

Pathogenesis and laboratory diagnosis of hereditary angioedema

Bruce L. Zuraw, M.D.,¹ and Sandra C. Christiansen, M.D.²

ABSTRACT

Hereditary angioedema (HAE) was first described in the 19th century. Over the past 50 years, many details of the pathophysiology and molecular biology of HAE have been elucidated. Two types of HAE, type I and type II, result from mutations in the gene for the broad-spectrum protease inhibitor C1 inhibitor (C1INH). Type I HAE is characterized by low antigenic and functional C1INH levels and type II HAE has normal antigenic but low functional C1INH levels. Type III HAE, by contrast, has normal antigenic and functional C1INH levels. In some families, type III HAE has been linked to mutations in Hageman factor. C1INH is the primary inhibitor of the complement proteases C1r and C1s as well as the contact system proteases activated Hageman factor (coagulation factor XIIa and XIIb) and plasma kallikrein. It is also an inhibitor of plasmin and coagulation factor XIa. The primary mediator of swelling in HAE has now been unequivocally shown to be bradykinin, generated from activation of the plasma contact system. The knowledge gained concerning the underlying mechanisms of the different types of HAE allow the clinician to approach the laboratory diagnosis with confidence and provides opportunities for novel therapeutic strategies.

(Allergy Asthma Proc 30:487–492, 2009; doi: 10.2500/aap.2009.30.3277)

Key words: Angioedema, bradykinin, C1 inhibitor, C2 kinin, complement, contact system, HAE, Hageman factor, high molecular weight kininogen, mutation, plasma kallikrein

In 1888, William Osler published the first description of a familial form of angioedema associated with significant morbidity and mortality.¹ He called this disease hereditary angioneurotic edema, a name that has subsequently been shortened to hereditary angioedema (HAE). The prevalence of HAE is not known for certain but has been estimated to range from 1:30,000 to 1:80,000 in the general population without any known gender or ethnic or racial differences.²

HAE is clinically characterized by recurrent episodes of angioedema that generally involve the extremities, gastrointestinal tract, face, oropharynx, larynx, or external genitalia. Patients with HAE present with a his-

tory of discrete episodes of nonpruritic nonpitting angioedema. These attacks typically involve the extremities, genitourinary tract, abdomen, face, oropharynx, or a combination of all of these.^{2,3} HAE attacks are usually distinguished from allergic or idiopathic angioedema by their duration, absence of accompanying urticaria, and failure to respond to antihistamines or corticosteroid therapy.

Most often, patients with HAE begin swelling and experiencing abdominal pain during childhood. Fifty percent of HAE patients begin swelling under the age of 10 years, with some patients manifesting angioedema by the age of 1 year.^{4,5} Most patients then experience a worsening of symptoms around puberty.³ Occasionally, patients with HAE do not begin to show evidence of angioedema until their late teens or early adulthood. Rarely, patients with HAE have been reported who never experience angioedema.^{5,6} Although some patients appear to experience decreased symptoms as they age, other patients continue to experience HAE attacks throughout their lives.

C1 INHIBITOR AND HAE

The pathophysiological basis of HAE as a deficiency of a plasma inhibitor was discovered in the early 1960s. Landerman *et al.* reported that patients with HAE

From the ¹Department of Medicine, University of California San Diego and San Diego Veteran's Affairs Medical Center, La Jolla, California, and ²Department of Allergy, Kaiser Permanente and Department of Medicine, University of California San Diego, La Jolla, California

Presented at the Hereditary Angioedema Update symposium at the Eastern Allergy Conference, Palm Beach, Florida, May 1, 2009

Supported by an unrestricted educational grant from ViroPharma. B. Zuraw receives grant/research support from Lev and Pharming and is a consultant for Lev, Pharming, Jerini, CSL Behring and Dyax. S. Christiansen has nothing to disclose pertaining to this article

Address correspondence and reprint requests to Bruce L. Zuraw, M.D., 9500 Gilman Drive, Mailcode 0732, La Jolla, CA 92093-0732

E-mail address: bzuraw@ucsd.edu

Copyright © 2009, OceanSide Publications, Inc., U.S.A.

