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The radioallergosorbent test: Uses and abuses

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It has now been more than a decade since the introduction of the radioallergosorbent test (RAST) for in vitro measurement of IgE antibodies.¹ This remarkable serological assay has greatly facilitated fundamental research in allergy, and has shown promise in clinical applications as well. But, like many new technological advances, it has become subject to a variety of abuses. An appreciation of the capabilities and limitations of the RAST can help to guide both researchers and clinicians in its proper application.

The development of the RAST has been a boon for research studies of IgE-mediated diseases. The precision of the test has allowed quantitative measurement of fluxes in serum levels of IgE antibody which were previously laborious or impossible with bioassays. Using the RAST, the increase in IgE antibody synthesis induced by seasonal allergen exposure can now be monitored quantitatively.^{2,3} The long-term effects of various immunotherapy regimens on specific IgE antibody synthesis can be determined independently of confounding biologic variables such as end-organ sensitivity and mediator releasability.^{2,4,5} The RAST is currently being used in exciting prospective studies of the immunologic development of atopic disease in high-risk pediatric populations.^{6,7} RAST technology is also being successfully applied to the problem of allergen standardization.^{8,9} Unlike many immu-

nochemical methods for protein standardization, the RAST inhibition assay has the distinct advantage of focusing standardization efforts on those allergens which are capable of eliciting a human IgE antibody response.

In recent years technical modifications have increased the utility of RAST measurements in a number of ways. It is now possible, using several methods, to standardize RAST assays such that estimates of IgE antibody can be obtained in weight per volume terms.¹⁰⁻¹² Much effort has been devoted to optimizing the RAST assay for both precision and sensitivity.¹³⁻¹⁵ It is beginning to be possible to design a RAST system which best suits the requirements of the investigator. As an example, Gleich et al. report in this issue of the JOURNAL¹⁶ their efforts in the development of a "mini-RAST" which in some systems allows the use of much less allergen without compromising sensitivity. Still, despite numerous technical modifications during the 12 years since its introduction, there continues to be room for improvement. Especially vexing is the potential influence of high levels of IgG "blocking" antibodies on the quantitation of specific IgE.^{17,18} This interference is most commonly observed in sera from patients receiving intensive immunotherapy with the allergen of interest. However, in RAST systems in which an insufficient amount of allergen is insolubilized, even modest amounts of IgG antibodies may totally mask the presence of small amounts of IgE antibody.¹⁹ Despite

such difficulties, in 1980 there is still no other *in vitro* assay for IgE antibody which can match the accuracy, sensitivity, and precision of the RAST.

Using a paper disk support system for ease of manipulation and washing, a commercial form of the RAST was introduced for clinical diagnosis in the United States in 1974. Prior to its introduction in the United States, the RAST had been used extensively for clinical diagnosis of atopic disease in Europe, particularly in Scandinavia, where it is commonly employed in conjunction with skin testing for clinical diagnosis.^{20, 21}

In recent years there has been an increasing movement in this country toward the use of the RAST as an adjunct to or substitute for intradermal skin testing. Favorable attributes of the RAST which commend its use as a diagnostic test include its amenability to standardization, its low rate of false positive results, and its potential for quantitation.

Intradermal skin testing, on the other hand, is clearly slightly more sensitive than most RAST systems, but it has yet to be shown that this increased sensitivity is important for clinical diagnosis of inhalant allergy. In their article in this issue of the JOURNAL, Gleich et al.¹⁶ make an important contribution to this question by reporting their evaluation of 27 patients, all of whom had an equivocal history of ragweed hay fever. Of these 27 patients, 25 had clearly positive skin tests to ragweed extract and about half had a marginally positive RAST test. The authors conclude that "RAST is only a partial aid in the classification of these patients [with equivocal clinical histories] and might be best employed as a possible adjunct to skin test and history in the diagnosis of ragweed hay fever." The underlying issue of how much specific IgE antibody is required to put a patient at risk for clinical symptoms from airborne allergens remains to be answered definitively, but observations such as those of Gleich et al. demonstrate that the presence of low levels of IgE antibody as determined by either skin testing or RAST may not be accompanied by clinically significant allergic symptoms. In such cases, skin tests, and to a lesser extent RAST may provide erroneous indications of clinical sensitivity, and, in that sense, represent biologically "false positive" results. This fact serves to underline the need to interpret results of any test of IgE antibody in the light of clinical history.

Currently the principal advantage of skin testing over the RAST test for clinical diagnosis of inhalant allergy is its economy. The average RAST test today costs from four to ten times that of equivalent skin testing depending upon the skin-test method and degree of patient sensitivity. The future holds out the

possibility of automating RAST techniques; this could reduce the cost per test appreciably if performed in high volume in large regional laboratories. For the present, economic consideration will continue to favor limited use of the RAST for routine diagnostic purposes.

