Hemodynamic Disorders
Thrombosis and Shock

- Edema
- Congestion
- Infarction
- Hemorrhage
- Thrombosis
- Embolism
- Shock
Edema
Edema

- Edema can be defined as the accumulation of abnormal amounts of fluid (predominantly water) in interstitial spaces or body cavities.
Edema

• In various body cavities fluid collections are variously designated hydrothorax, hydropericardium, hydroperitoneum (more commonly called ascites)

• Anasarca is a severe and generalized edema with profound subcutaneous tissue swelling
Edema

• In general, the opposing effects of vascular hydrostatic pressure and plasma colloid osmotic pressure are the major factors that govern movement of fluid between vascular and interstitial spaces
To thoracic duct and eventually to left subclavian vein

Hydrostatic pressure

Increased interstitial fluid pressure

Plasma colloid osmotic pressure

Arterial end  CAPILLARY BED  Venous end

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Causes of Edema

- Inflammatory
- Non-Inflammatory
Causes of Edema

- Inflammatory: tissue injury alters blood flow and vascular permeability. Water accumulates in the interstitium as a consequence of changes in hydrostatic pressure and colloid osmotic pressure.
Causes of Edema

Non-Inflammatory causes include:

- increased hydrostatic pressure
- decreased plasma osmotic pressure
- lymphatic obstruction
- sodium and water retention
### Table 5-1: Pathophysiologic Categories of Edema

#### 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
  - Neurohumoral dysregulation

#### Reduced Plasma Osmotic Pressure (Hypoproteinemia)
- Protein-losing glomerulopathies (nephrotic syndrome)
- Liver cirrhosis (ascites)
- Malnutrition
- Protein-losing gastroenteropathy

#### Lymphatic Obstruction
- Inflammatory
- Neoplastic
- Postsurgical
- Postirradiation

#### Sodium Retention
- Excessive salt intake with renal insufficiency
  - Increased tubular reabsorption of sodium
    - Renal hypoperfusion
    - Increased renin-angiotensin-aldosterone secretion

#### Inflammation
- Acute inflammation
- Chronic inflammation
- Angiogenesis
Edema

• The edema fluid occurring in hydrodynamic derangements is typically a protein-poor TRANSUDATE, with a specific gravity below 1.012.

• Conversely, because of increased vascular permeability, inflammatory edema is a protein-rich EXUDATE, with a specific gravity usually over 1.020.
Edema: Clinical Correlation

- The effects of edema may range from a mere annoyance to being fatal.

- Subcutaneous tissue edema in cardiac or renal failure is important mainly because it signals the underlying disease; pulmonary edema can cause death by interfering with normal ventilatory function; brain edema is serious because of the closed cavity.
Edema : lung
Edema: lung
Early mild pulmonary edema. Most alveoli contain air; but a few contain pink, acellular proteinaceous fluid.
Edema: lung

enlarged alveolar spaces, filled with pink staining edema fluid.
Hyperemia and Congestion
Hyperemia and Congestion

• Hyperemia & congestion indicate a local increased volume of blood in a particular tissue

• Hyperemia is an active process resulting from augmented tissue inflow because of arteriolar dilation

• Congestion is a passive process resulting from impaired outflow from a tissue
Congestion

- Congested tissue has a blue-red color (cyanosis) particularly as worsening congestion leads to accumulation of deoxygenated hemoglobin

- Congestion of capillary beds is closely related to the development of edema, so that congestion and edema commonly occur together
Congestion and Hyperemia

HYPEREMIA
erythema

Increased inflow
(e.g., exercise, inflammation)

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Congestion and Hyperemia

CONGESTION
cyanosis/hypoxia

Decreased outflow
(e.g., local obstruction, congestive heart failure)

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Congestion of Lung

- Sections of fresh pulmonary parenchyma.
- Note deep red color with preservation of underlying architecture.
- Normal should be pink-tan.
Pulmonary congestion

Note markedly distended and engorged blood vessels.
Pulmonary congestion

Note congested vessels engorged with blood.
Chronic Passive Congestion, Liver Nutmeg Liver
Liver -- Passive congestion Centrilobular necrosis with hemorrhage and hemosiderin.
Hemorrhage
Hemorrhage

- Is the flow of blood from a ruptured blood vessel
- The flow may be into a tissue, body cavity or outside the body
- May occur as the result of mechanical force (trauma) or as a result of a pathologic process (inflammation)
Hemorrhage

• Hemorrhage, as noted, may be external or may be enclosed within a tissue; the accumulation is referred to as a HEMATOMA.

