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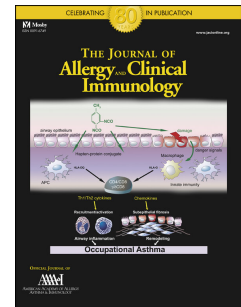
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The Discovery of IgE

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Abstract

In 1919 the search in serum of allergic individuals for the factor, later called reagin, that could mediate an allergy, e.g. allergic asthma. In 1967 the fifth class of immunoglobulins, IgE, was discovered and found to be able to carry regain activity. The discovery has had an immense importance for understanding, diagnosis and treatment of allergic diseases.

Summary

The discovery of IgE, its physico-chemical and immunological characterization and the understanding of its key-role in allergic inflammation, have been of immense importance for the specialty allergology and have had a significant impact on diagnosis and treatment of allergy.

Abbreviations

PK-test=the Prausnitz and Küstner test

RAST=Radio Allergo Sorbent Test

Key words

Allergy, inflammation, mast cell, immunoglobulin, sensitization, reagin

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In 1919, one of Dr. Ramirez patients with aplastic anemia that just had received a blood transfusion developed an asthma attack when taking a horse ride in Central Park in New York. Ramirez was observant and noticed that the blood came from a donor with allergy to horses. He published a case report that obviously blood could transfer allergy to horses and cause asthma. Two years later, 1921, Prausnitz and Küstner passively sensitized the skin of healthy individuals and transferred positive skin tests, a method referred to as the PK-test.

The search for the reagin, the factor in plasma causing the positive PK-test, was unsuccessful for about 45 years. When immunology was further understood it was thought to be an immunoglobulin. For some years several scientific articles suggested that the reagin was IgA and in 1964 K. and T. Ishizaka (Figure 1) published in *Immunochemistry*, a journal for basic science, the definitive proofs (1). However, many scientists were confused and the results were never reproduced. Ishizakas explanation was that a low concentration of a factor carrying the skin-sensitizing activity had contaminated the IgA serum used in the tests.

However, this factor was not sensitive to reduction and alkylation in contrast to what they found for reaginic activity (2). In 1966 and onwards the Ishizakas published several most interesting articles describing an antiserum that could block the PK-test indicating that it reacted with a key factor in allergic inflammation, perhaps the reagin. They called this factor γ E-antibody (3). However, they did never succeed to isolate and characterize γ E which is not surprising considering the very low concentration in serum.

In June, 1965, working during my medical studies, as a laboratory technician in Uppsala, I detected a myeloma protein, M-component that could not be identified as any of the four known immunoglobulin classes, IgG, IgM, IgA or IgD (Figure 2) (4). During close to two years of intensive work with Hans Bennich (Figure 3), the unique immunological and

physicochemical characteristics of the immunoglobulin were obtained showing that it represented a new immunoglobulin class. The results were documented and published (5). The “nick-name” given to the “newborn immunoglobulin class” was IgND after the initials of the patient, following the routine at the time.

Several scientists participated enthusiastically in the work to characterize IgND. One was Denis R. Stanworth in Birmingham who’s experience with the PK-test was most important. He found that very small amounts of IgND did, in dose-response, block the PK-test (6) (Figure 4) and the active structure was located to the Fc-fragment (7). Leif Wide, Uppsala, had a long experience in immunassays of hormones and when he became interested to apply his knowledge to IgND an immunoassay for IgND was developed. Extremely low serum concentrations, in the order of a few nanogram per ml, of IgND were found in healthy individuals but, interestingly, 10-100 fold higher levels were found in patients with allergic diseases, e.g. allergic asthma (Figure 5) (8). Using radiolabeled anti-IgND allergen specific IgND antibodies to common allergens could be determined and thus the first laboratory test for allergy diagnosis, the Radio Allergo Sorbent Test, RAST, (9) (Figure 6), a technically advanced update of the well-known Coombs test (10), was developed.

