Comenius University

Jessenius Faculty of Medicine

Pathophysiology for Surgery

Textbook for Medical Students

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Introduction

Many medical students in the 5th or 6th year have already partially forgotten the information learned in the 3rd year during the course of pathophysiology, because the main focus of the study has moved onto clinical subjects. However, during the preparation for the state exam from surgery as well as for other clinical exams the students often discover that they need the knowledge of pathophysiology in order to manage the content of the questions for the exams. This is especially true for the topics in general surgery.

The aim of our effort was to prepare a textbook in which the students will find the essential up-to-date pathomechanisms of surgical diseases. It is based on the requirements of surgical scientific-pedagogical faculty who are the members of the state exam committee. The textbook is focused not only on pathophysiological aspects of general surgery, but also includes a substantial part of the pathophysiology pertinent to special surgery.

The textbook is based on latest e-learning courses for theoretical training of surgeons. The text is original and is based on the principles of clinical pathophysiology, which are familiar to students that are well-oriented in the study of clinical subjects. The textbook is designed by utilizing an extensive experience gained from the active participation in conducting the state exams in surgery.

We believe that the textbook will help students of general medicine in an effective theoretical preparation for the state examination from surgery. In addition, this textbook also has an ambition to help the physicians in their specialized studies.

Authors

PHYSICAL NOXAS INJURIES

Mechanical injuries
- Crush syndrome
- Compartment syndrome

Pressure injuries
- Decompression sickness
- Dysbarism (barotrauma)
- Blast injuries

Electrical injuries

Burns
- Thermal
- Chemical
- Electrical

Cold injury

Mechanical Injuries

Crush Syndrome

The clinical crush syndrome occurs as a **consequence of traumatic events**, either accidental or disasters. As a result of muscular compression, myocytes are damaged, and this is followed by the release of intracellular constituents into the systemic circulation. This process is called **rhabdomyolysis**. One of the key compounds released is myoglobin, an oxygen carrier similar to haemoglobin. It contains only one haeme moiety. Myoglobin is filtered by the glomeruli and reaches the tubules, where it provokes obstruction and failure of renal function.

Other intracellular components such as protons, phosphate, potassium, and nucleotides (precursors of uric acid) are released from

the damaged muscles as well, and play an important role in crush-associated pathophysiology. Finally, **volume depletion** of the victim where they are activated and release free radicals and other injurious compounds. Process is further enhanced by the ample availability of oxygen.

Compartment phenomenon

Many striated muscles are contained within rigid compartments formed by fasciae, bones and other structures. If **muscle cell swell**, the intracompartmental pressure rises and this causes additional damage and necrosis. Compartment pressures above 30 mmHg produce significant muscular ischemia.

Pathophysiology of acute renal failure in rhabdomyolysis

The main pathophysiologic events are renal vasoconstriction, intraluminal cast formation, and direct haeme-protein-induced cytotoxicity. Myoglobin is easily filtered through the glomerular membrane. When water is reabsorbed from tubular fluid, the concentration of myoglobin rises until it precipitates, causing **obstructive cast formation**. This process is aggravated by **renal vasoconstriction** resulted from intravascular hypovolaemia caused by uptake of water by damaged muscles. In damaged limbs more than 10 litres of fluid can accumulate. Another factor in the precipitation of myoglobin and uric acid is a low pH in tubular fluid. The intratubular disintegration of the myoglobin leads to the **release of iron, which catalyses free radical production**. In addition, gastrointestinal ischaemia favours endotoxin absorption and release of cytokines, which further enhances the inflammatory reaction and haemodynamic instability.

Compartment Syndrome

Extremity

Compartment syndrome is a limb-threatening and life-threatening condition observed when **perfusion pressure falls below tissue pressure in a closed anatomic space**. Untreated compartment syndrome leads to

tissue necrosis, permanent functional impairment, and, if severe, renal failure and death. The original description of the consequences of unchecked intracompartmental pressures was documented as nerve injury and subsequent contracture following supracondylar fracture (Volkmann contracture). Although long bone fractures are a common cause of compartment syndrome, vascular and crush injuries are also common antecedents to compartment syndrome. Almost any injury can cause this syndrome, including injury resulting from vigorous exercise.

Compartment syndrome pathophysiology follows the path of **ischemic injury**. Intracompartmental structures cannot withstand infinite pressure. If fluid is introduced into a fixed volume, pressure rises. Various osseofascial compartments have a relatively fixed volume; introduction of excess fluid or extraneous constriction increases pressure and decreases tissue perfusion, until no oxygen is available for cellular metabolism.

As intracompartmental pressure rises, autoregulatory mechanisms are overwhelmed and a cascade of injury develops. As intracompartmental pressure rises, venous pressure rises. When venous pressure is higher than capillary perfusion pressure, capillaries collapse. At this point, blood flow through the capillaries stops. Hypoxic injury causes cells to release vasoactive substances (e.g., histamine, serotonin), which **increase endothelial permeability**. Capillaries allow continued fluid loss, which increases tissue pressure and advances injury. Nerve conduction slows, tissue pH falls due to anaerobic metabolism, surrounding tissue suffers further damage, and muscle tissue suffers necrosis, releasing myoglobin.

Abdominal

Normally, the abdominal pressure is about 5 mm Hg. The intraabdominal pressure may increase with acute and **substantial accumulation of fluid within the abdomen**. “Abdominal compartment syndrome” is defined as intraabdominal pressure of at least 20 mm Hg with dysfunction of at least one thoracoabdominal organ.

Primary abdominal compartment syndrome results from injury or disease in the abdominopelvic region. *Secondary abdominal compartment*

syndrome occurs from disease originating from outside the abdomen, such as from major burns or sepsis.

As intraabdominal pressure rises, progressive organ failure occurs. **The kidneys and lungs are the most affected**. With abdominal pressure of 15–20 mm Hg, the urinary output is reduced. When the pressure exceeds 30 mm Hg, anuria ensues. Renal failure is caused by external pressure on the renal vasculature and parenchyma. Ureteric obstruction is not thought to be a cause.

Mesenteric blood flow reduces to 70% of normal when intraabdominal pressure is about 20 mm Hg and falls to 30% of normal at 40 mm Hg. Intestinal oxygenation is impaired above a pressure of 15 mm Hg. **Bowel mucosal hypoxia** results in impaired gut–mucosal barrier function, allowing bacterial translocation and sepsis.

In abdominal compartment syndrome, the diaphragm becomes elevated with reduced excursion. The thoracic volume and compliance are reduced. The ensuing compressive atelectasis and **ventilatory perfusion mismatch** lead to hypercarbia and respiratory acidosis. Oxygen delivery decreases with increasing abdominal pressure. Hypoxia is found in patients when the pressure exceeds 35 mm Hg. Decompression usually results in prompt reversal of respiratory failure.

Pressure Injuries

Decompression Sickness

Although decompression sickness includes high-altitude–related and aerospace-related events, this article focuses on decompression as related to the **sudden decrease in pressures from ascending under water**. The increasing popularity of SCUBA (self-contained underwater breathing apparatus) diving and growth of commercial diving have increased the incidence of deep pressure injuries.

Effects of increasing pressure occur only on compressible substances in the body. The human body is made primarily of water, which is

noncompressible; however, the gases of hollow spaces and viscous organs and those dissolved in the blood are subject to pressure changes. Physical characteristics of gases are described by the following 3 gas laws, which quantify the physics and problems involved in descending under water.

Boyle law

$PV = K$

(P = pressure, V = volume, K = a constant)

Simply stated, this means that if the pressure is doubled, the volume is halved and vice versa. Going from 30 m to the surface without venting (exhaling) would cause the lungs, with minimal ability to expand further, to increase pressure to 3 times normal, with the greatest change occurring in the last 10 m, where it would double. This is the key law explaining the pressurization injuries.

Dalton law

$Pt = PO_2 + PN_2 + Px$

(Pt = total pressure, PO_2 = partial pressure of oxygen, PN_2 = partial pressure of nitrogen, Px = partial pressure of remaining gases)

Dalton's problem: As an individual descends, total pressure of breathing air increases; therefore, the partial pressures of the individual components of breathing air have to increase proportionally. As the individual descends deeper under water, an increasing amount of nitrogen dissolves in the blood. Nitrogen at higher partial pressures alters the electrical properties of cerebral cellular membranes, causing an anesthetic effect termed **nitrogen narcosis**. Every 15 m of depth is equivalent in its effects to one alcoholic drink. Thus, at 45 m divers may experience alterations in reasoning, memory, response time, and other problems such as idea fixation, overconfidence, and calculation errors.

Henry law

$\%X = (PX / Pt) \times 100$

(%X = amount of gas dissolved in a liquid, PX = pressure of gas X, Pt = total atmospheric pressure)

Henry's problem: With increasing depth, nitrogen in compressed air equilibrates through the alveoli into the blood. Over time, increasing amounts of nitrogen dissolve in the lipid component of tissues, where it accumulates. When a critical amount of nitrogen is dissolved in the tissues, ascending too quickly causes the **dissolved nitrogen to return to gas** form while still in the blood or tissues, causing bubbles to form. If the bubbles are still in the tissue, they can cause local problems; if they are in the blood, embolization may result.

Organ involvement associated with decompression sickness

Decompression sickness results from the effects of these bubbles on organ systems. The **bubbles may disrupt cells** and cause loss of function. They may act as **emboli** and block circulation, as well as cause **mechanical compression and stretching** of the blood vessels and nerves. The blood-bubble interface may act as a foreign surface, activating the early phases of blood coagulation and the release of vasoactive substances from the cells lining the blood vessels.

Type I decompression sickness is characterized by mild pains that begin to resolve within 10 minutes; pruritus or "skin bends" that cause itching or burning sensations; and/or skin rash.

Type II decompression sickness is characterized by pulmonary symptoms, hypovolemic shock, or nervous system involvement:

Nervous system

- Symptoms mimic spinal cord trauma. Low back pain may progress to paresis, paralysis, paresthesia, and loss of sphincter control.
- Other common symptoms include headaches or visual disturbances, dizziness, tunnel vision, and changes in mental status.
- Labyrinthine involvement causes a combination of nausea, vomiting, vertigo, and nystagmus.

Lungs

- Pulmonary dysfunction is characterized by burning substernal discomfort on inspiration, nonproductive coughing that can become paroxysmal, and severe respiratory distress.

Circulatory system

- Fluid shifts from the intravascular spaces to the extravascular ans it causes hypovolemic shock.
- Thrombi may form from activation of the early phases of blood coagulation.

Arterial gas embolization

Pulmonary overpressurization can cause large gas emboli when rupture into the pulmonary vein allows alveolar gas to enter systemic circulation. Gas emboli can lodge in coronary, cerebral, and other systemic arterioles. These gas bubbles continue to expand as ascending pressure decreases. Symptoms and signs depend on where the emboli travel.

Dysbarism (Barotrauma)

The effects of increasing pressure occur only on compressible substances in the body. The human body is made primarily of water, which is noncompressible. The gases of hollow spaces and viscous organs and those dissolved in the blood, however, are at the mercy of pressure changes. The physical characteristics of gases are described by the 3 gas laws (decompression sickness). It is these laws that quantify the physics and problems involved in descending under water.

Organ involvement

The areas affected by the Boyle law can be divided into compressible and noncompressible spaces. Compressible spaces include the lungs, the hollow visci of the gastrointestinal system, and the space behind the facemask. Examples of noncompressible spaces include the sinuses, air spaces in tooth fillings, middle ear canals, and occluded external ear canals.

Pulmonary

- As an individual descends, the lungs decrease in size according to the Boyle law. This is true only if the diver is holding his or her breath. Since a SCUBA diver breathes from a compressed air source, the loss of volume from depth is negated. Normally, divers are taught to ascend no faster than a rate of 30 cm per second or slower. They also are instructed to breathe normally during ascent. This slow rate of ascent allows for a gradual offloading of nitrogen and emptying of air-filled spaces (e.g., the lungs).
- A too-rapid ascent, especially if emptying of the lungs is incomplete, causes the **lung volume to expand rapidly**. The musculoskeletal cage limits expansion, which then causes overpressurization of the lung. Resulting injuries include pneumothorax, pneumomediastinum, subcutaneous emphysema, and rupture into the pulmonary vein causing a large air embolism.

Ear squeeze

- Dysbarism most commonly affects the ears. The Eustachian tube functions to equalize middle ear and ambient environment pressures. Rapid descent increases **external pressure on the tympanic membrane** and requires the diver to add air pressure in the pharynx to equalize. Large pressure differences can stretch the tympanic membrane excessively and cause hemorrhage or rupture.
- If the round window membrane is ruptured, the leading symptom is the sudden loss of hearing.
- Vertigo can result for several reasons. On descent, an obstruction of one ear canal (e.g., by cerumen or a tight-fitting hood) can allow cold water to enter unilaterally, causing caloric stimulation.

Headache

- In a larger context, many causes of headache can be associated with scuba diving. Ear, sinus, and tooth squeeze are potential etiologies of headache. Inadequate ventilation can cause retention of carbon dioxide. Contamination of the pressurized air from

exhaust fumes can produce carbon monoxide toxicity. Pressure on the face from the mask can irritate the facial or scalp nerves. Prolonged extension at the neck can cause impingement on the occipital nerve.

Tooth squeeze

- Barodontalgia is caused by air trapped under a filling. Barodontalgia is more likely to occur in older or temporary fillings.

Gastrointestinal problems

- Diving does not usually pose a major problem in the GI tract because gas present at the surface will be compressed and then reexpanded to the same volume as before the dive. Small amounts of air may be swallowed during a dive due to the unnatural breathing from a regulator and ear and sinus pressure-equalization techniques.
- Bowel gas volume changes usually only cause discomfort. Excessive amounts of gastric air or intestinal air trapped by constipated stool or external issues, such as adhesions, can yield rupture and occurrence of pneumoperitoneum.

Blast Injuries

In general, most blast tends to be accidental, including firework mishaps, unintended occupational or industrial fuel eruptions.

Blast injuries traditionally are divided into 4 categories: primary, secondary, tertiary, and miscellaneous injuries.

- A primary blast injury is caused solely by the direct effect of blast overpressure on tissue. Air is easily compressible, unlike water. As a result, a primary blast injury almost always affects air-filled structures such as the lung, ear, and gastrointestinal tract.
- A secondary blast injury is caused by flying objects that strike people.

- A tertiary blast injury is a feature of high-energy explosions. This type of injury occurs when people fly through the air and strike other objects.
- Miscellaneous blast-related injuries encompass all other injuries caused by explosions. For example, the resulting fire and building collapse.

Electrical Injuries

To fully understand such injuries, understanding certain basic electrical principles is necessary. Direct current (DC) flows in a constant direction. Batteries, for example, deliver DC. Alternating current (AC) changes direction. A **volt** is a unit of electromotive force or pressure that causes current to flow. Most electrical shocks come from constant voltage sources. Electric voltage of 380 volts or less is considered low voltage and above 380 volts, high voltage. An **ampere** is a unit of electrical current. More precisely, it is the flow of a certain number of electrons per second. An **ohm** is a unit of electrical resistance. The resistance of a material to current flow depends on the physical and chemical properties of the material. The amount of current flow often determines the magnitude of injury. Heat generated in a material due to current flow is an indication of power. The heat produced is proportional to the resistance and the square of the current. A **watt** is the unit of electrical power that is delivered when 1 ampere flows through 1 ohm for 1 second. Power is equal to voltage multiplied by current (P=VxI). Energy is defined in terms of a watt-second. One watt-second is equal to 1 joule. One watt of power delivered for 1 second produces 0.24 calories of heat.

The 3 major **mechanisms of electricity-induced injury** are

1. electrical energy causing direct tissue damage, altering cell membrane rest potential, and eliciting muscle tetany;
2. the conversion of electrical energy into thermal energy, causing massive tissue destruction and coagulative necrosis; and

3. mechanical injury with direct trauma resulting from falls or violent muscle contraction.

Systemic effects and tissue damage are directly proportional to the magnitude of current delivered to the victim. As a general rule, **high voltage is associated with greater morbidity and mortality**, although fatal injury can occur at household current (230 volts).

Body tissues differ in their resistance. In general, **tissues with high fluid and electrolyte content conduct electricity better**. Bone is the tissue most resistant to the flow of electricity. Nerve tissue is the least resistant. Skin resistance is the most important factor impeding current flow. The **resistance of skin depends on its thickness**. It varies from 1000 ohms for humid thin skin to several thousand ohms for dry calloused skin. Skin resistance can be reduced substantially by moisture, sweat, or contamination, converting an ordinarily low-voltage injury into a life-threatening one.

AC is substantially more dangerous than DC. Contact with AC may cause **tetanic muscle contraction**. Thoracic muscle tetany involving the diaphragm and intercostal muscles can result in **respiratory arrest**. The repetitive nature of AC increases the likelihood of current delivery to the myocardium during the vulnerable recovery period of the cardiac cycle, which can precipitate **ventricular fibrillation**. In contrast, DC usually causes a **single violent muscle contraction**, often thrusting the victim away from the source.

The current pathway determines which tissues are at risk and what type of injury is observed. **Electrical current that passes through the head or thorax is more likely to produce fatal injury**. Transthoracic currents can cause fatal arrhythmia, direct cardiac damage, or respiratory arrest. Transcranial currents can cause direct brain injury, seizure, respiratory arrest, and paralysis.

Current travels down the path of least resistance. **Nerve and muscle tissues have lower resistance than skin tissue**. Understanding that an injured extremity may not show external signs of injury is important.

Moreover, **injury to deeper tissues may lead to edema and increased intracompartmental pressure**.

Burns

Burns Thermal

Burn wounds can be classified into **6 separate groups** based on the mechanism of injury: scalds, contact burns, fire, chemical, electrical, and radiation. Scald burn injuries can be caused by liquids, grease, or steam. Liquid scalds can be further divided into spill and immersion scalds. Fire burn injuries can be divided into flash and flame burns.

Severity of burn injury is related to the rate at which heat is transferred from the heating agent to the skin. The skin is the largest organ of the body. While not very active metabolically, the **skin serves multiple functions essential to the survival of the organism**, including the following:

- Thermal regulation and prevention of fluid loss by evaporation
- Hermetic barrier against infection
- Contains sensory receptors that provide information about environment

Temperature

Initial temperature of a material at the instant of contact is an important determinant of burn severity. Many materials (e.g., water) cannot be heated beyond a certain temperature without changing state. Water can only be heated to 100°C at atmospheric pressure before it ceases to be a liquid and vaporizes. Because more joules are required to produce steam, this additional heat transfer accounts for the severe burns caused by steam injury.

A flammable liquid is defined as any liquid having a flash point less than 37.8°C. Liquids with a flash point above this temperature are considered combustible. In addition to their high temperatures, burning

liquids also may **ignite the victim's clothing**, thereby further exacerbating severity of the injury.

Duration of contact

Human skin can tolerate temperatures as high as 44°C (111°F) for a relatively long time (6 hours) before irreversible injury occurs. Temperatures greater than this level cause an almost logarithmic increase in tissue destruction. Viscous oils and greases usually cling to a victim's skin, prolonging duration of exposure and extent of injury. In immersion scalds, duration of contact between the hot liquid and the skin is considerably longer than that with spill scalds, thereby increasing the severity of injury.

Tissue conductivity

Water content, natural oils or secretions of the skin, and the presence of insulating material (e.g., cornified keratin layer of skin) influence tissue conductivity. In addition, alterations in local tissue blood flow produce a profound effect on heat transfer and distribution.

Burn wound injury

During the first day after burn injury, **3 concentric zones** of tissue injury characterize a full-thickness burn: zones of coagulation, stasis, and hyperemia. The central zone consists of dead or dying cells as a result of coagulation necrosis and absent blood flow. It usually appears white or charred. The intermediate zone of stasis usually is red and may blanch on pressure, appearing to have an intact circulation; however, after 24 hours, circulation through its superficial vessels often has ceased. Petechial hemorrhages may be present. By the third day, the intermediate zone of stasis becomes white because its superficial dermis is avascular and necrotic. The outer zone of hyperemia is a red zone that blanches on pressure, indicating that it has intact circulation. By the fourth day, this zone has a deeper red color. Healing is present by the seventh day.

Transformation of the zone of stasis to coagulation occurs and has been related to many factors, including progressive dermal ischemia.

Prostaglandins, histamine, and bradykinin as the chemical mediators of this progressive vascular occlusion have been implicated. They can produce edema by altering endothelial cell and basement membrane function to enhance permeability. When this ischemia persists, the zone of stasis eventually becomes a full-thickness burn injury. It is suggested that an imbalance in the vasoconstrictive and vasodilatory prostanoids produces a progressive tissue loss in the zone of stasis.

Systemic inflammatory response

Cytokines and other mediators are released into the systemic circulation, causing a systemic inflammatory response. Because vessels in burned tissue exhibit increased vascular permeability, **an extravasation of fluids into the burned tissues** occurs. Hypovolemia is the immediate consequence of this fluid loss, which accounts for decreased perfusion and oxygen delivery. In patients with serious burns, release of catecholamines, vasopressin, and angiotensin causes **peripheral and splanchnic bed vasoconstriction** that can compromise in-organ perfusion. Myocardial contractility also may be reduced by the release of inflammatory cytokine tumor necrosis factor-alpha.

A **decrease in pulmonary function** can occur in severely burned patients without evidence of inhalation injury from the **bronchoconstriction caused by humoral actors**, such as histamine, serotonin, and thromboxane A_2. A decrease in lung and tissue compliance is a manifestation of this reduction in pulmonary function. Burned skin exhibits an increased **evaporative water loss** associated with an obligatory concurrent heat loss, which can cause hypothermia.

A significant proportion of the morbidity and mortality of severe burns is attributable to the ensuing **hypermetabolic response**. This response can last as long as a year after injury and is associated with impaired wound healing, increased infection risk, and erosion of lean body mass.

Nutritional support

Because burn injury causes a hypermetabolic state that is characterized by a dramatic **increase in resting energy expenditure**,

nutritional support is essential, especially via the enteral route, to reduce intestinal villous atrophy. A syndrome of decreased bowel mucosal integrity, capillary leak, and decreased mesenteric blood flow, which allowed **bacterial translocation into the portal circulation** could occur. These translocated bacteria significantly alter hepatocyte function and spread systemically to cause systemic **sepsis**. Adequate resuscitation that ensures mesenteric blood flow can prevent potential development of multisystem organ failure.

Infection

In patients with major burn injuries, infection remains the major cause of death. Immune consequences of this injury have been identified and are **specific deficits in neutrophil chemotaxis, phagocytosis, and intracellular bacterial killing**. Cell-mediated immunity also is compromised and has been related to both decreased lymphocyte activation and suppressive mediators present in the serum of burn patients. A reduction in immunoglobulin synthesis also has been encountered in these seriously ill patients.

Burn shock

Severe burn injury causes a coagulation necrosis of tissue that initiates a physiologic response in every organ system that is directly proportional to the size of the burn. Tissue destruction results in **increased capillary permeability** with profound egress of fluid from the intravascular space to the tissues adjacent to the burn wound. Inordinate amounts of **fluid are lost by evaporation** from the damaged surface that is no longer able to retain water. This increase in capillary permeability, coupled with evaporative water loss, causes **hypovolemic shock**.

Other physiologic changes

Immediate cardiovascular response to thermal injury is a **reduction in cardiac output** accompanied by an elevation in peripheral vascular resistance. In the absence of heart disease, ventricular ejection fraction and velocity of myocardial fiber shortening are actually increased during thermal injury. With replacement of plasma volume, cardiac output

increases to levels that are above normal. This **hyperdynamic state** is a reflection of the hypermetabolic flow phase of thermal injury.

In the immediate postburn period, **glomerular filtration rate and renal blood flow are reduced** in proportion to the reduction in intravascular volume.

Burn shock may be complicated by an acute erythrocyte **hemolysis** caused by both direct heat damage and by a decreased half-life of damaged red blood cells.

Burns Chemical

Most acids produce a **coagulation necrosis** by denaturing proteins, forming a coagulum that limits the penetration of the acid. Bases typically produce a more severe injury known as **liquefaction necrosis**. This involves denaturing of proteins as well as saponification of fats, which does not limit tissue penetration.

