EMBOLISM

EMBOLISM

- Embolus definition:
  - a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin

EMBOLISM

- Virtually 99% of all emboli represent some part of a dislodged thrombus, hence the term *thromboembolism*

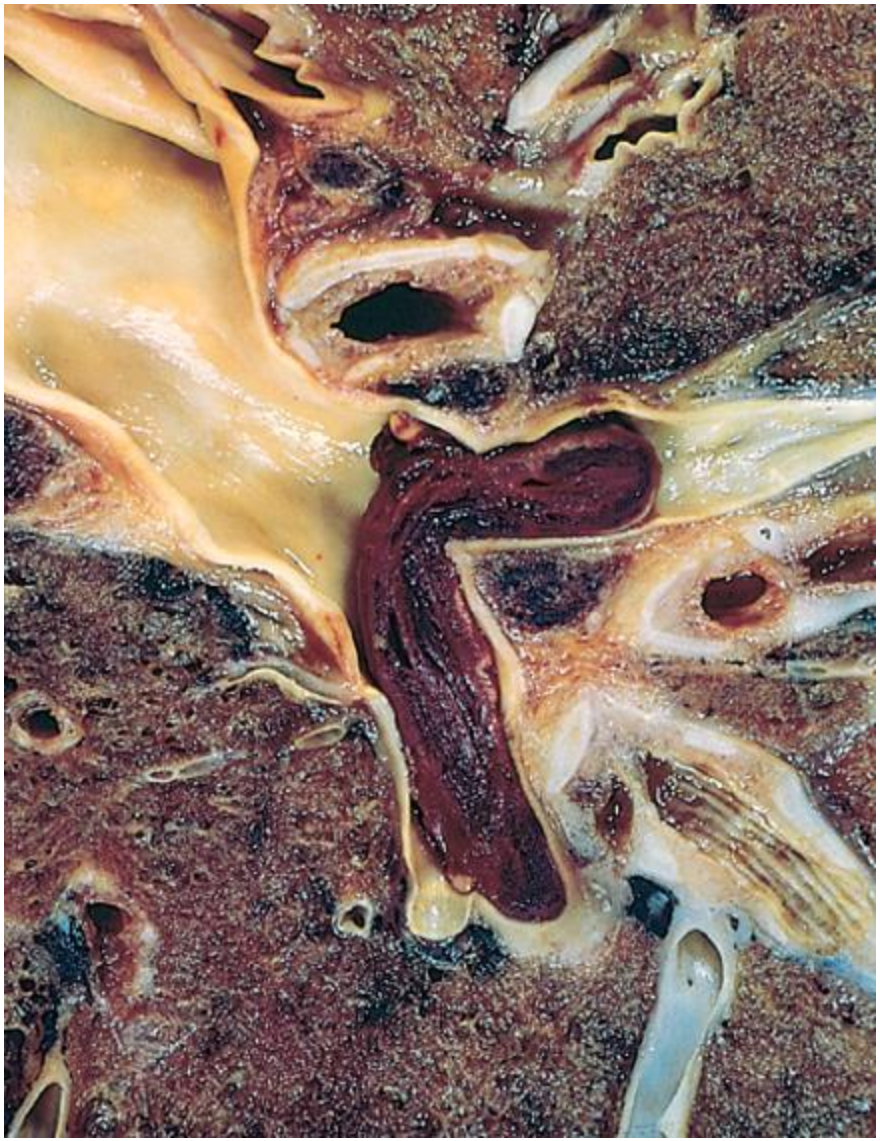
- Rare forms of emboli include:
  - fat droplets
  - bubbles of air or nitrogen
  - atherosclerotic debris (*cholesterol emboli*)
  - tumor fragments
  - bits of bone marrow
  - foreign bodies (such as bullets)

EMBOLISM

- Pulmonary Thromboembolism:
  - In more than 95% of cases, venous emboli originate from deep leg vein thrombi above the level of the knee → progressively larger channels and pass through the right side of the heart → entering the pulmonary vasculature
  - Depending on the size of the embolus, it may:
    - occlude the main pulmonary artery
    - impact across the bifurcation (*saddle embolus*)
    - pass out into the smaller, branching arterioles
  - Frequently, there are multiple emboli (perhaps sequentially, or as a shower of smaller emboli from a single large thrombus)
  - In general, *the patient who has had one pulmonary embolus is at high risk of having more*