In 1967, purified IgND was sent to the Ishizakas and was found to react with their anti- γ E. In February 1968 the WHO International Reference Centre in Lausanne, where studies on IgND had been performed for some months, invited the two groups to review comparative laboratory studies of IgND and γ E. In contrast to IgND, no information on physico-chemical properties, requested by the Reference Centre, was available for γ E. However, there was a link to the mast cell sensitizing properties of the reagin. The official report, “birth announcement”, of the fifth immunoglobulin class, IgE, was published in February, 1968 (11). Today almost 50 000 articles with IgE have been published.

The discovery of IgE has had a significant impact on the diagnosis and management of allergic disease, enabling clinicians to differentiate between IgE-mediated allergic diseases and other hypersensitivity reactions, and to appropriately handle the IgE antibody driven inflammation causing IgE-mediated allergic diseases. RAST, and other tests developed from RAST, became available and allowed a more simple and reliable identification of the allergen-specific IgE-sensitization, covering a very broad spectrum of allergens. The characterization and standardization of allergen preparations for clinical diagnosis and allergen specific immunotherapy has improved, although slowly, over the years. An injectable

monoclonal anti-IgE, omalizumab, that eliminates most of IgE in the circulation, is now available and is useful in the management of severe allergic asthma, severe food allergy and chronic urticaria.

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Legends to figures

Figure 1 Professors Kimishige and Teruko Ishizaka.
(picture from ref. 4)

Figure 2 Immuno-electrophoresis of serum ND, below, and a normal serum, above, using
a mixture of antibodies to IgG, IgA, IgD, IgM and kappa and lambda light
chains. Note below the black area in the agar close to the left of the starting hole
indicating a high protein concentration which does not fit with the very weak
precipitate. The precipitate at the left end is free light chains.
(picture from ref. 4)

Figure 3 Hans Bennich, left, and S.O. Johansson, right, in 1967.

Figure 4 A schematic drawing of blocking, with IgND, the specific binding of reagin to
mast cell and basophil receptors.

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151 Figure 5 Serum IgND levels in patients with allergic and non-allergic asthma.

152 (picture from ref. 8)

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154 Figure 6 The principle of the Radio Allergo Sorbent Test, RAST.

