Lecture 2C:
Evaluation of Hemostasis
Disorders of Hemostasis

Evaluation of Hemostasis

Clinical Assessment of Bleeding Problems

- Family history (of hemophilia or von Willebrand disease, for example)
- Location, duration, severity of bleeding
  - Vascular and platelet defects (primary hemostasis disorders) are associated with **immediate** brief bleeding in skin or mucous membranes.
  - Coagulation disorders (secondary hemostasis disorders) are associated with **delayed** bleeding into deeper structures such as muscles or joints.
- Systemic disease: liver disease, lupus, cancer
- Medication history: aspirin, NSAIDs, antibiotics, alcohol, chemotherapy, thrombolytics
- Evidence of hemarthosis—bleeding into joints.

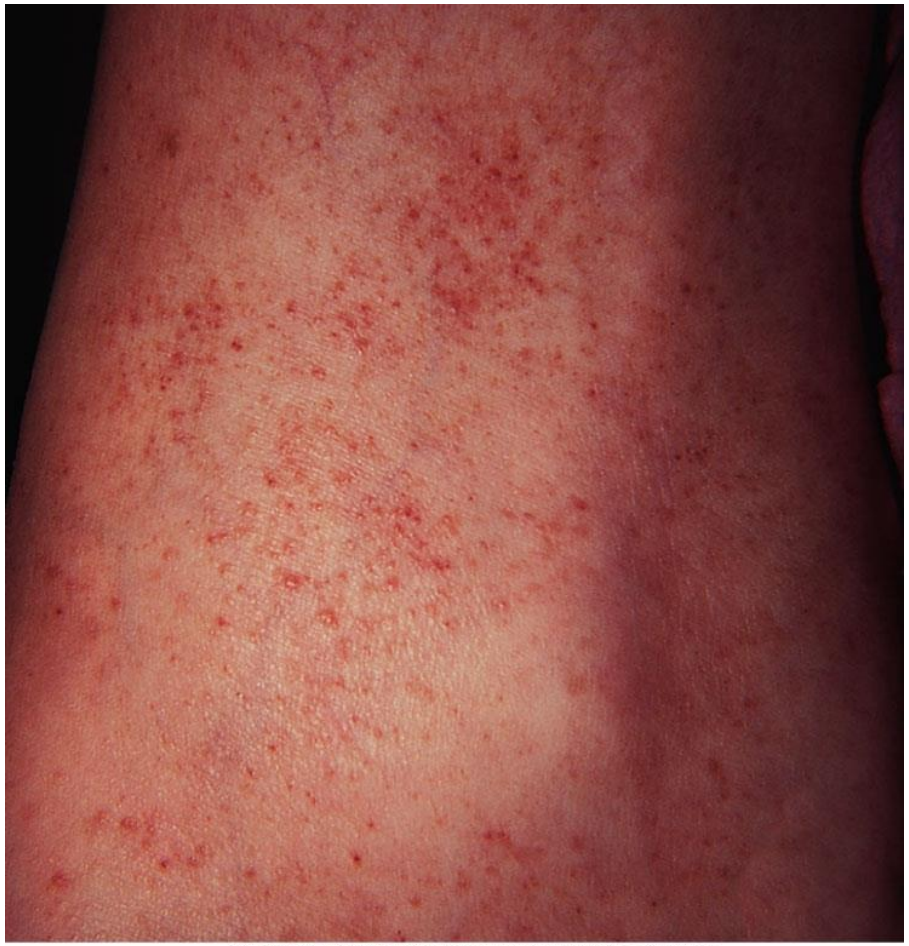
Evaluation of Hemostasis 1

External signs of bleeding disorders

- **Pallor** (pale skin) or **jaundice** (yellow skin and sclera)
- **Epistaxis** (bleeding from the nose)
- **Telangiectasia** (spider or star angiomas)
  - Caused by **dilation** of dermal capillaries and small arteries
  - Red to violet in color and blanch with pressure
- **Purpura**
  - Flat, non-blanching red or purple spots in the skin
  - Caused by dermal capillary **hemorrhage** that is NOT due to blunt force trauma. (Bruises are due to blunt force trauma.)
  - May indicated vascular or platelet disorders
  - Pinpoint purpura areas are called **petechiae.**
  - Purpura areas larger than 5 mm in diameter are called **ecchymoses**.

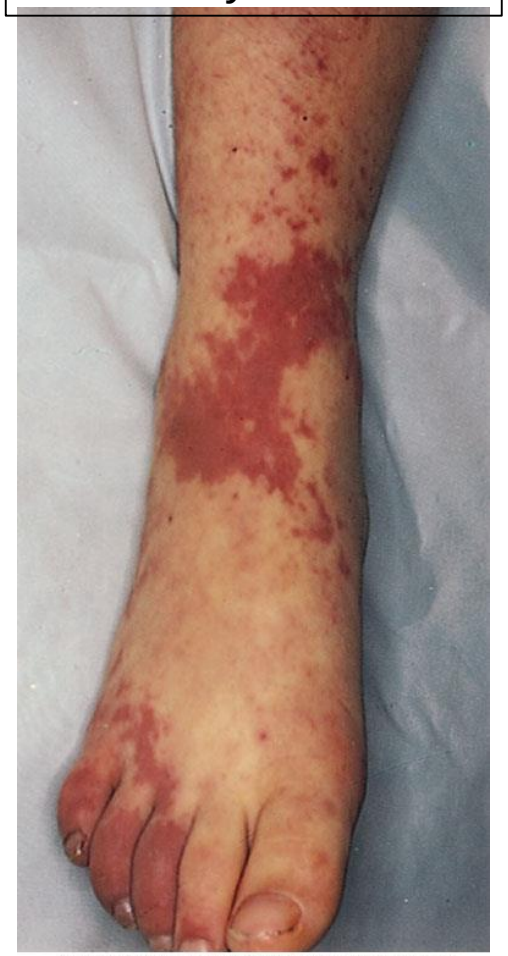
Evaluation of Hemostasis 2

Purpura: Petechiae



From Dockery GL: Cutaneous disorders of the lower extremity, Philadelphia, 1997, Saunders.

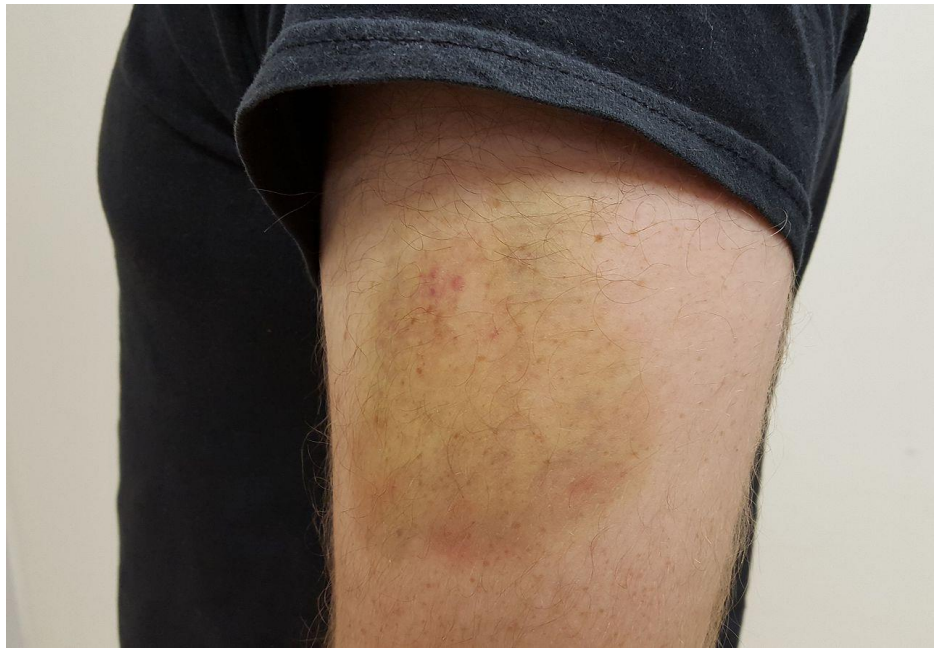
Purpura: Ecchymoses



From Hurwitz S: Clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence, ed 2, Philadelphia, 1993, Saunders, p 269.

Evaluation of Hemostasis 3

Bruise



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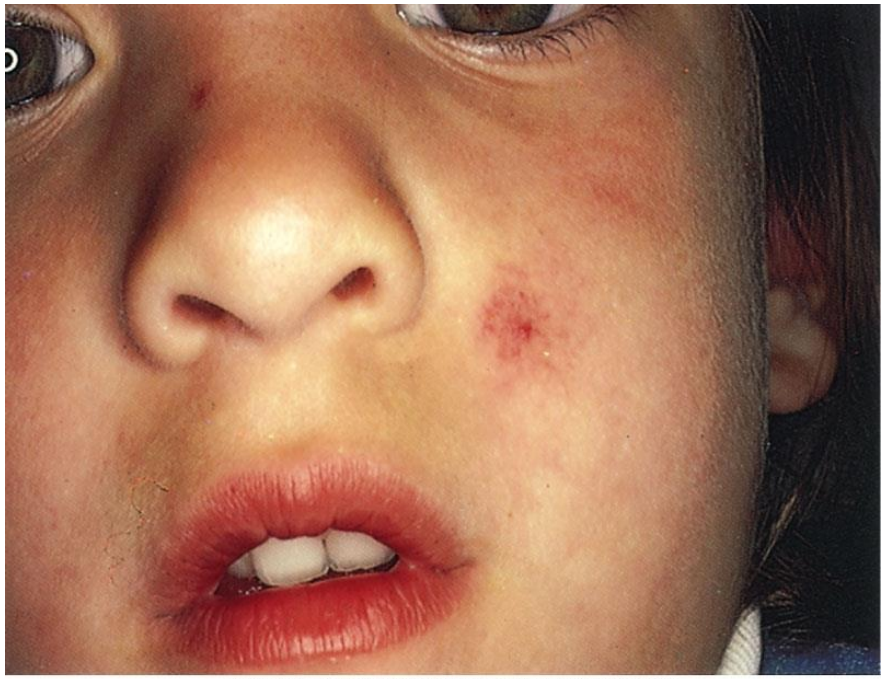
Telangiectasia



From Hurwitz S: Clinical pediatric dermatology: a textbook of skin disorders in childhood and adolescence, ed 2, Philadelphia, 1993, Saunders, p 266.

Evaluation of Hemostasis 4

Evidence of Internal Bleeding:

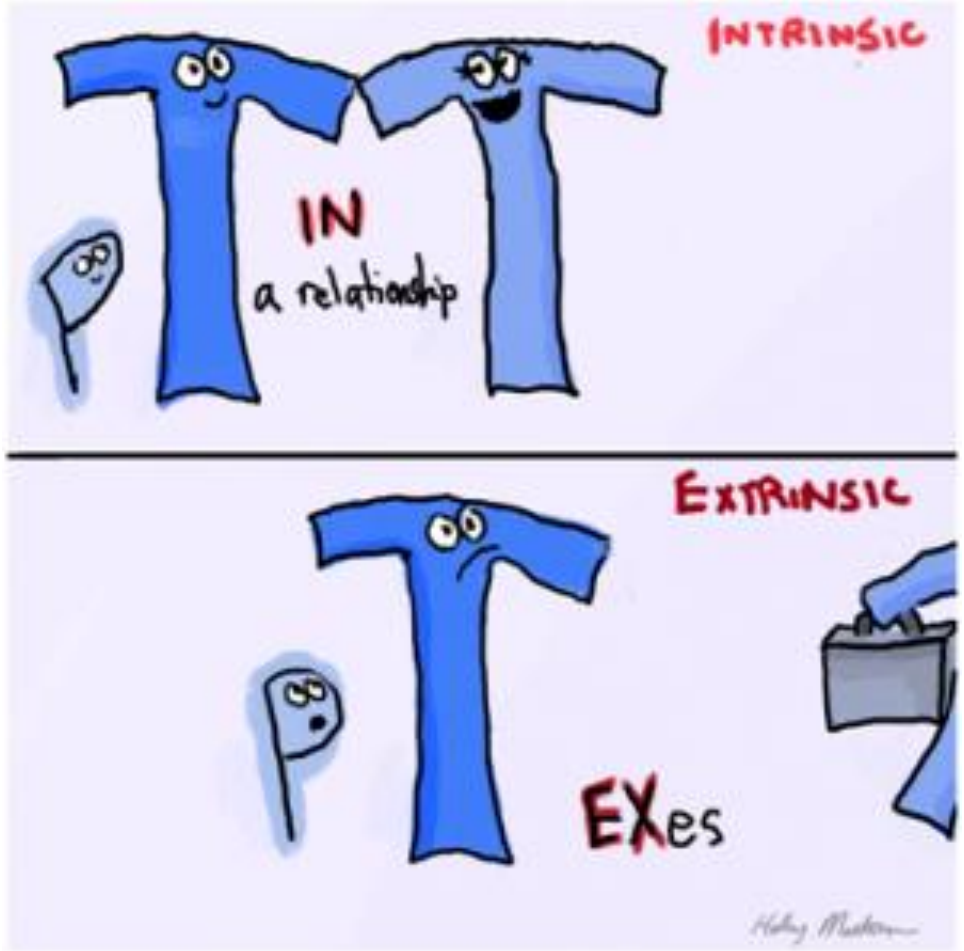
- **Blood in excretions or secretions**
  - Hematochezia or melena (feces)
  - Hematuria (urine)
  - Hemarthosis (joints, synovial fluid)
  - Hematemesis (vomit)
  - Hemoptysis (gastric drainage or saliva)
  - Menorrhagia (excessive menstrual bleeding)
  - Epistaxis (nose bleed)
- **Acute abdominal or flank pain**
- **Hypovolemia** (reduced vascular volume) may lead to shock.
- The two sites at which bleeding is most life-threatening are the oropharynx (can block the airway) and brain tissue.