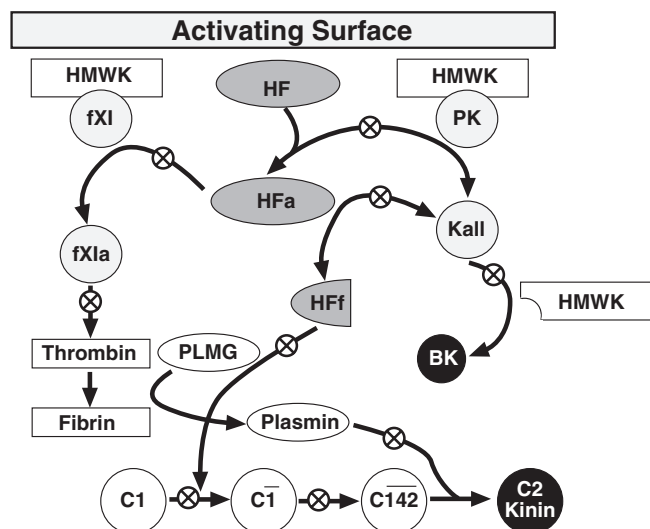


Figure 1. Interrelated plasma proteolytic cascades inhibited by C1INH. When exposed to an appropriate stimulus such as an activating surface, several plasma proteolytic cascades are activated, including the contact system, the intrinsic coagulation pathway, the fibrinolytic system, and the classic complement pathway. Steps that are inhibited by C1INH are shown as circles with an "X" inside. C1INH, C1 inhibitor; HF, Hageman factor; HFa, activated Hageman factor; HFf, Hageman factor fragment; PK, plasma prekallikrein; Kall, plasma kallikrein; BK, bradykinin; fXI, coagulation factor XI; fXIa, activated fXI; PLMG, plasminogen. Complement proteases shown with a bar on the top are activated.

lacked an inhibitor of serum globulin permeability factor (activated Hageman factor) or plasma kallikrein.⁷ The next year, in a seminal publication, Donaldson and Evans identified the missing inhibitor as C1 inhibitor (C1INH).⁸ The identification of C1INH deficiency as the basis of HAE allowed the pathophysiological and molecular mechanisms of HAE to be explored.

C1INH is a broad-spectrum serine protease inhibitor that is a member of the serpin serine protease inhibitor superfamily, with significant homology to α_1 -antitrypsin. It is the major inhibitor of several complement proteases (C1r, C1s, MASP-1, and MASP-2) and contact system proteases (plasma kallikrein and activated Hageman factor [coagulation factors XIIa and XIIIf]).⁹ C1INH is also a relatively less important inhibitor of the fibrinolytic protease plasmin and the coagulation protease factor XIa. Figure 1 illustrates these pathways and shows where they are inhibited by C1INH.

Like other serpins, C1INH functions as a "molecular mousetrap," undergoing large-scale rearrangement and trapping the target protease when it is cleaved.¹⁰ C1INH is a suicide inhibitor, forming a 1:1 stoichiometric complex with the target protease followed by clearance of the entire complex. In cases of overwhelming proteolytic activation, C1INH can be cleaved into a modified inactive form without forming a complex with or inhibiting the protease.¹¹

The 2.1-kb C1INH cDNA was initially cloned and sequenced in 1986.¹² C1INH is a 110-kDa single chain glycoprotein consisting of 478 amino acids plus a 22-residue signal peptide.¹² The protein is organized into two domains: the N-terminal 100 amino acids contain the N- and O-linked carbohydrates and the carboxy 378 amino acids contain the active site in a stressed loop conformation typical of the serpins.¹² The 17,159 basepair genomic sequence of the gene was published in 1991.¹³ The gene, now named *SERPING1*, is located on chromosome 11 (p11.2-q13), contains 8 exons and 7 introns, does not contain a 5' TATA box, and is distinguished by 17 Alu repeats in introns 3–7. More recently, the crystal structure has been solved.¹⁴

