

Clinical significance of measurement of reaginic (IgE) antibody by RAST

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Introduction

It was shown in 1966 that reaginic antibodies, which are involved in hypersensitivity of the atopic type, belong to a particular immunoglobulin class (IgE) (Ishizaka, Ishizaka & Hornbrook, 1966a,b). Soon thereafter, the finding of an atypical myeloma protein, which did not belong to immunoglobulin classes A, D, G or M, was reported by Johansson & Bennich (1967a,b). This myeloma protein had a corresponding protein in normal human serum (Johansson, Bennich & Wide, 1968) and was shown to belong to the same immunoglobulin class E as found by Ishizaka and collaborators (Bennich *et al.*, 1968; Bennich *et al.*, 1969) and be present in serum in extremely low concentrations. However, the availability of the IgE myeloma together with the development of the radioimmunosorbent techniques (RIST) (Wide & Porath, 1966; Wide, Axén & Porath, 1967a) made it possible to construct a sensitive *in vitro* method for the assay of reaginic (IgE) antibodies to particular allergens. This method was called the radioallergosorbent technique (RAST) (Wide, Bennich & Johansson, 1967b). During the past 6 years the RAST has been used clinically as a method for the diagnosis of atopic allergy and as a means of quality control of allergen extracts. This paper will discuss the clinical significance of the use of the RAST in these respects.

The radioallergosorbent test (RAST)

The principle of the RAST is shown in Fig. 1: reaginic (IgE) antibodies in a serum react with the allergen which is chemically coupled to an insoluble matrix. The bound reagins are then detected by their ability to bind ^{125}I -labelled antibodies directed against IgE and the uptake of labelled antibodies measured in terms of radioactivity on the solid phase, is directly correlated with the level of specific reaginic (IgE) antibodies to that particular allergen (Fig. 2). Common allergens such as pollen, animal dandruff, food allergens, moulds etc. can easily be coupled to a solid phase like cellulose or cross-linked dextran (Sephadex®) and the solid phase may be either in the form of fine particles or as a paper disc (Wide *et al.*, 1971). The insoluble allergens seem to be stable for some years and with the simplified technical procedure

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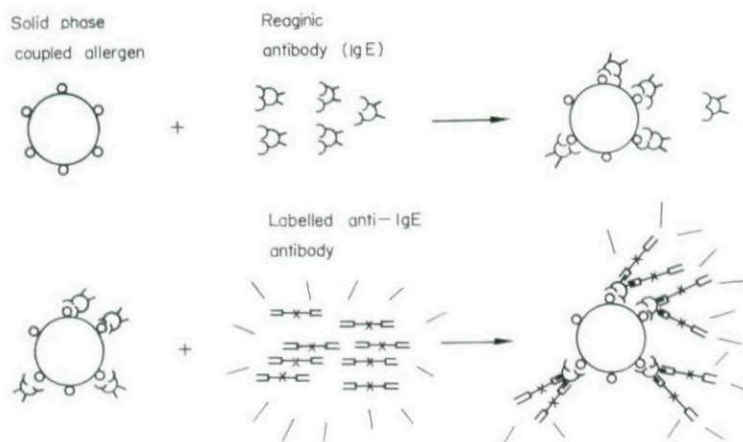


Fig. 1. The principle of the radioallergosorbent technique (RAST) for detection of reagenic (IgE) antibodies to different allergens (from: Wide, 1971).

outlined in Fig. 3 it is possible for one technician to perform up to a 1000 tests per week. The results of RAST can be expressed semi-quantitatively in arbitrary units, either in sorbent units (SU) (Stenius & Wide, 1969) or per ml of activity of a laboratory standard serum tested against a particular allergen extract (Johansson, Bennich & Berg, 1971). When expressed in SU the uptake of ^{125}I -labelled antibodies on the solid phase in the RAST is compared with the binding of these antibodies on solid phase coupled IgE.