• Minute 1-2 mm hemorrhages into skin, mucous membranes or serosal surfaces are called PETECHIAE.
Hemorrhage

• Slightly larger (> or =3mm) hemorrhages are called PURPURA

• Large (.1 to 2 cm) subcutaneous hematomas are called ECCHYMOSES

• Large accumulations of blood in the different body cavities are variously designated hemothorax, hemopericardium, hemoperitoneum or hemarthrosis
Hemorrhage

- Hemorrhage can occur as a result of low platelet counts (thrombocytopenia)

- RBCs in hemorrhages are degraded and phagocytosed by macrophages; the hemoglobin (red-blue color) is then enzymatically converted into bilirubin (blue-green color) and eventually into hemosiderin (gold-brown color)
Hemorrhage

- Patients with extensive hemorrhages occasionally develop jaundice from the massive breakdown of red cells and systemic release of bilirubin.
The clinical significance of hemorrhage depends on the volume and rate of blood loss.

Rapid removal of up to 20% of blood volume or slower losses of even more may have little effect on healthy adults.

Greater losses however may result in hemorrhagic (hypovolemic) shock.
Hemorrhage

• The site of hemorrhage is important, e.g. into brain tissue

• The loss of iron from hemorrhage may cause iron-deficiency anemia which is problematic
Subarachnoid Hemorrhage

- A view of the base of the brain, showing dark reddish blood in the subarachnoid space over the optic and other cranial nerves and brainstem from a ruptured anterior communicating artery berry aneurysm.
- Note how generally swollen the brain is.
Intracerebral Hemorrhage

- A coronal section of brain through the thalamus showing a large intracerebral hemorrhage.
- Note the shift of structures toward the opposite side including the cingulate gyrus, lateral and third ventricles and thalamus.
- There is blood in the ventricles as well.
Gastric Hemorrhage

- Opened stomach demonstrates innumerable small punctate gastric mucosal hemorrhages

- Large numbers of small mucosal hemorrhages associated with mucosal erosions are often seen in severe illnesses "stress ulcers" or NSAID

- Esophageal-gastric junction is seen at left (arrow)
Petechial Hemorrhages

- This is a lateral view of the brain with the frontal lobes to the left and the occipital lobes and cerebellum to the right.

- The arrows point to numerous petechial hemorrhages which could be due to blood dyscrasias such as seen in terminal leukemias, ITP, etc. or due to toxins such as arsenic.
Hemostasis and Thrombosis
Hemostasis and Thrombosis

• Normal hemostasis is a well-regulated process which:
  1) maintains blood in a fluid, clot-free state in normal vessels and
  2) is ready to induce a rapid and localized hemostatic plug at the site of vascular injury

• Thrombosis can be thought of as the pathologic opposite to hemostasis
Hemostasis and Thrombosis

• Both hemostasis and thrombosis depend on three general components
  1) the vascular wall
  2) platelets
  3) coagulation cascade
NORMAL HEMOSTASIS

1. Integrity of small blood vessels
2. Adequate numbers of platelets
3. Normal amounts of coagulation factors
4. Normal amounts of coagulation inhibitors
5. Adequate amounts of calcium ions in the blood
The vessel constituents and coagulation

- **Endothelial cells are antithrombotic**
  - Antiplatelet effects
  - Anticoagulant effects
  - Fibrinolytic effects

- **Prothrombotic**
  - Pro-platelet adhesion – vwf
  - Procoagulant – activated to secrete tissue factor
  - Antifibrinolytic – inhibitors of plasminogen activators that depress fibrinolysis
A. VASOCONSTRICION

Endothelium
Basement membrane
Arteriole smooth muscle

Site of injury

Endothelin release causes vasoconstriction

Reflex vasoconstriction

ECM (collagen)
C. SECONDARY HEMOSTASIS

1. Tissue factor
2. Phospholipid complex expression
3. Thrombin activation
4. Fibrin polymerization

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Abnormalities of coagulation

• Abnormalities of small blood vessels

• Abnormalities of platelet numbers
  ▫ Thrombocytopenia
    • Insufficient production
    • Peripheral destruction

• Decrease in coagulation factors
  ▫ Hemophilia
  ▫ Prothrombin deficiency
    • Anticoagulants
    • Inadequate synthesis or absorption of vitamin k
    • Severe liver disease
The coagulation cascade

• A series of enzyme reactions ultimately resulting in the formation of thrombin which converts fibrinogen (soluble) into fibrin (insoluble)
D. THROMBUS AND ANTITHROMBOTIC EVENTS