The severity of the burn is related to a number of factors, including the pH of the agent, the concentration of the agent, the length of the contact time, the volume of the offending agent, and the physical form of the agent. The ingestion of solid pellets of alkaline substances results in prolonged contact time in the stomach, thus, more severe burns. In addition, concentrated forms of some acids and bases generate significant heat when diluted, resulting in **thermal and caustic injury**.

The long-term effect of caustic burns is scarring and, depending on the site of the burn, can be significant. Esophageal and gastric burns can result in significant **stricture formation**.

Burns Electrical

Recently, **electroporation** of skeletal muscle and nerve cells was suggested as an additional mechanism of injury in electrical burns. This mechanism is different from Joule heating, even though it is influenced by temperature. It is the enlargement of cellular-membrane molecular-scale defects that results when electrical forces drive polar water

molecules into such defects. Electroporation effects can mediate significant skeletal muscle necrosis without visible thermal changes.

These life-threatening consequences of low-voltage electric burns usually occur without any lesions of the skin at entrance and exit points of the current. An absence of local lesions indicates that the surface area of contact (current density) is large and that there is insufficient heat to produce a thermal injury; however, the smaller the surface area of the contact, the greater the density of the current and the more energy is transformed into heat that can cause local burn injury.

Cold Injury

Exposure to cold can produce various injuries that occur as a result of the **human inability to adapt to cold**. These injuries can be divided into localized injury to a body part or parts (peripheral cold injuries), generalized cooling of the entire body (systemic hypothermia), or a combination of both.

Systemic Hypothermia

Body temperature may fall as a result of heat loss by radiation, evaporation, conduction, and convection. **Radiation causes 55-65% of the body's heat loss**. Evaporation occurs via the skin and airway and accounts for 30% of the heat loss. Normally, in a dry environment, only 15% of the body's heat loss results from conduction. However, the thermal conductivity of water is approximately 30 times that of air, so the **body loses heat rapidly when immersed in water or covered in wet clothing**, leading to a rapid decline in body temperature. Convection accounts for a minor amount of heat loss, but it becomes more significant in a **windy environment**. The amount of heat dissipated by any of these mechanisms is proportional to the temperature difference between the body and environment.

Opposing the loss of body heat are the mechanisms of heat conservation and gain. In general, a thermostat in the preoptic region of

the hypothalamus controls these mechanisms. It responds to thermoregulatory mechanisms, the temperature of blood, and temperature receptors deep within the body and in the skin. When the sympathetic nerves are excited, they cause the blood vessels in the skin to markedly constrict. The flow of warm blood from the core of the skin is depressed, thereby reducing the transfer of heat to the body surface. This **reduction of blood flow in the skin is the prime physiologic regulator of heat loss from the body**. The temperature of the skin decreases to approach the temperature of surrounding air, which lowers the temperature gradient and further decreases heat loss.

Stimulation of the sympathetic nerves also causes secretion of epinephrine and norepinephrine by the adrenal medullae. These **hormones increase the metabolic rate of all cells**, thereby enhancing heat production. Impulses from the preoptic hypothalamus also activate the primary motor center for shivering, which, in turn, increases the tone of muscles. The resulting enhancement of muscle metabolism can increase heat production by as much as 500%.

DISTURBANCES OF HOMEOSTASIS

Dehydration, hypovolemia

Hypernatremia

Hyponatremia

Hyperkalemia

Hypokalemia

Hypercalcemia

Hypocalcemia

Acid-base dysbalances

- Metabolic acidosis
- Metabolic alcalosis
- Respiratory acidosis
- Respiratory alcalosis

Hypoglycemia

Dehydration, Hypovolemia

The negative fluid balance that causes dehydration results from decreased intake, increased output (renal, gastrointestinal, or insensible losses), or fluid shift (ascites, effusions, and capillary leak states such as burns and sepsis). The **decrease in total body water** causes reductions in both the intracellular and extracellular fluid volumes. Clinical manifestations of dehydration are most closely related to intravascular volume depletion. As dehydration progresses, hypovolemic shock ultimately ensues, resulting in end organ failure and death.

The terms dehydration and volume depletion are commonly used interchangeably to denote intravascular fluid depletion. However, it is useful for clinicians to understand that **volume depletion is distinct from dehydration**. Volume depletion denotes contraction of the total

intravascular plasma pool, whereas dehydration denotes loss of plasma free water disproportionate to loss of sodium, the main intravascular solute. The distinction is important because volume depletion can exist with or without dehydration, and dehydration can exist with or without volume depletion.

In volume depletion the entire plasma pool is contracted with solutes (mostly sodium) and solvents (mostly water) lost in proportionate quantities. Intravascular sodium levels are within the reference range. This is **volume depletion without dehydration**. The most common cause is excessive extrinsic loss of fluids in conditions such as vomiting and diarrhea.

Sodium considerations

Volume depletion can be concurrent with **hyponatremia**. This is characterized by plasma volume contraction with free water excess. An example is a child with diarrhea who has been given tap water to replete diarrheal losses. Free water is replenished, but sodium and other solutes are not. In hyponatremic volume depletion, the patient may appear more ill clinically than fluid losses indicate. Serum sodium levels less than **120 mmol/l may result in seizures**. If intravascular free water excess is not corrected during volume replenishment, the shift of free water to the intracellular fluid compartment may cause cerebral edema.

With **true dehydration**, plasma volume contracts with a disproportionately larger loss of free water. In hypernatremic volume depletion, the patient may appear less ill clinically than fluid losses indicate. As in hyponatremia**, hypernatremic volume depletion may result in serious central nervous system effects** as a result of structural changes in central neurons. However, cerebral shrinkage occurs instead of cerebral edema. This may result in intracerebral hemorrhage, seizures, coma, and death. Overly rapid correction of hypernatremia, however, may result in cerebral edema. For this reason, volume restoration must be performed gradually over 24 hours or more. Gradual restoration

prevents a rapid shift of fluid across the blood-brain barrier and into the intracellular fluid compartment.

Acid and base problems

Derangements of acid-base balance may occur with volume depletion. Some degree of **metabolic acidosis** is common, especially in infants. Mechanisms include **bicarbonate loss** in stool and **ketone production**. Hypovolemia causes decreased tissue perfusion and increased **lactic acid production**. Decreased renal perfusion causes decreased glomerular filtration rate, which, in turn, leads to **decreased hydrogen (H^+) ion excretion**. These factors combine to produce a metabolic acidosis. In most patients, acidosis is mild and easily corrected with volume restoration; increased renal perfusion permits excretion of excess H^+ ions in the urine. Administration of glucose-containing fluids further decreases ketone production.

Hypernatremia

Hypernatremia is caused by serum sodium concentration of **more than 150 mmol/l**. Usually, it reflects an underlying defect in water metabolism. Hyperosmolality stimulates **thirst**, which usually prevents the development of hypernatremia.

Hypernatremia occurs in the following 3 ways:

1. Pure water depletion (e.g. diabetes insipidus)
2. Sodium excess (e.g. salt poisoning)
3. Water depletion exceeding sodium depletion (e.g. diarrhea)

These mechanisms cause hypernatremia either alone or in concert. Search for any cause of extrarenal fluid losses (eg, burns, vomiting, diarrhea, fevers). The patient can complain of polyuria or polydipsia (ie, signs of diabetes insipidus or osmotic diuresis). Search for the patient intact thirst response is important, this often is impaired in elderly persons.

Diabetes insipidus can be due to a lack of a central stimulus to concentrate the urine (ie, lack of antidiuretic hormone production [central type]) or to a lack of renal response to such stimulus (ie, nephrogenic type).

As a result of increased extracellular sodium, **plasma tonicity** increases. This increase in tonicity results in removal of fluid from within the cells. Extracellular volume remains normal at the expense of intracellular dehydration, which is responsible for the clinical manifestations of hypernatremia.

Hypernatremia causes **decreased cellular volume** as a result of water efflux from the cells in order to maintain equal osmolality inside and outside the cell. **The effects of cellular dehydration are seen principally in the CNS**, where stretching of shrunken neurons and alteration of membrane potentials from electrolyte flux lead to ineffective functioning. If shrinkage is severe enough, stretching and rupture of bridging veins may cause intracranial hemorrhage.

Cells immediately respond to combat this shrinkage and osmotic force by transporting electrolytes across the cell membrane, thus altering rest potentials of electrically active membranes. After an hour of hypernatremia, **intracellular organic solutes are generated** in an effort to restore cell volume and to avoid structural damage. This protective mechanism is important to remember when treating a patient with hypernatremia. Cerebral edema ensues if water replacement proceeds at a rate that does not allow for excretion or metabolism of accumulated solutes.

Hyponatremia

Hyponatremia is defined as a serum sodium concentration of **less than 130 mmol/l**. This is the most common electrolyte abnormality encountered in clinical practice. Symptoms and signs of hyponatremia are related to the absolute level and rate of fall of serum sodium from

baseline. Symptoms do not correlate with specific sodium levels. However, symptoms may appear when the serum sodium concentration is less than 125 mmol/l.

Causes

Three general mechanisms are as follows:

1. Deficiency in sodium intake
2. Excessive loss of sodium (renal or extrarenal)
3. Excessive water retention

Risk factors

Because the human body protects itself from hyponatremia through an intact thirst mechanism, conditions associated with **alteration in thirst mechanism** are more prone to induce hyponatremia.

Hyponatremia rarely is caused by a deficient intake, except in infants fed with hypotonic fluids. The most common cause of hyponatremia in children is **loss of sodium from the gastrointestinal tract**. **Diarrhea** is responsible for most incidents of hyponatremia in children. Sodium loss also occurs via the kidneys. **Diuretics** are the most common culprit, followed by less common causes (e.g. salt-losing nephritis, mineralocorticoid deficiency).

Excessive antidiuretic hormone (ADH) secretion causes water retention and subsequent **dilutional hyponatremia**. Excessive secretion of ADH occurs in response to pain, nausea, vomiting, and morphine intake in postoperative patients. Excessive secretion of ADH can occur without physiologic stimuli (e.g. increased serum osmolality, decreased intravascular volume); hence, the condition is named syndrome of inappropriate secretion of ADH (SIADH). In patients with cirrhosis, cardiac failure, or renal failure, hyponatremia may be caused by one of many mechanisms.

Hyponatremia is physiologically significant when it indicates a state of **extracellular hyposmolarity** and a tendency for free water to shift from the vascular space to the intracellular space. Although cellular edema is well tolerated by most tissues, it is not well tolerated within the rigid

confines of the bony calvarium. Therefore, clinical manifestations of hyponatremia are related primarily to **cerebral edema**. The rate of development of hyponatremia plays a critical role in its pathophysiology and subsequent treatment. When serum sodium concentration falls slowly, over a period of several days or weeks, the brain is capable of compensating by extrusion of solutes and fluid to the extracellular space. Compensatory extrusion of solutes reduces the flow of free water into the intracellular space, and symptoms are much milder for a given degree of hyponatremia. Chronic hyponatremia may not result in neurologic dysfunction even at serum sodium levels less than 100 mmol/l. When serum sodium concentration falls rapidly, over a period of 24-48 hours, this compensatory mechanism is overwhelmed and severe cerebral edema may ensue, resulting in **brainstem herniation and death**. Symptoms range from mild anorexia, headache, and muscle cramps, to significant alteration in mental status including confusion, obtundation, coma, or status epilepticus.

Hyperkalemia

Potassium is the primary intracellular cation and plays a key role in **intracellular volume regulation**. Almost 100% of body potassium is contained in the intracellular fluid space, most in skeletal muscles. Both animal and vegetable food sources contain significant amounts of potassium. However, despite the level of consumption, a balance between intake and excretion maintains plasma potassium levels within a narrow range (3.5-4.5 mmol/l). Less than 10% of potassium is excreted through sweat and stools, while more than 90% is excreted by the kidneys.

Within the kidneys, a large amount of filtered potassium is reabsorbed (along with sodium) at the proximal convoluted tubule, thus regulating potassium excretion. Normally, considerable amounts of potassium are

secreted into the distal tubules and some into the collecting tubules and ducts. Significant reabsorption occurs in the descending loop of Henle.

Aldosterone affects potassium secretion in the distal nephron by its action on the Na^+/K^+-ATPase. Elevated levels of aldosterone stimulate potassium secretion, while low levels inhibit potassium secretion by the cortical collecting duct. Increased sodium reabsorption and potassium secretion is due to its effects on the transport system. In addition, potassium levels are partly responsible for a negative feedback to the adrenal cortex such that high levels of potassium decrease aldosterone production, while low levels depress the secretion of aldosterone.

Factors Affecting Plasma Potassium

Factor	**Effect on Plasma K^+**	**Mechanism**
Mineralocorticoids	Increase	Activation of Na^+/K^+-ATPase pump
Filtrate flow rate	Decrease	Increased flow rate leads to increased filtrate load in kidneys with increased K^+ reabsorption
Aldosterone	Decrease	Increases sodium reabsorption, which increases filtrate load to kidneys, leading to increased K^+ reabsorption
Insulin	Decrease	Stimulates K^+ entry into cells by increasing sodium efflux (energy-dependent process)
Beta-adrenergic agents	Decrease	Increase skeletal muscle uptake of K^+
Alpha-adrenergic agents	Increase	Increase K^+ release from the liver

Increased pH	Increase	Favors K^+ entry into cells

Hyperkalemia results from the following:

- Decreased or impaired potassium excretion - acute or chronic renal failure, especially in patients who are on dialysis
- Additions of potassium into extracellular space - trauma, including crush injuries (rhabdomyolysis), hemolysis (eg, blood transfusions, burns, tumor lysis)
- Transmembrane shifts (ie, shifting potassium from the intracellular to extracellular space) - as observed with acidosis, medication effects (eg, acute digitalis toxicity) and catabolic states

Levels of 7 mmol/l can lead to significant **hemodynamic and neurologic consequences**. Levels exceeding 8.5 mmol/l cause **respiratory paralysis and cardiac arrest** and can quickly be fatal. High levels of potassium cause abnormal heart and skeletal muscle function by lowering resting action potential and by preventing repolarization and muscle paralysis. ECG findings are classic and begin with tenting of the T wave, followed by lengthening and eventual disappearance of the P wave and widening of the QRS complex. Just before the heart stops, the QRS and T wave merge.

Hypokalemia

Hypokalemia is defined as a plasma potassium level of less than 3.5 mmol/l. The ratio of intracellular to extracellular potassium is important in determining the cellular membrane potential. Potassium homeostasis is integral to normal cellular function and tightly regulated by sodium-potassium adenosine triphosphatase (ATPase) pumps.

Hypokalemia may be due to a total body deficit of potassium, which may result from long-term inadequate intake, long-term diuretic or laxative use, and chronic diarrhea, or hyperhidrosis. Acute causes of

potassium depletion include **alkalosis** (movement of potassium from serum into cells), severe gastrointestinal losses from vomiting and diarrhea, or dialysis. Other recognizable causes include renal tubular disorders, such as **distal renal tubular acidosis and hyperaldosteronism**. Other mineralocorticoid excess states that may cause hypokalemia include Cushing syndrome, and exogenous steroid administration.

Hypokalemia should be suggested by a constellation of symptoms that involve the GI, renal, musculoskeletal, cardiac, and nervous systems. Findings that are consistent with severe hypokalemia may include the following:

- Signs of ileus
- Hypotension
- Ventricular arrhythmias
- Cardiac arrest
- Hypoventilation, respiratory distress
- Lethargy or other mental status changes
- Decreased muscle strength
- Decreased tendon reflexes
- Polyuria, nocturia

Hypercalcemia

Hypercalcemia is a disorder that most commonly results from malignancy or primary **hyperparathyroidism**. Hypercalcemic crisis does not have an exact definition, although marked elevation of serum calcium is associated with acute signs and symptoms of hypercalcemia.

Calcium enters the body through the small intestine and eventually is excreted via the kidney. Bone can act as a storage depot. This entire system is controlled through a feedback loop. For hypercalcemia to develop, the normal calcium regulation system must be overwhelmed by an excess of PTH, calcitriol, some other serum factor that can mimic these hormones.

PTH-mediated hypercalcemia

Primary hyperparathyroidism originally was the disease of "stones, bones, and abdominal groans." In most primary hyperparathyroidism cases, the calcium elevation is caused by **increased intestinal calcium absorption**. This is mediated by the PTH-induced calcitriol synthesis. The increase in serum calcium results in an increase in calcium filtration at the kidney. Because of PTH-mediated absorption of calcium at the distal tubule, less calcium is excreted than might be expected. In PTH-mediated hypercalcemia, bones do not play an active role because most of the PTH-mediated osteoclast activity that breaks down bone is ofset by hypercalcemic-induced bone deposition.

Non–PTH-mediated hypercalcemia

Hypercalcemia associated with **malignancy** commonly is the result of multiple myeloma, breast cancer, or lung cancer and is caused by **increased osteoclastic activity** within the bone. Granulomatous disorders with high levels of calcitriol may be found in patients with sarcoidosis, tuberculosis, and histoplasmosis.

Increased calcium levels may cause the following:

- Nausea
- Vomiting
- Alterations of mental status
- Abdominal pain
- Constipation
- Lethargy
- Polyuria, polydipsia, nocturia

Severe elevations in calcium levels may cause **coma**.

Hypocalcemia

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling.

PTH directly targets the bone and the kidneys to increase serum calcium levels. Indirectly, through vitamin D, it causes intestinal calcium absorption. **Vitamin D** directly targets GI absorption of calcium to increase calcium levels. **Calcitonin** lowers calcium by targeting bone, renal, and GI losses. Calcium also is affected by **magnesium and phosphorus.**

Distribution

Approximately 99% of calcium is found in bone, and 1% is found in extracellular fluid. Of this 1%, 50% is in the free (active) ionized form, 40% is bound to protein (predominantly albumin), and 10% is complexed with anions (eg, citrate).

Homeostasis is maintained by an extracellular to intracellular gradient, which is largely due to abundant high-energy phosphates intracellularly. Intracellular calcium regulates cAMP-mediated messenger systems and most cell organelle functions. Variations of **extracellular calcium level depend upon serum pH, protein and anion levels, and calcium-regulating hormone** function.

Effects

- The patient may complain of muscle cramping, shortness of breath secondary to bronchospasm, tetanic contractions.
- Chronic manifestations include cataracts, dry skin, brittle nails, and poor dentition.
- Acute hypocalcemia may lead to syncope, congestive heart failure, and angina due to the multiple cardiovascular effects.

Neuromuscular and cardiovascular findings predominate. Neural hyperexcitability due to acute hypocalcemia causes smooth and skeletal muscle contractions.

The causes of hypocalcemia include hypoalbuminemia, hypomagnesemia, hyperphosphatemia, multifactorial enhanced protein binding and anion chelation, PTH deficiency or resistance, and vitamin D deficiency or resistance.

- **Hypoalbuminemia** is the most common cause of hypocalcemia and is due to cirrhosis, nephrosis, malnutrition, burns, chronic illness, and sepsis.
- **Hypomagnesemia** causes end-organ resistance to PTH and inhibits the hypocalcemic feedback loop through uncertain mechanisms.
- **Hyperphosphatemia** may be seen in critical illness. Phosphate binds calcium avidly, causing acute hypocalcemia.
- **Vitamin D deficiency/resistance**; hepatorenal disease: the liver and the kidney provide intermediary enzymes to form active $1,25(OH)_2$ D.

Acid-base Dysbalances

Basic definitions

An acid is a substance that can donate hydrogen ions (H^+), and a base is a substance that can accept H^+ ions, regardless of the substance's charge. H_2CO_3 is a weak acid because it is ionized incompletely, and, at equilibrium, all 3 reactants are present in body fluids.

H_2CO_3 (acid) $\Leftrightarrow$ $H^+ + HCO_3^-$ (base)

The addition of H^+ or bicarbonate (HCO_3^-) drives this reaction to the left.

In body fluids, the concentration of hydrogen ions [H^+] is maintained within very narrow limits, with the normal physiologic concentration being **40 nmol/l**. The concentration of HCO_3^- (**24 mmol/l**) is 600,000 times that of [H^+]. The tight regulation of [H^+] at this low concentration is crucial for normal cellular activities because **H^+ at higher concentrations can bind strongly to negatively charged proteins, including enzymes, and impair their function**. Under normal conditions, acids and, to a lesser extent, bases are being added constantly to the extracellular fluid

compartment, and for the body to maintain a physiologic [H^+] of 40 nmol/l, the following 3 processes must take place:

- Buffering by extracellular and intracellular buffers
- Alveolar ventilation, which controls $PaCO_2$
- Renal H^+ excretion, which controls plasma [HCO_3^-]

Buffers

Buffers are weak acids or bases that are able to minimize changes in pH by taking up or releasing H^+. Buffers work as a first-line of defense to blunt the changes in pH that would otherwise result from the constant daily addition of acids and bases to body fluids.

HCO_3^-/H_2CO_3 buffering system

The major extracellular buffering system is HCO_3^-/H_2CO_3; its function is illustrated by the following reactions:

$$H_2O + CO_2 \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + HCO_3^-$$

One of the major factors that makes this system very effective is the ability to control $PaCO_2$ by **changes in ventilation**. As can be noted from this reaction, increased carbon dioxide concentration drives the reaction to the right, whereas a decrease in CO_2 concentration drives it to the left. Put simply, **adding an acid load to the body fluids results in consumption of HCO_3^-** by the added H^+, and the formation of carbonic acid; the carbonic acid, in turn, forms water and CO_2. CO_2 concentration is maintained within a narrow range via the respiratory drive, which eliminates accumulating CO_2. The kidneys regenerate the HCO_3^- consumed during this reaction. That **HCO_3^- and $PaCO_2$ can be managed independently** (kidneys and lungs, respectively) makes this a very effective buffering system. At equilibrium, the relationship between the 3 reactants in the reaction is expressed by the **Henderson-Hasselbalch equation**, which relates the concentration of dissolved CO_2 (ie, H_2CO_3) to the partial pressure of CO_2 (0.03 x $PaCO_2$) in the following way:

$pH = 6.10 + \log ([HCO_3^-]/0.03 \times PaCO_2)$

Changes in pH or $[H^+]$ are a result of relative changes in the ratio of $PaCO_2$ to $[HCO_3^-]$ rather than to absolute change in either one. In other words, if both $PaCO_2$ and $[HCO_3^-]$ change in the same direction, the ratio stays the same and the pH or $[H^+]$ remains relatively stable. **In chronic metabolic acidosis, intracellular buffers (eg, hemoglobin, bone) may be more important than HCO_3^-** when the extracellular HCO_3^- level is low.

Renal acid handling

Acids are added daily to the body fluids. These include volatile (eg, carbonic) and nonvolatile (eg, sulfuric, phosphoric) acids. The metabolism of dietary carbohydrates and fat produces approximately 15,000 mmol of CO_2 per day, which is excreted by the lungs. The metabolism of proteins (ie, sulfur-containing amino acids) and dietary phosphate results in the formation of nonvolatile acids, H_2SO_4 and H_3PO_4. These acids first are buffered by the HCO_3^-/H_2CO_3 system as follows:

$$H_2SO_4 + 2NaHCO_3 \Leftrightarrow Na_2SO_4 + 2H_2CO_3 \Leftrightarrow 2H_2O + CO_2$$

To maintain normal pH, the kidneys must perform 2 physiologic functions. The first is to reabsorb all the filtered HCO_3^-, a function principally of the proximal tubule. The second is to excrete the daily H^+ load, a function of the collecting duct.

HCO_3^- reabsorption

With a serum HCO_3^- concentration of 24 mmol/l, the daily glomerular ultrafiltrate of 180 l, in a healthy subject, contains 4300 mmol of HCO_3^-, all of which has to be reabsorbed. Approximately 90% of the filtered HCO_3^- is reabsorbed in the **proximal tubule**, and the remainder is reabsorbed in the thick ascending limb and the medullary collecting duct.

The $3Na^+$-$2K^+$/ATPase (sodium-potassium/adenosine triphosphatase) provides the energy for this process, which maintains a low intracellular Na^+ concentration and a relative negative intracellular potential. The low

Na^+ concentration indirectly provides energy for the apical Na^+/H^+ exchanger, which transports H^+ into the tubular lumen. H^+ in the tubular lumen combines with filtered HCO_3^- in the following reaction:

$$HCO_3^- + H^+ \Leftrightarrow H_2CO_3 \Leftrightarrow H_2O + CO_2$$

Carbonic anhydrase present in the brush border of the proximal tubule accelerates the dissociation of H_2CO_3 into $H_2O + CO_2$, which shifts the reaction shown above to the right and keeps the luminal concentration of H^+ low. CO_2 diffuses into the proximal tubular cell, where carbonic anhydrase combines CO_2 and water to form HCO_3^- and H^+. The HCO_3^- formed intracellularly returns to the pericellular space and then to the circulation via the basolateral $Na^+/3HCO_3^-$ cotransporter.

