PATHOLOGIC HEMORRHAGE

RUSSELL L. HADEN, M.D.

From the Proceedings of the Interstate Postgraduate Medical Association of North America, October 19 to 23, 1931, pages 325-330.

Every clinician sees at times patients who bleed without injury or who bleed excessively from a minor injury, and hence are subject to pathologic hemorrhage. The proper treatment of this condition depends on the correct classification of the homorrhagic disease and, if possible, recognition of the underlying cause. All pathologic hemorrhage is the result of an abnormal permeability of the capillaries, an increased tendency of the blood to penetrate the vessel walls, or a disturbed coagulation of the blood.

Normally, as we know, the blood does not penetrate the endothelial barrier of the capillaries, and when vessel injury occurs, a clot is quickly formed, preventing an abnormal loss of blood. According to Howell, the factors in blood coagulation are as follows: (1) prothrombin, the precursor of thrombin, is held neutral in the blood plasma by antiprothrombin (heparin); (2) on adding zymoplastic substances (tissue juice, platelets) to blood, the thromboplastin (cephalin) which these substances contain neutralize the antiprothrombin leaving the prothrombin in an active state; (3) prothrombin combines with ionized calcium to form thrombin; (4) thrombin unites with fibrinogen to form fibrin, the clot. A disturbance in any factor in the chain may lead to abnormal hemorrhage.

The important factors in blood coagulation, then are: (1) *prothrombin*, derived partly, but not solely, from platelets; (2) *antiprothrombin*, formed probably in the liver; (3) *calcium*, derived from calcium salts in the blood plasma; (4) *fibrinogen*, a globulin formed principally in the liver; and (5) *thromboplastin*, a phospholipin derived from tissue juices or platelets. This summary emphasizes the great importance of the liver which is the source of antiprothrombin and fibrinogen and of the platelets formed in the bone marrow which supply prothrombin and thromboplastin.

Increased permeability of the endothelium is also a factor in many cases of abnormal bleeding. Some observers believe that in purpura this is by far the most important factor. Normal endothelium is not permeable to normal blood. When a lowering of the viscosity of the blood occurs, as in marked anemia, there is an increased tendency for the blood to penetrate the capillary walls. In numerous conditions the capillary wall becomes more permeable

through injury from toxic substances. Purpura developing in infections or following the use of drugs is due largely to damage to the capillary wall. Certain substances are almost specific toxins for endothelium. Classic examples of these are snake venom and bacillus Welchii toxin.

Abnormal hemorrhage may be dependent primarily upon an abnormality of the blood or blood-forming organs and in such case is spoken of as primary hemorrhagic disease. In this group are included: (1) hemophilia, (2) acute and chronic purpura hemorrhagica, and (3) hemorrhage of the newborn. More frequently abnormal bleeding is secondary to some disease in the course of which the blood or blood vessels are so altered as to lead to hemorrhage. Under the head of secondary hemorrhagic disease we include abnormal bleeding due to: (1) platelet deficiency in aplastic anemia, in intoxications such as benzol poisoning, in leukemia, and in some infections; (2) damage to capillary endothelium in Schönlein-Henoch's purpura, and in infections just as cerebrospinal or typhus fever, in drug rashes, such as that caused by turpentine, or with toxins such as snake venom; (3) a deficiency in fibrinogen due to liver disease such as cirrhosis or chloroform poisoning; (4) a decrease in ionized calcium in some cases of jaundice.

In many cases of secondary hemorrhagic disease more than one factor is operative.

A carefully elicited history and a thorough physical examination will often suggest the proper diagnosis in instances of abnormal hemorrhage, but the cases can be classified definitely only by special blood studies in addition to the routine counts and the hemoglobin estimation. The following examinations should be made in the case of every patient suffering from hemorrhagic disease:

1. *Determination of the coagulation time.* For this examination the blood must be obtained from the vein and must be free from admixture of tissue juices. The Lee and White modification of the Howell method[1] is the method of choice. Blood is obtained from the vein by means of a syringe and a fairly large needle. After the needle has been removed from the vein, 1 cc. of blood is run into a test tube 8 mm. in diameter, slightly dampened with salt solution. Clotting should be complete so that the tube may be inverted in from eight to ten minutes without altering the form of the clot.

