MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

February 7, 1963.

SOME CLINICAL ASPECTS OF PLATELET DISEASES

CASE #1: [redacted]

[redacted], a 24-year-old [redacted] female followed during 1961 while pregnant. Post-partum uterine bleeding necessitated a D&C for cystic hyperplasia. In [redacted] 1962 she presented with uterine bleeding and was found to be six months pregnant. Platelets were noted to be 18,000 and a bone marrow revealed normal numbers of megakaryocytes with no platelet budding. Most of the megakaryocytes were at the basophilic stage of maturation. She was started on Meticorten 60 mg/day with a prompt platelet response and steroids were maintained at reduced dosage until her delivery in late [redacted] 1962. No abnormal physical findings were noted. L.E. and anti-nuclear tests were repeatedly negative. Post-partum she was discharged on 20 mg. of Meticorten/day which maintained her platelets at about 100,000. A readmission was necessary two weeks post-partum because of bleeding and P.I.D. and platelets were found to be 23,000. Meticorten was increased to 30 mg/day and platelets rose to 98,000 and she was discharged in mid-September 1962. We first saw her in [redacted] 1962 and while on 30 mg. Meticorten her platelets were 105,000. Steroids were tapered to evaluate her response and platelets slowly decreased to 14,000 range. She was electively admitted for splenectomy in [redacted] 1962. Physical exam was within normal limits; the spleen was not palpable. She was prepared with steroids 60 mg. prednisone/day for seven days without significant rise in platelet levels, so she was prepped with platelet transfusions and an uneventful splenectomy and accessory splenectomy performed. Postoperatively platelets rose to 450,000 and have remained in that range.

CASE #2: [redacted]

This 34-year-old [redacted] female was well until about two years prior to admission, at which time she noted ease of bruising. These bruises were variable in size, measuring between 1 cm. and up to 10 or 12 cm. in diameter, frequently spontaneous and seemed to occur just prior to or during her menstrual periods. During the past 18 months, she has noted the recurring pattern of ecchymoses unassociated with trauma. Petechiae have not been noted. In addition, the patient has noted gingival bleeding. Prior to this time, the patient denies all previous bleeding episodes. The patient further notes that there is an increase in such bleeding associated with the premenstrual period. During the past 12 to 18 months, there also has been some change in her normal menstrual pattern, which is now irregular and associated with a considerable number of clots.

The patient's drug history includes Daprisal, employed for menstrual cramps, a Dexamyl spansule, employed at various times during the month, and Phenergan, used for bedtime sedation. The patient denies the use of all other drugs and states that she is allergic to many of the "narcotic-like" drugs.

Pertinent past history reveals 6 previous pregnancies, yielding 4 normal children, 1 stillbirth at 8 months and 1 early miscarriage. All of these pregnancies were carried with ease and increased bleeding at the time of parturition was not recorded in any. Pertinent family history reveals no bleeding tendency.

Physical examination revealed a well-developed, well-nourished [redacted] female. Pertinent positive physical findings included normal retina and normal oral, nasal and conjunctival mucous membranes. A few small petechiae were present on the hard palate. There was no significant lymphadenopathy or sternal tenderness. Examination of the skin revealed several resolving ecchymoses, largely characterized by residual hemosiderin pigment. No petechiae were present and no fresh ecchymoses were noted. The liver and spleen were not palpable.

Initial laboratory examination revealed a positive Rumpel-Leeds test. The initial bleeding time by the Ivy method was 12 minutes. The upper limit of normal by the Ivy method in this laboratory is 5 to 5.5 minutes. Hemoglobin was 13.7 gm.%, white blood count 6,700 and the platelets 237,500. Platelet morphology revealed that the platelets were quite loose, somewhat abnormal in size and structure, with an increased abnormal granulomere, and poor viscous metamorphosis was noted on phase microscopy. Other coagulation studies revealed that the prothrombin time was 11.5 seconds, the same as the control. The partial thromboplastin time was 60 seconds with the upper limit of our normal range extending to 100. Gross clot retraction was noted to be poor at 2 hours and 24 hours. A thromboplastin generation test carried out employing the patient's plasma and normal serum demonstrated borderline to slightly decreased levels.

