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Langdell R D, Wagner R H & Brinkhous K M. Effect of antihemophilic factor on one-stage clotting tests. *J. Lab. Clin. Med.* **41**:637-47, 1953.
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This article describes a laboratory procedure that has been applied as a screening test for a number of hemostatic disorders and is the basis for the assay of what at the time was called the antihemophilic factor (AHF) and is now known as factor VIII:C. The principle of the bioassay has been the basis for the measurement of several other plasma coagulation factors. [The *SCI*® indicates that this paper has been cited in over 655 publications since 1955.]

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"At the time these studies were done, much of the research activity in the Department of Pathology at the University of North Carolina centered on a bleeding disorder that arose apparently as a mutation in a group of inbred dogs. Genetic, clinical, and coagulation studies indicated that the disorder was very similar to human hemophilia.[1] As in humans, transfusion of normal plasma corrected the clotting defect and controlled the hemorrhagic phenomena. We attributed this effect to the antihemophilic factor (AHF) that could be fractionated along with fibrinogen from normal plasma. Efforts to characterize the trace protein were impeded by the methodology for measuring AHF based on the utilization of prothrombin in clotting hemophilic blood. To simplify the measurement of AHF, we utilized an observation that in one-stage clotting tests, some extracts of normal or hemophilic tissue could compensate for the factor missing in hemophilia (complete thromboplastin), while others, such as natural or synthetic cephalins, could not (partial thromboplastin).

"The partial thromboplastin time, a new procedure based on these observations, was used in our laboratory for over three years before the article was submitted for publication. This was in part due to observations indicating that the method was sensitive to coagulation factors other than the plasma factor deficient in hemophilia, reports that other hemorrhagic states could easily be confused with hemophilia, and studies that were in progress indicating that there were mild forms of human hemophilia.[2] It was ultimately determined that the corrective effect of a test sample on canine or human hemophilic plasma used as a substrate was dependent on what is now known as factor VIII:C.

"The partial thromboplastin time is now widely used in clinical laboratories as a screening test not only for hemophilia but also for coagulation factors that were unrecognized at the time the procedure was published.[3] Although the bioassay method was developed for measuring factor VIII:C, by using plasma deficient in any one of several other clotting factors as a substrate, it is used as an assay method for other coagulation factors. The original method has been modified by a number of investigators, and reagents are now available commercially. In view of the tendency of authors to cite their own work, it is surprising that the original publication has been cited frequently.

"It is of interest that our efforts to characterize the coagulation defect in hemophilia have general applicability and have contributed to the recognition of other clotting factors and to the recently announced production of factor VIII:C through genetic splicing techniques."

1. **Graham J B, Buckwalter J A, Hartley L J & Brinkhous K M.** Canine hemophilia: observations on the course, the clotting anomaly, and the effect of blood transfusions. *J. Exp. Med.* 90:97-111, 1949. (Cited 75 times since 1955.)
2. **Brinkhous K M, Langdell R D, Penick G D, Graham J B & Wagner R H.** Newer approaches to the study of hemophilia and hemophilioid states. *J. Amer. Med. Assn.* 154:481-6, 1954. (Cited 90 times since 1955.)
3. **Brinkhous K M & Dombrose F A.** Partial thromboplastin time. (Schmidt R M, ed.) *CRC handbook series in clinical laboratory science. Section I: hematology.* Boca Raton, FL: CRC Press, 1980. Vol. 3. p. 221-46.