

This Week's Citation Classic

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Donaldson V H & Evans R R. A biochemical abnormality in hereditary angioneurotic edema. Absence of serum inhibitor of C'1-esterase. *Amer. J. Med.* **35**:37-44, 1963.
[Res. Div. and Dept. Allergy, Cleveland Clinic Foundation, and Dept. Med., Western Reserve Univ. Sch. Med., Cleveland, OH]

Affected members of kindred with hereditary angioneurotic edema were markedly deficient in the serum inhibitor of the activated first component of complement (C'1-esterase inhibitor, C1-Inhibitor, or C1-INH). The deficiency and susceptibility to attacks of edema were transmitted as autosomal dominant traits. [The SCI® indicates that this paper has been cited over 330 times since 1963.]

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"The serum complement system consists of a group of proteins, some of which are enzymes, which participate in immune reactions. When the first component of complement (C1) is activated it acquires esterase activity.¹ Normally, an α -2 glycoprotein called serum inhibitor of C1 (C1-INH) regulates the action of activated C1 or C'1-esterase.² The deficiency of this serum inhibitor in hereditary angioneurotic edema was inadvertently observed during laboratory studies examining the effect of the fibrinolytic enzyme, plasmin, upon serum complement. The goal of these experiments was to determine if C1 became activated by plasmin through a two-step mechanism in which plasmin first destroyed C1-Inhibitor, thus permitting autocatalytic activation of C1.

"While at lunch with a colleague during these studies, my attention was drawn to a patient with hereditary angioneurotic edema whose symptoms had been treated with a large

amount of adrenalin, albeit to no avail. Adrenalin is known to activate fibrinolytic mechanisms in *vivo*, but does not accomplish this *in vitro*, and it was possible that it might have an effect on complement in *vivo* not demonstrable in the test tube. I therefore pursued the possibility that this means of plasminogen activation might affect C1-Inhibitor and C1. When the patient's serum was found to lack C1-Inhibitor activity it was thought that this might have occurred through this hypothetical mechanism. The same observation, however, was made on serum collected after swellings had subsided, and when other members of the family who were subjected to these swellings were tested, all affected adults were found to have this deficiency even when their symptoms were in remission. Moreover, some of the children in this and other kindred who had not yet had attacks of hereditary angioneurotic edema were deficient in serum C1-Inhibitor; these children have since developed the classical symptoms of the disease. Therefore, the detection of this deficiency is a diagnostic feature of hereditary angioneurotic edema, and this inherited defect demonstrates the participation of the complement system in a human disease. In the face of this deficiency there is ready activation of the first component of complement with consequent destruction of the hemolytic activity of the fourth component, because it is easily destroyed by active C1.

"This disorder represents a unique disease due to an inherited deficiency of an inhibitor protein of blood plasma. This study is probably frequently cited because it was the first published description of a disease process associated with a deficiency of a clearly defined regulatory protein of serum, and because it was the first description of a disease picture associated with perturbed serum complement reflecting an inherited abnormality of the system."

1. **Ratnoff O D & Lepow I H.** Some properties of an esterase derived from preparations of the first component of complement. *J. Exp. Med.* **106**:327-43, 1957.
2. **Levy L R & Lepow I H.** Assay and properties of serum inhibitor C'1-esterase. *Proc. Soc. Exp. Biol. Med.* **101**:608-11, 1959.