Two patients had atrophic gastritis. Interstitial hemorrhage into the lamina propria was present in four of the seven biopsy specimens.

There was histological evidence of mild superficial gastritis in two cases, and atrophic gastritis in one other, when these conditions were not suspected from the gross appearance of the mucosa.

The pathogenesis and possible importance of gastritis in the herniated stomach in patients with sliding esophageal hiatus hernia have been discussed.

REFERENCES

1. DAGRADI, A. E., KILLEEN, R. N. AND SCHINDLER, R.: *Gastroenterology*, 35: 54, 1958.
2. PALMER, E. D.: *Amer. J. Dig. Dis.*, 3: 45, 1958.
3. ATKINS, L. AND BENNEDICT, E. B.: *New Engl. J. Med.*, 254: 641, 1956.
4. SELESNICK, S. AND KINSELLA, E. D.: *Ibid.*, 248: 842, 1953.
5. YLVISAKER, R. S. *et al.*: *Gastroenterology*, 28: 88, 1955.
6. DOIG, R. K. AND WOOD, I. J.: *In*: Modern trends in gastroenterology, edited by A. F. Jones, Butterworth and Co., London, 1958, p. 208.
7. PALMER, E. D.: *Medicine (Balt.)*, 33: 199, 1954.
8. SAHLER, O. D. AND HAMPTON, A. O.: *Amer. J. Roentgenol*, 49: 433, 1943.
9. PALMER, E. D.: *In*: The esophagus and its diseases, Paul B. Hoeber, Inc., New York, 1952, p. 131.
10. STEMPIEN, S. J. AND SILK, A. D.: *Calif. Med.*, 78: 499, 1953.
11. MARCHAND, P.: *Brit. J. Surg.*, 47: 515, 1960.
12. AYLWIN, J. A.: *Thorax*, 8: 38, 1953.
13. JOSKE, R. A., FINCKH, E. S. AND WOOD, I. J.: *Quart. J. Med.*, 24: 269, 1955.
14. JACOBS, W. H.: *J. Mount Sinai Hosp. (N.Y.)*, 26: 464, 1959.
15. FELDER, S. L., MASLEY, P. M. AND WOLFF, W. I.: *A.M.A. Arch. Int. Med.*, 105: 873, 1960.
16. JOHNS, T. N. P. AND CLEMENTS, E. L.: *J. Thor. Cardiov. Surg.*, 41: 737, 1961.
17. WOOD, I. J. AND TAFT, L. I.: *In*: Diffuse lesions of the stomach, Edward Arnold Ltd., London, 1958, p. 50.
18. *Idem*: *Ibid.*, p. 65.

Congenital Hypofibrinogenemia in Five Members of a Family

R. HASSELBACK, M.D., F.R.C.P.[C], RITA B. MARION, A.R.T.
and J. W. THOMAS, M.D., *Vancouver, B.C.*

ABSTRACT

The bleeding tendency in five members of one family with fibrinogen levels ranging from 58 mg. % to 158 mg. % was mild and chiefly related to dental extractions. Abruptio placentae in one patient produced severe bleeding. Reports of menstrual bleeding patterns in patients with defects of hemostatic mechanisms suggest that normal platelets, vascular function and extrinsic and possibly intrinsic coagulation systems, except for fibrinogen, control menstrual blood loss. An autosomal dominant gene with variable penetrance may determine fibrinogen levels.

OVER 30 cases of congenital afibrinogenemia have been reported to date.[11, 14, 29] Hypofibrinogenemia, sometimes referred to as fibrinogenopenia, has been reported much less frequently and only a few cases of this disorder have been described in the literature.[10, 31, 35, 43] This report concerns five members of one family with moderately low levels of fibrinogen.

