**Iron Deficiency Anemia.** This is a disease that can be, but often not, associated with improper iron intake (for example, duodenal resection). More often, it is associated with a slow occult bleed, such as colorectal cancer or menorrhea, or with pregnancy, where the parasite steals mom’s iron. Because the body does not have enough iron, labs are marked by decreased serum iron, decreased serum Ferritin, and increased total iron binding capacity (TIBC). Without the iron to make hemoglobin, the red blood cells are not “filled up” and thus are small (microcytic) and have an increased central pallor (Hypochromic). This can be treated with either Enteral or parenteral administration of iron. When found with esophageal webs and esophageal cancer, it is called Pummel-Vinson Syndrome.

**α-thalassemia.** α-thalassemia is genetic disease. It is an autosomal recessive disorder resulting from deletions on the α gene of chromosome 16. Each individual carries 4 copies of the α gene, 2 on each of their chromosomes. α-chain is required for all forms of hemoglobin, thus deficiencies can lead to serious anemia. If the patient is lacking only one gene, the condition is asymptomatic. If the patient is lacking two genes, either (-/α, α/α) or (-/-, α/α) then there is a mild anemia. However, if there are 3 mutations (-/-, -/α) then there is what is called Hemoglobin H, which is marked by a decreased MCV, marked anemia, and hemolysis from abnormal red blood cells with aggregates of unpaired β-chains. 4 mutations (-/-, -/-) is called hydrops fetalis and is incompatible with life. All thalassemias contain target cells on peripheral smear. In severe cases, frequent transfusions are required.

**β-Thalassemia.** β-thalassemia is an autosomal recessive disorder resulting from point mutations of the β gene on chromosome 11 causing mutations in splice sites. There are only two copies of the β-gene in each cell, one on each chromosome. The heterozygous condition (-/β) presents with a minor anemia, but risks passing on the mutation to their offspring. The homozygous condition (-/-) is marked by hemolytic anemia, splenomegaly, overexpression of fetal hemoglobin. In severe cases, frequent transfusions are required. You will get target cells just like in α-thal. However, you will see immediate changes in electrophoresis (minor = some fetal hemoglobin, major = almost all fetal hemoglobin)
Anemia of Chronic Disease. This is a disease whereby the body has the iron, its stores are filled, it just can’t USE the iron it’s got. Iron is stored in macrophages. Under chronic inflammatory disease, macrophages may retain the iron and prevent its release. The body knows the iron is there so it won’t try to get more, but it just can’t use it. This results in a **decreased TIBC with a decreased Serum Iron**. This also presents as a **Hypochromic microcytic anemia**, and may trick you into thinking its Iron Deficiency.

Glucose-6-Phosphate Dehydrogenase Deficiency. This is an **X-linked recessive disorder** more common in Mediterranean descent. G6PD is an enzyme that generates NADPH as it enters glucose into the **hexose monophosphate shunt**. The NADPH will be used to ultimately reduce diglutathione back to glutathione, the only means of protecting RBC membrane from oxidative free radicals. Patients with this disease, when exposed to oxidative stress (fava beans or malarial medications such as quinolone or primaquine) experience a **paroxysmal hemolytic anemia**. Often presents with **jaundice**, **hepatomegaly**. There are **Heinz bodies** within RBCs and **Bite Cells** are present on peripheral smear.

Warm Autoimmune Hemolytic Anemia (WAHA). This can be very long winded to learn. Essentially, what you must know is that this is **IgG associated**; hemolysis occurs at **warm temperatures** (your core, aka the spleen) and has a positive Coombs test at warm temperatures (37°C). While not hereditary, this disease presents with **spherocytes** on peripheral smear because RBCs have their proteins stripped by the spleen identifying the Fc portion of IgG, bound to the RBC membrane. Associated with **Lupus**

Cold Agglutinin Hemolytic Anemia. This is **IgM associated**, with hemolysis occurring in the liver. IgM identifies the **I antigen** on RBC surfaces at **colder temperatures** (nose, tips of fingers), and is then recognized in the liver by Kupfer cells. Histologically, **clumping** of RBCs (or a **HUGE MCV** which is in fact reading the one clump as one cell) is indicative of Cold Agglutinin Disease. It is associated with a recent **walking pneumonia** such as mycoplasma. Positive Coombs test at cold temperature (4°C)

Hereditary Spherocytosis. An autosomal dominant disease effecting either spectrin, ankrin or band 4.2. These are RBC membrane-protein associated and their loss results in deformity of the RBC membrane. It becomes vulnerable to osmotic forces, and the weakened membrane structure forces the RBC to take on a **spherical shape**, appearing as **spherocytes without central pallor** on peripheral smear. The increased volume and size causes the RBCs to spend longer in the spleen, resulting in extravascular hemolysis, **splenomegaly**, and reticulocytosis. It is the only disease with an increased **MCHC**.