EMBOLISM

- Pulmonary Thromboembolism, consequences:
  - 60% to 80% are clinically silent because they are small
    - they eventually become organized and become incorporated into the vascular wall
    - in some cases, organization of the thromboembolus leaves behind a delicate, bridging fibrous ***web***
  - When 60% or more of the pulmonary circulation is obstructed with emboli →
    - sudden death
    - right ventricular failure (*cor pulmonale*)
    - cardiovascular collapse
  - Embolic obstruction of medium-sized arteries can cause pulmonary hemorrhage but usually **not** pulmonary infarction:
    - the lung has a dual blood supply and the intact bronchial arterial circulation continues to supply blood to the area
  - Embolic obstruction of small end-arteriolar pulmonary branches usually does result in associated infarction
  - Many emboli occurring over a period of time may cause:
    - pulmonary hypertension → right ventricular failure
  - ***Paradoxical embolism*:**
    - **Rarely, an embolus can pass through an interatrial or interventricular defect, thereby entering the systemic circulation**



Embolus derived from a lower extremity deep venous thrombosis and now impacted in a pulmonary artery branch

EMBOLISM

- Systemic Thromboembolism
  - Emboli in the arterial circulation
  - Most (80%) arise from intracardiac mural thrombi:
    - two-thirds of which are associated with left ventricular wall infarcts
    - quarter with dilated left atria (e.g., secondary to mitral valve disease)
  - The remainder originate from:
    - aortic aneurysms
    - thrombi on ulcerated atherosclerotic plaques
    - fragmentation of valvular vegetations
  - The **major sites** for arteriolar embolization:
    - the lower extremities (75%)
    - the brain (10%),
    - the intestines, kidneys, and spleen affected to a lesser extent

EMBOLISM

- Fat Embolism:
  - Microscopic fat globules can be found in the circulation after fractures of long bones (which contain fatty marrow), burns or after soft-tissue trauma
  - Although fat and marrow embolism occurs in some 90% of individuals with severe skeletal injuries, fewer than 10% of such patients show any clinical findings
  - *Fat embolism syndrome is characterized by:*
    - *pulmonary insufficiency*
    - *neurologic symptoms*
    - *anemia*
    - *thrombocytopenia*

EMBOLISM

- Air embolism:
  - Gas bubbles within the circulation can obstruct vascular flow almost as readily as thrombotic masses can
  - Air may enter the circulation during obstetric procedures or as a consequence of chest wall injury
  - Generally, more than 100 mL of air are required to produce a clinical effect
  - *decompression sickness:*
    - occurs when individuals are exposed to sudden changes in atmospheric pressure
      - e.g. Scuba and deep-sea divers are at risk
    - When air is breathed at high pressure (e.g., during a deep-sea dive)→ increased amounts of gas (particularly nitrogen) become dissolved in the blood and tissues → If the diver then ascends (depressurizes) too rapidly → the nitrogen expands in the tissues and bubbles out of solution in the blood → gas emboli
    - can induce focal ischemia in a number of tissues:
      - brain and heart
      - skeletal muscles , causing pain (*the bends*)
      - In the lungs, respiratory distress, (the *chokes)*