Evaluation of Hemostasis 5

Laboratory Tests

- **CBC** (complete blood cell) with platelet count
- **Peripheral blood smear**-histological examination of blood
- **Coagulation Tests**
  - **Prothrombin time (PT)** aka Pro-Time
    - Normal is 11-12.5 sec
    - Evaluates clotting Factor VII of the **extrinsic** pathway and Factors I, II, V and X of the **common** pathway.
  - **INR** (international normalized ratio)-expresses prothrombin time as an internationally accepted ratio; most often used to assess anticoagulation therapy
    - Normal depends on Coumadin dose, varies between 1.5 and 4.0
  - **Activated Partial Thromboplastin Time (aPTT)**
    - Normal is 30-40 sec
    - Evaluates clotting factors VIII, IX, XI and XII of the **intrinsic** pathway.

To help you remember aPTT vs PT tests☺



Evaluation of Hemostasis 6

Coagulation Tests, cont.

- **Fibrin Split Products (FSP) aka D-Dimer Test** assesses the degradation of fibrin into smaller molecules (fibrin split products aka d-dimers). The test is elevated in cases of embolism or thrombosis when the body is attempting to break down a clot or clots.
- **Bleeding Time Test**
  - Used to assess **platelet function**. A cut is made on the forearm with an inflated blood pressure cuff in place. The cuff is deflated and the time it takes for the bleeding to stop is measured. It normally stops in 1 to 9 min. The cut is dabbed every 30 seconds.

Evaluation of Hemostasis 7

- **Bleeding Time Test, cont.**
  - If bleeding time is significantly prolonged and coagulation values are normal, the bleeding problem is likely due to a platelet defect (Primary Hemostasis defect).
  - If the bleeding time is normal or slightly prolonged and the coagulation values are abnormal, an abnormal or missing clotting factor is likely the cause.

- **Tourniquet Test (aka Hess Test or Rumpel-Leede Test)**
  - This is a test for **capillary fragility**. (Primary Hemostasis defect)
  - A blood pressure cuff is inflated to a pressure between the patient's systolic and diastolic blood pressure for 10 minutes, and then the cuff is removed. The number of petechiae within a 5 cm diameter circle in the area under pressure are counted. Normally less than 15 are present.

Disorders of Primary Hemostasis

Vascular Disorders

- Vascular Purpura
- Hereditary Hemorrhagic Telangiectasia

Platelet Disorders

- Thrombocytopenia (Platelet count <100,000/µL)
- Thrombocytosis (Platelet count > 400,000/µL)
- Thrombasthenia
- Von Willebrand Disease

Disorders of Primary Hemostasis 1

Vascular Purpura:

- Due to alterations in blood vessel wall structure; several mechanisms:
  - **Allergic purpura**
    - Due to immune reactions related to infection, drug treatment, or autoimmunity
  - **Scurvy**
    - Vitamin C deficiency causes defective collagen synthesis.
  - **Corticosteroid purpura**
    - Corticosteroid treatment and associated gluconeogenesis causes protein catabolism and weakens vessel walls.
  - **Senile purpura**
    - Loss of fat and connective tissue mobility (due to aging) allows vessel shearing.

Disorders of Primary Hemostasis 2

Vascular Purpura

- **Clinical Manifestations**
  - Location of purpura varies with cause.
- **Diagnosis**
  - Normal platelet count
  - Normal coagulation values
  - Presence of purpura
  - Positive tourniquet test (Hess test of Rumpel-Leede test)
- **Treatment**
  - Removal of causative agents and relief of symptoms such as itching.

Disorders of Primary Hemostasis 3

Hereditary Hemorrhagic Telangiectasia

- **Etiology and Pathogenesis**
  - Autosomal dominant
  - Abnormality in blood vessel development causes **deficient connective tissue**
  - More prominent after puberty, peaks occurrence at age 40-50 years
  - Frequency and severity of bleeding from lesions increase over time.
  - Malformed vessels in the liver, spleen, lung, and brain are the most serious complications. Internal bleeding occurs.

Disorders of Primary Hemostasis 4

Hereditary Hemorrhagic Telangiectasia

- **Clinical Manifestations**
  - Bright red to purple spider-like lesions on nasal mucous membranes, lips, palate, tongue, face, trunk, palms, and soles. May also occur internally in mucous membranes.
  - The most common clinical problem is bleeding, especially epistaxis
  - Anemia may result.
- **Diagnosis**
  - Multiple telangiectases with repeated episodes of bleeding
  - Normal or increased bleeding time
  - Tourniquet test is usually positive.
  - Normal platelet count
  - Normal coagulation values

Disorders of Primary Hemostasis 5

Hereditary Hemorrhagic Telangiectasia

- **Treatment:**
  - Topical hemostatic agents
  - Cauterization or laser treatments for accessible lesions
  - For epistaxis: nasal tamponade and use of estrogen or estrogen with progesterone.
  - For uncontrolled bleeding: transfusion, iron replacement, or surgery.

Disorders of Primary Hemostasis 6

Thrombocytopenia (Platelet count <100,000/µL)

- **Etiology and Pathogenesis**
  - **Decreased platelet production**
    - Cancer chemotherapy
    - Aplastic anemia
    - Drugs
    - Vitamin B12/folic acid deficiency (cell cycle stalling)
    - Bone marrow cancer (crowding prevents normal production)
  - **Decreased platelet survival**
    - Antibody-mediated destruction of platelets aka **idiopathic thrombocytopenia purpura (ITP)**
      - Acute ITP occurs following a viral infection.
      - Chronic ITP occurs secondary to diseases of altered immunity: lupus, AIDS.

Disorders of Primary Hemostasis 7

Thrombocytopenia (Platelet count <100,000/µL)

- **Etiology and Pathogenesis**
  - Decreased platelet survival, cont.
    - Increased consumption of platelets by unwanted clotting
    - Direct trauma to platelets by vascular or valvular prostheses.
    - Splenic sequestration of platelets by an enlarged spleen.
    - Platelet depletion as a result of blood transfusion (Platelets degenerate in stored blood after 24 hours.)
- **Clinical Manifestations**
  - Increased bruising and prolonged bleeding with minor trauma
  - Petechiae and purpura occur at or below 50,000 platelets/µL.
  - Spontaneous bleeding occurs below 20,000 platelets/µL.

Disorders of Primary Hemostasis 8

Thrombocytopenia

- **Diagnosis**
  - Low platelet count is diagnostic.
  - Bleeding time test is prolonged.
  - Normal coagulation values
- **Treatment**
  - Discontinued used of suspected drugs, avoid aspirin
  - Corticosteroids to decrease splenic sequestration and anti-platelet antibody production
  - Splenectomy may be necessary.

Disorders of Primary Hemostasis 9

Thrombocytosis (Platelet count > 400,000/μL)

- **Etiology and Pathogenesis**
  - **Transitory** thrombocytosis
    - Occurs in relation to stress or physical exercise.
  - **Primary** thrombocytosis
    - Abnormal **proliferation of megakaryocytes** in the bone marrow usually associated with polycythemia vera
    - There may be a15-fold increase in platelet production.
  - **Secondary** thrombocytosis (**most common form**)
    - Response to hemorrhage, inflammation, malignancy, infection, hemolysis, or splenectomy.

Disorders of Primary Hemostasis 10

Thrombocytosis

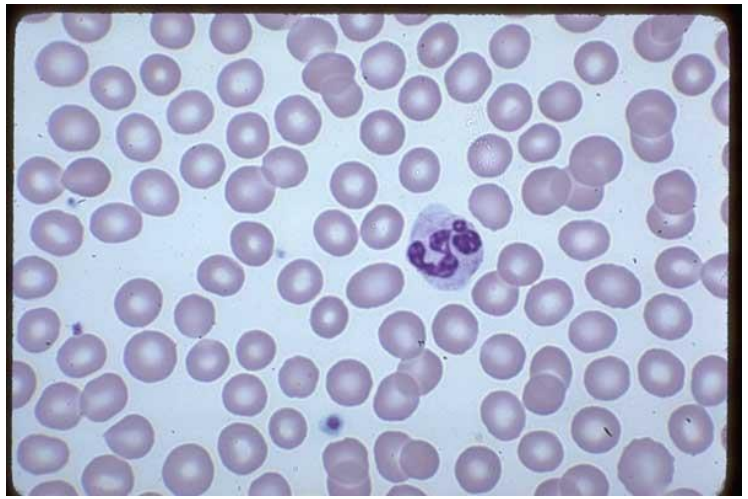
- **Clinical Manifestations**
  - Transitory and secondary thrombocytosis rarely result in hemorrhage or thrombosis.
  - Primary thrombocytosis
    - May cause hemorrhage into skin or mucous membranes due to platelet abnormality.
    - Thrombosis and peripheral vascular ischemia or pulmonary embolism may also occur.
- **Diagnosis**
  - The platelet count is diagnostic.
  - Bleeding time may be normal or prolonged;
  - Platelet aggregation may be normal or impaired.

Disorders of Primary Hemostasis 11

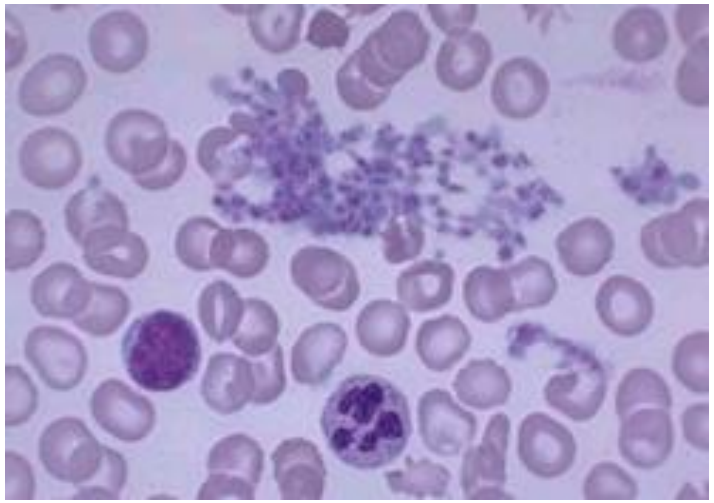
Thrombocytosis

- **Treatment**
  - No treatment is needed in transitory and secondary.
  - Primary form may be treated with drugs to reduce platelet count.
  - Plasma exchange temporarily controls platelet count.

Thrombocytopenia



Thrombocytosis



Disorders of Primary Hemostasis 12

Qualitative Platelet Disorders

- **Etiology and Pathogenesis**
  - Inherited defects in platelet function are rare.
    - **von Willebrand disease**
      - Lack or defect in von Willebrand protein
      - Inherited as an autosomal dominant in most cases
      - **Platelet adhesion** (to damaged vessel walls) is decreased.
    - **Thrombasthenia**
      - Lack or defect in platelet **fibrinogen receptor protein**
      - Usually inherited as an autosomal recessive disorder
      - May be acquired as an autoimmune disorder
      - **Platelet aggregation** (to each other) is decreased.

Disorders of Primary Hemostasis 13

Qualitative Platelet Disorders

- **Etiology and Pathogenesis, cont.**
  - **Acquired disorders** in platelet function are common.
    - Drugs
      - Aspirin and other NSAIDs inhibit production of thromboxane A2 by the arachidonic acid pathway.
      - **Platelet aggregation** is decreased.
      - **Platelet release reaction** (degranulation) is decreased.
    - Uremia (toxins in blood due to kidney failure)
    - Leukemia and other hematopoietic diseases.
- **Clinical Manifestations**
  - Petechiae, purpura, epistaxis
  - GI bleeding or menorrhagia.

Disorders of Primary Hemostasis 14

Qualitative Platelet Disorders

- **Diagnosis**
  - Bleeding time is prolonged
  - Normal platelet count
  - Normal coagulation values
  - Special laboratory tests are required to determine the nature of the defect.
- **Treatment**-Platelet transfusion or drug treatment

Disorders of Secondary Hemostasis

Coagulation Disorders

- Hemophilia
- von Willebrand Disease
- Vitamin K Deficiency Bleeding of Infancy
- Acquired Vitamin K Deficiency
- Disseminated Intravascular Coagulation (DIC)
- Hepatic Disease

Disorders of Secondary Hemostasis 1

Hemophilia

- **Etiology and Pathogenesis**
  - Inability to form blood clots causes bleeding.
  - **Hemophilia A**-85% of all hemophilia cases
    - Factor VIII deficiency
    - X-linked recessive inheritance
    - Displayed by members of the European royal families
  - **Hemophilia B** (aka Christmas disease)
    - Factor IX deficiency
    - X-linked recessive inheritance
  - Note: About 20% of hemophilia cases are due to spontaneous mutations rather than heritable mutations.