Microangiopathic Hemolytic Anemia. This one is interesting. There is nothing wrong with the RBC itself. However, increased fibrosis in the vessels causes the RBCs to be literally clotheslined by the collagen. This is the only condition where you will see **Schistocytes** on peripheral smear. Associated with severe sepsis, usually of **gram negative bacteria**.

Sickle Cell Anemia. This is a long one. You have to know all the details. This is an **Autosomal Recessive** disorder common in African Americans. There is a point mutation at the 6th amino acid of the β-globin chain, switching hydrophilic glutamate for hydrophobic valine. In the heterozygous form, called **sickle cell trait**, which is for all intents and purposes asymptomatic, the patient may not even know they have it. The homozygous condition, called **sickle cell disease** (or ss disease), results in a **sickle-shaped RBC** in peripheral smear. Under low oxygen tensions, the β-chains aggregate and form long chains, giving rise
Path Heme Paragraph

to the rigid, abnormal shape of the RBC. Since RBCs must deform to get through capillaries and other small vessels, these sickle cells get stuck. They either occlude the vessel, causing ischemia or infarct (vaso-occlusive crisis) which is extremely painful and generally affects the joints, or they lyse from pressure pushing them through. Thus patients have bouts of vasoocclusive crises, anemias, and jaundice throughout the year. Early in childhood, repeated infarcts of the spleen will lead to autosplenectomy, making these patients effectively Asplenic. This predisposes them to infection by capsulated organisms and is why salmonella is the most common form of osteomyelitis in ss patients, where Staph Aureus is most common in everyone else. In addition, infection with parvovirus B19 which infects hematopoietic stem cells of the bone marrow and temporarily terminates their production, can induce aplastic crisis in ss patients. Since the virus pauses the production of RBCs and ss patients lyse their cells so frequently (therefore relying on new cells for them to live) these patients may in fact deplete their RBCs. Transfusions are almost a certainty. Hydroxyurea induces formation of fetal hemoglobin, which uses the gamma chain (without mutation) and limits crises. Bone marrow transplant is dangerous (because of the asplenia) and is a new therapy. If the patient has a single gene for sickle cell, and another for hemoglobin C (another point mutation at the 6th position) the patient is said to have sc disease, which is essentially the same disease, just much milder, usually without vasoocclusive crises. Gel electrophoresis of hemoglobin can reveal which disease a patient has (A1/A1 = normal, A1/S = sickle trait, A1/C = Hemoglobin C, S/S = ss disease, S/C = sc disease)

Vitamin B12 Deficiency. Vitamin B12, or cobalmin, has huge stores in the body, lasting years to a decade without depletion. Vitamin B12 is ingested, bound to haptocorrin (R-Factor) secreted by parietal cells in the acidic pH of the stomach. There in the stomach parietal cells also release intrinsic factor (IF) as well as haptocorrin. In the alkaline pH of the duodenum, B12 dissociates from haptocorrin and associates with intrinsic factor and is absorbed in the terminal ileum. B12 deficiency is seen in strict vegans (since B12 is attached only to animal products), ileal resections (Crohn’s Disease), and pernicious anemia (an autoimmune disorder that either destroys the parietal cells, forms IgA to IF, or both). B12 is required for DNA synthesis and therefore division. Cells lacking B12 are therefore huge. They are not broken, so the cytoplasm still works, just the nucleus will not divide. You see a megaloblastic erythrocytes and Hypersegmented neutrophils on peripheral smear. Labs show elevated homocysteine and methyl malonic acid. The MCV is high (duh). Severe deficiencies result in demyelination of the dorsal and lateral horns of the spinal cord resulting in ataxia and loss of vibratory sense. B12 can be administered enterally or parenterally, though the neurologic symptoms are permanent.