HISTORY OF PROPOSITI

CASE 1.—M.N., a 27-year-old married woman, was admitted to the Vancouver General Hospital in February 1960, for excision of a Bartholin cyst. From the age of 20 she had noted excessive bruising after minor trauma, bleeding lasting up to two days after dental extractions, and a postpartum hemorrhage at the age of 24 which required two transfusions after the birth of her only child. She had had no bleeding which could be described as spontaneous, no joint hemorrhages, and her menses had always been lighter than average. After excision of the Bartholin cyst, she developed a large hematoma of the vulva that had to be evacuated 36 hours postoperatively; no transfusions or blood products were administered. Excision of skin tags that were causing dyspareunia was carried out five months later, without excessive bleeding. The results of the investigations of this patient are shown in Table I.

CASE 2.—J.B., the 19-year-old sister of M.N., presented at another hospital with vaginal hemorrhage during the 32nd week of her first pregnancy. Her previous history of bleeding was limited to one to two days' oozing after dental extractions on two occasions; two heavy, prolonged menstrual periods at the ages of 12 and 13; and one very heavy period at age 18 which required the transfusion of two bottles of blood. Otherwise her menses had been normal. Neither the patient nor her mother had noted any other bleeding episodes. On admission, a diagnosis of abruptio placentae was made. The addition of thrombin to the patient's plasma gave only a delayed poor clot suggesting an associated defibrination syndrome. After 16 hours of ineffective labour, a classical Cesarean section was carried out. At operation, there were multiple small, blue hematomas in the uterus, with a large hematoma involving the right tube and ovary. Liquid blood, to 1500 ml., was free in the uterine cavity, external to the amniotic sac. A 1420-g. female infant was delivered live, but expired almost immediately. The patient received 2500 ml. of blood, 500 ml. of polyvinylpyrrolidone, and 2.2 g. of fibrinogen concentrate before and during the procedure. Moderate oozing but no extensive

From the Department of Pathology, Vancouver General Hospital, and the Department of Medicine, The University of British Columbia, Vancouver, B.C.

TABLE I.

	Bleeding time (minutes)	*Capillary fragility*	*Platelet count (per c.mm.)*	*Clot retraction*	*Clotting time (minutes)*	*Prothrombin activity %*	*Thrombin time (seconds)*	*Fibrinogen (mg./100 ml.)*	*Inhibitors*	*Screening thrombo-plastin test*
M.N.	1½	Negative	310,000	Small	14	63	Abnormal	76	Negative	Normal
				*	10	75	Abnormal	80	Negative	
					8	*	*		Negative	
J.B.	2½	Negative	540,000	Small	12	60	Abnormal	58		Normal
	3			*	10	100	*			
						*				
A.B.	1		510,000	Small	13	100	Abnormal	86		Normal
				*		*	*			
T.B.	2		350,000	Small	12	100	Abnormal	158	Negative	Normal
				*		*	*			
P.B.	2		330,000	Good	10	85	Normal	225		Normal
S.B.	3		340,000	Good	12	100	Normal	142		Normal
S.N.	1		730,000	Good	5	100	Normal	205		Normal

*Clots formed appeared smaller than normal.

bleeding was noted during the operation. The fibrinogen level five days postoperatively was reported as 250 mg. %, and 10 days postoperatively as 210 mg. %. A mild thrombophlebitis of the right leg in the postoperative period responded to conservative management. A fibrinogen level of 58 mg. % was determined several weeks later at the Vancouver General Hospital.

Two months later, the patient was admitted to this hospital with acute abdominal pain and leukocytosis. Fibrinogen, 1.6 g., was administered before laparotomy. At operation, no pathological lesion adequate to explain the pain and leukocytosis was found; a normal appendix was removed. Careful hemostasis was carried out and no unusual bleeding was encountered. The fibrinogen level 12 hours postoperatively was 91 mg. %. The patient had an uneventful postoperative course, but she has since been subject to recurrent episodes of similar abdominal pain.

As a result of the investigations of these two sisters, other members of the family were studied. None have ever required transfusion or been considered bleeders. There is no known consanguinity in the family.