The autosomal dominant pattern of HAE was recognized by Osler in 1888. Each child of an affected patient has a 50% chance of having HAE. Importantly, HAE does not skip generations. The C1INH deficiency in HAE has been shown to result from mutations of the gene coding for C1INH, *SERPING1*. A large number of *SERPING1* mutations have been identified,^{9,15–18} with additional mutations still being reported. A database tabulating known *SERPING1* gene mutation database currently lists over 150 different mutations identified in patients with HAE.¹⁹

Lack of a positive family history of angioedema can not, however, be used to exclude the diagnosis. Although ~75% of patients give a compatible history of having an affected parent, the remaining 25% of patients presumably have a *de novo* mutation of the C1INH gene that results in HAE.²⁰ More recently, a form of HAE (type III), not associated with C1INH deficiency, has been described (see later in text).

MEDIATOR OF SWELLING

Identification of the mediator of swelling in patients with HAE has important implications for developing more effective treatment of the disease. Incubation of plasma from HAE patients *ex vivo* at 37°C was shown to generate a factor that caused smooth muscle contraction and increased vascular permeability.²¹ It was quickly recognized that this vascular permeability enhancing factor was likely to be the mediator of swelling in HAE; however, the identity of this factor was an area of significant controversy for many years. As reviewed previously, C1INH is a major inhibitor of several complement proteases and contact system proteases as well as a minor inhibitor of coagulation factor XIa and plasmin. During HAE attacks, each of these plasma proteolytic cascades is activated and several vasoactive substances are potentially generated. Based on these considerations, two potential mediators of swelling in HAE were identified: C2 kinin, generated through activation of the classic complement pathway,²² or bradykinin, generated through activation of the contact system.²³

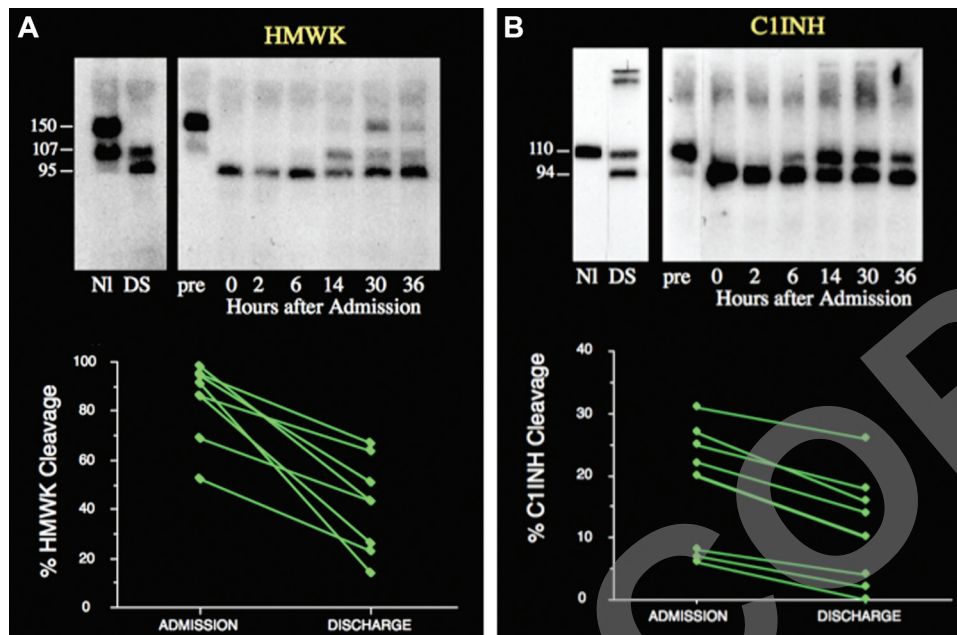


Figure 2. Activation of the contact system with cleavage of HMWK and C1INH during attacks of angioedema in HAE patients. (A) HMWK is cleaved during attacks of HAE. Top shows an immunoblot of plasma HMWK. The first two lanes show normal plasma and plasma in which the contact system is activated by treatment with dextran sulfate. The final seven lanes show an HAE patient at various times: during remission and then at the indicated times after admission for a severe attack of angioedema. The bottom graph shows the percentage of HMWK cleaved in eight separate HAE patients at admission for attacks of HAE and at the time of discharge. (B) C1INH is cleaved during attacks of HAE. The top shows an immunoblot of plasma C1INH. The lanes and graph below are the same as described for panel A. C1INH, C1 inhibitor; HAE, hereditary angioedema; HMWK, high molecular weight kininogen.