Like all technological advances, the RAST technique is subject to abuse. Abuses of the RAST have taken three forms: user abuses, commercial abuses, and abuses due to unvalidated interpretation of RAST results.

User abuses for RAST are simply those common to many sophisticated laboratory tests. The most common of these is its inappropriate use, often by physicians who have little experience with the evaluation of IgE-mediated diseases and who are poorly prepared to interpret the results obtained. As with other clinical laboratory tests, RAST results cannot be interpreted outside of the clinical context in which they were obtained. Thus, to order a battery of RAST to "screen" for allergic disease is no more useful or cost-effective than ordering a battery of hormone studies to screen for endocrine disease. Another misuse of the RAST is in the evaluation of life-threatening anaphylactic states in which diagnosis by RAST (as opposed to skin tests) has not been thoroughly validated. This calls to mind the current status of the RAST for anaphylactic sensitivity to insect venoms²² or allergenic drugs like penicillin* where the extra sensitivity afforded by skin testing may be clinically important. Lastly, we have the abuse of overuse, the indiscriminate ordering of batteries of RAST in clinical settings in which they are unlikely to be helpful, or where more economic diagnostic methods (such as skin testing) can be employed. This potential for overuse of the RAST, as for any laboratory test, may be increased when physicians incorporate the technical capability of performing RASTs into their practice setting.

Of much greater concern are the commercial abuses of the RAST. The principal form that this has taken is extension of RASTs to substances which are most unlikely to be responsible for IgE-mediated disease. Insurance carriers and various regulatory agencies have legitimized the RAST as a diagnostic test *per se*, without any attention to what substances are being insolubilized on the allergosorbent. The result is that any licensed medical laboratory is at liberty to develop and market RASTs for virtually any substance it chooses. Unlike the RAST kits which are commercially marketed to individual physicians or medical

*Adkinson NF Jr: Unpublished observations.

laboratories, these in-house "supplementary" RASTs are not subject to any requirements for demonstration of validity or quality control. Thus, it is possible at the present time to order from a number of commercial laboratories in this country RASTs to detect IgE antibody specific for foods like strawberries and lettuce and drugs like codeine and contrast media. In each of these cases there is no scientific basis for a belief that an IgE antibody response is associated with adverse reactions to these materials. For this reason, it seems highly unlikely that laboratories offering these tests have any positive sera for such RAST systems. Even the existence of a serum which scores positive in a RAST system is not proof of the test's validity; specificity must also be shown (preferably by inhibition studies), and correlation with clinical risk or symptoms is equally important.

It is ironic that in a decade in which Food and Drug Administration panels have undertaken a sweeping review of the safety and efficacy of drugs and biologicals, including allergenic extracts, that not only is it legally permissible to offer a RAST for "kitchen sink," but in many states the cost for such a test is reimbursed by third-party payers. This state of affairs is due in part to confusion among a number of federal and state regulatory agencies about which agency has jurisdiction and by what authority it can act to eliminate or at least attenuate this clear abuse. Undoubtedly this will eventually get sorted out, but until that time thousands of dollars will continue to be wasted on worthless RASTs.

Finally, we have recently seen a more insidious abuse of the RAST which is of great concern. I refer to recent commercialization of various schemes by which the results of legitimate RASTs are reclassified in a manner claimed to increase the sensitivity of the test.² The proponents of such measures are not laboratory scientists attempting to design a better mousetrap, but rather reinterpreters of RAST results who claim to have improved the sensitivity of RAST by rescaling its results in terms of a total IgE assay.²⁴ The net effect is to create new positive grades (score 1 and part of score 2) from binding levels considered by the manufacturer to be indistinguishable from negative controls. Such a manipulation is likely to lead to a striking increase in the rate of low-level positive results which do not correlate with clinical symptomatology. The tie-in of such schemes with recommended regimens for immunotherapy^{24, 25} may well result in inappropriate injection therapy being administered to a large number of individuals, and with a larger number of allergens, than would otherwise be the case. Since immunotherapy with allergens to which a patient is not already sensitive may actually

induce clinical sensitivity,²⁶ such inappropriate injection therapy is to be avoided at all costs. These alternative RAST scoring schemes and the commercial laboratories which promote them must be viewed with skepticism until scientific evidence validating the claims made by them is forthcoming.

In summary, the RAST is now a valuable research tool in allergic diseases, and when employed judiciously it can be of diagnostic value in the clinic. Further studies are needed to establish the diagnostic utility of the RAST in a variety of IgE-mediated diseases, particularly with regard to whether RAST sensitivity is sufficient for recognizing all clinically significant disease. Technological modifications of the RAST which will reduce its ultimate cost must continue to be sought. The attention of appropriate governmental regulatory agencies should be drawn to the commercial abuses of the RAST which fall under their jurisdiction. Finally, those of us in the profession of allergy and clinical immunology must shoulder the responsibility of educating our medical colleagues, especially medical students and house officers, concerning both the uses and abuses of this major technological advance within our specialty.

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