Folate Deficiency. Folate, like B12, is required for DNA synthesis. However, the stores of Folate are low, and folate is found in leafy greens. Alcoholics (who rarely eat salads) are the most likely in the general population to present with folate deficiency. You see the same megaloblastic erythrocytes and Hypersegmented neutrophils on peripheral smear. Only homocysteine levels are elevated. You do not see the demyelination of the spinal cord. You do see folate deficiency in pregnant females who don’t know their pregnant, leading to neural tube defects in pregnancy. There are enteral and parenteral options for supplemental administration. Keep in mind that you can treat a B12 deficiency by throwing a lot of Folate at it. The problems will subside until they develop the irreversible neurologic effects. You must distinguish one from the other.
**Acute Lymphoblastic Leukemia.** This is the most common leukemia of childhood and responds very well to treatment (which is usually radiation and bone marrow transplant). This is an acute (problems with differentiation) lymphoblastic (precursors of lymphocytes) leukemia (spread in the blood). Patients are young, present with bone pain and frequent nose bleeds, and may have a petechial rash. The blast cells are in both the bone and the periphery, crowding out the good stuff. Thusly, they present with hypercellularity in the bone marrow and a pancytopenia with multiple undifferentiated blasts on peripheral smear. Remission/Cure rate is quite high.

**Acute Myeloid Leukemia.** This occurs in middle age and responds very poorly to treatment. This is an acute (problems with differentiation) myeloid (precursors of RBCs) leukemia (present in the blood). Patients are middle aged, present with fatigue, infection, and bleeding and may have lymphadenopathy and hepatosplenomegaly. Since there are multiple erythroid precursors, there are multiple subtypes, named M0-M7. The one you must know is M3, characterized by a 15:17 translocation to the retinoic acid receptor. While most AML responds poorly to therapy, administration of Vitamin A (retinoic Acid) will aid in the differentiation of the myeloblasts, avoiding much of the symptoms. Patients will present with pancytopenia and auer rods on peripheral smear. If you see an Auer rod, it is automatically AML, and the prognosis is poor.

**Chronic Myelogenous Leukemia.** This occurs both in young men in their 20s and in older patients. It is the leukemia you must know. Characterized by FISH studies, it is caused by a 9:22 translocation (called the Philadelphia Chromosome) with the formation of the BCR-ABL fusion protein. This expresses ABL, a tyrosine kinase, constitutively in the cytoplasm, overactivating growth pathways. Targeted therapy with Imatinib (Gleevec) works by binding the ATP-binding pocket, inhibiting the tyrosine kinase, inhibiting the proliferation. It is characterized by a proliferation of granulocytes, with basophilia or neutrophilia on peripheral smear, appearing as a leukocytosis with left shift (lots of WBCs, some of them immature). The marrow is hypercellular but the granulocytes crowd out everything else, and thus the patient is at risk for thrombocytopenia/bleeding and anemia. If the disease is allowed to progress, there can be a
Path Heme Paragraph

cataclysmic reversion to AML, called a **blast crisis** which is generally the marker of death. Even with treatment, life expectancy does not exceed 10 years.

**Chronic Lymphoblastic Leukemia.** This is the **leukemia of old age** (greater than 60). It is **chronic** (cells are differentiated) **lymphoblastic** (T or B Cells) **leukemia** (in the blood). This is a proliferation of **B cells** that express **T Cell marker CDS** in the bone marrow. **Smudge cells** are present in the periphery. There are few B symptoms, except for **lymphadenopathy** that can result in **hypogammaglobulinemia** (infection) and **WAHA** (hemolytic anemia). These cells are **TDT** and **CALLA** positive (immature markers).

**Polycythemia Vera.** This is a disease of **middle aged, hypertensive, obese males.** Essentially, hematopoietic stem cells become **hypersensitive to erythropoietin**, a result of a **JAK-STAT mutation**. Thus the labs will come back with a **decreased epo level** (the body is trying to compensate) despite **panmyelosis** (elevated Hgb, Hct, and platelets). In the early states there is a hypocellularity of the marrow with an increased Hematocrit. The late stage is called the **spent phase**, where there is a **fibrotic marrow** with significant **extramedullary hematopoiesis**. This late stage resembles Primary Myelofibrosis. Patients are prone to **bleeds** and **clots**, often occurring in the extremities. **Phlebotomy** works really well to treat these patients. Myelosuppressive or chemotherapeutic agents may lead to AML.

**Essential Thrombocytosis.** This is more of a Tulane examable than Board testable. The exact mechanism is unknown, but it is thought to be a similar mutation to **PV** (a JAK mutation) that occurs only in platelet precursors. This leads to clots, bleeds, **burning in the hands and feet**, though is **indolent** (comes and goes). The peripheral smear reveals **giant platelets** within a **thrombocytosis**.