Acid excretion

Excretion of the daily acid load (50-100 mmol of H^+) occurs principally through H^+ secretion by the apical H^+/ATPase in α intercalated cells of the collecting duct.

HCO_3^- formed intracellularly is returned to the systemic circulation and H^+ enters the tubular lumen via apical proton pumps. Urine pH cannot be lowered much below 5.0 because the gradient against which H^+/ATPase has to pump protons (intracellular pH 7.5 to luminal pH 5) becomes too steep. More than 99.9% of the H^+ load excreted is buffered by the weak bases NH_3 or phosphate.

Ammonia

A more important urine-buffering system for secreted H^+ than phosphate, ammonia (NH_3) buffering occurs via the following reaction:

$$NH_3 + H^+ \Leftrightarrow NH_4^+$$

Ammonia is produced in the **proximal tubule** from the amino acid glutamine. Ammonia is converted to ammonium (NH_4^+) by intracellular H^+ and is secreted into the proximal tubular lumen. The thick ascending limb

of the loop of Henle transports NH_4^+ into the medullary interstitium, where it dissociates back into NH_3 and H^+. The NH_3 is transported into the lumen of the collecting duct, where it is available to buffer H^+ ions and becomes NH_4^+. NH_4^+ is excreted as the Cl salt, and every H^+ ion buffered is an HCO_3^- gained to the systemic circulation.

Acidosis and alkalosis

An increase in $[H^+]$ and a fall in pH are termed **acidemia**, and a decrease in $[H^+]$ and an increase in pH are termed **alkalemia**. The underlying disorders that lead to acidemia and alkalemia are **acidosis** and **alkalosis**, respectively. Rarely, metabolic acidosis can be part of a mixed or complex acid-base disturbance in which 2 or more separate metabolic or respiratory derangements occur together. In these instances, pH may not be reduced or the HCO_3^- concentration may not be low.

As a compensatory mechanism, metabolic acidosis leads to **alveolar hyperventilation** with a fall in $PaCO_2$. The only definitive way to diagnose metabolic acidosis is by simultaneous measurement of serum electrolytes and arterial blood gases, which shows both pH and $PaCO_2$ to be low; calculated HCO_3^- also is low. In persons with chronic uremic acidosis, bone salts contribute to buffering, and the serum HCO_3^- level usually remains greater than 12 mmol/L. This bone buffering can lead to significant **loss of bone calcium**, with resulting osteopenia and osteomalacia.

Anion gap

Plasma, like any other body fluid compartment, is neutral; **total anions match total cations**. The major plasma cation is Na^+, and major plasma anions are Cl^- and HCO_3^-. The anion gap (AG) is the difference between the concentration of Na^+ and Cl^- and HCO_3^-. An increase in the AG can result from either a decrease in unmeasured cations (eg, hypokalemia, hypocalcemia, hypomagnesemia) or an increase in unmeasured anions (eg, hyperphosphatemia, high albumin levels). In certain forms of metabolic acidosis, other anions accumulate; by

recognizing the increasing AG, the clinician can formulate a differential diagnosis for the cause of that acidosis.

$$HA + NaHCO_3 \Leftrightarrow NaA + H_2CO_3 \Leftrightarrow CO_2 + H_2O$$

This reaction indicates that the addition of an acid (HA, where H^+ is combined with an unmeasured anion A^-) results in the **consumption of HCO_3^- with an addition of anions that will account for the increase in the AG**. Metabolic acidosis is classified on the basis of AG into normal- (also called non-AG or hyperchloremic MA) and high-AG metabolic acidosis.

Potassium and renal acid secretion

Renal acid secretion is influenced by serum K^+ and may result from the transcellular shift of K^+ when **intracellular K^+ is exchanged for extracellular H^+ or vice versa**. In hypokalemia, an intracellular acidosis can develop; in hyperkalemia, an intracellular alkalosis can develop. HCO_3^- reabsorption is increased secondary to relative intracellular acidosis. The increase in intracellular H^+ concentration promotes the activity of the apical Na^+/H^+ exchanger. Renal production of NH_3 is increased in hypokalemia, resulting in an increase in renal acid excretion. Patients with **hypokalemia may have relatively alkaline urine because hypokalemia increases renal ammoniagenesis**. Excess NH_3 then binds more H^+ in the lumen of the distal nephron and urine pH increases. The most common cause for hypokalemia and metabolic acidosis is GI loss (eg, diarrhea, laxative use).

Hyperkalemia has an effect on acid-base regulation opposite to that observed in hypokalemia. **Hyperkalemia impairs NH_4^+ excretion through reduction of NH_3 synthesis** in the proximal tubule and reduction of NH_4^+ reabsorption in the thick ascending limb, resulting in reduced medullary interstitial NH_3 concentration. This leads to a **decrease in net renal acid secretion**.

Metabolic Acidosis

Metabolic acidosis is a clinical disturbance characterized by an increase in plasma acidity. Metabolic acidosis is typically classified as having a normal AG (ie, non-AG) or a high AG.

Non-AG metabolic acidosis is also characterized by **hyperchloremia** and is sometimes referred to as hyperchloremic acidosis. Hyperchloremic or non-AG metabolic acidosis occurs principally **when HCO_3^- is lost from either the GI tract or the kidneys or because of a renal acidification defect**. Some of the mechanisms that result in a non-AG metabolic acidosis are the following:

- Addition of HCl to body fluids: H^+ buffers HCO_3^- and the added Cl^- results in a normal AG.
- Loss of HCO_3^- from the kidneys or the GI tract: The kidneys reabsorb sodium chloride to maintain volume.
- Rapid volume expansion with normal saline: This results in an increase in the chloride load that exceeds the renal capacity to generate equal amounts of HCO_3^-.

Causes of non-AG metabolic acidosis: acid load, chronic renal failure, carbonic anhydrase inhibitors, renal tubular acidosis, ureteroenterostomy, expansion/extra-alimentation, diarrhea.

Specific causes of hyperchloremic or non-AG metabolic acidosis:

Loss of HCO_3^- via the GI tract

Diarrhea is the most common cause of external loss of alkali resulting in metabolic acidosis. Biliary, pancreatic, and duodenal secretions are alkaline and are capable of neutralizing the acidity of gastric secretions. In normal situations, a **luminal Na^+/H^+ exchanger in the jejunal mucosa effectively results in sodium bicarbonate ($NaHCO_3$) reabsorption**, and the 100 ml of stool excreted daily has very small amounts of bicarbonate.

The development of diarrheal states and **increased stool volume (potentially several l/d) may cause a daily loss of several hundred millimoles of bicarbonate**. Because diarrheal stools have a higher

bicarbonate concentration than plasma, the net result is a metabolic acidosis with volume depletion.

Other GI conditions associated with external losses of fluids may lead to large alkali losses. These include enteric fistulas and drainage of biliary, pancreatic, and enteric secretions; ileus secondary to intestinal obstruction, in which up to several liters of alkaline fluid may accumulate within the intestinal lumen.

Distal renal tubular acidosis (RTA) - type 1

The defect in this type of RTA is a **decrease in net H^+ secreted by the collecting duct**. The secreted H^+ is excreted as free ions (reflected by urine pH value) or titrated by urinary buffers, phosphate, and NH_3. A decrease in the amount of H^+ secreted results in a reduction in its urinary concentration (ie, increase in urine pH) and a reduction in total H^+ buffered by urinary phosphate or NH_3.

Patients have a **reduction in serum HCO_3^-** to various degrees, in some cases to less than 10 mmol/l. Several different mechanisms are implicated in the development of distal RTA. These include a **defect in proton pumps**, that can be acquired or congenital. Another mechanism is a **defect in the basolateral Cl^-/HCO_3^- exchanger**, or the **intracellular carbonic anhydrase** that can be acquired or congenital. Back-diffusion of the H^+ from the lumen via the paracellular or transcellular space is another mechanism; this occurs if the integrity of the tight junctions is lost or permeability of the apical membrane is increased.

Urine pH is high secondary to the renal acid secretion defect. Patients with type 1 RTA may develop **nephrocalcinosis and nephrolithiasis**. This is thought to occur for the following reasons:

- Patients have a constant release of calcium phosphate from bones to buffer the extracellular H^+.
- Patients have decreased reabsorption of calcium and phosphate, leading to hypercalciuria and hyperphosphaturia.
- Patients have relatively alkaline urine, which promotes calcium phosphate precipitation.

Type 1 RTA occurs sporadically; the causes are shown as follows:

- Primary - Genetic
- Drug-related - Amphotericin B, lithium, analgesics
- Autoimmune disease - Systemic lupus erythematosus, chronic active hepatitis, rheumatoid arthritis, primary biliary cirrhosis
- Related to other systemic disease - Sickle cell disease, hyperparathyroidism, light chain disease
- Tubulointerstitial disease - Obstructive uropathy, medullary cystic kidney disease, hypercalciuria

Proximal RTA - type 2

The hallmark of type 2 RTA is **impairment in proximal tubular HCO_3^- reabsorption**. In the euvolemic state and in the absence of elevated levels of serum HCO_3^-, all filtered HCO_3^- is reabsorbed, 90% in the proximal tubule. Normally, HCO_3^- excretion occurs only when serum HCO_3^- exceeds 24-28 mmol/l. Patients with type 2 RTA, however, have a **lower threshold for excretion of HCO_3^-,** leading to a loss of filtered HCO_3^- until the serum HCO_3^- concentration reaches the lower threshold.

Type 2 RTA can be found either as a **solitary proximal tubular defect**, in which reabsorption of HCO_3^- is the only abnormality (rare), or as part of a more generalized defect of the proximal tubule characterized by glucosuria, aminoaciduria, and phosphaturia, also called **Fanconi syndrome**.

Any disorder that leads to **decreased ATP production** or a disorder involving Na^+ -K^+ –ATPase can result in Fanconi syndrome. In principle, loss of function of the apical Na^+/H^+ antiporter or the basolateral $Na^+/3HCO_3^-$ cotransporter or the intracellular carbonic anhydrase results in selective reduction in HCO_3^- reabsorption.

Type 4 RTA

This is the most common form of RTA in adults and results from **aldosterone deficiency or resistance**. The collecting duct is a major site of aldosterone action; there it stimulates Na^+ reabsorption and K^+ secretion in the principal cells and stimulates H^+ secretion in the A-type

intercalated cells. Hypoaldosteronism, therefore, is associated with **decreased collecting duct Na^+ reabsorption, hyperkalemia, and metabolic acidosis**.

Hyperkalemia also reduces proximal tubular NH_4^+ production and decreases NH_4^+ absorption by the thick ascending limb, leading to a reduction in medullary interstitial NH_3 concentration. This diminishes the ability of the kidneys to excrete an acid load and worsens the acidosis.

The following are causes of type 4 RTA:

- Hypoaldosteronism (low renin) - Hyporeninemic hypoaldosteronism (diabetes mellitus/mild renal impairment, chronic interstitial nephritis, nonsteroidal anti-inflammatory drugs)
- Hypoaldosteronism (high renin) - Primary adrenal defect (isolated: congenital hypoaldosteronism; generalized: Addison disease), inhibition of aldosterone secretion (heparin, ACE inhibitors)

Early renal failure

Metabolic acidosis is usual in patients with renal failure, and, in **early to moderate stages of chronic kidney disease (glomerular filtration rate of 20-50 ml/min), it is associated with a normal AG (hyperchloremic)**. In more advanced renal failure, the acidosis is associated with a high AG.

In hyperchloremic acidosis, **reduced ammoniagenesis** (secondary to loss of functioning renal mass) is the primary defect, leading to an inability of the kidneys to excrete the normal daily acid load. Note that patients with hypobicarbonatemia from renal failure cannot compensate for additional HCO_3^- loss from an extrarenal source (eg, diarrhea) and severe metabolic acidosis can develop rapidly.

High AG metabolic acidosis:

- Lactic acidosis – L-Lactate, D-lactate
- Ketoacidosis - Beta-hydroxybutyrate, acetoacetate
- Renal failure - Sulfate, phosphate, urate, and hippurate
- Ingestions - Salicylate, methanol or formaldehyde (formate),

- Massive rhabdomyolysis (release of H^+ and organic anions from damaged muscle)

Specific causes of high-AG metabolic acidosis

Lactic acidosis

L-lactate is a product of pyruvic acid metabolism in a reaction catalyzed by lactate dehydrogenase. Daily lactate production in a healthy person is substantial (approximately 20 mmol/kg/d), and this is usually metabolized to pyruvate in the liver, the kidneys, and, to a lesser degree, in the heart. Thus, production and use of lactate (ie, Cori cycle) is constant, keeping plasma lactate low.

The major metabolic pathway for pyruvate is to acetyl coenzyme A, which then enters the citric acid cycle. In the presence of **mitochondrial dysfunction**, pyruvate accumulates in the cytosol and more lactate is produced. Type A lactic acidosis occurs in hypoxic states, while type B occurs without associated tissue hypoxia.

D-lactic acidosis is a form of lactic acidosis that occurs from overproduction of D-lactate by intestinal bacteria. It is observed in association with **intestinal bacterial overgrowth syndromes.**

Ketoacidosis

Free fatty acids released from adipose tissue have 2 principal fates. In the major pathway, triglycerides are synthesized in the cytosol of the liver. In the less common pathway, fatty acids enter mitochondria and are metabolized to ketoacids (acetoacetic acid and beta-hydroxybutyric acid) by the beta-oxidation pathway. Ketoacidosis occurs when **delivery of free fatty acids to the liver or preferential conversion of fatty acids to ketoacids is increased**. This pathway is favored when **insulin is absent** (as in the fasting state), in certain forms of diabetes, and when glucagon action is enhanced.

Alcoholic ketoacidosis occurs when excess alcohol intake is accompanied by poor nutrition. Alcohol inhibits gluconeogenesis, and the **fasting state leads to low insulin and high glucagon levels**. These patients tend to have a mild degree of lactic acidosis.. Patients may have

more than one metabolic disturbance (eg, mild lactic acidosis, metabolic alkalosis secondary to vomiting). Starvation ketoacidosis can occur after prolonged fasting and may be exacerbated by exercise.

Diabetic ketoacidosis is usually precipitated in patients with type 1 diabetes by stressful conditions (eg, infection, surgery, emotional trauma), but it can also occur in patients with type 2 diabetes. The metabolic acidosis in diabetic ketoacidosis is commonly a **high-AG acidosis secondary to the presence of ketones in the blood**. However, after initiation of treatment with insulin, ketone production ceases, the liver uses ketones, and the acidosis becomes a non-AG type that resolves in a few days (ie, time necessary for kidneys to regenerate HCO_3^-, which was consumed during the acidosis).

Advanced renal failure

Patients with advanced chronic kidney disease **(glomerular filtration rate of less than 20 ml/min) present with a high-AG acidosis.** The acidosis occurs from reduced ammoniagenesis leading to a decrease in the amount of H^+ buffered in the urine. The increase in AG is thought to occur because of the **accumulation of sulfates, urates and phosphates** from a reduction in glomerular filtration and from diminished tubular function. Bone buffering can lead to significant loss of bone calcium with resulting osteopenia and osteomalacia.

Metabolic Alkalosis

Metabolic alkalosis is an acid-base disturbance caused by an **elevation in plasma bicarbonate** concentration. This condition is not a disease; it is a sign or state encountered in certain disease processes. Although metabolic alkalosis may not be referred to as often as metabolic acidosis, it is the most common acid-base abnormality in hospitalized adults. The 2 types of metabolic alkalosis (ie, chloride-responsive, chloride-resistant) are classified based upon the amount of chloride in the urine.

Chloride-responsive metabolic alkalosis involves urine chloride levels less than 10 mmol/l, and it is characterized by **decreased extracellular fluid volume and low serum chloride** such as occurs with **vomiting**.

Chloride-resistant metabolic alkalosis involves urine chloride levels more than 20 mmol/l, and it is characterized by **increased extracellular fluid volume**. As the name implies, this type resists administration of chloride salt. **Primary aldosteronism** is an example of chloride-resistant metabolic alkalosis.

In most cases, metabolic alkalosis is caused by loss of HCl through the kidney or GI tract, especially from loss due to vomiting, nasogastric tube suctioning, severe gastroesophageal reflux or pyloric stenosis. Occasionally, the condition is caused by disproportionate loss of chloride.

Other causes of metabolic alkalosis include loss of hydrogen ions from renal acid losses that exceed acid production from cellular metabolism.

The consequences of metabolic alkalosis on organ systems depend on the severity of the alkalemia and the degree of respiratory compensation. If the elevated plasma HCO_3 concentration is not accompanied by a rise in PCO_2, the elevation of pH is much more severe.

Effects

Oxygen delivery: An increase in blood pH shifts the oxygen-hemoglobin dissociation curve to the left. This creates a tighter bond between hemoglobin and oxygen, causing **decreased oxygen delivery to tissues**. Hypoxemia is worsened by a compensatory hypoventilation to elevate PCO_2.

Cardiovascular system: **Life-threatening arrhythmias** are the most significant adverse effect of metabolic alkalosis.

Neuromuscular system: Patients with severe metabolic alkalosis can develop **obtundation**.

Ionized calcium concentration: Metabolic alkalosis may cause a decrease in ionized calcium because of **increased binding of calcium to plasma proteins**; consequences include tetany and **seizures**.

Compensation mechanisms

Buffering of excess HCO_3: Intracellular buffering occurs through sodium/hydrogen and potassium/hydrogen ion exchange, with eventual formation of CO_2 and water from HCO_3.

***Hypoventilation*:** Within several hours, elevated levels of HCO_3 and metabolic alkalosis stimulate a chemoreceptor inhibition of the respiratory center, resulting in hypoventilation and increased PCO_2 levels. Hypoventilation may actually occur to an extent sufficient to cause **hypoxemia**.

Respiratory Acidosis

Respiratory acidosis is a clinical disturbance that is due to **alveolar hypoventilation**. Alveolar hypoventilation leads to an increased $PaCO_2$ (ie, hypercapnia). The removal of CO_2 by the lungs is less than the production of CO_2 in the tissues. The increase in $PaCO_2$ in turn decreases the $HCO_3^-/PaCO_2$ and decreases pH.

The metabolism of fats and carbohydrates leads to the formation of a large amount of CO_2. The CO_2 combines with H_2O to form carbonic acid (H_2CO_3). The lungs excrete the volatile fraction through ventilation, and acid accumulation does not occur.

Alveolar ventilation is under the control of the central respiratory centers, which are located in the pons and the medulla. Ventilation is influenced and regulated by chemoreceptors for $PaCO_2$, PaO_2, and pH located in the brainstem, as well as by neural impulses from lung stretch receptors and impulses from the cerebral cortex. Failure of ventilation quickly increases the $PaCO_2$.

Respiratory acidosis can be acute or chronic. In acute respiratory acidosis, the $PaCO_2$ is elevated above the upper limit of the reference range (ie, >47 mm Hg) with an accompanying acidemia (pH <7.35). In chronic respiratory acidosis, the $PaCO_2$ is elevated above the upper limit of the reference range, with a normal or near-normal pH secondary to renal compensation and an elevated serum bicarbonate (HCO_3^- > 30 mmol/l).

Acute respiratory acidosis occurs when an abrupt failure of ventilation occurs. This failure in ventilation may be caused by **depression of the central respiratory center** by cerebral disease or drugs, **inability to ventilate adequately** due to neuromuscular disease (eg, myasthenia gravis, amyotrophic lateral sclerosis), or **airway obstruction** related to asthma or chronic obstructive pulmonary disease (COPD) exacerbation.

Chronic respiratory acidosis may be secondary to many disorders, including COPD. Hypoventilation in COPD involves multiple mechanisms, including decreased responsiveness to hypoxia and hypercapnia, **increased ventilation-perfusion mismatch** leading to increased dead space ventilation, and **decreased diaphragm function** secondary to fatigue and **hyperinflation**. Chronic respiratory acidosis also may be secondary to **obesity hypoventilation syndrome** (ie, pickwickian syndrome), and **severe restrictive ventilatory defects** as observed in interstitial fibrosis and thoracic deformities.

Lung diseases that primarily cause abnormality in alveolar gas exchange usually do not cause hypoventilation but tend to cause stimulation of ventilation and hypocapnia secondary to hypoxia. Hypercapnia only occurs if severe disease or respiratory muscle fatigue occurs.

In acute respiratory acidosis, compensation occurs in 2 steps. The initial response is cellular buffering that occurs over minutes to hours. Cellular buffering elevates plasma bicarbonate only slightly. The second step is renal compensation that occurs over 3-5 days. With **renal compensation**, renal excretion of carbonic acid (H^+) is increased and bicarbonate reabsorption is increased.

Respiratory acidosis does not have a great effect on electrolyte levels. Some small effects occur on calcium and potassium levels. Acidosis decreases binding of calcium to albumin and tends to increase serum ionized calcium levels. In addition, acidemia causes an extracellular shift of potassium, but respiratory acidosis rarely causes clinically significant hyperkalemia.

Respiratory Alkalosis

Respiratory alkalosis is a clinical disturbance due to **alveolar hyperventilation**. Alveolar hyperventilation leads to a decreased $PaCO_2$ (hypocapnia). In turn, the decrease in $PaCO_2$ increases the ratio of bicarbonate concentration (HCO_3^-) to $PaCO_2$ and increases pH. **Hypocapnia** develops when the lungs remove more carbon dioxide than is produced in the tissues. Respiratory alkalosis can be acute or chronic. In **acute respiratory alkalosis**, the $PaCO_2$ is below the lower limit of normal and the serum is alkalemic. In **chronic respiratory alkalosis**, the $PaCO_2$ is below the lower limit of normal, but pH is normal or near normal because of renal compensation.

Respiratory alkalosis is **the most common acid-base abnormality observed in patients who are critically ill**. It is associated with numerous illnesses and is a common finding in patients undergoing **mechanical ventilation**. Many cardiac and pulmonary disorders can present with respiratory alkalosis as an early or intermediate finding.

Acute hypocapnia causes a reduction of serum levels of potassium and phosphate secondary to increased cellular uptake of these ions. A reduction in free serum calcium also occurs. Calcium reduction is secondary to increased binding of Ca^{++} to serum albumin. Many of the symptoms present in persons with respiratory alkalosis are related to the hypocalcemia. Hyponatremia and hypochloremia may also be present. After a period of 2-6 hours, respiratory alkalosis is renally compensated by a decrease in bicarbonate reabsorption.

Hypoglycemia

It can be caused by a variety of different conditions. The most common cause of mild or severe hypoglycemia in childhood is **insulin-treated type 1 diabetes** and a mismatch among food, exercise, and insulin.

The body normally defends itself against hypoglycemia by decreasing insulin secretion and increasing glucagon, epinephrine, growth hormone, and cortisol secretion. These **hormonal changes combine to cause increased hepatic glucose output, increased alternative fuel availability, and decreased glucose utilization**. The increase in hepatic glucose production comes initially from the breakdown of liver glycogen stores due to lower insulin and increased glucagon. When glycogen stores become depleted and protein breakdown increases due to increased cortisol levels, hepatic gluconeogenesis replaces glycogenolysis as the primary source of glucose production. This breakdown of protein is reflected by increased plasma levels of the gluconeogenic amino acids, alanine, and glutamine.

Decreased peripheral glucose use again occurs initially because of a fall in insulin levels and later because of increases in epinephrine, cortisol, and growth hormone. All 3 events **increase lipolysis and plasma free fatty acids**, which are available as an alternative fuel and competitively inhibit glucose use. **Increased plasma and urinary ketone** levels indicate the use of fat as an energy source. Plasma free fatty acids also stimulate glucose production.

Hypoglycemia occurs when one or more of these counterregulatory mechanisms fail, either through glucose overutilization as in hyperinsulinism, underproduction as in the glycogen storage diseases, or a combination of the two as in growth hormone or cortisol deficiency.