Several lines of evidence appeared to favor C2 kinin as the mediator of swelling in HAE. Because of the deficiency in C1INH, the classic complement pathway is continuously activated in patients with HAE with increased activation during attacks.^{24–26} Evidence suggested that C4 and C2 were required for generation of vascular permeability enhancing activity in HAE plasma, and the factor transducing this effect appeared to be distinct from bradykinin.^{22,27} Furthermore, purified mixtures of active C1s, C2, and plasmin generated a vascular permeability enhancing factor along with a peptide cleaved from C2 and a synthetic C2 peptide had weak vascular permeability enhancing factor activity on its own.²⁸

Gradually, however, compelling laboratory and clinical data have shown that bradykinin is the primary mediator that enhances vascular permeability in HAE. Bradykinin is a nanopeptide generated by activation of the contact system, in which active plasma kallikrein cleaves high molecular weight kininogen (HMWK) to release bradykinin. The generated bradykinin can potentially increase vascular permeability by binding to its cognate receptor (the B2 bradykinin receptor) on vascular endothelial cells. Active plasma kallikrein was detected in the blister fluid of HAE patients but not in normal controls.²³ Incubation of HAE plasma *ex vivo* was shown to generate bradykinin.^{29,30} Furthermore,

evidence of *in vivo* activation of the contact system during attacks of angioedema in HAE patients was found (Fig. 2 A),^{31–33} and increased levels of bradykinin measured in plasma during attacks of angioedema.³⁴

Contact system activation was also shown to cleave C1INH into a nonfunctional form,¹¹ and the plasma level of cleaved nonfunctional C1INH was increased during attacks of angioedema in HAE patients (Fig. 2 B).³⁵ Importantly, the vascular permeability enhancing activity generated by *ex vivo* incubation of C1INH-deficient plasma was shown to be independent of C2 but completely dependent on HMWK (the substrate for bradykinin).³⁶ The C1INH knockout mouse showed a persistent increase in vascular permeability, which could be corrected by administration of exogenous C1INH.³⁷ Additionally, the vascular permeability defect was shown to be dependent on both plasma kallikrein activity and bradykinin receptor signaling. In view of the overwhelming evidence supporting the predominant role of bradykinin as the mediator of swelling in HAE, it was of little surprise that drugs targeting bradykinin generation or action have shown efficacy in clinical trials for treatment of acute attacks of angioedema in HAE.^{38,39}

Several stressors have been associated with precipitating HAE attacks, especially trauma (even relatively

minor trauma such as sitting on a hard surface for a prolonged time) and emotional stress.³ The mechanism by which these stressors enhance bradykinin signaling in HAE remains unclear. Because angiotensin-converting enzyme (ACE) inhibitors decrease the catabolism of bradykinin,⁴⁰ ACE inhibitors are contraindicated in HAE patients.⁴¹

Hormonal changes can also affect disease severity.^{3,42,43} The impact of pregnancy on HAE disease severity is variable with some women worsening and other women having less swelling during their pregnancy. Universally, women appear to be relatively protected against swelling at the time of parturition; however, their risk of swelling increases dramatically during the postpartum period.⁴⁴ Birth control pills containing estrogen and estrogen replacement therapy both appear to increase frequency of swelling. Estrogens have been shown to increase expression of the contact system protease Hageman factor,^{45,46} providing a potential mechanism by which they may enhance bradykinin generation.

MOLECULAR BASIS OF HAE

Three different forms of HAE have been identified. Type I and type II HAE involve a deficiency of C1INH and can be distinguished depending on whether the plasma C1INH antigenic levels are low or normal, respectively. Type III HAE, however, has been clearly shown to not involve C1INH deficiency. Each of these three types of HAE will be discussed separately, later.

