Pathophysiology of blood disorders 2

Clinkic Medicine and Integrated Science Author: Howard Franklin Bunn, John K. Astaire ISBN: 0071713786 / 9780071713788 Purchase Investors Foreword 1. Introduction to the blood and hematopoetic tissues of John K. Astaire 2. Hemathoposis David Scudden and John C. Astaire 3. Review of anemia by H. Franklin Bunn 4. Anemia due to bone marrow failure or infiltration by H. Franklin Bunn 5. Iron Homeostasis: Deficit and overload by H. Franklin Bunn and Matthew M. Heaney 6. Megaloblast anemia H. Franklin Bunn and Matthew Heaney 7. Anemia associated with chronic diseases by H. Franklin Bunn 8. Thalassemia H. Franklin Bunn and David G. Nathan 9. Sickle cell disease H. Franklin Bunn 10. Hemolytic disorders of the membrane of red cells and the metabolism of red cells H. Franklin Bunn and Samuel E. Lux 11. Acquired hemolytic anemia H. Franklin Bunn 12. Erythrocytosis H. Franklin Bunn 13. Review of Gemostas H. Franklin Bunn and Bruce Fury 14. Platelet disorders by H. Franklin Bunn and Bruce Fury 15. 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Antin Answers The Issues Index Go to the Basic Content A Brief Full Color Review of The Mechanisms of Blood Diseases and Disorders - based on Harvard Medical School Hematology Course 4 STAR DOODY'S REVIEW! It's an excellent book. Deceptively small but packs wallop. The emphasis on principles rather than practice is welcome.... The text is clear, concise and surprisingly appropriate for what could be a very dense and dry discussion. I couldn't put this book down and read it completely in one sitting. When was the last time someone found a hematology textbook so riveting? --Doody's Review Service hematological pathophysiology is a well-illustrated, easy-to-absorb introduction to the physiological principles underlying the regulation and function of blood cells and hemostasis, as well as the pathophysiological mechanisms responsible for the development of blood diseases. Thanks to a strong emphasis on key principles, the book covers diagnosis and management primarily within the pathogenesis. Written by a world-renowned clinician/educator at Harvard Medical School, pathophysiology features the content and organization of the organization the second year of students at the school was offered in the hematology course. The book is logically divided into four sections: anemia and disorders of red blood cells, disorders of hemostasis and thrombosis, disorders of leukocyte and transfusion medicine; it opens with an important overview of blood and hemathopoetic tissues. Features brief, in point coverage that reflects the current medical education More than 200 full-color photos and visualization of the mechanisms of diseases and diseases of the blood Each chapter includes the purpose of teaching and self-assessment issues Numerous tables and charts encapsulate important information includes feedback from 180 Harvard medical students, which reviewed the first project -- so you know you're studying the most relevant materials of J. Ben Davoren, MD, PhD, s Sunny Wang, MD NORMAL STRUCTURE -- is an extremely complex fluid consisting of both formed elements (red cells, white cells, platelets) and plasma. Red blood cells (erythrocytes) are the most common forming elements that carry oxygen to the body's cells through their main component, hemoglobin. White blood cells are usually present at about 1/700th in the number of red blood cells and function as mediators of the immune response to infection or other stimuli of inflammation. Platelets are formed elements that are involved in coagulation. Plasma is mainly water, electrolytes and plasma proteins. Plasma proteins, the most important in blood clotting, are factors of blood clotting. Because blood circulates throughout the body, changes in normal blood physiology - either formed elements or plasma proteins - can have widespread negative effects. FORMED ELEMENTS OF BLOOD Anatomy A. Bone Marrow and Hematopoiesis Although mature blood cells are very different from each other in both structure and function, all these cells develop from the general hematopoietic stem cell population that is found in the bone marrow. The development process is called hematopoise and is a huge metabolic challenge for the body. More than 100 billion cells are produced every day. This makes the bone marrow one of the most active organs in the body. In adults, most of the active bone marrow is found in the vertebrae, sternum and ribs. In children, bone marrow is more active in long bones. The process of differentiation from stem cells to mature red blood cells, granulocytes, lymphocytes, monocytes or platelets is shown in figure 6-1. It is not clear what early events lead to stem cell division along a certain pathway, but many different peptides, called cytokines, are clearly involved (table 6-1); See also Chapter 3. Perhaps because mature white blood cells have a much shorter period of semi-life in circulation, white blood cell precursors usually outperform the precursors of red blood cells in a 3:1 ratio in the bone marrow. FIGURE Hematopoiesis: the development of formed blood cells from bone marrow stem cells. Cells below the horizontal line is in normal peripheral blood. The basic cytokines are shown to stimulate each cell line to differentiation. (EPO, erythropoietin; TPO, thrombopotin; CSF, the colonial-stimulating factor; G, granulocyte; M, macrophag; IL, interleukin; SCF, stem cell factor.) See the details in table 6-1. (Reprision, with permission, from Ganong WF. Review of Medical Physiology, 22nd Ed. McGraw Hill, 2005.) TABLE 6-1 Cytokines, which regulate hematoposes. The main hormone that stimulates the production of red blood cells (erythropoietis) is erythropoietin. This peptide is produced by the kidneys and regulates the production of red blood cells by the feedback system: when the level of hemoglobin in the blood drops (anemia), oxygen delivery to the kidneys drops and they produce more erythropoietin, resulting in the brain producing more red cells. When hemoglobin levels rise, the kidney produces less erythropoietin and the brain has fewer red cells. For white blood cells, the situation is more complicated. The most common cells are granulocytes, so named because their cytoplasm are filled with pellets. Of these, neutrophils are the most common and most important cells in the production of inflammation. The production of granulocytes (myelopoeza) can be affected by many cytokines at different stages of development. Figure 6-1 shows that interleukin-3 (IL-3), the granulocyte colony stimulant factor (G-CSF), and the colonocyte-macrophagion of the colony stimulant factor (GM-CSF) are the most important. All three proteins were cleaned, sequenced and cloned. The last two proteins are used therapeutically. Unlike G-CSF, GM-CSF also stimulates the maturation of another line of white blood cells, the monocyte-macrophages line. These cells are part of the immune system as well (e.g. ingest foreign bacteria) and can be found in the skin and other tissues, not just blood. Their function, along with the function of B- and T-lymphocyte populations, is more fully discussed in Chapter 3. Platelets are not cells, but fragments of larger multi-nuclear cells in the bone marrow called megacariocytes. Platelets are crucial for normal blood clotting. The production of platelets is also stimulated by several cytokines, but depends mainly on the action of IL-3, IL-6 and IL-11 and thrombopoethin (TPO). This peptide is produced by the liver, kidneys, skeletal muscles and bone marrow strobe. One of the models of thrombopoese suggests that the production of TPO occurs at a constant rate. However, the amount of this hormone to freely interact with platelet precursors rises and falls, probably as a result of the absorption by TPO receptors (c-Mpl) on existing platelets in the blood. Thus, a low number of platelets (with less c-Mpl mass) stimulates thromboposis as a result of increased circulating levels of TPO. The second model suggests that low platelet levels may cause an increase in TPO production in bone marrow cells, using various cytokines, including platelet growth factor (PDGF) and fibroblast growth factor (FGF). These two are two are not necessarily mutually exclusive. Inflammation can also lead to plateletosis through IL-6-mediated increase in liver TPO production. For all its complexity and metabolic activity, there is a huge regulation of the bone marrow through the interaction of different cytokines. Typically, only the most mature elements in each cell line are released into the general circulation, demonstrating this exquisite control over development. To maintain the circulating quantities of each formed element at the agreed levels at which they are located, complex negative feedback mechanisms must work. The study of the feasibility of the development of blood cells is best conducted with a microscope, using a thin blood smear (Figure 6-2). Modern technical equipment, which can optically sort cells by size and various optical reflective parameters, provides important information, especially as to whether the cell numbers are from conventional ranges (table 6-2). However, a microscopic blood smear examination, usually using Wright's spots, provides additional information once an anomaly is detected and should always be done when a blood disorder is suspected on a clinical basis. FIGURE 6-2 Normal thin blood smear, seen at low power (40×) with Wright's stain. Red blood cells prevail and can be seen as thin discs with central pallor (see text). Platelets are numerous small dark bodies. Large cells with lobulated nuclei are mature neutrophils. Lymphocytes and monocytes are not present on this smear. TABLE 6-2 Normal values obtained by automatic blood count form elements of blood. Physiology A. Erythrocytes Mature red blood cells are double disk-shaped cells filled with hemoglobin that function as an oxygen-carrying component of the blood. Unlike most other cells, they have no nuclei in maturity; their nuclei are produced in the final stages of red blood cell development. The presence of red blood cells with nuclei in the peripheral blood smear indicates the condition of the underlying disease. Normal red cells have a diameter of about 8 microns, which is larger than the smallest capillaries. However, their two-see shape gives them enough flexibility to slip through small capillaries and deliver oxygen to the tissue. After extrusion from the bone marrow, individual red blood cells function for 120 days before they are removed from the bloodstream of the spleen. In a typical blood smear (stained by Wright's stain), red blood cells dominate the microscopic field, and their bi-barrel shape of the disc resembles the shape of a doughnut. There is a thicker outer rim that appears red due to the hemoglobin present and the area of central pallor where the disc is thinner. Young red blood cells (reticulocytes) appear more pigeon (basophilic) because they still contain some ribosomes and mitochondria in a few days after the cores have been extruded. Hemoglobin is the most important substance in red blood cells. This protein is actually a tetramer made from β protein subunit subunit two α protein subunicies (in a normal adult haemoglobin called hemoglobin A). Each β- or α-sub-unit contains the actual oxygen-binding part of the complex, heme. Heme is a compound whose central important atom is iron; it is this atom that actually binds oxygen to the lungs and then releases it into the body's tissues. Low levels of haemoglobin in the blood, from various causes (see later discussion), is anemia, the most common blood disease. B. Granulocytes: Neutrophils, Eosinophils and basophilic granulocytes are the most common white blood cells; of these, the most common are neutrophils, followed by eosinophils and basophils (table 6-2). In development, all three types are similar: as their nuclei grow older, they become more tangled and multi-layered, and each of them develops a cytoplasm filled with pellets. These pellets contain various enzymes, prostaglandins and mediators of inflammation, and specific factors depend on the type of cell. Early precursor cells for each type of granulocytes (explosions) are indistinguishable from microscopic bone marrow examination, but under the influence of different cytokines they become morphologically different types of cells. Basophils contain very dark blue or purple pellets when painted with either a Giemsa or a Wright stain. Basophilic pellets are large and usually obscure the core because of their density. Basophils usually act in hypersensitivity responses (as described in Chapter 3). However, their number can be increased in non-sensitivity diseases such as chronic myeloid leukemia. Eosinophils contain large, strikingly eosinophil pellets (painting red with a spot of Wright or Gims). The nuclei of eosinophils are usually bile. Typically, eosinophils function as part of an inflammatory response to parasites too large to be absorbed by individual immune cells. They are also involved in some allergic reactions. Neutrophils contain pellets that are neutrophilic (i.e. neither eosinophilic nor basophilic). Although they predominate in the blood, their main function is actually in the tissues; they must leave blood inserting themselves between the endothelial vascular cells to reach the sites of injury or infection. Their pellets contain very active enzymes such as