats having a circulating *N. brasiliensis* reagin titre of 2048 were passively sensitized with 1 ml egg-albumin reaginic serum of titre 1600. Both groups were challenged 24 hr later with ID injections of egg albumin and IV injections of Evans blue

ID dose of egg albumin in μg	Mean Reaction size (three rats)		% inhibition
	Control rats	Infected rats	
125	19·6	8·2	60
62	13·7	6·3	58
31	17·3	5·1	71
16	19	6·6	64
4	15·6	5	100
2	17	4	100
1	16	3	100
0·5	18	3	100

Experiment 2(*b*). *The result of PCA titrations* (*of EaS*) *in normal rats and in rats producing large quantities of circulating N. brasiliensis reagins*

The above results suggested that the titre of a serum tested for reagins in the PCA reaction might be influenced by the reaginic status of the rat on which the PCA is performed. To test for this the EaS was retitrated in normal rats and infected rats remaining from Experiment 2(a), the titrations being carried out in triplicate. The titre in the normal rats was again 1600 whereas it did not go above 64 in the infected animals.

Experiment 3. *Skin tests in rats actively producing two reagins; attempt to demonstrate interference by egg-albumin reagins on N. brasiliensis skin test sensitivity*

Egg albumin potentiated rats (see Materials and Methods) were used in an attempt to demonstrate that competition for mast cell sensitization sites would occur by two actively produced reagins. Fig. 3 shows in diagrammatic form the time course of both the circulating egg albumin and *N. brasiliensis* reagin response in potentiated rats, and the *N. brasiliensis* reagin response in rats which have had the infection only. It can be seen that the maximum circulating egg albumin titre in the potentiated rats occurs 12–14 days after the parasitic infection, followed by a rapid decline (Orr, Riley & Doe, 1971). *N. brasiliensis* reagins on the other hand appear in the circulation 16–18 days after infection and the titre is maintained at the peak level for a long time after infection (Ogilvie, 1967).

In this experiment an attempt was made to demonstrate in potentiated rats an interference effect of egg-albumin reagins on *N. brasiliensis* sensitivity during the short period when both reagins are present in the circulation. Rats infected with *N. brasiliensis* only, served as controls.

On days 12 and 18 after the infection animals from both groups were injected intradermally with dilutions of *N. brasiliensis* antigen and egg albumin as shown in Table 4.

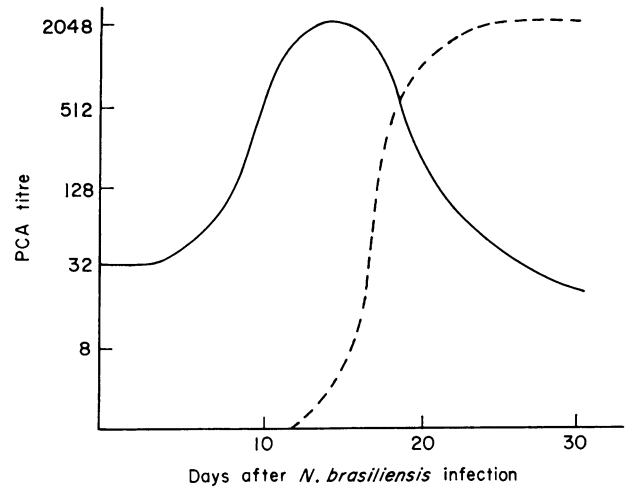

FIG. 3. Kinetics of the circulating reagin response in egg albumin potentiated rats. ———, Egg-albumin reagins; — — —, *N. brasiliensis* reagins (also produced to a similar titre in rats infected with *N. brasiliensis* only).

TABLE 4. Skin tests in rats producing both egg albumin and *N. brasiliensis* reagins (potentiated rats) and in rats producing *N. brasiliensis* reagins alone (control rats)

Dose of antigen injected intradermally	Mean reaction sizes (three rats) on day 12 after infection		Mean reaction sizes on day 18 after infection	
	Potentiated	Control	Potentiated	Control
25 worm equivalents	13·3	13	15·6 (13)*	18
10 worm equivalents	11	11	15·3 (10)	17
1 worm equivalent	5	5	10 (23)	13
100 ng egg albumin	14	< 5	14·6	< 5
10 ng egg albumin	8	< 5	10	< 5

* Figures in parentheses indicate % inhibition compared to controls.

The results are shown in Table 4. On day 12 after infection the control rats showed no greater sensitivity to *N. brasiliensis* antigen than did the potentiated rats which were found to have a circulating egg albumin titre of 2048. At this time neither group had circulating *N. brasiliensis* reagins. Eighteen days after infection some inhibition was noted; the potentiated rats having somewhat smaller skin reactions to injected *N. brasiliensis* antigen than the controls. At this time the egg-albumin reagin titre had fallen to 256 while the anti-*N. brasiliensis* titre of both groups was 512.

DISCUSSION

It has been shown in man and the rat (Ishizaka, Ishizaka & Hornbrook, 1966a, b; Stechschulte, Orange & Austen, 1970) that reaginic antibodies belong to an antigenically distinct immunoglobulin class, IgE (see Bull. Wld. Hlth. Org. 1968, **38,** 151), and that the unique tissue sensitizing property resides in the Fc fragment of the immunoglobulin molecule (Stanworth *et al.*, 1968; Ishizaka, Ishizaka & Lee, 1970).