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Causes

Sepsis

Septic shock

SIRS defines a **clinical response** to a nonspecific insult of either infectious or noninfectious origin. SIRS is defined as 2 or more of the following variables:

- Fever of more than 38°C or less than 36°C
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or a PaCO2 level of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/µl or < 4,000/µl or >10% bands)

SIRS is nonspecific and can be caused by ischemia, inflammation, trauma, infection, or a combination of several insults. **SIRS is not always related to infection**. **Infection** is defined as "a microbial phenomenon characterized by an inflammatory response to the microorganisms or the invasion of normally sterile tissue by those organisms." **Inflammation** is the body's response to nonspecific insults that arise from chemical, traumatic, ischemic or infectious stimuli.

Bacteremia is the presence of bacteria within the blood stream, but this condition does not always lead to SIRS or sepsis. **Sepsis** is the systemic response to infection and is defined as the presence of SIRS in addition to a documented or presumed infection. **Severe sepsis** meets the aforementioned criteria and is associated with organ dysfunction, hypoperfusion, or hypotension. **Sepsis-induced hypotension** is defined as

"the presence of a systolic blood pressure of less than 90 mm Hg or a reduction of more than 40 mm Hg from baseline in the absence of other causes of hypotension." Patients meet the criteria for **septic shock** if they have persistent hypotension and perfusion abnormalities despite adequate fluid resuscitation. **Multiple organ dysfunction syndrome** (MODS) is a state of physiological derangements in which organ function is not capable of maintaining homeostasis.

SIRS, independent of the etiology, has the same pathophysiologic properties, with minor differences in inciting cascades. Many consider **the syndrome a self-defense mechanism**. **The inflammatory cascade** is a complex process that involves humoral and cellular responses, complement, and cytokine cascades. The relationship between these complex interactions and SIRS are sumarized as the following 3-stage process:

- **Stage I**: Following an insult, **local cytokine** is produced with the goal of inciting an inflammatory response, thereby promoting wound repair and recruitment of the monocyte-macrophage system.
- **Stage II**: Small quantities of **local cytokines are released into circulation** to improve the local response. This leads to growth factor stimulation and the recruitment of macrophages and platelets. This **acute phase response is typically well controlled** by a decrease in the proinflammatory mediators and by the release of endogenous antagonists. **The goal is homeostasis.**
- **Stage III**: If homeostasis is not restored, a significant systemic reaction occurs. **The cytokine release leads to destruction rather than protection.** A consequence of this is the activation of numerous humoral cascades and subsequent **loss of circulatory integrity**. This leads to end-organ dysfunction.

Theory behind the progression of SIRS to organ dysfunction and possibly MODS: the event that initiates the SIRS cascade primes the pump. With each additional event, an altered or exaggerated response

occurs, leading to progressive illness. The key to preventing the multiple hits is adequate identification of the cause of SIRS and appropriate resuscitation and therapy.

Trauma, inflammation, or infection leads to the activation of the **inflammatory cascade**. When SIRS is mediated by an infectious insult, the inflammatory cascade is often initiated by endotoxin or exotoxin. Tissue macrophages, monocytes, mast cells, platelets, and endothelial cells are able to produce a multitude of cytokines. The cytokines tissue necrosis factor-a (TNF-α) and interleukin (IL)–1 are released first and initiate several cascades. The release of IL-1 and TNF-α induces the production other **proinflammatory cytokines**.

IL-6, IL-8, and interferon gamma are the **primary proinflammatory mediators**. TNF-α and IL-1 have been shown to be released in large quantities within 1 hour of an insult and have both local and systemic effects; cause severe lung injury and hypotension when given together, they are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system).

The proinflammatory interleukins either function directly on tissue or work via secondary mediators to activate the coagulation cascade, complement cascade, and the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes. Numerous proinflammatory polypeptides are found within the **complement cascade**. Protein complements C3a and C5a have been the most studied and are felt to contribute directly to the release of additional cytokines and to cause vasodilatation and increasing vascular permeability. Prostaglandins and leukotrienes incite **endothelial damage**, leading to multiorgan failure.

The correlation between inflammation and coagulation is critical to understanding the potential **progression of SIRS**. IL-1 and TNF-α directly affect endothelial surfaces, leading to the expression of tissue factor, thereby promoting coagulation. Fibrinolysis is impaired. This coagulation

cascade leads to complications of microvascular thrombosis, including organ dysfunction.

To counteract the acute inflammatory response, the body is equipped to reverse this process via counter inflammatory response syndrome (**CARS**). IL-4 and IL-10 are cytokines responsible for decreasing the production of TNF-α, IL-1, IL-6, and IL-8. The acute phase response also produces antagonists to TNF-α and IL-1 receptors. These antagonists either bind the cytokine, and thereby inactivate it, or block the receptors. The balance of SIRS and CARS determines a patient's prognosis after an insult. Because of CARS, many of the new medications meant to inhibit the proinflammatory mediators may lead to deleterious **immunosuppression**.

The mortality rates were 7% (SIRS), 16% (sepsis), 20% (severe sepsis), and 46% (septic shock).

Causes

The differential diagnosis of SIRS is broad and includes infectious and noninfectious conditions, surgical procedures, trauma, and medications and therapies.

- ***Infectious causes of SIRS***:
    - Bacterial sepsis
    - Burn wound infections
    - Cholecystitis
    - Community-acquired pneumonia
    - Diabetic foot infection
    - Erysipelas
    - Intraabdominal infections (eg, diverticulitis, appendicitis)
    - Gas gangrene
    - Nosocomial pneumonia
    - Pseudomembranous colitis
    - Pyelonephritis
    - Septic arthritis

    - Urinary tract infections
- ***Noninfectious causes of SIRS***:
    - Acute mesenteric ischemia
    - Adrenal insufficiency
    - Autoimmune disorders
    - Burns
    - Chemical aspiration
    - Cirrhosis
    - Dehydration
    - Drug reaction
    - Electrical injuries
    - Hemorrhagic shock
    - Intestinal perforation
    - Pancreatitis
    - Substance abuse (stimulants such as cocaine and amphetamines)
    - Surgical procedures
    - Transfusion reactions
    - Upper gastrointestinal bleeding

Sepsis

Sepsis is not a random occurrence and is usually associated with other conditions, such as perforation, compromise, or rupture of an intra-abdominal or pelvic structure. Intrarenal infection (pyelonephritis), renal abscess (intrarenal or extrarenal), acute prostatitis, or prostatic abscess may cause urosepsis in immunocompetent hosts. Sepsis or septic shock may be associated with the direct introduction of microbes into the bloodstream via intravenous infusion (eg, device-associated infections) and may be caused by overwhelming pneumococcal infection in patients with impaired or absent splenic function.

The **pathophysiology** of sepsis is complex and results from the effects of circulating bacterial products, mediated by cytokine release, caused by sustained bacteremia. Cytokines, previously termed endotoxins, are responsible for the clinically observable effects of the bacteremia in the host. Impaired pulmonary, hepatic, or renal function may result from excessive cytokine release during the septic process. Sepsis is defined as the presence of **infection in association with SIRS**.

Patients with nonspecific symptoms are usually acutely ill with **fever**, with or without **shaking chills**. **Mental status** may be impaired in the setting of fever or hypoperfusion. Patients with bacteremia from any source often display an **increased breathing rate** due to **respiratory alkalosis**. The skin of patients with sepsis may be warm or cold, depending on the adequacy of organ perfusion and dilatation of the superficial vessels of the skin.

Pseudosepsis

Pseudosepsis is a common cause of misdiagnosis in hospitalized patients, particularly in the emergency department and in medical and surgical intensive care units. The most common causes of pseudosepsis include gastrointestinal hemorrhage, pulmonary embolism, acute myocardial infarction, acute pancreatitis (edematous or hemorrhagic), diuretic-induced hypovolemia, and relative adrenal insufficiency. Patients with pseudosepsis may have fever, chills, leukocytosis, with or without hypotension.

Septic Shock

Not all patients with bacteremia have signs of sepsis. Clinical syndrome of sepsis is the result of **excessive activation of host defense mechanisms** rather than the direct effect of microorganisms. Serious bacterial infections at any body site, with or without bacteremia, are usually associated with important **changes in the function of every organ system in the body**. These changes are mediated mostly by elements of

the host immune system against infection. Shock is deemed present when **volume replacement fails to increase blood pressure** to acceptable levels and associated clinical evidence indicates inadequate perfusion of major organ systems, with progressive failure of organ system functions. Multiple organ dysfunctions, the extreme end of the continuum, are incremental degrees of physiologic derangements in individual organs.

Definitions of key terms

The basis of sepsis is **the presence of infection associated with a systemic inflammatory response that results in physiologic alterations at the capillary endothelial level**. The difficulty in diagnosis comes in knowing when a localized infection has become systemic and requires more aggressive hemodynamic support. No criterion standard exists for the diagnosis of endothelial dysfunction, and patients with sepsis may not initially present with frank hypotension and overt shock.

In the presence of infection, an increase in the number of SIRS criteria observed should alert the clinician to the possibility of endothelial dysfunction, developing organ dysfunction, and the need for aggressive therapy. With sepsis, at least 1 of the following **manifestations of inadequate organ function/perfusion** is typically included:

- Alteration in mental state
- Hypoxemia (arterial oxygen tension [PaO_2] < 72 mm Hg at fraction of inspired oxygen [FiO_2] 0.21; overt pulmonary disease not the direct cause of hypoxemia)
- Elevated plasma lactate level
- Oliguria (urine output < 30 ml or 0.5 ml/kg for at least 1 h)

Severe sepsis is defined as sepsis complicated by end-organ dysfunction, as signaled by altered mental status, an episode of hypotension, elevated creatinine concentration, or evidence of disseminated intravascular coagulopathy.

Septic shock is defined as a state of acute circulatory failure characterized by persistent arterial hypotension despite adequate fluid

resuscitation or by tissue hypoperfusion (increased lactate concentration) unexplained by other causes.

Multiple organ dysfunction syndrome **(MODS)** is defined as the presence of altered organ function in a patient who is acutely ill and in whom homeostasis cannot be maintained without intervention.

The pathophysiology of septic shock is not precisely understood, but it involves a complex interaction between the pathogen and the host's immune system. The normal physiologic response to localized infection includes the activation of host defense mechanisms that result in the influx of activated neutrophils and monocytes, the release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of coagulation pathways. These mechanisms are in play during septic shock, but on a systemic scale, leading to **diffuse endothelial disruption, vascular permeability, vasodilation, and thrombosis of end-organ capillaries**. Endothelial damage itself can further activate inflammatory and coagulation cascades, creating in effect a positive feedback loop, and leading to further endothelial and end-organ damage.

Mediator-induced cellular injury

Inflammatory mediators are the key players in the pathogenesis. An initial step in the activation of innate immunity is the synthesis de novo of small polypeptides, called cytokines, that induce protean manifestations on most cell types, from immune effector cells to vascular smooth muscle and parenchymal cells. Several cytokines are induced, including tumor necrosis factor (TNF) and interleukins (ILs), especially IL-1**. Both of these factors also help to keep infections localized, but, once the infection becomes systemic, the effects can also be detrimental**.

High levels of IL-6 are associated with mortality. IL-8 is an important regulator of neutrophil function, synthesized and released in significant amounts during sepsis. IL-8 contributes to the lung injury and dysfunction of other organs. The chemokines (monocyte chemoattractant protein–1) orchestrate the migration of leukocytes. The other cytokines that have a

supposed role in sepsis are IL-10, interferon gamma, IL-12, macrophage migration inhibition factor, granulocyte colony-stimulating factor (G-CSF), and granulocyte macrophage colony-stimulating factor (GM-CSF). In addition, cytokines activate the coagulation pathway, resulting in capillary microthrombi and end-organ ischemia.

Several of the harmful effects of bacteria are mediated by **proinflammatory cytokines** induced in host cells (macrophages/monocytes and neutrophils) by the bacterial cell wall component. The most toxic component of the gram-negative bacteria is the lipid A moiety of lipopolysaccharide. The complement system is activated and contributes to the clearance of the infecting microorganisms but probably also enhances the tissue damage.

Hypotension, the cardinal manifestation of sepsis, occurs via induction of **nitric oxide** (NO). NO plays a major role in the hemodynamic alterations of septic shock, which is a hyperdynamic form of shock.

Abnormalities of coagulation and fibrinolysis

An imbalance of homeostatic mechanisms leads to **disseminated intravascular coagulopathy** and microvascular thrombosis, causing organ dysfunction and death. Inflammatory mediators instigate direct injury to the vascular endothelium; the endothelial cells release tissue factor, triggering the extrinsic coagulation cascade and accelerating production of thrombin.

The process is initiated via binding of factor XII to the subendothelial surface. This activates factor XII, and then factor XI and eventually factor X are activated by a complex of factor IX, factor VIII, calcium, and phospholipid. The final product of the coagulation pathway is the production of thrombin, which converts soluble fibrinogen to fibrin. The insoluble fibrin, along with aggregated platelets, forms intravascular clots. **The imbalance among inflammation, coagulation, and fibrinolysis results in widespread coagulopathy and microvascular thrombosis and suppressed fibrinolysis, ultimately leading to multiple organ dysfunction and death. The insidious nature of sepsis is such that microcirculatory**

dysfunction can occur while global hemodynamic parameters such as blood pressure may remain normal.

Circulatory abnormalities

Septic shock falls under the category of **distributive shock**, which is characterized by **pathologic vasodilation and shunting of blood from vital organ to nonvital tissues** such as skin, skeletal muscle, and adipose. The endothelial dysfunction and vascular maldistribution characteristic of distributive shock result in global tissue hypoxia or inadequate delivery of oxygen to vital tissues.

The predominant hemodynamic feature of septic shock is **arterial vasodilation**. The potassium-ATP channels are directly activated by lactic acidosis. Potassium efflux from cells results in hyperpolarization, inhibition of calcium influx, and vascular smooth muscle relaxation. The resulting **vasodilation can be refractory to endogenous vasoactive hormones** (eg, norepinephrine and epinephrine) that are released during shock.

Vasodilation to result in hypotension and shock is insufficiently compensated by a **rise in cardiac output**. Early in septic shock, the rise in cardiac output often is limited by hypovolemia and a fall in preload because of low cardiac filling pressures. Even though cardiac output is elevated, the performance of the heart, reflected by stroke work as calculated from stroke volume and blood pressure, usually is depressed. Factors responsible for **myocardial depression** of sepsis are myocardial depressant substances, coronary blood flow abnormalities.

The arterial-mixed venous oxygen difference usually is narrow, and the blood lactate level is elevated. This implies that low global tissue oxygen extraction is the mechanism that may limit total body oxygen uptake in septic shock. This disparity is termed **maldistribution of blood flow**, either between or within organs, with a resultant **defect in capacity to extract oxygen locally.**

The peripheral blood flow abnormalities result from the balance between local regulation of arterial tone and the activity of central

mechanisms (eg, the autonomic nervous system). The regional regulation and the release of vasodilating substances (eg, NO, prostacyclin) and vasoconstricting substances (eg, endothelin) affect regional blood flow.

Increased systemic microvascular permeability also develops, remote from the infectious focus, and contributes to edema of various organs, particularly the lung microcirculation, and to the development of ARDS. The delivery of oxygen is relatively high, but the global oxygen extraction ratio is relatively low. The oxygen uptake increases with a rise in body temperature despite a fall in oxygen extraction. **Maldistribution of blood flow, disturbances in the microcirculation**, and, consequently, **peripheral shunting of oxygen** are responsible for diminished oxygen extraction and uptake, pathologic supply dependency of oxygen, and **lactate acidemia.**

Mechanisms of organ dysfunction

Sepsis is described as an **autodestructive process** that permits the extension of the normal pathophysiologic response to infection (involving otherwise normal tissues), resulting in multiple organ dysfunction syndrome. Organ dysfunction or organ failure may be **the first clinical sign of sepsis**.

MODS is associated with widespread endothelial and parenchymal cell injury:

- **Hypoxic hypoxia** - The septic circulatory lesion disrupts tissue oxygenation, alters the metabolic regulation of tissue oxygen delivery, and contributes to organ dysfunction. Reactive oxygen species, lytic enzymes, vasoactive substances (eg, NO), and endothelial growth factors lead to microcirculatory injury.
- **Direct cytotoxicity** - Endotoxin, TNF-α, and NO may cause damage to mitochondrial electron transport.
- **Apoptosis** (programmed cell death) - The proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils, but other tissues, such as the gut epithelium, may undergo accelerated apoptosis.

- **Immunosuppression** - The interaction between proinflammatory and anti-inflammatory mediators may lead to an imbalance and an inflammatory reaction, or immunodeficiency may predominate, or both may occur.
- **Coagulopathy**.

Cardiovascular dysfunction

Significant **derangement in the autoregulation** of the circulatory system is typical in patients with sepsis. Vasoactive mediators cause **vasodilatation** and increase the **microvascular permeability** at the site of infection. NO plays a central role in the vasodilatation of septic shock.

Changes in both systolic and diastolic ventricular performance occur in patients with sepsis.

Abnormal distribution of systemic blood flow to organ systems; therefore**, core organs may not receive appropriate oxygen delivery.**

The **microcirculation** is the key target organ for injury:

- decrease in the number of functional capillaries,
- intrinsic and extrinsic compression of capillaries and plugging of the capillary lumen by blood cells,
- increased endothelial permeability leads to widespread tissue edema involving protein-rich fluid.

Hypotension is caused by redistribution of intravascular fluid volume resulting from reduced arterial vascular tone, diminished venous return from venous dilation, and release of myocardial depressant substances.

Pulmonary dysfunction

The pathogenesis of sepsis-induced ARDS is a pulmonary manifestation of SIRS. Injury to the **endothelial and epithelial cells** of the lung increases **alveolar capillary permeability**; edema fluid is protein rich.

Injury to **type II pneumocytes** decreases surfactant production; these enhance the surface tension at the air-fluid interfaces, producing diffuse **microatelectasis**. Neutrophil entrapment within the pulmonary microcirculation initiates and amplifies the injury to alveolar capillary

membrane. Migration of macrophages and neutrophils into the interstitium and alveoli produces many different mediators, which contribute to the alveolar and epithelial cell damage. A progressive **respiratory failure** and pulmonary fibrosis develop. 40% of patients with severe sepsis develop ARDS.

Gastrointestinal dysfunction

The GI tract may help to propagate the injury of sepsis. Overgrowth of bacteria in the upper GI tract may aspirate into the lungs and produce nosocomial pneumonia. The gut's normal **barrier function** may be affected, thereby allowing **translocation of bacteria and endotoxin** into the systemic circulation and extending the septic response.

Hepatic dysfunction

The abnormal synthetic functions contribute to both the initiation and progression of sepsis. The monocyte-macrophage system of the liver acts as a first line of defense in **clearing bacteria and their products**; liver dysfunction leads to a spillover of these products into the systemic circulation.

Renal dysfunction

Acute renal failure caused by acute tubular necrosis often accompanies sepsis. The mechanism involves systemic hypotension, direct renal vasoconstriction, release of cytokines (eg, TNF), and activation of neutrophils by endotoxins and other peptides, which contribute to renal injury.

Central nervous system dysfunction

Central nervous system involvement in sepsis produces **encephalopathy and peripheral neuropathy**. The pathogenesis is poorly defined.

CIRCULATORY SHOCK

Shock state

Classification of shock

Hypovolemic, hemorhagic shock

Distributive shock

Cardiogenic shock

Heart failure

Shock State

Shock state, irrespective of the etiology, is described as a syndrome initiated by acute systemic hypoperfusion that leads to tissue hypoxia and vital organ dysfunction. All forms of shock are characterized by **inadequate perfusion to meet the metabolic demands of the tissues**. A maldistribution of blood flow to end organs begets cellular hypoxia and end organ damage, the well-described multisystem organ dysfunction syndrome. The organs of vital importance are the brain, heart, and kidneys.

- A decline in higher cortical function may indicate diminished perfusion of the brain, which leads to an **altered mental status** ranging from confusion and agitation to flaccid coma. The heart plays a central role in propagating shock. Depressed coronary perfusion leads to worsening **cardiac dysfunction** and a cycle of self-perpetuating progression of global hypoperfusion. Renal compensation for reduced perfusion results in diminished glomerular filtration, causing **oliguria** and subsequent renal failure.
- The general appearance of a patient in shock is very dramatic. The **skin** will have a pale, ashen color, usually with diaphoresis. The

patient may appear confused or agitated and may become obtunded.

- The **pulse** first becomes rapid and then becomes dampened as the pulse pressure diminishes. Systolic blood pressure may be in the normal range during compensated shock.
- **Temperature** is at such an extreme that you may have hyperthermia or hypothermia.
- **Blood pressure** may besurprisingly increased in the early stages of shock as heart output increases but declines rapidly as shock progresses. Hypotension is not required to make the diagnosis of shock. Hypotension, however, is common.
- The **central nervous system** is also affected. The earliest findings include a change in personality and may progress to restlessness. In the advanced stages of shock, confusion and ultimately coma may occur.
- **Cardiovascular problems**, including chest pain, may develop in addition to the heart rate and blood pressure changes. With profound acidosis, cardiac dysrhythmias are more prevalent and are potentially fatal.
- **Respiratory rate** increase is seen. This increase compensates as the body attempts to remove excess acids in the form of carbon dioxide. This condition can put a gradually worsening demand on the body and ultimately lead to respiratory distress or failure.
- **Gastrointestinal problems** arise most often from the shunting of blood away from this system. The intestines can stop working and become distended, they can start to die because of a lack of blood flow, or bleeding may occur in the stomach or intestines. These problems show themselves as abdominal pain, nausea, vomiting, or diarrhea. The vomit or stool may appear bloody or have a black/tarry appearance. Any of these features may indicate gastrointestinal bleeding or tissue death in the intestines.

- **Skin** becomes pale, dusky, and clammy. A cyanosis is seen under states of extreme low blood oxygen content.
- **Renal problems** occur as shock progresses to the kidneys. The urinary output declines. In profound shock states, the urine output is nearly none as a result of decreased blood flow to the kidneys.

Classification of Shock

Shock is identified in most patients by hypotension and inadequate organ perfusion, which may be caused by either low cardiac output or low systemic vascular resistance. Circulatory shock can be **subdivided into 4 distinct classes** on the basis of underlying mechanism and characteristic hemodynamics, as follows:

- Hypovolemic shock
- Distributive shock
- Cardiogenic shock
- Obstructive shock

Hypovolemic shock results from the loss of blood volume.

Distributive shock is caused by such conditions as direct **arteriovenous shunting** and is characterized by decreased resistance or increased venous capacity from the vasomotor dysfunction. These patients have high cardiac output, hypotension, large pulse pressure, a low diastolic pressure, and warm extremities with a good capillary refill. These findings on physical examination strongly suggest a working diagnosis of **septic shock**.

Neurogenic shock is manifested by the triad of **hypotension, bradycardia, and hypothermia**. Shock tends to occur more commonly in injuries above T6, secondary to the **disruption of the sympathetic outflow** from T1-L2 and to unopposed vagal tone, leading to decrease in vascular resistance with associated vascular dilatation.

Cardiogenic shock is characterized by **primary myocardial dysfunction**, resulting in the inability of the heart to maintain adequate

cardiac output. These patients demonstrate clinical signs of low cardiac output, while evidence exists of adequate intravascular volume.

Obstructive shock results from **impedance of circulation** by an intrinsic or extrinsic obstruction. Pulmonary embolism and pericardial tamponade both result in obstructive shock. **Clinical features are very similar to cardiogenic shock**. Heart function decrease is not primarily caused by myocardial dysfunction.

Hypovolemic, Hemorrhagic Shock

Hypovolemic shock results from an absolute deficiency of intravascular fluid volume.

Causes of hypovolemic shock

- Intravascular volume loss
    - Gastroenteritis
    - Burns
    - Diabetes insipidus
    - Heat stroke
- Hemorrhage
    - Trauma
    - Major surgery
    - Gastrointestinal bleeding
- Interstitial loss
    - Severe burns
    - Sepsis
    - Nephrotic syndrome
    - Intestinal obstruction
    - Ascites

Physiologically, rapid **loss of intravascular volume reduces ventricular preload**, resulting in decreased stroke volume and cardiac output and thus decreased oxygen delivery. In addition, a hemorrhagic component may reduce hemoglobin content, resulting in decreased oxygen content

(CaO_2). **Hemorrhagic shock reduces both CaO_2 and preload**, resulting in decreased oxygen delivery to the tissues.