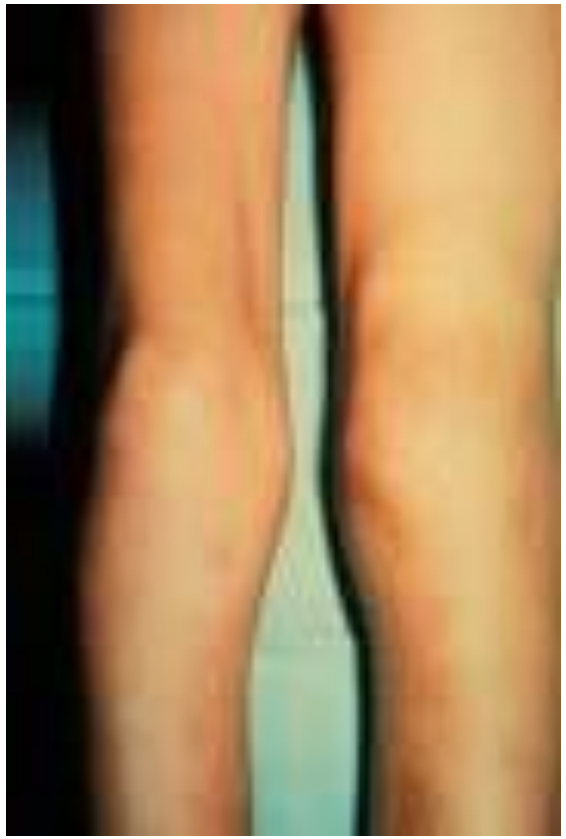
Disorders of Secondary Hemostasis 2

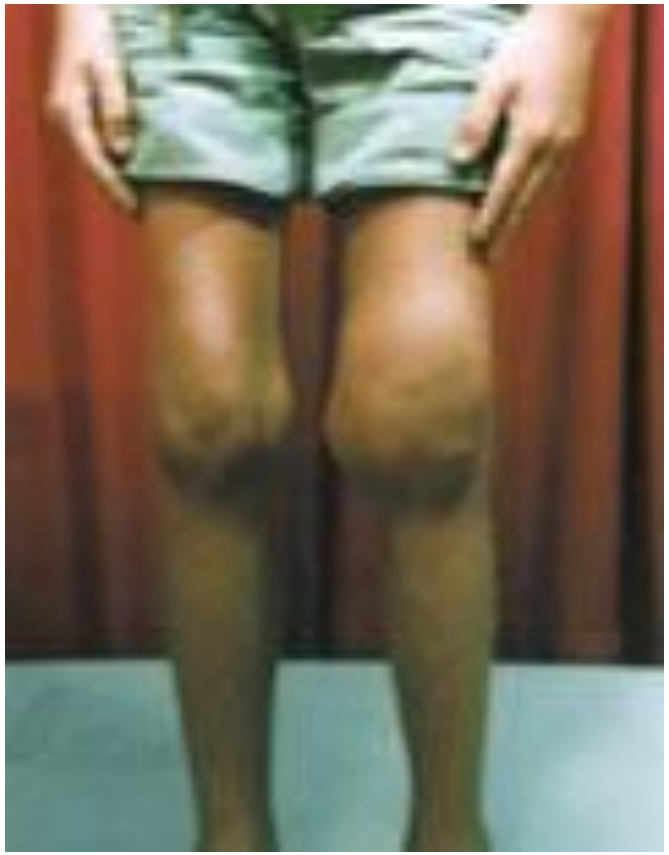
Hemophilia

- **Classification**
  - Severe hemophilia=less than 1% normal coagulation factor activity
  - Mild hemophilia=5%-25% normal coagulation factor activity.
- **Clinical Manifestations (severe form)**
    - Prolonged bleeding from minor trauma and spontaneous bleeding
    - The hallmark of hemophilia is **hemarthosis**, bleeding into the joints; causes joint deformity
    - Before improved donor blood screening procedures were in place hepatitis, cirrhosis, and AIDS were common in hemophiliacs due to administration of virus-contaminated blood or clotting factor concentrates.

Disorders of Secondary Hemostasis 3

Hemarthosis in Hemophilia A





Disorders of Secondary Hemostasis 4

Hemophilia

- **Diagnosis**
  - Positive family history for bleeding in males
  - History of hematomas and hemarthosis (The knees and elbows are most affected.)
  - Normal platelet count
  - Normal or slightly prolonged bleeding time
  - Normal PT/INR
  - Prolonged aPTT (Factors VIII and IX are part of the intrinsic pathway.)
  - Factor assay by electrophoresis verifies the deficiency as factor VIII or factor IX.
  - Prenatal diagnosis is possible through chorionic villus sampling or amniocentesis.

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Disorders of Secondary Hemostasis 5

Hemophilia

- **Treatment for Hemophilia**
  - Patient and family must be educated about hemophilia.
  - Aspirin and other drugs that reduce platelet activity must be avoided.
  - Transfusion of clotting factors
    - Cryoprecipitate is a precipitate that forms when plasma is frozen. It is rich in **Factor VIII and von Willebrand factor.**
    - Factor VIII and IX (produced by recombinant DNA technology) are also available in purified forms.
  - The goal of therapy is to obtain a factor VIII or IX level of at least 40% of normal, higher if internal bleeding occurs.
  - About 20% of severe hemophilia A patients develop **factor VIII inhibitor**—antibody against factor VIII. Plasmapheresis and immunosuppressive therapy are used to manage this problem.

Disorders of Secondary Hemostasis 6

von Willebrand Disease

- **Etiology and Pathogenesis**
  - Inherited, usually as an **autosomal** dominant; rarely as an autosomal recessive.
  - von Willebrand factor and factor VIII normally circulate in the plasma as a complex.
  - von Willebrand factor is necessary for
    - Stabilization of factor VIII in the circulation
    - Normal platelet adherence to damaged vessel walls.
  - In von Willebrand disease **von Willebrand factor** is absent or deficient and **factor VIII** may be mildly to severely depressed.

Disorders of Secondary Hemostasis 7

von Willebrand Disease

- **Clinical Manifestations**
  - Epistaxis, mucosal bleeding, ecchymoses, and menorrhagia are common.
  - Hemarthosis is rare (opposite of hemophilia)
  - Bleeding manifestations decrease during pregnancy because levels of von Willebrand factor and factor VIII normally rise during this time.
- **Diagnosis**
  - Prolonged bleeding time test due to decreased platelet adherence
  - Prolonged aPTT due to decreased Factor VIII
  - Normal PT
  - Normal platelet count

Disorders of Secondary Hemostasis 8

von Willebrand Disease

- **Treatment**
  - **Desmopressin,** a synthetic version of ADH, increases the release of von Willebrand factor from **endothelial cells**. VWF then stabilizes Factor VIII.
  - Hormonal suppression of menstruation in women.
  - Cryoprecipitate and/or purified **factor VIII** replacement therapy.
  - Avoidance of aspirin

Disorders of Secondary Hemostasis 9

Vitamin K Deficiency Bleeding of Infancy

- **Etiology and Pathogenesis**
  - Occurs from 2 days postnatal up to 6 month of age
  - Rare in Western countries due to routine administration of Vitamin K to newborns.
  - Bleeding is due to deficiency in the **Vitamin K-dependent clotting factors: II, VII, IX and X**
  - Immaturity of the liver contributes. Vitamin K is a fat-soluble vitamin, so it requires the phospholipids in bile (for micelle formation) in order to be absorbed into the blood.
  - The microflora (resident bacteria) of the digestive tract is undeveloped in newborns. Once it is established, **bacteria will synthesize Vitamin K for absorption.**
  - **Human breast milk** is low in Vitamin K compared to infant formulas, so breast-fed babies should receive supplementation.

Disorders of Secondary Hemostasis 10

Vitamin K Deficiency Bleeding of Infancy

- **Clinical Manifestations**
  - Melena (tarry, black feces composed of partially digested blood), bleeding from the umbilicus, and hematuria, appear on the second or third day of life.
  - Severe complications include intracranial hemorrhage and hypovolemic shock.
  - **Diagnosis**
    - Prolonged PT (Loss of Factor VII is the most serious defect.)
    - Prolonged aPTT
    - Deficient Vitamin K-dependent clotting factors (II, VII, IX, X)
- **Treatment to control bleeding**
    - Whole blood for anemia and avoidance of shock
    - Fresh plasma for clotting factor replacement

Disorders of Secondary Hemostasis 11

Acquired Vitamin K Deficiency

- **Etiology and Pathogenesis**
  - Vitamin K is obtained via the diet and intestinal flora, absorbed through intestinal wall in micelles, absorbed into the lymph in chylomicrons, enters the blood, and is stored in the liver.
  - Deficiency is acquired by malnutrition, malabsorption, chronic liver disease, antibiotic therapy, or Coumadin therapy.
    - Liver disease or bile duct obstruction causes bile deficiency in the small intestine. Bile is necessary for the absorption of nonpolar, fat-soluble molecules (the Vitamins A, D, E and K, for example).
    - Coumadin-type drugs are antagonists of vitamin K activity; clotting factors are synthesized but have reduced activity.
- **Clinical Manifestations**
    - Mucosal bleeding, ecchymoses, menorrhagia, and hematuria may be present; surgical bleeding is a risk
- **Diagnosis and Treatment**-same as for newborns

Disseminated Intravascular Coagulation (DIC)

Disseminated Intravascular Coagulation (DIC)

- **Etiology**
  - DIC is an acquired syndrome associated with certain disease conditions. It causes the widespread formation of microemboli in small blood vessels. Obstruction of blood flow leads to organ damage.
  - In some forms of DIC the fibrinolytic system is triggered leading to bleeding.
  - Most cases of DIC occur **secondary to** sepsis, leukemia or solid tumor cancer.
  - Other causes include severe infection, severe burns, placental abruption (premature separation from the uterine wall), crushing injuries, mismatched blood transfusion, shock, and severe liver disease.
  - DIC occurs in 1 in 900-2400 adult hospital admissions.
  - Mortality rates range from 50% to 80%.
- **Pathogenesis**
  - Clotting is initiated by contact of blood with **damaged endothelium** (sepsis, burns, placental abruption, aortic aneurysm), release of **procoagulants** (snake venom, malignancy), or **stagnant** blood flow (shock).

Disseminated Intravascular Coagulation (DIC) 1

Disseminated Intravascular Coagulation (DIC)

- **Pathogenesis, cont.**
  - In the case of sepsis, inflammation leads to the release of excessive **TF-tissue factor** by endothelial cells that line blood vessels. The **extrinsic pathway** of coagulation then begins. Fibrinolysis is **not** a major factor. Microemboli cause organ damage.
  - In most cases of malignancy the cancer cells **release TF**. Fibrinolysis and clotting tend to exist in a **balanced** state. DIC may become a **chronic** state.
  - In certain cases (dissected aortic aneurysm, placental abruption, prostate cancer and APL (acute promyelocytic leukemia) **fibrinolysis** becomes the major factor and bleeding is extensive.
- **Clinical Manifestations**
  - Excessive blood clot formation:
    - Acrocyanosis (cold, bluish fingers and toes) due to thrombi
    - Dyspnea, hemoptysis (bloody sputum) due to thrombi in pulmonary microvasculature
    - Acute renal failure due to thrombi in renal microvascular
  - Excessive bleeding:
    - Crackles or rales (abnormal breath sounds) as blood fills the alveoli (air sacs of the lungs).
    - Petechiae, ecchymoses, bleeding from orifices, and injury sites

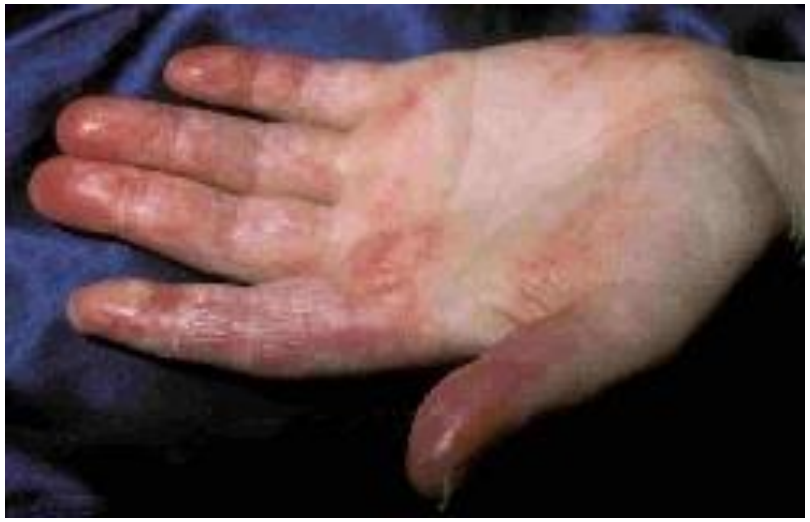
Disseminated Intravascular Coagulation (DIC) 2

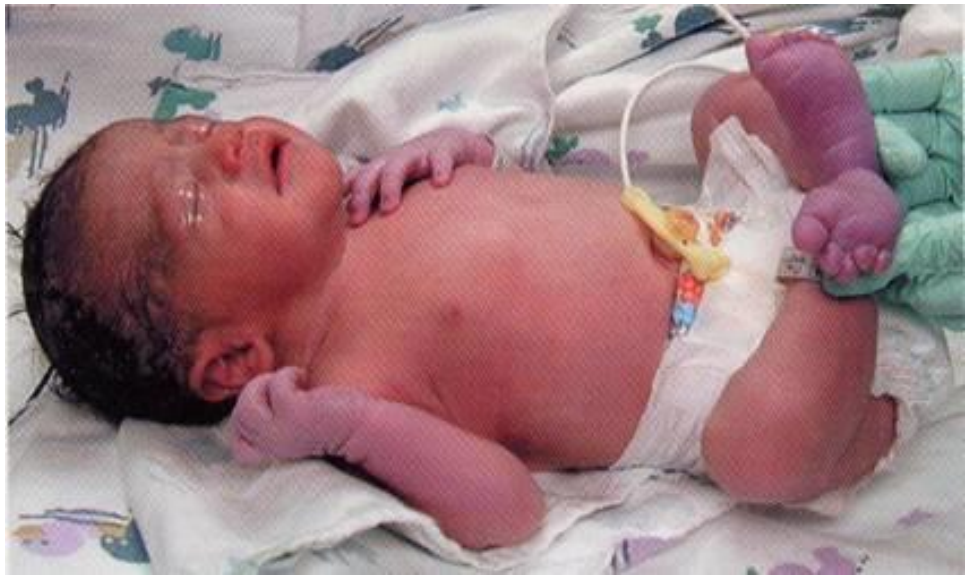
Disseminated Intravascular Coagulation (DIC)

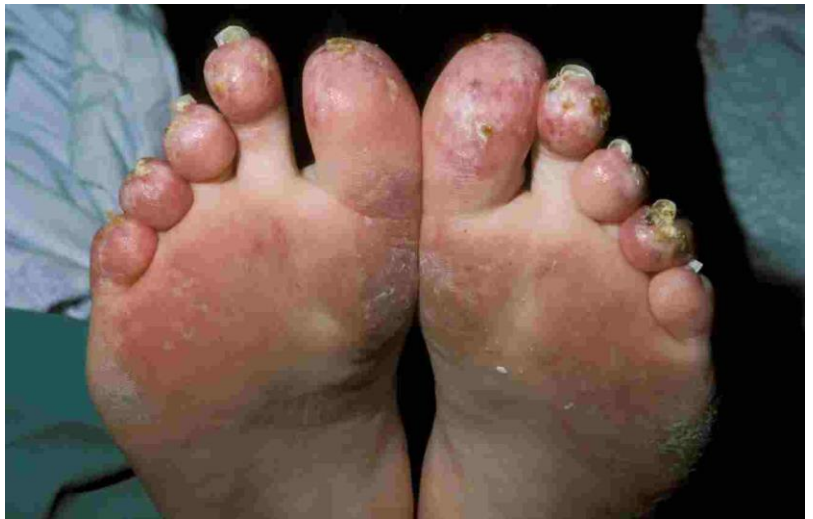
- **Diagnosis**
  - Prolonged bleeding time, PT, aPTT
  - Decreased fibrinogen
  - Decreased platelet count
  - FSP (D-Dimer) test indicates increased fibrinolysis.
  - Antithrombin complex level is increased
- **Treatment**
  - Removal of the underlying cause; support of major organ systems.
  - Replacement of depleted clotting factors
  - Anti-fibrinolytics if there is a life-threatening hemorrhage.
- In cases of sepsis and severe trauma the **chances of death are multiplied** by a factor of 1.5 to 2 if DIC occurs.