The scarcity of the myeloma-IgE protein required for the purification of specific antihuman IgE antibodies for labelling with ^{125}I has hitherto been a limitation in the widespread use of the RAST. However, Sarsfield & Gowland (1973) have recently shown that it was possible to perform the RAST by using the IgG fraction of an anti-human IgE antiserum. Furthermore, it now seems that in the near future the reagents

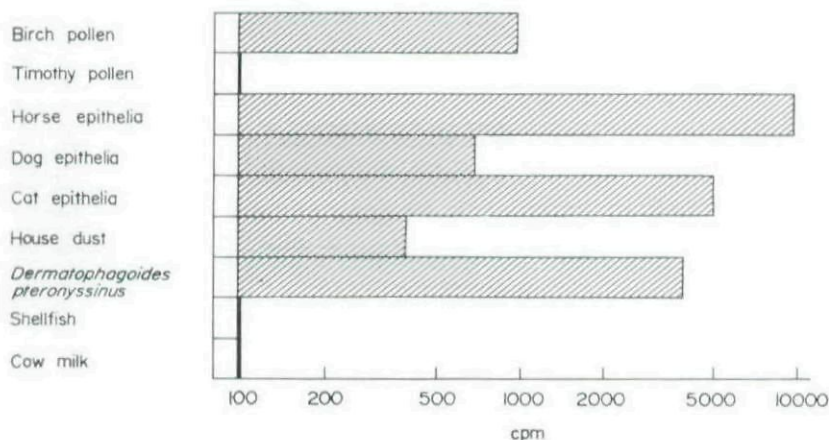


Fig. 2. Reagenic (IgE) antibody activity to nine different allergen extracts in one serum sample assayed by RAST. The activities are expressed in counts per minute (cpm). The reaction is positive for six allergens and negative for three (timothy, shellfish and cow milk).

for RAST, ^{125}I -labelled antibodies to IgE and solid phase coupled allergens, will be commercially available and this will make it possible for many research units and hospitals to use the RAST as an aid in the clinical diagnosis of allergy.

RAST versus provocation and skin tests in allergic asthma and allergic rhinitis

In diagnosing hypersensitivity of the atopic type, i.e. 'extrinsic' asthma, allergic conjunctivitis, allergen-induced urticaria and atopic eczema, skin tests and provocation tests are usually made as a complement to a thorough case history. These tests can sometimes be time-consuming and there are occasions where both skin or provocation tests are difficult to perform and evaluate, e.g. due to psychological reasons or to the medical treatment of the patients. In these cases in particular, an *in vitro* test like the

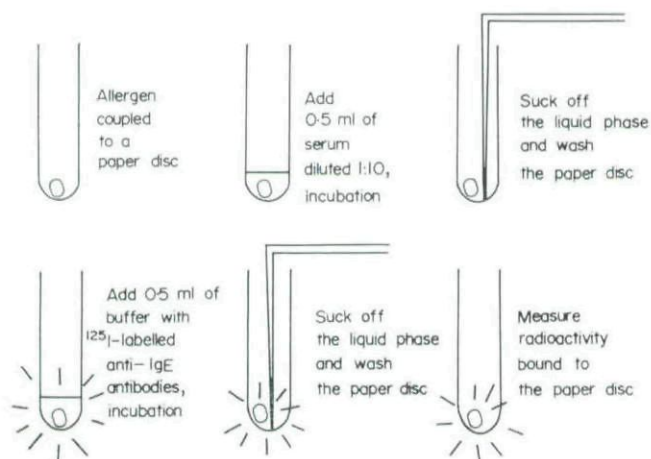


Fig. 3. The principle of RAST using paper disc coupled allergens (from: Wide *et al.*, 1971).

RAST would be extremely valuable. Provocation tests are not completely free of risk and it was therefore of interest to see if the RAST had any advantage when compared with *in vivo* tests and could perhaps replace these in some cases or be a valuable addition in others.

A number of studies have been made on the comparison between clinical history and the results of skin tests, provocation tests and the RAST. In most of these investigations good correlations have been obtained between results of the RAST and the *in vivo* tests. In the first report (Wide *et al.*, 1967b) a 68% agreement was found between results of 140 intracutaneous (i.c.) tests and RAST using fourteen different allergens. A greater correlation (96%) was found when results of fifty-one provocation tests and RAST were compared. A 79–82% agreement between RAST and skin-prick tests with extracts of house dust and of house dust mite (*Dermatophagoides culinae*) was found by Stenius & Wide (1969) in patients with a history suggestive of house dust allergy. Where the prick test and RAST results were discordant the skin test was usually positive and the RAST negative, and negative RAST results corresponded with negative provocation tests. Comparisons of quantitative estimations of prick tests and RAST revealed a highly significant ($P < 0.001$) correlation between results of the two methods with four different extracts. A group of thirty-five adults with asthma and suspected allergy to dog epithelium were investigated by Fagerberg & Wide (1970)

and there was a 97% agreement between the results of RAST and clinical diagnosis of dog hypersensitivity as obtained from both history and provocation tests. The concordance between results of RAST, provocation tests and i.c. tests was much higher for mixed dog-breed epithelia extracts than for individual breed extracts although the same batches of extracts were used in all three tests, Table 1. Skin tests and RAST, for example, agreed in 84% with mixed extracts of dog epithelia and in 64% with individual dog breed epithelia extracts. These results indicated that the quality of the allergen

