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The discovery of IgE 50 years on

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Introduction

In 1906, Von Pirquet used the term “supersensitivity without immunity” to describe; (i) the symptoms of inhalant allergy, (ii) the positive immediate skin tests and (iii) the fact that other tests of immunity were not positive in these patients [1]. The other tests he referred to were precipitin tests and complement fixation. Thus he opened up the question of serum tests for “supersensitivity”. In 1919, Ramirez reported that a patient, who had received a blood transfusion from a horse allergic donor, became allergic to horse dander [2]. At this point, Prausnitz set out to investigate whether the serum of allergic subjects contained a factor or factors that could sensitize the skin. In 1921, he reported that the local injection of serum from a fish allergic subject, Kuestner, to an individual who was only allergic to pollen, Prausnitz, would transfer specific sensitivity [3]. This transfer of sensitivity came to be known as the P-K test and was used widely to study sensitivity not only to common allergens but also to extracts as diverse as those obtained from Schistosomes [4, 5].

Furthermore, Cooke and his colleagues in New York identified that there were other antibodies in the serum that increased during desensitization treatment and could block the skin sensitizing activity [6]. By the 1950’s, it was clear that the transferred sensitivity was specific, that it could be diluted extensively and that the skin remained locally sensitive for days if not weeks after the injection of serum [7, 8]. It was also already clear that the ability to sensitize the skin was lost after moderate heating of the serum [7]. Several studies had also been reported on the physical properties of P-K activity. Indeed Dan Campbell and his

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colleagues at Cal Tech reported on the sedimentation properties of skin sensitizing antibodies in 1960 [9]. However, the studies prior to 1964 had not succeeded in defining the nature of these antibodies.

The Purification of P-K activity and evidence that it represented a new isotype of immunoglobulin

Around 1960, Kimishige Ishizaka set out to purify P-K activity from the serum of patients who were allergic to pollen. At that time, seasonal hay fever was much the most common form of allergic disease and these were the sera that had the highest titers of P-K activity. In 1964, his group reported that P-K activity was present in a serum fraction that contained molecules larger than IgG and that included monomeric IgA [10]. Those experiments actually suggested that P-K activity might be a property of IgA. However, he went on to disprove that idea based on two observations. Firstly partially purified human IgA antibodies to group A blood substance did not have P-K activity and secondly the P-K activity separated with molecules slightly larger than IgA [11]. The separation of P-K activity from serum IgA was dependent on using two 100 cm upward flowing, gravity fed, size exclusion columns in series and also on the development by Pharmcia of the cross linked dextran Sephadex G200 as a molecular sieve. This column produced a P-K rich fraction which was further depleted of other immunoglobulins and used to immunize rabbits. Thus by 1966, an antiserum specific for P-K activity had been produced that could deplete the P-K activity from serum, as well as give a precipitin line in a gel [12]. They provided evidence at that time that this activity could not be ascribed to IgM, IgG, IgA or IgD antibodies and suggested that it should be regarded as a new isotype which they named gamma E [13, 14].

Demonstration that a myeloma derived protein ND was not IgM, IgG, IgA or IgD and could block sensitization of the skin

Meanwhile "back in Europe" the immunochemists Hans Bennich and Gunnar Johansson had become very interested in the nature of the immunoglobulin present in the serum of a patient (ND) who required regular plasmapheresis for multiple myeloma. From a large bank of myeloma sera this was the only one that could not be typed i.e. it was not IgM, IgG, IgA, or the newly defined IgD. The serum from this patient provided an ideal source to study since it contained 10 mg/ml of the myeloma protein. However, it is important to remember that myeloma proteins do not have known antigen specificity which made it difficult to investigate the biological activity. Nonetheless, in 1967 working with Dennis Stanworth and John Humphrey in the UK they digested the molecule with Papain and reported that the Fc fragment of the ND protein could inhibit PK activity [15–17]. One of the most remarkable things about the whole story is that the Radio-Allergo Sorbent test (RAST) for IgE antibodies was also published in 1967 [18]. That paper by Wide, Bennich and Johansson reported assays of IgE to more than twenty different allergens and a significant correlation between the assay results and the results of challenge tests. The availability of myeloma protein, ND, was invaluable in the development of assays of total IgE and IgE antibodies in serum, because there was sufficient fully purified protein not only for the digestion with Papain but also for radiolabeling and production of specific anti-IgE. The protein also made

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it possible to carry out a detailed structural analysis of the molecule which was found to have an extra domain in the heavy chain thereby explaining its molecular weight of close to 190,000. In that same year, the two groups exchanged reagents and it became clear that Ishizaka's purified P-K activity and the ND protein purified by Johansson and Bennich carried the same isotype specific determinants. By 1968, the two groups together had enough information to present their results to WHO [19], and the new isotype was officially named IgE.

Studies on the function and biology of IgE at Johns Hopkins

The importance of the discovery of IgE to our understanding of allergic disease really became obvious from the research that came from each of the groups over the next few years. In 1969, Dr. Ishizaka's group moved from the Children's Asthma Research Institute (CARI) in Denver to Johns Hopkins in Baltimore. There they pursued both the mechanisms of sensitization and release of histamine and also the biology of IgE antibody responses. The work on the role of IgE antibodies addressed the nature of the cells both in the skin and the circulation that bound IgE and contained histamine as well as the role of IgE in triggering these cells [20]. Those experiments with Terruko Ishizaka and Hisaio Tomioka included, identifying the IgE receptor, demonstrating that the same receptor was present on basophils and mast cells and proving that histamine release from basophils required physical cross linking of two IgE receptor molecules [21].