CASE #3: [redacted]

On [redacted]/62, this 74-year-old [redacted] man was brought to the EOR in an unconscious state from a nursing home where he had been cared for for several years because of "old age". The patient had been in his usual state of health which consisted of being confined to bed for the most part with trips to the dining table in a wheelchair. He was lucid up till the evening of admission, when he had a "jerking spell" followed by unconsciousness. His hospital chart revealed that this patient had first been seen at [redacted] in 1959 with complaints of dyspnea progressive for 8 years. BP was 210/110. He was felt to have hypertension and emphysema. Treatment with cardilin and reserpine was started but only one follow-up visit was made.

At the time of admission, which was 3 hours after he became unconscious, the patient appeared as a small, markedly emaciated [redacted] male who was comatose and had Cheyne-Stokes respiration. BP 170/120, pulse 80 and regular. The skin was cool, dry and had poor turgor. Purpuric lesions were noted over the dorsum of both hands. The pupils were constricted, equal and reactive. The remainder of the examination was unremarkable. The spleen was not felt.

Shortly after admission the patient because apneic and had to be maintained with automatic assisted respiration. BP remained stable. 45 minutes after admission a blood glucose determination of 15 mg.% was obtained and the patient was given 50 cc. of D50W and maintained on a constant infusion of glucose. 35 minutes later the patient became somewhat responsive and was breathing without assistance. At 0800 on 8/29 the patient was found in bed unconscious, cool and perspiring profusely. He was given 25 cc. of D50W and responded immediately. Blood glucose at this time was 44 mg.%. Two other similar episodes during the day responded to increasing the rate at which the glucose infusion was given.

On [redacted]/62 three episodes of unconsciousness relieved by glucose were observed. On [redacted] the patient was found unconscious; shortly thereafter he became apneic and expired in spite of IV glucose.

	[redacted]/59	[redacted]/62	[redacted]	[redacted]	[redacted]
Hemoglobin	13.3	9.2	10.6	8.2	7.9
Hematocrit				28.5	29.5
MCV/MCHC				66/27	74/24
WBC	15,250	27,000	56,000	62,000	41,000
Polys/bands	75/4	81/6	87/10	76/21	55/42
Lymphs/monos	18/2	9/3	3/-	3/-	1/1
Eos	1	1	-	-	-
ESR				32	
Platelets		reported increased		1,900,000	2,212,500
Retics			0.3	0.8	
Total eosinophiles					22
Bleeding time					1'45"
Clotting time					10'30"
Urine pH	5.0		7.5		
sp.gr.	1.021			1.014	
Alb/sugar/acetone	N/N/N		N/N/N		
Hgb. elect.				AA	
BUN/creatinine		18/-	36/-	49/1.6	45/1.4
Uric acid/amylase					-/320
Glucose			15,<25,430	44,442,<25	<25, 66
CO2/Cl		25/90	22/96	25/100	24/93
Na/K				125/5.3	127/5.8
TSP				4.5	
A/G				2.4/2.1	
Ca/PO4				7.5/5.4	
Cholesterol				too low to measure	
BSP				18%	
Bilirubin				0.7	
Ceph Floc				2+/2+	
TT				1.9	
Alk. p'tase				7.3	
Acid p'tase				3.2	
SGOT/control				65/55	
Stool guaiac/VDRL	-/neg.			neg/neg	
Pro time/control=100					18.5/12.5
Cellular alkaline phosphatase:		196			

REFERENCES

I.T.P.

1. Frank, E.: Die essentielle Thrombopenie: I. Klinisches Bild. II. Pathogenesese. Berl. Klin. Wchnschr. 52:454,490, 1915.
Although not the first description of I.T.P., it was the most lucid, complete and clearest recognition of the disease to that time.

2. Kagnelson, P.: Verschwenden der hämorrhagischen Diathese bei einem Falle von Essentiellen Thrombopenie (Frank) nach Milzextirpation. Wien. Klin. Wchnschr. 29: 145, 1916.
This report from Prague was the first description that splenectomy was dramatically effective in Werlhof's disease (ITP).

