HEMOSTASIS AND BLOOD COAGULATION

A woman brings her 13-year old son to the pediatrician's clinic. The boy's problems go back to the neonatal period, when he bled unduly after circumcision. When his deciduous (baby) teeth first erupted, he bit his lower lip, and the wound oozed for 2 days. As he began to crawl and walk, bruises appeared on his arms and legs. Occasionally he would sustain a nosebleed without having had an obvious injury. By the time he was 3 years of age, his parents became aware that occasionally he would have painful swelling of a joint ---- a knee, shoulder, wrist, or ankle ---- but his fingers and toes seemed spared. The joint swelling would be accompanied by exquisite tenderness; the swelling would subside in 2 to 3 days. The patient's mother noted that when her son was a baby, she had noted what appeared to be blood in his stool, and the boy tells the doctor that twice his urine appeared red for 1 or 2 days.

The doctor ordered 4 tests:

1) Platelet count
2) Bleeding time
3) Prothrombin time
4) Clotting time

The patient's platelet count was found to be 260,000/μl of blood. This finding ruled out a deficiency or excess of platelets as the cause of bleeding.

Q.1 What is the role of platelets in hemostasis?

Q.2 What purpose is served by drawing blood into a solution of sodium citrate? What is the purpose of adding a solution of calcium chloride? Does the prothrombin time measure the intrinsic or extrinsic pathway of coagulation?

Q.3 With the given data, can you guess in general the site of the clotting abnormality in this patient?

intrinsic pathway

Q.4 Which clotting factors participate in the early steps of the intrinsic pathway of thrombin formation?

Q.5 It is possible that the patient is functionally deficient in one of two clotting factors. Which are these? Can you propose a way to determine which of these two clotting factors is deficient?

Q.6 Had the bleeding time been long, what diagnosis must be considered?

Q.7 How does the bleeding time help to further delineate the diagnosis?

CHAPTER 21 HEMOSTASIS (KEY)

1. Platelets accumulate at the site of vascular endothelial damage, adhere to the site of injury, and clump together to form a plug that can seal small injuries. Platelets also promote clotting by furnishing phospholipids (needed for clotting) and receptors (for plasma-clotting factors that potentiate the clotting process). (See pp. 353-356 in *Physiology* 3rd ed.)

   In the second test, blood is drawn into a solution of sodium citrate, the plasma is separated by centrifugation, tissue thromboplastin is added to the plasma, and a solution of calcium chloride is added to the mixture. The interval until the mixture clots is designated as the *prothrombin time*, and the normal value is usually 12 to 14 seconds. This patient's prothrombin time was 12.5 seconds.

2. Sodium citrate forms a soluble complex with plasma calcium ions, and it inhibits clotting. Addition of calcium chloride after addition of tissue thromboplastin restores these necessary ions and allows clotting to proceed. The prothrombin time is a measure of the extrinsic pathway of thrombin formation; it is called extrinsic because tissue thromboplastin is not a normal constituent of plasma. (See pp. 347-348 in *Physiology* 3rd ed.)

3. (a) Deficiency of any plasma constituents of the extrinsic pathway, except calcium ions (which are added from a bottle), and of fibrin-stabilizing factor (factor XIII), which acts to form covalent bonds between adjacent fibrin monomers. (b) The presence of an abnormal inhibitor of thrombin formation, for example, therapeutically administered heparin. (c) The presence of an extrinsic pathway clotting factor that is structurally abnormal; hence a clot cannot form within a normal time. The most common such defect is the presence of a species of fibrinogen that has an amino acid substitution that results in delayed clotting. (See pp. 341-348 in *Physiology* 3rd ed.)

   In the third test, blood is drawn into a solution of sodium citrate (as for the prothrombin time), the plasma is separated, and the clotting time is measured after sequential additions to the plasma of a suspension of phospholipids and a solution of calcium chloride. The term *partial thromboplastin* is derived from the fact that tissue thromboplastin is a complex of phospholipids and protein. In contrast to the prothrombin time, here only the phospholipid moiety of tissue thromboplastin is added to plasma. The normal partial thromboplastin time, as usually measured, varies from about 25 to 32 seconds. In this patient the partial thromboplastin time was 52 seconds.

4. B, Because the prothrombin time is normal, one must assume that the patient's clotting abnormality lies within the early steps of the intrinsic pathway of thrombin formation before the participation of Stuart factor (factor X), proaccelerin (factor V), prothrombin (factor II), and fibrin-stabilizing factor (factor XIII or fibrinogen). (See pp. 344-347 in *Physiology* 3rd ed.)

5. H, Hageman factor (factor XII), plasma prekallikrein, high-molecular-weight kininogen, plasma thromboplastin antecedent (PTA, factor XI), antihemophilic factor (factor VIII), and Christmas factor (factor IX). (See pp. 344-345 in *Physiology* 3rd ed.)

6. A, A deficiency of either antihemophilic factor (factor VIII) or Christmas factor (factor IX) would explain the patient's symptoms. To test this, the patient's plasma is mixed with that of patients with either classic hemophilia (factor VIII deficiency) or Christmas disease (factor IX deficiency). Determination of the partial thromboplastin time of the mixture will indicate which factor the patient lacks. In the present case, the partial thromboplastin time of the mixture of the patient's plasma with the plasma deficient in Christmas factor (factor IX) shortened the partial thromboplastin time to 28 seconds. This indicates that the patient was deficient in factor VIII, which was furnished by the plasma deficient in factor IX. (See pp. 344-348 in *Physiology* 3rd ed.)

   The fourth test, the bleeding time, is the time it takes for bleeding to stop after a small, deliberately incised wound; several different techniques have been described. Paradoxically, the bleeding time is usually normal in defects of blood coagulation. It was normal in the present instance.

7. D, The bleeding time measures hemostasis at the site of a minor injury to the blood vessel wall. It is not surprising, then, to learn that the bleeding time is abnormally long if too few platelets are present in the circulating blood (thrombocytopenia) or if the circulating platelets are abnormal (thrombocytopathia). The bleeding time is not expected to be long when the number of circulating platelets is greatly increased (thrombocytosis or thrombocythemia); the mechanism is not clear.

   In the present case, we know that the patient's plasma is deficient in factor VIII (antihemophilic factor).

8. I, In patients with classic hemophilia, the bleeding time is normal. In those with von Willebrand's disease, the bleeding time is long because the patient's plasma is deficient in von Willebrand factor, which is needed to promote adhesion of platelets to the edges of the vascular injury created by the deliberately incised wound. Von Willebrand's disease can be further distinguished from hemophilia, because its mode of inheritance is autosomal dominant and not X chromosome linked. (See p. 346 in *Physiology* 3rd ed.)