Type I HAE

Type I HAE is the most common form of HAE, accounting for ~85% of cases. As mentioned previously it is associated with decreased antigenic levels of C1INH in the plasma. A large number of different *SERPING1* mutations have been associated with type I HAE including missense, nonsense, frameshift, deletion, and insertion mutations. In general, type I HAE is caused by mutations in the C1INH gene that result in either truncated proteins or misfolded proteins that cannot be secreted.⁴⁷

Type II HAE

Another ~15% of HAE patients have type II HAE. This type of HAE is characterized by normal plasma antigenic levels of C1INH with decreased plasma functional C1INH levels.^{48,49} The vast majority of *SERPING1* mutations associated with type II HAE involve residues at or near the active site on the reactive mobile loop that result in a mutant C1INH protein that is secreted but is dysfunctional.⁵⁰

Type III HAE

A hereditary form of angioedema that does not involve C1INH has been recently described.^{51,52} This

additional form of HAE has been called type III HAE or estrogen-dependent/associated angioedema. The clinical pattern of angioedema attacks is similar to that seen in types I/II HAE with prolonged angioedema episodes and marked differences in severity from patient to patient.⁵³ At the current time, there is no definitive laboratory or clinical parameter to definitively diagnose type III HAE and the diagnosis can only be considered in patients with a strong family history suggestive of an autosomal dominant pattern. Therefore, the frequency of type III HAE relative to type I and type II HAE are difficult to assess.

The original descriptions of type III HAE described families in which all of the affected subjects were women. Furthermore, attacks of angioedema were felt to mirror states of high endogenous estrogen (*i.e.*, pregnancy) or administration of exogenous estrogen. Subsequently, a number of families have been described with affected male subjects and with affected female subjects whose angioedema does not depend on high estrogen levels.⁵⁴

Recently, several of the type III HAE kindreds have been shown to have a gain-of-function mutation in coagulation factor XII that may result in enhanced generation of bradykinin.^{55–57} Other families with type III HAE, however, were screened for this mutation and found not to have it. It is conceivable, but not proven, that the coagulation factor XII gain-of-function mutation is responsible for the disease in the affected kindreds.

DIAGNOSIS

When a diagnosis of HAE is suspected, confirmation requires laboratory testing.^{58,59} The typical patterns for type I HAE, type II HAE, type III HAE, acquired C1INH deficiency, ACE-I-associated angioedema, and allergic or idiopathic angioedema is shown in Table 1. In addition, an algorithm for the diagnosis of HAE is shown in Fig. 3.

In general, measuring the complement C4 level is the best cost-effective screening test to exclude a diagnosis of HAE.^{60,61} An analysis of screening tests for the diagnosis of HAE showed that measurement of the C4 level had a sensitivity of 65%, a specificity of 94%, positive predictive value of 23%, and a negative predictive value of 99%.⁶¹ On occasion, the C4 can be normal, particularly if the patient is already being treated for a presumed diagnosis of HAE.⁶⁰ When repeated during an HAE attack, however, the C4 should be low in HAE. A normal C4 level during an attack of HAE strongly suggests that a diagnosis of HAE may be incorrect.

In a patient suspected of having HAE after confirmation of a low C4, the next step should be to measure C1INH antigen (and function if the antigenic level is normal).³ The combination of low C4 and low C1INH function had a 98% specificity for C1INH deficiency and

Table 1 Usual complement profile in various types of angioedema

	Antigenic C1INH Level	Functional C1INH Level	C4 Level	C1q Level	C3 Level
HAE type I	Decreased	Decreased	Decreased	Normal	Normal
HAE type II	Normal	Decreased	Decreased	Normal	Normal
HAE type III	Normal	Normal	Normal	Normal	Normal
Acquired C1INH deficiency	Decreased	Decreased	Decreased	Decreased	Normal or decreased
ACE-I associated	Normal	Normal	Normal	Normal	Normal
Allergic/idiopathic	Normal	Normal	Normal	Normal	Normal

ACE-I = angiotensin-converting enzyme I; C1INH = C1 inhibitor; HAE = hereditary angioedema.

