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-esterase inhibitor, C1-INH) is activated it acquires esterase activity.1 Normally, an α-2 glycoprotein called serum inhibitor of C1-esterase (C1-INH) regulates the action of activated C1 or C1-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 plasminogen activation might affect C1-esterase inhibitor and C1. When the patient’s serum was found to lack C1-esterase 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-esterase 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.