Disseminated Intravascular Coagulation (DIC) 3

Acrocyanosis in DIC

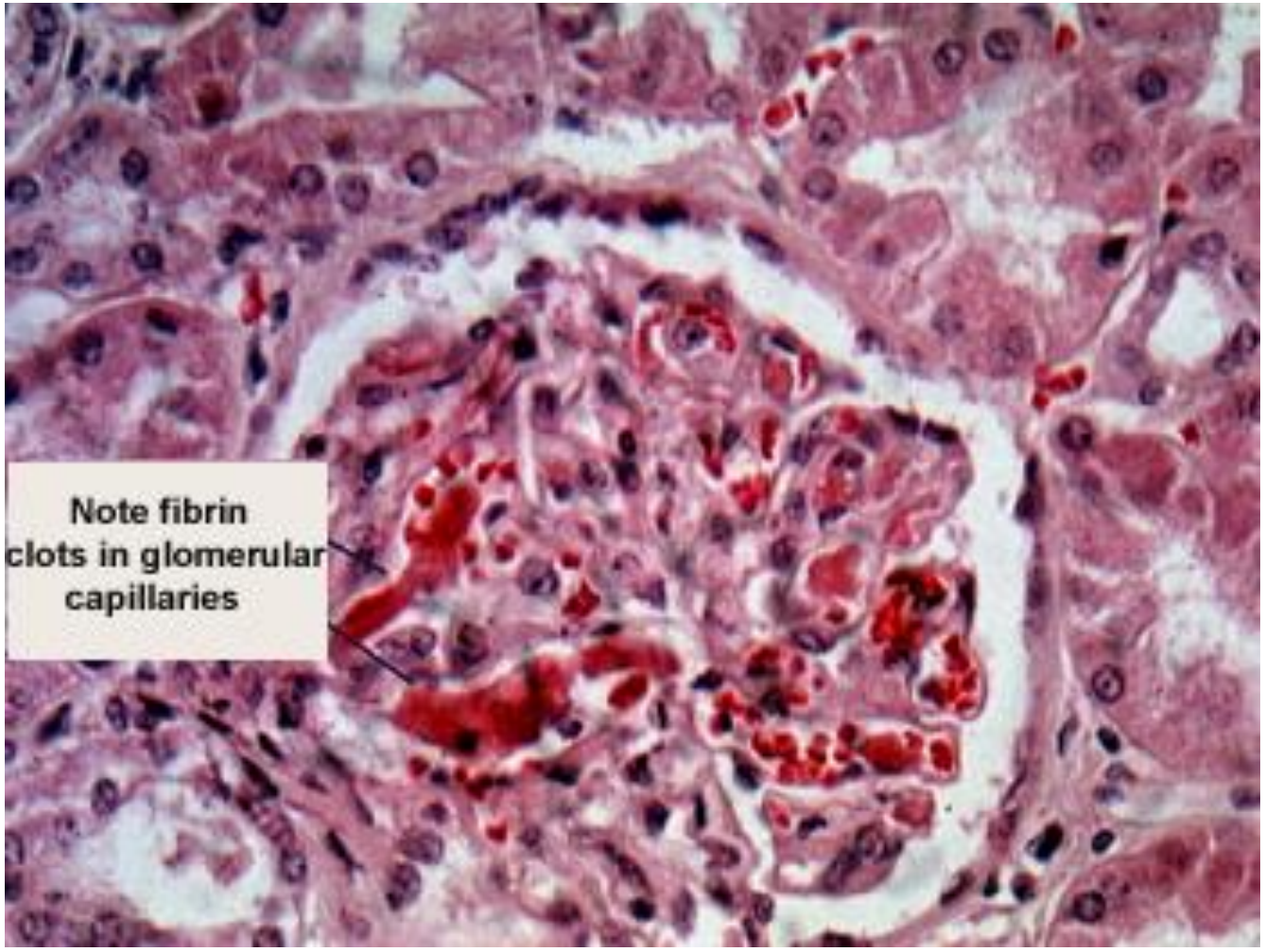






Disseminated Intravascular Coagulation (DIC) 4

Kidney Tissue: Glomerular Thrombosis in DIC



Liver Disease and Bleeding Problems

Why Hepatic Disease Causes Bleeding Problems

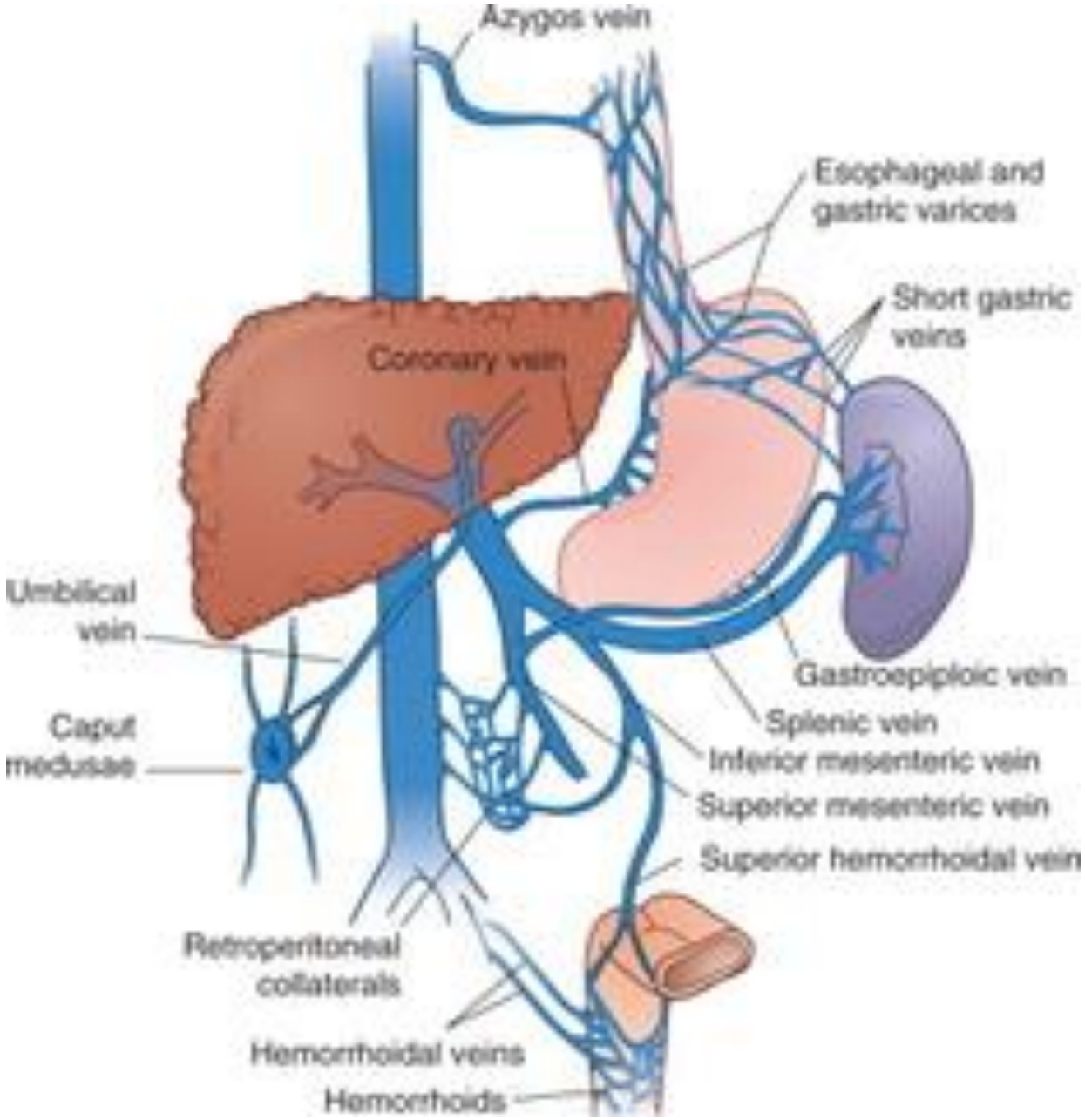
- **Liver Disease Interferes With Blood Clotting Functions:**
  - The plasma proteins involved in coagulation and fibrinolysis are synthesized by liver hepatocytes.
  - The liver synthesizes **bile**. The phospholipids in bile are required for micelle formation and vitamin K absorption in the small intestine.
  - The liver is responsible for removing excess activated clotting factors and fibrinolytic factors from the blood.
  - Portal hypertension (high blood pressure in the **hepatic portal vein** and its branches) is often due to **cirrhosis** of the liver, the end result of many liver diseases. Cirrhosis is the replacement of healthy liver tissue with scar tissue. It is difficult for blood to flow through the liver when cirrhosis is present.

Liver Disease and Bleeding Problems 1

Why Hepatic Disease Causes Bleeding Problems

- **Roles of the Liver in Blood Clotting, cont.**
  - The hepatic portal vein collects blood from the digestive organs and the spleen and transports it to the liver.
    In **portal hypertension** blood “backs up” from the liver into the veins that normally empty into the hepatic portal vein causing congestion (excess fluid and pressure) in those veins.
  - Blood backs up into the spleen leading to **splenomegaly** (The splenic vein empties into the hepatic portal vein.). And platelet sequestering is associated with splenomegaly.
  - The back up of blood into the veins of the digestive tract adds to bleeding problems, especially bleeding from **esophageal varices and hemorrhoids** that form in the small veins of the digestive tract wall. Varices and hemorrhoids are both due to **stretching and coiling** of blood vessels subjected to increased blood pressure.

The Hepatic Portal System



Lecture 2D:
Infectious Processes

Infection Terminology

- **Infection** is an assault on the human body caused by invasive microorganisms. Many species of beneficial microorganisms normally live on the surface of the human body. Even though the surface the human body has multiple mechanisms to prevent penetration by both beneficial and dangerous species, **penetration of the body surface** does occur.
- Multiple **immune system mechanisms**, both nonspecific and specific, are aimed at thwarting the replication of microorganisms that have penetrated the body surface. Still microorganisms regularly overcome those mechanisms to cause disease.
- Even with the advent of **antibiotics and vaccinations**, infectious disease remains a healthcare challenge worldwide.
- The overuse or incomplete use of antibiotics has lead to the existence of multiple **drug-resistant microbes.**
- **Globalization** and the import and mass distribution of **perishable foods** has led to the spread of dangerous infectious diseases.

Infection Terminology 1

- Two agencies are front and center in **infective epidemiology**, the study of the incidence, distribution and prevention of infectious diseases. Visit these websites and have a look around.

- Center for Disease Control and Prevention (CDC)
- World Health Organization (WHO)

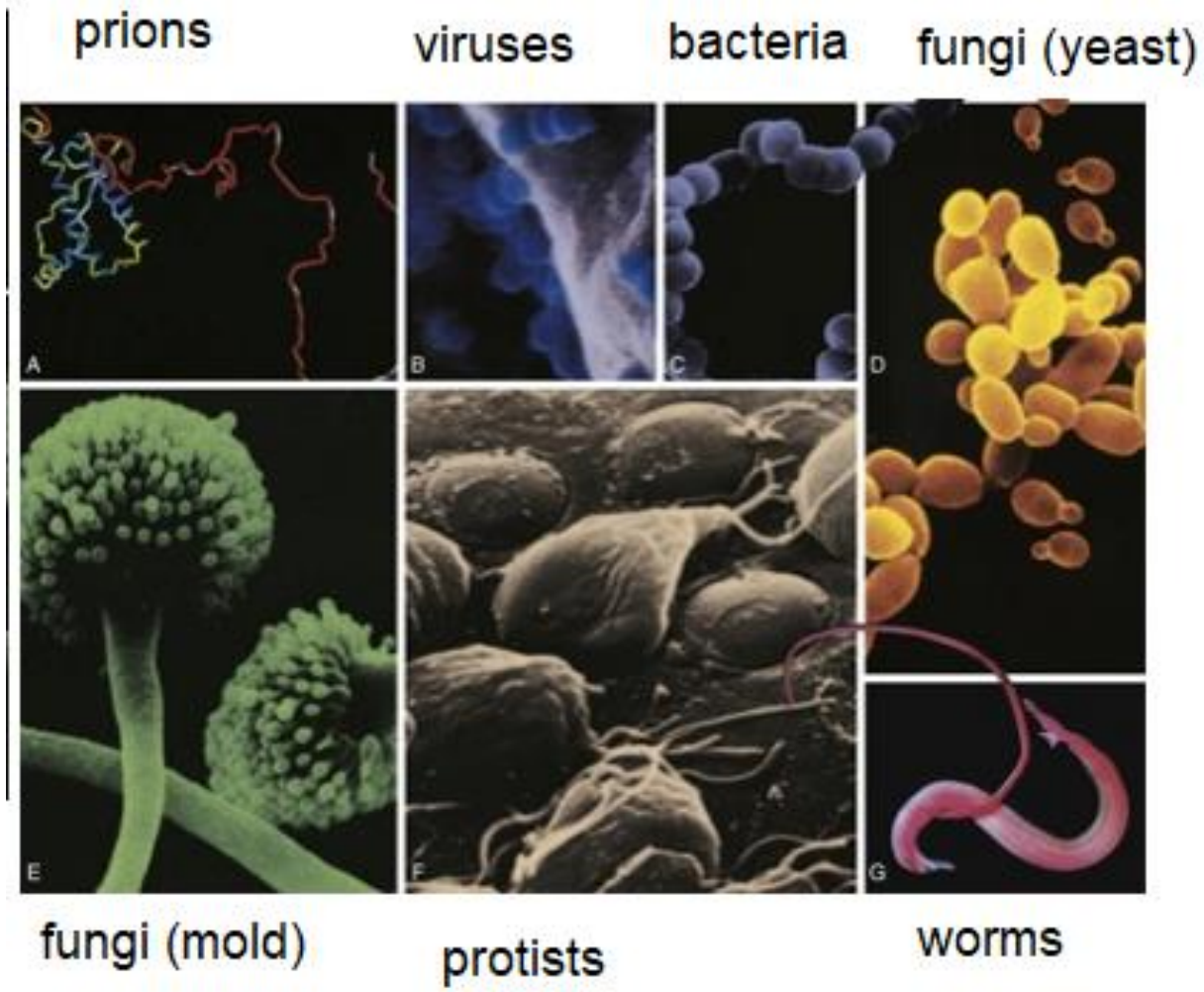
Infection Terminology 2

- **Incidence**-number of **new** cases of an infectious disease in a given population in one year
- **Prevalence**-number of **active** cases of an infectious disease in a given population in one year
- **Endemic infection**-stable incidence and prevalence of an infectious disease in a **specific** population
- **Epidemic infection**-sudden increase in incidence of an infectious disease in a **specific** population
- **Pandemic infection**-spread of an infectious disease beyond continental borders.
- **Resident flora**- live in or on the host and recolonize quickly if disturbed; a symbiotic relationship exists with the host
- **Transient flora**- reside temporarily in or on the host; for example, secondary infections that occur during antibiotic therapy.