Release of:
- t-PA (fibrinolysis)
- thrombomodulin (blocks coagulation cascade)

Trapped neutrophil
Trapped red blood cells
Polymerized fibrin

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How do we stop this

• Fibrinolytic system
  ▫ Predominantly by action of plasmin
    • Plasmin formed by action of tissue plasminogen activator and urokinase
    • Leads to breakdown of fibrin into fibrin split products
Thrombosis

- Formation of a thrombus or blood clot can result from: endothelial injury, altered blood flow or hypercoaguable states
Thrombosis

• Three primary influences predispose to thrombus formation (Virchow’s triad):
  1) endothelial injury
  2) stasis or turbulence of blood flow
  3) blood hypercoagulability
Factors predisposing to thrombosis

• **ABNORMALITIES OF BLOOD FLOW**

• **TURBULENCE**
  - Endothelial injury
  - Local areas of stasis
  - Disrupt laminar flow
    • Moves platelets from center of flow to the vessel wall
    • Prevent dilution of activated clotting factors by flowing blood
    • Slow down the inflow of clotting factor inhibitors
    • Promotes endothelial cell activation
Factors predisposing to thrombosis

• Hypercoaguability
  ▫ Any alteration of the coagulation pathway that predisposes to thrombosis
    • Primary (genetic)
      • Factor v gene mutation and prothrombin gene mutations most frequent
        • V becomes resistant to protein c inactivation
        • Prothrombin levels elevated
    • Secondary (acquired)
      • Bed rest – immobilization, obesity, cancer, atrial fibrillation, myocardial infarction, tissue damage (surgery, burns)
### Table 5-2: Hypercoagulable States

<table>
<thead>
<tr>
<th><strong>Primary (Genetic)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations in factor V</td>
<td></td>
</tr>
<tr>
<td>Antithrombin III deficiency</td>
<td></td>
</tr>
<tr>
<td>Proteins C or S deficiency</td>
<td></td>
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<tr>
<td>Fibrinolysis defects</td>
<td></td>
</tr>
<tr>
<td>Homocysteinemia</td>
<td></td>
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<tr>
<td>Allelic variations in prothrombin levels</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Secondary (Acquired)</strong></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>High risk for thrombosis</td>
<td></td>
</tr>
<tr>
<td>Prolonged bed rest or immobilization</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
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<tr>
<td>Tissue damage (surgery, fracture, burns)</td>
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<tr>
<td>Cancer</td>
<td></td>
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<tr>
<td>Prosthetic cardiac valves</td>
<td></td>
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<tr>
<td>Disseminated intravascular coagulation</td>
<td></td>
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<tr>
<td>Heparin-induced thrombocytopenia</td>
<td></td>
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<tr>
<td>Antiphospholipid antibody syndrome (lupus anticoagulant syndrome)</td>
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<tr>
<td>Lower risk for thrombosis</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Nephrotic syndrome</td>
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<tr>
<td>Hyperestrogenic states</td>
<td></td>
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<tr>
<td>Oral contraceptive use</td>
<td></td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
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</tbody>
</table>
Fate of Thrombi

• If the patient survives the thrombotic vascular obstruction thrombi may undergo:
  1) propagation
  2) embolization
  3) dissolution
  4) organization and recanalization
Thrombi fates

- Resolution
- Embolization to lungs
- Organized and incorporated into wall
- Organized and recanalized

- Propagation towards heart
- Inferior vena cava
- Iliac vein

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Thrombi: Clinical Correlation

• Thrombi are significant because they:
  1) cause obstruction of arteries and veins
  2) are possible sources of emboli
• The significance of each depends on where the thrombus occurs
Venous Thrombosis

• The great preponderance of venous thrombi occur in either the superficial or deep veins of the leg
• Deep thrombi (of the larger veins) are more serious because they may embolize and approximately 50% of these thrombi are asymptomatic
Venous Thrombi: Fates

- **Organization**
  - Ingrowth of cells into thrombus with incorporation into wall

- **Resolution**
  - It goes away

- **Embolization**
  - Travels from its site of origin to a distal part of circulation
Venous Thrombi: Clinical
Arterial Thrombosis

• Atherosclerosis is a major initiator of thromboses, related to abnormal vascular flow and loss of endothelial integrity

• Myocardial infarcts and rheumatic heart disease also provide sites for thromboses
Arterial Thrombi Morphology