myeloperoxidase, which, along with free radical oxygen ion produced by membrane enzymes such as nicotinamide adenine dinucletide phosphate (NADPH) oxidase, kill bacteria that neutrophils ingest through endocytosis or phagocytosis. They are the first line of protection against bacterial pathogens, and a small amount of them (leukopenia) directly leads to a high incidence of significant bacterial infections (see later discussion). Of all the cells produced by the bone marrow, neutrophils make up the largest proportion. their life in the blood, only 8 hours, is much shorter than that of any other cell type. Evidence of their importance and their short survival is it is manifested because the study of blood smear under a microscope in a patient with active infection can show not only an increase in the number of mature, multibrow neutrophils (neutrophilia), but also an increase in the number of less mature cells. These less mature cells, released from a large storage pool in the bone marrow, are called strips and have a characteristic subshoe-shaped nucleus that is not yet fully lobulated. The phenomenon of finding these cells in the peripheral blood is called the left change of the line of granulocytes. C. Other white blood cells: monocytes and lymphocytes of both monocytes and lymphocytes arise from a common stem cell. It is the widespread pluripotential ability of stem cells to differentiate into these cells in addition to granulocytes, red blood cells and platelets, making bone marrow transplantation a therapeutic option for immune system disorders and malignancies. Monocytes have a very long lifespan, probably a few months, but spend only about 3 days in circulation. They are mainly found in tissues and act there as immune cells that absorb (phagocytosis) bacteria and can then present the components of these bacteria in lymphocytes in such a way that further strengthen and clarifies the immune response (Chapter 3). When assessing blood smears, monocytes are the largest cells seen, with irregular but not multi-probaic nuclei and pale blue cytoplasm, often with prominent vacuoles. Precursor lymphocytes leave the brain early and require extramedalular (outside the bone marrow) maturation to become normally functioning immune cells in the blood or lymphatic system (Figure 6-3). Their crucial role in recognizing I am against not myself and in modulating almost all aspects of the immune response described in Chapter 3. In microscopic blood smear examinations, lymphocytes are small cells, slightly larger than red blood cells, with dark nuclei essentially filling the entire cell; only the thin edge of the light blue cytoplasm is usually seen. The pellets are rare or non-existent. FIGURE 6-3 The development of the immune system from the common stem cell of the bone marrow. (Reprision, with permission, from Ganong WF. Review of Medical Physiology, 22nd Ed. McGraw Hill, 2005.) D. Platelets are the smallest formed elements in the blood. These are fragments of larger, multi-celled cells, which are the largest discrete components of bone marrow (megacariocytes), but platelets do not have their own nuclei. Most platelets remain in circulation, but a significant minority are trapped in the spleen; this phenomenon becomes important in various immune-mediated reductions in platelets (thrombocytopenia; see later discussion). Under normal platelet counts, they have a semi-seven circulation of about 10 days. In cases of thrombocytopenia, their semi-shift decreases, as they are consumed in routine maintenance of vascular integrity. Platelets integral components of the coagulation system. Coagulation. The membranes provide an important source of phospholipids (PLs), which are essential for the function of the coagulation system proteins (Figure 6-4), and contain important receptors that allow attachment to endothelial cells (platelet adhesion), so that candle platelets can be formed in response to damage to blood vessels. This prevents further blood loss after injury and limits the coagulation response to the trauma scene, rather than allowing the clotting to continue improperly. FIGURE 6-4 Coagulation and thrombolytic systems showing balanced activity between them. Cytoplasm is also important for platelet function, especially intracellular dense pellets and alpha pellets. The phenomenon of platelet activation is also called degranulation and can be triggered by the effects of platelets on the activated platelet factor of thrombosis thrombosis, adenosine 5 -diphosphate (ADP), or collagen. This last reaction is probably the most important occurring when collagen, usually in the basement membrane below the endothelial cells, is exposed to blood after injury. Activation of platelets can also be caused by exposure to platelet activation factor (PAF) (phospholipid cytokines, thrombocan A2, serotonin and epinephrine. During platelet activation, dense and alpha pellets release additional platelet activators such as ADP, and platelet factor 4, which can also bind to endothelial cells. Finally, up to a flat shape, allowing adequate coverage of the site of damage to the vessel. The last step in platelet activity is platelet aggregation, where platelets stick to each other, tightening the fork of platelets. When examining blood swab platelets are small, irregularly shaped blue or purple granular bodies. CHECKPOINT 1. What is the ratio of red blood cells to white blood cells in the blood? 2. What is the number of cells produced daily by the bone marrow? 3. What are the different blood elements formed and how can they be distinguished and their subtypes? COAGULATION FACTORS - The Anatomy of COAGULATION SYSTEM Coagulation System, schematically 6-4, is a very complex, regulated interaction between cells and plasma proteins. The coagulation system provides immediate activation when bleeding control (hemostasis) is required and limits its activity to the place of blood loss. Otherwise, coagulation can occur throughout the circulatory system, which would be incompatible with life. Key components are platelets (discussed earlier), endothelial cells (lining blood vessels), other tissue factors (TF)-bearing (TF)-bearing and coagulation factors, which are plasma proteins. The end result of the activated coagulation system is the formation of a complex of cross molecules fibrin and platelets that stop hemorrhaging after injury. To maintain a well-regulated balance between prothrombotic and antithrombotic factors, a complex coagulation system provides multiple control points (Figure 6-4). Coagulation factors generally do not circulate in active forms. Most of them are enzymes (proteas serin) and remain at rest until they are needed. This is achieved by the presence of other enzymes (other proteases in the coagulation system) that can break down inactive factors into active ones. All factors have Roman numerals, and inactive forms are written without annotation (e.g. Factor II, also known as prothrombin). Activated forms of factors are indicated by the letter A (e.g. IIa factor, also known as thrombone). Most clotting factors are made by the liver, but the factor XIII comes from platelets and factor VIII is made of endothelial cells. Factors II, VII, IX and X are particularly important factors (table 6-3) because they all depend on the liver enzyme γ carboxylase. Gammacarboxylase depends on vitamin K, and oral warfarin anticoagulant acts by interfering with the activity of vitamin K. Two anticoagulant proteins, protein S and C protein (see later discussion), also depend on vitamin K. TABLE 6-3 Coagulation factors of plasma. The physiology of hemostasis is divided into three main processes: primary hemostasis, secondary hemostasis and fibrinalis. Primary hemostasis includes vasoconstriction and platelet adhesion and activation in places of endothelial injury. Collagen and thrombone activate platelets, leading to an increase in intracellular calcium, platelet secretion and activation of various signaling pathways. Secondary hemostasis is the process of formation of fibrin. The classic coagulation cascade, which includes internal, external and common pathways, better describes coagulation in vitro, as has been tested by coagulation analyses: activated partial time thromboplastin (aPTT) and prothrombin time (PT). The cell clotting model replaced the coagulation cascade as a more accurate depiction of the in vivo clotting process (Figure 6-4). Secondary hemostasis is further divided into three overlapping phases: initiation, amplification and distribution. Initiation occurs on the surface of injured cells. It starts with the release of TF injured cells. TF, also called thromboplastin, is a lipid-rich protein material that is exposed to plasma when the vascular wall is damaged. It directly activates Factor VII, forming a TF-VIIa complex that activates both factor IX and X factor. (IIa). Trombon, a serene protease, breaks down the ubiquitous plasma protein fibrinogen into fibrin monomers, small insoluble proteins that can polymerize with each other to form complex fibrin; however, the amount of thrombin produced at the site of the cell injury is not enough in itself to obtain enough fibrin to stabilize the platelet cork. Amplification, unlike the initiation phase, occurs on the platelet surface. During this phase, the thrombone produced in the initiation phase activates platelets and clotting factors V, VIII and XI found on the platelet surface. Factor VIII is usually combined with the von Willebrand factor (vWF), a protein that allows platelets to stick to endothelial cells. Tromborin activates factor VIII by releasing it from vWF. It also activates V and XI, allowing them to communicate with the platelet surface. The XIa factor is then catalysis of activation IX in IXa, providing an additional factor IXa on the platelet surface. Distribution involves activated platelets recruiting other circulating platelets to the site of ship damage and forming two large complexes: thenasis and prothrombinase, which are crucial for the production of fibrin. Factors VIIIa and IXa form a tenase complex on the surface of platelets in the presence of LP and calcium (VIIIa-IXa-Ca2-PL). Together they activate the X factor on the surface of the platelets. The Xa factor then forms a prothrombinaz complex with the Va factor on the platelet surface, again in the presence of LP and calcium (Xa-Va-Ca2-PL). This complex catalysis of the fission of prothrombin (II) into thrombin (IIa) and can convert several molecules into complex. As activated platelets gain more circulating platelets to the site of damage, a critical mass of platelets leads to a surge in thrombin generation. This, in turn, leads to sufficient fibrin formation to stabilize the platelet cork. This fibrin polymer further hardens the chemical cross compounds catalyzed by the XIIIa factor, which itself is activated by thrombo as it is activated. The XIIIa factor also includes the antiplasmin No.2 clot to protect it from fibrinolytic proteases. Fibrinolise involves the process of breaking fibrin into degradation products. Plasmin is the main catalytic enzyme in the process. It is a serum protease that breaks down fibrin, leading to the breakdown of the clot and creating fibrin degradation products that suppress thrombone. Tromborin, which works in negative fashion feedback, actually helps catalyze the formation of plasmin from the inactive precursor protein, plasminogen. Plasminogen can also be split by a tissue plasminogen activator (t-PA) to form plasmin; t-PA and associated proteins are used clinically to break down blood clots, which are formed in coronary arteries in patients with a new myocardial infarction, as well as in the brain in patients with a new stroke. Fibrinolysis inhibitors include a plasminogen activator inhibitor and antiplasmin. In addition to the fibrinolitic track, checks the coagulation coagulation system anticoagulant system) also include various feedback loops and inhibitors. The Xa factor is associated with another plasma (and lipid) protein called tissue factor inhibitor (TFPI). TFPI not only inhibits the further activity of the Xa factor itself, but also prevents Xa from binding to the platelet surface, and the combination of the Xa and TFPI factor significantly inhibits the TF-VIIa. In addition, downstream prothrombinase activity can only be sustained if the initial injury continues to generate enough factors IXa and VIIIa (in the form of a tenase complex) to activate more X factor on platelet surfaces. Other anticoagulants include a group of coagulation inhibitors. They consist of antithrombin (AT), protein S and protein C (see later discussion). AT is a protease inhibitor and physically blocks the action of seroine protease in the coagulation system. Its activity is enhanced up to 2,000 times by heparin. Protein C activated by throbin breaks down the Va factor into an inactive form, so that the complex of prothrombinase cannot break down prothrombine (II) into thrombin. Protein C requires protein S as a cofactor. This complex also inactivates the VIIIa factor. LABORATORY TESTING OF THE COAGULATION PROCESS Assays are available to determine both the absolute level and activity of each of the coagulation factors, but in practice there are two common tests in the test tube coagulation function, both reported as seconds needed to form the clot: PT and APTT. The tests are designed so that the results will be extended from the normal range in various pathological conditions, but significant changes in the pathway of coagulation inevitably lead to changes in both tests due to the numerous interactions involved. PT evaluates the external TF-dependent and common pathways of the classical cascade of coagulation and is used clinically to monitor the effects of warfarin. Since all levels of vitamin K-dependent factor are reduced by warfarin, eventually APTT will also become abnormal with high enough doses; but Factor VII has the shortest period of semi-individuality of these factors, so its levels fall first. Because of its critical role in blood clotting, thrombone is a major factor whose activity needs to be reduced to achieve and maintain therapeutic anticoagulation. APTT evaluates internal non-TF-dependent and common pathways and is extended most easily when there are decreases in factor VIII or factor IX activity, regardless of whether these factors are present at low concentrations or present in normal concentrations, but are actively suppressed by other molecules. APTT is also very sensitive to the presence of heparin associated with AT and is used to monitor the anticoagulant effects of non-fractional heparin. Low molecular weight heparins (specific purified subset of unfractional heparin) in combination with AT inhibit the Xa factor. In low molecular heparin doses, it is usually common prevention or treatment of thrombosis, aPTT will not be extended (at least not in the usual therapeutic range for unfractional heparin), despite strong evidence of the effectiveness of anticoagulation if the Xa activity factor is measured directly. CHECKPOINT 4. What are the clotting factors of vitamin K and the organ in which they are synthesized. 