Table 1. Correlation between the results of RAST, bronchial provocation tests and i.c. tests (data from: Fagerberg & Wide, 1970)

	Number	Agreement (%)	Doubtful (%)	Disagreement (%)
Mixed extracts of dog epithelia				
RAST and provocation tests	66	95	3	2
i.c. tests and provocation tests	66	83	6	11
RAST and i.c. tests	68	85	7	7
Extracts of epithelia of individual dogs				
RAST and provocation tests	54	59	9	32
i.c. tests and provocation tests	68	60	6	34
RAST and i.c. tests	188	65	8	27

extract to a large extent influenced the degree of concordance between results from the three tests. That the correlation between results of different allergy tests varied with the allergen extracts used, was also found by Aas & Johansson (1971). The agreement between RAST and provocation tests varied between 93% for fish allergy to 59% for allergy to house dust. Using a highly purified allergen from cod, Aas & Lundkvist (1973) found a 100% correlation between results of RAST and provocation tests in 112 allergic children.

The relationship of reaginic IgE antibodies against extracts of *Dermatophagoides* spp. and grass pollen compared to the results of skin and nasal tests and history was investigated in ninety-four patients by Stenius *et al.*, (1971). There was a significant correlation between the RAST and the size of the prick test wheal ($P < 0.001$). In budgerigar fanciers reaginic (IgE) antibodies to budgerigar serum proteins were present in the atopic subjects with asthma due to budgerigar allergens but not in the non-atopic subjects with allergic alveolitis (Faux *et al.*, 1971). The RAST has furthermore been found to be of value in making the diagnosis of hypersensitivity of the immediate type to proteolytic enzymes from *Bacillus subtilis* in 'biological' detergents for household use both in consumers and factory workers (Belin *et al.*, 1970; Göthe *et al.*, 1972). Berg, Bennich & Johansson (1971) compared results of RAST and provocation tests on ninety-six children, 3-15 years of age and found an overall agreement of 74%. This relatively low figure may have been due to some factor related to the age of the patients or to the fact that blood sampling and provocation tests were not performed at the same time. In only a minor part of the study was the same batch of allergen extracts used for both provocation tests and RAST. Different allergen extracts of the same type can vary considerably even between different batches prepared in the same way by the same firm (Aronsson & Wide, 1973).

When results of RAST and provocation tests are to be compared it is important that, (1) the same extract is used in both provocation tests and the RAST, (2) the provocations are performed at the time of blood sampling, (3) note is made if the patients have been hyposensitized or are treated with any medical drugs, and (4) only batches of allergen extracts which have proved to be of high quality as judged from skin tests and RAST are used. In a study which fulfilled these criteria a good correlation was found in 128 non-hyposensitized patients (Wide *et al.*, 1971) using extracts