**Primary Myelofibrosis.** This is a problem of **fibroblasts**. An overproduction of PDGF or TGF-β in the **marrow** causes an overgrowth of fibroblasts and collagen deposition. Essentially, the collagen crowds out everything. RBCs from the marrow are “squeezed through” the fibrosis and appear as **tear-drop cells** on peripheral smear. There is **extensive extramedullary hematopoiesis** in the spleen and in the liver leading to hepatosplenomegaly. The inability to produce marrow cells results in **anemia** and a **decreased hematocrit**.

**Multiple Myeloma.** This is a disorder of **plasma cells**, which are the final determinants of B cells. In this disease there is a **monoclonal expansion** of plasma cells. Since plasma cells secrete Ig, and all the plasma cells from this expansion secrete the same Ig, there is an **M Spike** on Ig electrophoresis from increased production of that one Ig molecule. In addition, there are **Bence-Jones proteins** (pieces of the Ig light chain) in the urine, **anemia, hypercalcemia, lytic bone lesions** (that appear “punched out” on x-ray). The bone marrow contains a **fried egg appearance**. An **autologous** bone marrow transplant can be performed.

**Hairy Cell Leukemia.** This is stupid. You will see more questions on this in practice books than there are patients. Why? Because its treatable. This is a **T cell proliferative disorder** characterized by **lymphocytes with fibrous projections** on peripheral smear. It is positive for the **TRAPP test** and is treated with dichlorodeoxyadenosine (2-CI-DNA). If you go for a bone marrow biopsy you might encounter a **dry tap**.
These next “two” are complicated. Hodgkins and Non-Hodgkins Lymphomas are actually about 9 diseases in one. What separates a Hodgkins from a Non-Hodgkins is the presence or absence of Reed-Sternburg Cells. These are the “Owl Eye” cells similar to what we learned in CMV, except these are in lymph nodes. They are CD45 negative CD30/CD15 positive. All these diseases are lymphomas (contained proliferations of the lymph = marrow, spleen and lymph nodes) versus the leukemias (which were in the peripheral blood). Tulane did a brief survey of the different diseases; Kaplan seemed to care very little with you knowing everything about each subtype of the disease.

Hodgkins Lymphoma. This is the more benign, less painful, less killing, more curable form of lymphoma. Patients will present with mild or absent B symptoms (B symptoms are the presence of nontender rubbery lymphadenopathy with fever, fatigue, and weight loss). Hodgkin lymphomas spread contiguously, that is, invading a chain of lymph nodes linearly. When caught early, when benign, and without B symptoms, the end result is greater. There are 5 subtypes of Hodgkins Lymphoma.

- **Nodular Sclerosis** = fibrous bands divide tumor into nodules, forming lacunar cells where the nucleus appears to be sitting in an empty space.
- **Mixed Cellularity** = mononuclear reed-sternburg with eosinophilic background
- **Lymphocyte Rich** = rare, seen in older patients, with predominantly reactive T cells, EBV
- **Lymphocyte Depleted** = Rarest, older males, associated with HIV and EBV, poorest prognosis
- **Nodular Lymphocyte Predominant** = rare, younger males, popcorn reed-sternburg cells

Hodgkins Lymphomas are staged according to lymph involvement.

- Stage (1) = One lymph node involved
- Stage (2) = Multiple lymph nodes on one site of the diaphragm
- Stage (3) = Multiple lymph nodes on both sides of the diaphragm
- Stage (4) = Extralymphatic Masses (spleen counts as inside the lymph)

Non Hodgkins Lymphoma. This is the worse, more severe, poorer prognosis form of lymphoma. Patients present with an abundance of B symptoms, are usually older (or are from Africa), do not spread contiguously and pretty much mark a patient’s death. Like hodikins, there are multiple types with much greater relevance than the subtypes of Hodgkins. The first two are the most significant; the others should be looked at for Tulane, but probably will not show up on the Boards.