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Figure 1



Figure 2

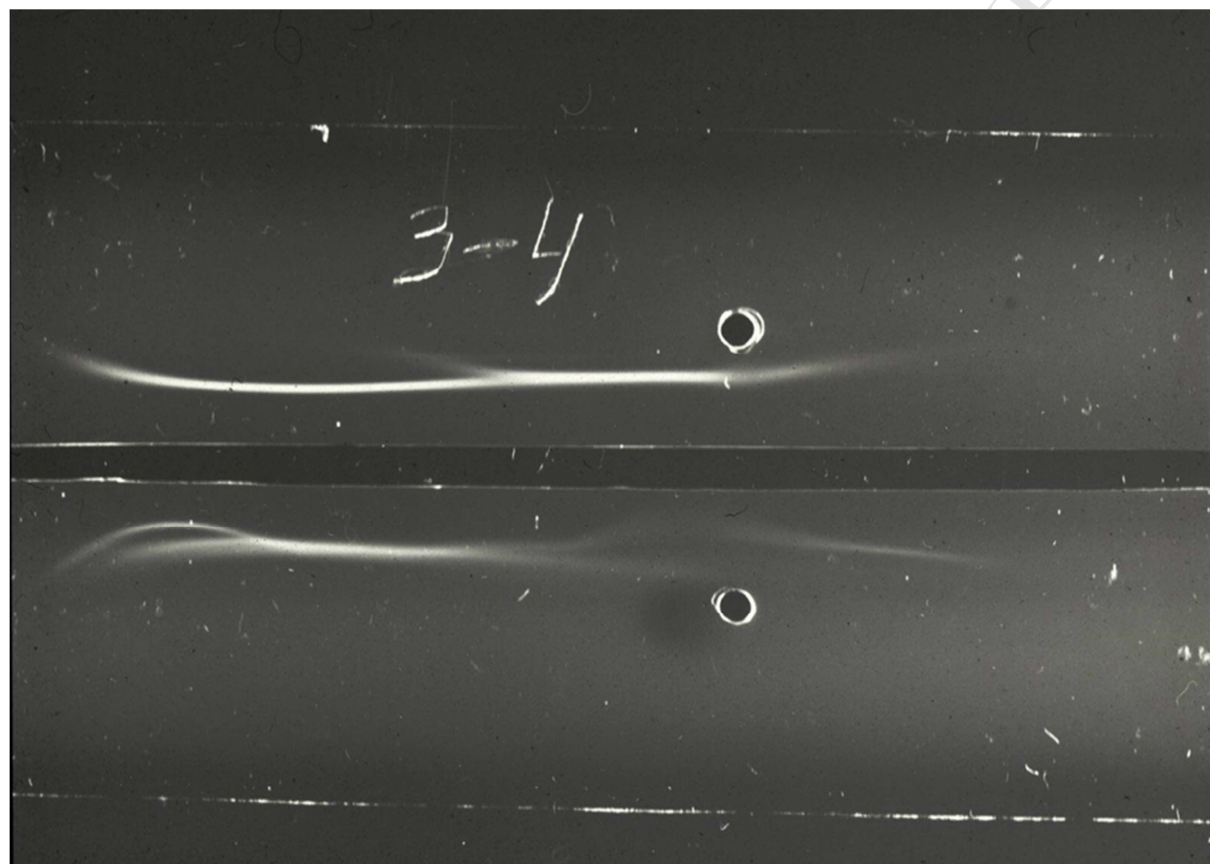


Figure 3