Stanworth *et al.* (1967) showed that the PK reaction in man could be inhibited by an IgE myeloma protein which competed with a test serum for reagin-binding tissue sites. This finding indicated that the sensitivity of skin tests used for the detection or assay of reaginic antibodies might vary inversely with total IgE.

Until recently such interference effects between reagins have not been analysed in an experimental system because of the difficulty of raising high reagin titres to more than one antigen in experimental animals. This problem was recently resolved by the finding of Orr & Blair (1969) that the production of egg-albumin reagins in rats by inoculation of the antigen with *B. pertussis* suspension, can be greatly potentiated by subsequent infection of the animals with the nematode parasite *N. brasiliensis*. Rats undergoing this treatment produce large amounts of circulating reaginic antibody against egg albumin and subsequently also against *N. brasiliensis* with a short period intervening during which both reagins are present in the circulation. This system has enabled us to test the inhibiting effect of one reagin on sensitization by another in situations involving either passive or active sensitization or a combination of the two.

Where both reagins are given passively by intraperiotoneal injection and the animals are challenged after 24 hr by skin tests with antigen (Exp. 1a), the degree of inhibition of skin test reactions was shown to be related directly to the dose of the second or interfering reaginic serum (Fig. 1). The finding that the two reagins did not interfere with sensitization to the same degree might imply that there are differences in affinity for mast cell attachment sites between individual reagins. However, it cannot be excluded that the presence of reagins to other unknown antigens contributed to the stronger inhibiting effect of the *N. brasiliensis* serum.

The inhibition phenomenon is of obvious importance in the PCA test if it is suspected that reagins other than the one being titrated are present in the test serum. For instance, it became apparent in the PCA titration of sera from egg albumin potentiated rats that when *N. brasiliensis* reagins began to appear in the serum they had an inhibiting effect which resulted in an apparently dramatic drop in egg-albumin reagin titre. The results of Exp. 1(b) showed that in a mixed serum each reagin could, depending on relative proportions, partially or completely inhibit the PCA reaction of the other reagin.

The inhibiting effect of actively produced reagins on passive sensitization was also demonstrated. Rats producing a large quantity of *N. brasiliensis* reagin were far less effectively sensitized by egg-albumin reagins than control animals. This was demonstrated by their almost complete protection against the 'shocking' effect of doses of intravenous antigen which caused fatal systemic anaphylaxis in the control rats, and by the marked inhibition of skin reactions to an intradermal injection of antigen.

The practical importance of these results is emphasized in Exp. 2(b) in which it was shown that the titre of a serum in the PCA test is markedly influenced by the reaginic status of the rats on which the PCA reactions are performed. It is clearly apparent that

infection with a nematode parasite could markedly distort the result of PCA tests. The finding of Johansson that the IgE myeloma patient N.D. could not be passively sensitized for the PK reaction (personal communication) is of interest since this is almost certainly an example of complete pre-emption of mast cell receptors by actively produced IgE. A somewhat similar phenomenon was noted by Austen *et al.* (1965) in that mast cells from young or germ free rats were found to have a much greater capacity for *in vitro* passive sensitization with anaphylactic antibody than cells from older rats. It was suggested that the sensitization sites of the mast cells from the older rats had been pre-empted by anaphylactic antibody to naturally occurring antigens, or alternatively were blocked due to steric hindrance by another immunoglobulin.

In animals which were actively producing both egg albumin and *N. brasiliensis* reagins (Exp. 3) interference effects were not so readily demonstrable. We do not know why there was no inhibition of *N. brasiliensis* skin test reactions on day 12 after infection when the egg albumin reagin titre is at its peak. Clearly the animals are sensitive to *N. brasiliensis* antigen at this time although no circulating *N. brasiliensis* reagins are present. (It may be noted in passing that *N. brasiliensis* antigen contains a mast cell degranulating factor similar to that of Ascaris (Uvnas & Wold, 1967) capable of causing large skin reactions in unsensitized rats. This factor can be diluted out, negligible reaction occurring when the saline extract of 25 or less worms is injected.)

When viewed in the light of previous experiments it is probable however that the small degree of inhibition observed on day 18 after infection is real. Thus it has been shown in a mutual system that the interfering ability of egg-albumin reagins is much less than that of *N. brasiliensis* reagins. It has also been shown that for marked interference to occur it is necessary for the blocking reagin to be present in excess. From Fig. 1 it can be seen that when both reagins are present in approximately equal proportions the percentage inhibition is in fact of the same order as that observed on day 18 after infection in Exp. 3.

The results of these experiments could indicate that in animal or human subjects with multiple allergies the results of skin tests for individual sensitivities might be made misleading by high total IgE levels. This would particularly apply in subjects infected with nematode parasites, such as those described by Johansson, Melbin & Vahlquist (1968) who were shown to have very high levels of this immunoglobulin. It is also possible that the intensity of naturally occurring allergic reactions in the hypersensitive individual is subject to modification by the competitive effect of reagins of other specificities, either actively produced or passively administered. It is tempting to speculate that unrelated reagins or IgE myeloma protein could be used therapeutically to inhibit selected hypersensitive reactions. However some preliminary results with the rat system indicate that the displacement of an actively sensitizing reagin by another passively administered reagin is very difficult to achieve (Jarrett & Henderson, 1971, unpublished results).

There may be more future in the artificial stimulation of production of the individual's own IgE preferably of a completely non-specific kind, or in response to a potent but seldom encountered allergen.

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