- **Burkitt’s Lymphoma.** Associated with EBV, there is both the African Endemic form (worse) and the nonendemic form we see in the US. It is still maintained by an 8:14 translocation with overexpression of c-MYC oncogene. This is a rapidly growing tumor (doubling time is about 2 days). This is characterized by a starry-sky appearance on histology. Patients may present with tumor lysis syndrome with therapy, resulting in a hyperkalemia, hypophosphatemia, and renal failure. Picture the African boy with a giant tumor stretching his face off.
- **Follicular Lymphoma.** It is an indolent and common disease of adulthood. It is associated with a 14:18 translocation with overexpression of the anti-apototic gene BCL-2. There is the diagnostic buttock cell in peripheral smear. For the board’s use buttock cell, for life, we use immunohistochemistry to scan for the BCL-2 overexpression
- **Mantle.** 11:14 translocation, overexpression of Cyclin D1
- **Marginal.** 11:18 translocation, associated with autoimmune malomas, h pylori induced
- **Diffuse Large B Cell Lymphoma.** This is an aggressive tumor that can arise anywhere, is associated with **immunocompromised states**, and may be associated with viruses. These are diseases you have already encountered thus far: post-transplant proliferation disorder (EBV) and Kaposi sarcoma (HHV8)

**Waldenstrom Macroglobulinemia.** Passing mention in Tulane, stuck on to the end of every Board review I’ve seen. Be aware of it, details can be left out. This is a **plasma cell dyscarias** that results in the secretion of the very large **IgM**. This causes **hyperviscosity syndrome** leading to the sluggish moving of blood resulting in infarction, clotting, and edema. It looks just like Multiple Myeloma with Bence Jones protein, M-spike, and hyperlg. If you see a question where your reaction is multiple myeloma, but it just doesn’t sound right, pick Waldenstrom.

<table>
<thead>
<tr>
<th>PATHOGNOMONIC CELL TYPE</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smudge Cell</td>
<td>Chronic Lymphoblastic Leukemia</td>
</tr>
<tr>
<td>Hairy Cell</td>
<td>Hairy Cell Leukemia</td>
</tr>
<tr>
<td>Tear-Drop Erythrocyte</td>
<td>Primary Myelofibrosis</td>
</tr>
<tr>
<td>Bite Cell or Heinz Bodies</td>
<td>G6PD Deficiency</td>
</tr>
<tr>
<td>Ballerina Skirt or Down Cell</td>
<td>Epstein-Barr, Burkitt’s Lymphoma</td>
</tr>
<tr>
<td>Buttock Cell</td>
<td>Follicular Non Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>Auer Rods</td>
<td>Acute Myelogenous Leukemia</td>
</tr>
<tr>
<td>“Owl Eye” in Lymph = Reed-Sternburg Cells</td>
<td>Hodgkins Lymphoma</td>
</tr>
<tr>
<td>Starry Sky Histology</td>
<td>Hodgkins Lymphoma</td>
</tr>
<tr>
<td>Cerebiform T Cells</td>
<td>Sezary Syndrome</td>
</tr>
<tr>
<td>Flower Pedal Nucleus</td>
<td>HLTV-1 T cell Leukemia</td>
</tr>
<tr>
<td>Howell-Jolly Bodies</td>
<td>Sickle Cell Anemia</td>
</tr>
<tr>
<td>Bence-Jones Protein</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Spherocytes</td>
<td>Hereditary Spherocytosis or Autoimmune Hemolytic Anemia</td>
</tr>
<tr>
<td>Schistocytes</td>
<td>Microangiopathic Hemolytic Anemia (TTP/HUS/DIC)</td>
</tr>
<tr>
<td>Target Cells</td>
<td>Thalassemias (any symptomatic, alpha or beta)</td>
</tr>
<tr>
<td>Basophilic Stippling</td>
<td>Lead poisoning (we didn’t do this in this block)</td>
</tr>
<tr>
<td>Ring Sideroblasts</td>
<td>Sideroblastic Anemia</td>
</tr>
</tbody>
</table>

| **TRANSLLOCATION TO DISEASE** (in order of importance) |
|-------------------------|---------------------------------------------|
| Translocation | Disease                                      | Protein/Pathology |
| 9:22               | Chronic Myelogenous Leukemia | BCR-ABL protein |
| 15:17              | Acute Myeloid Leukemia, M3    | Retinoic Acid Receptor - PML |
| 8:14               | Burkitt’s Lymphoma            | c-MYC            |
| 14:18              | Follicular Non Hodgkin’s Lymphoma | BCL-2          |
| 11:18              | Marginal Non Hodgkins         | H. Pylori Maltoma |
| 11:14              | Mantle Non Hodgkins (lowest yield) | Cyclin D        |
HOW PLATELETS CLOT

