

This Week's Citation Classic

Ishizaka K, Ishizaka T & Hornbrook M M. Physicochemical properties of reaginic antibody. V. Correlation of reaginic activity with yE-globulin antibody. *J. Immunology* **97**:840-53, 1966. [Children's Asthma Res. Inst. and Hosp., Denver, CO]

This paper provided convincing evidence that reaginic antibodies in the serum of ragweed sensitive patients are associated with a new immunoglobulin, which we called yE. The physicochemical properties and antigenic structure of yE corresponded to those of reaginic antibodies. [The SC® indicates that this paper has been cited over 210 times since 1966.]

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"When my wife, Teruko Ishizaka, and I were at the California Institute of Technology and Johns Hopkins University from 1957 to 1959, we studied the mechanisms of anaphylaxis in the guinea pig. We reached a hypothesis that bridging of antibody molecules by antigen would induce new biologic activities which trigger allergic reactions. Naturally, we wished to test this hypothesis in humans, and began to study human reaginic antibodies in 1962 after we joined Children's Asthma Research Institute and Hospital in Denver, Colorado.

"The nature of reaginic antibodies in the serum of allergic patients had remained unknown for 40 years since Prausnitz detected skin-sensitizing activity in Küstner's serum! At one time, many immunochemists and allergists reached the conclusion that reaginic antibodies belong to IgA. Indeed, the antibodies were enriched in the IgA fraction of the serum of hay fever patients. We realized, however, that IgA antibodies against conventional antigens, such as blood group

substance, did not have the ability to sensitize human skin for allergic reactions. This finding suggested to us the possibility that reaginic antibodies against allergens may belong to impurities present in the IgA fraction. By 1965, we accumulated evidence that the antibodies do not belong to any of the known immunoglobulin classes such as IgG, IgA, IgM, and IgD. In order to detect 'unknown' immunoglobulin with which reaginic antibody is associated, we tried to prepare rabbit antibodies specific for human reaginic antibodies. At that time, the only way to select an antiserum was to assess the skin sensitizing activity of a mixture of a patient's serum and a rabbit antiserum on our skin. Fortunately, we obtained an appropriate rabbit antiserum and detected a new immunoglobulin in a reaginrich fraction of patient's sera. As we believed that the protein had skin-sensitizing activity, and caused erythema-wheal reactions, we tentatively called this protein yE.²

"The paper cited followed studies in which we studied the correlation between yE and reaginic antibodies. Data showed that the distribution of reaginic activity paralleled yE antibody detected in vitro when a serum of ragweed sensitive patients was fractionated by various methods and that yE is an immunoglobulin.

"Probable reasons for more frequent citation of this paper than the previous one is that more compelling evidence was provided in the second paper. This work led to purification of yE and confirmed our conclusion. After an atypical myeloma protein with the same antigenic structure as yE was found, yE was approved to represent the fifth immunoglobulin class which is now called IgE. Discovery of IgE enabled us to study immunological mechanisms of reaginic hypersensitivity and led to radioimmunoassay of reaginic antibodies in hay fever patients."

1. Prausnitz C & Küstner H. Studien über die überempfindlichkeit.

Zbl. Bakt. Parasitenk. 86:160-9, 1921.

2. Ishizaka K, Ishizaka T & Hornbrook M M. Physicochemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J. Immunology* **97**:75-85, 1966.