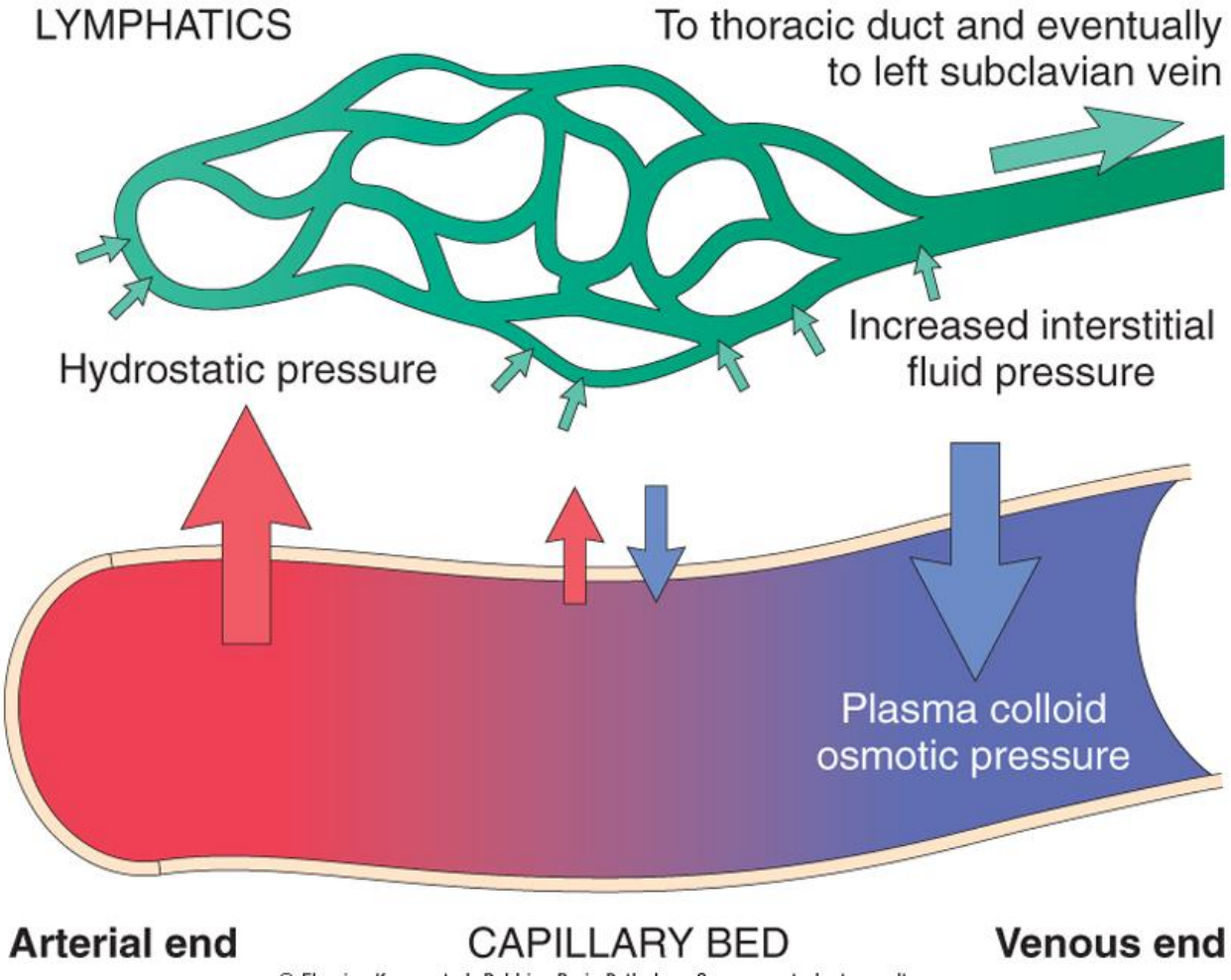
EMBOLISM

- Amniotic embolism:
  - A grave but fortunately uncommon
  - Complication of labour and the immediate postpartum period
  - The onset is characterized by sudden severe dyspnea, cyanosis, and hypotensive shock, followed by seizures and coma
  - If the patient survives the initial crisis, the patient may develope:
    - pulmonary edema and diffuse alveolar damage
    - disseminated intravascular coagulation (DIC), due to release of thrombogenic substances from amniotic fluid
  - The underlying cause is entry of amniotic fluid (and its contents) into the maternal circulation via a tear in the placental membranes and rupture of uterine veins

EDEMA

EDEMA

- increased fluid in the interstitial tissue spaces
- fluid collections in different body cavities are variously designated:
  - *Hydrothorax*
  - *Hydropericardium*
  - *Hydroperitoneum* (more commonly called *ascites*)
- *Anasarca*
  - a severe and generalized edema with profound subcutaneous tissue swelling



Variables affecting fluid transit across capillary walls. Capillary hydrostatic and osmotic forces are normally balanced so that there is no *net* loss or gain of fluid across the capillary bed. However, *increased* hydrostatic pressure or *diminished* plasma osmotic pressure leads to a net accumulation of extravascular fluid (edema). As the interstitial fluid pressure increases, tissue lymphatics remove much of the excess volume, eventually returning it to the circulation via the thoracic duct. If the ability of the lymphatics to drain tissue fluid is exceeded, persistent tissue edema results.