5. What are the two main complexes on the surface of activated platelets that are essential for a surge in thrombin production? Describe the coagulation factors that form these complexes, and what complexes specifically activate. 6. What is the main catalytic enzyme in fibrinilism? Name two fibrinilism inhibitors. BLOOD DISORDERS FORMED ELEMENT DISORDERS Disorders of red cells, white cells and platelets are separated for discussion because one or the other proved to be the most abnormal during laboratory tests. However, due to the clonal nature of hemathopose, many disorders affect all formed elements of blood. This is perhaps best demonstrated in the explosive crisis phase of chronic myeloid leukemia, in which most of both myeloid and lymphoid cells in the blood can be shown to express identical permutations of genes, called the bcr-abl or Philadelphia chromosome, which originated in one abnormal precursor cell. 1. Red cell disorders there are many anomalies of red cells, but the main ones are different anemia. Anemia is defined as abnormally low concentration of haemoglobin in the blood. There are several classification methods, but existing systems are based on the size and shape of red cells. In normal people, red blood cells have a single size and shape, and an automatic blood test shows an average corpuscular volume (MCV) of about 90 ml, which is the estimated volume of a single cell. Automated systems typically report red cell abnormalities like changes in hemoglobin concentrations, red cell number, and MCV. Small cells (low MCVs) are called microcytes, and cells are more conventionally called macrocytic cells. The relative non-uniformity of cellular forms (puilocecytosis) or size (anisocytosis) can further help in the subclassification of red blood cell disorders. The morphological classification of anemia is set out in table 6-4 and figure 6-5. In general, microcytastic anemia is caused by anomalies in the production of hemoglobin, either by the number of hemoglobin molecules per cell, or by the type of hemoglobin molecules (hemoglobinopathy). Iron deficiency anaemia as a result of chronic blood loss and thalassemia are examples of microcytic anemia. TABLE 6-4 Morphological classification and common causes of anemia. FIGURE 6-5 Thin blood smear the appearance of red blood cells in various morphological types of anemia. (1, Poikilocytosis (shape change); 2, anisocytosis (size change).) (Repainting, with permission, from Chandrasoma P et al. Brief Pathology, 3rd ed. published by Appleton and Lange. Image © copyright McGraw-Hill, McGraw-Hill, 1998 Macrocytastic anemia reflects either abnormal nuclear maturation or a higher proportion of young, large red cells (cyticulocytes). When the nuclei of maturing red cells seem too young and large for the amount of hemoglobin in the cytoplasm, macrocytical anemia is called megaloblast. These anemias are most often due to vitamin deficiency (vitamin B12 or folic acid) or drugs that interfere with DNA synthesis. Abnormal nuclear maturation can also be associated with clonal spread in the bone marrow, producing prelucemics called myelodysplastic syndromes. Normocytic anemia can be caused by several causes: a decrease in the number of precursors of red cells in the bone marrow (primary deficiency is called aplastic anemia, replacement of bone marrow elements with cancer, some viral infections, or autoimmune inhibition, called pure red cell aplasia), low levels of erythropoietin (as a result of chronic kidney disease), or chronic diseases of the brain. Other normocytic anemia may be secondary to the reduced life expectancy of the cells that are produced. Examples of this phenomenon are acute blood loss; autoimmune hemolytic anemia, in which antibodies or supplements bind to red cells and cause their destruction; sickle cell anemia, in which abnormal hemoglobin polymerizes and destroys the usual resistance of the red cell; and hereditary spherocytosis or hereditary elliptocytosis, in which red blood cell membrane defects affect their ability to squeeze through capillary microcirculation. Anemia is very common. In contrast, the increased concentration of hemoglobin, called red blood cellosis, is a rarity. Increased hemoglobin concentrations can occur as a secondary phenomenon due to increased levels of erythropoietin, for example, in smokers or people who live at high altitudes (low blood oxygen stimulates the production of erythropoietin). Some tumors, especially kidney tumors, can also make erythropoietin. Primary polycythemia is an anomaly of the bone marrow itself. This myeloproliferinative syndrome leads to an increase in the mass of red cells and, as a result, low levels of erythropoietin by the negative feedback mechanism discussed earlier. 2. White blood cells Anomaly disorder in white cell numbers occur normally (table 6-5), while function abnormalities are rare. Neoplastic transformation in the form of leukemia (granulocytes and monocytes) or lymphoma (lymphocytes) is quite common. Leukemia is discussed in Chapter 5. TABLE 6-5 Causes of abnormal neutrophils counts. Changes in the calculation of neutrophils are the most common anomaly of white cells, found in automatic blood counting. Increase in the number of neutrophils suggest an acute or chronic infection or inflammation, but can be a sign of many conditions. These include stress because adrenal corticosteroids cause demargination of neutrophils from the walls of blood vessels. Reducing the number of neutrophils (neutropenia) may be in overwhelming infections and benign diseases such as cyclical neutropenia (see later discussion), but can also be seen when the bone marrow penetrates the tumor or is involved in myelodysplastic syndromes. Many drugs can also directly inhibit bone marrow production, and because neutrothylous drugs have the shortest period of semi-life in the blood of any brain cell, their number can quickly fall. The number of lymphocytes can vary significantly (table 6-6). The number of lymphocytes is classically increased in viral infections such as infectious mononucleosis. However, persistent elevations suggest malignancies, especially chronic lymphocytic leukemia, which may not cause any symptoms and, incidentally, are detected on a routine blood test. TABLE 6-6 Causes of abnormal lymphocytes. The decrease in lymphocytes (lymphopedia) is a common complication of corticosteroid therapy, but the most worrying for the condition of immunodeficiency; HIV directly infects lymphocytes, and the likelihood of opportunistic infections increases as the number of lymphocytes decreases, leading to AIDS. 3. Violations of platelet abnormalities in platelet number are quite common, especially low bills (thrombocytopenia). The reasons are listed in table 6-7. Reducing platelet production occurs when the bone marrow is affected by various diseases or when the production of TPO by the liver is disrupted, as in cirrhosis of the liver. Increased platelet destruction is much more common. There are three common mechanisms. Since a significant number of platelets are usually found in the spleen, any increase in the size of the spleen or activity (hyperspleism) leads to a decrease in the number of platelets. The consumption of platelets that is associated with current clotting will also reduce the amount. More often than not, however, there is immune-mediated consumption caused by either drugs or autoantio. The latter are usually directed against the platelets membrane of the antigen gpIIb/IIIa. TABLE 6-7 Causes platelet anomalies. Functional platelet disorders are common, especially acquired disorders resulting from urmia (kidney failure) or aspirin, which suppresses platelet cyclooxygenase and reduces platelet agregability. Inherited anomalies are unusual, with the exception of von Willebrand's disease, which is the result of a quantitative or qualitative vWF defect carrying protein for factor VIII. vWF also acts as a bridge between platelets and endothelium and is thus crucial for platelet formation in the coagulation cascade. Rises in the number of platelets above the norm (thrombocytosis) are relatively common and are especially prone to recovery from iron deficiency anemia in iron shake. In myeloproliferative disorders such as polycythemia, platelets are often high. With the necessary platelet platelets may be above 1,000,000/L. COAGULATION FACTOR CONTRIBUTING CONTRIBUTING CONTRIBUTING THE most important coagulation factor disorders are quantitative rather than qualitative and generally hereditary rather than hereditary (Table 6-8). Exceptions to this rule are acquired factor inhibitors, which are antibodies that bind to one of the clotting factors, most often factor VIII. The quantitative disorders that most often cause haemophilia (factor VIII deficiency) and haemophilia B (factor IX deficiency). Both X chromosomes are bound by recessive traits, and the affected males have very low levels of Factor VIII or IX. It is unclear why all affected males do not have a complete lack of factor VIII or IX activity. Hemophilia A is more common, with a prevalence of 1:10,000 men worldwide. Both disorders lead to spontaneous and excessive post-traumatic bleeding, especially in joints and muscles. Females with a trait have 50% of the normal amount of any factor and usually do not have any bleeding problems; In general, you only need half of the normal number of most factors coagulation the clot normally. The APTT test is usually designed to become abnormal when the activity of factor VIII or IX falls below 50% of the norm. TABLE 6-8 Coagulation Factor Deficit. Vitamin K deficiency also leads to a quantitative reduction in factors such as FACTORS II, VII, IX and X, as well as proteins C and C; extending prothrombin time can result. The quantitative inherited anomalies of anticoagulation systems also occur. Protein S deficiency, protein C deficiency, and AT deficiency all occur and lead to abnormal blood clotting problems, as discussed in the next section. Finally, the condition for the consumption of coagulopathy or common intravascular coagulation (DIC) should be included. This condition is usually due to an overwhelming infection, specific leukemia or lymphoma, or massive hemorrhage. In DIC, coagulation factors are depleted. Often there is a simultaneous activation of the fibrinolitic system as well, and uncontrolled bleeding can occur throughout the circulatory system. PT and APTT are usually as abnormal. CHECKPOINT 7. Identify anemia and suggest three causes of macrocytic and microcytastic anemia. 8. What are some categories of explanations for white blood cell analysis that increases or decreases significantly compared to the normal range? 9. What are the three common thrombocytopenia mechanisms? 