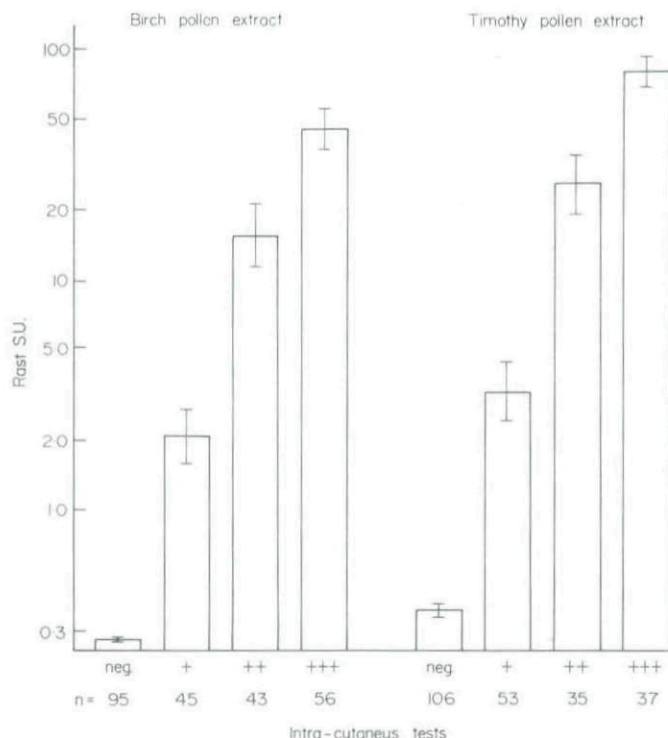


Fig. 4. Correlation between results of 470 RAST and skin tests. The bars represent mean reaginic (IgE) antibody activity expressed in s.u. with $\pm$ s.e. mean indicated at the top (from: Wide *et al.*, 1971).

of birch and timothy pollen, cat, dog and horse epithelia and house dust, Table 2. A 95% agreement was then found between the results of 220 RAST and provocation tests (64 inhalation tests and 156 nasal tests). The results were doubtful with one of the methods in 3.6% and disagreed in only 1.4%. When, in the same investigation, results of i.c. tests and the RAST were compared a high degree of correlation ($P < 0.001$) was obtained in 470 tests (Fig. 4).

It can thus be concluded that in almost all studies on the clinical usefulness of RAST as a method for diagnosis of atopic allergy in patients with asthma or hay fever significant correlations between results of RAST and provocation or skin tests have been found. It is possible that with the routine use of RAST, the number of skin tests made can be reduced and in particular provocation tests may become superfluous in a large number of cases.

Drug allergy and reaginic IgE antibodies

The most serious complication of penicillin therapy is anaphylactic shock or other hypersensitivity reactions of the immediate type. Penicilloyl is the principal allergen derived from penicillin and is commonly used in the form of penicilloyl polylysine for intradermal testing. This test may provoke severe generalized reactions and the RAST has been suggested as an alternative or complement to the skin tests in these cases (Wide & Juhlin, 1971; Juhlin & Wide, 1972). In the study of sixty-nine patients with a possible penicillin allergy, sera from fifteen gave a positive RAST reaction to peni-

Table 2. Correlation between results of 220 RAST and provocation tests on 128 patients (data from: Wide *et al.*, 1971)

		RAST		
		Positive	Doubtful	Negative
Provocation tests (64	positive	112	3	0
inhalation tests and	doubtful	0	0	3
156 nasal tests)	negative	3	2	97

Allergen extracts of birch and timothy pollen, cat, dog and horse epithelia and of house dust.

Agreement 95%, doubtful 3.6%, disagreement 1.4%.

cilloyl. Results from skin tests and RAST agreed in all cases. It is our experience that in patients with a history of penicillin allergy and a positive RAST reaction skin tests should be avoided or made with caution. However, to be able to exclude penicillin allergy of the immediate type with certainty, it might be important to include minor determinant allergens of the penicillin group in the test battery (Siegel & Levine, 1964; Voss, Redmond & Levine, 1969).

In patients treated with hormones, particularly from animal sources, reaginic (IgE) antibodies might develop and cause severe complications with even a fatal outcome. By using the RAST method, reaginic (IgE) antibodies in serum were found in patients who had reacted with anaphylactic shock or urticaria to insulin, bovine thyroid stimulating hormone and pork adrenocorticotrophic hormone. In some of these cases the complications were not due to the hormone itself but merely to contaminating proteins from the animal.

In this context it may be of interest to note that antibodies of the IgE-type might be present in serum without causing any noticeable clinical effect. For instance, in patients treated with daily intravenous or intramuscular injections of L-asparaginase, IgE antibodies developed in some patients who showed no signs of hypersensitivity (Dohlwitz *et al.*, 1970). It has also been shown (Wiholm, 1972) that immunization with tetanus toxoid can lead to sensitization in both allergic and non-allergic subjects, with development of skin fixed reagins and circulating reaginic (IgE) antibodies to the toxoid, the latter being detected both by Prausnitz-Küstner (PK) tests and the RAST. This sensitization, however, seemed to be of no practical importance since no allergic reactions were caused by further injections of the toxoid.