2. *Determination of the prothrombin time.* The prothrombin time should be determined in all cases in which the coagulation time is prolonged. Varying amounts of 0.5 per cent calcium chloride solu-

tion are added to a set of tubes each containing 5 drops of oxalated plasma. The normals are as follows:

PROTHROMBIN TIME

Tube No.	1	2	3	4	5	6	7
Plasma (drops)	5	5	5	5	5	5	5
0.5% calcium chloride solution (drops)	2	3	4	5	6	7	8
Normal prothrombin time	6	8	8	10	10	12	12

3. *Determination of clot retraction.* A sample of blood is obtained by the method used for determining the coagulation time. Agitation of the specimen should be avoided as this will inhibit clot retraction. The specimen should be placed in an incubator at 37 degrees centigrade and observed for from twelve to twenty-four hours. Normally, a definite retraction is observed in one hour although the process is not complete until eighteen hours have elapsed. Retraction is often satisfactory at room temperature and may take place in a very short time. Pathologic blood may show no retraction even after days. Absence of clot retraction is usually associated with a diminution of platelets since the phenomenon is caused by some substance associated with the platelets.

4. *Enumeration of blood platelets.* An idea of the number of platelets present is obtained from a stained film properly made on a cover glass. The platelets may be satisfactorily counted by the Rees-Ecker method. The normal number is 250,000 to 300,000 per c. mm.

5. *Measurement of the bleeding time.* This determination is made by Duke's method. The lobe of the ear or the finger tip is punctured with a sharp needle or a blood lancet and the blood wiped up at regular intervals on filter paper, preferably every minute. Normally, bleeding ceases in less than three minutes, a bleeding time of over ten minutes being definitely prolonged. A diminution of platelets is nearly always present with a prolonged bleeding time.

6. *Capillary resistance test* (Leede-Rumpel test). A blood pressure band is placed on the upper arm and the pressure maintained at 100 mm. for from two to three minutes. In positive cases a crop of petechiae appears below the arm band and under it. The appearance of petechiae indicates an increased permeability of the capillary walls and is usually associated with a platelet deficiency.

In cases of jaundice the calcium time should also be determined and occasionally determinations of fibrinogen are indicated.

The typical clinical and blood findings in the various types of hemorrhagic disease are given below, and are illustrated by cases.

A. Primary Hemorrhagic Diseases

I. *Hemophilia:* An abnormal tendency to bleed, appearing early in life in the male sex and transmitted only by the unaffected females. The typical blood findings are an increased coagulation and prothrombin time with normal clot retraction, and a normal platelet count and bleeding time. The hemorrhagic tendency appears early in life; there is no bleeding from the mucous membranes but there are usually hemorrhages into the joints. The prolongation of coagulation time is seemingly due to a qualitative defect in the platelets, with an increased resistance to dissolution.

The following cases are typical examples of hemophilia:

Case 1. The patient was a boy, 6 years of age, who, following circumcision at one week, had had a severe hemorrhage from the wound which lasted for two days and was finally relieved by transfusion. He had had many hemorrhages into all the large joints and into the skin and subcutaneous tissues of various parts of the body but there was no bleeding from mucous membranes. The boy had been perfectly well except for the abnormal bleeding. The findings from the physical examination were negative except for swelling of the right elbow and the left knoe. X-rays of knees and elbows revealed joint changes characteristic of hemophilia. The patient had no brothers and there was no family history of hemorrhagic disease. The blood findings were as follows:

Red blood cells, 3,790,000; white blood cells, 7,000; hemoglobin, 76 per cent, differential count, normal. Coagulation time, 2 hours (slight clot formation at one hour); prothrombin time, 45 minutes. Clot retraction, normal. Platelets, 384,000. Bleeding time, 3 minutes. Capillary resistance test, normal.

This was a typical case of severe true hemophilia in the absence of familial hemorrhagic disease. The patient was made sensitive to sheep serum and at intervals small doses of serum were administered intradermally, to induce a mild anaphylactic reaction. No improvement followed this treatment.

Case 2. A boy, 13 years of age, has bled excessively since infancy upon receiving the slightest injury. He often bleeds from one to three weeks from an injury, and has had recurrent hemorrhages into the joints. His mentality is below par and there is a speech impairment which is probably due to a cerebral hemorrhage at birth. The patient was admitted to the hospital on account of pro-

longed bleeding following the extraction of a tooth. He was relieved by transfusion. There have been 13 known male bleeders in the family but no hemorrhagic disease has been found in the females.

The examination showed no petechiae. Examination of the joints gave negative findings. The tonsils were large and there was a slight general adenopathy.

The blood findings were as follows: Erythrocytes, 3,050,000; leucocytes, 10,500; hemoglobin, 56 per cent; differential count, normal. Coagulation time, 22 minutes. Prothrombin time, 22 minutes. Clot retraction, normal. Platelets, abundant. Bleeding time, normal. Capillary resistance test, normal.