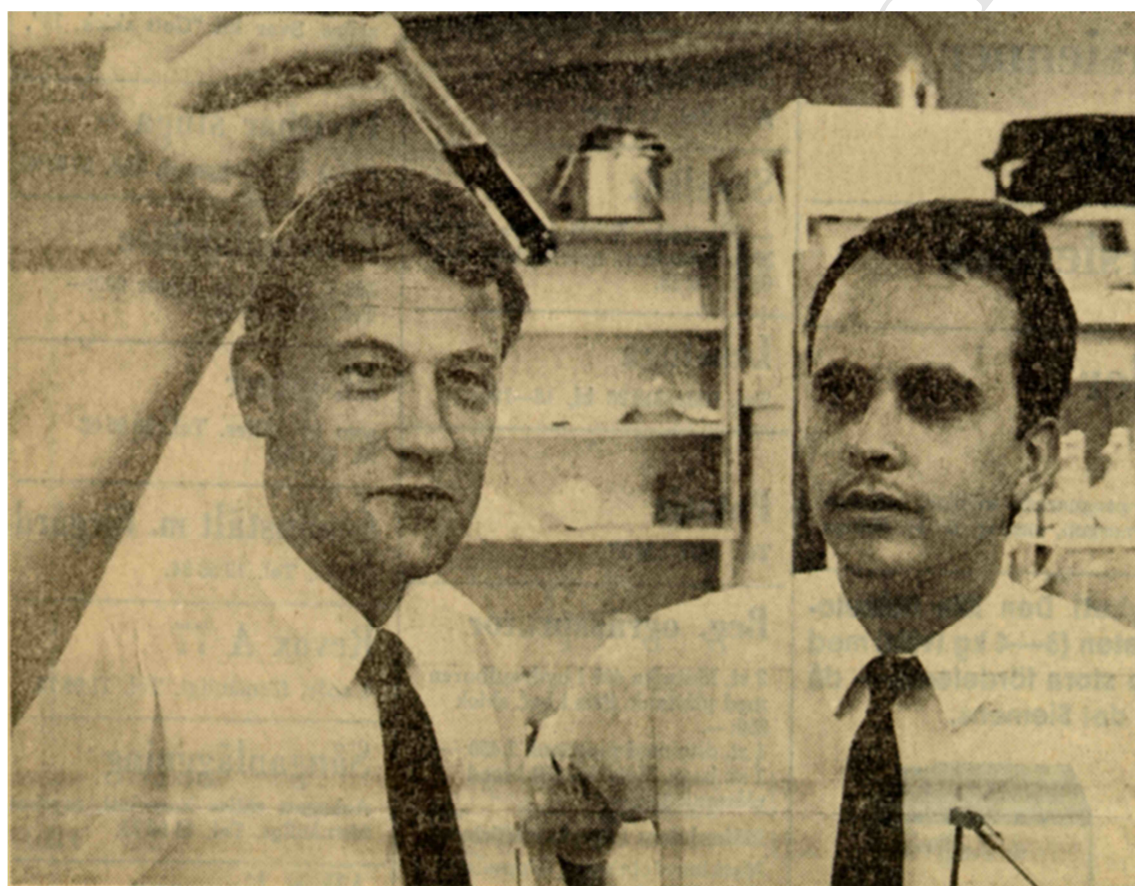


Figure 4

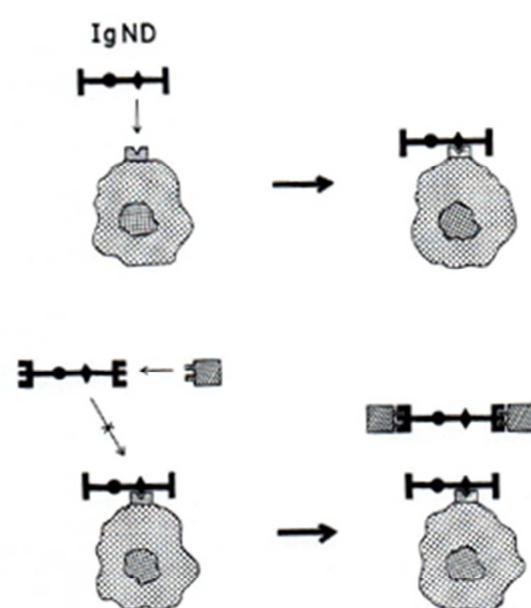


Figure 5

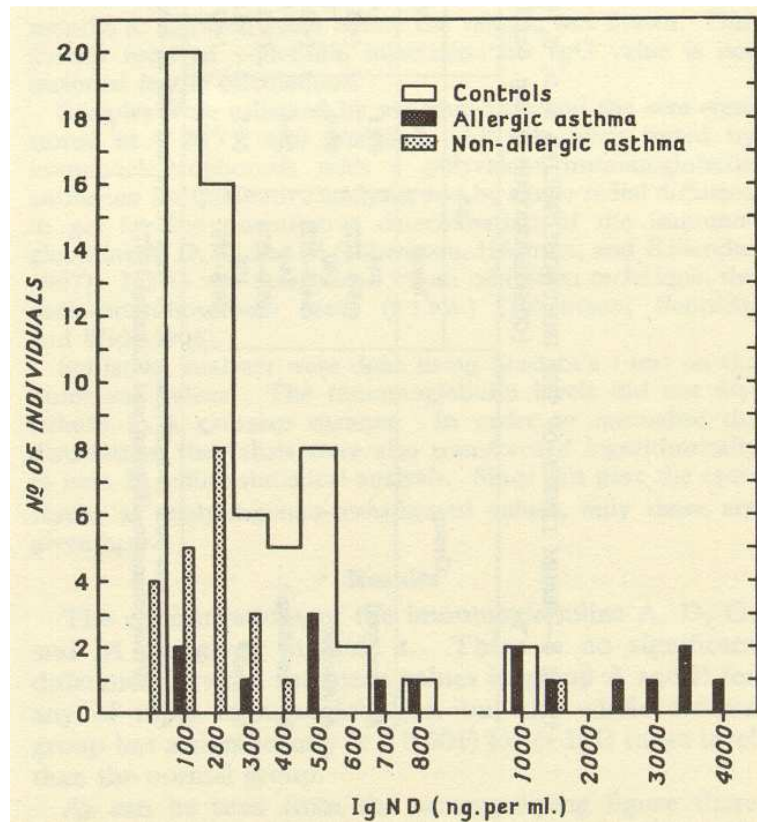


Figure 6