EDEMA
Causes

- **Increased Hydrostatic Pressure**
  - Impaired venous return
    - Congestive heart failure
    - Constrictive pericarditis
    - Ascites (liver cirrhosis)
    - Venous obstruction or compression:
      - Thrombosis
      - External pressure (e.g., mass)
      - Lower extremity inactivity with prolonged dependency
  - Arteriolar dilation
    - Heat
- **Reduced Plasma Osmotic Pressure (Hypoproteinemia)**
  - Protein-losing glomerulopathies (nephrotic syndrome)
  - Liver cirrhosis (ascites)
  - Malnutrition
  - Protein-losing gastroenteropathy
- **Lymphatic Obstruction** (*lymphedema)*
  - Inflammatory (e.g. Filariasis)
  - Neoplastic (e.g. breast cancer)
  - Postsurgical
  - Postirradiation
- **Sodium Retention**
  - Excessive salt intake with renal insufficiency
  - Increased tubular reabsorption of sodium
  - Renal hypoperfusion
  - Increased renin-angiotensin-aldosterone secretion
- **Inflammation**
  - Lead to increased endothelial permeability

EDEMA
Notes to remember

- Congestive heart failure:
  - Although increased venous hydrostatic pressure is contributory, the pathogenesis is more complex
  - reduced cardiac output →

    reduced renal perfusion →

    activate renin-angiotensin-aldosterone axis → sodium and water retention by the kidneys (*secondary aldosteronism*)
  - This is not unique to CHF (e.g. can be observed in decreased osmotic pressure)

EDEMA

- Exudate
  - increased vascular permeability
  - protein-rich *exudate*
  - specific gravity that is usually greater than 1.020
- Transudate
  - volume or pressure overload, or under conditions of reduced plasma protein
  - protein-poor
  - specific gravity less than 1.012

SHOCK

SHOCK

- Definition:
  - the final common pathway for a number of potentially lethal clinical events
  - *gives rise to **systemic hypoperfusion***
  - *caused either by reduced cardiac output or by reduced effective circulating blood volume*
  - *the end results are:*
    - *hypotension*
    - *impaired tissue perfusion*
    - *cellular hypoxia*

SHOCK

Types

Type of Shock	Clinical Example	Principal Mechanisms
CARDIOGENIC		
	Myocardial infarction Ventricular rupture Arrhythmia Cardiac tamponade Pulmonary embolism	Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow
HYPOVOLEMIC		
	Fluid loss (e.g., hemorrhage, vomiting, diarrhea, burns, or trauma)	Inadequate blood or plasma volume
SEPTIC		
	Overwhelming microbial infections (bacterial and fungal) Superantigens (e.g., toxic shock syndrome)	Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage, disseminated intravascular coagulation; activation of cytokine cascades

SHOCK
also..

- *Neurogenic shock*
  - Less common
  - shock may occur in the setting of an anesthetic accident or a spinal cord injury
  - as a result of loss of vascular tone and peripheral pooling of blood
- *Anaphylactic shock:*
  - represents systemic vasodilation and increased vascular permeability caused by an immunoglobulin E hypersensitivity reaction
  - in these situations, acute severe widespread vasodilation results in tissue hypoperfusion and cellular anoxia

SHOCK
Stages

- Shock tends to evolve through three general (albeit somewhat artificial) stages:
  - **Initial *non-progressive stage:***
    - reflex compensatory mechanisms is activated
    - perfusion of vital organs is maintained
    - These include:
      - baroreceptor reflexes
      - release of catecholamines
      - activation of the renin-angiotensin axis
      - antidiuretic hormone release
      - generalized sympathetic stimulation
    - The net effect:
      - ***tachycardia***
      - ***peripheral vasoconstriction***
      - ***renal conservation of fluid***
      - Cutaneous vasoconstriction:
        - » characteristic coolness and pallor of skin in shock (although septic shock may initially cause cutaneous *vasodilation* and thus present with *warm, flushed skin*)
    - Coronary and cerebral vessels are **less sensitive** to the sympathetic response → maintain relatively normal caliber, blood flow, and oxygen delivery to their respective vital organs