CASE 3.—A.B., the father of M.N. and J.B., has sometimes but not consistently bled after tooth extractions. Drainage of an antrum at age 37 and a tonsillectomy and adenoidectomy at the age of nine years were not accompanied by excessive bleeding. He had not noted easy bruising or excessive bleeding from minor cuts.

CASE 4.—T.B., aged 57, a brother of A.B., and uncle of M.N. and J.B., bled excessively after all tooth extractions and after a repeat tonsillectomy at age 14. A previous tonsillectomy at age 8, a submucous resection at age 14, and an appendectomy at age 30 were not accompanied by bleeding. He is known to have a peptic ulcer which has never bled.

CASE 5.—Mrs. F.B., the mother of T.B. and A.B., now dead, was said to bruise excessively and to have bled at delivery of one of her children. She underwent thyroidectomy and cholecystectomy with no significant bleeding. Mr. J.B., the father of A.B. and T.B., died at age 86; he had never exhibited any bleeding tendency. P.B., aged 18, the younger brother of M.N. and J.B. has never exhibited a bleeding tendency, nor has S.N., the 3-year-old daughter of M.N.

The results of investigations performed on the family are reported in Table I.

METHODS

Duke's method was used for estimation of the bleeding time; by this method the normal bleeding time is less than three minutes. The whole blood clotting time was performed by a modified Lee and White method, with a normal range of 6-14 minutes. Platelet counts were performed by the indirect method, normal being 200,000-500,000/c.mm. Clot retraction was observed by incubating the whole blood clot at 37° C. and is normally complete in four hours. The thromboplastin times (Quick one-stage prothrombin) were determined with a commercial thromboplastin-calcium mixture (Simplastin, Warner-Chilcott). Thrombin times were determined on citrated plasma with thrombin dilutions chosen to give a time of 15 to 25 seconds with normal plasma. The thromboplastin screening test was performed by the method of Hicks and Pitney.[16] Fibrinogen was determined by a micro-Kjeldahl assay of thrombin-clottable plasma protein. Testing for inhibitors was carried out by mixing various proportions of the test plasma with normal plasma and comparing the thrombin time of this mixture with that of the normal plasma.

DISCUSSION

The bleeding tendency in this family may be described as mild at most. None of the subjects were considered to be bleeders until the episodes reported above in the two young women led to the investigation of their hemostatic mechanisms. Bleeding after dental extractions was the commonest manifestation in this family. Other surgical procedures, such as tonsillectomy, have been per-

formed in some members of the family without abnormal bleeding. The only life-endangering episode of bleeding that has occurred in the family happened when a 19-year-old girl with a usual fibrinogen level of 58 mg. % developed abruptio placentae, a condition which is commonly responsible for a defibrination syndrome. Bleeding under these circumstances may have been contributed to by a further fall in fibrinogen level owing to defibrination. During the hemorrhagic episode, the low fibrinogen level was recognized by examination of the whole blood clot, and the performance of a thrombin time, but no quantitative determination of fibrinogen was carried out at the time. It seems unlikely that the postoperative fibrinogen levels of 250 mg. % and 210 mg. % are accurate.

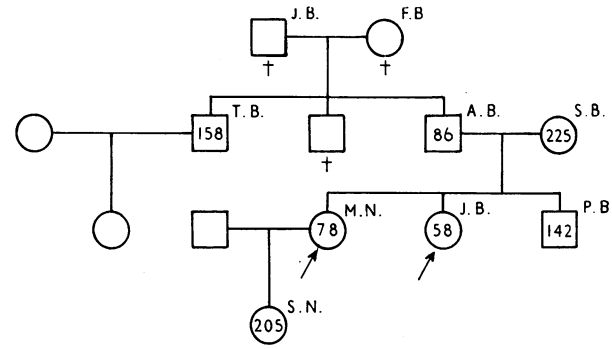
Although patient J.B. had three heavy periods in her life, one requiring transfusion, menorrhagia has not been a feature of this condition. Four cases of afibrinogenemia in females who have passed puberty have been reported in the literature.[11, 15, 19, 21] In all, the menstrual history was normal. Lawson[19] noted this fact and assumed that the principal hemostatic mechanism involved in limiting menstrual blood loss was vascular constriction. This is in keeping with current thinking concerning the mechanisms of menstruation.[32] In contrast to fibrinogen deficiency, congenital deficiency of other hemostatic components—vascular, platelets, and coagulation factors—are frequently associated with menorrhagia.