3. Dameshek, W. and Miller, E. B.: Megakaryocytes in I.T.P., form of hypersplenism. Blood 1:27, 1946.

The above articles, as well as Frank's, propose that a splenic humoral material acting on megakaryocytes prevents production of platelets.

4. Evans, R. S.: Primary ITP and acquired hemolytic anemia: Evidence for a common etiology. Arch. Int. Med. 87:48, 1951.
This first correlated cases of AIHA with ITP and demonstrated a platelet agglutinin in ITP.

5. Dameshek, W., Rubio, F., Jr., Mahoney, J. P., Reeves, W. H. and Burgin, L. A.: Treatment of I.T.P. with prednisone. JAMA 166:1805, 1958.

6. Harrington, W. J., Mennich, V. and Arimura, G.: The autoimmune thrombocytopenias. In: Progress in Hematology, Ed. L. M. Tocantina. Grune & Stratton, Inc., New York, 1956, vol. I:166.
A review of the experience and techniques of platelet antibody evaluation.
The methods and enthusiasm for platelet agglutinin studies are reflected in the above paper as well as the following three. These are but a sampling of the better of such studies.

7. Stefanini, M. and Mele, R. H.: The significance of platelet antibodies: With special reference to platelet agglutinins. Acta Haemat. 20:195, 1958.

8. Tullis, J. L.: Role of leukocyte and platelet antibody tests in the management of diverse clinical disorders. Ann. Int. Med. 54:1165, 1961.

9. Tullis, J. L.: Identification and significance of platelet antibodies. NEJM 255: 541, 1956.

The next six papers sum up the Dameshek argument against splenectomy in I.T.P.

10. Dameshek, W.: Systemic lupus erythematosus: A complex autoimmune disorder. Ann. Int. Med. 48:707, 1958.

11. Dameshek, W.: I.T.P. — Tricky disease. Med. Clin. No. Amer. 46:1135, 1962.

12. Dameshek, W., Schwartz, R. and Oliner, H.: Current concepts of auto-immunization: An interpretive review. Blood 17:6, 1961.

13. Dameshek, W.: Controversy in I.T.P. JAMA 173:123, 1960.
A stirring review of the controversy as seen by one of the major protagonists.

14. Rabinowitz, Y. and Dameshek, W.: S.L.E. after "idiopathic" thrombocytopenic purpura: Review. Ann. Int. Med. 52:1, 1960.

15. Dameshek, W. and Reeves, W. H.: Exacerbation of L.E. following splenectomy in "idiopathic" thrombocytopenic purpura and autoimmune hemolytic anemia. Am. J. Med. 21:560, 1960.
This describes 2 cases of occult L.E. presenting with AIHA and 1 case as I.T.P.

16. Smith, C. H., Erlandson, M., Schulman, I. and Stern, G.: Hazard of severe infections in splenectomized infants and children. Am. J. Med. 22:390, 1957.
The above is a good study of the problems encountered in children following splenectomy.

17. Meyers, M. C.: Results of treatment in 71 patients with idiopathic thrombocytopenic purpura. Am. J. Med. Sci. 242:295, 1961.
An excellent review of an approach to therapy from the experience at the University of Michigan.

18. Carpenter, A. F., Wintrobe, M. W., Fuller, E. A., Haut, A. and Cartwright, G. E.: Treatment of I.T.P. JAMA 171:1911, 1959.
Good review of treatment in 85 cases.

19. Doan, C. A., Bouroncle, B. A. and Wiseman, B. K.: Idiopathic and secondary thrombocytopenic purpura: Clinical study and evaluation of 381 cases over a period of 28 years. Ann. Int. Med. 53:861, 1960.

20. Best, W. R. and Darling, D. R.: A critical look at the splenectomy - S.L.E. controversy. Med. Clin. No. Amer. 46:19, 1962.
They do not feel true I.T.P. is S.L.E. nor does splenectomy increase the propensity to or severity of S.L.E. when it does develop.

21. Baldini, M. and Ebbe, S.: Platelet disorders and their management. Med. Clin. No. Amer. 46:1349, 1962.
60 to 80% of patients with chronic I.T.P. will respond to splenectomy.