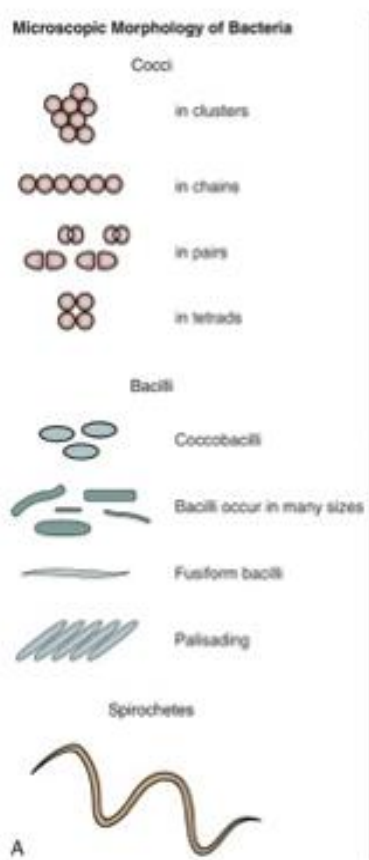
Infection Terminology 3

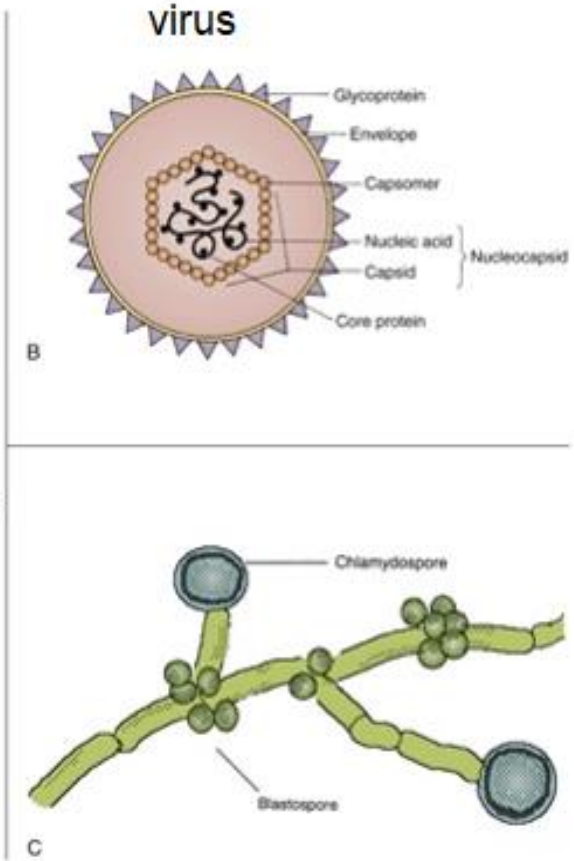
- **Opportunistic infections**-occur in a host with a compromised immune system
- **Virulent infections**-involves microorganisms that are consistently capable of causing disease
- **Nosocomial infections**-arise in a hospital or clinical situation. They may be opportunistic or virulent in nature. MRSA (methicillin resistant *Staphlococcus aureus*) is an example.
- **Infectious agents**-organisms that infect the human body: bacteria, viruses, fungi, protozoans, worms
- **Transmission of infection or disease-**any mechanism by which an infectious agent is spread through the environment to a new host.

Infectious Agents



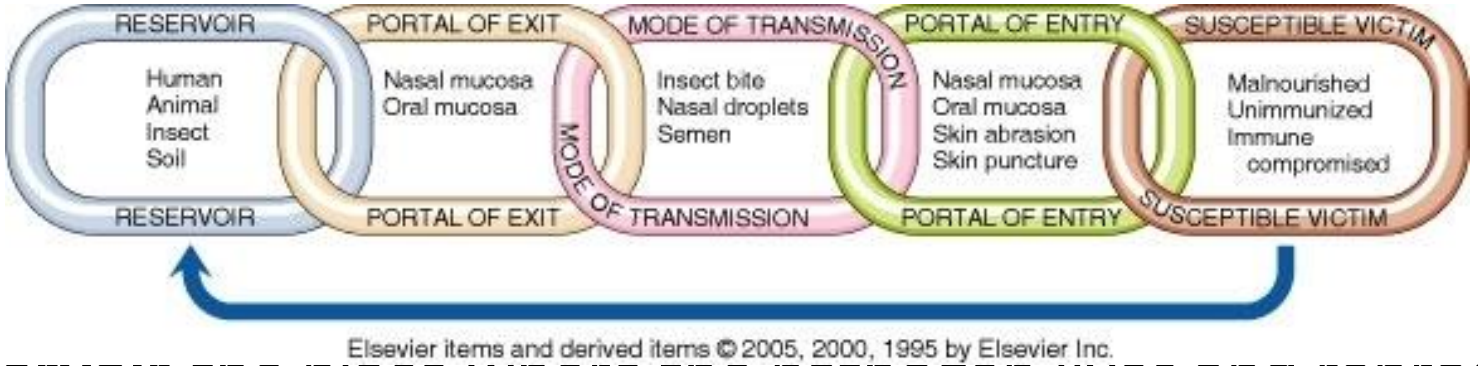
Infectious Agents 2





fungus

The Chain of Infection



- **reservoir**-the place where the pathogen lives and reproduces; may be an animal (human, another mammal, insect) or part of the environment (water or soil).
- **portal of exit**-the site where the pathogen leaves the reservoir (For example, in sexually-transmitted diseases, the portal of exit is the urethra of the male or the vagina of the female.)
- **mode of transmission**-how the pathogen travels to a new host; may be direct or indirect
- **portal of entry**-site where the body surface of the host is penetrated (skin, conjunctiva or mucous membrane)

Modes of Transmission

- **DIRECT modes of transmission require physical contact between the old host and the new host**
  1. **exchange of bodily fluids**-kissing or sexual intercourse; pathogen enters the new host through conjunctiva or mucous membrane
  2. **through the placenta or through breast milk from mother to child**
- **INDIRECT modes of transmission do not require physical contact between the old host and the new host.**
  1. **vehicle-borne**-the infectious agent is transported from the old host to the new host by a nonliving entity: contaminated water, food, clothing, plasma or tissue (dirty needles).
  2. **airborne**-the infective agent (usually one that is present in the upper respiratory tract) is transported through the air from reservoir to host. Coughing or sneezing by a current host followed by inhalation of the resulting aerosol (tiny liquid droplets suspended in air) most often causes airborne transmission.

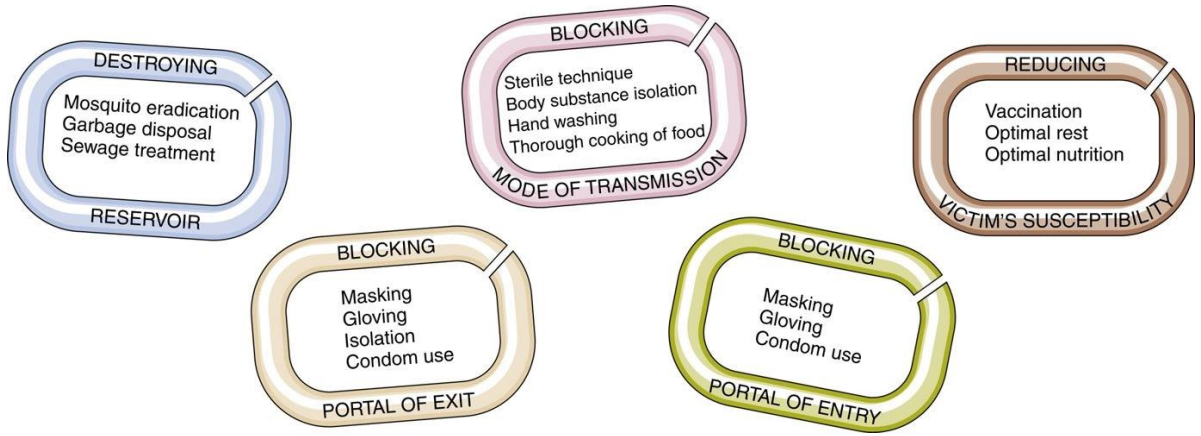
Modes of Transmission 2

3. **vector-borne**-the pathogen is transmitted from the old host to the new host by a living organism. The pathogen develops and reproduces in the organism (vector) prior to infecting the new host. (The pathogens that cause West Nile disease and malaria develop and reproduce in mosquitos. The mosquitos then bite the new host.)

- Some pathogens may be transmitted by both direct and indirect means.
- The ability of an agent to cause disease depends on the availability of a host, the effective transmission to the host, and its ability to invade and reproduce in the host.
- The resident flora of the body can become disease-causing, if the flora moves to a new location (bacteria enter deeper tissue through a wound) or if the body's defenses are weakened (by chemotherapy or immune diseases).

Breaking the Chain of Transmission

- Breaking the chain of events that causes an infectious disease includes any or all of the following:
  - Killing the reservoir
  - Blocking the portal of exit
  - Blocking the transmission
  - Blocking the portal of entry
  - Reducing the victim's susceptibility
  - NOTE examples of each below.



Pathogen Characteristics That Affect Infection

- The mechanisms by which pathogens cause disease include one or more of the following:
  - Direct destruction of the host cell.
  - Interference with the host cell's metabolic function.
  - Exposing the host cell to toxins produced by the pathogen.
- **Pathogenicity** of an organism involves factors such as:
  - **Virulence**-the level to which the pathogen causes **severe** disease in a **large** portion of exposed individuals.
  - **Infectivity**-the level of host exposure required for the pathogen to take hold, multiply and cause disease.
  - **Toxigenicity**-the level to which the pathogen is able to produce chemicals that harm host cells.
  - **Antigenicity**-the level to which the pathogen is recognized as foreign by the host immune system.
  - **Antigenic variability**-the ability of the pathogen to alter its foreign antigens in order to thwart host defenses.
  - **Pathogenic defenses**-mechanisms that protect the pathogen from the host defenses (bacterial capsules, for example)

Host Characteristics That Affect Infection

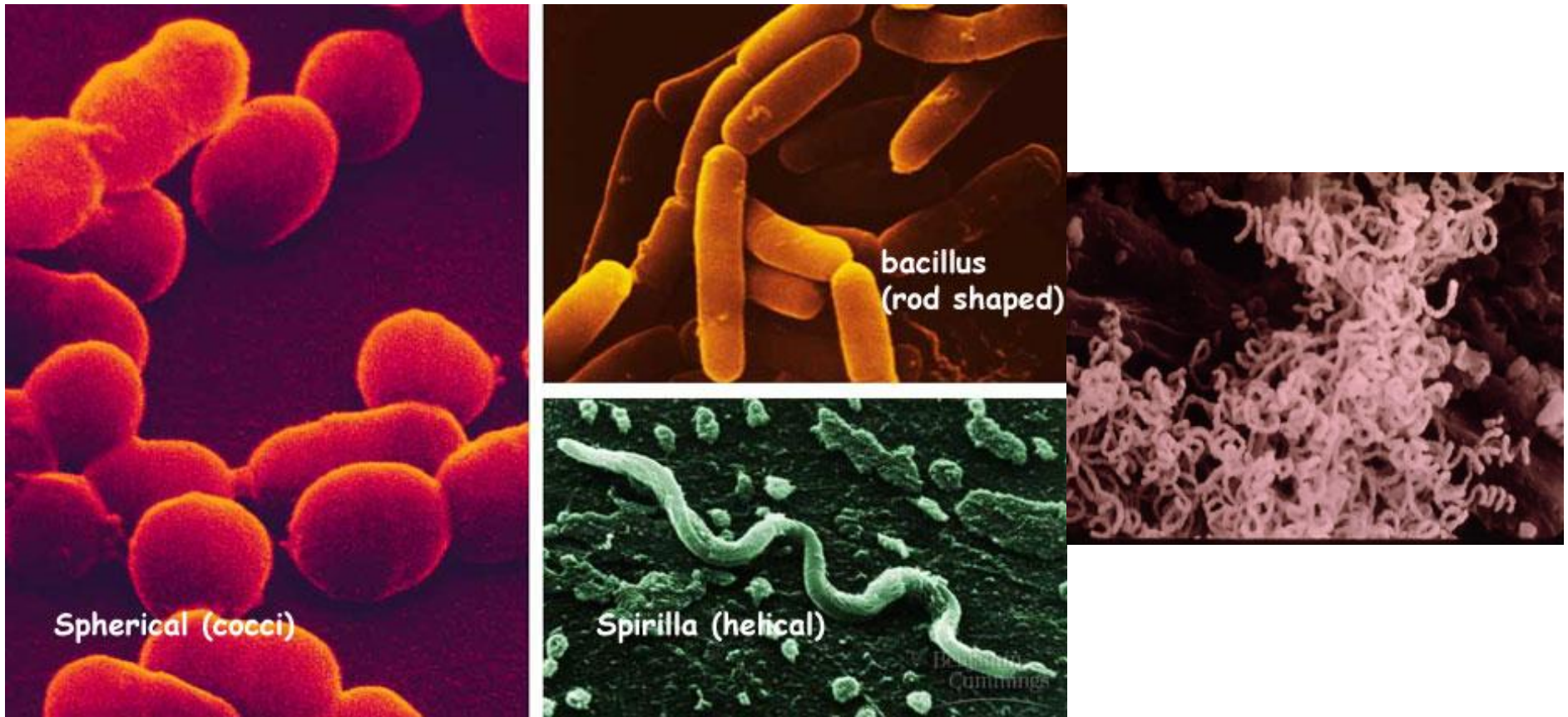
- **Susceptibility** of the host to infection is affected by factors such as:
  - **Environment-**access to clean air and water, adequate housing
  - **Personal Hygiene**-hand washing
  - **Social Behavior**-alcohol, drugs, sexual behavior
  - **Travel-**proper immunizations for foreign countries
  - **Immune Status**-current immunizations
  - **Chronic illness** (non-infectious): diabetes, cancer, kidney disease, heart disease
  - **Nutritional Status-**malnutrition, vitamin and mineral deficiencies
  - **Age**-some infections are more dangerous to infants, others are more dangerous to the elderly
  - **Exposure to Antibiotics**-always take the full course of the prescription to avoid antibiotic resistance!!