- Adherent masses of blood that demonstrate areas of pale alternating with areas of red
  - Lines of Zahn
Arterial Thrombi Morphology
Disseminated Intravascular Coagulation (DIC)

• DIC is not a primary disease but rather a potential complication of any condition associated with widespread activation of thrombin

• DIC may result in a variety of disorders ranging from obstetric complications to advanced malignancy
Embolism
Embolism

- An embolus is an intravascular substance (solid, liquid, gas) which is carried by the blood from a point of origin to a distant site.
Types of Emboli

- Fragments of thrombus
- Amniotic fluid
- Air (gas)
- Fat
Emboli

• Approximately 99% of all emboli represent dislodged thrombi, hence the commonly used term thromboembolism
Pulmonary Thromboembolism

- Pulmonary embolism has an incidence of 20/25 per 100,000 hospitalized patients with a death rate of 2%

- In greater than 95% of cases the venous embolus originated from deep leg veins above the knee
Pulmonary Thromboembolism

- Depending on size, an embolus may occlude the main pulmonary artery, impact across the bifurcation (saddle embolus), or pass out into the smaller branching arterioles.

- Most pulmonary emboli (60-80%) are clinically silent because they are small.
Pulmonary Thromboembolism

• Sudden death, rt. heart failure (cor pulmonale), or cardiovascular collapse occurs when 60%+ of the pulmonary circulation is obstructed.

• Embolic obstruction of medium-sized arteries may result in hemorrhage but usually not infarction because of the dual blood supply.
Pulmonary Thromboembolism

• Embolic obstruction of small end-arteriolar pulmonary branches usually does result in an infarct

• Multiple emboli over time may cause pulmonary hypertension with rt. heart failure

• A patient who has had one pulmonary embolus is at high risk of having more
The main pulmonary trunk and pulmonary arteries to right and left lungs are seen here opened to reveal a large "saddle" pulmonary thromboembolus. Patients with such an embolus will have a high mortality rate.
This is the microscopic appearance of a pulmonary embolus (PE) in a major pulmonary artery branch.
Fat Embolism

• Most fat emboli occur after fractures of long bones; 90% of pts. with severe skeletal injuries have fat emboli but only 10% have clinical findings

• Fat embolism syndrome begins 1-3 days after injury with sudden onset of tachypnea, dyspnea and tachycardia; pulmonary insufficiency, neurologic symptoms and rash may occur
Air Embolism

• Gas bubbles within the circulation can obstruct vascular flow

• Usually, an excess of 100cc is required to have a clinical effect

• A particular form of gas embolism called decompression sickness occurs when individuals are exposed to sudden changes in atmospheric pressure
Air Embolism

• Acutely, the formation of painful gas bubbles within the skeletal muscles and tissues in and around the joints is responsible for what is called the bends.

• In the lungs, edema, hemorrhages, and focal atelectasis or emphysema may appear leading to respiratory distress, the so-called chokes.
Air Embolism

• Caisson disease, is a chronic form of decompression sickness in which gas emboli persist in the skeletal system leading to multiple foci of ischemic necrosis

• Caisson disease usually effects the femur, tibia and humerus most commonly
Amniotic Fluid Embolism

• This form of embolism is a grave but uncommon complication of labor and the immediate postpartum period

• The underlying cause is the infusion of amniotic fluid into the maternal circulation via a tear in the placental membranes and rupture of uterine veins
Ischemia
Ischemia

• Occurs when the tissue has become deficient in blood from its local arterial supply or when the demand of the tissue for oxygenated blood exceeds the capacity of the vascular supply

• May lead to cell death or infarction (ischemic necrosis)
Ischemic Colitis

- Intact surface colonic mucosa is seen at the upper right.
- Laminar propria has a pink amorphous appearance representing necrosis with escape of red cells and fibrin into the interstitial tissue.
- The heavy neutrophile infiltrate involving both crpts and lamina propria is a response to tissue necrosis.
Infarction
Infarction

• An infarct is an area of ischemic necrosis within a tissue or organ, produced by the occlusion of either its arterial supply or venous drainage.

• The majority are associated with thromboembolism and involve arterial occlusions
Factors Which Influence the Development of an Infarct

1. Nature of the vascular supply; the availability of an alternative blood supply is the most important factor in determining whether an infarct will occur.