Other causes of hypovolemia include **capillary leak and tissue third spacing**, which results in leakage of fluid out of the intravascular space into the interstitial tissues. Etiologies include burns, sepsis, and other systemic inflammatory diseases. Patients with such etiologies may appear "puffy" and **total-body fluid overloaded while actually being significantly intravascularly depleted** with inadequate preload and in significant shock.

Hypovolemic shock refers to a surgical condition in which rapid fluid loss results in multiple organ failure due to inadequate circulating volume and subsequent inadequate perfusion. Most often, hypovolemic shock is secondary to rapid blood loss. Acute **external blood loss secondary to penetrating trauma and severe GI bleeding** disorders are 2 common causes of hemorrhagic shock. Hemorrhagic shock can also result from significant acute internal blood loss into the thoracic and abdominal cavities. Two common causes of rapid internal blood loss are **solid organ injury and rupture of an abdominal aortic aneurysm**. Hypovolemic shock can result from significant fluid (other than blood) loss. Two examples of hypovolemic shock secondary to fluid loss include **refractory gastroenteritis and extensive burns**.

The causes of hemorrhagic shock are traumatic, vascular, gastrointestinal, or pregnancy related.

- **Traumatic causes** can result from penetrating and blunt trauma. Common traumatic injuries that can result in hemorrhagic shock include the following: myocardial laceration and rupture, major vessel laceration, solid abdominal organ injury, pelvic and femoral fractures, and scalp lacerations.
- **Vascular disorders** that can result in significant blood loss include aneurysms, dissections, and arteriovenous malformations.

- **Gastrointestinal disorders** that can result in hemorrhagic shock include the following: bleeding esophageal varices, bleeding peptic ulcers, Mallory-Weiss tears, and aortointestinal fistulas.
- **Pregnancy-related disorders** include ruptured ectopic pregnancy, placenta previa, and abruption of the placenta.

The human body responds to acute hemorrhage by activating the following major physiologic systems: the hematologic, cardiovascular, renal, and neuroendocrine systems. These responses act to systematically divert circulating volume away from nonvital organ systems so that **blood volume may be conserved for vital organ function**.

The hematologic system responds to an acute severe blood loss by **activating the coagulation cascade and contracting the bleeding vessels** (by means of local thromboxane A_2 release). In addition, platelets are activated (also by means of local thromboxane A_2 release) and form an immature clot on the bleeding source. The damaged vessel exposes collagen, which subsequently causes fibrin deposition and stabilization of the clot.

Acute hemorrhage causes a **decreased cardiac output** and decreased pulse pressure. These changes are sensed by baroreceptors in the aortic arch and atrium. With a decrease in the circulating volume, neural reflexes cause an **increased sympathetic outflow** to the heart and other organs. The cardiovascular system initially responds to hypovolemic shock by increasing the heart rate, increasing myocardial contractility, and constricting peripheral blood vessels. The cardiovascular system also responds by redistributing blood to the brain, heart, and kidneys and away from skin, muscle, and gastrointestinal tract.

Concurrently, a **multisystem hormonal response** to acute hemorrhage occurs. Corticotropin-releasing hormone is stimulated directly. This eventually leads to glucocorticoid and beta-endorphin release. Vasopressin from the posterior pituitary is released, causing water retention at the distal tubules, the collecting ducts, and the loop of Henle. Renin is released by the juxtamedullary complex in response to

decreased mean arterial pressure, leading to increased aldosterone levels and eventually to sodium and water resorption and subsequent water conservation. Hyperglycemia commonly is associated with acute hemorrhage. This is due to a glucagon and growth hormone–induced increase in gluconeogenesis and glycogenolysis. Circulating catecholamines relatively inhibit insulin release and activity, leading to increased plasma glucose.

In addition to these global changes, many **organ-specific responses** occur. The brain has remarkable autoregulation that **keeps cerebral blood flow constant** over a wide range of systemic mean arterial blood pressures. The kidneys can tolerate a 90% decrease in total blood flow for short periods of time. With significant decreases in circulatory volume, intestinal blood flow is dramatically reduced by splanchnic vasoconstriction.

Classes of hemorrhage have been defined, based on the percentage of blood volume loss.

- **Class I hemorrhage** (loss of 0-15%)
    - In the absence of complications, only minimal tachycardia is seen.
    - Usually, no changes in BP, pulse pressure, or respiratory rate occur.
    - A delay in capillary refill of longer than 3 seconds corresponds to a volume loss of approximately 10%.
- **Class II hemorrhage** (loss of 15-30%)
    - Clinical symptoms include tachycardia (rate >100 beats per minute), tachypnea, decrease in pulse pressure, cool clammy skin, delayed capillary refill, and slight anxiety.
    - The decrease in pulse pressure is a result of increased catecholamine levels, which causes an increase in peripheral vascular resistance and a subsequent increase in the diastolic BP.
- **Class III hemorrhage** (loss of 30-40%)

    - By this point, patients usually have marked tachypnea and tachycardia, decreased systolic BP, oliguria, and significant changes in mental status, such as confusion or agitation.
- **Class IV hemorrhage** (loss of >40%)
    - Symptoms include the following: marked tachycardia, decreased systolic BP, narrowed pulse pressure (or immeasurable diastolic pressure), markedly decreased (or no) urinary output, depressed mental status (or loss of consciousness), and cold and pale skin.
    - This amount of hemorrhage is immediately life threatening.

Distributive Shock

In certain clinical states, normal peripheral vascular tone becomes inappropriately relaxed. Common causes include anaphylaxis, neurologic injury, sepsis, and drug-related causes. Such vasodilation **increases venous capacitance**, resulting in a relative hypovolemia even if the patient has not actually lost any net fluid. However, the common physiologic disturbance that affects oxygen delivery in all forms of distributive shock is a **decrease in preload** resulting from inadequate effective intravascular volume as a result of massive vasodilation.

Common causes of distributive shock

- Anaphylaxis
    - Medications (eg, antibiotics, vaccines, other drugs)
    - Blood products
    - Envenomation
    - Foods
    - Latex
- Neurologic causes
    - Head injury
    - Spinal shock
- Drugs

- Sepsis (SIRS chapter)

Anaphylaxis results in **mast cell degranulation** with resultant sytemic histamine release and vasodilation.

Neurologic injury can **interrupt sympathetic input to vasomotor neurons**, resulting in vasodilation. Spinal shock may result from cervical cord injuries above T-1, which interrupt the sympathetic chain, allowing for unopposed parasympathetic stimulation. Such patients may present with the clinical picture of hemodynamic instability and hypotension accompanied by **bradycardia** because they may lose sympathetic vascular tone (resulting in vasodilation) while being unable to mount an appropriate sympathetic-mediated tachycardic response.

Drugs may also cause **vasodilation**.

Finally, sepsis results in the release of many vasoactive mediators that may cause **profound vasodilation** resulting in an aspect of distributive shock, along with others.

Cardiogenic Shock

Impairment of cardiac contractility defines cardiogenic shock. A decreased contractile state results in decreased systolic volume and cardiac output and, therefore, in decreased oxygen delivery. Causes include congestive heart failure, ischemic heart disease, cardiomyopathy, cardiac tamponade, sepsis, and drugs.

Cardiac failure with cardiogenic shock continues to be a frustrating clinical problem. Cardiogenic shock is a physiologic state in which inadequate tissue perfusion results from cardiac dysfunction, most commonly following acute myocardial infarction.

Hemodynamic criteria for cardiogenic shock are **sustained hypotension** (systolic blood pressure < 90 mm Hg for at least 30 min) and a reduced cardiac index in the presence of elevated pulmonary capillary pressure.

Heart Failure

Heart failure is the **pathophysiologic state in which the heart, via an abnormality of cardiac function, fails to pump blood at a rate commensurate with the requirements of the metabolizing tissues** or is able to do so only with an elevated diastolic filling pressure.

Heart failure may be caused by myocardial failure but may also occur in the presence of near-normal cardiac function under conditions of high demand. To maintain the pumping function of the heart, compensatory mechanisms increase blood volume, cardiac filling pressure, heart rate, and cardiac muscle mass. However, despite these mechanisms, there is **progressive decline in the ability of the heart to contract and relax**, resulting in worsening heart failure.

Signs and symptoms of heart failure include **tachycardia** and manifestations of **venous congestion** (eg, edema) and **low cardiac output** (eg, fatigue). Breathlessness is a cardinal symptom of left ventricular failure that may manifest with progressively increasing severity.

Compensatory mechanisms exist on every level of organization. Most important among the adaptations are the following:

- The **Frank-Starling mechanism**, in which an increased preload helps to sustain cardiac performance
- **Alterations in myocyte regeneration** and death
- **Myocardial hypertrophy** with or without cardiac chamber dilatation, in which the mass of contractile tissue is augmented
- **Activation of neurohumoral systems**

The release of **norepinephrine** by adrenergic cardiac nerves augments myocardial contractility and includes activation of the **renin-angiotensin-aldosterone** system [RAAS], the sympathetic nervous system [SNS], and

other neurohumoral adjustments that act to maintain arterial pressure and perfusion of vital organs.

The primary myocardial response to chronic increased wall stress is myocyte hypertrophy, death/apoptosis, and regeneration. This process eventually leads to remodeling, usually the eccentric type. **Eccentric remodeling** further worsens the loading conditions on the remaining myocytes and perpetuates the deleterious cycle.

In addition, the activation of the RAAS leads to **salt and water retention**, resulting in increased preload and further increases in myocardial energy expenditure.

In diastolic heart failure (heart failure with normal ejection fraction), the same pathophysiologic processes occur that lead to decreased cardiac output in systolic heart failure. **Altered relaxation and increased stiffness** of the ventricle occur in response to an increase in ventricular pressure overload. The impaired relaxation of the ventricle then leads to impaired diastolic filling of the left ventricle.

TRAUMA

Abdominal blunt trauma

Abdominal penetrating trauma

Abdominal vascular injouries

Splenic injury

Biliary trauma

Blunt chest trauma

Flail chest

Penetrating chest trauma

Hemothorax

Pneumothorax

Diaphragmatic rupture

Pneumomediastinum

Esophageal rupture

Diaphragmatic hernias, acquired

Head trauma

Abdominal Blunt Trauma

Auto-to-auto and auto-to-pedestrian collisions have been cited as causes in 50-75% of cases. Blunt force injuries to the abdomen can generally be explained by 3 mechanisms:

1. **Rapid deceleration** causes differential movement among adjacent structures. As a result, shear forces are created and cause hollow, solid, visceral organs and vascular pedicles to tear, especially at relatively fixed points of attachment. For example, the distal aorta is attached to the thoracic spine and decelerates much more quickly than the relatively mobile aortic arch.

2. **Intra-abdominal contents are crushed between the anterior abdominal wall and the vertebral column or posterior thoracic cage**. This produces a crushing effect, to which solid viscera (eg, spleen, liver, kidneys) are especially vulnerable.
3. **External compression forces** that result in a sudden and dramatic rise in intra-abdominal pressure and culminate in rupture of a hollow viscous organ.

Penetrating Abdominal Trauma

It could be caused by a **missile** propelled by combustion of powder. It implies high-energy transfer and unpredictability of the extent of intra-abdominal injuries. Not only is the missile track unpredictable, but also, **secondary missiles** such as bone fragments or fragments of the bullet are capable of inflicting additional injuries.

Stab wounds are caused by a **sharp object** penetrating the abdominal wall.

Abdominal Vascular Injouries

In blunt trauma, **rapid deceleration** results in an avulsion of the small branches of major vessels (eg, mesenteric tear). Another mechanism of injury is related to a **direct crush or blow** to the major vessels, resulting in an intimal tear or vessel rupture.

Penetrating injuries **directly disrupt** the vessel wall. Hemorrhagic shock often occurrs. This self-perpetuating cycle is responsible for deaths in patients with major vascular injury.

Splenic Injury

Though normally protected by its anatomic position, preexisting illness or disease can markedly increase the risks and severity of splenic injury.

Infectious mononucleosis, malaria, and hematologic abnormalities can lead to **acute or chronic enlargement** of the spleen. This is often accompanied by a thinning of the capsule, **making the spleen more fragile** as well as engendering a greater mass effect in decelerating trauma.

With **free intraperitoneal blood**, diffuse abdominal pain and rebound are more likely. If the intra-abdominal bleeding exceeds 5-10% of blood volume, clinical signs of early shock may manifest. With increasing blood loss into the abdominal cavity, abdominal distension, peritoneal signs, and overt shock may be observed.

Biliary Trauma

Isolated injury to the extrahepatic biliary tract and gallbladder may occur from a **thoracoabdominal injury** or an **iatrogenic trauma**. Typically, a mechanism of crushing or shear injury to the right upper quadrant causes biliary disruption leading to bile peritonitis. The retroduodenal region of the superior portion of the pancreas is the most common site of biliary transection following blunt trauma.

Hypovolemic shock can occur from intense chemical peritonitis. This can be followed by **septic shock** from bacterial overgrowth within a period of hours to days.

Jaundice is usually observed 3-5 days after injury, along with the passage of clay-colored stools and dark-colored urine.

Blunt Chest Trauma

Blunt injury to the chest **can affect any one or all components of the chest wall and thoracic cavity**. These components include the bony skeleton, lungs and pleurae, tracheobronchial tree, esophagus, heart, great vessels of the chest, and the diaphragm. The most important cause

of significant blunt chest trauma is motor vehicle accidents. Blast injuries can also result in significant blunt thoracic trauma.

The major pathophysiologies encountered in blunt chest trauma involve derangements **in the flow of air, blood, or both in combination**. **Sepsis** due to leakage of alimentary tract contents, as in esophageal perforations, also must be considered.

Blunt trauma commonly results in chest wall injuries (eg, rib fractures). The pain associated with these injuries can make breathing difficult, and this may **compromise ventilation**. Direct lung injuries, such as pulmonary contusions, are frequently associated with major chest trauma and may impair ventilation by a similar mechanism.

Shunting and dead space ventilation produced by these injuries can also **impair oxygenation**.

At the molecular level, a **mediator-driven inflammatory process** further leading to respiratory insult after chest trauma. Following blunt chest trauma, several blood-borne mediators are released, including interleukin-6, tumor necrosis factor, and prostanoids. These mediators are thought to induce secondary cardiopulmonary changes. Blunt trauma that causes significant cardiac injuries or severe great vessel injuries (eg, thoracic aortic disruption) frequently results in death before adequate treatment can be instituted. This is due to immediate and devastating exsanguination or loss of cardiac pump function. This causes hypovolemic or cardiogenic shock and death.

Flail Chest (Blunt Chest Trauma)

Flail chest is the paradoxical movement of a segment of chest wall caused by **fractures of 3 or more ribs** anteriorly and posteriorly within each rib. Mechanically, flail chest generally requires a significant force diffused over a large area (ie, the thorax) to create multiple anterior and posterior rib fractures.

The actual motion of the flail segment is usually limited by the surrounding structural components, the intercostals, and the surrounding musculature. This mechanical limitation of motion affects the actual size of the changes in thoracic volume and patient-generated tidal volume.

Respiratory insufficiency in flail chest is much more likely to be a result of the underlying severity of pulmonary contusion and ventilation perfusion mismatch than the actual structural defect to the chest wall.

Flail chest is a clinical anatomic diagnosis noted in blunt trauma patients with paradoxical or reverse motion of a chest wall segment while spontaneously breathing. This clinical finding disappears after intubation with positive pressure ventilation, which occasionally results in a delayed diagnosis of the condition.

Patients may demonstrate only the paradoxical chest wall motion, and they may have minimal-to-incapacitating respiratory insufficiency, although they usually show some **tachypnea** with a notable decrease in resting tidal volume due to fracture pain.

Penetrating Chest Trauma

Penetrating chest trauma comprises a **broad spectrum of injuries**: the most important are hemothorax, pneumothorax, diaphragmatic rupture, and pneumomediastinum.

Hemothorax

Hemothorax refers to a **collection of blood within the pleural cavity**. Although the most common etiology of hemothorax is blunt or penetrating trauma, it can also result from a number of nontraumatic causes or can occur spontaneously.

Bleeding into the pleural space can occur with virtually any disruption of the tissues of the chest wall and pleura or the intrathoracic structures. The physiologic response to the development of a hemothorax is

manifested in 2 major areas: hemodynamic and respiratory. The degree of hemodynamic response is determined by the amount and rapidity of blood loss.

Hemodynamic response

Hemodynamic changes vary **depending on the amount of bleeding and the rapidity of blood loss**. Blood loss of up to 750 ml in a 70-kg man should cause **no significant hemodynamic change**. Loss of 750-1500 ml in the same individual will cause the **early symptoms of shock**. Significant signs of **shock with signs of poor perfusion** occur with loss of blood volume of 30% or more (1500-2000 ml). Because the pleural cavity of a 70-kg man can hold 4 or more liters of blood, **exsanguinating hemorrhage** can occur without external evidence of blood loss.

Respiratory response

The space-occupying effect of a large accumulation of blood within the pleural space may **hamper normal respiratory movement**. In trauma cases, abnormalities of ventilation and oxygenation may result, especially if associated with injuries to the chest wall.

In some cases of nontraumatic origin, especially those associated with pneumothorax and a limited amount of bleeding, respiratory symptoms may predominate. A large enough collection causes the patient to complain of **dyspnea** and may produce the clinical finding of **tachypnea**. Dyspnea is a common symptom in cases in which hemothorax develops in an insidious manner, such as those secondary to metastatic disease. Blood loss in such cases is not acute as to produce a visible hemodynamic response, and dyspnea is often the predominant complaint.

Physiologic resolution of hemothorax

Blood that enters the pleural cavity is exposed to the motion of the diaphragm, lungs, and other intrathoracic structures. This results in some degree of **defibrination of the blood** so that incomplete clotting occurs. Within several hours of cessation of bleeding, lysis of existing clots by pleural enzymes begins. **Lysis of red blood cells** results in a marked increase in the protein concentration of the pleural fluid and an increase

in the osmotic pressure within the pleural cavity. This **elevated intrapleural osmotic pressure** favors transudation of fluid into the pleural space. In this way, a small and **asymptomatic hemothorax can progress into a large and symptomatic bloody pleural effusion**.

Late physiologic sequelae of unresolved hemothorax

Two pathologic states are associated with the later stages of hemothorax. These include empyema and fibrothorax. **Empyema** results from bacterial contamination of the retained hemothorax. If undetected or improperly treated, this can lead to **bacteremia and septic shock**. **Fibrothorax** results when fibrin deposition develops in an organized hemothorax and coats both the parietal and visceral pleural surfaces, trapping the lung. The **lung is fixed** in position by this adhesive process and is unable to fully expand. **Persistent atelectasis** of portions of the lung and reduced pulmonary function result from this process.

Pneumothorax

Pneumothorax is defined as the presence of air or gas in the pleural cavity. The result is **collapse of the lung** on the affected side. Air can enter the intrapleural space through a communication from the chest wall (ie, trauma) or through the lung parenchyma across the visceral pleura.

Primary spontaneous pneumothorax occurs in people **without underlying lung disease** and in the absence of an inciting event. However, many patients have subclinical lung disease.

Secondary spontaneous pneumothorax occurs in people with a wide variety of parenchymal lung diseases. Air enters the pleural space via **distended, damaged, or compromised alveoli**.

Iatrogenic pneumothorax is a type of traumatic pneumothorax that results from incursion into the pleural space secondary to diagnostic or therapeutic medical intervention.

Traumatic pneumothorax results from injury, typically blunt or penetrating trauma that disrupts the parietal or visceral pleura.

Spontaneous pneumothorax

Spontaneous pneumothoraces in most patients occur from the **rupture of bullae**. Primary spontaneous pneumothorax is typically observed in tall, young people without parenchymal lung disease and is thought to be related to increased shear forces in the apex.

The pleural space has a negative pressure, with the chest wall tending to spring outward and the lung's elastic recoil tending to collapse. If the pleural space is invaded by gas from a ruptured bullae, the lung collapses until equilibrium is achieved or the rupture is sealed. As the pneumothorax enlarges, the lung becomes smaller. The main physiologic consequence of this process is a **decrease in vital capacity and partial pressure of oxygen**.

Lung inflammation and oxidative stress are hypothesized to be important to the pathogenesis of primary spontaneous pneumothorax. Current smokers have increased numbers of inflammatory cells in the small airways with the extent of **emphysematous like changes**. These changes result from degradation of lung tissue due to imbalances of enzymes and antioxidants released by innate immune cells. There is a growing body of evidence that indicates **genetic factors** may be important in the pathogenesis of many cases of primary spontaneous pneumothorax.

Tension pneumothorax

Tension pneumothorax occurs anytime a **disruption involves the visceral pleura, parietal pleura, or the tracheobronchial tree**. This condition develops when injured tissue forms a **1-way valve**, allowing air inflow into the pleural space and prohibiting air outflow. The volume of this nonabsorbable intrapleural air increases with each inspiration because of the 1-way valve effect.

As the pressure increases, the **ipsilateral lung collapses** and causes hypoxia. Further pressure build-up causes the **mediastinum to shift**

toward the contralateral side and impinge on and **compress both the contralateral lung and the vasculature entering the right atrium** of the heart. Hypoxia results as the collapsed lung on the affected side and the compressed lung on the contralateral side compromise effective gas exchange. This **hypoxia and decreased venous return** caused by compression of the relatively thin walls of the atria impair cardiac function. The **inferior vena cava** is thought to be the first to kink and restrict blood flow back to the heart.

Arising from numerous causes, this condition rapidly progresses to **respiratory insufficiency, cardiovascular collapse**, and, ultimately, death if unrecognized and untreated. Cardiovascular collapse develops from a combination of mechanical and hypoxic effects. The mechanical effects manifest as kinking or compression of the superior and inferior vena cava, because the mediastinum deviates and the intrathoracic pressure increases. Hypoxia leads to **increased pulmonary vascular resistance** via vasoconstriction. In either event, decreasing cardiac output and worsening metabolic acidosis secondary to decreased oxygen delivery to the periphery occur, thus inducing anaerobic metabolism. If the underlying problem remains untreated, the hypoxemia, metabolic acidosis, and decreased cardiac output lead to **cardiac arrest** and death.

Diaphragmatic Rupture

Diaphragmatic injuries are relatively rare and result from either blunt trauma or penetrating trauma. Presently, 80-90% of blunt diaphragmatic ruptures result from motor vehicle crashes. The mechanism of rupture is related to the **pressure gradient between the pleural and peritoneal cavities**. Lateral impact cause a rupture, since it can distort the chest wall and shear the ipsilateral diaphragm. Frontal impact can cause an increase in intra-abdominal pressure, which results in long radial tears in the posterolateral aspect of the diaphragm, its embryologic weak point.

Blunt trauma typically produces large radial tears measuring 5-15 cm, most often at the posterolateral aspect of the diaphragm.

Penetrating injuries to the chest or abdomen also may injure the diaphragm. This occurs most often from gunshot wounds but can result from knife wounds.

Pneumomediastinum

With pneumomediastinum, excessive intra-alveolar pressures lead to **rupture of perivascular alveoli**. Air escapes into the surrounding connective tissue and dissects into the mediastinum. **Esophageal trauma** or elevated pressures may also allow air to dissect into the mediastinum. Air may then travel superiorly into the visceral, retropharyngeal, and subcutaneous spaces of the neck. From the neck, the subcutaneous compartment is continuous throughout the body; thus, **air can diffuse widely**. Mediastinal air can also pass inferiorly into the retroperitoneum and other extraperitoneal compartments. If the mediastinal pressure rises abruptly or if decompression is not sufficient, the mediastinal parietal pleura may rupture and cause a **pneumothorax**.

Esophageal Rupture

Spontaneous esophageal rupture is known as Boerhaave syndrome. As technology improved, instrumental perforation became more common.

The esophagus lacks a serosal layer and is, therefore, more vulnerable to rupture or perforation. Once a perforation occurs, retained gastric contents, saliva, bile, and other substances may enter the mediastinum, resulting in **mediastinitis**.

The degree of mediastinal contamination and the location of the tear determine the clinical presentation. Within a few hours, a polymicrobial invasion of bacteria supervenes, which can lead to **sepsis**. The mediastinal pleura often ruptures, and gastric fluid is drawn into the

pleural space by the negative intrathoracic pressure. Even if the mediastinal pleura is not violated, a **pleural effusion** often occurs.