II. *Purpura hemorrhagica (essential thrombocytopenia):* This disease may be congenital or acquired, and is found more commonly in women than in men. Hemorrhage from the mucous membranes may be the only evidence of the disease, but in addition, numerous petechiae are usually found on the body.

The characteristic blood findings are a normal or only slightly prolonged coagulation time but there is no clot retraction. The platelets are usually markedly diminished and the bleeding time much prolonged. The capillary resistance test is practically always positive.

The following cases are typical examples of purpura hemorrhagica:

Case 1. A female school teacher, 23 years of age, for two months had noticed large hemorrhagic areas and numerous petechiae on the skin following a slight injury or without injury. She had also had three attacks of nosebleed without apparent cause. Recently she had noted bleeding from the gums and also the mentrual flow had been excessive. There had been no previous infections.

The physical examination was entirely negative except for the hemorrhagic disease. There were many petechiae over the entire body and several large ecchymoses.

The blood examination showed: 3,250,000 red cells; 4,850 lucocytes; hemoglobin, 42 per cent; differential count, normal. Coagulation time, 15 minutes. Prothrombin time, not determined. Clot retraction, none. Platelets, 10,000. Bleeding time, 35 minutes. Capillary resistance test, positive.

This patient showed no improvement after viosterol and ultraviolet therapy, and numerous transfusions gave but little benefit. X-ray treatment to the spleen did not help. A few hours before the death of the patient, antivenin serum was administered with no change in the bleeding.

In a serious acute case of purpura hemorrhagica such as this a great increase in capillary permeability evidently occurs for which treatment avails little. Splenectomy in acute cases has usually ended fatally.

Case 2. A boy, seven years of age, two weeks before admission had had a rash which was considered German measles by his father, a physician. One week previous to his admission petechiae had developed. He had had some bleeding from the nose and gums.

On admission, in addition to the anemia which was evidently present ecchymoses and petechiae were visible over the entire body. The tonsils were enlarged and cryptic. The cervical and inguinal glands were enlarged. The spleen was not palpable.

The blood examination showed: Red blood cells, 4,000,000; white blood cells, 8,500; hemoglobin, 70 per cent. Differential count: polymorphonuclears, 38 per cent; eosinophiles, 4 per cent; lymphocytes, 52 per cent; monocytes, 6 per cent. Coagulation time, 10 minutes. Prothrombin time, 8 minutes. Clot retraction, none. Platelets, 32,000. Bleeding time, much prolonged. Capillary resistance test, positive. Blood transfusion brought about a rapid diminution of symptoms. Later a tonsillectomy was performed without abnormal bleeding. After three years the child is entirely well and has had no recurrence of the abnormal bleeding.

This is evidently a case in which the decrease in platelets was due to infection and was transitory. It is very probable that the infection was tonsillar in origin.

Case 3. For two years previous to admission, this patient, a boy, 9 years old, had had several severe nosebleeds lasting for hours in each instance. He bruised easily, large ecchymotic areas being formed, and some bleeding from the gums was present constantly. The patient was unable to attend school, and other activities were much limited by the abnormal tendency to bleed.

When the boy was admitted he was suffering from a nosebleed. There were many petechiae over the entire body. The liver and spleen were not palpable. The tonsils were large and infected.

The blood findings were as follows: Red blood cells, 3,440,000; white blood cells, 4,100; hemoglobin, 64 per cent. Differential count, normal. Coagulation time, 12 minutes. Prothrombin time, 10 minutes. Clot retraction, none. Platelets, 50,000. Bleeding time, much prolonged. Capillary resistance test, positive.

A splenectomy was performed, followed by a normal convalescence. The pathological diagnosis was chronic splenitis with an unusual eosinophilic infiltration.

The patient continued to have occasional nosebleeds which, however, were not severe. He gained in weight, improved rapidly, and was able to lead a normal life which he had not been able to do before splenectomy was performed.

The platelet count rose immediately after operation and then fell and remained low.

The counts are as follows:

	Platelets	Hemoglobin
Before operation	50,000	64 per cent
24 hours after operation	150,000	55 per cent
72 hours after operation	100,000	65 per cent
5 months after operation	64,000	80 per cent
2 years after operation	80,000	80 per cent

Case 4. A woman, 46 years of age, had had severe nosebleeds since the age of three years. At times she had unexplained hemorrhages from the gums, rectum and uterus and stated that for years she had passed blood with every stool. Two years previous to her admission linear streaks developed on the shins, followed by bleeding.