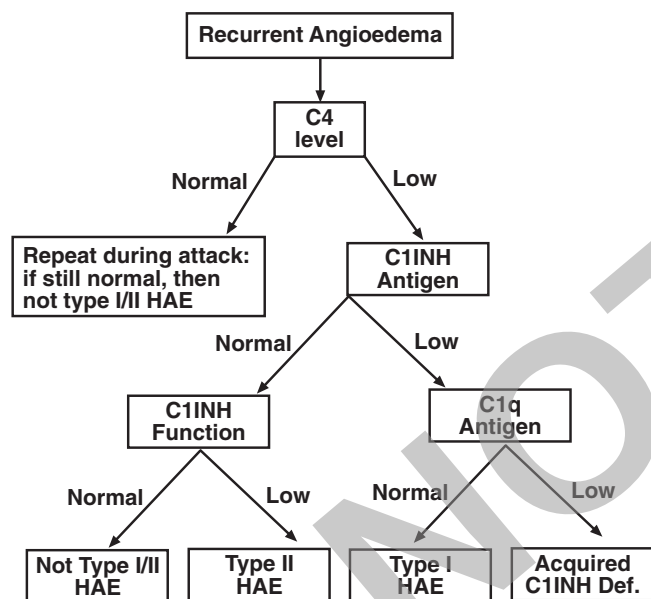


Figure 3. Diagnostic algorithm for the evaluation of recurrent angioedema.

a 96% negative predictive value.⁶¹ As indicated previously, type III HAE patients have normal C1INH antigenic and functional levels. Some type III families have been shown to have a mutation in factor XII; however, the clinical utility of looking for this mutation in patients suspected of having type III HAE is unclear at the current time.

REFERENCES

- Osler W. Hereditary angio-neurotic oedema. *Am J Med Sci* 95:362–367, 1888.
- Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
- Frank MM, Gelfand JA, and Atkinson JP. Hereditary angioedema: The clinical syndrome and its management. *Ann Intern Med* 84:586–593, 1976.
- Farkas H, Varga L, Szeplaki G, et al. Management of hereditary angioedema in pediatric patients. *Pediatrics* 120:e713–e722, 2007.
- Agostoni A, and Cicardi M. Hereditary and acquired C1-inhibitor deficiency: Biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 71:206–215, 1992.

- Molina C, Brun J, Coulet M, et al. Diagnostic and therapeutic problems associated with hereditary deficiency of the C1 esterase inhibitor. *Clin Allergy* 7:127–135, 1977.
- Landerman NS, Webster ME, Becker EL, and Ratcliffe HE. Hereditary angioneurotic edema. II. Deficiency of inhibitor for serum globulin permeability factor and/or plasma kallikrein. *J Allergy* 33:330–341, 1962.
- Donaldson VH, and Evans RR. A biochemical abnormality in hereditary angioneurotic edema: Absence of serum inhibitor of C'1- esterase. *Am J Med* 35:37–44, 1963.
- Davis AE III. C1 inhibitor and hereditary angioneurotic edema. *Annu Rev Immunol* 6:595–628, 1988.
- Lomas DA, Belorgey D, Mallya M, et al. Molecular mousetraps and the serpinopathies. *Biochem Soc Trans* 33:321–330, 2005.
- Zuraw BL, and Curd JG. Demonstration of modified inactive first component of complement (C1) inhibitor in the plasmas of C1 inhibitor-deficient patients. *J Clin Invest* 78:567–575, 1986.
- Bock SC, Skriver K, Nielsen E, et al. Human C1 inhibitor: Primary structure, cDNA cloning, and chromosomal localization. *Biochemistry* 25:4292–4301, 1986.
- Carter PE, Duponchel C, Tosi M, and Fothergill JE. Complete nucleotide sequence of the gene for human C1 inhibitor with an unusually high density of Alu elements. *Eur J Biochem* 197:301–308, 1991.
- Beinrohr L, Harmat V, Dobo J, et al. C1 inhibitor serpin domain structure reveals the likely mechanism of heparin potentiation and conformational disease. *J Biol Chem* 282:21100–21109, 2007.
- Bissler JJ, Aulak KS, Donaldson VH, et al. Molecular defects in hereditary angioneurotic edema. *Proc Assoc Am Physicians* 109:164–173, 1997.
- Verpy E, Biasotto M, Brai M, et al. Exhaustive mutation scanning by fluorescence-assisted mismatch analysis discloses new genotype-phenotype correlations in angioedema. *Am J Hum Genet* 59:308–319, 1996.
- Zuraw BL, and Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol* 105:541–546, 2000.
- Gosswein T, Kocot A, Emmert G, et al. Mutational spectrum of the C1INH (SERPING1) gene in patients with hereditary angioedema. *Cytogenet Genome Res* 121:181–188, 2008.
- Kalmár L, Hegedűs T, and Tordai A. HAEdb C1 inhibitor gene mutation database. Available online at hae.enzim.hu/; last accessed August 2009.
- Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the C1inhibitor gene of patients with angioedema. *J Allergy Clin Immunol* 106:1147–1154, 2000.
- Donaldson VH, Ratnoff OD, Da Silva WD, and Rosen FS. Permeability-increasing activity in hereditary angioneurotic edema plasma. II. Mechanism of formation and partial characterization. *J Clin Invest* 48:642–653, 1969.

