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This Week's Citation Classic®

Hathaway W E, Belhasen L P & Hathaway H S. Evidence for a new plasma thromboplastin factor. I. Case report, coagulation studies and physicochemical properties. *Blood* 26:521-32, 1965.
[Depts. Pediatrics, Univ. Kentucky Med. Ctr., Lexington, KY, and Univ. Colorado Med. Ctr., Denver, CO]

A markedly prolonged partial thromboplastin time in four siblings was shown to be corrected by prolonged incubation with kaolin and addition of all known deficient plasmas. None of the siblings showed any bleeding tendency. Physicochemical properties related this plasma defect to the contact coagulation factors. [The *SCI*® indicates that this paper has been cited in over 165 publications since 1965.]

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While I was establishing my first coagulation laboratory at the new University of Kentucky Medical Center, a pediatrician in Lexington called to ask about a prolonged whole-blood clotting time performed prior to tonsillectomy in an 11-year-old girl with a negative bleeding history. The child was in the midst of her first pediatric evaluation after having been brought to Lexington for convalescent care of frostbitten feet. She was one of 11 children of a poor family and had walked from a burned-out mountain cabin in the snowy hills of eastern Kentucky. This remarkable series of events led to the performance of a kaolin partial thromboplastin time on her plasma.

The strikingly abnormal results, which corrected on prolonged incubation with kaolin, stimulated the further investigations that convinced my research assistants and me that we had evidence for a new clotting factor, which we tentatively designated "Fletcher factor" because it was the patient's family name. Family studies and plasma procurement frequently involved hiking trips into the hollows of eastern Kentucky. These efforts helped establish rapport with family members, who remain cooperative to this day.

From the beginning of our studies, it appeared that the Fletcher factor was part of the contact system of the coagulation cascade and perhaps represented the "missing" contact factor predicted by Schiffman, Rapaport, and others.[1] Although the Fletchers moved to Michigan and were "lost to follow-up" for a while, we continued to study the relation of the new factor to factors XI and XII.[2] In 1970 the second group of patients with Fletcher factor deficiency was reported by Hattersley and Hayse.[3] Although previously there were hints that the contact system of coagulation was related to the kinin system, it was not until 1973 that these systems were closely entwined.

The observation that the Fletcher factor was the same as plasma prekallikrein was made by Kirk Wuepper in 1973.[4] The clinical significance of prekallikrein deficiency in man was then addressed by Wuepper, me, and others in a study of two siblings of the original Fletcher family. These studies suggested that severe plasma prekallikrein deficiency is not associated with any clinically significant impairment in hemostasis, fibrinolysis, inflammatory responses, or leukocyte function.[5] The increased interest in coagulation and inflammatory responses[6] is probably responsible for the frequent citation of our original publication.

1. **Schiffman S, Rapaport S I, Ware A G & Mehl J W.** Separation of plasma thromboplastin antecedent (PTA) and Hageman factor (HF) from human plasma. *Proc. Soc. Exp. Biol. Med.* 105:453-4, 1960.
2. **Hathaway W E & Abever J.** The relation of 'Fletcher factor' to factors XI and XII. *Brit. J. Haematol.* 18:161-9, 1970. (Cited 65 times.)
3. **Hattersley P E & Hayse D.** Fletcher factor deficiency. A report of three unrelated cases. *Brit. J. Haematol.* 18:411-16, 1970.
4. **Wuepper K D.** Prekallikrein deficiency in man. *J. Exp. Med.* 138:1345-55, 1973. (Cited 125 times.)
5. **Hathaway W E, Wuepper K D, Weston W L, Humbert J R, Rivers R P A, Genton E, August C S, Montgomery R R & Mass M F.** Clinical and physiologic studies of two siblings with prekallikrein (Fletcher factor) deficiency. *Amer. J. Med.* 60:654-64, 1976.
6. **Bennet J S.** Blood coagulation and coagulation tests. *Med. Clin. N. Amer.* 68:557-76, 1984.

