Observations on the Hereditary Nature of Hageman Trait

By Alvin Margolius, Jr. and Oscar D. Ratnoff

In previous reports, three patients with an unusual disorder of blood coagulation have been described. These patients, two females and one male, do not have a history suggestive of a bleeding disorder; the discovery of their abnormality was fortuitous. In each, the clotting time of whole blood, measured both in glass and in silicone-coated tubes was greatly prolonged, to a degree comparable to that observed in hemophilia. The defect appeared to be localized to the early stages of coagulation, namely, the elaboration of thromboplastic activity in shed blood. However, the syndrome could be differentiated from classic hemophilia, Christmas disease (deficiency of plasma thromboplastin component), and deficiencies of plasma thromboplastin antecedent and the fourth thromboplastin component. It was possible to prepare a globulin fraction of normal plasma which would correct the patient's defect. A fraction, prepared in the same manner from the plasma of a patient with this disorder, was inert. Since the mechanism of action of the corrective factor is unknown, it has been given the tentative name of Hageman factor, after the first patient observed. The condition in which this factor appears to be absent has been named Hageman trait.

Since two of the three patients thus far observed were sisters, it seemed likely that the defect was inherited. All three patients were of Germanic stock, but there is no indication that Mr. Hageman is related in any manner to the two sisters. The two sisters have a large family so located geographically that it was possible to make a detailed study of the hereditary nature of Hageman trait. These studies indicate that this disorder is inherited as an autosomal recessive, in a manner predictable from Mendelian theory.

Materials and Methods

Blood was drawn from the antecubital vein of 39 relatives of the sisters (Patients II and III), using No. 18 gauge needles coated with tris (2-hydroxyethyl) dodecyl-ammonium chloride (Armour Needle Coating Solution) and glass syringes coated with silicone (Desi-cote, Beckman). In most cases the blood was drawn at a distance from the laboratory and kept in ice for as long as six hours before centrifugation.

Oxalated plasma was prepared by mixing nine parts of venous blood with one part of 0.1 M sodium oxalate solution, and removing the cells by centrifugation at 2500 r.p.m. for 15 minutes in an International SB size 1 centrifuge. This plasma was kept in ice water and used within a few hours or stored at −27 C. for as long as 4 months until used.

The buffer solution consisted of 7.30 Gm. of sodium chloride, 2.76 Gm. of barbital and...
The clotting time of whole blood was measured by a modification of the method of Lee and White using dry Pyrex or silicone-coated tubes (internal diameter 11 mm.)]. In 144 normal individuals, the clotting time at 25 C. in Pyrex tubes averaged 30.8 minutes (range 11 to 56 minutes; standard deviation of the mean 8.3 minutes). In silicone coated tubes, the clotting time in 105 normal persons averaged 103.4 minutes (range 55 to 185 minutes; standard deviation of the mean, 18.5 minutes). Measurement of the clotting time at 25 C. and in wider tubes than those used in the original method of Lee and White prolongs the clotting time compared with conventional methods and exaggerates the difference between normal and abnormal bloods. In our hands, these modifications have increased the ease of detecting minor abnormalities in the clotting mechanism.

The recalified clotting time of oxalated plasma was determined at 25 C. in Pyrex tubes (internal diameter 8 mm.). In duplicate, 0.2 ml. of plasma and 0.2 ml. of 0.025 M calcium chloride solution were mixed in tubes immersed in ice water and then rapidly transferred to a water bath at 25 C. The clotting time was determined by tilting both tubes at approximately 30 second intervals. After 20 or 30 minutes the tubes were observed at progressively longer intervals. The clotting time was the period which elapsed from the time that the tubes were transferred to the 25 C. bath until the appearance of a solid clot. The longer of the duplicate clotting times is recorded. When the clotting time was 12 minutes or less, the duplicate tubes almost always clotted within one minute of each other. In 92 presumably normal subjects the recalified clotting time of fresh oxalated plasma at 25 C averaged 7.0 minutes (range 3 to 15 minutes; standard deviation 2.4 minutes). The measurement of the recalified clotting time at 25 C. results in longer clotting time with normal plasma than at 37 C. At the same time, the difference in the clotting times between normal and abnormal plasma is usually greater than at 37 C., increasing the ease of distinguishing between the normal and the abnormal.

Assay for Hageman factor. The concentration of Hageman factor in oxalated plasma was estimated by determining the plasma's capacity to correct the abnormality of plasma known to be deficient in Hageman factor. The plasma to be tested was diluted with buffer to the desired concentration. In duplicate, 0.1 ml. of plasma deficient in Hageman factor, 0.1 ml. of the diluted plasma, and 0.1 ml. of 0.025 M calcium chloride were mixed in Pyrex tubes (internal diameter 8 mm.) immersed in ice water. The tubes were then transferred to a water bath at 25 C., and the clotting time was determined as described for the recalified clotting time. The clotting times were determined in duplicate; the longer clotting time of each pair is recorded. In this system, normal oxalated plasma diluted 1:160 shortened the prolonged recalified time of Hageman factor deficient plasma (always greater than 30 minutes) to 14 or less minutes. Normal plasma diluted 1:320 shortened the prolonged recalified time of Hageman factor deficient plasma to 17 minutes or less.