22. Donaldson VH, Rosen FS, and Bing DH. Role of the second component of complement (C2) and plasmin in kinin release in hereditary angioneurotic edema (H.A.N.E.) plasma. *Trans Assoc Am Physicians* 40:174–183, 1977.
23. Curd JG, Prograis L Jr, and Cochrane CG. Detection of active kallikrein in induced blister fluids of hereditary angioedema patients. *J Exp Med* 152:742–747, 1980.
24. Austen KF, and Sheffer AL. Detection of hereditary angioneurotic edema by demonstration of a profound reduction in the second component of human complement. *N Engl J Med* 272: 649–656, 1965.
25. Carpenter CB, Ruddy S, Shehadeh IH, et al. Complement metabolism in man: Hypercatabolism of the fourth (C4) and third (C3) components in patients with renal allograft rejection and hereditary angioedema (HAE). *J Clin Invest* 48:1495–1505, 1969.
26. Laurell AB, Martensson U, and Sjöholm AG. C1 subcomponent complexes in normal and pathological sera studied by crossed immunoelectrophoresis. *Acta Pathol Microbiol Scand C* 84C: 455–464, 1976.
27. Klemperer MR, Donaldson VH, and Rosen FS. Effect of C1 esterase on vascular permeability in man: Studies in normal and complement-deficient individuals and in patients with hereditary angioneurotic edema. *J Clin Invest* 47:604–611, 1968.
28. Strang CJ, Cholin S, Spragg J, et al. Angioedema induced by a peptide derived from complement component C2. *J Exp Med* 168:1685–1698, 1988.
29. Curd JG, Yelvington M, Burrige N, et al. Generation of bradykinin during incubation of hereditary angioedema plasma. *Mol Immunol* 19:1365, 1983.
30. Fields T, Ghebrehiet W, and Kaplan AP. Kinin formation in hereditary angioedema plasma: Evidence against kinin derivation from C2 and in support of “spontaneous” formation of bradykinin. *J Allergy Clin Immunol* 72:54–60, 1983.
31. Lammle B, Zuraw BL, Heeb MJ, et al. Detection and quantitation of cleaved and uncleaved high molecular weight kininogen in plasma by ligand blotting with radiolabeled plasma prekallikrein or factor XI. *Thromb Haemost* 59:151–161, 1988.
32. Berrettini M, Lammle B, White T, et al. Detection of in vitro and in vivo cleavage of high molecular weight kininogen in human plasma by immunoblotting with monoclonal antibodies. *Blood* 68:455–462, 1986.
33. Schapira M, Silver LD, Scott CF, et al. Prekallikrein activation and high-molecular-weight kininogen consumption in hereditary angioedema. *N Engl J Med* 308:1050–1054, 1983.
34. Nussberger J, Cugno M, Amstutz C, et al. Plasma bradykinin in angio-oedema. *Lancet* 351:1693–1697, 1998.
35. Zuraw BL, Lammle B, Sugimoto S, et al. Cleavage of high molecular weight kininogen in plasma during attacks of angioedema in hereditary angioedema. *J Allergy Clin Immunol* 79:177, 1987.
36. Shoemaker LR, Schurman SJ, Donaldson VH, and Davis AE. Hereditary angioneurotic oedema: Characterization of plasma kinin and vascular permeability-enhancing activities. *Clin Exp Immunol* 95:22–28, 1994.
37. Han ED, MacFarlane RC, Mulligan AN, et al. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 109:1057–1063, 2002.
38. Zuraw BL, and Christiansen SC. New promise and hope for treating hereditary angioedema. *Expert Opin Investig Drugs* 17:697–706, 2008.
39. Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 119:1497–1503, 2007.
