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Wide L, Bennich H & Johansson S G O. Diagnosis of allergy by an in-vitro test for allergen antibodies. *Lancet* 2:1105-7, 1967.

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An *in vitro* method, the radioallergosorbent test (RAST), was developed for the detection and assay of allergen-specific antibodies of a new immunoglobulin class, later termed IgE. The method was a noncompetitive radioimmunoassay using labeled antibodies. [The SC® indicates that this paper has been cited in over 740 publications since 1967.]

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The conception of this paper was the result of some remarkable coincidences. My interest in the development of a test for the diagnosis of an allergy arose from a seminar presented at our hospital. Lennart Juhlin, a dermatologist, held the seminar when he returned from the US in August 1966. He described the basophil degranulation tests¹ and discussed the need for very high sensitivity in measuring reagins in serum. At that time, I had developed the prototype of an extremely sensitive new principle for radioimmunoassay (RIA), which was noncompetitive and used a labeled binding reagent. I suggested that this method might be used for the assay of reagins, and we decided to collaborate using penicillin allergy as a model.

At about the same time, Hans Bennich and Gunnar Johansson informed me that they had tested a large number of sera with a single radial immunodiffusion test (SRD) and failed to find a normal counterpart to a myeloma protein called ND. We decided to try a solid-phase competitive RIA, the radioimmunosorbent technique,² which was about 1,000 times more sensitive than the SRD. With their collaboration, I labeled the ND protein with ¹²⁵I and coupled the antibodies to Sephadex. About six months later, we concluded that a protein corresponding to ND was present in

all human sera tested and that it represented a new class of immunoglobulins.³

One serum specimen had a remarkably high level of the protein. The individual it represented turned out to be hypersensitive to dog epithelium. As it was a possibility that this elevated protein level in the serum specimen arose as reaginic antibodies to dog epithelium, I constructed a noncompetitive sandwich RIA to detect allergen-specific antibodies of the new immunoglobulin class in the serum. The presumptive reagins were first bound to a solid phase-coupled allergen and then detected by binding ¹²⁵I-labeled antibodies to the ND protein. An increased amount of radioactivity was bound to the solid phase when the serum was tested with dog epithelium, and all controls were negative. Sera from patients with hay fever and allergic asthma were tested with different allergens, and the results correlated well with those of provocation tests. These results, together with a number of other observations, indicated that the reagins belonged to the new immunoglobulin class and that this class was related to the gamma-E (later IgE) described by Ishizaka *et al.*⁴

The noncompetitive sandwich technique combined two important properties: a very high sensitivity and a two-sided specificity. Used as an allergy test, only antibodies against a particular allergen were detected, and only those belonging to IgE. The method was called the radioallergosorbent technique (RAST). For the next few years, I examined the clinical significance of RAST and summarized the results in 1973.⁵

I believe that this paper is frequently cited for two reasons. First, RAST has become extensively used as a test for diagnosis of allergy and for quantitation of allergen-specific IgE. RAST is also used as a method for control of allergen extracts. Second, it was the first noncompetitive RIA and the first quantitative assay using labeled antibodies. Similar sandwich techniques have come to be used more and more in many different fields of research as well as routinely in the clinical laboratory.

Honors received for the studies include the Anniversary Medal of the Swedish Society of Medicine, in 1969, for the allergy test and, in 1983, the Clinical Ligand Assay Society Senior Investigator Award for the noncompetitive "sandwich" ligand-binding assay.

1. Shelley W B & Juhlin L. A new test of detecting anaphylactic sensitivity: the basophil reaction. *Nature* 191:1056-8, 1961. (Cited 85 times.)
2. Wide L & Porath J. Radioimmunoassay of proteins with the use of Sephadex-coupled antibodies. *Biochim. Biophys. Acta* 130:257-60, 1966. (Cited 480 times.)
3. Johansson S G O, Bennich H & Wide L. A new class of immunoglobulin in human serum. *Immunology* 14:265-72, 1968. (Cited 295 times.)
4. Ishizaka K, Ishizaka T & Hornbrook M H. Physico-chemical properties of reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J. Immunology* 97:75-85, 1966. (Cited 305 times.)
5. Wide L. Clinical significance of measurement of reaginic (IgE) antibody by RAST. *Clin. Allergy* 3:583-95, 1973. (Cited 50 times.)