Patients with bleeding tendencies due to vascular defects sometimes have menorrhagia. In Blackburn's series of patients with primary capillary hemorrhage,[5] 16 of 81 females of all ages had had menorrhagia; some of these patients had associated deficiencies of Factor VIII (antihemophilic globulin) or Factor IX (Christmas factor, PTC).

Menometrorrhagia is a common manifestation of thrombocytopenia. Qualitative defects of platelet functions such as thrombocytasthenia ("thrombocytopathic purpura with impaired clot retraction") have been recognized as a cause of menorrhagia.[30, 37]

Deficiencies of components of the extrinsic coagulation system other than fibrinogen, including hypoproaccelerinemia,[7, 24, 40] hypoprothrombinemia,[6] hypoproconvertinemia[41] and Factor X deficiency,[39] are commonly associated with menorrhagia.

The occurrence of menorrhagia in patients with deficiencies of coagulation factors which are active only in the intrinsic coagulation system is more difficult to establish, as the two pure deficiency states which occur with any frequency, i.e. deficiencies of Factors VIII and IX, are almost confined to males. Six reports of Factor VIII deficiency occurring in females past the menarche have been noted; four of these were said to have a normal menstrual history[18, 26-28] and two to exhibit some degree of menorrhagia.[12, 38] Two patients reported by Mersky[23] had severe menorrhagia, but as a family history of father-to-son transmission through four generations and positive tourniquet tests and prolonged bleeding times in the patients or members of their families was found, the possibility of Factor VIII deficiency associated with a vascular defect, "vascular hemophilia", must be considered in these cases. Taylor and Biggs[38] have stated that the diagnosis of female hemophilia in Mersky's cases had since been "confirmed". Factor IX deficiency in teen-age sisters has been reported by Cook and Douglas.[9] One had questionable menorrhagia and the other had no bleeding manifestations of any sort. Some reported cases of plasma thromboplastin antecedent deficiency have had menorrhagia (Case 1 of Cavins and Wall[8]) but others seem to have normal menses.[33]



FAMILY TREE

Fig. 1.—The B. family. Squares represent males, circles females; the numbers indicate the fibrinogen levels in mg. %. The propositi are indicated by arrows.

The evidence from a consideration of congenital defects of the hemostatic mechanism therefore suggests that a normal vascular mechanism, normally functioning platelets, an intact extrinsic coagulation system and possibly an intact intrinsic coagulation system, except for fibrinogen, are necessary for the limitation of blood loss and the production of hemostasis in the endometrium during menstruation.

The sequence of events in endometrial transplants in the eyes of Rhesus monkeys during menstruation was described in detail by Markee in 1940.[22] Stasis in vessels for one to five days and vasoconstriction of coiled arteries for four to 24 hours preceded the onset of the menstrual period. Blood escaped into endometrial lakes or hematomas by periodic relaxation of these vessels. The hematomas eventually were discharged when the endometrial tissue sloughed. Clotting occurred in only one of the five types of bleeding observed, which Markee named "secondary hemorrhages"; these hemorrhages occurred only when the animals were frightened or struggling. Dislodging these clots from the vessels never initiated fresh bleeding, and the conclusion was reached that clotting was not necessary to terminate these hemorrhages. The clots that formed disintegrated apparently by lysis

in three to six hours. Markee made no mention of the presence of platelet plugs on blood vessels.