Types of Infectious Agents: Bacteria

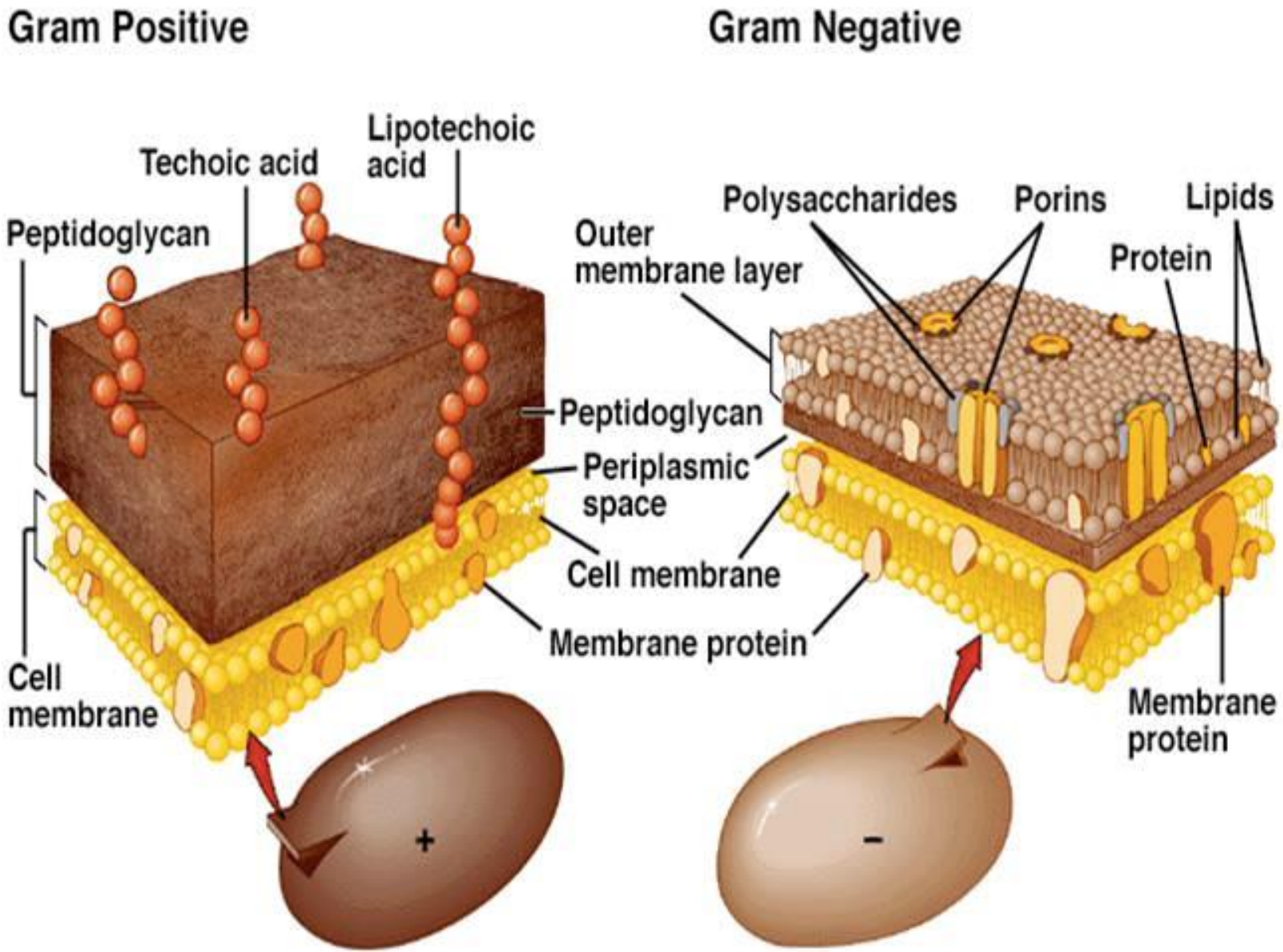
- Bacteria, in general, are single-celled prokaryotic organisms with **rigid cell walls**. Bacterial infections are **usually extracellular (free-living)**, but a few types are due to bacteria that live inside our cells. There are multiple ways of classifying bacteria.
- **Free-living bacteria with rigid cell walls: classified by shape**
  - Cocci-round and immobile: *Staphlococcus aureus*
  - Bacilli-rod shaped and may be motile: *Escherichia coli*
  - Spiral-spiral shaped (like a cork screw): *Spirillum volutans*
- **Free-living bacteria with rigid cell walls are classified by their response to Gram staining , a four-step process.**
  - Gram-positive bacteria retain dark blue dye (*Staphlococcus aureus)*
  - *Gram-negative bacteria resist dark blue dye, but stain pink after exposure to red dye (Escherichia coli)*

Types of Infectious Agents: Bacteria 1

Types of Bacteria by Shape



Gram negative and Gram positive bacteria differ in their responses to the Gram staining technique because of differences in their cell wall structures.



Types of Infectious Agents: Bacteria 2

- The cell wall characteristics of Gram- and Gram+ bacteria have much to do with the behavior of the two groups of organisms.

Characteristic	Gram +	Gram -
Cell Wall Structure	20-30 nm thick, smooth	8-12 nm thick, wavy
	No outer plasma membrane	Outer plasma membrane
	High peptidoglycan content	Lower peptidoglycan content
	Virtually no lipopolysaccharide	High lipopolysaccharide
	Teichoic acid in some	No teichoic acid
Toxins Produced	Exotoxins	Endotoxins or exotoxins
Lysozyme effect	High susceptibility	Low susceptibility
Penicillin effect	High susceptibility	Low susceptibility
Streptomycin effect	Low susceptibility	High susceptibility

Types of Infectious Agents: Bacteria 3

- Bacteria of the **normal flora** live and reproduce on the body surface (skin and mucus membranes). But they can become **opportunistic pathogens** when the body surface is broken by trauma or when the immune system is suppressed. Recall that mucous membranes line all body tracts: digestive, respiratory, urinary, reproductive
- The human body contains **10 times more** bacterial cells (10^{14}) than human cells (10^{13})!
- The normal flora is established beginning **at birth**. *Lactobacilli* grow rapidly in the mother's vagina just before birth. They represent the first resident bacteria of the newborn. Other bacteria of the normal flora are introduced by contact, eating and breathing.
- The bacteria of the normal flora assist in the **development** of the digestive system and the immune system. In the human digestive tract they assist with **digestion** of cellulose, and they also synthesize **vitamins (Vitamin K and Vitamin B12)** that are absorbed into the blood.

Types of Infectious Agents: Bacteria 4

- The highest concentration of resident bacteria is in the **digestive tract**.
  - The number of resident bacteria in the **stomach** is relatively low due to the low pH. But ***Heliobacter pylori*** thrives in the stomach and causes stomach ulcers.
  - The **small intestine** has a moderate number of resident bacteria due to the inhibition by the high concentration of bile salts and digestive enzymes.
  - The **large intestine** contains the **highest** number of bacteria of any body site. The harsh conditions of the stomach and small intestine don’t exist there.

Types of Infectious Agents: Bacteria 5

- The bacteria of the **normal flora** compete with disease-causing bacteria for resources and thus help to prevent illness. **Disturbances** in the normal flora increase susceptibility to infectious diseases.
- The normal flora of the **digestive tract** can be disturbed by emotional stress, antacids, changes in diet, diarrhea or antibiotic therapy.
- The normal flora of the **skin** may be disturbed by antibacterial soaps or antibacterial deodorants.
- The normal flora of the **vagina** is affected by female hormones. It is sparse before puberty and after menopause. It contains a mixture of skin bacteria and colon bacteria. ***Lactobacilli*** predominate during the child-bearing years. Their production of lactic acid keeps the vaginal pH acidic (pH 3.6- 4.5).

Types of Infectious Agents: Bacteria 6

- Bacteria of the genus ***Staphlococcus*** and the genus ***Corynebacteria*** are part of the normal flora of essentially every external body surface region (skin and body tracts).
- ***Staphlococcus aureus*** is a potential pathogen. It is the **leading cause** of bacterial disease in humans. It is usually transmitted from the nasal cavity of an **asymptomatic** carrier to a **susceptible** host.
- Some ***Corynebacteria*** species are associated with acne.
- ***Streptococcus mutans*** is part of the normal flora of the mouth and throat. It is also the cause of **dental caries**, one of the most expensive human infections.
- ***Streptococcus pneumoniae*** is part of the normal flora of the upper respiratory tract, but if it invades the lower respiratory tract it can cause **pneumonia**. It is the cause of 95% of all bacterial pneumonias.

Types of Infectious Agents: Bacteria 7

- ***Haemophilus influenza***, part of the normal flora of the respiratory tract, is a secondary invader to viral influenza (reflected in its name). It was the major cause of **meningitis** in infants and children until the development of the Hflu type B (HIB) vaccine.
- ***Bacteroides*** is the most common genus of the normal flora of the **large intestine**. Some species have been implicated in the development of **colitis and colon cancer**.
- ***Pseudomonas aeruginosa*** is a common opportunistic species that can invade any tissue. It is the leading cause of **nosocomial Gram- infections**, but its source, in these cases, is often exogenous.
- ***Clostridium difficile ("C.diff")***is the most important cause of **nosocomial diarrhea.** Certain antibiotics allow it to thrive, causing "antibiotic-induced diarrhea" (pseudomembranous colitis).

Types of Infectious Agents: Bacteria 8

- **Intracellular bacterial infections** are much **less common** than extracellular infections. Three examples of causative organisms:
  - ***Rickettsiae*** are Gram- obligate intracellular parasites. They cannot replicate outside the host cell. They target the endothelial cells of the blood vessels and capillaries. They are usually spread by vectors. **Rocky Mountain spotted fever** is due to infection by ***Rickettsia rickettsii***. It is spread by tick bites.
  - ***Chlamydia*** are Gram- obligate intracellular parasites***. Chlamydia trachomatis*** is the cause of a **sexually transmitted disease.**
  - ***Mycoplasmas*** don't have rigid cells walls. They have many shapes and are among the **smallest** bacteria. ***Mycoplasma pneumoniae*** causes an atypical form of **pneumonia** due to intracellular infection.

Types of Infectious Agents: Bacteria 9

- Once bacteria have penetrated the body surface, they reproduce to establish a **colony. Then:**
- The immune system reacts with an acute **inflammatory reaction**. Immune cells such as **macrophages and neutrophils** are recruited to the site where they ingest and destroy bacteria.
- If the inflammatory response doesn't remove all of the bacteria, they spread into the lymphatic system**. Further immune responses** will be generated in the **lymph nodes** and other lymphatic tissues and organs.
- If the infection overwhelms the lymph nodes, clumps of bacteria (emboli) may circulate in the blood causing **bacteremia** and micro-abscesses.
- In the most severe cases **sepsis** occurs. Rampant inflammation causes **hypotension** leading to **shock**. In shock, blood pressure is too low to get blood to the tissues. Organ failure and death may occur.

Types of Infectious Agents: Viruses

- Viruses are the **smallest** pathogens (20-300 nm). They are composed of **nucleic acid** (DNA or RNA) surrounded by a **protein capsid.** Some viruses have a covering outside the capsid called an envelope. A **viral envelope** is derived from the plasma membrane of a host cell.
- **Viruses are obligate intracellular parasites.** They are totally dependent on a host cell for energy and for reproduction. They have no organelles and no ribosomes. Viral infection is spread by release of viral progeny from the host cell.
- **Invasion of the host cell by a virus:** two possibilities
  - **Adherence to and endocytosis by the host cell**. Once inside the viral capsule is removed from the virus exposing the viral genetic material to the host cell environment.
  - **Adherence to the host cell and injection of the viral genetic material into the host cell.** Once inside the cell the host cell's machinery is used to manufacture new virus particles (virions).

Types of Infectious Agents: Viruses 1

- **Release of progeny viruses from the host cell:** two possibilities
  - Progeny viruses may manufacture an **envelope** of host proteins and then be released by **budding** from the host cell surface. Budding is not the same as exocytosis, because the host cell is not in control of the process. The host cell is not destroyed and continues to manufacture progeny viruses.
  - The photomicrograph below depicts **HIV (AIDS virus)** budding from the surface of a helper T lymphocyte.
  - Progeny viruses that do not manufacture envelopes are usually released by **lysing the host cell**, thus destroying it.

Types of Infectious Agents: Viruses 2

- Viral infections are difficult to treat. Antibiotics have no effect on them.
- Since viruses spend most of their time inside host cells the only really effective means of getting rid of them is to kill the infected host cells. That is just what the immune system attempts to do.
- Viruses are classified in various ways. One simple means of classification is based on the **type of genetic material** the virus contains as well as the means by which the genetic material is replicated.