10. What is the nature of haemophilia defects A and B? PATHOPHYSIOLOGY OF INDIVIDUAL BLOOD DISORDERS OF RED CELL DISORDER 1. Iron Anaemia Deficiency Iron Etiology Deficiency Anemia is the most common form of anemia. Although iron deficiency may occur in many developing countries, iron loss is almost always the result of loss of blood from the gastrointestinal tract in developed countries. Due to periodic menstrual blood loss, women in premenopausal represent with the highest frequency of iron deficiency. Incidence in this group is even higher due to iron loss during pregnancy, pregnancy, the developing fetus effectively extracts the mother's iron for use in its own hematopes. In men or postmenopausal women with iron deficiency, G.I. bleeding is usually the cause. Blood loss in this case can be caused by relatively benign disorders such as ulcers, arteriovenous malformations or angiodysplasia (small vascular abnormalities along the intestinal walls). More serious causes are inflammatory bowel disease or malignancies. An endoscopic study to rule out malignancies is mandatory in patients without the known cause of iron deficiency. There are other less common causes of iron deficiency, but most are associated with blood loss: Bleeding disorders and heoptysis are major opportunities. When no source of bleeding is detected, G.I. malabsorption should be considered as a possible cause of iron deficiency anemia. Such malabsorption occurs in patients with coeliac disease, helicobacter pylori infection, partial gastrectomy, or gastric bypass surgery. Other mechanisms of iron deficiency anemia include intravascular hemolysis (paroxysmal nocturnal hemoglobinuria or cardiac insidious disease) and erythropoietin treatment. The pathogenesis of the body's iron reserves is usually enough to last several years, but there is a constant loss of iron in perfectly healthy people, so the balance of iron depends on adequate consumption and absorption. Diet iron is mainly absorbed into the duodenum. Absorption increases in the conditions of anemia, hypoxia and systemic iron deficiency. The iron is also processed from senile red blood cell through macrophagus phagocytosis and lys. Exports of iron to plasma from these cell areas are regulated by heppydin, a 25-amino acid peptide produced by the liver. Geptidine binds to ferroportin, a transmembred protein, causing its internalization and lysosomal degradation. When iron reserves are low, heptsydine production decreases and ferroportin molecules are expressed on the basolateral membrane of enterocytes, where they transfer iron from the enterocyte cytoplasm to plasma transferrin. Conversely, when iron reserves are adequate or elevated, heppydine production increases, leading to internalization of ferroportin and reduced iron exports to plasma. In inflammatory conditions, the production of heptsydine increases, which leads to internalization of ferroportin on macrophagues and capture of processed iron in macrophagent stores. Iron is stored in most of the body's cells, like ferritin, a combination of iron and protein apoferritine. It is also stored as hemoosiderin, which is a ferritin partially devoid of the apoferritine protein shell. The iron is transported in the blood bound to its carrier of the carrier protein. Because of the complex interactions between these molecules, a simple measurement of the serum iron reflects the reserves of the body's iron (see later discussion). Iron is mainly found in hemoglobin and is also present in myoglobin, an oxygen-stored protein of skeletal muscles. The main role of iron is that in the center of the molecule that is carrying oxygen in the body, heme. Held in the form of iron by other atoms in the heme, iron reversible binds oxygen. Each protein unit of hemoglobin contains one heme molecule; because hemoglobin exists as a tetramer, each hemoglobin block requires four iron molecules. In the case of iron deficiency, the last step in the synthesis of hem (figure 6-6) is interrupted. At this stage, iron ferroscus is inserted into protoporphyrin IX by the enzyme ferrochelatase; when heme synthesis is interrupted, there is insufficient heme production. Globin biosynthesis is inhibited by heme deficiency with a heme-regulated translation inhibitor (HRI). Increased activity of HRI (as a result of heme deficiency) suppresses the key factor of initiation of transcription for the synthesis of heme, eIF2. Thus, each precursor of red cells has less heme and less globin chains. It directly causes anemia, a decrease in the concentration of haemoglobin in the blood. FIGURE 6-6 Synthesis of heme, emphasizing the role of iron and heme insertion into individual globin chains to make hemoglobin, and the role of heme-regulated translation inhibitor (HRI) of globin synthesis. Normal heme concentrations keep HRI activity low, maintaining normal globin synthesis. As noted, heme is also an oxygen intake in myoglobin; therefore, iron deficiency will also reduce the production of myoglobin. Other proteins also depend on iron; most of them are enzymes. Many use iron in the heme molecule, but some use elementary iron. Although the exact effects of iron deficiency on their activity are not known, these enzymes are crucial for metabolism, energy production, DNA synthesis and even brain function. Pathology As iron reserves are depleted, the peripheral model of blood smear develops. In early iron deficiency, the level of haemoglobin in the blood drops, but individual red blood cells look normal. In response to a drop in oxygen levels, the level of erythropoietin increases and stimulates the brain, but the level of hemoglobin cannot rise in response due to iron deficiency. Other hormones are presumably also stimulated, however, and as a result revved-up bone marrow usually causes elevated blood platelet levels. The increased number of white cells is less common. Reticulocytes are noticeably absent. Eventually, the concentration of hemoglobin of individual cells drops, leading to a classic picture of microcyte, hypochromic red blood cells (figure 6-5). It is most commonly found as abnormally low MCV red cells on an automated hemogram. There is also substantial anisocytosis and puycocytosis, seen on a peripheral smear, and target cells can be seen. The target form occurs because there is a relative excess of the membrane of red cells compared to the amount of hemoglobin in the cell, so the membrane beams in the center. The results of laboratory studies are often confusing. Low levels of ferritin in blood is a diagnosis of iron deficiency, but even in obvious cases, cases Can be normal. Ferritin levels are increased in acute or chronic inflammation or significant diseases, which in themselves can cause iron (blood loss). Serum iron levels are falling in many diseases, and the levels of its serum carrier, transferrin, also fluctuate, so none of them is a consistent indicator of iron deficiency, nor is their ratio, weight saturation. If ferritin levels are not diagnostic, measuring the soluble transferrin receptor in the serum (sTfR) can help. TfRs are membrane glycoproteins that facilitate the transport of iron from plasma transferrin to the body's cells. Red blood precursors increase the expression of the TfR membrane in conditions of iron deficiency, but not chronic anaemia. Some TfR membranes are released into the serum as sTfR. The amount of sTfR in the serum reflects the amount of the TfR membrane. High sTfR ratio to ferritin predicts iron deficiency when ferritin is not diagnostically low. While this is helpful, this test has limited acceptance in clinical practice. In addition to observing the hematological response to empirical iron supplements, a bone marrow biopsy can confirm a diagnosis of iron deficiency. Iron is usually found in macrophagues of the bone marrow, where it supplies red blood cell precursors; intracellular hemosiderin is easy to visualize with a Prussian blue spot. These macrophagues are not spot at all if there is an iron deficiency. Clinical manifestations of all anemia lead to the classic symptoms of reduced oxygen-carrying ability (i.e. fatigue, weakness and shortness of breath, especially shortness of breath during load), and iron deficiency is no exception. Reducing the ability to transport oxygen leads to a decrease in oxygen delivery to metabolically active tissues, which nevertheless must have oxygen; this leads directly to fatigue. The body's compensatory mechanisms lead to additional symptoms and signs of anemia. Some patients seem pale not only because the blood unit is smaller than hemoglobin (oxygen hemoglobin is red and gives color to the skin), but also because the surface blood vessels of the skin are compressed, distracting the blood to more vital structures. Patients may also respond to anemia with tachycardia. This increase in cardiac output is appropriate because one way to increase the delivery of oxygen to the tissue is to increase the number of times each hemoglobin molecule is saturated with oxygen in the lungs every hour. This tachycardia can cause benign heart murmurs due to increased blood flow. Gastrointestinal abnormalities occur because iron is also necessary for cell reproduction. Glossitis, where normal tongue suckers are absent, can occur, as well as stomach atrophy with chlorhydria (lack of stomach acid). Achlorhydria can exacerbate iron deficiency because iron is best in an acidic environment, but this complication is quite unusual. Children may have significant developmental problems, both physical and mental. Children with iron deficiency, mainly in developing regions, are bad compared to the iron children. Iron therapy can reverse these findings if it started early enough in childhood. The exact mechanism of cognitive loss of iron deficiency is not known. Another inexplicable but often observed phenomenon with acute iron deficiency is peak, craving for non-nutrient substances such as clay or dirt. Many patients do not have specific symptoms or findings at all, and their iron deficiency is detected due to anemia noted on a blood test obtained for another purpose. It is interesting that mild anemia (hemoglobins 11-12 g/dL) can be tolerated very well, because they develop slowly. In addition to the previously discussed physiological compensatory mechanisms (increase of cardiac output, diversion of blood flow from less metabolically active areas), there is also biochemical adaptation. The ability to transmit oxygen from hemoglobin to cells depends in part on a small molecule in red blood cells called 2.3-biphosphoglycerate (2.3-BPG). In high concentrations, the ability to unload oxygen in tissues increases. Chronic anemia leads to an increased concentration of 2.3-BPG in red blood cells. Other patients who are not present with symptoms directly related to anemia present are now instead with symptoms or signs related directly to blood loss. Since the most common place of unexpected (non-menstrual) blood loss is the gastrointestinal tract, patients often have visible changes in the stool. There may be gross blood (hematocosis) that is more common with bleeding sites near the rectum, or black, belated, metabolized blood (melen) from more proximal areas. Significant blood loss of the urinary tract is very rare. CONTROL 11. What is the most common form of anaemia and its most likely cause in a woman in premenopausal? A man? 12. Why is serum ferritin often not a good indicator of whether iron deficiency is caused by anemia? 13. What disorders are associated with iron deficiency anaemia? 14. What are the physiological adaptations to slow-moving iron deficiency anemia? 2. The pernicious anemia of the etiology of pernicious anemia is mega-regional anemia, in which there is an abnormal maturation of red blood cells. Unlike many other types of anemia, such as iron deficiency, hemoglobin synthesis is normal. Pernicious anemia is the end result of a cascade of events that are autoimmune in origin. The end effect is the loss of adequate supplies of vitamin B12 (comalamine), which is a cofactor involved in DNA synthesis. Rapidly multiplying cells are the most commonly affected, predominantly bone marrow cells and epithelium G.I. The nervous system is also affected, demonstrating that it is a systemic disease. Anemia is only the most common manifestation. In addition to harmful anaemia, comalamine deficiency may be associated with bacterial growth in the gut (because bacteria compete with the host for comalamine), intestinal malabsorbtion of vitamin B12involving terminal ile (e.g. in Crown Crown surgical removal of the stomach antrum (gastrectomy) and, less often, a dietary deficiency that occurs only in strict vegetarians. In the diet of comalamine can be found mainly in animal products. Prevalent anaemia is most common in older patients of Scandinavian origin and is more common in patients of European and African descent than of Asian descent. In the United States, black women are one of the most common groups. However, harmful anaemia accounts for only a small percentage of anaemia patients. Pathogenesis Initial events in the pathogenetic cascade begin in the stomach (figure 6-7). The lumnal cells of the stomach initially suffer from an autoimmune phenomenon, which leads to two discrete effects: loss of stomach acid (acchlorhydria) and loss of internal factor. Pernicious anemia interferes with both the initial availability and absorption of vitamin B12: gastric acid is needed to release comalamine from food, and the internal factor is glycoprotein, which binds cobalamin and is necessary for effective absorption of cobaalamine in terminal ileum. Both stomach acid and internal factor are made exclusively by the parietal cell. FIGURE 6-7 Pathogenesis and the effects of harmful anemia (autoimmune atrophic gastritis). (Repainting, with permission, from Chandrasoma P et al. Brief Pathology, 3rd ed. Originally published by Appleton and Lange. 