Upon physical examination no petechiae were found. The spleen was palpable but not large. There was no apparent infection. Gastric analysis showed no free hydrochloric acid.

The blood examination showed: Red blood cells, 1,980,000; white blood cells, 3,500; hemoglobin, 22 per cent. Differential count, normal. Coagulation time, 10 minutes. Prothrombin time, 10 minutes. Clot retraction, none. Platelets, 40,000. Bleeding time, much prolonged. Capillary resistance test, positive.

This patient is evidently an example of congenital platelet deficiency. A splenectomy should have been performed but the patient refused operation. Treatment had little effect on the blood condition and the clinical symptoms.

III. *Hemorrhagic disease of the newborn:* This condition which occurs only in infants during the first few days of life is characterized by spontaneous hemorrhages occurring usually not later than the second week of life. Relatively few careful blood studies have been made. The platelets seem to be normal but the coagulation and bleeding times were prolonged. Gelstron[2] found a prothrombin deficiency.

B. Secondary Hemorrhagic Disease

1. *Platelet deficiency:* In this condition the blood findings are much like those in purpura hemorrhagica. The following cases are typical examples:

Case 1 (aplastic anemia). A boy 15 years of age, had been well until one month before admission when his throat became sore and began to bleed. Soon afterwards hemorrhagic areas appeared on the skin. Three weeks previous to admission, toothache developed, the neck became swollen, and the gums began to bleed. During the past two weeks the patient had passed blood in stools and urine.

The physical examination revealed many petechiae, retinal hemorrhages and several badly infected carious teeth with enlarged glands on the side of the infection. The liver and spleen were not palpable. The capillary resistance test was positive. The urine was negative.

The blood examination showed: Erythrocytes, 800,000; leucocytes, 400; hemoglobin, 13 per cent. Differential count: Polymorphonuclears, 46 per cent; lymphocytes, 50 per cent; monocytes, 4 per cent. The coagulation period was twelve minutes. The prothrombin time was not determined. Clot retraction, none. Platelets, 10,000. Bleeding time, 45 minutes. Capillary resistance test, positive.

After transfusion the patient showed much improvement. The infected tooth roots were removed. The leucocyte count remained low, however, and the number of platelets did not rise above 60,000. Death resulted from lobar pneumonia which developed two weeks after the patient was admitted to the hospital. At autopsy the diagnosis of aplastic anemia was confirmed.

In this case the abnormal bleeding was due to the platelet deficiency which, however, was only a phase of the aplastic anemia.

Case 2 (tuberculosis of liver and spleen). This patient, a woman, aged 35 years, had had recurring attacks of fever accompanied by few other symptoms. On examination the liver was found to be much enlarged and the spleen a hand's breadth below the costal margin. An exploratory operation was performed and some tissue was removed. The pathologic picture was typical of tuberculosis. The avian type of tuberculosis was suggested but not proven. Several months later this patient returned complaining of bleeding from the kidneys, uterus, nose and gums. There were many petechiae. The liver and spleen were unchanged in size.

The blood findings were as follows: Red blood cells, 3,100,000; white blood cells, 6,300; hemoglobin, 55 per cent. Differential count, normal. Coagulation time, twenty-five minutes. Prothrombin time, not determined. Clot retraction, none. Platelets, none. Bleeding time, much prolonged.

This patient responded well to transfusion and the abnormal bleeding ceased. The platelet deficiency here was probably due to the tuberculous infection of the spleen.

II. *Damage to capillary endothelium:* In this condition abnormal hemorrhage occurs without alteration in the blood.

Case 1 (Henoch-Schönlein's disease). For the past year a clerk, 25 years of age, had had recurring attacks of abdominal pain accompanied by nausea and vomiting. During each attack the large joints had been painful and red splotches had appeared on the extremities. After the first attack of pain the appendix was removed but no improvement resulted.

On admission of the patient a generalized petechial rash was present. Several joints were painful and tender on palpation. The tonsils were of moderate size. Evidence of chronic prostatitis was found and there were several infected teeth. The capillary resistance test was negative.

The blood examination showed: Red blood cells, 5,590,000; white blood cells, 11,600; hemoglobin, 102 per cent; differential count, essentially normal. Coagulation time, 9 minutes. Prothrombin time, not determined. Clot retraction, normal. Platelets, 290,000. Bleeding time, five minutes.