Menstrual fluid has been shown to contain no fibrinogen and to be incoagulable on the addition of thrombin.[2, 3, 13, 17, 20] Furthermore, it has been found to possess a high plasminogen activator activity, as does endometrium.[1, 3] Albrechtsen[2] has postulated that menstrual blood is clotted by tissue thromboplastin in the endometrium and that the fibrin formed immediately undergoes lysis by plasmin which has been activated from the plasminogen normally present in the plasma. The fact that fibrinogen deficiency does not produce excessive menstrual loss is therefore not remarkable, as fibrin deposition which does occur is apparently lysed, while other mechanisms maintain hemostasis.

Why then do defects of other coagulation factors, particularly those involved in the extrinsic coagulation system, lead to menorrhagia? A possible explanation is the role of the coagulation products in platelet function in hemostasis. Viscous metamorphosis appears to be an essential stage in the development of a platelet plug which is impermeable to blood. Some authors consider thrombin the coagulation intermediary which is active in inducing viscous metamorphosis,[25, 35] while others attribute this activity to an earlier coagulation product. One can postulate that the extrinsic and possibly the intrinsic coagulation system must be intact down to thrombin formation, but not including fibrinogen, to permit platelets to function normally to limit menstrual blood loss.

The inheritance pattern in this family suggests that the defect is due to an autosomal gene acting as a dominant with incomplete penetration. This is in keeping with the previous suggestion of Schönholzer.[34]

The prolonged thrombin time reaction in the patient's plasma compared to the thrombin time reaction in normal plasma when diluted to a comparable fibrinogen level is of interest. A possible reason for this prolongation of thrombin time may be that a normal concentration of antithrombin in the patient's plasma partially impairs the activity of the added thrombin, whereas in normal plasma the antithrombin is diluted to the same degree as the fibrinogen. Other cases have been seen, however, in which a normal thrombin time reaction compared with normal plasma has been obtained in patients with comparable fibrinogen levels. This test can therefore not be relied upon to permit recognition of patients with mild or moderate hypofibrinogenemia.

SUMMARY

Five members of one family with fibrinogen levels ranging from 58 mg. % to 158 mg. % are reported. The bleeding tendency which they exhibited was generally mild, principally involving bleeding after dental extractions. A 19-year-old girl, however, had a severe hemorrhage in association with abruptio placentae, control of which required five transfusions and the administration of fibrinogen.

A consideration of defects of hemostatic components suggests that a normal vascular system, normally functioning platelets, an intact extrinsic coagulation system and possibly an intact intrinsic coagulation system, except for fibrinogen, are necessary for hemostasis during menstruation.

Congenital hypofibrinogenemia appears to be due to an autosomal dominant gene with incomplete penetration.