Atopic dermatitis and reaginic IgE antibodies

Patients with pure atopic dermatitis have circulating (IgE) antibodies to common

allergens such as animal dandruff, pollens, house dust and to different kinds of food (Öhman, 1971). Such reaginic (IgE) antibodies were demonstrated by RAST in children with both high and normal serum levels of IgE. Patients with more extensive skin changes had a higher mean serum IgE level than those with mild dermatitis. The agreement between results of skin tests and RAST depended very much on the allergen tested and was best for birch pollen extract. The RAST was positive in 86% of strongly positive skin tests and a strongly positive RAST reaction always had a corresponding skin test result. There was an agreement with history and illness in 48% of the positive skin tests and in 51% of the RAST positive reactions. However, these figures are difficult to evaluate as there is no provocation test for atopic dermatitis.

Relationship between reaginic IgE antibodies and clinical manifestations

Studies on the relationships between reaginic IgE antibodies in serum of patients hypersensitive to *Dermatophagoides* spp. and grass pollen showed no correlation with early or late onset of asthma, the age of the patient, duration, severity and frequency of symptoms (Holford-Strevens *et al.*, 1970; Stenius, Wide & Seymor, 1973). In patients allergic to penicillin there was no obvious correlation between the severity of the drug reaction and the strength of the RAST reaction to penicilloyl (Wide & Juhlin, 1971).

Several patients have been investigated by the RAST at different intervals during periods of several months. Foucard (1973) who studied a group of children with asthmatic bronchitis found that reaginic (IgE) antibodies to animal dandruff or pollen were often detected by RAST before allergy was clinically apparent. The results indicate some predictive value in the use of RAST for assay of reaginic (IgE) antibodies and RIST for assay of serum IgE.

Berg & Johansson (1971a) found considerable increases of serum reaginic (IgE) antibodies to pollen during the pollination season. Wide & Juhlin (1971) examined a group of penicillin hypersensitive patients over a period of 2–20 months for their serum content of reaginic (IgE) antibodies to penicilloyl. In seven of nine patients who were not exposed to penicillin, except for skin tests the concentration in serum of reaginic (IgE) antibodies decreased significantly during the period of investigation and there was also a significant decrease of serum IgE for this group of patients.

Effect of allergen inhalation tests and hyposensitization on serum reaginic IgE antibodies

The effect of allergen inhalation tests on the reaginic (IgE) antibody concentration in serum was studied by Holmgren *et al.* (1972). No effect was observed either with or without treatment with sodium cromoglycate. Berg & Johansson (1971b) and Johansson, Berg & Foucard (1971) studied the effect of hyposensitization on the level of reaginic (IgE) antibodies in serum. They found large variations in the response but in the majority of children an increase was found 2–4 weeks after the start of the treatment, often starting during the first few days. A few patients were investigated for up to 20 months and in most cases the levels decreased after the initial rise but were still higher than before treatment. It is not yet known if the observed changes are of any clinical significance.

RAST compared with Prausnitz-Küstner tests and chopped human lung tests

The RAST can be regarded as being an *in vitro* Prausnitz-Küstner test. Comparisons of results of PK tests and RAST are of interest as both tests, the *in vivo* tests in particular, may be dependent on factors other than the concentration of reaginic (IgE) antibodies. Wiholm (1972) compared results of PK and RAST on fractions of sera

from thirteen subjects sensitized to tetanus toxoid. The distributions of the two activities agreed very well and it was found that the RAST was the most sensitive of the two tests. Foucard, Aas & Johansson (1973) compared the RAST with the PK test on children allergic to cod. They found a significant correlation between the tests which were equally sensitive. The chopped human lung test (CHLT) *in vitro* is analogous to the PK test *in vivo*. Comparisons of results from CHLT and RAST using sera from forty-seven patients with allergy to horse dandruff, birch or timothy pollen (Foucard, 1972) or from thirteen children with cod induced bronchial asthma (Foucard *et al.*, 1973a) showed significant ($P < 0.001$) correlations between the two methods. The RAST would seem to be the most practicable of the three tests.

RAST applied to studies of allergen activity

The RAST has been applied to the study of allergen activity defined as reagenic (IgE) antibody binding capacity. Stenius & Wide (1969) first used the inhibition method for this purpose to see if extracts of house dust had allergens in common with extracts of *Dermatophagoides culinae*. The allergen extract and the test serum were preincubated before the RAST was performed. An inhibition of the RAST reaction indicated the presence of determinants common to the extract in solution and the polymer coupled one. It was concluded that the two extracts shared common determinants and in addition, each extract had specific allergenic components. Similar inhibition studies with RAST on dog epithelia extracts showed that there were both breed-specific determinants and allergenic structures common to several dog breeds (Fagerberg & Wide, 1970).

