MILESTONE 6

IgE and the quest to understand allergy

In 1919 a clinical case report noted a curious phenomenon: allergy could be transferred to an otherwise healthy person through the donation of blood from an allergic patient. That observation was subsequently expanded on by Otto Prausnitz and Heinz Küstner in the 1920s through their demonstration that subcutaneous injection of serum from an allergic donor followed by challenge with a specific antigen resulted in a characteristic erythema and wheal response. This so-called 'PK reaction' would become a 'go-to' technique of early allergy research. Collectively these findings suggested that a factor—which came to be known as 'reagin'—was present in the serum of allergic people and was responsible for mediating allergy. The suspicion was that reagin was an antibody of some kind; however, a 'smoking gun' proved elusive.

The field largely languished for decades until the husband-and-wife team of Kimishige and Teruko Ishizaka entered the fray. Frequently experimenting on himself using the PK reaction, Kimishige Ishizaka made the surprising discovery that reagin was indeed an antibody but not one of the known immunoglobulin isotypes of IgM, IgG or IgA, as initially suspected; instead, it was an entirely new isotype. Although IgA was able to transfer allergy, the Ishizakas speculated that in fact a very dilute contaminating component was the culprit. Backing up that idea was their seminal 1966 paper showing that a serum preparation with all IgA removed still retained its 'PK activity'. The Ishizakas called this reagenic component 'γE', as it triggered a PK reaction to the E antigen of ragweed pollen; however, it was so rare in normal or even allergic serum that it defied the purification technologies of the day.

Around that time, Hans Bennich and S.G.O. Johansson in Sweden noted that an unusual protein referred to as 'ND', isolated from a patient with myeloma (MILESTONE 9), had properties almost identical to those of the Ishizakas' γE. Their serendipitous yet key advance here was that because ND was produced by a myeloma, it could be isolated in meaningful amounts and examined experimentally. The two groups exchanged reagents and collaborated in a series of classic experiments that definitively proved that ND and γE were indeed identical and represented the long-sought-after reagin. Shortly thereafter reagin was officially renamed by the World Health Organization as immunoglobulin E (IgE)—its name recalling the original association with the allergenic ragweed E antigen and its ability to trigger erythema. Kimishige Ishizaka went on to become the first scientific director of the La Jolla Institute for Allergy and Immunology, a leading research center.

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IgE is now well established as the critical mediator of allergy and is therefore central to everything from asthma to food allergy. Subsequent studies by the Ishizakas, Henry Metzger and others have shown that IgE mediates its functions by triggering basophils and mast cells through interaction with the unique membrane receptor FcεRI that binds IgE's Fc portion (MILESTONE 7). The importance of IgE for allergy has made it a major drug target, and clinical studies have already shown that blocking its activity can be beneficial in the treatment of asthma. On the plus side, IgE has a key function in the clearance of multicellular parasites such as helminths. The potentially harmful effects of IgE mean that under normal conditions, the immune system keeps it at only vanishingly small concentrations in the serum; it is this property that made it initially so difficult to study and led to its distinction as being the final human antibody type to be discovered.

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IgE was the final human antibody type to be discovered and has a central role in allergy.
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