Types of Infectious Agents: Viruses 3

- This is the seven part Baltimore Virus Classification Scheme.
- I: dsDNA viruses

(e.g. Adenoviruses, Herpesviruses, Poxviruses)

- II: ssDNA viruses **(+ strand or "sense") DNA**

(e.g. Parvoviruses)

- III: dsRNA viruses

(e.g. Reoviruses)

- IV: (+)ssRNA viruses **(+ strand or sense) RNA**

(e.g. Corona virus, Picornaviruses, Togaviruses)

- V: (–)ssRNA viruses **(– strand or antisense) RNA (e.g. Orthomyxoviruses, Rhabdoviruses)**
- VI: ssRNA-RT viruses **(+ strand or sense) RNA with DNA intermediate in life-cycle**

(e.g. Retroviruses)

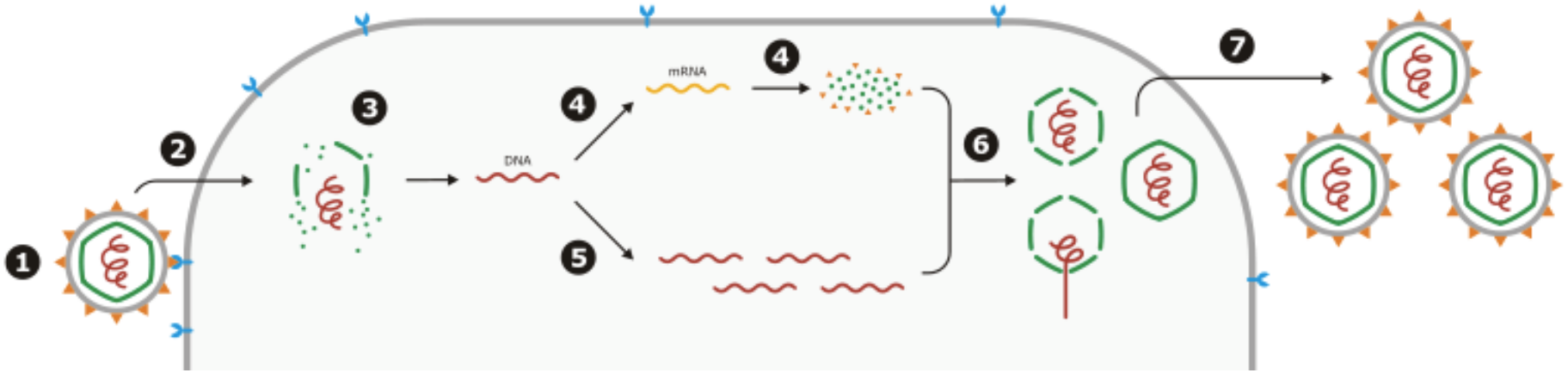
- VII: dsDNA-RT viruses **DNA with RNA intermediate in life-cycle**

(e.g. Hepadnaviruses)

- Note that viral chromosomes may be double-stranded DNA, single-stranded DNA, double-stranded RNA or single stranded RNA.

Types of Infectious Agents: Viruses 4

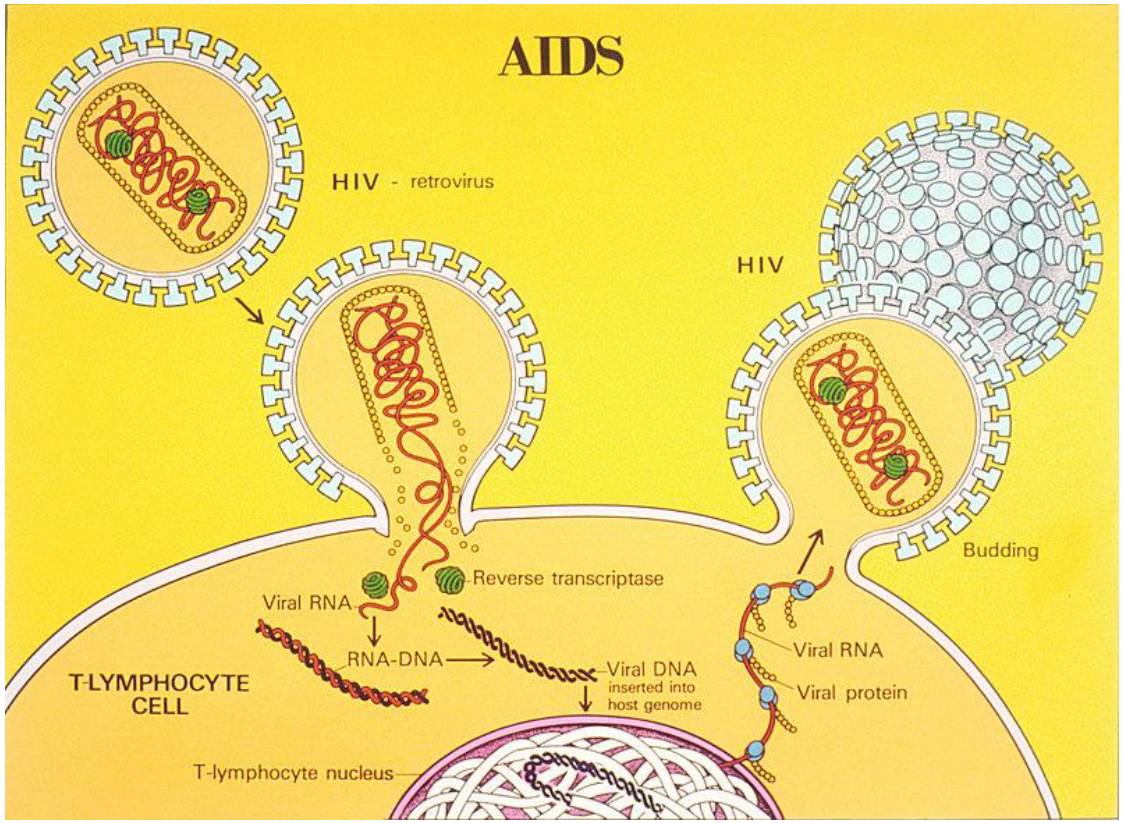
Typical DNA Virus (**herpes simplex virus**) Life Cycle
Invasion by Endocytosis; Release by Budding



Note the viral envelope.

Types of Infectious Agents: Viruses 5

Typical RNA Retrovirus **(HIV)** Life Cycle
Invasion by Nucleic Acid Injection; Release by Budding

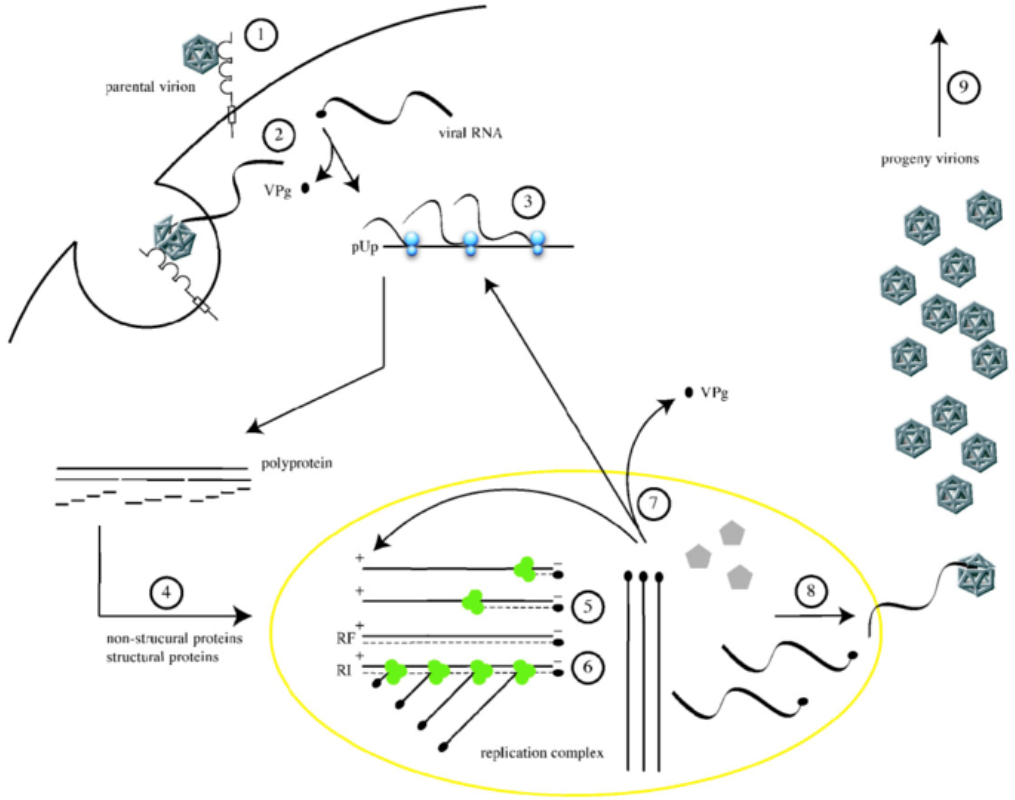


Note the viral envelope.

By Trudy Nicholson (Illustrator) [Public domain or Public domain], via Wikimedia Commons

Types of Infectious Agents: Viruses 6

Typical RNA Virus **(polio virus)** Life Cycle
Invasion by Endocytosis; Release by Lysis



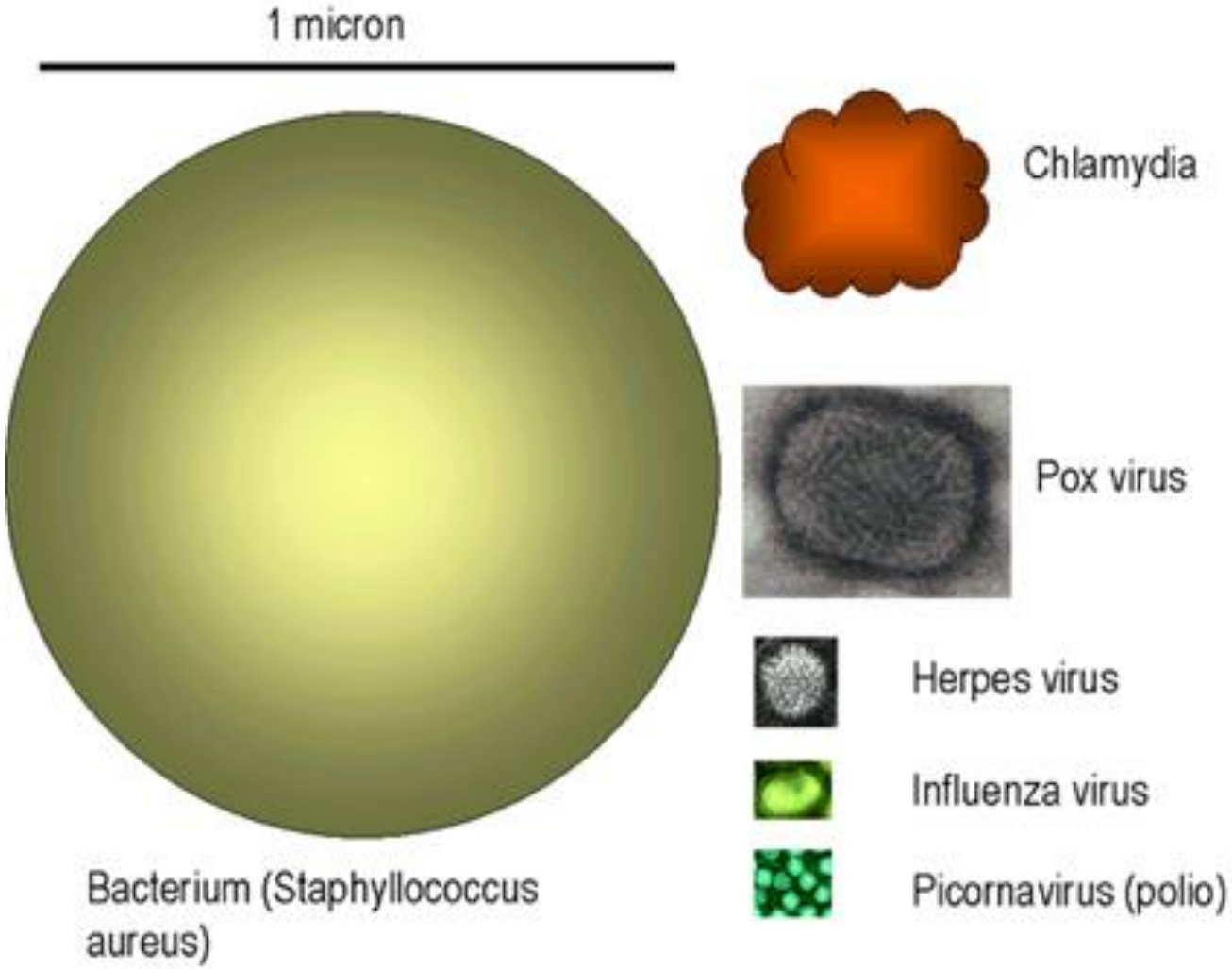
By Nidia H De Jesus (image and caption) [CC BY 2.0 (http://creativecommons.org/licenses/by/2.0)], via Wikimedia Commons

In this case the viral RNA is translated into a polyprotein that must be cut into functional pieces. Note the lack of viral envelope.

Types of Infectious Agents: Viruses 7

- Covid-19, also know as SARS-CoV-2, is an RNA virus.
- Its life cycle is rather complicated. Here's a link to a diagram with a detailed caption.

