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Immunoglobulin E: From horses to myeloma

Let me tell you a story about a horse. In 1919, a previously healthy man living in New York City developed an undisclosed anemia that caused fatigue. He received a blood transfusion from an individual donor, and his fatigue symptoms improved. Two weeks after the transfusion he felt well enough to go to Central Park and take a horse-drawn carriage ride. Upon entering the carriage, he felt his chest tighten and his breathing became more laborious. Understandably concerned, he walked home and called on a doctor, who likely heard wheezing on examination of the man's lungs, leading to an injection of epinephrine, "bringing the paroxysm to a rapid end."[1] The man had never experienced anything like this before.

Associate Editor, Adam Brown, MD, discusses an angle related to the article "How should I evaluate allergic disease in patients with asthma?" on page 586.

A few days later he went back to Central Park, and his symptoms returned as soon as he was near the horses. At this point, he was seen by allergy expert Dr. Maximilian Ramirez, who "tested him against a large number of food and bacterial proteins, pollens, etc., with negative results, finally … obtaining a positive reaction to horse dandruff."[1] Perplexed, Ramirez reached out to the man who donated his blood to treat the anemia, and the man told the doctor he was allergic to many animals, including horses. He came into Ramirez's office and also underwent a skin-prick test, again revealing the same reaction to horse dander. Ramirez was shocked, wrote about it in a case report published in the *Journal of the American Medical Association*,[1] and even cautioned people with allergies against donating blood.

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What was this mysterious reagent that seemingly transferred allergies from one person to another?

Most people know immunoglobulin (Ig) E to the extent that we blame it for allergic reactions. Weird rash after eating an almond? Probably IgE-mediated. A simplified framework looks like this: a person sensitized to a certain allergen produces IgE, which then binds to mast cells in tissues (such as in the airway). When the IgE is exposed to the allergen again, it binds to the allergen and triggers mast cell degranulation, releasing histamine and other mediators that result in bronchoconstriction. Understanding this immune system response took decades of work, from astute clinical observations to painstaking translational research.

In this article, we'll explore the unusual history of IgE, including how difficult it was to isolate, and elucidate its interaction with mast cells and histamine. But first we need to talk about a technique developed to trigger a reaction to fish, which became a way to conduct reproducible research on allergies in the laboratory.

THE FISH TEST

In 1921, German physicians Dr. Heinz Küstner and Dr. Carl Prausnitz, inspired by the story of the horse allergy, designed an experiment. Küstner, it turns out, was severely allergic to fish, so he took a sample of his serum and injected it subcutaneously into the skin of Prausnitz's arm. A few days later, he injected boiled fish extract subcutaneously into Prausnitz's arm in the area where Küstner's serum was previously injected and into the other arm to act as a control. Within minutes, the area on the arm that received Küstner's serum erupted into a wheal and flare, whereas the other arm had no reaction.[2] The observed response became known as the Prausnitz-Küstner reaction, and

the experiment showed researchers how to reliably reproduce an allergic response in a controlled manner within a laboratory setting.

THE DISCOVERY OF IgE

It would take 45 years to discover what was being transferred from person to person, well after IgG, IgA, IgD, and IgM were identified. IgE was discovered in 1966 by Dr. Kimishige Ishizaka and Dr. Teruko Ishizaka in Denver, Colorado. Taking advantage of technology, they used rabbit antibody to the unknown reagin and radiolabeled ragweed antigen, performed immunodiffusion through agarose gel, and found that the antibody to the unknown protein aligned perfectly with the radiolabeled ragweed antigen.[3] IgE was also discovered independently around the same time by another group in Sweden who were trying to identify the antibody in a patient with multiple myeloma. It was not IgG, IgM, or the recently described IgD, but turned out to be an extremely rare form of IgE myeloma.[4]

After IgE was discovered, it quickly became clear why it was so difficult to find—IgE makes up the smallest fraction of circulating immunoglobulin.[5] In fact, researchers struggled to experiment with IgE because of its scarcity. It took the willingness of the second patient ever described with an IgE myeloma to donate his plasma weekly for a year before he died for researchers to acquire enough IgE to conduct experiments on the newly discovered antibody.[6] To prove IgE was the transferable reagin in the Prausnitz-Küstner reaction, it was isolated from an individual with a ragweed allergy and transferred into the skin of a person without the allergy, triggering the wheal and flare when exposed to ragweed pollen.[7]

HOW DOES IgE TRIGGER AN ALLERGIC RESPONSE?

To understand how IgE works, we must begin by turning to mast cells, which were first described by Friedrich von Recklinghausen in 1863.[8] In 1878, they were named by Paul Ehlich who, as a medical student at the time, recognized an unusual granular cell attached to various tissues. He incorrectly thought the granules inside the cell were nutrient stores and named the cells *mastzellen* (well-fed cells).[6,8]

The link between mast cells and histamine storage was clarified in 1953 when tissues with higher amounts of mast cells were found to have a corresponding greater ability to release histamine when triggered by an antigenic stimuli, but the mechanism that triggered the release remained a mystery.[9] Because of the known association between mast cells and histamine, once IgE was discovered, mast cells were quickly suspected of somehow interacting with the antibody.

In 1974, IgE was radiolabeled by researchers and then exposed to tissue with a high concentration of mast cells; repeated washing to clear any unbound immunoglobulin revealed abundant IgE binding.[10] IgG, IgA, and IgM, which were radiolabeled as controls, were not bound to mast cells. Another study from France used mouse peritoneal tissue with mast cells that were either incubated with anti-ovalbumin IgE or control IgE and then exposed to ovalbumin.[11] The mast cells incubated with anti-ovalbumin IgE were the only ones to release histamine. These experiments demonstrated the IgE–mast cell–histamine framework of allergic reactions.

THE FINISH LINE

The road to unraveling the connection among IgE, mast cells, and histamine took nearly a century of work. A clinical scenario of a man suddenly becoming allergic to a horse after a blood transfusion piqued scientific curiosity, leading to the development of the reproducible Prausnitz-Küstner reaction, aiding scientific investigation of allergies. While mast cells, histamine, IgG, IgA, IgD, and IgM were all discovered much earlier, technology had to advance to the point where it could detect a type of antibody that makes up a small fraction of all serum immunoglobulin. Once IgE was isolated, with help from a patient with an extremely rare IgE myeloma, a working framework of allergic reactions fell into place relatively rapidly, finally explaining how one man's IgE to horse dander was transfused into another, binding to the recipient's mast cells and then triggering an allergic response once he was exposed to the allergen.

Now the next time you accidentally ingest that almond you're not supposed to have and you feel your face begin to swell, you can appreciate the work it took to understand the reaction you're experiencing while you desperately search for your EpiPen.

DISCLOSURES

Dr. Brown has disclosed consulting and teaching and speaking for Amgen and Sanofi.

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