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The important role of IgE in the pathogenesis of most allergic disorders makes it appropriate to celebrate the 50th anniversary of its discovery and identification as the allergy-associated Ig isotype and to recall the role of two papers published in *The Journal of Immunology* on this milestone. First, however, it is helpful to briefly recount the earlier advances that led to the discovery.

In 1919, Maximilian Ramirez described a case in which blood transfusion from a horse-allergic donor caused a horse-incited asthma attack in the recipient (1). Two years later, Carl Prausnitz, influenced by Ramirez’s case report, injected serum from his fish-allergic colleague, Heinz Küstner, intradermally into his own arm and 24 h later injected a tiny quantity of a fish extract into the same and other sites; swelling and erythema developed at the site of injection of Küstner’s serum, but not at the other locations (2). These observations established that a factor in serum, later labeled reagin (3) and shown to be Ag specific (4), could sensitize the skin to develop the immediate hypersensitivity response characteristic of allergy and provided an assay [called the Prausnitz-Küstner (P-K) test] for reagin activity that was crucial for later discoveries. What remained was to isolate reagin and characterize it. However, what today would be a relatively trivial task was not feasible at the time; the required technology was not available. It was only in the 1960s with the development of purification techniques such as ammonium sulfate precipitation, zone electrophoresis, ion exchange chromatography, sucrose density gradient ultracentrifugation and gel filtration, and the development of Ig isotype-specific antisera that the identification of reagin could be accomplished.

Even with this improved technology, the initial identification of reagin was incorrect. Several investigators, including the team of Ishizaka and Ishizaka that later correctly identified reagin as IgE, initially reported reagin to be IgA (5–7). The mis-identification of IgA as reagin was based on observations published from 1962 to 1964 that reagin activity could be removed from serum with a sheep antiserum thought to be specific for human IgA, and that the P-K reaction could be blocked by what was thought to be purified IgA and by IgA heavy (α) chains (6, 8). However, an observation that reagin activity was present in a man who lacked IgA [published by Mary Loveless as an abstract in 1964 (9)] led the Ishizakas to re-examine their earlier conclusion.

Fractionation studies of sera from ragweed- and egg-allergic individuals, published by the Ishizakas in 1966 (10), demonstrated a lack of correlation between serum IgA or IgG levels and reagin activity in a P-K assay. Absorption studies with improved isotype-specific antisera showed reagin activity was barely removed by elimination of IgG and IgA, but was removed by precipitation with an anti-Ig L chain antiserum. It was also shown that the quantity of reagin required for skin sensitization in a P-K assay was very small, probably <1 ng of Ab nitrogen. Consequently, it was suggested a novel Ig isotype that could be present in very low concentration in the serum of an allergic individual might be fully responsible for reagin activity.

This set the stage for the two papers in *The Journal of Immunology*, both published a few months later in 1966, which coined the term γE (later changed to IgE). The first (11) used ion exchange chromatography, gel filtration, and [125I]-enhanced gel double diffusion and immunoelectrophoresis to confirm some of the observations in the *Journal of Allergy* paper (10) and show that: 1) a rabbit antiserum prepared against the serum fraction from ragweed-allergic patients that had the highest reagin activity and that was absorbed with human IgA, IgM, IgG, and IgD still bound to a molecule in the high reagin fraction of serum; 2) this molecule bound ragweed allergen; and 3) absorption of the high reagin fraction of serum with this rabbit antiserum eliminated reagin activity, as determined by the P-K reaction. On the basis of this and the evidence from the *Journal of Allergy* paper that reagin has Ig light chains, it was concluded that reagin was a novel Ig isotype, which was labeled γE. This study was complemented by the second paper in *The Journal of Immunology* (12), which used the same techniques and preparative agar gel zone electrophoresis to demonstrate a close correlation between γE levels in serum and serum fractions (determined by immunoprecipitation studies with the rabbit anti-human γE antiserum and [125I]-labeled ragweed allergens) and reagin activity (determined by P-K reaction). Studies in this article also established γE had physical properties that differed from IgG and IgA: most importantly, a higher apparent m.w., as determined by gel filtration and sucrose density gradient ultracentrifugation. This increased m.w. was later shown to reflect an extra Ig domain in the IgE H chain, as compared with the heavy chains of IgA and IgG.

These studies and their conclusions, however, were limited by the inability to produce a truly monospecific anti-γE antiserum using available technology; this left open the possibility that reagin and γE were separate molecules that copurified. This possibility was eliminated over the next two...
years when Bennich, Johansson, and colleagues discovered a novel myeloma protein that had reagin activity, detected by its ability to block the P-K reaction (13), and found that their novel myeloma protein was bound by the Ishizakas’ (14) anti-\(\gamma\)E antiserum. These achievements were formally recognized by the designation of the reagin-associated isotype as IgE by the World Health Organization in 1968 (15).

The discoveries by the Ishizakas and their colleagues were characterized by remarkable intuition, state-of-the-art protein chemistry, and an admirable willingness to challenge their own previous conclusions. The identification of reagin as IgE set the stage for rapid elucidation of the mechanisms by which IgE contributes to allergy, the mechanisms that mediate IgE responses, the roles played by IgE in diverse allergic disorders, and most recently, the treatment of allergic disorders with a monoclonal anti-human IgE Ab.

**Disclosures**
The author has no financial conflicts of interest.

**References**