Diaphragmatic Hernias, Acquired

Acquired diaphragmatic hernias stem from all types of trauma, with blunt forces accounting for the majority.

The pathophysiology of acquired diaphragmatic hernias includes **circulatory and respiratory depression** secondary to decreased function of the diaphragm, intrathoracic abdominal contents leading to compression of the lungs, shifting of the mediastinum, and cardiac compromise. Smaller diaphragmatic hernias are often not found until months or years later, when patients present with strangulation of intra-abdominal organs, dyspnea, or nonspecific gastrointestinal complaints.

Head Trauma

The brain has several features that distinguish it from other organ systems. The most important of these differences is that the **brain is contained within the skull**, a rigid and inelastic container. Because the brain is housed within this inelastic container, only small increases in volume within the intracranial compartment can be tolerated before pressure within the compartment rises dramatically.

In the typical adult, the intracranial volume is approximately 1500 ml, of which the brain accounts for 85-90%, intravascular cerebral blood volume accounts for 10%, and cerebrospinal fluid accounts for the remainder (<3%). When a significant head injury occurs, **cerebral edema** often develops, which increases the relative volume of the brain. Because the intracranial volume is fixed, the **pressure within this compartment rises** unless some compensatory action occurs, such as a decrease in the volume of one of the other intracranial components. The brain has very limited compliance and cannot tolerate significant increases in volume

that can result from diffuse cerebral edema or from significant mass lesions such as a hematoma.

Cerebral perfusion pressure is defined as the difference between the mean arterial pressure and the intracranial pressure. Cerebral perfusion pressure is the net pressure of blood delivery to the brain. In the noninjured brain in individuals without long-standing hypertension, cerebral blood flow is constant in the range of mean arterial pressures of 50-150 mm Hg. This is due to **autoregulation** by the arterioles, which will constrict or dilate within a specific range of blood pressure to maintain a constant amount of blood flow to the brain. When the mean arterial pressure is less than 50 mm Hg or greater than 150 mm Hg, the arterioles are unable to autoregulate and blood flow becomes entirely dependent on the blood pressure.

When the mean arterial pressure falls below 50 mm Hg, the brain is at **risk of ischemia** due to insufficient blood flow, while a mean arterial pressure greater than 160 mm Hg causes excess cerebral blood flow that may result in **increased intracranial pressure**. Autoregulation is impaired in the injured brain. As a result, increased flow occurs within and around injured areas and, perhaps, globally in the injured brain.

Traumatic brain injury may be divided into 2 categories, primary brain injury and secondary brain injury. **Primary brain injury** is defined as the initial injury to the brain as a direct result of the trauma. This is the initial **structural injury** caused by the impact on the brain, and, like other forms of neural injury, patients recover poorly. **Secondary brain injury** is defined as any subsequent injury to the brain after the initial insult. Secondary brain injury can result **from systemic hypotension, hypoxia, elevated intracranial pressure**, or as the biochemical result of a series of physiologic changes initiated by the original trauma.

Elevated intracranial pressure may result from the initial brain trauma or from secondary injury to the brain. Elevations are deleterious because they can result in decreased cerebral perfusion pressure and **decreased cerebral blood flow**, which, if severe enough, may result in

cerebral ischemia. In addition to creating a significant risk for ischemia, uncontrolled intracranial pressure may cause herniation. **Herniation** involves the movement of the brain across fixed dural structures, resulting in irreversible and often fatal cerebral injury.

The brain essentially floats within the cerebrospinal fluid; as a result, the brain can undergo significant translation and deformation when the head is subjected to significant forces. In a **deceleration injury**, the skull stops moving almost instantly. However, the brain continues to move. This results in significant forces acting on the brain as it undergoes both translation and deformation.

The forces that result from either deceleration or acceleration of the brain can cause injury by direct mechanical effects on the various cellular components of the brain or by shear-type forces on axons. In addition to the translational forces, the brain can experience significant **rotational forces**, which can also lead to shear injuries.

The intracranial compartment is divided into 3 compartments by 2 major dural structures, the falx cerebri and the tentorium cerebelli. The **tentorium cerebelli** divides the posterior fossa or **infratentorial compartment** (the cerebellum and the brainstem) from the **supratentorial compartment** (cerebral hemispheres). The **falx cerebri** divides the supratentorial compartment into 2 halves and separates the left and right hemispheres of the brain. Both the falx and the tentorium have central openings and prominent edges at the borders of each of these openings. When a significant increase in intracranial pressure occurs, caused by either a large mass lesion or significant cerebral edema, the brain can slide through these openings, a phenomenon known as herniation.

Transtentorial herniation occurs when the medial aspect of the *temporal lobe* (uncus) migrates across the free edge of the tentorium. This causes pressure on the *third cranial nerve*, interrupting parasympathetic input to the eye and resulting in a **dilated pupil**. In

addition to pressure on the third cranial nerve, transtentorial herniation **compresses the brainstem**.

Subfalcine herniation occurs when the cingulate gyrus on the medial aspect of the *frontal lobe* is displaced across the midline under the free edge of the falx. This may compromise the blood flow through the anterior cerebral artery complexes.

Central herniation occurs when a diffuse increase in intracranial pressure occurs and each of the cerebral hemispheres is displaced through the tentorium, resulting in significant pressure on the upper *brainstem*.

Upward, or ***cerebellar herniation*** occurs when either a large mass or increased pressure in the posterior fossa is present and the *cerebellum* is displaced in an upward direction through the tentorial opening. This also causes significant *upper brainstem* compression.

Tonsillar herniation occurs when increased pressure develops in the posterior fossa. In this form of herniation, the *cerebellar tonsils* are displaced in a downward direction through the foramen magnum, causing compression on the *lower brainstem* and *upper cervical spinal* cord as they pass through the foramen magnum.

WOUND HEALING

Biology of wound healing

Categories of wound healing

Common chronic wounds

Hypertrophic scar, keloids

Biology of Wound Healing

With the wounding of healthy tissue, a predictable progression of physiologic events unfolds. This progression can be divided into the phases of inflammation, proliferation, and maturation

The inflammatory phase

The inflammatory phase simultaneously launches **hemostatic mechanisms and pathways** that create the clinically recognizable cardinal signs of inflammation: *rubor* (redness), *calor* (warmth), *tumor* (swelling), *dolor* (pain), and *functio laesa* (loss of function).

Injury to vascular tissue initiates the **extrinsic coagulation cascade** by releasing intracellular calcium and tissue factor that activate factor VII. The resulting **fibrin plug** achieves hemostasis aided by reflex vasoconstriction. This plug acts as a lattice for the aggregation of platelets, the most common and "signature" cell type of the early inflammatory phase.

Platelets elaborate a number of proinflammatory substances. Growth factors act on surrounding cells and stimulate **chemotaxis of neutrophils, monocytes, and fibroblasts** to the area of injury. Injured tissues catalyze arachidonic acids to produce vasoactive prostaglandins and thromboxane. **Eicosanoids** mediate activity influencing platelet plug formation, vascular permeability, and cellular chemotaxis to influence

wound healing. After initial vasoconstriction, the classic signs of inflammation manifest from **increased vascular permeability**. Rubor results from **vasodilation**. Tumor and calor develop as vascular endothelial gaps enlarge, allowing the egress of plasma protein and fluid into the interstitial space. These changes allow the ingress of inflammatory cells into the area of injury. Dolor is sensed as eicosanoids act on peripheral nociceptors.

In the second stage of the inflammatory phase, **leukocytes** supplant platelets. White blood cells are the predominant cells for the first 3 days after wounding. **Polymorphonucleocytes** are the first to begin bactericidal activities using inflammatory mediators and oxygen free radical metabolites. Another leukocyte, the **helper T cell**, elaborates interleukin-2 to promote further T cell proliferation to augment the immunogenic response to injury.

As polymorphonuclear leukocytes begin to wane after 24-36 hours, circulating monocytes enter the wound and mature into tissue **macrophages**. These cells debride the wound and produce a wide variety of important substances, such as IL-1 and basic fibroblast growth factor. IL-1 promotes **angiogenesis** through endothelial cell replication.

Toward the end of the inflammatory cycle eicosanoids in the wound interact with the cell types present, resulting in fibroblast synthesis of **collagen** and ground substance. Macrophage-derived growth factors strongly influence the influx of fibroblasts and then keratinocytes and endothelial cells into the wound. As mononuclear cells continue to replace leukocytes and macrophages, the proliferative phase begins.

The proliferative phase

Two to three days after wounding, **fibroblasts** migrate inward from wound margins over the fibrinous matrix established during the inflammatory phase. During the first week, fibroblasts begin producing glycosaminoglycans and proteoglycans, the ground substance for **granulation tissue**, as well as collagen. Fibroblasts become the dominant cell type, peaking at 1-2 weeks. **Collagen** is the major component of acute

wound connective tissue, with net production continuing for the next 6 weeks.

Endothelial expansion contributes to angiogenesis, as intact vessels generate buds in granulation tissue. Neovascularization facilitates growth of the advancing line of fibroblasts into the wound. Degradation of the fibrin clot and provisional matrix is accompanied by the deposition of granulation tissue (ground substance, collagen, capillaries). Decreasing hyaluronic acid (in ground substance) levels and increasing chondroitin sulfate levels slow fibroblast migration and proliferation while inducing fibroblast differentiation, transitioning to the maturation phase of wound healing.

The maturation phase

For the first 6 weeks, new **collagen** production dominates the wound healing process. As the wound matures, collagen is remodeled into a more organized structure with increased tensile strength. Gradually, type I collagen replaces type III until the normal skin ratio of 4:1 is achieved. Superficial to this activity, **epithelial cells** continue to migrate inward from the wound edge until the defect is covered. At this point, contact inhibition induces transformation of fibroblasts into **myofibroblasts**, which contain contractile actin fibers. Wound contraction follows, replacing injured tissue volume with new tissue.

Deterrents to wound healing

Various physiologic and mechanical factors may impair the healing response, resulting in a chronic wound. Local infection, hypoxia, trauma, or systemic problems such as diabetes mellitus, malnutrition, immunodeficiency, or medications are most frequently responsible.

All wounds are contaminated, but most successfully resist invasive infection. High concentration of microorganisms or the immune system becomes compromised, infection frequently ensues. **Cellulitis** prolongs the inflammatory phase by maintaining high levels of proinflammatory cytokines and tissue proteases, which degrade granulation tissue and tissue growth factors, and by delaying collagen deposition.

Debridement removes **devitalized tissue**, which can be a source of endotoxins that inhibit fibroblast migration into the wound. **Foreign bodies** may also require removal, as the presence of a silk suture reduces the number of bacteria required to incite infection 10,000-fold.

Cellular **hypoxia** retards wound healing through various means. Collagen fibril crosslinking requires oxygen to hydroxylate proline and lysine and fails when tissue pressure is below 40 mm Hg. The bactericidal potency of leukocyte oxidative phosphorylation also suffers in a hypoxic environment.

Glycosylation in diabetes mellitus impairs neutrophil and macrophage phagocytosis of bacteria, prolonging the inflammatory phase. The proliferative phase is also protracted in the same disease as **erythrocytes become less pliable** and less able to deliver oxygen to the wound.

Malnutrition results in diminished fibroblast proliferation, impaired neovascularization, and decreased cellular and humoral immunity. Amino acids such as methionine, proline, glycine, and lysine, are essential for normal cell function and the repair of cutaneous wounds. Fatty acids are critical constituents of cell membranes and are the substrate for the eicosanoids that mediate the inflammatory process**.**

Adequate vitamins and minerals must be available for cell metabolism, acting as cellular signals and cofactors. **Vitamin C and iron** are required for the hydroxylation of lysine and proline, which crosslink and stabilize the triple helix structure of collagen. **Vitamin A** plays an important role in modulating collagen production and degradation and is particularly important in epithelialization. A potent antioxidant, **vitamin E** appears to accelerate dermal and bone healing.

Categories of Wound Healing

Primary healing, delayed primary healing, and healing by secondary intention are the 3 main categories of wound healing. A fourth category is healing that transpires with wounds that are only partial skin thickness.

Primary wound healing

Healing by first intention occurs within hours of repairing a full-thickness surgical incision. This surgical insult results in the mortality of a minimal number of cellular constituents.

Delayed primary healing

If the **wound edges** are not reapproximated immediately. This type of healing may be desired in the case of **contaminated wounds**. By the fourth day, phagocytosis of contaminated tissues is well underway, and the processes of epithelization, collagen deposition, and maturation are occurring. Foreign materials are walled off by macrophages that may metamorphose into epithelioid cells, which are encircled by mononuclear leukocytes, forming **granulomas**. Usually the wound is closed surgically at this juncture, and if the "cleansing" of the wound is incomplete, chronic inflammation can ensue, resulting in **prominent scarring**.

Healing by secondary intention

Results in an **inflammatory response that is more intense** than with primary wound healing. In addition, a **larger quantity of granulomatous tissue** is fabricated because of the need for wound closure. Secondary healing results in pronounced contraction of wounds. Fibroblastic differentiation into myofibroblasts, which resemble contractile smooth muscle, is believed to contribute to wound contraction. These myofibroblasts are maximally present in the wound from the 10th-21st days.

Common Chronic Wounds

Common chronic skin and soft tissue wounds include the diabetic foot ulcer, the pressure ulcer, and the venous stasis ulcer.

Diabetic foot ulcer

Pathogenesis is due to **neuropathic impairment** of musculoskeletal balance as well as **immune compromise** from leukocyte dysfunction and **peripheral vascular disease**, complicating these wounds with infection. Chronic wounds have decreased levels of growth factors, and topical platelet-derived growth factor. Platelet-derived wound healing factor have been demonstrated to speed the healing of diabetic ulcers.

Pressure ulcer

Result from **ischemia** due to prolonged pressure over a bony prominence. They typically occur in paralyzed or unconscious patients who unable to either sense or respond to the need for periodic repositioning.

Venous stasis ulcer

Venous stasis ulcers result from hypoxia in areas of **venous congestion** in the lower extremity. Possibly, the thick perivascular fibrin cuffs impede oxygen diffusion into surrounding tissues. Alternately, macromolecules leaking into perivascular tissue may **trap growth factors** needed for the maintenance of skin integrity. A third potential cause may be leukocytes migrating through capillaries more slowly than usual, even occluding them, becoming activated, and **damaging the vascular endothelium**.

Hypertrophic Scar, Keloids

A keloid is an abnormal proliferation of scar tissue that forms at the site of cutaneous injury. Keloids should not be confused with hypertrophic scars, which are raised scars that do not grow beyond the boundaries of the original wound and may reduce over time.

The most important risk factor for the development of abnormal scars such as keloids is a **wound healing by secondary intention**, especially if healing time is greater than 3 weeks.

Keloids are **dermal fibrotic lesions** that are a variation of the normal wound healing process. They usually occur during the **healing of a deep skin wound**. Hypertrophic scars and keloids are both included in the

spectrum of fibroproliferative disorders. These abnormal scars result from the **loss of the control mechanisms that normally regulate the fine balance of tissue repair and regeneration**.

The excessive proliferation of normal tissue healing processes results in both hypertrophic scars and keloids. The production of extracellular matrix proteins, collagen, elastin, and proteoglycans presumably is due to a **prolonged inflammatory process** in the wound.

Keloid formation can occur within a year after injury. The most frequently involved sites of keloids are areas of the body that are constantly subjected to **high skin tension**. Wounds on the anterior chest, shoulders, flexor surfaces of the extremities (eg, deltoid region), and anterior neck are more susceptible to abnormal scar formation.

After the initial insult to the skin and the formation of a wound clot, the balance between granulation tissue degradation and biosynthesis becomes essential to adequate healing. Keloids have an **increased blood vessel density, higher mesenchymal cell density, a thickened epidermal layer, and increased mucinous ground substance**. The alpha–smooth muscle actin fibroblasts, myofibroblasts important for contractile situations, are few.

Collagenase activity, ie, prolyl hydroxylase, has been found to be 14 times greater in keloids than in both hypertrophic scars and normal scars. Collagen synthesis in keloids is 3 times greater than in hypertrophic scars and 20 times greater than in normal scars. Collagen cross-linking is greater in normal scars, while keloids have immature cross-links that do not form normal scar stability.

Immunohistochemical studies of keloids demonstrate an amplified production of tumor necrosis factor **(TNF)–alpha**, interferon **(INF)–beta**, and **interleukin-6**. The concentration of immunoglobulin G in the keloids is elevated when compared to hypertrophic and normal scar tissue.

The difference between a keloid and a hypertrophied scar is that a keloid continues to enlarge beyond the original size and shape of the wound, while a hypertrophied scar enlarges within the confines of the

original wound. Although both can be red and raised, **keloids continue to grow and hypertrophied scars tend to regress over time**. Both can recur after surgical excision; however, the recurrence of keloid scars is more common.

Normal wound healing requires a balance of catabolic and anabolic activities. Although multiple factors are involved in abnormal scar formation, keloid and hypertrophied scars result from **increased collagen production (anabolic) and decreased collagen degradation (catabolic)**.

GASTROINTESTINAL TRACT

Esophagitis

- Gastroesophageal reflux disease
- Barrett esophagus

Esophageal motility disorders

- Achalasia
- Esophageal spasm
- Scleroderma esophagus

Esophageal strictures

Esophageal diverticula

Mallory-Weiss syndrome

Gastric ulcer desease

- Zollinger-Ellison syndrome

Gastroparesis

Dumping syndrome

Pyloric obstruction

Bacterial overgrowth syndrome

Appendicitis

- Mesentheric lymphadenitis

Crohn disease

Ulcerative colitis

Hirschsprung´s disease

Malabsorption

Ileus

Small bowel obstruction

Colonic obstruction

Intestinal volvulus

Intussusception

Abdominal hernias

Intestinal perforation

- Peritonitis and abdominal sepsis
- Abdominal abscess

Lower gastrointestinal bleeding

Diverticulosis

- Diverticulitis
- Meckel diverticulum

Constipation

Hemorrhoids

Anal fissure

Fistula-in-ano

Perianal abscess

Rectal prolaps

Gastrojejunostomy

Esophagitis

The most common cause of esophagitis is gastroesophageal reflux disease. Other important, but less common, types of esophagitis include infectious esophagitis, radiation esophagitis, and esophagitis from direct erosive effects of ingested medication or corrosive agents. Other causes of esophagitis include systemic disease and trauma.

Reflux esophagitis

Reflux esophagitis develops when gastric contents are passively regurgitated into the esophagus. Reflux happens commonly; in most cases, it does not cause major harm, because natural peristalsis of the esophagus clears the refluxate back to the stomach. In other cases, where acid **reflux from the stomach is persistent**, the result is damage to the esophagus, causing symptoms and macroscopic changes. **Gastric acid,**

pepsin, and bile irritate the squamous epithelium, leading to inflammation, erosion, and ulceration of the esophageal mucosa.

Infectious esophagitis

Infectious esophagitis is most commonly observed in **immunosuppressed hosts**. A wide range of abnormalities in host defense may predispose an individual to opportunistic infections, such as neutropenia, impaired chemotaxis and phagocytosis, alteration in humoral immunity, and impaired T-cell lymphocyte function.

Patients with **systemic diseases** (eg, diabetes mellitus, adrenal dysfunction, alcoholism) can be predisposed to infectious esophagitis because of altered immune function. Steroids, cytotoxic agents, and antibiotics that suppress the normal bacterial flora may contribute to the invasive ability of commensal organisms.

Fungal overgrowth typically occurs in the setting of esophageal stasis resulting from **abnormal esophageal motility.**

Radiation and chemoradiation esophagitis

Radiation therapy over 30 Gy to the mediastinum typically causes retrosternal burning and painful swallowing, which is usually mild and limited to the duration of therapy.

Gastroesophageal Reflux Disease

Gastroesophageal reflux is a normal physiologic phenomenon experienced intermittently by most people, particularly after a meal. Gastroesophageal reflux disease (GERD) occurs when **the amount of gastric juice that refluxes into the esophagus exceeds the normal limit**, causing symptoms with or without associated esophageal mucosal injury (ie, esophagitis).

Typical symptoms include **heartburn, regurgitation, and dysphagia**. Atypical symptoms include **noncardiac chest pain, asthma, pneumonia, hoarseness, nighttime coughing and aspiration**.

The esophagus, lower esophageal sphincter, and stomach can be envisioned as a simple plumbing circuit. The esophagus functions as an antegrade pump, the lower esophageal sphincter as a valve, and the stomach as a reservoir. The abnormalities that contribute to GERD can stem from any component of the system. Poor esophageal motility **decreases clearance** of acidic material. A **dysfunctional lower esophageal sphincter** allows reflux of large amounts of gastric juice. **Delayed gastric emptying** can increase volume and pressure in the reservoir until the valve mechanism is defeated.

Esophageal defense mechanisms

Esophageal defense mechanisms against the noxious substances in the refluxate include an **antireflux barrier**, **an efficient clearing mechanism**, and **epithelial defense factors**. The antireflux barrier is a high-pressure zone at the esophageal gastric junction that is generated by tonic contraction of the lower esophageal sphincter coupled with extrinsic compression by the right crus of the diaphragm.

This system is imperfect due to the existence of physiologic transient lower esophageal sphincter relaxations. Transient lower esophageal **sphincter relaxations** occur primarily after meals but in the absence of a preceding swallow. About 95% of reflux episodes in healthy controls occur during the transient lower esophageal sphincter relaxations. Most reflux in patients with GERD occurs via this same mechanism. **The duration of esophageal acidification, and not the frequency, correlates best with presence of erosive esophagitis**.

A healthy individual clears the esophagus through various means, including gravity, bicarbonate secretion from the salivary and esophageal glands, and peristalsis. **Dysfunctional esophageal motility with failed or weak peristalsis** is a contributing factor in GERD.

An acid (pH < 4) contact time of 1-2 hours per day is considered normal in the distal esophagus. This physiologic reflux occurs in completely asymptomatic individuals. The esophagus, therefore, must have additional local means of protection. The esophagus is composed of

a thick epithelial layer, with cells joined by tight junctions with lipid-rich intercellular spaces. This arrangement resists the diffusion of noxious substances by limiting entry of H^+ into both cells and intercellular spaces. In addition, scattered submucosal glands in the distal esophagus that secrete bicarbonate and have an adequate blood supply to deliver bicarbonate and remove H^+ help to maintain tissue acid-base balance.

The aggressors in the GERD battle reside in the refluxate. Lower pH of the refluxate and extended contact with the esophagus increases the time required for intraesophageal pH to return to normal and increases the risk for mucosal injury.

Dysfunction of the lower esophageal sphincter

The lower esophageal sphincter (LES) is defined by manometry as a zone of elevated intraluminal pressure at the esophagogastric junction. For proper LES function, this junction must be located in the abdomen so that the diaphragmatic crura can assist the action of the LES, thus functioning as an extrinsic sphincter. LES dysfunction occurs via one of several mechanisms: **transient relaxation of the LES (most common mechanism), permanent LES relaxation, and transient increase of intra-abdominal pressure that overcomes the LES pressure**.

Delayed gastric emptying

The postulated mechanism by which delayed gastric emptying may cause GERD is an **increase in gastric contents** resulting in increased intragastric pressure and, ultimately, increased pressure against the lower esophageal sphincter. This pressure eventually defeats the LES and leads to reflux.

Hiatal hernia

A hiatal hernia occurs when **a portion of the stomach prolapses through the diaphragmatic esophageal hiatus**. By far, most hiatal hernias are asymptomatic and are discovered incidentally.

Hiatal hernia may contribute to reflux via a variety of mechanisms. The **lower esophageal sphincter may migrate proximally into the chest** and lose its abdominal high-pressure zone. **The diaphragmatic hiatus**

may be widened by a large hernia, which impairs the ability of the crura to function as an external sphincter. Finally, **gastric contents may be trapped in the hernial sac** and reflux proximally into the esophagus during relaxation of the LES. The presence of a hiatal hernia compromises this reflux barrier not only in terms of reduced LES pressure but also reduced esophageal acid clearance. Patients with hiatal hernias also have longer transient LES relaxation episodes particularly at night time.

Obesity as contributing factor

Some studies have shown that GERD is highly prevalent in patients who are morbidly obese. The mechanism by which a high BMI increases esophageal acid exposure is not completely understood. Increased intragastric pressure and gastroesophageal pressure gradient, incompetence of the LES, and increased frequency of transient LES relaxations may all play a role in the pathophysiology.