Following tonsillectomy and the removal of the infected teeth the patient gained 40 pounds in weight and made a complete recovery. In this case the abnormal bleeding was doubtless due entirely to increased permeability of the capillaries.

III. *Fibrinogen deficiency:* Abnormal bleeding due to a deficiency in fibrinogen is uncommon and occurs only in extreme hepatic disease. Fibrinogen is an exceedingly labile substance which seemingly is easily mobilized. A slight injury to the liver or to other tissues causes a rapid and usually marked increase in fibrinogen. Extensive hepatic injury, however, causes a decrease in the circulating fibrinogen.

IV. *Altered coagulation time due to decreased calcium ions in jaundice:*

Case 1 (obstructive jaundice). A woman, 78 years of age, had a chronic, progressive, painless jaundice. Mild diabetes and hypertension had been present for many years. On admission marked jaundice was present, accompanied by extreme itching. The liver was only slightly enlarged and the gall bladder was not palpable. The icterus index was 100.

The blood examination showed: Erythrocytes, 4,460,000; white cells cells, 9,400; hemoglobin, 78 per cent. Differential count, normal. Coagulation time, 35 minutes. Prothrombin time, 5 minutes. Clot retraction, normal. Platelets, 440,000. Bleeding time, not determined.

An exploratory operation disclosed gall stones with blockage of the common duct. The patient had been given calcium chloride intravenously peroperatively and did not bleed excessively following operation.

The convalescence was satisfactory although prolonged. The jaundice cleared very slowly. Three weeks after operation the patient had multiple hemorrhages from the intestines from which she died.

In this case the hemorrhagic disease was evidently due to the jaundice and liver disease. The coagulation time was much prolonged, with normal prothrombin time.

Treatment

Primary hemorrhagic disease. The treatment of *hemophilia* is most unsatisfactory. The transfusion of blood will often stop the bleeding for a time. In some cases much improvement has been brought about by making the patient serum sensitive, preferably to sheep serum and then by giving serum intradermally to induce a mild anaphylactic reaction. I have not seen any striking results from this method. More recently Birch[8] has suggested a new line of treatment with ovarian extract.

The acute phases of *purpura hemorrhagica* usually respond well to transfusion, but the platelets supplied by the normal blood live only for three or four days so that bleeding usually begins again even after relief has been obtained by the transfusion. Often, however, the patient can be tided over the acute phase of the disease by transfusion. Since in many cases infection seems to be a very definite etiologic factor in idiopathic thrombocytopenic purpura, the removal of infection is most important.

It is well known that untraviolet light and vitamin D definitely increase the platelet count; therefore ultraviolet therapy and viosterol should be used in every case.

In chronic cases of purpura due to a platelet deficiency, splenectomy must always be considered. Excellent results have been obtained by this procedure in properly selected cases. Deep x-ray therapy may also be tried. The use of serum and other thromboplastic agents is of little value in purpura and hemophilia.

Hemorrhagic disease of the new born usually responds quickly to normal blood given intramuscularly. If the bleeding does not stop after the intramuscular administration of blood, transfusion should be employed. I once transfused through the longitudinal sinus, a new-born baby who was bleeding constantly from the point of separation of the umbilical cord. Blood given intramuscularly and

other thromboplastic agents had no effect. The bleeding ceased after a few cubic centimeters of citrated blood had been run in, and did not recur.

In *secondary hemorrhagic disease* the primary cause should be treated or removed if possible, as well as the immediate cause of the bleeding. If the bleeding is due to a platelet deficiency the treatment is the same as that indicated in idiopathic thrombocytopenic purpura. Antivenin serum has been used to decrease the capillary permeability. A deficiency in fibrinogen is best treated by transfusion. In cases in which there is a deficiency of ionized calcium, the oral or intravenous use of calcium is indicated, in addition to transfusion.

Summary

Cases of pathologic hemorrhage can usually be correctly classified if the various factors concerned are thoroughly studied. These for the most part are simple tests which can be done in every well-equipped laboratory. The special tests should always include: coagulation time by a correct method, retractility of the clot, platelet count, prothrombin time if the coagulation be prolonged, bleeding time and tourniquet test for capillary resistance. The different types of hemorrhagic disease present quite typical findings when grouped on the basis of these tests.

It should always be determined whether the patient is suffering from primary hemorrhagic disease or secondary hemorrhagic disease. The primary cases constitute separate clinical entities. The exact factor on which the secondary cases depend can usually be found.

The indications for the proper treatment in each case are usually clear-cut if the disease has been properly studied and classified.

References

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