2. Rate of development of the occlusion; slowly developing occlusions are less likely to cause infarction especially if collateral circulation can be developed.
Factors Which Influence the Development of an Infarct

3. Vulnerability to hypoxia; neurons are irreversibly damaged in 3-4 minutes

4. Oxygen content of blood; partial flow obstruction of a small vessel in an anemic or cyanotic patient might lead to tissue infarction, whereas it would be without effect with normal oxygen tension
Infarction: Types of Infarcts

Red Infarcts occur:

• with venous occlusions (ovarian torsion)
• in loose tissues which allow blood to collect (lungs)
• in tissues with dual circulations (lung & intestines)
• in tissues that were previously congested
• when flow is reestablished
Infarction: Types of Infarcts

• White infarcts occur with arterial occlusions or in solid organs (heart, spleen, kidney) where the solidity of the tissue limits the amount of hemorrhage than can seep into the damaged area.
Myocardial infarctions
- Note the copious exudate of PMN's between the muscle fibers.
- Note the absence of nuclei in the myocardial fibers indicating necrosis, i.e., infarction.
- PMN's have a life span of 24 hours, and then undergo karyorrhexis, which is not seen here, suggesting that this lesion is less than 2 days old.
Shock
Shock

- Constitutes widespread hypoperfusion of tissues due to reduction in blood volume or cardiac output, or redistribution of blood, resulting in an inadequate effective circulating volume
Types and Causes of Shock

• Anaphylactic - type I hypersensitivity (allergy)
• Hypovolemic - loss of blood
• Cardiogenic - reduced cardiac output
• Septic - septicemia
• Neurogenic - traumatic injury (pain, crushing injury)
### Table 5-3: Three Major Types of Shock

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>Clinical Examples</th>
<th>Principal Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
<td>Myocardial infarction</td>
<td>Failure of myocardial pump owing to intrinsic myocardial damage.</td>
</tr>
<tr>
<td></td>
<td>Ventricular rupture</td>
<td>extrinsic pressure, or obstruction to outflow</td>
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<tr>
<td></td>
<td>Arrhythmia</td>
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<tr>
<td></td>
<td>Cardiac tamponade</td>
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<tr>
<td>Hypovolemic</td>
<td>Pulmonary embolism</td>
<td>Inadequate blood or plasma volume</td>
</tr>
<tr>
<td>Septic</td>
<td>Hemorrhage</td>
<td>Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; disseminated intravascular coagulation; activation of cytokine cascades</td>
</tr>
<tr>
<td></td>
<td>Fluid loss, e.g., vomiting, diarrhea, burns, or trauma</td>
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<tr>
<td></td>
<td>Overwhelming microbial infections</td>
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<td></td>
<td>Endotoxic shock</td>
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<tr>
<td></td>
<td>Gram-positive septicemia</td>
<td></td>
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<tr>
<td></td>
<td>Fungal sepsis</td>
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<tr>
<td></td>
<td>Superantigens</td>
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</tr>
</tbody>
</table>
Cardiogenic Shock

Clinical Examples:

• Myocardial infarction
• Ventricular rupture
• Arrhythmia
• Cardiac tamponade
• Pulmonary embolism

Principal Mechanisms:

• Failure of myocardial pump owing to intrinsic myocardial damage, extrinsic pressure, or obstruction of outflow
Hypovolemic Shock

Clinical Examples:

• Hemorrhage
• Fluid loss, e.g. vomiting, diarrhea, burns or trauma

Principal Mechanisms

• Inadequate blood or plasma volume
Septic Shock

Clinical Examples:

- Overwhelming microbial infections
- Endotoxic shock
- Gram-positive septicemia
- Fungal sepsis
- Superantigens

Principal Mechanisms:

- Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage; DIC, activation of cytokine cascades
Effects of lipopolysaccharide (LPS) and secondarily-induced effector molecules. LPS initiates the cytokine cascade described in Figure 5-20; in addition, LPS and the various factors can 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 is seen. DIC, disseminated intravascular coagulation; ARDS, adult respiratory distress syndrome. (Modified from Abbas AK, et al: Cellular and Molecular Immunology, 3rd ed. Philadelphia, WB Saunders, 1997.)
Shock: Clinical Features

- In hypovolemic and cardiogenic shock, the patient presents with hypotension, a weak, rapid pulse, tachypnea and cool, clammy, cyanotic skin.

- In septic shock, the skin may initially be warm and flushed because of peripheral vasodilation.
Shock: Clinical Features

- The original threat to life stems from the underlying catastrophe that precipitated the shock state
- Soon cardiac, cerebral and pulmonary changes secondary to the shock state worsen the problem
- Electrolyte disturbances and metabolic acidosis further exacerbate the situation
THANK YOU