22. Cohen, P. and Gardner, F. H.: The thrombocytopenic effect of sustained high-dosage prednisone therapy in thrombocytopenic purpura. NEJM 265:611, 1961.
Report of 7 cases of sustained high-dosage therapy initially manifesting a rise in platelets and then a later penic state.

23. Landing, B. H., Strauss, L., Crochen, A. C., Bravinstein, H., Henley, W. L., Will, J. R. and Sanders, M.: Thrombocytopenic purpura with histiocytosis of the spleen. NEJM 265:572, 1961.

The above paper gives 9 cases of ITP with a lipid histiocytosis of the spleen found.

Some of the problems of platelet storage and transfusion are reviewed in the following five articles. Techniques of platelet transfusions and criteria of therapy are discussed from many points of view.

24. Conley, C. L.: Blood platelets and platelet transfusions. Arch. Int. Med. 107:67, 1961.

25. Baldini, M., Costen, N. and Dameshek, W.: The viability of stored human platelets. Blood 16:1669, 1960.

26. Raccuglia, G. and Bethell, F. H.: Platelet transfusions and administration of platelet derivatives in man.
I. Evaluation of laboratory techniques used for prognostic purposes. Am. J. Clin. Path. 34:495, 1960.
II. Evaluation of systemic hemostatic properties of various preparations. Am. J. Clin. Path. 34:505, 1960.

27. Ivy, A. C., Shapiro, P. and Melnick, P.: The bleeding tendency in jaundice. S.G. & O. 60:781, 1935.

28. Swank, R.: Alteration of blood on storage: Measurement of adhesiveness of "aging" platelets and leukocytes and their removal by filtration. NEJM 265:728, 1961.

Megakaryocyte and Platelet Kinetics:

29. Odell, T. T., Jr., McDonald, T. P. and Asano, M.: Response of rat megakaryocytes and platelets to bleeding. Acta Haemat. 27:171, 1962.

30. Craddock, C. G., Adams, W. S., Perry, S. and Lawrence, J. S.: The dynamics of platelet production as studied by a depletion technique in normal irradiated dogs. J. Lab. & Clin. Med. 45:906, 1955.

31. Rosenthal, R. L., Pickering, B. I. and Goldschmidt, L.: A semi-quantitative study of bone marrow in rats following total body x-radiation. Blood 6:600, 1951.

32. Witte, S.: Megakaryocyten und Thrombocytopoese bei der experimentellen Thrombocytopenischen Purpura. Acta Haemat. 14:215, 1955.

33. Jackson, D. P. and Krevens, J. R.: Survival of platelets transfused into thrombocytopenic recipients. Bull. Johns Hopk. Hosp. 107:349, 1960.

34. Zucker, M. B., Ley, A. B. and Mayer, K.: Studies on platelet life span and platelet depots by use of DFP 32. J. Lab. & Clin. Med. 58:405, 1961.

35. Heyssel, R. M.: Determination of human platelet survival utilizing C^{14}-labeled serotonin. JCI 40:2134, 1961.
Platelet half-life of 5-6 days.

36. Aas, K. A. and Gardner, F. H. Survival of blood platelets labeled with chromium 51. JCI 37:1257, 1958.

37. Adelson, E., Rheingold, J. J. and Crosby, W. H.: Studies of platelet survival by tagging in vivo with P^{32}. J. Lab. & Clin. Med. 50:570, 1957.
Platelet half life of 2-3 days.

38. Leeksma, C.H.W. and Cohen, J. A.: Determination of the life span of human blood platelets using labeled diisopropylflurophosphonate. JCI 35:964, 1956.
Platelet half life of 5 days.

39. Odell, T. T., Jr. and Anderson, B.: Production and life span of platelets. In: The Kinetics of Cellular Proliferation, Ed. F. Stohlman, Jr. Grune & Stratton, Inc., New York, 1959, p. 278.
Platelet half life of 5 days using S^{35}.

40. Born, G.V.R. and Gillain, R. E.: Studies on the uptake of 5-hydroxytryptamine by blood platelets. J. Physiol. (Lond.) 146:472, 1959.

41. Feinendegen, N., Odartchenko, N., Cottier, H. and Bond, V. P.: Kinetics of megakaryocyte proliferation. Proc. Soc. Exp. Biol. & Med. 111:177, 1962.