SHOCK

Stages

– ***Progressive stage:***

- characterized by tissue hypoperfusion and onset of worsening circulatory and metabolic imbalances
- it occurs when the underlying causes are not corrected
- intracellular aerobic respiration is replaced by anaerobic glycolysis→ *lactic acidosis* → *lowers the tissue pH* → *blunts the vasomotor response* → arterioles dilate→ blood begins to pool in the microcirculation (Peripheral pooling) → worsens the cardiac output and puts endothelial cells at risk of developing anoxic injury → may lead to subsequent DIC
- with widespread tissue hypoxia, vital organs are affected and begin to fail

SHOCK

Stages

- ***Irreversible stage:***
  - The body has incurred cellular and tissue injury so severe that even if the hemodynamic defects are corrected, survival is not possible
  - Widespread cell injury → lysosomal enzyme leakage→ aggravating the shock state.
  - Myocardial contractile function worsens
  - If ischemic bowel allows intestinal flora to enter the circulation →endotoxic shock may also be superimposed
  - At this point, the patient has complete renal shutdown due to ischemic acute tubular necrosis
  - Almost inevitably culminates in death

SHOCK

Morphology

- The cellular and tissue changes induced by shock are non-specific and are essentially those of hypoxic injury, due to some combination of hypoperfusion and microvascular thrombosis
- The changes are particularly evident in the brain (hypoxic encephalopathy), heart (e.g. Contraction band and necrosis), kidneys, adrenal glands, and gastrointestinal tract
- Fibrin thrombi may be identified in virtually any tissue, although they are usually most readily visualized in kidney glomeruli
- With the exception of neuronal and myocyte ischemic loss, virtually all tissues may revert to normal if the patient survives
- Unfortunately, most patients with irreversible changes due to severe shock die before the tissues can recover

SHOCK
Morphological changes, examples

- **kidneys** :
  - typically reveals acute tubular necrosis → oliguria, anuria, and electrolyte disturbances
- **Gastrointestinal tract:**
  - may manifest focal mucosal hemorrhage and necrosis
- **Lungs:**
  - seldom affected in pure hypovolemic shock, because they are somewhat resistant to hypoxic injury
  - however, when shock is caused by bacterial sepsis or trauma, changes of **diffuse alveolar damage** may develop, the so-called shock lung
  - Pulmonary edema
- **Liver:**
  - Fatty change
  - **Centrilobular necrosis:** necrotic hepatocytes around terminal hepatic venule