After vascular injury there is an immediate vasoconstriction to reduce blood flow and facilitate clots. The damaged vasculature exposes collagen, which is sticky to platelets. Endothelial Cells produce von Willebrand Factor which binds to the collagen. vWF interacts with Glycoprotein Ib on platelets, tethering them to the vasculature. This interaction of vWF to Glyc-1b is called adhesion (the platelet adheres to the vascular wall). Adhesion allows the platelets to release ADP and localizes the platelets as the endothelial cells release Thromboxane A2. ADP and TXA2 cause the platelets to stick to each other, a process called aggregation. The platelets get linked together by fibrinogen and vWF, attaching to each other by Glycoprotein Ib/IIa. Eventually, fibrin stabilizes the platelet plug. Now, the body isn't going to just let the platelets clot without control. The endothelial cells also produce prostaglandins (PGI2) and nitric oxide which inhibits platelet aggregation. Platelets are tested with bleed time.

Ok, great. That’s how platelets work. How about coagulation; the clotting cascade? Everything we just learned about was focused on platelets. The Factor System is annoying and difficult. They are not named in the order they occur and there are many intermediates. However, in its simplest form we have the intrinsic system that starts with factor 12 (Hageman’s Factor) and leads to fibrin and the extrinsic system that starts with factor 7 and leads to fibrin (as well as facilitate the intrinsic system). The critical factors are Factor X (activated by both the intrinsic and extrinsic pathways), Factor V (required for Factor X to activate thrombin), Thrombin (which is required to activate fibrin) and Factors 7 and 12 (as discussed above). You might want to look at the outline format for the picture. It’s not worth memorizing the clotting cascade in every detail, but it’s worth looking at a good 5 times. Just like the platelets weren’t allowed to clot like crazy, neither is general coagulation. Protein C is activated by endothelial cells, a vitamin K dependent plasma protein that acts to cleave factors Va and VIIIa inhibiting coagulation. Without Factor 7 there is no extrinsic system, without factor5 there is no activation of thrombin. Protein S is an endothelial cell derived protein that is a cofactor for activated protein C.

Intrinsic System is tested with PTT. Extrinsic System is tested with PT.
Path Heme Paragraph

MAKES YOU BLEED

Immune Thrombocytopenia Purpura (ITP). Formerly called idiopathic, we now know it is an autoimmune disorder. Being autoimmune, it primarily targets women in early adulthood. This forms antibodies to glycoprotein2a/3b preventing platelet aggregation. The spleen generates these antibodies and, once tagged by immunoglobulins, the platelets are destroyed by macrophages. Therefore, these patients have a chronically depressed platelet count (the thrombocytopenia). This causes an elevated bleeding time. However, since the clotting factors are not affected, there is no change in the PT or the PTT. Since this is a disease of platelet destruction (as opposed to failed platelet formation), the bone marrow will demonstrate abundant megakaryocytes as the marrow attempts to produce the missing platelets. The disease can be treated by immunosuppressants (since it is autoimmune) followed by splenectomy, since that is where immunoglobulins are coming from.

Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS). These two diseases are “the same” but on opposite ends of a spectrum. TTP is a disease of adulthood presenting with neural symptoms. HUS is a disease of childhood, primarily affecting the kidneys, usually after infection with E Coli 0157:H7 (EHEC). TTP causes platelet clots that occur throughout the body. This is not a coagulopathy since the clotting cascade is not involved, and these platelet clots do NOT contain fibrin. However, blood vessels fill with the pink protein of platelets, giving rise to the name hyaline clots. Since the platelets are being used up in the clots, when we take a blood sample, the platelet count is decreased, and there is an increased bleeding time. Again, since there coagulation cascade is not involved, PT and PTT are normal. Both HUS and TTP are characterized by a classic pentad: fever, thrombocytopenia, neurologic symptoms (adults and TTP), renal symptoms (kids and HUS), and Microangiopathic anemia (presence of Schistocytes on blood smear). So, if you see a kid with renal problems, think HUS; if you see an adult with Neuro symptoms think TTP, but the pathogenesis is the same for both.

Hemophilia A. This is an x-linked recessive disease that is caused by a deficiency in factor VIII. Factor VIII was required for the extrinsic pathway to lead into the common pathway, activating Factor X. These patients are usually boys that develop deep bruising, characterized by spontaneous hemorrhage into the joints (hemarthrosis), profuse postoperative bleeding, and easy bruising after minor trauma. Give these kids Factor VIII concentrate.