40. Byrd JB, Adam A, and Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 26:725–737, 2006.
41. Shepherd GM. Possible contraindication of angiotensin converting enzyme inhibitors in patients with hereditary angioedema. *Am J Med* 88:446, 1990.
42. Frank MM. Effect of sex hormones on the complement-related clinical disorder of hereditary angioedema. *Arthritis Rheum* 22:1295–1299, 1979.
43. Bouillet L, Longhurst H, Boccon-Gibod I, et al. Disease expression in women with hereditary angioedema. *Am J Obstet Gynecol* 119:484 e1–4, 2008.
44. Chappatte O, and De Swiet M. Hereditary angioneurotic oedema and pregnancy. Case reports and review of the literature. *Br J Obstet Gynaecol* 95:938–942, 1988.
45. Farsetti A, Misiti S, Citarella F, et al. Molecular basis of estrogen regulation of Hageman factor XII gene expression. *Endocrinology* 136:5076–5083, 1995.
46. Citarella F, Misiti S, Felici A, et al. Estrogen induction and contact phase activation of human factor XII. *Steroids* 61:270–276, 1996.
47. Verpy E, Couture-Tosi E, Eldering E, et al. Crucial residues in the carboxy-terminal end of C1 inhibitor revealed by pathogenic mutants impaired in secretion or function. *J Clin Invest* 95:350–359, 1995.
48. Rosen FS, Charache P, Pensky J, and Donaldson VH. Hereditary angioneurotic edema: Two genetic variants. *Science* 148:957–958, 1965.
49. Rosen FS, Alper CA, Pensky J, et al. Genetically determined heterogeneity of the C1 esterase inhibitor in patients with hereditary angioneurotic edema. *J Clin Invest* 50:2143–2149, 1971.
50. Wagenaar-Bos IG, and Hack CE. Structure and function of C1-inhibitor. *Immunol Allergy Clin North Am* 26:615–632, 2006.
51. Bork K, Barnstedt SE, Koch P, and Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 356:213–217, 2000.
52. Binkley KE, and Davis A III. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 106:546–550, 2000.
53. Bork K, Gul D, Hardt J, and Dewald G. Hereditary angioedema with normal C1 inhibitor: Clinical symptoms and course. *Am J Med* 120:987–992, 2007.
54. Bork K. Hereditary angioedema with normal C1 inhibitor activity including hereditary angioedema with coagulation factor XII gene mutations. *Immunol Allergy Clin North Am* 26:709–724, 2006.
55. Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet* 79:1098–1104, 2006.
56. Dewald G, and Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun* 343: 1286–1289, 2006.
57. Duan QL, Binkley K, and Rouleau GA. Genetic analysis of factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. *J Allergy Clin Immunol* 123:906–910, 2009.
58. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: A current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol* 100:S30–S40, 2008.
59. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: Consensus document. *Clin Exp Immunol* 139:379–394, 2005.
60. Zuraw BL, Sugimoto S, and Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. *J Allergy Clin Immunol* 78:1115–1120, 1986.
61. Gompels MM, Lock RJ, Morgan JE, et al. A multicentre evaluation of the diagnostic efficiency of serological investigations for C1 inhibitor deficiency. *J Clin Pathol* 55:145–147, 2002. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.