Barrett Esophagus

The definition of Barrett esophagus currently is the finding of specialized **intestinal metaplasia** anywhere within the tubular esophagus. Barrett esophagus is well recognized as a complication of gastroesophageal reflux disease (GERD). Patients with GERD who develop Barrett esophagus tend to have a combination of clinical features, **including hiatal hernia, reduced lower esophageal sphincter pressures, delayed esophageal acid clearance time, and duodenogastric reflux** (as documented by the presence of bile in the esophageal lumen).

Prolonged exposure of the esophagus to the refluxate can erode the esophageal mucosa, promote inflammatory cell infiltrate, and ultimately cause **epithelial necrosis**. This chronic damage is believed to promote the replacement of healthy esophageal epithelium with the **metaplastic columnar cells**, the cellular origin of which remains unknown. This likely is an adaptive response of the esophagus, which, if not for the increased risk of cancer, would have been beneficial.

Esophageal Motility Dysorders

Esophageal motility disorders include the following:

- Achalasia
- Spastic esophageal motility disorders, including diffuse esophageal spasm (DES), nutcracker esophagus, and hypertensive LES
- Secondary esophageal motility disorders related to scleroderma, diabetes mellitus, alcohol consumption, and psychiatric disorders.

Achalasia

Achalasia is a primary esophageal motility disorder characterized by **failure of a hypertensive lower esophageal sphincter to relax** and the **absence of esophageal peristalsis**. These abnormalities cause a **functional obstruction at the gastroesophageal junction**.

Lower esophageal sphincter pressure and relaxation are regulated by excitatory (eg, acetylcholine, substance P) and inhibitory (eg, nitric oxide, vasoactive intestinal peptide) neurotransmitters. Persons with achalasia **lack nonadrenergic, noncholinergic, inhibitory ganglion cells**, causing an imbalance in excitatory and inhibitory neurotransmission.

The physiologic process of achalasia is correlated most directly to the loss of the inhibitory nerves at the sphincter, resulting in failure of the lower esophageal sphincter to completely relax and causing relative obstruction.

Esophageal Spasm

The esophagus is comprised of 2 layers of muscle, the inner circular and the outer longitudinal layers. Arbitrarily, the esophagus can be divided into 3 zones.

Diffuse fragmentation of vagal filaments, increased endoneural collagen, and mitochondrial fragmentation are described. There appears to be a **functional imbalance between excitatory and inhibitory postganglionic pathways, disrupting the coordinated components of peristalsis**.

Esophageal zones

Upper zone: Comprised entirely of striated muscle, this zone initiates the contractions that propel the food bolus down the esophagus. The upper esophageal sphincter, named the cricopharyngeus muscle, is located in the upper zone.

Middle zone: Comprised of striated and smooth muscles, the inner circular muscle layer and the outer longitudinal muscle layer work in conjunction to propel the food bolus.

Lower zone: The lower segment is the lower esophageal sphincter. This sphincter is a thickening of the smooth muscle that is contracted tonically to prevent reflux. For food to pass into the stomach, the lower esophageal sphincter relaxes.

Diffuse esophageal spasms

Contractions of several segments of the esophagus are uncoordinated and they contract simultaneously, preventing the propagation of the food bolus. The usual presentation is **intermittent dysphagia with occasional chest pain**.

Nutcracker esophagus

Nutcracker esophagus occurs when the amplitude of the contractions exceeds 2 standard deviations from normal. The contractions proceed in an organized manner, **propelling food down the esophagus**. These patients often present with **chest pain**, but they present with **dysphagia less often** than patients with diffuse esophageal spasms.

Scleroderma Esophagus

In scleroderma, the primary defect in this systemic process is related to **smooth muscle atrophy and fibrosis**. Esophageal dysmotility develops

as the smooth muscle of the esophagus is replaced by scar tissue, gradually leading to progressive **loss of peristalsis and a weakening of LES**. Motility is preserved at the proximal striated muscle portion of the esophagus.

Esophageal Strictures

Disease processes that can produce esophageal strictures can be grouped into 3 general categories:

1. **intrinsic diseases that narrow the esophageal lumen** through inflammation, fibrosis, or neoplasia (acid peptic, autoimmune, infectious, caustic, congenital, iatrogenic, medication-induced, radiation-induced, malignant, and idiopathic disease processes);
2. **extrinsic diseases that compromise the esophageal lumen** by direct invasion or lymph node enlargement;
3. diseases that **disrupt esophageal peristalsis** and/or lower esophageal sphincter function by their effects on esophageal smooth muscle and its innervation.

Esophageal Diverticula

A diverticulum is a sac or pouch arising from a tubular organ, such as the esophagus. **True diverticula** contain all layers of the intestinal tract wall. **False diverticula**, also known as pseudodiverticula, occur when herniation of mucosa and submucosa through a defect in the muscular wall occurs (eg, Zenker diverticulum diverticulum that arises from the posterior hypopharynx).

Finally, **acquired diverticula** of the esophagus and hypopharynx also may be classified according to their pathogenesis as pulsion diverticula or traction diverticula. **Pulsion diverticula** form as a result of high intraluminal pressures against weaknesses in the GI tract wall. **Zenker diverticulum** occurs due to increased pressure in the oropharynx during

swallowing against a closed upper esophageal sphincter. An **epiphrenic diverticulum** occurs from increased pressure during esophageal propulsive contractions against a closed lower esophageal sphincter. In contrast**, traction diverticula** occur as a consequence of pulling forces on the outside of the esophagus from an adjacent inflammatory process (eg, involvement of inflamed mediastinal lymph nodes in tuberculosis or histoplasmosis).

Mallory-Weiss Syndrome

The syndrome is characterized by **esophageal bleeding** caused by a **mucosal tear** in the esophagus as a result of **forceful vomiting**. Predisposing medical conditions include portal hypertension, liver cirrhosis, and severe gastroesophageal reflux disease.

Mallory-Weiss tear develops as a linear laceration at the gastroesophageal junction because the esophagus and stomach are cylindrical. These tears have been postulated to occur either by a **rapid increase in intragastric pressure and distention**, which increases the forceful fluid ejection through the esophagus, or secondary to a significant change in transgastric pressure (ie, difference in pressure across the gastric wall) because negative intrathoracic pressure and positive intragastric pressure leads to distortion of the gastric cardia, resulting in a gastric or esophageal tear.

Gastric Ulcer Disease

- *Epigastric pain* is the most common symptom of both gastric and duodenal ulcers and occurs after meals—classically, shortly after meals with gastric ulcer and 2-3 hours afterward with duodenal ulcer.
- "*Alarm features*" include bleeding, anemia, early satiety, unexplained weight loss, progressive dysphagia or odynophagia, and recurrent vomiting.

- Testing for *H pylori* infection is essential in all patients with peptic ulcers.
- In patients with *NSAID-associated peptic ulcers*, discontinuation of NSAIDs (non steroid antiinflammatory drugs) is paramount.
- Patients with gastric ulcers are also at risk of developing *gastric malignancy*.

Peptic ulcers are **defects in the gastric or duodenal mucosa that extend through the muscularis mucosa**. The **epithelial cells** of the stomach and duodenum **secrete mucus** in response to irritation of the epithelial lining. The superficial portion of the gastric and duodenal mucosa exists in the form of a gel layer, which is impermeable to acid and pepsin. Other **gastric and duodenal cells secrete bicarbonate**, which aids in buffering acid that lies near the mucosa. **Prostaglandins** of the E type (PGE) have an important protective role, because PGE increases the production of both bicarbonate and the mucous layer.

In the event of acid and pepsin entering the epithelial cells, additional mechanisms are in place to reduce injury. Within the epithelial cells, ion pumps in the basolateral cell membrane help to regulate intracellular pH by removing excess hydrogen ions. Through the **process of restitution**, healthy cells migrate to the site of injury. **Mucosal blood flow** removes acid that diffuses through the injured mucosa and provides bicarbonate to the surface epithelial cells.

Under normal conditions, a physiologic balance exists between gastric acid secretion and gastroduodenal mucosal defense. **Mucosal injury** and, thus, peptic ulcer occur when the **balance between the aggressive factors and the defensive mechanisms is disrupted**. Aggressive factors, such as NSAIDs, *H pylori* infection, alcohol, bile salts, acid, and pepsin, can alter the mucosal defense by allowing **back diffusion of hydrogen ions** and subsequent epithelial cell injury. The defensive mechanisms include tight intercellular junctions, mucus, mucosal blood flow, cellular restitution, and epithelial renewal.

The gram-negative spirochete **H pylori** contributes to primary peptic ulcer disease. The unique microbiologic characteristics of this organism, such as **urease production**, allows it to alkalinize its microenvironment and survive for years in the hostile acidic environment of the stomach, where it causes **mucosal inflammation**. The causal association between H pylori gastritis and duodenal ulceration is now well established.

Most patients with duodenal ulcers have **impaired duodenal bicarbonate secretion**, which has also proven to be caused by H pylori because its eradication reverses the defect. The combination of increased gastric acid secretion and reduced duodenal bicarbonate secretion lowers the pH in the duodenum, which promotes the development of **gastric metaplasia**. H pylori infection in areas of gastric metaplasia induces **duodenitis** and enhances the susceptibility to acid injury, thereby predisposing to duodenal ulcers.

Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome is caused by a non–beta islet cell, **gastrin-secreting tumor** of the pancreas that stimulates the acid-secreting cells of the stomach to maximal.

Hypergastrinemia, which causes hypertrophy of the gastric mucosa, leading to **increased numbers of parietal cells** and increased maximal acid output. Gastrin by itself also stimulates acid secretion, resulting in increased basal acid secretion. The large quantity of acid produced leads to **gastrointestinal mucosal ulceration**. It also leads to diarrhea and malabsorption. **Malabsorption** is usually multifactorial, being caused by direct mucosal damage by acid, inactivation of pancreatic enzymes, and precipitation of bile salts.

Gastroparesis

Gastroparesis is a condition of abnormal gastric motility characterized by **delayed gastric emptying in the absence of mechanical outlet obstruction**.

Gastric motility results from the integration of tonic contractions of the fundus, phasic contractions of the antrum, and inhibitory forces of pyloric and duodenal contractions. These contractions require a complex interaction between gastric smooth muscle, the enteric nervous system and specialized pacemaker cells. Motor dysfunction of the stomach may result from autonomic neuropathy, enteric neuropathy, abnormalities of pacemaker cells, and fluctuations in blood glucose. **Autonomic neuropathy** is a likely contributor to the pathogenesis of delayed emptying in patients with long-standing diabetes.

Gastroparesis **may complicate surgery** performed on the stomach. In many instances, it is uncertain whether gastric motor impairments were present preoperatively or whether they occurred as a consequence of the surgery. Abnormal antral peristalsis and fundic tone are demonstrable with postsurgical gastroparesis. Patients with gastroparesis had no fasting motor cycles. Increases in intragastric volumes, impaired fundic responses to meals, and heightened perception of gastric distention are also observed after vagotomy, documenting **combined motor and afferent defects** in this condition.

Dumping Syndrome

The primary functions of the stomach are to act as a reservoir, to initiate the digestive process, and to release its contents downstream into the duodenum in a controlled fashion. Gastric motility is regulated by the enteric nervous system, which is influenced by extrinsic innervation and by circulating hormones.

Dumping is the effect of **altered gastric reservoir function**, and abdominal postoperative gastric motor function. It is observed **after a variety of gastric surgical procedures**, such as vagotomy, pyloroplasty, gastrojejunostomy, and laparoscopic Nissan fundoplication and it has characteristic alimentary and systemic manifestations. Dumping syndrome can be separated into early and late forms, depending on the occurrence of symptoms in relation to the time elapsed after a meal. Both forms occur because of **rapid delivery of large amounts of osmotically active solids and liquids into the duodenum**.

The severity of dumping syndrome is proportional to the rate of gastric emptying. Postprandially, the function of the body of the stomach is to store food and to allow the initial chemical digestion by acid and proteases before transferring food to the gastric antrum. In the antrum, high-amplitude contractions triturate the solids, reducing the particle size to 1-2 mm. These particles are able to pass through the pylorus. Gastric emptying is controlled by fundic tone, antropyloric mechanisms, and duodenal feedback. Gastric surgery alters each of these mechanisms in several ways.

Gastric resection reduces the fundic reservoir, thereby reducing the stomach's receptiveness (accommodation) to a meal. **Vagotomy** increases gastric tone, similarly limiting accommodation. An operation in which the **pylorus is removed, or bypassed**, increases the rate of gastric emptying. Duodenal feedback inhibition of gastric emptying is lost after a bypass procedure, such as **gastrojejunostomy**.

Early dumping

Rapid emptying of gastric contents into the small intestine or colon may result in high amplitude propagated contractions and **increased propulsive motility**.

Symptoms of early dumping syndrome (**30-60 min postprandial**) are believed to result from accelerated gastric emptying of hyperosmolar contents into the small bowel. This leads to **fluid shifts from the intravascular compartment into the bowel lumen**, resulting in rapid

small bowel distention and an increase in the frequency of bowel contractions. Bowel distention may be responsible for GI symptoms, such as **crampy abdominal pain, bloating, and diarrhea**. Intravascular volume contraction due to osmotic fluid shifts is perhaps responsible for vasomotor symptoms, such as **tachycardia and lightheadedness**.

Peripheral and splanchnic vasodilatory response seems to be pivotal in the pathogenesis of dumping.

Late dumping

Late dumping occurs **1-3 hours** after a meal. The pathogenesis is related to the early development of **hyperinsulinemic (reactive) hypoglycemia**. Rapid delivery of a meal to the small intestine results in an initial high concentration of carbohydrates in the proximal small bowel and **rapid absorption of glucose**. This is countered by a hyperinsulinemic response. The high insulin levels are responsible for the subsequent hypoglycemia.

Pyloric Obstruction

Gastric outlet obstruction is not a single entity; it is the clinical and pathophysiological consequence of any disease process that produces a mechanical impediment to gastric emptying.

Pyloric obstruction is categorized into 2 well-defined groups of causes—benign and malignant. In the past, when peptic ulcer disease was more prevalent, benign causes were the most common; however, today the **obstruction secondary to malignancy is much more frequent**.

Patients present with intermittent symptoms that progress until obstruction is complete. **Vomiting** is the cardinal symptom. Initially, patients may demonstrate better tolerance to liquids than solid food.

In a later stage, patients may develop significant **weight loss** due to poor caloric intake. **Malnutrition** is a late sign, but it may be very profound in patients with concomitant malignancy.

In the acute or chronic phase of obstruction, continuous vomiting may lead to **dehydration and electrolyte abnormalities**.

When obstruction persists, patients may develop significant and progressive **gastric dilatation**. The stomach eventually loses its contractility. Undigested food accumulates and may represent a constant **risk for aspiration**.

Pediatric hypertrophic pyloric stenosis

Hypertrophic pyloric stenosis occurs secondary to **diffuse hypertrophy and hyperplasia of the muscular layers of the antrum of pylorus**. The antral region is elongated and thickened to as much as twice its normal size. In response to outflow obstruction and vigorous peristalsis, stomach musculature becomes uniformly hypertrophied and dilated. **Gastritis** may occur after prolonged stasis. Hematemesis is occasionally noted. The patient may become **dehydrated** as a result of vomiting and develop marked **hypochloremic alkalosis**.

No definitive cause for hypertrophic pyloric stenosis has been found. However, various environmental and hereditary factors have been implicated. Suspected environmental factors include infantile hypergastrinemia, abnormalities in the myenteric plexus innervation, cow's milk protein allergy, and exposure to macrolide antibiotics. The etiology is probably **multifactorial**, with both genetic and environmental factors contributing. Molecular studies have concluded that smooth muscle cells are not properly innervated.

Bacterial Overgrowth Syndrome

Bacterial overgrowth syndrome is a term that describes clinical manifestations that occur when the **normally low number of bacteria that inhabit the stomach, duodenum, jejunum, and proximal ileum significantly increases** or becomes overtaken by other pathogens.

Low concentrations of various bacteria are now widely accepted to live within or attached to its luminal surface. This symbiotic relationship

is thought to be vital for normal digestive processes, immunity, and intestinal development. Bacterial species usually present include lactobacilli, enterococci, oral streptococci, and other gram-positive aerobic or facultative anaerobes.

Various etiological processes can disrupt mechanisms that keep the number of these bacteria low. These include **structural abnormalities (congenital or surgical) and disorders that cause decreased gastric acidity, reduced peristaltic activity, and mucosal damage or atrophy**.

Normally, colony counts of gram-positive bacteria and fungi in the duodenum and jejunum are less than $1X10^5$ organisms/ml. This is in sharp contrast to the $1 X 10^{11}$ organisms/ml that colonize the colon**. Gastric acid and bile** destroy many micro-organisms before they leave the stomach. Enzymatic activity of intestinal, pancreatic, and biliary secretions helps destroy bacteria in the small intestine. The **bowel mucosal integrity, mucin layer, immunoglobulin secretion and immune cells** protect the gut from bacteria. Normal intestinal flora (eg, *Lactobacillus*) protects the gut from bacterial overgrowth by maintaining a low pH.

$1 X 10^{11}$ organisms/ml of aspirate fluid is diagnostic for bacterial overgrowth syndrome. Cultures grown from patients with bacterial overgrowth syndrome reveal abnormally **large numbers of anaerobic bacteria** in addition to normal flora.

Abnormal communications produce pathways that allow enteric bacteria to pass between the proximal and distal bowel. Anatomical defects can reduce peristaltic efficacy; for example, **blind pouches** result in a stagnant portion of the intestine.

Malabsorption of bile acids, fats, carbohydrates, proteins, and vitamins results in direct damage to the lining of the luminal surface by bacteria or by transformation of nutrients into toxic metabolites, leading to many of the symptoms of diarrhea and weight loss associated with bacterial overgrowth syndrome.

Anaerobes such as Bacteroides fragilis actively **deconjugate bile acids**, thereby preventing proper bile acid function and enterohepatic circulation. **Fatty acid absorption is reduced** because deconjugated bile acids cannot form micelles. Deconjugated bile acids **directly inhibit carbohydrate transporters**. These unabsorbed sugars ferment into organic acids, thereby reducing the intraluminal pH and producing **osmotic diarrhea**. The unconjugated bile acids also damage intestinal enterocytes and induce **water secretion** by the colonic mucosa.

Appendicitis

Appendicitis is defined as an inflammation of the inner lining of the vermiform appendix that spreads to its other parts. Appendicitis may occur for several reasons, such as an infection of the appendix, but the most important factor is the **obstruction of the appendicular lumen**. Independent of the etiology, obstruction causes an **increase in pressure** within the lumen. Such an increase is related to **continuous secretion of fluids and mucus** from the mucosa and the stagnation of this material. At the same time, intestinal **bacteria** within the appendix multiply, leading to the recruitment of **white blood cells** and the formation of **pus** and subsequent higher intraluminal pressure.

If appendiceal obstruction persists, intraluminal pressure rises ultimately above that of the appendiceal veins, leading to **venous outflow obstruction**. As a consequence, appendiceal **wall ischemia** begins, resulting in a loss of epithelial integrity and allowing bacterial invasion of the appendiceal wall.

Within a few hours, this localized condition may worsen because of **thrombosis** of the appendicular artery and veins, leading to **perforation and gangrene** of the appendix. As this process continues, a **periappendicular abscess or peritonitis** may occur. The location and extent of peritonitis (diffuse or localized) depends on the degree to which the omentum and adjacent bowel loops can contain the spillage of

luminal contents. If the contents become walled off and form an abscess, the **pain and tenderness may be localized to the abscess site**. If the contents are not walled off and the fluid is able to travel throughout the peritoneum, the **pain and tenderness become generalized**.

Mesenteric Lymphadenitis

It causes a clinical presentation that is often **difficult to differentiate from acute appendicitis**.

Microbial agents are thought to gain access to the lymph nodes via the intestinal lymphatics. Organisms subsequently multiply and, depending on the virulence of the invading pathogen, elicit varying degrees of inflammation and, occasionally, suppuration. The lymph nodes are enlarged and often soft. The adjourning mesentery may be edematous, with or without exudates.

Crohn Disease

Crohn disease is a **chronic, transmural inflammatory process** of the bowel that often leads to **fibrosis and obstructive symptoms** and can affect **any part of the gastrointestinal tract from the mouth to the anus**. This condition is the result of an **imbalance between proinflammatory and anti-inflammatory mediators**.

The characteristic presentation of Crohn disease is abdominal pain and diarrhea, which may be complicated by intestinal fistulization, obstruction, or both. Surgery plays an integral role in controlling symptoms and treating complications.

Chronic inflammation from **T-cell activation** leading to **tissue injury**. After activation by antigen presentation, unrestrained responses of helper lymphocytes type 1 (Th1) predominate in Crohn disease because of **defective regulation**. Th1 cytokines such as interleukin 12 and tumor necrosis factor alpha stimulate the inflammatory response. Inflammatory

cells recruited by these cytokines release nonspecific inflammatory substances, including arachidonic acid metabolites, proteases, platelet activating factor, and free radicals, which result in direct injury to the intestine.

Macroscopically, the initial abnormality is hyperemia and edema of the involved mucosa. Later, discrete superficial ulcers form over lymphoid aggregates. These can become deep, serpiginous ulcers. The **lesions are often segmental, being separated by healthy areas**.

Transmural inflammation results in **thickening of the bowel wall and narrowing of the lumen**. As Crohn disease progresses, it is complicated by deep ulceration leading to **fistulization, abscess formation, adhesions, and malabsorption**.

Obstruction is caused initially by significant **edema** of the mucosa and associated **spasm** of the bowel. With further disease progression, the obstruction becomes chronic because of **fibrotic scarry stricture** formation.

Fistulae may be enteroenteral, enterovesical, enterovaginal, or enterocutaneous. Serosal inflammation causes adhesions; thus, free perforations are less common in Crohn disease than in other inflammatory bowel conditions.

Malabsorption can occur as a result of **loss of functional mucosal absorptive surface**. This phenomenon can lead to protein-calorie malnutrition, dehydration, and multiple nutrient deficiencies. Involvement of the terminal ileum may result in malabsorption of bile acids, which leads to steatorrhea, fat-soluble vitamin deficiency, and gallstone formation. Fat malabsorption, by trapping calcium, may result in increased oxalate excretion (normally complexed by calcium), causing kidney stone formation.

Ulcerative Colitis

Ulcerative colitis characteristically involves the **large bowel**. The exact etiology of ulcerative colitis is unknown, but the disease appears to be multifactorial and polygenic. Proposed causes include **environmental factors, immune dysfunction, and a likely genetic predisposition**.

The disease is largely confined to the **mucosa** and, to a lesser extent, the submucosa. Early disease manifests as **hemorrhagic inflammation** with petechial hemorrhages and **bleeding**.

A variety of immunologic changes have been documented in ulcerative colitis. Subsets of T cells accumulate in the lamina propria of the diseased colonic segment. In patients with ulcerative colitis, these T cells are cytotoxic to colonic epithelium. This change is accompanied by an increase in the population of B cells and plasma cells, with increased production of immunoglobulin G (IgG) and immunoglobulin E (IgE). Anticolonic antibodies have been detected in patients with ulcerative colitis.

Excessive fibrosis is not a feature of the disease. The undermining of mucosa and an excess of granulation tissue lead to the formation of polypoidal mucosal excrescences, which are known as **inflammatory polyps or pseudopolyps**.

Hirschsprung´s Disease

Hirschsprung disease is a a congenital gastrointestinal motility disorder characterized by **an absence of neuronal cell bodies in the intestinal wall resulting in a functional obstruction**. During embryonic development, the neural crest cells migrate caudally where they differentiate amongst other cell types to ganglionic cells of the enteric nervous system. There is a delay or arrest in this migration, which results in the **neural crest cells failing to reach their correct positions in the distal intestine**.

Aganglionosis begins with the anus, which is always involved, and continues proximally for a variable distance. Both the myenteric (Auerbach) plexus and the submucosal (Meissner) plexus are absent, resulting in reduced bowel peristalsis and function.

Normal motility is primarily under the control of intrinsic neurons. These ganglia control both contraction and relaxation of smooth muscle, with relaxation predominating. Extrinsic control is mainly through the cholinergic and adrenergic fibers. The cholinergic fibers cause contraction, and the adrenergic fibers mainly cause inhibition.