Hemophilia B. This is also an x-linked recessive disease, only this is caused by a deficiency in factor IX. Factor 9 was required for the extrinsic pathway, used with factor VIII to activate Factor X. Since the pathogenesis is the same as Hemophilia A, the presentation is the same. They are usually boys that develop deep bruising, characterized by spontaneous hemorrhage into the joints (hemarthrosis), profuse postoperative bleeding, and easy bruising after minor trauma. The only difference between Hemophilia A and B is the factor assay. Hemophilia A is missing Factor 8, Hemophilia B is missing Factor 9. Hemophilia B is also called Christmas Disease. Give these kids Factor IX concentrate.

Vitamin K Deficiency. Vitamin K is necessary for gamma-carboxylation (activation) of Factors 2,5,7,9, and 10. Without Vitamin K, you have a broken Intrinsic Pathway and a broken Extrinsic Pathway, meaning that both PT and PTT go up. Vitamin K requires fat for absorption, so may occur in malnourished states. It comes from leafy greens. Please note that Vitamin K works in the liver; if there is a liver failure, there is a similar presentation to Vitamin K deficiency = ↑PT and PTT.
**Von Willebrand's Disease.** This is the most common bleeding disease caused by either a quantitative or qualitative deficiency of von Willebrand Factor. This presents like a problem with platelets, but it isn’t really a problem of platelets. The problem is that platelets have nothing to stick to. These patients present with, spontaneous mucosal bleeding (nosebleeds are common), exaggerated menorrhagia, and prolonged bleeding. Since this is a platelet disease, it makes sense that bleeding time is elevated. However, interestingly, platelet count is normal and PTT is also elevated. This is caused by a secondary Factor VIII deficiency. vWF circulates with Factor VIII, protecting it from degradation. With a decreased vWF, Factor VIII gets degraded, and there is a functional loss of Factor 8. In a minor deficiency, administration of demopressin releases vWF from Weibel-Palade bodies in endothelial cells and corrects levels. In severe cases, no treatment is available.

**Disseminated Intravascular Coagulopathy.** This is a bleeding disorder that is always secondary to something else. Usually it is secondary to an obstetrical emergency (abruptio placentae) or gram negative infection. It can be caused by saline fluid overload. What happens is essentially you clot all over the body, deplete your platelets and factors, then start to bleed from everywhere. In this case, there will be an elevated bleeding time, PT and PTT. The confirmatory test is D-dimer, also called Fibrin Split Products. This tells us there was a clot, and now there isn’t. You must be cautious when taking the exam. Do not jump to DIC when you see D-Dimer in the questions stem. This might be a clot that resolved itself, or it might be a clot you treated with fibrinolytics. If a patient is bleeding everywhere, is a female, and has D-Dimers, she is likely to have DIC.

**MAKES YOU CLOT**

**Factor V Leiden.** This is the most common congenital etiology of venous Hypercoagulability. There is a mutation in Factor V on the Protein C binding Site. This renders Factor V invulnerable to Protein C. That means that Factor V gets activated, and stays activated. It cannot be turned off, even when we want to turn off. This causes a Hypercoagulability that present with Deep Vein Thrombosis or Pulmonary Embolus that tends to run in families. These women get clots, and get them a lot. We treat these patients by giving them warfarin (chronic, target INR 2-3) or heparin (acute, in hospital).

**Prothrombin 20210A.** This is the second most common congenital etiology of venous Hypercoagulability. There is a mutation of the untranslated region of Prothrombin gene, leading to ↑ levels of Prothrombin. Increased levels of Prothrombin mean increased levels of thrombin, and more clotting.

**Protein C and Protein S Deficiency.** Protein S makes Protein C work better. Protein C inactivates Factor V. If there is a break in Protein S or in Protein C, factor V will stay on, presenting just like in Factor V Leiden.

There isn’t a disease associated with them, but you should be aware of the plasminogen system and the antithrombin system. Plasminogen is activated to plasmin which cleaves up fibrin clots into fibrin split products, called D-Dimers. This happens when you give TPA (a clot buster). Antithrombin binds to both Factor 10 and Thrombin to inhibit clotting. It requires Heparin to work. Low Molecular Weight Heparin is given when TPA cannot; it blocks Factor Xa activation, preventing further clots. It allows thrombin to work, reducing the chance of bleeding associated with Unfractionated heparin.
Path Heme Paragraph

SHOCK

Cardiogenic Shock. Shock caused by circulatory collapse in response to a failure of the pump. The heart tries to circulate the blood it needs to, but is unable to keep up. Blood vessels tighten up to maintain pressure, and are NOT defective. This usually follows a massive myocardial infarction, though may be the result of heart failure.