The allergenic activity (defined as binding capacity of reagenic (IgE) antibodies to penicilloyl) of different penicillin preparations was compared using the inhibition variant of RAST (Wide & Juhlin, 1971). Benzylpenicillin had the strongest capacity while cloxacillin and ampicillin had the weakest capacity to inhibit the reactions. The inhibition variant of RAST has also been found to be a useful tool for studying allergenic components of various horse epithelia extracts (Wide *et al.*, 1971; Aronsson & Wide, 1973) and for comparing the relationships between allergens in different deciduous trees (Zetterström, Fagerberg & Wide, 1972). By coupling various dilutions of different allergen extracts to the insoluble polymer and comparing the RAST reactions using these reagents it is also possible to get a rough estimation of allergenic activity in the different extracts (Ceska, Eriksson & Varga, 1972; Foucard *et al.*, 1973b; Ponterius *et al.*, 1973). It is most likely that both the inhibition variant and the direct RAST will be of great value as methods for quality control and standardization of allergen extracts.

Concluding remarks

The radioallergosorbent test is a sensitive *in vitro* method for the assay of reagenic IgE antibodies. The reagents of RAST can be prepared in batches for a large number of tests and the method is then simple to perform and has a high test capacity. Comparisons of results of RAST versus results of two other methods measuring reagenic antibodies, the PK test and the CHLT test, indicate that the three methods measure related or identical components and that they have about the same limit of sensitivity. With regard to practicability the RAST is the best of the three tests.

Studies on the clinical significance of the RAST for diagnosis of the atopic or immediate type of hypersensitivity have shown highly significant correlations between

results of this method and those of skin tests and provocation tests. The RAST has been found to be a clinically valuable tool for diagnosis of IgE mediated allergy. It seems most probable that in some cases, it can replace both skin and provocation tests and in other cases be a valuable complement to these tests.

Quantitative studies on the reaginic IgE antibodies in serum have shown that there is a rise during pollination season in pollen hypersensitive individuals and that if the patient is not exposed to the allergen the titre in serum will in most cases fall. Provocation tests do not seem to influence the concentration of reaginic IgE antibodies in serum while the effect of hyposensitization was an early increase in serum IgE antibodies. There is no close correlation between the severity of the allergic reaction and the concentration of reaginic IgE antibodies in serum. In young children such antibodies may be detected before clinical allergy is apparent.

Independent of the type of clinical allergy tests like provocation tests, skin tests or RAST, a prerequisite for the successful use of such a test is access to allergen extracts of high quality. The best correlation between results of these tests and clinical history is obtained with extracts containing the relevant allergenic components in a more purified form. The RAST has been applied also for the assay of allergenic activity (defined as IgE antibody binding capacity) and will most probably be an extremely valuable instrument for quality control of allergen extracts, in particular when used by the manufacturers for monitoring the preparation of such extracts.

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Discussion:

Brostoff: Taking into account the high affinity of IgE for mast cells and the fact that sensitization does not need circulating IgE, is it not surprising that there should be a good correlation between skin test size and RAST, when one might expect perhaps that after the serum IgE had reached a certain level there would be a plateau skin weal size?

Wide: The relation between skin test size and results of RAST show a wide variation but still a statistically highly significant correlation. We have no evidence for a plateau skin size at a certain IgE level.

Brostoff: Why isn't it possible to measure all the specific immunoglobulin levels on the RAST test?

Wide: IgE is present in such a low concentration that non-specific interference of other IgE molecules is very low. With IgG, for example, it may be difficult to eliminate all the non-specific IgG before the labelled anti-IgG is added.

Brostoff: You would also think that if there was much allergen specific IgG it would interfere very considerably with the RAST test which measures IgE. Does that not raise the question of the validity of the second IgE test.

Wide: When the IgG antibodies compete with the IgE antibodies for the allergen there must be a certain interference. However, it seems as if this interference is rather small in the RAST. The evidence that I have for this concept is from studies on sera from patients who have been hyposensitized. We have compared the results of PK tests and RAST on sera taken before and after hyposensitization. The results of PK tests and RAST did change but not very much due to hyposensitization in spite of evidence for development of blocking antibodies in most of the cases. It may be that the excess of allergen on the solid phase was large enough to take care of both IgE and blocking antibodies. With a small amount of allergenic components on the solid

phase the blocking antibodies will probably show a larger interference on the RAST reaction. The test is based upon the principle that there should be a large excess of solid-phase-coupled allergen in the first reaction and a large excess of labelled anti-IgE antibodies in the second reaction.