1998 Author's ©, 1998 by McGraw-Hill, Inc.) Evidence of autoimmune destruction of the parietal cell is strong: patients with harmful anemia have atrophy of the stomach mucosa, and pathological samples show penetration of lymphocytes, which are predominantly antibodies producing B-cells. In addition, 90% or more of patients have antibodies in the serum directed against the parietal cell membrane of proteins. The main protein antigen appears to be the H'-K-ATPase proton pump, which is responsible for the production of stomach acid. Cytotoxic T cells, whose receptors recognize H'-K ATPase, can also contribute to stomach atrophy. More than half of patients also have antibodies to the factor itself or the internal factor-comalamine complex. In addition, patients with harmful anaemia have a higher incidence of other autoimmune diseases, such as Graves' disease. Finally, corticosteroid therapy, used as a first-line therapy for many autoimmune disorders, can reverse pathological findings in pernicious anemia. Despite this evidence, the exact mechanism of incitement to the event remains unknown. A complete deficiency of vitamin B12 develops slowly, even after complete achlorhydria and loss of internal factor. Liver vitamin B12 stocks are sufficient for several years. However, the lack of this vitamin eventually leads to changes in DNA synthesis and in the nervous system altered by myelin synthesis. In the DNA synthesis of comalamine, with folic acid, is crucial as a cofactor in the synthesis of deoxythimidine from deoxyuridine (figure 6-8). Kobalamin takes a methyl group from which leads to the formation of two important intracellular compounds. First, it is methylcobalamin, which is essential for the production of the amino acid methionine from homocysteine. Secondly, tetrahydrofolate, which is needed as a single-carbon donor in the synthesis of purine, is reduced. Thus, the deficiency of comalamine depletes the reserves of reduced tetrahydrofolate and worsens the synthesis of DNA due to the decrease in purine production. In the case of copalamine deficiency, other reduced folates may replace tetrahydrofolate (and may explain why pharmacological doses of folic acid can partially reverse changes in megaloblast blood cells, but not neurological changes seen in harmful anemia). However, methyltetrahydrofolate, usually methyl donor comalamine, accumulates. This folate cannot be stored intracellularly because it cannot be polyglutamate; adding several remnants of glutamate results in a charged compound that does not freely dissipate from the cell. Thus, there is a relative deficiency of folic acid in pernicious anemia as well. In addition, methionine can serve as a major donor to methyl groups for these other substitutes for reduced folate; because methionine cannot be produced in the deficiency of comalamine, it exacerbates problems in the synthesis of purine. FIGURE 6-8 Role of comalamine (vitamin B12) and folic acid in the metabolism of nucleic acid and myelin. The absence of comalamine or folic acid slows down THE synthesis of DNA (A) and the absence of comalamine leads to the loss of folic acid, which cannot be carried out intracellularly, if not polyglutamatized. The lack of comalamine also leads to abnormal myelin synthesis, probably due to a deficiency in the production of methamphetamine (B). (Repainting, with permission, from Chandrasoma P et al. Brief Pathology, 3rd ed. Originally published by Appleton and Lange. 1998 Author's ©, 1998 by McGraw-Hill, Inc.) The exact mechanism of neurological consequences of harmful anemia, with demyelination (loss of myelin membranes around nerves), is not known. Defects in the pathway of methamphetamine synthesis have been proposed but not proven experimentally. Instead, observations in the coalamin-deficiency of rat gastrectomy imply an imbalance of cytokines and growth factors as a potential mediator of nerve damage. The synthesis of the tumor necrosis factor cytokines (TNF) is regulated by S-adenosyl-metion, a product of methionine. Methamphetamine deficiency can indirectly lead to neuropathy through unregulated production of TNF, myelinolitic cytokine, among other mechanisms. The production of succinyl-coenzyme A (CoA) also depends on the presence of comalamine. It is unclear whether the decline in production of succinyl-CoA, which can affect the synthesis of fatty acids, is also involved in demyelinating diseases. Pathology of gastric disorders associated with pernicious anemia dominates the pattern of chronic atrophic gastritis (Figure 6-7). Usually the high column epithelium is replaced by a very mucous membrane, and obviously obviously plasma cells and lymphocytes. Pernicious anemia also increases the risk of developing stomach adenocarcinoma. Thus, a pathological examination can also detect cancer. The peripheral pattern of blood smear (figure 6-5) varies, depending on the length of time the patient has had a comalamine deficiency. In the early stages, the patient may have mild macrocyte anemia, and large red blood cells of the egg (macro-ovalocytes) are usually found. In full-scale megaloblast anemia, however, there are anomalies in all cell lines. The classic picture shows significant anisocytosis and puycolytosis line of red cells, and there are hypersegmental neutrophils, revealing nuclear dysgenesis from abnormal DNA synthesis (Figure 6-9). In severe cases of pernicious anemia, the red-and-white cells of the series are easily mistaken for acute leukemia because the cells look so atypical. FIGURE 6-9 Megaloblastic hematopoiesis: morphological changes seen in microscopic examination of bone marrow or peripheral blood. (Repainting, with permission, from Chandrasoma P et al. Brief Pathology, 3rd ed. Originally published by Appleton and Lange. 1998 Author's ©, 1998 by McGraw-Hill, Inc.) Bone marrow aspiration and biopsy are not necessary in diagnosis and can be misleading, because bone marrow pathology can be confused with acute leukemia, hypercellularity, increased erythroblasts and even cytogenetic changes. Typical B12 deficit results include megaloblastic changes, nuclei that are too large and immature in cells with mature cytoplasm filled with hemoglobin, which are visible at every stage of red blood cell development. These cells are not visible in the peripheral blood, because abnormal red blood cells are usually destroyed in the bone marrow (intramedullary hemolysis) by unexplained processes. This exacerbates anemia. Megaloblast changes can be seen in the bone marrow even in the absence of obvious changes on the peripheral blood smear. Spinal cord abnormalities consist of demyelination of posterolateral spinal columns called sub-brain combined degeneration. Peripheral nerves can also show demyelination. Demyelination eventually leads to the death of neuronal cells, which is also evident in pathological examination. Because neurons do not divide, new neurons cannot replace the dead. Laboratory results include elevated lactate dehydrogenase (LDH) and, sometimes, indirect bilirubin consistent with hemolysis occurring in the bone marrow. LDH is directly released from the dehydrated red cells, and free hemoglobin is metabolized into bilirubin. Serum vitamin B12 levels are generally low, indicating a lack of condition. However, both false and negative test results remain high, as only 20% of the total measured amount of B12 serum is associated with cellular protein delivery, the rest is due to haptocorrin, which is not available for cells to use. Antibodies to the internal factor are usually detected. Height of methylmalonic acid serum (MMA) and/or homocystein homocysteine Figure 6-8) is a very predictive deficit B12. The Schilling test, which evaluates oral absorption of vitamin B12 with and without an additional internal factor, is no longer used due to the lack of radioactively labeled vitamin B12. Typically, the approach is the first measure of serum B12 and if ambiguous to get levels of serum MMA and/or homocysteine. Clinical manifestations Clinical representation consists of one or more symptoms associated with a major deficiency. Anemia is the most common anomaly and often very severe; Hemoglobin levels of 4 g/dL (less than a third of normal) can be seen. This degree of anemia is rare with other causes such as iron deficiency. Typical symptoms are fatigue, shortness of breath, or dizziness, because reducing the mass of red cells equals a decrease in oxygen-carrying blood capacity. High exit heart failure is relatively common, with tachycardia and signs of left ventricular failure (chapter 10). Since oxygen needs are constant (or grow with exercise) and oxygen carrying ability drops, the only way to keep tissue oxygenation in anemia is to increase cardiac production (i.e., the number of times per minute each red cell is completely oxygenated lung). In the end, however, the left ventricle fails. However, the symptoms may be mild because anemia develops slowly as a result of extensive liver storage of vitamin B12. Patients with anemia usually adapt over time to slow down changes in oxygen-carrying capacity. The same changes in 2.3-BPG that encourage the delivery of oxygen to tissues from hemoglobin in red cells in other anemia occur when vitamin B12 deficiency. GI symptoms are less common and include malabsorption, muscle waste (unusually), diarrhea (more often), and glossitis (most common). In glossitis, normal tongue soso hissonia is absent regardless of whether the tongue is painful, red, and beef or pale and smooth. Neurological symptoms are less likely to improve with comalamine replacement therapy. As with other neuropathies associated with the loss of myelin from large peripheral sensory nerves, numbness and tingling (paresthesia) are common and are the most common symptoms. The demyelination and death of neuronal cells in the posterolateral long tracts of the spinal cord interfere with the delivery of positional information to the brain stem, cerebellum and sensory cortex. Therefore, patients complain of loss of balance and coordination. The examination revealed a violation of proprioception (sense of position) and a sense of vibration. True dementia can also occur when demyelination involves the brain. Importantly, but somewhat unexpectedly, neurological symptoms may occur in the absence of any changes in peripheral blood smear suggestive pernicious anemia. Less frequently vitamin B12 can manifest itself in thrombosis and possibly in unusual places such as brain sinuses. Protrombotic condition may be secondary to hypermococysinemia, observed in heavy vitamins CONTROL 15. Name two of the most important

cofactors in DNA synthesis, the deficiency of which leads to harmful anemia. In what specific biochemical pathways do they participate in? 16. What neurological defects are observed in long-term pernicious anemia? 17. What symptoms of pernicious anaemia tend to be relatively mild? 18. Are changes in peripheral blood smear needed for the neurological effects of vitamin B12 deficiency? WHITE CELL DISORDERS 1. Malignant disorders The most important anomalies of white blood cells are malignant disorders of leukemia and lymphoma. They are discussed in Chapter 5. 2. Cyclic neutropenia Absolute neutropenia, characterized by the number of neutrophils less than 1500-2000/yl (zgt;2 SD below the average level in norms), is a widely encountered problem in medicine and can be caused by a large number of diseases (table 6-5). Cyclical neutropenia, however, is rare. This is of interest because it provides an understanding of the normal production of neutrophils and function. It is characterized by a lifelong history of neutrophil counts that decline to zero or near zero for 3-5 days at a time, every 3 weeks, and then rebound. Interestingly, the peripheral blood neutrophil counts and monocytes expect to fluctuate in opposite phases on this 3-week cycle. Etiology Classic, childhood onset of cyclical neutropenia as a result of heterozygous germ mutations in the gene ELANE (ELAstase, neutrophil expressed), formerly known as ELA2, which encodes for a single enzyme, neutrophil elastase (NE). NE is found in the primary azurophilic pellets of neutrophils and monocytes. There are about 100 cases in the literature, most of which are consistent with autosoom dominant inheritance. However, sporadic cases of adults also occur, and they are associated with mutations of neutrophil elastase. There does not appear to be a racial bias or gender bias against morbidity. Pathogenesis Number of neutrophils in the blood is stable in normal people, which reflects the fact that there is a large pool of granulocyte stores in the bone marrow. Bone marrow stock exceeds the circulating pool of neutrophils by 5-10 times. This large pool is necessary because it takes almost 2 weeks for the full development of neutrophil from the early stem cell in the bone marrow, but the average lifespan of mature neutrophil in the blood is less than 12 hours. In cyclical neutropenia, the repository is not adequate. Daily measurements of the number of neutrophils in the blood show striking differences in their number. Studies of neutrophil kinetics in affected patients show that the defect is in abnormal production, and not in the abnormal location of neutrophils. The production of neutrophils occurs in discrete waves even in normal individuals. As neutrophils differentiate from the earlier progenitor cells, they produce neutrophil which is thought to inhibit myeloblasts differentiation in a negative feedback loop. This leads to an oscillator wave with peaks and troughs produced by neutrophils. How neutrophil neutrophil increasing bone marrow, the peak is reached where enough neutrophil elastase causes a drop in neutrophil differentiation. Then, as the number of neutrophils drops again to nadir, the production of neutrophil elastase also decreases, allowing for a rise in the number of neutrophils again. In cyclical neutropenia, it is assumed that mutant neutrophil elastase may have an excessive inhibitory effect, causing long