RESULTS

Forty-one members of the family under study were tested for the presence of Hageman trait. It was possible to measure the clotting time of whole blood only in the six individuals who came to the laboratory. In patients II and III, as previously reported, the clotting time of venous blood was 86 and 90 minutes in glass and 330 and 300 minutes in silicone-coated tubes respectively. These are grossly abnormal values for the methods used. The clotting time of venous blood drawn from Mrs. R. P., a daughter of patient III, was 195 minutes in silicone-coated tubes, a moderately elevated value. However, there was evidence that this may have been due to a technical error, since the clotting time in the first two of the three tubes used in the test were within normal limits. The clotting times in glass tubes in this subject, and in both glass and silicone tubes in the other three subjects were normal.
Table 1.—Assay for Hageman Factor

Clotting time (min.) at 25°C in Pyrex tubes (internal diameter 8 mm.) of 0.1 ml. each of (1) oxalated plasma of patient III, (2) oxalated plasma of patient to be tested diluted with buffer as indicated, and (3) 0.025 M solution of calcium chloride.

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* Buffer substituted for test plasma.

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The recalified clotting time of oxalated plasma was determined in each of the 41 individuals studied. The recalified clotting time of plasma obtained from patients II and III was greatly prolonged on repeated occasions, ranging from 38 to 102 minutes. In two other subjects, the recalified clotting time was 17 and 23 minutes. The significance of these values is not clear, since a period of 5 to 6 hours elapsed between the time the blood was drawn and the time of testing in these subjects.

A more specific and sensitive test for the presence of Hageman factor was the assay for Hageman factor. A typical experiment is shown in Table 1. As little as one part in 80 parts of normal plasma shortened the prolonged recalified time of plasma deficient in Hageman factor from 35 minutes to 14 minutes. The plasma of the relative tested (niece of patient III) was similarly corrective. The plasma of patient I, as expected, failed to shorten significantly the prolonged recalified time of plasma deficient in Hageman factor. Thus the plasma of the
relative tested (niece of patient III) has a normal amount of Hageman factor, thereby ruling out the presence of the trait.

In this manner 37 relatives of Patients II and III, including those individuals with abnormalities in the clotting time of whole blood or recalcified plasma were tested for possible deficiency of Hageman factor. In none was any defect demonstrated by this technic.

Besides the 41 relatives studied in our laboratory, 5 other relatives were tested by Dr. Walter A. Stryker of Wyandotte, Michigan. In each case, the clotting time of venous blood was normal by the modification of the Lee White technic used in his laboratory.

The interrelationships of the various members of the family are demonstrated in figure 1. It will be noted that three of the four grandparents of the affected siblings were first cousins. Three children and four grandchildren of the affected individuals were tested, and found to be normal.

**DISCUSSION**

A study of 44 relatives of two sisters with Hageman trait failed to reveal any additional individuals with this disorder. Minor defects in the clotting time of whole blood in silicone-coated tubes or in the recalcified clotting time were found in several cases, but in each of these it was possible to demonstrate a normal concentration of Hageman factor.

The family tree of the two sisters with Hageman trait appears to provide an explanation for this result. Three of the patients' four grandparents were first cousins of each other. The defect appeared in two of three siblings. Three children and four grandchildren of the affected individual were tested, and in each case were normal. Moreover, neither of the two children of a fourth patient studied by Singer and his associates, was abnormal. The presence of consanguinity, and the absence of the trait in collateral lines and in the children of affected individuals are consistent with a hereditary trait carried by a recessive gene. Since the defect has been observed in both sexes, the gene is apparently not sex-linked. Hence, it appears likely that Hageman trait is transmitted as an autosomal recessive gene.

Among disorders of the coagulative mechanism, Hageman trait is thus transmitted in a unique manner. Congenital afibrinogenemia, parahemophilia and hypoproconvertinemia occur in both sexes. These disorders are sometimes described as the result of the transmission of recessive genes. However, in each case there is evidence that in some families individuals presumed to be heterozygous may have partial defects. It is well established that the defects in hemophilia and Christmas disease are transmitted by sex-linked recessive genes. A deficiency of plasma thromboplastin antecedent is thought to result from the inheritance of an autosomal dominant gene. The hereditary nature of deficiencies of prothrombin and the fourth plasma thromboplastin component is as yet unclarified. In contrast it has not been possible to detect individuals with a partial deficiency of Hageman factor among the many relatives of the two sisters with the disorder. This is not due to an inability to detect individuals with an incomplete defect, since in unpublished experiments it has been noted that the concentration of Hageman factor is subnormal in the blood of patients...
with severe hepatic disease, averaging between one-half and one-fourth the concentration in pooled normal plasma, barium sulfate-absorbed plasma or serum. Presumably, then, in this family the gene carrying the trait for a deficiency of Hageman factor is recessive.

**SUMMARY**

A study was made of the family tree of two sisters with Hageman trait, an asymptomatic disorder of blood coagulation. In this family the defect behaves genetically as if it is due to the transmission of an autosomal recessive gene.

**SUMMARIO IN INTERLINGUA**

Esseva executate un studio del arboe genealogic de duo sorores con le tracto de Hageman, que es un disordine asymptomatic del coagulatiom sanguinee. In le familia investigate le defecito se comporta geneticamente con le apparentia de esser debite al transmission de un autosomic gen recessive.

**REFERENCES**

5. Singer, K.: Personal communication.
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