The early evidence showing that P-K activity remained stable on the skin for many days implied that the receptor on the cells containing histamine must have a high affinity for IgE. After the discovery of IgE, this was confirmed and indeed it was suggested that the binding was not reversible. However, in 1973, it became clear that IgE could be stripped off histamine containing cells by low pH both in the mouse and in humans [22, 23]. Following directly on the early evidence about the Fc Receptor, there have been multiple investigations of the mechanism of histamine release and also on the structure of the IgE receptor focused on explaining its high affinity. The studies on the receptor have had a checkered history with arguments made for a role of many different parts of the IgE molecule [23] This included progressively refined studies by Jean Pierre Kinet and Henry Metzger. However, the full crystal structure of the receptor obtained by Brian Sutton, Hannah Gould, and their colleagues has now allowed a convincing model of the way in which IgE binds to the receptor [24].

Shortly after the registration of IgE, a second patient producing high levels of IgE was identified in New England, who also required repeated plasmapheresis to prevent excess viscosity. This made it possible to develop high affinity antibodies to IgE that were used to study IgE on basophils and also to develop binding assays to measure IgE antibodies [25, 26]. In Baltimore, Kishimoto and Ishizaka initiated studies to understand the mechanisms of IgE production using a rabbit model [27]. Those studies provided good evidence that the IgE responses were T cell dependent. In addition, they showed that Complete Freunds Adjuvant (CFA) could switch off IgE production even in rabbit strains that produced excellent IgE responses to the same allergen using alum [28]. However, it rapidly became obvious that these experiments would be easier in inbred strains of mice. Indeed, mice have provided an

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excellent model for studying the cellular basis of IgE production. In many senses the full understanding of TH1 and TH2 came from studies involving IgE production [29, 30]. Equally much of the understanding of the relevance of IL-4 and IL-13 came from studies on IgE production [31–33].

Sensitive and specific assays for IgE and IgE antibodies

After their initial work, Johansson and his colleagues focused on developing the assays for IgE and making them widely available [34]. This included both assays for specific IgE antibodies and also those for the total quantity of IgE in the circulation. The techniques for measuring total IgE ranged from inhibition radioimmuno assay (RIA) to different forms of assays using anti-IgE on the solid phase. Starting with different particles or paper discs, these assays became progressively more accurate and technically more reliable. The assays for total IgE are standardized relative to an IUIS international standard, and although the values are generally given in international units (IU) it is widely recognized that this unit is equal to 2.4 ng [35, 36]. Thus it became clear that a serum with 400 IU of IgE/ml contained 1 microgram of IgE/ml which is one ten thousandth of the average quantity of IgG. Although the units of IgE antibodies are often given in Allergy units/ml [or kilo AU/liter] there is good evidence that these IgE antibody units are quantitatively the same as the IU for IgE. This made it possible to estimate the percentage of total IgE that was explained by specific IgE. The initial observations of this kind were made by Gleich and Jacob on IgE to ragweed, but the same is true for grass pollen and dust mite [36, 37]. Most recently following IgE antibody responses to galactose alpha-1, 3-galactose after tick bites it is clear that this IgE response can be greater than 30% of the total IgE and that the specific IgE ab response can be an important contributor to elevated total IgE [38, 39]. It is important to recognize that this is the only isotype of immunoglobulin in the human where specific antibodies to one antigen are known to make an important contribution to the total.

Since it was known that anti-IgE could cross link molecules on the surface of basophils or mast cells and trigger histamine release there were obvious objections to using a polyclonal anti-IgE to treat allergic disease. However, once the full structures of circulating IgE and membrane IgE were known it became clear that there were two possible sites on the molecule that could be targeted. The first was the FC binding site that would be shielded as soon as the molecule was bound to Fc epsilon R1 and the second was a small section of the membrane bound IgE that is close to the B cell membrane. It took over twenty years from the first studies on monoclonal antibodies against the Fc binding site to achieve successful treatment of allergic asthma with omalizumab [40, 41].

Once the assays for IgE antibodies were possible, they became a normal part of epidemiologic studies as well as clinical practice [42]. When it became obvious that pediatric asthma had dramatically increased between 1960 and the 1980's these assays played a central role both in defining new allergens and in investigating the role of indoor allergens in asthma [37, 42–45]. From early on it was clear that IgE could be measured using either allergen extracts or purified proteins. However, it was not until the advent of recombinant proteins that widespread use of component assays became possible. With the dramatic rise in food allergy, IgE assays have played a central role both in the investigation and the management.

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This is particularly true for conditions such as peanut allergy and delayed anaphylaxis to red meat where the titer of IgE antibodies to Ara h 2 and Alpha-gal, respectively, has a direct relationship to the disease [39, 46–48]. However in Eosinophilic esophagitis (EoE) where the titers of IgE ab to milk are low or very low, IgE ab to milk components may nonetheless be relevant to designing management [49, 50].

Conclusions

There have been several previous reviews of the discovery of IgE with strikingly different emphasis [14, 17, 34]. Looking back we have to conclude that the joint success of two different research approaches was remarkably good luck for those of us who care about allergic disease. Just at the moment when Ishizaka's group had developed a rabbit antibody specific for the human antibodies that were responsible for P-K activity, Johansson and Bennich had identified a myeloma protein that appeared to be a novel isotype. In addition, they demonstrated that the Fc fragment of that protein would inhibit P-K activity. Once the two groups had collaborated to establish the identity of the new isotype, each group pursued their own research. What followed was a truly dramatic increase in research on allergic disease, ranging from mechanisms of histamine release, to cellular studies on the biology of IgE production, and the development of sensitive and accurate assays of IgE that became available worldwide. Thus the discovery of IgE spawned thousands of studies on the science of IgE as well as on the relevance of IgE antibodies to allergic disease. There have been few discoveries in the last 50 years that have directly resulted in such impressive progress in both the science and the clinical understanding of a major group of diseases.

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