periods of trough and inadequate pools to maintain a normal peripheral neutrophil count. However, once they are extruded from the bone marrow, neutrophils appear to have a normal lifespan (Figure 6-10). FIGURE 6-10 Feedback loops the hypothesis to explain hemathopoetic cycling. Neutrophil elastase (NE) is postulated to inhibit further myeloblastoma differentiation. The gray sinusoid wave denotes fluctuations in neutrophil countdown. In this model, NE produced a terminally differentiation of a cohort of neutrophils and eventually fed back to inhibit further production of neutrophils, resulting in the loss of the inhibitory cycle, at least for a while, until the production of neutrophils resumes and then again inhibiting the effect of NE in a cyclical manner. (Reprision of Horwitz MS et al. Neutrophil Elastase in cyclical and severe congenital neutropenia. Myeloid progenitor neutrophil can also produce monocytes. Thus, during neutrophil nadir, myeloid precursor cell can predominantly differentiate to the monocytes line, giving opposite oscillating waves of neutrophils and monocytes seen in these patients (see Figure 6-11). FIGURE 6-11 Regular cyclical changes in monocytes, cytoucytes and neutrophils in a patient with cyclic neutropenia. Note that monocytes and cytoucins tend to grow when neutrophils fall. (Repainting, with permission, from Dale D et al. Cyclical Neutropenia: Clinical Review. Waves are surprisingly constant in their frequency. Almost every patient has a cycle of 19 to 22 days, and each patient's cycle duration is constant during his or her lifetime. Neutrophils and monocytes are not the only bone marrow elements that cycle. The number of platelets and cytolucytes also cycle with the same cycle length, but unlike the amount of blood nytrophils, clinically significant reductions are not observed. Presumably, this is due to the fact that the lifespan of these elements in the blood is much longer than the lifespan of neutrophils. Since several cell lines are seen to cycle, it is believed that mutations of neutrophil elastase accelerate the process of apoptosis (programmed cell death) in the early progenitor cells, as well as if they are not saved by G-CSF. Clinically, introductions G-CSF (filgrasthim) doses for affected individuals have three interesting effects that partially overcome the condition. First, while cycling continues, the average number of neutrophils increases at each point of the cycle, cycle, that patients are rarely neutropenic. Secondly, the frequency of cycling decreases from 21 days to 14 days. Third, other fluctuations in the cell line change in parallel; their cycle frequency also decreases to 14 days, suggesting that the early progenitor cell is indeed at the center of the disease. However, the fact that cycling does not disappear shows that there are other anomalies that have yet to be discovered. It also suggests that cycling may be the inherent of all stem cells in normal people who are modulated by several cytokines in the bone marrow. Pathology Pathological features of cyclical neutropenia are visible mainly in the laboratory. Peripheral blood smears seem normal, except for a lack of neutrophils - mature or immature - during the nadir of each cycle. Individual neutrotrophils seem normal. The bone marrow, however, shows striking differences depending on the day of the cycle on which it is examined. During the nadir of each cycle, there are an increase in the number of early myeloid precursors, such as promyelocytes and myelocytes, and mature neutrophils are rare. This picture is similar to what is observed in acute leukemia, but 10 days later, as circulating neutrophil numbers grow, a perfectly normal brain appears is typical. Clinical manifestations In general, neutropenia from any cause places patients at risk of severe bacterial infections, usually from intestinal organisms, due to changes in host defense in the gastrointestinal tract. This is especially true when neutropenia is due to the introduction of chemotherapy agents, because chemotherapy also affects the lining of the gastrointestinal tract. Neutrophils, with their ability to absorb bacteria and deliver toxic enzymes and oxidization free radicals to the sites of infection, tend to serve as a first-line receiving protection against the bacteria that inhabit the intestines. Such patients are also at risk of fungal infections if neutropenia lasts more than a few days; This is because it takes longer for the fungi to reproduce and invade the bloodstream. Untreated infections of any type can be quickly fatal, especially if the number of neutrophils is less than about 250/L. In cyclic neutropenia, then, recurrent infections should be expected, and deaths from infections with intestinal organisms have been reported. Each cycle is characterized by malaise and the fever coincides with the time neutrophil counts fall. Cervical lymphadenopathy is almost always present, as are oral ulcers. These symptoms usually last about 5 days and then subside until the next cycle. When infections occur, the site is usually predictable. Skin infections, in particular small superficial piogenic abscesses (furunculosis) or bacterial invasion of dermis or epidermis (cellulite), are the most common and react to with a few sequels. The next most common place of infection is usually the gums, and chronic gingivitis occurs in about half of patients. In addition, the problem has improved markedly when patients receive therapy with filgrastomy. Other infections are unusual, but any neutropenic patient is at risk of infection by organisms that are in the GI system. In a few patients who need abdominal surgery during their neutropenia, ulcers similar to those seen in the mouth have been noted; this destruction of the normal mucous barrier presumably facilitates the entry of intestinal bacteria into the bloodstream. Since the period of greatest susceptibility to infection is only a few days in each cycle, most patients grow and develop normally. CONTROL 19. How long does it take for neutrophil to develop from stem cells in the bone marrow? Once fully mature, what is its life expectancy? 20. At what level of neutropenia is the incidence of infection increasing dramatically? 21. What are the most common places and types of infections observed in neutropenic patients? 22. What is the likely underlying anomaly in cyclical neutropenia? PLATELET DISORDERS 1. Drug-associated immune thrombocytopenia etiology thrombocytopenia, defined as platelet levels below normal laboratory range, is a commonly occurring anomaly. Although there are many causes (table 6-7), the possibility of a drug induced by immune thrombocytopenia should always be considered. Many drugs have been linked to this phenomenon, and the most common ones are listed in table 6-9. In practice, the link between a drug and thrombocytopenia is usually done clinically, rather than with specific tests. Thrombocytopenia usually occurs at least 5-7 days after exposure to the drug if given for the first time. The suspected drug stops and the platelet expects to rebound within days. Rechallenge with a drug that is rarely done, almost always reproduces thrombocytopenia. TABLE 6-9 Common drugs that can cause thrombocytopenia. Heparin is the most important cause of thrombocytopenia due to its frequent use in hospitalized patients; Its use also carries the potential to cause life-threatening thrombotic syndrome. The pathophysiology of thrombocytopenia caused by heparin is also the most fully described. Pathogenesis Although the phenomenon of drug-induced thrombocytopenia has been known for decades to be immune in nature, specific mechanisms have long been controversial. The connection of antibodies with platelets leads to their destruction through the spleen. The spleen acts as the main blood filter and recognizes platelets associated with antibodies as abnormal and thus removes them. The removal of the spleen also occurs in autoimmune (idiopathic) thrombocytopenia, which is relatively common and difficult to distinguish clinically from drug-induced thrombocytopenia. various mechanisms underlying the drug induced by immune thrombocytopenia. The quinine- or NSAID-induced thrombocytopenia involves the rigid binding of antibodies to normal thrombocytes only in the presence of sensitization drugs. Antibody Antibodies epitopes on Glycoprotein IIb/IIIa or Ib/IX complexes, the main platelet receptors for fibrinogen and vWF, respectively. Penicillin and cephalosporin antibiotics are thought to lead to the destruction of platelets through tactte-dependent antibodies. The drug acts as a hapten, a small molecule that only causes an immunological reaction when it is associated with a large carrier molecule or protein. Some drugs (golden salts, procainamide and possibly sulfonamides) can cause autoantibods, which are able to bind to platelets and destroy them even in the absence of sensitizing drug. Finally, antithrombotic agents that block the binding of fibrinogen to gpIIb/IIIa receptors (abciximab, tyrophyban or eptifibatide) can cause acute immunomediated thrombocytopenia, where patients develop severe thrombocytopenia within hours of exposure. The mechanism includes either natural antibodies that recognize the murine component of abciximab or structural changes in the gpIIb/IIIa receptor caused by binding tyrofiban or eptifibatide. For heparin there are clear signs of binding with platelet protein, platelet factor 4 (PF4). PF4 is found in alpha platelet pellets and released when activated. It binds back to the platelet surface through a specific PF4 receptor molecule, which further increases platelet activation. It also binds to a high affinity for heparin and heparin-like glycosamine glycominoglycan molecules present on vascular endothelium. This nonimunical-based adhesion to PF4 can lead to mild thrombocytopenia by promoting platelets binding to fibrinogen and subsequent aggregation, known as heparin-induced Thrombocytopenia (HIT) type I. This can occur in 30% of patients exposed to heparins without clinical sequels. However, the combination of heparin with PF4 can also act as an antigenic stimulus that triggers the production of immunoglobulin G (IgG) against the combination. This immunological response is known as heparin-induced thrombocytopenia (HIT) type II. About 10-20% of these patients with heparin-PF4 antibodies will develop a serious clinical syndrome, HIT (T) (heparin-induced thrombocytopenia and thrombosis), which paradoxically includes both thrombocytopenia 5-10 days after exposure to the drug and protrombotic state through increased thrombosis activation. There is a 10-fold increased risk of HIT infection in patients receiving non-fractional heparin (UFH) compared to those who receive low molecular-weight heparins. Patients with cardio or orthopedic surgery have a higher risk of clinical HIT (1-5%) (0.1-1%) when receiving UFH. Women are twice as likely to have a hit risk than men. Thrombocytopenia occurs in TYPE II HIT after a series of steps. First, PF4 is released from the or heparin itself or other stimuli. Heparin then binds to PF4, forming an antigenic complex that leads to the production of IgG antibodies that can bind directly to this compound. New complex complex binds to platelets through the Fc platelet receptor, through its end of IgG. The platelets associated with this antibody complex then destroy the spleen. Despite the resulting thrombocytopence, type II HIT leads to prothrombomatic condition through additional binding of the part of heparin-PF4 to the PF4 receptor on platelets, cross-contributing platelet compounds, activation and aggregation (Figure 6-12). FIGURE 6-12 Pathogenesis thrombocytopenia caused by heparin (HIT). IgG is an autoantibod against the heparin-PF4 complex. Platelets can bind to each other and be activated through the interaction of IgG-Fc receptors or the interaction of PF4-PF4 receptors or both. Thus, the formation of aggregation and blood clot may occur. In addition, IgG can bind to endothelial cells linked to the heparan-PF4 build and cause vascular damage, which can also trigger the formation of a blood clot. Since each end of this IgG-heparin-PF4 molecule can bind to platelets, it is possible that platelets can become a cross-single molecule. Many platelets can actually interact in this way, leading to further platelet aggregation and activation. Clinically, it reduces the number of circulating platelets, but it can also lead to a blood clot at the activation site. Thus, despite the fact that heparin is the most commonly used anticoagulant, in this case it can actually provoke coagulation. In addition, the activation of platelets using this mechanism leads to an increase in the number of circulating PF4, which can bind to more heparin and continue the cycle. Excess PF4 can also bind to the endothelial surface through glycerin-like glycosamine glycosamine glycosamines described earlier. Thus, it is possible that antibodies to the heparin-PF4 design may bind to endothelial cells as well, which can lead to endothelial cell injury, further increasing the risk of local thrombosis by releasing TF and eventually thrombin. Finally, there is some evidence that macrophases can release TF in response to these antibodies, further stimulating coagulation. The pathology of the peripheral blood smear is not startlingly abnormal if the number of platelets is less than about 75,000/ il, and then it is usually abnormal just because