42. Cohen, P., Gardner, F. H. and Barnett, G. O.: Reclassification of the thrombocytopenias by the Cr^{51}-labeling method for measuring platelet life span. NEJM 264: 1294, 1961.
Normal platelet T-1/2 was 2-3 days.

Vascular Hemophilia or Angiohemophilia:

43. Spurling, C. L. and Sacks, M. S.: Inherited hemorrhagic disorder with AHG deficiency and prolonged bleeding time (vascular hemophilia). NEJM 261:311, 1959.

44. Alexander, B. and Goldstein, R.: Dual hemostatic defect in pseudohemophilia. JCI 32:551, 1953.

45. Van Creveld, S., Jordan, F.L.J., Punt, K. and Veder, H. A.: Deficiency of AHF in women, combined with disturbance in vascular function. Acta Med. Scand. 151:381, 1955.

46. Schulman, I., Smith, C. H., Erlandson, M. and Fort, E.: Vascular hemophilia: Familial hemorrhagic disease in males and females characterized by combined AHG deficiency and vascular abnormality. Am. J. Dis. Child. 90:526, 1955.

47. Sanger, K. and Ramot, B.: Pseudohemophilia type B: Hereditary hemorrhagic diathesis characterized by prolonged bleeding time and decrease in AHG. Arch. Int. Med. 97:715, 1956.

48. Johnson, S. A., Monto, R. W. and Rebuck, J. W.: Nature of coagulation defect in pseudohemophilia B. J. Lab. & Clin. Med. 50:922, 1957.

49. Raccuglia, G. and Neel, J. V.: Congenital vascular defect associated with platelet abnormality and AHG deficiency. Blood 15:807, 1960.

50. Estren, S., Sanchez Medol, L. and Dameshek, W.: Pseudohemophilia. Blood 1:504, 1946.

51. Alexander, B. and Landevehr, G.: Thrombasthenia and thrombocytopenic purpura. NEJM 241:965, 1949.

52. Nilsson, I. M., Blombäck, M and Blombäck, B.: Willibrand's disease in Sweden. Acta Med. Scand. 164:263, 1959.

53. Nilsson, I. M., Blombäck, M. and von Franchen, I.: On an inherited autosomal hemorrhagic diathesis with AHG deficiency and prolonged bleeding time. Acta Med. Scand. 159:35, 1957.

54. Marle, J. B.: Vascular pseudohemophilia. In: Laboratory Medicine - Hematology. C. V. Mosby Co., St. Louis, 1962, 2nd Edition, p. 742.

Platelet Morphology: Adhesiveness, Clumping and Metamorphosis:

55. O'Brien, J. R.: The adhesiveness of native platelets and its prevention. J. Clin. Path. 14:140, 1961.
Describes a method for the determination of platelet adhesiveness and points out that alterations in local concentration of calcium and thrombin are the most crucial factors in initiating adhesiveness.

56. Nestel, P. J.: A note on platelet adhesiveness in ischemic heart disease. J.Clin. Path. 14:150, 1961.

57. Sharp, A. A.: Platelet (viscous) metamorphosis. In: Blood Platelets, Ed. S. Johnson. Little, Brown and Co., Boston, 1961, p. 67.

58. Rosenthal, R. L. and Vyas, S. B.: Morphological studies on the mechanism of viscous metamorphosis of platelets. From: Blood Platelets, Ed. S. Johnson. Little, Brown and Co., Boston, 1961, p. 89.

59. Haydon, G. B. and Corey, D. L.: Platelets in the thromboplastin generation test. Arch. Path. 71:615, 1961.
Describes the use of platelets in the T.G.T. to study the thrombopathies.

60. Hutter, R.V.P.: Electron microscopic observations on platelets from human blood. Am. J. Clin. Path. 28:447, 1957.

61. Sharp, A. A.: Viscous metamorphosis of blood platelets. Brit. J. Haemat. 4:29, 1958.

62. Bergsagel, D. E.: Viscous metamorphosis of platelets. Brit. J. Haemat. 2:130, 1956.

63. Schultz, H., Jürgens, R. and Hiepsier, E.: Die Ultrastruktur der Thrombozyten bei der Konstitutionellen Thrombopathie (v. Willibrand-Jürgens) mit einem Bertrag zur Submikroskopischen Orthologie der Thrombozyten. Thromb. et Diath. Haemat. 2:300, 1958.
Describes the abnormal granular architecture in electron microscopic studies of platelets in angiohemophilia.