Septic Shock. Caused by a gram-negative infection, it is generally in response to a systemic infection (aka, sepsis). Initially, vasodilation allows increased blood flow to fight the infection. Lipopolysaccharide from the gram negative organism’s cell wall is a direct stimulant to vasodilation. Combine that with the interleukins and other chemokines, massive systemic dilation causes venous pooling resulting in an effective hypovolemia. Pressors can be used to maintain pressure until the infection is cleared. There are some organisms that carry superantigens that may produce septic shock, such as Staph Aureus in the Toxic Shock Syndrome.

Neurogenic Shock. Seen in severe trauma with reactive vasodilation. Sympathetic control is lost due to damage of the nervous system. Without sympathetic tone, vessels dilate, permeability increases, and fluid shifts away from vasculature, pooling in the veins and interstitium.

Anaphylactic Shock. Massive degranulation of mast cells causes wide spread histamine release. This is a potent vasodilator. The reason we give epinephrine during anaphylaxis is not for its airway management (though it does cause bronchodilation) but rather for its vasoconstrictor properties. Blood pools in veins and interstitium as histamine causes a massive dilation.

Hypovolemic Shock. Usually associated with a loss of fluid, this may either be trauma/hemorrhage or simply diarrhea/vomiting. Pressors in this case are hazardous, fluid replacement should be initiated to expand the fluid volume.

EMBOLI

Arterial Thrombi. These thrombi are formed in areas of active blood flow. When mature, they demonstrate alternate dark grey layers of platelets interspersed with lighter layers of fibrin, termed the lines of Zahn. Arterial thrombi can occlude the lumen leading to impaired blood flow, ischemia, or infarction. They may either resolve or sustain. Collaterals or recanalization is required for reperfusion.

Venous Thrombi. These are formed in areas of less active blood flow, usually in the veins of the lower extremities. These are the “deep vein thrombosis” (DVT) we hear a lot about. They are dark red and have no lines of Zahn. They occur with venous stasis and congenital diseases of Hypercoagulability. It is important that bed-ridden hospital patients get up and move to prevent venous thrombi.

Thromboembolus. Both arterial and venous thrombi may become an embolus. Occlusion to blood flow may result simply as a thrombus. If a piece of the friable thrombus breaks off, it travels downstream. Venous Thrombi give rise to pulmonary embolism (see pulmonary block). Arterial Thrombi give rise to systemic emboli, such as the heart (MI, see cardio), brain (stroke, see Neuro), or extremity (infarction, gangrene).
Fat Emboli. Fat emboli are usually the result of **trauma to a long bone**. Fat from the marrow is released into the blood stream and goes systemic. The classic presentation is **pulmonary distress** (pulmonary embolism), **cutaneous petechiae** (stuck in the capillaries of the extremities), and **neurologic symptoms** (called a shower embolus, see Neuro).

Air Emboli. Always an **iatrogenic disease**. It may be caused by the injection of air through an improperly established IV or from divers who ascend too quickly (the bends). Follows the same course as blood flow, so can affect the lungs (venous air embolus) or any systemic organ (arterial air embolus).

Amniotic Fluid Embolus. If mom is delivering baby and ends up with DIC and fetal components in her blood, she has amniotic fluid embolus. This can be fatal.

Starting at “Shock” to the end of this segment is fairly curt. That is because you will get the details of these diseases and events later on in each subject. For example, when we discuss brain infarctions, a “shower embolus” has a special presentation; it is a fat embolus from a broken femur. This last section was written long after the block had ended, so are writing based on our review and on the outline format’s description of the vascular lecture. You are going to go over edema in GI-Liver block, Myocardial Infarction and Shock in Cardio Block, etc. You should really be focusing on the anemias, the leukemias/lymphomas, and the coagulopathies. Basically, what we are telling you is that if you go into a BRS or a Rapid Review, there is going to be a whole lot more than there is here for the vascular sections (check out chapter four in 3rd Edition BRS Pathology to see what I mean).

There is a lot in this block. A lot. It’s a big test, one of the largest. Make sure you check out the rapid review sheets at the end of the outline format; there are 4 pages of diseases with 2-4 high yield points about each one.