Soothill: What do you mean by a sorbent unit and would you discuss the limits of quantitation of this procedure? Will crowding of IgE molecules on your particle at the second stage of the reaction limit the access of anti IgE to them and so only lead to semi-quantitative results. Have you got any information on strength of binding using pH elution?

Wide: Indeed, this technique is semi-quantitative. The amount of allergenic components coupled on the solid phase is an important factor. The results may be quite different when different batches of the same type of allergen extract are coupled. For a particular allergen extract it is possible to compare results of different sera. However, as the reaction may be influenced by other factors in the serum, such as blocking antibodies, the RAST gives only a semi-quantitative estimation of the level of IgE antibodies to the particular solid-phase-coupled allergen extract. We have expressed the activity of RAST in sorbent units. (Stenius & Wide, 1969). A sorbent unit is the activity for a serum sample which when assayed in an aliquot of 1 μ l gives the same uptake of radioactivity as that obtained on a solid phase to which 1 pg of IgE was coupled. I have no information about the energy of these antigen-antibody reactions.

Morrison Smith: One finds if one does prick tests in children the results are remarkably repeatable provided your extracts are good and your operative is good, over periods of months or years. Is this true of IgE levels? Secondly, when one considers skin prick tests there is a very much greater correlation with a clinical history the larger the skin weal is, is this also true of provocation tests and of IgE levels? Does the correlation get better the higher the skin sensitivity? Finally in children with atopic eczema I have found a statistically significant correlation with positive skin reactions to egg, milk and fish, is this borne out in relation to IgE levels to these allergens?

Wide: Foucard, (Foucard, 1973) studied children with asthmatic bronchitis. He found that IgE antibodies to egg white or cow's milk were found in many cases during the first year of life. When the children grew older the titers decreased. In contrast to this, IgE antibodies to animal danders were not detected until 1½ years of age and those to pollen not until 3 years of age. These antibodies showed increasing titres with time.

With non-seasonal environmental allergies in adults the level of allergen specific IgE remains rather constant. The correlation with clinical history is greater with higher IgE levels in the RAST. It is also true that the agreement between results of RAST and skin tests is higher the higher the skin sensitivity.

Pepys: We have been looking at subjects in terms of their IgE antibody to the enzymes of *B. subtilis* which are contained in biological detergents (Pepys *et al.*, 1973). Here it is possible to estimate the degree of exposure, which is very difficult to do with natural allergens. We compared cord blood sera which we presumed to be free of specific

IgE antibodies as controls, with people we called non-consumers and then with two groups whom we called light and heavy consumers. We found highly significant increases of enzyme specific IgE as between each respective group from the cord bloods to the heavy consumers. None of those tested were skin test positive. There was therefore evidence of gradually increasing levels of IgE below the level that was clinically relevant. In the population there must be people who are constantly producing more and more IgE but still below the level required for skin test reactions or that we would regard as clinically relevant.

Levine: I believe that antigen binding avidity of IgE is an extremely important biological quality which determines the clinical importance of reagins. On the other hand what is measured by the RAST is not biological avidity but total antibody concentration. Generally the higher the avidity the greater the concentration as we saw in our studies on penicillin allergy. There are cases where one has IgE of high avidity and very low serum titres, as for example in hypersensitivity to guinea pig epithelium where patients can be exquisitely sensitive and have very low titre of antibodies as detected by PK testing. We also see this in penicillin hypersensitivity in about 25% of our cases. I also want to make a comment on penicillin allergy. We do not see penicillin anaphylaxis on skin testing, and we have been doing them for 15 years.

Wide: Even fatal outcomes of skin testing are described in the literature (Idsø *et al.*, 1968).

Levine: I am familiar with two published cases of generalized reaction to skin tests with benzylpenicilloyl-polylysine (BPL). In both cases the BPL was used in too high concentrations (Levine, 1966)

We do prick test first, wait 7 min, and if negative then do an intradermal test with 1×10^{-6} M BPL. Under these conditions we have had no generalized reactions in 10 years of clinical skin testing with BPL and the minor determinants. There is clearly a minimal danger of anaphylaxis to a skin test even when great care is taken. But with care, such an event is extremely infrequent, whereas the skin test gives an immediate answer at the bedside or in the clinic.

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