64. Rebuck, J. W., Riddle, J. M., Brown, M. G., Johnson, S. A. and Monto, R. W.: Volumetric and ultrastructural studies of abnormal platelets. From: Blood Platelets, Ed. S. Johnson, Little, Brown & Co., Boston, 1961, p. 533.

65. Uluten, O. N.: The qualitative platelet diseases. From : Blood Platelets, Ed. S. Johnson. Little, Brown & Co., Boston, 1961, p. 553.

66. Czernobilsky, H. and Alexander, B.: Some qualitative and quantitative aspects of platelet function in normal, thrombocytopenic and thrombocytopathic states. From: Blood Platelets, Ed. S. Johnson. Little, Brown & Co., Boston, 1961, p. 565.

67. Braunsteiner, H.: Electron microscopy of blood platelets. From: Blood Platelets, Ed. S. Johnson. Little, Brown & Co., Boston, 1961, p. 617.

Essential Thrombocythemia:

68. Wessler, S., Cohen, S. and Fleischner, F. G.: The temporary thrombotic state. NEJM 254:413, 1956.

69. Ozer, F. L., Truax, W. E., Miesch, D. C. and Levin, W. C.: Primary hemorrhagic thrombocythemia. Am. J. Med. 28:807, 1960.

70. Di Guglielmo, G.: Eritsoleucemia e Piastrinemia. Folia Med. 1:36, 1920.

71. Uotila, U.: On hemorrhagic thrombocythemia. Acta Med. Scand. 95:136, 1938.

72. Reid, J.: Hemorrhagic thrombocythemia. Lancet 2:584, 1940.

73. Rowlands, R. A. and Vaizy, J. M.: Primary thrombocythemia. Lancet 2:1217, 1938.

74. Monto, R. W.: Essential thrombophilia. Arch. Int. Med. 90:54, 1952.

75. Fountain, J. R. and Losowsky, M. S.: Haemorrhagic thrombocythemia and its treatment with radioactive phosphorus. Quart. J. Med. 31:207, 1962.

76. Hardisty, R. M. and Wolff, H. H.: Haemorrhagic thrombocythemia: A clinical and laboratory study. Brit. J. Haem. 1:390, 1955.

77. Fanger, H., Cella, L. J., Jr. and Litchman, H.: Thrombocythemia. NEJM 250:456, 1954.

78. Spart, T. H., Bauer, D. and Melamed, S.: Hemorrhagic thrombocythemia, a blood coagulation disorder. Arch. Int. Med. 98:377, 1956.

79. Dameshek, W.: Some speculation on the myeloproliferative syndromes. Blood 6:372, 1951.

80. Gunz, F. W.: Hemorrhagic thrombocythemia: A critical review. Blood 15:706, 1960.

81. Gunz, F. W.: The myeloproliferative disorders. New Zealand Med. J. 57:428, 1958.

The Chemistry of Platelets:

82. Corn, M., Jackson, D. and Conley, D. L.: Components of blood necessary for clot retraction. Bull. Johns Hopk. Hosp. 107:60, 1960.
Demonstrated crucial requirement of metabolically active platelets for clot retraction.

83. Detwiler, T. C., Odell, T. T., Jr. and McDonald, T. P.: Platelet size, ATP content and clot retraction in relation to platelet age. Am. J. Phys. 203:107, 1962.

84. Troup, S. B., Reed, C. F., Marinetti, G. V. and Swisher, S. N.: Thromboplastic factors in platelets and red blood cells: Observations on their chemical nature and function in in vitro coagulation. JCI 39:342, 1960.

85. Waller, H. D., Löhr, G. W., Grignani, F. and Gross, R.: Über den Energiestoffwechsel normaler menschlichen Thrombozyten. Thromb. Diath. Haem. 3:520, 1959.
An excellent review of the energy needs, pathways of metabolism and active enzymes in normal human platelets from Marburg.