REFERENCES

1. ALBRECHTSEN, O. K.: *Acta Endocr. (Kbh.)*, 23: 207, 1956.
2. *Idem*: *Ibid.*, 23: 219, 1956.
3. *Idem*: *Acta Physiol. Scand.*, 47: (Suppl. 165), 1, 1956.
4. BERGSAGEL, D. E.: *Brit. J. Haemat.*, 2: 130, 1956.
5. BLACKBURN, E. K.: *Ibid.*, 7: 239, 1961.
6. BORCHGREVINK, C. F. *et al.*: *Ibid.*, 5: 294, 1959.
7. BRINK, A. J. AND KINGSLEY, C. S.: *Quart. J. Med.*, 21: 19, 1952.
8. CAVINS, J. A. AND WALL, R. L.: *Amer. J. Med.*, 29: 444, 1960.
9. COOK, I. A. AND DOUGLAS, A. S.: *Brit. Med. J.*, 1: 479, 1960.
10. D'ABLAING, G. AND SEARCY, R. L.: *J. Amer. Osteopath. Ass.*, 58: 492, 1959.
11. DE VRIES, A. *et al.*: *Amer. J. Med.*, 30: 486, 1961.
12. FANTL, P. AND MARGOLIS, J.: *Brit. Med. J.*, 1: 640, 1955.
13. GLUECK, H. I. AND MIRSKY, I. A.: *Amer. J. Obstet. Gynec.*, 42: 267, 1941.
14. GROSSMAN, B. J. AND CARTER, R. E.: *J. Pediat.*, 50: 708, 1957.
15. HARDISTY, R. M. AND PINNIGER, J. L.: *Brit. J. Haemat.*, 2: 139, 1956.
16. HICKS, N. D. AND PITNEY, W. R.: *Ibid.*, 3: 227, 1957.
17. HUGGINS, C., VAIL, V. C. AND DAVIS, M. E.: *Am. J. Obstet. Gynec.*, 46: 78, 1943.
18. ISRAELS, M. C. G., LEMPERT, H. AND GILBERTSON, E.: *Lancet*, 1: 1375, 1951.
19. LAWSON, H. A.: *New Engl. J. Med.*, 248: 552, 1953.
20. LOZNER, E. L., TAYLOR, Z. E. AND TAYLOR, F. H. L.: *Ibid.*, 226: 481, 1942.
21. MACKINNON, H. H.: Cited in: *Ibid.*, 248: 552, 1953.
22. MARKEE, J. E.: *Contrib. Embryol. Carneg. Inst.*, 177: 223, 1940.
23. MERSKY, C.: *Quart. J. Med.*, 20: 299, 1951.
24. OWREN, P. A.: *Lancet*, 1: 446, 1947.
25. *Idem*: The mechanism of hemostasis, presented at the VIIIth International Congress of Hematology, Tokyo, 1960, Paper No. 402.
26. PAVLOVSKY, A.: Personal communication 1961.
27. PINNIGER, J. L. AND FRANKS, R. B.: *Lancet*, 2: 82, 1951.
28. POLA, V. AND SVOJITKA, J.: *Folia haemat.* (Lpz.), 75: 43, 1957.
29. PRICHARD, R. W. AND VANN, R. L.: *A.M.A. J. Dis. Child.*, 88: 703, 1954.
30. RATNOFF, O. D.: *In*: Bleeding syndromes: A clinical manual, Charles C Thomas, Springfield, Ill., 1960, p. 170.
31. RISAK, E.: *Z. Klin. Med.*, 128: 605, 1935.
32. ROCK, J., GARCIA, C.-R. AND MENKIN, M. F.: *Ann. N.Y. Acad. Sci.*, 75: 831, 1959.
33. ROSENTHAL, R. L., DRESKIN, O. H. AND ROSENTHAL, N.: *Blood*, 10: 120, 1955.
34. SCHÖNHOLZER, G.: *Deutsch. Arch. Klin. Med.*, 184: 496, 1939.
35. SETNA, S. S. AND ROSENTHAL, R. L.: *Acta Haemat. (Basel)*, 19: 209, 1958.
36. SHARP, A. A.: *Brit. J. Haemat.*, 4: 28, 1958.
37. SOULIER, J. P. AND LARRIEU, M. J.: *Rev. Hémat. (Par.)*, 9: 77, 1954.
38. TAYLOR, K. AND BIGGS, R.: *Brit. Med. J.*, 1: 1494, 1957.
39. TELFER, T. P., DENSON, K. W. AND WRIGHT, D. R.: *Brit. J. Haemat.*, 2: 308, 1956.
40. THOMAS, J. W. AND HASSELBACK, R.: Unpublished observations.
41. VOSS, D. AND WAALER, B. A.: *Thromb. Diath. Haemorrh.*, 3: 375, 1959.
42. WAALER, B. A.: Contact activation in the intrinsic blood coagulation system, Thesis, Oslo, Oslo University Press, 1959.
43. WOLFF, J.: *Jb. Kinderheilk.*, 148: 33, 1936.

INDEX TO VOLUME 87, 1962

Reprints of the Index to Volume 87, July-December 1962, are available for the convenience of readers who would like to have a separate copy of the Index published in the issue of December 29. Requests should be addressed to: The Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.