Comparisons Among Microorganisms



Types of Infectious Agents: Fungi

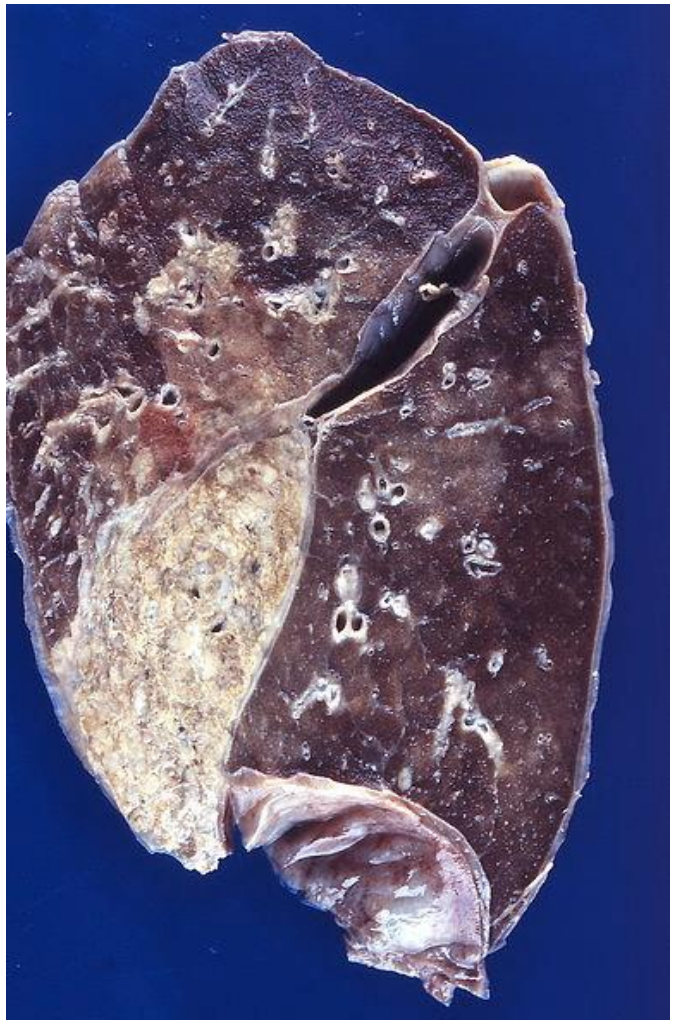
- Fungi are non-photosynthetic, **eukaryotic** organisms. They are disseminated throughout the environment.
- Because both fungal and human cells are eukaryotic cells, fungal infections are difficult to treat. Medications that kill fungal cells are usually capable of harming human cells too.
- Fungi reproduce by simply dividing (asexually) or by combining their genetic information before dividing (sexually).
- They have **chitin** in their cell walls. Bacteria do not.
- Unicellular fungi are called **yeasts**. Yeast cells reproduce by budding and form an elongated chain called a **pseudohyphae**.
- Multicellular fungi have tubules that branch to form **hyphae**. Clusters of hyphae form a fuzzy mat called a **mycelium**. Reproduction occurs by formation of a **fruiting body** that forms and releases spores.

Types of Infectious Agents: Fungi 1

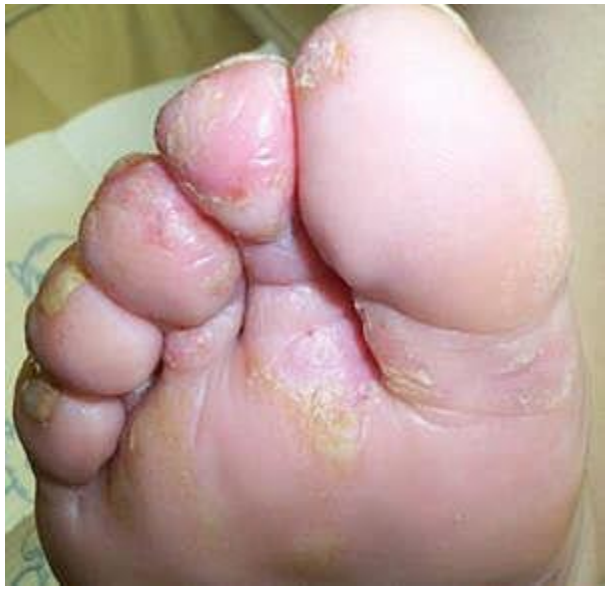
- Infections caused by fungi are called **mycotic infections** or **mycoses**.
  - **Opportunistic mycoses**-normal flora become bothersome
  - **Superficial mycoses** occur only on dead, keratinized tissue
  - **Subcutaneous mycoses** occur due to body surface trauma
  - **Systemic mycoses** are life-threatening and usually opportunistic. They may affect the lungs, kidneys or heart.
- Fungi are common residents of the body surface. They are kept at bay by intact integument and mucous membranes, the immune system and by resident bacteria.
- Bacteria of the normal floral compete with fungi of the normal flora for resources. **Antibiotic treatment** disturbs this balance and may allow fungal overgrowth because of lowered competition from bacteria.
- Fungal infections are often opportunistic. A very common opportunistic yeast infection is **candidiasis.** *It is caused by* ***Candida albicans.*** Yeast grow best in warm, moist dark regions: diaper area in infants, under the breasts in women, the vagina, the mouth and between the toes.
- **Histoplasmosis**, a fungal lung infection, is caused by ***Histoplasma capsulatum.***

Types of Infectious Agents: Fungi 2

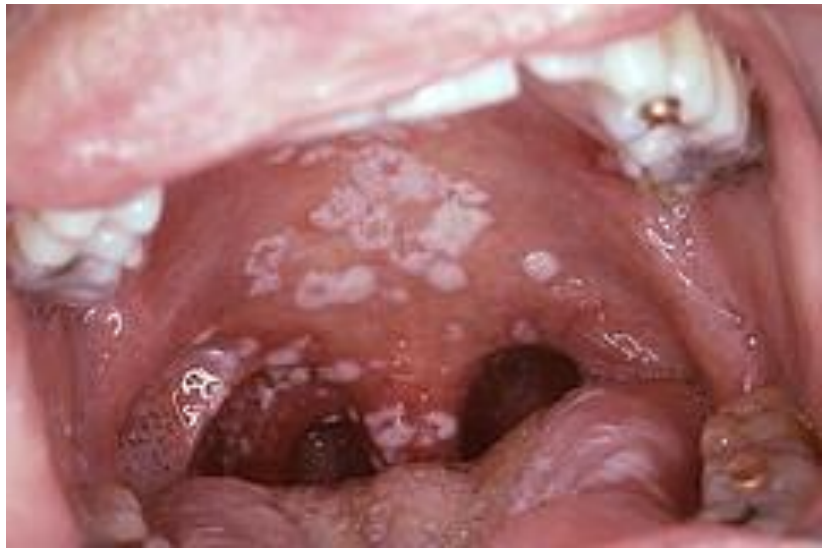
Histoplasmosis: Lung infected by inhaling fungus from pigeon feces.



Types of Infectious Agents: Fungi 3



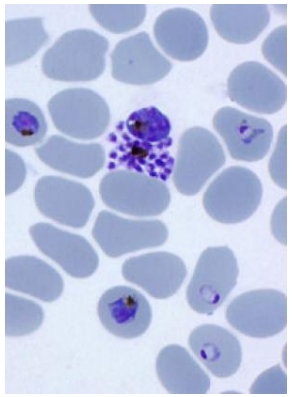
Athlete’s Foot



Oral Candidiasis

Types of Infectious Agents: Protozoans

- **Protozoans** are single-celled **eukaryotic protists**. They have no cell walls. Many shapes exist and most forms are motile due to the presence of cilia or flagella.
- Although some protists (algae) are autotrophs, protozoans are heterotrophs.
- Protozoans usually reproduce asexually, but sexual reproduction is possible in some forms.
- Transmission of protozoan infections may be by sexual contact, contaminated food or water or vector.
- **Malaria** is caused by protozoans of the genus ***Plasmodium*** that specifically infect **red blood cells** causing severe anemia. It is transmitted by mosquito bite.



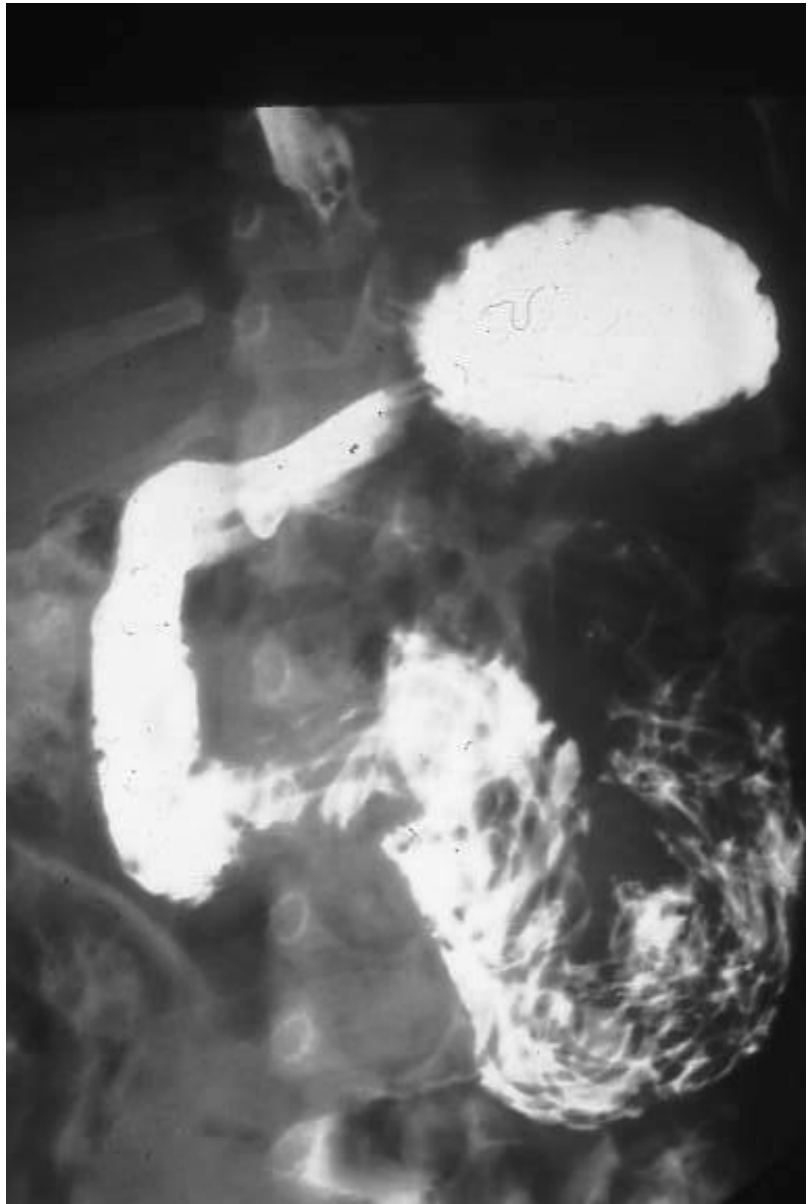
Red blood cells infected with malarial parasites.

Types of Infectious Agents: Other

- Other eukaryotic animal organisms that cause or act as vectors for human infections include:
- **Nematodes**-round worms
- **Platyhelmintes**-flat worms (tapeworms)
- **Arthropods** (insects) act as **vectors** for many infections
  - Mosquitos: malaria (protozoan, ***Plasmodium faciparum***), dengue fever (virus), West Nile virus
  - Ticks: Lyme disease (bacteria, ***Borrelia burgdorferi***)
  - Fleas: Bubonic plague (bacteria, ***Yersinia pestis***)
  - Tsetse fly: African sleeping sickness (protozoan, ***Trypanosoma brucei***)
- Infections by eukaryotic organisms are **difficult to treat.** Any medication that would kill the eukaryotic parasite would also likely do harm to human cells.

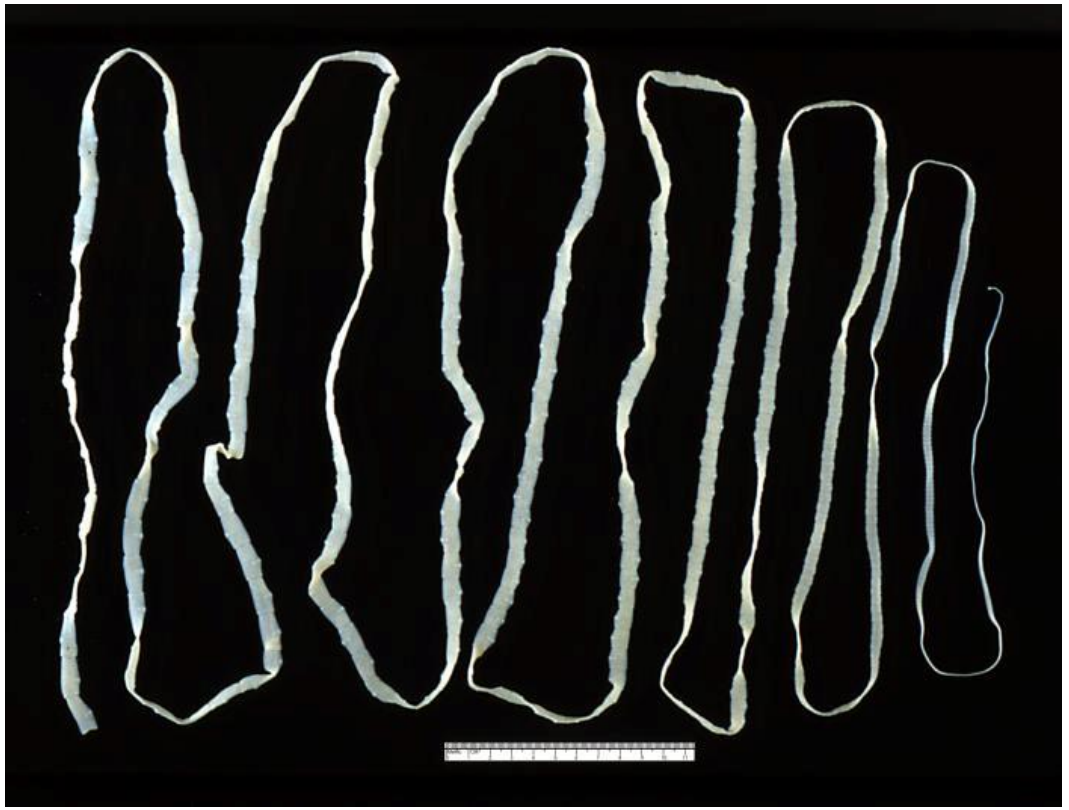
Types of Infectious Agents: Other 1

X-ray of the digestive tract using barium contrast medium. The dark areas in the intestine are clumps of **roundworms.**



Platyhelminthes (Tapeworm)

Tapeworm with 12” ruler



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QUIZ 2CD

- COMPLETE QUIZ 2CD.
- THEN PREPARE FOR EXAM 2.

EXAM 2

- COMPLETE EXAM 2.
- THEN GO ON TO MODULE 3AB PPT.