relatively few platelets are seen. Platelet morphology, however, is usually normal, although large platelets can be seen. These large platelets are less mature and are bone marrow compensation for low amounts of peripheral platelets, with the production of platelets from megacariocytes increasing. Although drugs, particularly heparin, can cause platelet aggregation in vivo and in vitro, this usually does not manifest itself when considering a blood smear. Bone marrow usually seems normal, although the number of megakaryocytes can be relatively increased, presumably reflecting an attempt to increase platelets (fragments of megakaryocytes) in circulation. In some cases, immune-mediated thrombocytopenia, however, can be reduced the number of megacariocytes. There are many hypothesis hypotheses why this might happen, but it most likely means that an antigenic combination of the drug-platelet protein also occurs on megacariocytes, so that they as well as platelets in peripheral circulation are being immunologically destroyed. This destruction will not involve the spleen, of course, but will require antibody-dependent killing cells. Patients who develop thrombocytopenia and thrombosis, there is thrombosis, which is relatively rich in platelets compared to typical thrombobacteria, which can be seen in other situations. They are described as white clots. Blood clots can be both arterial and venous. Clinical manifestations Despite the fact that the number of platelets in the immune medial thrombocytopenia can be extremely low (lt; 10,000/L, compared to the normal value of more than 150,000/L), severe bleeding is unusual. Most often there are mild bruises with minimal injuries. When platelets are counted at less than 5000/L, point hemorrhages (petehia) can spontaneously occur in the skin or mucous membranes. They are self-mutilated because plasma clotting factors are still intact, and only a small number of aggregated platelets are needed to provide an adequate PL for clotting. The relationship between the likelihood of bleeding and the number of platelets is not linear. Bleeding time, a test used clinically to assess platelet function, does not even begin to be abnormally long, until the number of platelets is less than 90,000/L. Spontaneous bleeding is unlikely until the number of platelets is less than 20,000/il, but still rare until the number is less than about 5,000/L, assuming that patients have no other hemostasis abnormalities. For example, aspirin inhibits platelet aggregation and increases the likelihood of bleeding. When bleeding from thrombocytopenia occurs, it is most commonly mucosa or superficial in the skin. It is most commonly seen as nosebleed (epistaxis), but bleeding of the gums, gastrointestinal tract, or lining of the bladder can be seen. As mentioned, however, when immune thrombocytopenia occurs as a result of heparin, paradoxical clotting can occur instead of bleeding. This can cause a very confusing picture because heparin may have been given therapeutically for another thrombosis; It can be difficult to determine whether the new thrombosis is an extension of the original clot or a new one due to exposure to heparin. However, the occurrence of simultaneous thrombocytopenia gives a clue. When heparin-induced thrombocytopenia and thrombosis occur, the clinical manifestation of the new thrombosis will depend on the location of the clot. Most studies of this disorder show that when thrombosis occurs, it is in place of a previous vascular injury or abnormality. For example, patients with atherosclerotic vascular disease thrombosis is much more common than venous clots. Patients have a rapid onset of severe pain, usually in the limb, with a cool, pale limb. There are no impulses. It could be (5-10% mortality) or at least limbs are threatened because the flow of oxygen to the affected area is cut off, and emergency removal of a clot or vascular bypass may be necessary. Venous clots also occur in the same way as typical venous clots (see later discussion). In addition to stopping heparin, patients with type II HIT need anticoagulation to prevent and treat thrombosis. Direct thrombotin inhibitors (argatroban, lepirudin or bivalirudin) provide a direct means of blocking the effects of thrombin, the main mediator of the coagulation system. CONTROL 23. What is the most common category of thrombocytopenia? 24. What are the antibodies to which the platelet protein is implicated in the pathogenesis of heparin-induced thrombocytopenia? 25. With what mechanism can heparin-induced thrombocytopenia actually increase the formation of a blood clot? 26. Why are large bleeding unusual in thrombocytopenia caused by drugs? COAGULATION DISORDERS 1. Inherited Hypercoagulable State Etiology The formation of blood clots otherwise normal blood vessels are clearly abnormal, because the coagulation system in mammalian species is positively and negatively balanced by so many factors. However, there are a number of diseases that lead to abnormal blood clotting (thrombosis). Abnormal blood clotting states can be either primary, in that the anomalies are caused by genetic predisposition associated with the coagulation factors themselves, or secondary (i.e. acquired) due to changes in clotting factors, blood vessels or blood flow. As virkhov's pathologist first noted more than 150 years ago, there are three possible contributors to the formation of an abnormal clot (blood clot): reduced blood flow, vascular damage or inflammation, and changes in the internal properties of the blood. Persistent physiological changes in any of these three factors (the Virkhov Triad) are called hypercoagulation states. Primary, or inherited, hypercoagulal states are autosoom-dominant genetic defects. This means that carriers (heterozygots) suffer. With the exception of hyperprotrombinemy, all lead to only moderate (50%) reducing the levels of relevant factors. Despite the relatively modest drop, the affected people are predisposed to abnormal thrombosis. These disorders are relatively rare in the general population, but they make up a significant proportion of young patients who come to medical care with thrombosis. Specific states to be discussed are activated protein C (APC) resistance (most commonly occurring abnormalities), protein C deficiency, protein deficiency S, AT deficiency, and prothrombin 20210 AG anomalies. Hyperhomocystinemia, a congenital metabolic error, is also a hereditary hypercoagulant condition, but because it is not related to coagulation, it is not discussed here. Pathogenes in the coagulation cascade, activated factor V (Va) plays a key role (Figure 6-13). This is necessary for prothrombinase complex with Xa factor, which leads to a surge of thrombin and fibrin generation during hemostasis. The Va factor thus makes an excellent negative control point, so that once the clot formation begins, it does not go on unchecked. FIGURE 6-13 The central role of Factor V in the management of the coagulation cascade. The effect of each of the negative control factors - protein S, protein C and antithromin - is shown in color. Protein C is a major inhibitor of the Va factor. Although it is a factor of anticoagulation, its production depends on vitamin K-dependent γ-carboxylation, just as coagulation factors II, VII, IX and X. Protein C, when activated the presence of clotting, which generates thrombone, breaks down the Va factor in an inactive form, and activation of the X factor thus slows down. By itself, however, protein C only has little effect on the Va factor; its negative effect on the Va factor is amplified by the protein cofactor, the S. Factor V protein does not provide a single negative point of control, however. Protein C also suppresses the activated VIIIa factor, which is crucial for the formation of the IXa tenase factor, which is needed to activate the X factor on activated platelets leading to the generation of protrombinase. Factors II, IX, X and XI (cerine proteases) are suppressed by another molecule, AT. The action of AT itself is also regulated and heavily dependent on binding accelerator, heparin, or similar molecules that are present in abundance along the endothelial cells that stick out the vessels. Evidence suggests that AT may also interfere with the TF-VIIa complex. The fact that deficiencies in protein S, protein C and AT activity cause clinically significant thrombosis demonstrates an important concept: it is the lack of adequate anticoagulant activity, rather than overproduction of procoagulant activity, that characterizes most hypercoagulant states. A. Activated C-APC protein resistance is the most common inherited hypercoagulable state, with as much as 3-7% of the total heterozygous population for abnormality. Up to 25% of patients who have venous thrombosis without inciting event found to resist APC in a large series of patients. Most cases occur due to a single DNA mutation in the V gene, where guanine (G) is replaced by adenine (A). This one basic change results in the replacement of the amino acid glutamine with arginine at position 506, while the modified V factor is called Factor V Leiden, named after the city in the Netherlands where it was discovered. This change in the amino acid alters the three-dimensional conformation of the fission area in the Va factor, where the APC is usually binds to inactivate it. Thus, the Va molecule factor can continue to strengthen the Xa factor converting prothrombin into thrombin (the IIa factor), through prothrombinase complex, and coagulation is not suppressed. This mutation also leads to the loss of the fission product, which формируется при факторе V V inactivated by APC, a cofactor that is important in inactivating the APC factor VIIIa. Thus, the loss of this cofactor leads to a decrease in anticoagulant activity and contributes to a hypercoagulated state. B. Protein deficiency C- Protein C deficiency is common; to 1 out of every 200 individuals in the heterozygote population. However, thrombosis is a rarity among these people. Families who are prone to thrombosis are thought to carry additional genetic factors, in addition to protein C deficiency, which increase the risk of thrombosis. As noted earlier, protein C inactivates Va and VIIIa factors, but requires protein S for its own action. Protein C also depends on the presence of PL platelets and calcium. In a deficiency of protein C less inhibition of prothrombinous complex, which leads to relatively unlimited blood clots. Typically, a part of the thrombin is generated by binds to the endothelial cell protein, thrombomodulin, and this complex activates the C protein in the first place. Thus, this negative feedback loop is lost in protein deficiency C. Protein C deficiency is not all one disease, however, unlike factor V Leiden anomalies discussed earlier. Type I deficiency refers to people with reduced protein C. Type II deficiency refers to cases with normal protein C levels but low protein C activity. C. Protein deficiency S-Protein S deficiency is also an unusual heterogeneous disorder. Type I protein S deficiency refers to cases of low free and overall protein S. Type II deficiency, which is least common, refers to abnormal functioning protein S. Type III deficiency refers only to low levels of free protein S. In the cascade of coagulation, when va and Xa factors are complex together, the place of inactivation on the Va factor is hidden from the protein C. Protein S. rather than the protease itself, exposes this site so that protein C can break down Va. Because the S protein is so important, protein S deficiency also leads to an unregulated procoagulant Xa factor. D. Deficiency of antithrombin- CIN deficiency is less common than any of the previously discussed disorders, with approximately 1 in 2,000 cases in the general population. AT binds and suppresses not only thrombone (where its name comes from), but also activated forms of factors IX, X, XI and XII and possibly the VII-TF complex factor as well. Unlike the proteolytic fission of the Protein C Factor Va, AT binds to each factor by directly blocking their activity; it's not an enzyme. This action is accelerated - up to 2,000 times - by the reversible anticoagulant heparin molecule, which binds to AT through its pentasacharid sequence. The fondaparinux anticoagulant is a synthetic version of this five-sugar sequence, and thus it can also bind to AT. In the deficit of AT, then, several steps of clotting are unbalanced, and the cascade of coagulation can continue rampant. More than 100 мутаций AT. Молекулярные дефекты типа I I parallel decrease in antigen and activity, while type II defects are associated with a dysfunctional molecule that has reduced activity but normal or near normal antigen levels. E. Hyperprotrombemia - Mutation in the untranslated region of the prothrombin gene (mutation of one base pair called 20210 AG) is associated with elevated plasma prothrombin (II) and increased risk of thrombosis. Presumably, this leads to excessive production of thrombin when activating the prothrombinaous complex. It is probably the second most common hereditary hypercoagulation condition after the V Leiden factor. This is the first hereditary thrombophilia associated with overproduction of procoagulant factors. Pathology Pathological features of blood clots in hypercoagulation states are indistinguishable from genetically normal individuals on a rough anatomical or microscopic basis, except that there is a