SHOCK

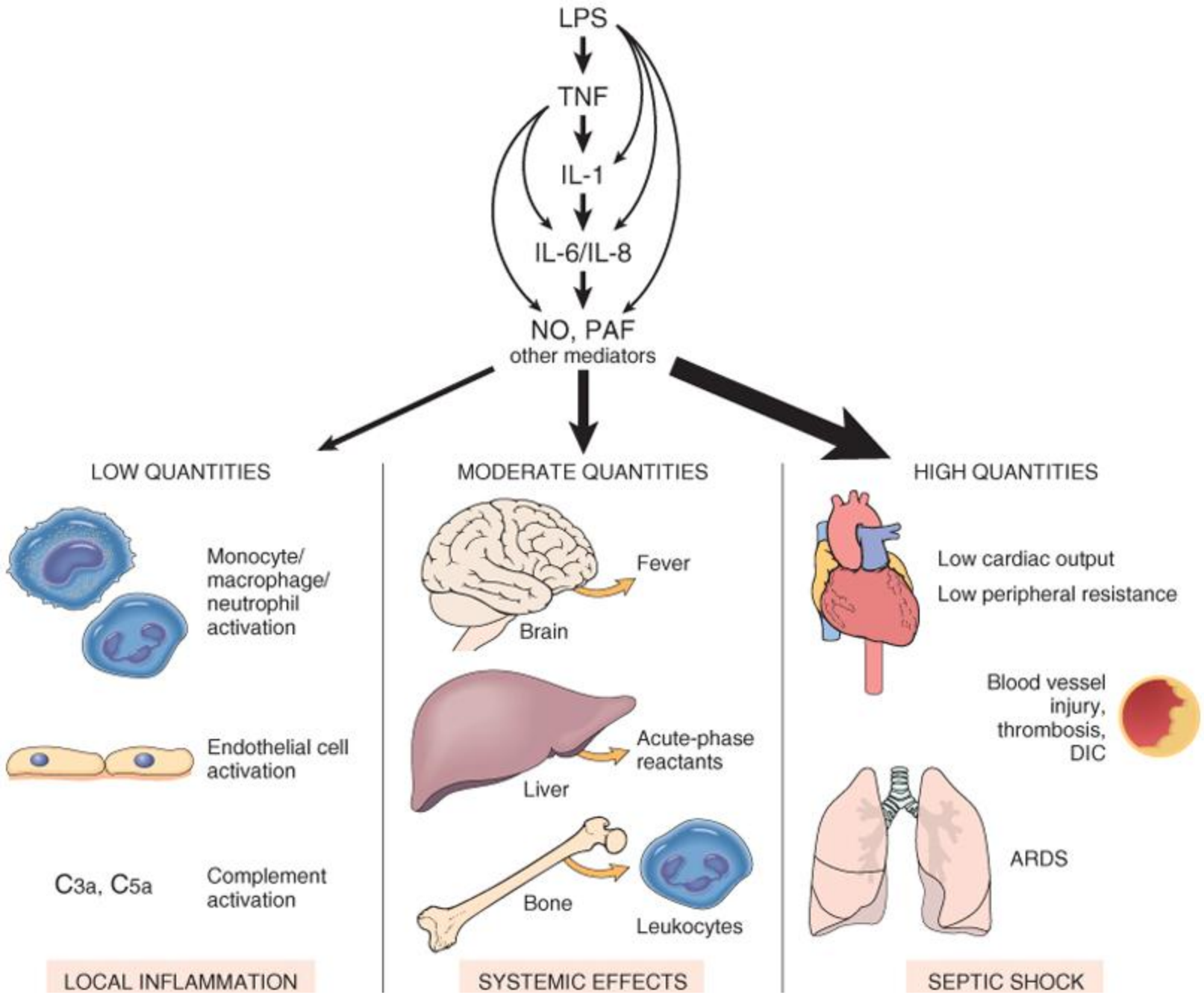
- **Septic shock pathophysiology <u>(Not included in 1430 path211 curriculum) but read it when you can :</u>**
  - results from the host innate immune response to bacterial or fungal cell molecules
  - Most cases of septic shock were thought to be caused by endotoxin-producing gram-negative bacilli - hence the term *endotoxic shock*
  - **Currently (Robbins 2010)**, septic shock is most frequently triggered by gram-positive bacterial infections, followed by gram-negative bacteria and fungi
  - systemic production of cytokines, such as TNF and IL-1 → endothelial and inflammatory cell activation
  - Hypotension, DIC, and metabolic disturbances constitute the clinical triad of septic shock

SHOCK

- Septic shock (continued):
  - Endotoxins:
    - Bacterial wall lipopolysaccharides (LPS) consisting of:
      - a toxic fatty acid (*lipid A*) core common to all gram-negative bacteria
      - a complex polysaccharide coat (including *O antigen*) unique for each species
    - Analogous molecules in the walls of gram-positive bacteria and fungi can also elicit septic shock

SHOCK

- Septic shock (continued):
  - Cytokines that were activated by LPS effects, act on endothelial cells and have a variety of effects including reduced synthesis of anticoagulation factors
  - **But**, Higher LPS levels tip the endothelium toward a net procoagulant phenotype



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Caption of above figure

Effects of lipopolysaccharide (LPS) and secondarily induced effector molecules. LPS initiates the cytokine cascade. In addition, LPS and the secondary mediators can also directly stimulate downstream cytokine production, as indicated. Secondary effectors that become important include nitric oxide(NO) and platelet-activating factor (PAF). At low levels, only local inflammatory effects are seen. With moderate levels, more systemic events occur in addition to the local vascular effects. At high concentrations, the syndrome of septic shock supervenes. ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation; IL-1, interleukin 1; IL-6, interleukin 6; IL-8, interleukin 8; TNF, tumor necrosis factor

Shock

- *Septic shock (continued):*
  - *Also note that Immune suppression is a factor n the septic shock pathophysiology*
    - The hyperinflammatory state initiated by sepsis can activate counter-regulatory immunosuppressive mechanisms
    - Proposed mechanisms for the immune suppression include a shift from pro-inflammatory (T_H1) to anti-inflammatory (T_H2) cytokines
    - It is still debated whether immunosuppressive mediators are deleterious or protective in sepsis.