high probability in hypercoagulable states of having a blood clot in unusual places. (See Clinical Appearances section.) Most pathological features of hereditary hypercoagulation states consist of laboratory abnormalities. In assessing patients suspected of hereditary hypercoagulated condition, there are two main types of laboratory abnormalities. The first type is quantitative: Specific immunological tests can determine the relative amount of protein C, protein S, AT or fibrinogen present in the serum of this patient, but they do not assess the function of any of these molecules. The second type is qualitative: tests on the activity of protein C or protein S (rather than quantity) measure the ability (or inability) of a patient's protein C or S to extend the clotting time in the test tube. APC resistance can be evaluated with different clot analysis, but the general sweetness of the specific mutation in the factor V Leiden is estimated by the polymerase chain response, because the total sequence of the molecule is known. The chain reaction polymerase is also used to detect 20210 AG prothrombin anomaly. Prothrombin levels can also be measured and are consistently found in the highest quartile levels of prothrombin found. Clinical manifestations Of most thromboembolic events encountered in clinical practice are secondary, not primary. Patients usually have blood clots in the deep veins of the legs for two reasons: (1) due to sluggish blood flow (in high capacity, low-flow veins) compared to other areas, especially when inactive (bedridden after surgery or as a result of illness); and (2) because the limbs are more likely to get injured than the trunk. Injury causes compression of blood vessels or injury; thus, the two elements of the Virginia Triad are more easily observed in the legs than anywhere else. These venous clots in the legs (commonly referred to as deep venous thrombosis DVTs) are usually present with pain, swelling and redness below the level of the blood clot, with arterial impulses and perfusion of the distal limb. Because the blood comes back in Circulation is blocked in these high-capacity vessels, the superficial accompanying veins only under the skin can be noticeable and engorged. The tumor is mechanical because normal arterial blood flow continues to the limb, while the venous return is compromised, leading to engorgement. Pain occurs primarily as a result of swelling alone, but can also occur from the accumulation of lactic acid in the leg muscles. This occurs when the pressure in the legs increases to such an extent that it jeopardizes the arterial blood flow and adequate oxygen delivery to these muscles. Pulmonary embolisms, the main source of morbidity and mortality after DVT of the lower extremities, are usually present with acute onset of shortness of breath, hypoxemia, and history suggesting the initial DVT, which has now broken down and migrated through the right side of the heart into the pulmonary arterial system. The presence of a blood clot blocks blood flow from the heart to part of the lungs, leading to hypoxemia, which can be exacerbated by any major lung disease. Clinical presentations of all hypercoaglyable states are similar, but there are some interesting differences. DVT tends to occur (whether hypercoagly or not) in patients with a history of trauma, pregnancy, use of oral contraceptives, or immobility, but rarely in adolescents or young adults. Hereditary hypercoagulating conditions are suspected in patients who are present with a thromboembolic event, usually because they are young or have recurrent clots. Events that occur without any specific risks are particularly suspicious. Because of the dominant pattern of inheritance, suspicion is aroused when other family members have been winding down the problem, emphasizing the importance of adopting family history. Despite various anomalies in coagulation, most thrombosis still occur in normal places (i.e. deep veins of the legs with or without pulmonary embolism). Other unusual areas (sagittal sinuses of the skull or mesenterical veins in the abdominal cavity) are more likely to be found in patients with concomitant coagulation disorders than those who do not. However, arterial thrombosis is extremely rare. Interestingly, only a minority of patients with hereditary hypercoagulation develop symptomatic thrombosis; this is especially true for heterozysto. Each disorder is slightly different, presumably due to redundancy factors in the coagulation cascade, and the performance of each condition varies in individual patients due to factors that we do not yet understand. Heterozygates, which develop thrombosis, are usually present in conditions of typical risk factor: trauma maintenance, immobilization of limbs, surgery or pregnancy. The gomoygous protein C or protein S flaws have the highest probability of causing the disease. Both conditions usually lead to thrombosis, which deadly at an early age (neonatal purple fulminans), although some patients may not be present until adolescence. Age. Protein C deficiency is unlikely to develop thrombosis throughout life, although they are about 4-6 times more likely to do so than the general population. Heterozygates for protein deficiency S have a 1 to 10 times increased relative risk of thrombosis. At DEFICIENCY is another significant defect in terms of the likelihood of thrombosis. In these patients, a lifelong 5-10-fold increased relative risk of thrombosis. The situation is complicated in the case of APC resistance. Heterozygates for APC resistance are likely to account for more than one third of all patients with family thrombosis. Although there is a 3 to 5 times increased relative risk of thrombosis for heterozygous of this mutation, heterozygousness rarely leads to thrombosis unless there is an additional risk factor for hypercoagulation. In heterozygous, proteins C and S can still break down the VIIIa factor, and the V factor is a relative, not an absolute insensitivity to APC. There is still a negative control of the cascade winding down on the X step TFPI factor as well. Even the homosigotic factor V Leiden does not inevitably cause thrombosis. Families in which homosigotic women are repeatedly pregnant have been easily described. This is somewhat surprising because pregnancy, a hypercoagulated condition in itself, leads to a decrease in the concentration of protein S, which is expected to increase resistance to protein C. However, there is at least a 20 to 50 times increased risk of thrombosis compared to the general population for homoigote for factor V Leiden. Individuals with prothrombin 20210 AG mutations are almost all heterozygates, with approximately 2-3 times higher risk of thrombosis than the general population. CONTROL 27. What is the Virginia triad of factors that predispose to the formation of intravascular blood clots? 28. The disadvantages are which proteins can lead to clinically significant thrombosis? 29. What is the basis for activating protein C resistance? CASE STUDIES Yeong Kwok, MD (see chapter 25, page 705 for answers) CASE 23 A 65-year-old formerly a good person presents to the clinic complaining of fatigue from a 3-month period. The survey shows diffuse weakness and a sense of wind when walking uphill or climbing more than one flight of stairs. All symptoms gradually worsen over time. There are no other complaints, and the review of the systems is otherwise negative. The patient has no significant medical history, social history or family history. On physical examination, he looks somewhat pale, with normal life signs. The physical examination is unremarkable, except for its rectal examination, which reveals a brown, guayak-positive stool (suggests the presence of blood in the stool). A blood test revealed anemia. A. What is the most likely form of anemia in this person? What is the probable root cause? B. What is the mechanism by which this disorder leads to anemia? C. What could have been see in the peripheral blood swab? D. What other tests can be ordered to confirm the diagnosis? E. What is the pathophysiological mechanism of fatigue, weakness and shortness of breath of this patient? Why is he pale? CASE 24 58-year-old black woman poses in the emergency room complaining of progressive fatigue and weakness over the past 6 months. She was short of breath after walking a few blocks. When reviewing systems, she mentions mild diarrhea. She noticed intermittent numbness and tingling of the lower limbs and loss of balance while walking. She denies other neurological or cardiac symptoms and has no history of black or bloody stools or other blood loss. When she is physically examined, she has tachycardia up to 110 b/d; other vital signs are within the normal range. The examination of the head and neck is distinguished by pale conjunctivas and muscular red tongue with loss of salt. The cardiac examination shows a fast regular rhythm with a 2/6 class of systolic murmur on the left stern boundary. The findings of the lung, abdominal and rectum examinations are normal. Neurological examination shows a decrease in the sensation of light touch and vibration in the lower extremities. The call hematology consultant is asked to see this patient because of the low level of hematocrit. A. What vitamin deficiency is the likely cause of this woman's anemia? How does this lead to anemia? B. How can you expect a stroke of peripheral blood to look like? What other blood tests can be ordered and what results are expected? What test can differentiate the various causes of this vitamin deficiency? C. Workup detects pernicious anaemia. What is the pathogenesis of this disease? What is the evidence to prove an autoimmune origin? D. What is the pathophysiological mechanism of symptoms of tachycardia, paresthesia and disturbance of this woman's proprioception? CASE 25 6-year-old boy represents the pediatric emergency department. His mother claims he had three days of general malaise and fever up to 38.5 degrees Celsius. He has no other localizing symptoms. The history of the disease is notable for multiple feverish diseases. His mother says: He seems to get sick every month. Physical examination is distinguished by lymphaderopathy of the cervix and oral ulcers. Blood tests show that the number of neutrophils is 200/L. The patient is hospitalized. The culture of blood, urine and cerebrosal fluid is negative, and within 48 hours the amount of his neutrophils returns to normal. Then he is discharged. A. What is the likely pathogenesis of cyclical neutropenia? What evidence supports this theory? B. What aspects of this presentation case support the diagnosis of cyclical neutropenia? What is the expected clinical course? C. Assuming that the diagnosis of cyclical neutropenia is correct, what would one expect a peripheral blood smear to look like? will the results of the bone marrow examination at this second appointment? What will they be like in two weeks? CASE 26 36-year-old man was hospitalized in after sustaining multiple fractures of the lower limbs by jumping from a three-high-rise building in a suicide attempt. His fractures required surgical repairs. He doesn't have a significant medical history. Current medications include morphine for pain and subcutaneous heparin for prevention from deep venous thrombosis. Consultation with the hematologist is requested due to the fall of platelets. During physical examination, the patient has multiple bruises, and the lower limbs are cast on a bilateral basis. Examination is otherwise normal. Laboratory tests over the past few days show the number of platelets, which has decreased from 170,000/L when taken to 30,000/L 5 days later. A. What is the most likely cause of this person's thrombocytopenia? B. What mechanisms do heparin sometimes cause thrombocytopenia? C. What are the possible clinical effects of this patient's thrombocytopenia? CASE A 27-year-old woman poses in the emergency room with a major complaint of acute onset of shortness of breath. This is due to right-sided chest pain, which increases with inspiration. She denies fever, chills, cough or other respiratory symptoms. She had no swelling of her lower limbs. She was not sick, bedridden, or motionless for long periods of time. Her medical history is notable for an episode about 2 years ago of deep venous thrombosis in the right lower limb when taking oral contraceptives. She was otherwise healthy and currently does not take any medication. Family history is remarkable for his father, who died of a pulmonary embolism. During physical examination, it appears alarmingly and in mild respiratory failure. She had tachycardia until 110 bpm, with a 20/min breathing rate. She doesn't have a fever, and her blood pressure is stable. The rest of the medical examination is normal. The chest X-ray film is normal. Vented perfusion scans show a high probability of pulmonary embolism. Given her history of deep vein thrombosis, a hypercoagulation condition is suspected. A. What is the Virginia triad of predisposing factors of venous thrombosis? What components of the triad can be present in this patient? B. What are some of the causes of hereditary hypercoagulating conditions specifically associated with the coagulation cascade? How do they lead to hypercoagulability? C. How can this woman be assessed for a inherited hypercoagulation condition? REFERENCES General Hematology Baker DC et al. 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