In Hirschsprung disease, **ganglion cells are absent, leading to a marked increase in extrinsic intestinal innervation, leading to an increase in smooth muscle tone**. With the loss of the intrinsic enteric inhibitory nerves, the increased tone is unopposed and leads to an imbalance of smooth muscle contractility, **uncoordinated peristalsis, and a functional obstruction**.

Malabsorption

Symptoms, such as **diarrhea and weight loss**, may be common.

To understand the mechanisms of malabsorption, understanding the normal physiologic process of digestion and absorption by the intestinal tract is necessary. In general, the digestion and absorption of food materials can be divided into **3 major phases: luminal, mucosal, and postabsorptive**. The luminal phase is the phase in which dietary fats, proteins, and carbohydrates are hydrolyzed and solubilized by secreted digestive enzymes and bile. The mucosal phase relies on the integrity of the brush-border membrane of intestinal epithelial cells to transport digested products from the lumen into the cells. In the postabsorptive phase, reassembled lipids and other key nutrients are transported via lymphatics and portal circulation from epithelial cells to other parts of the body. **Perturbation by disease processes in any of these phases frequently results in malabsorption**.

Ileus

Ileus occurs from **hypomotility of the gastrointestinal tract in the absence of mechanical bowel obstruction**. Presumably, **the muscle of the bowel wall is transiently impaired and fails to transport intestinal contents**. This lack of coordinated propulsive action leads to the **accumulation of gas and fluids within the bowel**.

Although ileus has numerous causes, the **postoperative state** is the most common setting for the development of ileus. Indeed, ileus is an expected consequence of abdominal surgery. Physiologic ileus spontaneously **resolves within 2-3 days**, after sigmoid motility returns to normal. Ileus that persists for more than 3 days following surgery is termed postoperative adynamic ileus or **paralytic ileus**. Frequently, ileus occurs after **intraperitoneal** operations, but it may also occur after **retroperitoneal and extra-abdominal** surgery. The longest duration of ileus is noted to occur after colonic surgery.

The clinical consequences of postoperative ileus can be profound. Patients with ileus are immobilized, have **discomfort and pain**, and are at increased **risk for pulmonary complications**. Ileus also **enhances catabolism** because of poor nutrition.

Postoperative ileus is mediated via activation of **inhibitory spinal reflex arcs**. Anatomically, 3 distinct reflexes are involved: ultrashort reflexes confined to the bowel wall, short reflexes involving prevertebral ganglia, and long reflexes involving the spinal cord. The long reflexes are the most significant. Spinal anesthesia, abdominal sympathectomy, and nerve-cutting techniques have been demonstrated to either prevent or attenuate the development of ileus.

The **surgical stress** response leads to systemic generation **of endocrine and inflammatory mediators** that also promote the development of ileus. Laparotomy, eventration, and bowel compression lead to increased numbers of macrophages, monocytes, dendritic cells, T

cells, natural killer cells, and mast cells. Macrophages residing in the muscularis externa and mast cells are probably the key players in this inflammatory cascade. Calcitonin gene–related peptide, nitric oxide, vasoactive intestinal peptide, and substance P function as inhibitory neurotransmitters in the bowel nervous system.

Small Bowel Obstruction

A small-bowel obstruction is caused by a variety of pathologic processes. The leading cause in industrialized countries is **postoperative adhesions, followed by malignancy, Crohn disease, and hernias**. Surgeries most closely associated with small-bowel obstruction are appendectomy, colorectal surgery, and gynecologic and upper gastrointestinal procedures.

Small-bowel obstructions can be **partial or complete, simple (ie, nonstrangulated) or strangulated**. Strangulated obstructions are surgical emergencies.

Small-bowel obstruction leads to **proximal dilatation of the intestine** due to accumulation of GI secretions and swallowed air. This bowel dilatation **stimulates cell secretory activity**, resulting in more **fluid accumulation**. This leads to **increased peristalsis** above and below the obstruction, with frequent loose stools and flatus early in its course.

Vomiting occurs if the level of obstruction is proximal. Increasing small-bowel distention leads to **increased intraluminal pressures**. This can cause compression of mucosal lymphatics, leading to bowel **wall lymphedema**. With even higher intraluminal hydrostatic pressures, increased hydrostatic pressure in the capillary beds results in **massive third spacing of fluid, electrolytes, and proteins into the intestinal lumen**. The fluid loss and **dehydration** that ensue may be.

Strangulated small-bowel obstructions are most commonly associated with adhesions and occur when a **loop of distended bowel twists on its**

mesenteric pedicle. The arterial occlusion leads to **bowel ischemia** and **necrosis**. If left untreated, this progresses to perforation, peritonitis, and death.

Bacteria in the gut proliferate proximal to the obstruction. Microvascular changes in the bowel wall allow translocation to the mesenteric lymph nodes. This is associated with an increase in the incidence of **bacteremia** due to *Escherichia coli*.

Colonic Obstruction

Large bowel obstruction may be caused by **neoplasms or anatomic abnormalities, such as volvulus, incarcerated hernia, stricture, or obstipation**. The challenges in managing this condition are distinguishing colonic obstruction from ileus, ruling out nonsurgical causes, and determining the best surgical management.

Large bowel obstruction from an anatomic abnormality leads to **colonic distention, abdominal pain, anorexia, and, late in the course, feculent vomiting**. Persistent vomiting may result in dehydration and electrolyte disturbances.

Intestinal Volvulus

Intestinal volvulus is defined as a complete **twisting of a loop of intestine around its mesenteric attachment site**. It is related to but not precisely synonymous with malrotation, a more general term used when the normal process of rotation and fixation of the midgut goes awry.

Volvulus can occur at various sites in the gastrointestinal tract, including the **stomach, small intestine, cecum, transverse colon, and sigmoid colon**. Midgut volvulus refers to twisting of the entire midgut around the axis of the superior mesenteric artery. Midgut volvulus secondary to intestinal malrotation is more common in infants and

children, but it can occur in persons of all ages. **Sigmoid volvulus** is more common in elderly persons.

Volvulus involving the GI tract can cause severe clinical problems; the most feared complication is **ischemia and necrosis** of the entire midgut, which can be fatal.

Volvulus of the midgut may result in several manifestations, depending on the degree of twisting. **Venous and lymphatic obstructions occur first** because of lower intravascular pressures. Vascular congestion leads to **bowel edema** and possible oozing of blood, potentially causing **GI bleeding**. Lymphatic congestion causes the formation of a mesenteric cyst and/or chylous ascites

If volvulus is **intermittent**, children may have **chronic malabsorption** from congestion and edema or intermittent bouts of symptoms, usually vomiting and possibly alternating diarrhea and constipation. Arterial compromise is seen when the twisting is significant enough to occlude venous and arterial vessels. This represents an acute and dangerous event. Sequelae include ischemia, mucosal necrosis, intramural air formation, bacterial translocation, gram-negative sepsis, full-thickness intestinal wall necrosis, perforation, peritonitis, and death.

Intussusception

Intussusception is a process in which a **segment of intestine invaginates into the adjoining intestinal lumen**, causing bowel obstruction**.** Intussusception presents in 2 variants: idiopathic intussusception, which usually starts at the **ileocolic junction** and affects infants and toddlers, and **enteroenteral** intussusception (jejunojejunal, jejunoileal, ileoileal), which occurs in older children.

The pathogenesis of idiopathic intussusception is not well established. It is believed to be secondary to an imbalance in the longitudinal forces along the intestinal wall. In enteroenteral intussusception, this imbalance

can be caused by a **mass acting as a lead point** or by a **disorganized pattern of peristalsis** (eg, an ileus in the postoperative period).

If the mesentery of the intussusceptum is lax and the progression is rapid, the intussusceptum can proceed to the distal colon or sigmoid and even prolapse out the anus. The mesentery of the intussusceptum is invaginated with the intestine, leading to the classic pathophysiologic process of any **bowel obstruction**.

Early in this process, lymphatic return is impeded; then, with increased pressure within the wall of the intussusceptum, venous drainage is impaired. If the obstructive process continues, the pressure reaches a point at which arterial inflow is inhibited, and **infarction** ensues. The intestinal mucosa is extremely sensitive to ischemia because it is farthest away from the arterial supply. Ischemic mucosa sloughs off, leading to the **heme-positive stools**. If untreated, transmural **gangrene** and **perforation** of the leading edge of the intussusceptum occur.

Lead points

Examples of lead points are as follows:

- Meckel diverticulum
- Enlarged mesenteric lymph node
- Benign or malignant tumors of the mesentery or of the intestine
- Inverted appendiceal stumps
- Sutures and staples along an anastomosis
- Intestinal hematomas secondary to abdominal trauma
- Foreign body
- Hemangioma

Other causes

Electrolyte derangements associated with various medical conditions can produce **aberrant intestinal motility**, leading to enteroenteral intussusception.

Abnormal intestinal release of **nitric oxide**, an inhibitory neurotransmitter, caused relaxation **of the ileocecal valve**, predisposing to ileocecal intussusception.

Abdominal Hernias

Inguinal hernias

The pinchcock action of the musculature of the internal ring during abdominal muscular straining prohibits protrusion of the intestine into a patent processus. **Paralysis or injury to the muscle** can disable the shutter effect. In addition, the transversus abdominis aponeurosis flattens during tensing, thus reinforcing the inguinal floor. A congenitally high position of the aponeurotic arch might preclude the buttressing effect. Neurapraxic or neurolytic sequelae of appendectomy or femoral vascular procedures may contribute to a greater incidence of hernia in these patients.

Repetitive stress as a factor in hernia development is suggested by clinical presentations. **Increased intra-abdominal pressure** is seen in a variety of disease states and seems to contribute to hernia formation. Elevated intra-abdominal pressure is associated with chronic cough, ascites, increased peritoneal fluid from biliary atresia, peritoneal dialysis or ventriculoperitoneal shunts, intraperitoneal masses or organomegaly, and obstipation.

The rectus sheath adjacent to groin hernias is thinner than normal. The rate of fibroblast proliferation is less than normal, while the rate of collagenolysis appears increased.

Umbilical hernias

Umbilical hernias in children are secondary to **failure of closure of the umbilical ring**, but only 1 in 10 adults with umbilical hernias reports a history of this defect as a child. The adult umbilical hernia occurs through a canal bordered anteriorly by the linea alba, posteriorly by the umbilical fascia, and laterally by the rectus sheath. **Multiparity**, increased

abdominal pressure, and a single midline decussation are associated with umbilical hernias.

Congenital abdominal wall defects

The underlying embryogenic factor in omphalocele and gastroschisis is deficient closure of the developing anterior wall at the umbilical stalk. Variations in lateral fold migration can result in **omphalocele and gastroschisis**.

Other hernias

Aberrant formation of the **decussations of the linea alba**, leading to a midline pattern of single anterior and posterior lines, predisposes to the formation of **epigastric** hernias. Abnormal orientation of the semilunar and semicircular lines, in combination with obesity, increased intra-abdominal pressure, aging, and rapid weight loss, leads to the production of **spigelian** hernias.

Intestinal Perforation

Normally, the stomach is relatively free of bacteria and other microorganisms because of its high intraluminal acidity. Most persons who experience abdominal trauma have normal gastric functions and are not at risk of bacterial contamination following **gastric perforation**. However, those who have a preexisting gastric problem are at risk of peritoneal contamination with gastric perforation. Leakage of acidic gastric juice into the peritoneal cavity often results in profound **chemical peritonitis**. If the leakage is not closed and food particles reach the peritoneal cavity, chemical peritonitis is succeeded by gradual development of bacterial peritonitis. Patients may be **free of symptoms for several hours** between the initial chemical peritonitis and the later occurrence of bacterial peritonitis.

The **microbiology** of the small bowel changes from its proximal to its distal part. Few bacteria populate the proximal part of the small bowel, whereas the distal part of the small bowel (the jejunum and ileum)

contains aerobic organisms (eg, *Escherichia coli*) and a higher percentage of anaerobic organisms (eg, *Bacteroides fragilis*). Thus, the likelihood of intra-abdominal or wound infection is increased with perforation of the distal bowel.

The presence of bacteria in the peritoneal cavity stimulates an influx of **acute inflammatory cells**. The omentum and viscera tend to localize the site of inflammation, producing a **phlegmon**. The resulting **hypoxia** in the area facilitates growth of anaerobes and produces impairment of bactericidal activity of granulocytes, which leads to increased phagocytic activity of granulocytes, degradation of cells, hypertonicity of fluid forming the abscess, osmotic effects, shift of more fluids into the abscess area, and enlargement of the **abdominal abscess**. If untreated, bacteremia, generalized sepsis, multiorgan failure, and shock may occur.

Peritonitis and Abdominal Sepsis

Peritonitis is defined as inflammation of the serosal membrane that lines the abdominal cavity and the organs contained therein. The peritoneum, which is an otherwise sterile environment, reacts to various pathologic stimuli with a fairly uniform inflammatory response. Depending on the underlying pathology, the resultant **peritonitis may be infectious or sterile (ie, chemical or mechanical**). **The inflammatory process may be localized (abscess) or diffuse** in nature.

Peritonitis is most often caused by introduction of an **infection** into the otherwise sterile peritoneal environment through organ perforation, but it may also result from other irritants, such as **foreign bodies, bile** from a perforated gall bladder or a lacerated liver, or **gastric acid** from a perforated ulcer. Women also experience localized peritonitis from an **infected fallopian tube** or a **ruptured ovarian cyst**. Patients may present with an acute or insidious onset of symptoms, limited and mild disease, or systemic and severe disease with septic shock.

Peritoneal infections are classified as **primary** (ie, from hematogenous dissemination, usually in the setting of immunocompromise), **secondary**

(ie, related to a pathologic process in a visceral organ, such as perforation or trauma, including iatrogenic trauma), or **tertiary** (ie, persistent or recurrent infection after adequate initial therapy).

Intra-abdominal sepsis from a perforated viscus (ie, secondary peritonitis or suppurative peritonitis) results from **direct spillage of luminal contents into the peritoneum** (eg, perforated peptic ulcer, diverticulitis, appendicitis, iatrogenic perforation). **Endotoxins** produced by gram-negative bacteria lead to the release of **cytokines** that induce **cellular and humoral cascades, resulting in cellular damage, septic shock, and multiple organ dysfunction syndrome**.

A host of factors contributes to the formation of peritoneal inflammation and bacterial growth in the ascitic fluid. A key predisposing factor may be the **intestinal bacterial overgrowth** found in people with cirrhosis, mainly attributed to decreased intestinal transit time.

Fibrinolysis

The production of fibrin exudates is an important part of the host defense, but large numbers of **bacteria may be sequestered within the fibrin matrix**. This may retard systemic dissemination of intraperitoneal infection, but it also is integral to the development of **residual infection** and **abscess** formation. As the fibrin matrix matures, the bacteria within are protected from host clearance mechanisms.

Abscess formation

Abscess formation occurs when the host defense is unable to eliminate the infecting agent and attempts to control the spread of this agent by **compartmentalization**. This process is aided by a impairment of phagocytotic killing.

Cytokines

The role of cytokines in mediation of the body's immune response and their role in the development of the **systemic inflammatory response syndrome and multiple organ failure** have been a major focus of research over the past decade. Bacterial peritonitis is associated with an immense intraperitoneal compartmentalized cytokine response. Higher

levels of certain cytokines (ie, tumor necrosis factor-alpha, interleukin-6) have been associated with worse outcomes.

Abdominal Abscess

Intra-abdominal abscesses are localized collections of pus that are confined in the peritoneal cavity by an **inflammatory barrier**. This barrier may include the **omentum, inflammatory adhesions, or contiguous viscera**. The abscesses usually contain a mixture of aerobic and anaerobic bacteria from the gastrointestinal tract.

Bacteria in the peritoneal cavity, in particular those arising from the large intestine, stimulate an influx of **acute inflammatory cells**. The omentum and viscera tend to localize the site of infection, producing a **phlegmon**. The resulting **hypoxia** in the area facilitates the growth of **anaerobes** and impairs the bactericidal activity of granulocytes. The phagocytic activity of these cells degrades cellular and bacterial debris, creating a **hypertonic milieu** that expands and enlarges the abscess cavity in response to osmotic forces. If untreated, the process continues until **bacteremia** develops, which then progresses to generalized **sepsis with shock.**

Lower Gastrointestinal Bleeding

Lower gastrointestinal bleeding encompasses a wide spectrum of symptoms, ranging from trivial hematochezia to massive hemorrhage with shock. Acute lower gastrointestinal bleeding is of recent duration, originates beyond the **ligament of Treitz**, results in instability of vital signs, and is associated with signs of **anemia** with or without need for blood transfusion.

Diverticulosis

The **vessel becomes draped over the dome of the diverticulum, separated from the bowel lumen only by mucosa**. Subsequent chronic trauma to the vasa recta along the luminal aspect, as well as contraction

and relaxation of the surrounding muscularis propria, leads to eccentric thinning of the media. Ultimately, **erosion of the vessel** and bleeding can occur.

Angiodysplasia

Colonic angiodysplasias are **arteriovenous malformations** located in the cecum and ascending colon; these are acquired lesions that affect elderly persons older than 60 years. Most colonic angiodysplasias are degenerative lesions that arise **from chronic, intermittent, low-grade colonic contraction that obstructs the mucosal venous drainage**. Over time, mucosal capillaries dilate, become incompetent, and form an arteriovenous malformation.

Colitis

Ulcerative colitis causes **bloody diarrhea** in most cases.

Ischemic colitis is a disease of the elderly population and is commonly observed after the sixth decade of life. Ischemia causes mucosal and partial-thickness **colonic wall sloughing, edema**, and bleeding.

Colon carcinoma

Colorectal carcinoma causes occult bleeding as a result of **mucosal ulceration or erosion**.

Anorectal disease

Benign anorectal disease (eg, **hemorrhoids, anal fissures, anorectal fistulas**) can cause intermittent rectal bleeding.

Diverticulosis

Small intestinal diverticulosis refers to the clinical entity characterized by the presence of multiple saclike mucosal herniations through weak points in the intestinal wall. **Small intestinal diverticula are far less common than colonic diverticula**. The **sigmoid colon has the highest intraluminal pressures** and is most commonly affected. It appears to be associated with a low-fiber diet, constipation, and obesity.

It is believed to develop as the result of **abnormalities in peristalsis**, intestinal dyskinesis, and **high segmental intraluminal pressures**.

The resulting diverticula emerge on the mesenteric border, ie, sites where **mesenteric vessels penetrate** the small bowel. Diverticula are classified as true and false. True diverticula are composed of all layers of the intestinal wall, whereas false diverticula are formed from the herniation of the mucosal and submucosal layers.

Diverticulitis

Diverticulitis is defined as an inflammation of one or more diverticula. **Fecal material or undigested food particles** may collect in a diverticulum, causing obstruction. This **obstruction** may result in distension of the diverticula secondary to mucous secretion and overgrowth of normal colonic bacteria. **Vascular compromise** and subsequent microperforation or macroperforation then ensue. Alternatively, increased intraluminal pressure or inspissated food particles cause erosion of the diverticular wall, resulting in inflammation, focal necrosis, and **perforation**. The disease is frequently mild when pericolic fat and mesentery wall off a small perforation. However, larger perforations and more extensive disease lead to **abscess formation** and, rarely, intestinal rupture or **peritonitis**.

Fistula formation is a complication of diverticulitis. Fistulas to adjacent organs and the skin may develop, especially in the presence of an abscess. In men, **colovesicular fistulas are the most common**. In women, the uterus is interposed between the colon and the bladder, and this complication is only seen following a hysterectomy.

Recurrent attacks of diverticulitis can result in the formation of scar tissue, leading to narrowing and **obstruction** of the colonic lumen.

Meckel Diverticulum

A Meckel diverticulum is a vestigial remnant of the **omphalomesenteric duct**. As a congenital anomaly, it is a. Generally, a

Meckel diverticulum ranges from 1-12cm in length and is found 45-90cm proximal to the ileocecal valve. It frequently contains **heterotropic tissue**; pluripotential cells line the omphalomesenteric duct; thus, gastric, colonic, duodenal, and pancreatic mucosa may be present. The diverticulum may or may not be attached to the umbilicus with a fibrous cord.

Although most commonly discovered as an incidental finding on laparotomy or laparoscopy, Meckel diverticulum can be **associated with life-threatening disease** states.

Hemorrhage

Hemorrhage is the most common complication. It is more common in children younger than 2 years. The patient complains of passing bright red **blood in the stools**. Bleeding may vary from minimal, recurrent episodes of hematochezia to massive, shock-producing hemorrhage.

The gastric mucosa found in the diverticulum may form a **chronic ulcer** and may also damage the adjacent ileal mucosa because of **acid production**. Ectopic gastric mucosa is found in about 50% of all Meckel diverticulum.

Perforation

Perforation may occur, and the patient then presents with an **acute abdomen**, often associated with air under the diaphragm.

Intestinal obstruction

Various mechanisms of intestinal obstruction occur with Meckel diverticulum as a causative factor. Because the omphalomesenteric duct may be attached to the abdominal wall by a fibrotic band, a **volvulus** of the small bowel around the band may occur. The diverticulum may also form the lead point of an **intussusception** and cause obstruction. Infrequently, a tumor arising in the wall of the diverticulum may form the lead point for intussusception.

Diverticulitis

It is occurring more often in the elderly population. **Perforation** of the inflamed diverticulum leads to peritonitis.

Stasis in the diverticulum, especially in one with a narrow neck, causes inflammation and secondary infection leading to diverticulitis. Diverticular inflammation can lead to adhesions, which cause **intestinal obstruction**.

Neoplasm

This is the least commonly associated pathology. Of the various types of tumors reported, leiomyoma is the one that is most frequent found, followed by leiomyosarcoma, carcinoid tumor, and fibroma.

Constipation

It is a symptom rather than a disease and, despite its frequency, often remains unrecognized until the patient develops sequelae, such as anorectal disorders or diverticular disease.

Acute or subacute constipation in middle-aged or elderly patients should prompt a search for an obstructing colonic lesion. Acute constipation **must be carefully distinguished from ileus** secondary to intra-abdominal emergencies, including infections.

Constipation is divided, with considerable overlap, into issues of **stool consistency** (hard, painful stools) and issues of **defecatory behavior** (infrequency, difficulty in evacuation, straining during defecation). Although hard stools frequently result in defecatory difficulties, **soft bulky stools may also be associated with constipation**, particularly in elderly patients with anatomic abnormalities and in patients with impaired colorectal motility.

Constipation may originate primarily from within the colon and rectum or may originate externally. Processes involved in constipation originating from the colon or rectum include the following:

- Colon obstruction (neoplasm, volvulus, stricture)
- Slow colonic motility, particularly in patients with a history of chronic laxative abuse

- Outlet obstruction (anatomic or functional) - rectal prolapse, and rectocele; functional outlet obstruction may derive from puborectalis or external sphincter spasm when bearing down, short-segment Hirschsprung disease, and damage to the pudendal nerve, typically related to chronic straining or vaginal delivery
- Hirschsprung disease in children

Factors involved in constipation originating outside the colon include poor **dietary habits** (the most common factor, generally involving inadequate fiber or fluid intake and/or overuse of caffeine or alcohol), **medications, systemic endocrine or neurologic diseases, and psychological issues**. Nearly 50% of patients with diverticular or anorectal disease, when asked, deny experiencing constipation.

Hemorrhoids

Hemorrhoids are **swollen blood vessels** in the lower rectum. Hemorrhoidal venous cushions are normal structures of the anorectum. Because of their rich vascular supply, highly sensitive location, and tendency to engorge and prolapse, hemorrhoidal venous cushions are common causes of anal pathology. Symptoms can range from **pruritus** to **rectal bleeding**.

Hemorrhoids are present in healthy individuals. Hemorrhoids generally cause symptoms when they become enlarged, inflamed, thrombosed, or prolapsed.

Most symptoms arise from **enlarged internal hemorrhoids**. Abnormal swelling of the anal cushions causes dilatation and engorgement of the arteriovenous plexuses. This leads to **stretching of the suspensory muscles** and eventual **prolapse of rectal tissue** through the anal canal. The engorged anal mucosa is easily traumatized, leading to **rectal bleeding** that is typically bright red due to high blood oxygen content within the **arteriovenous anastomoses**. Prolapse leads to mucus

discharge (triggering pruritus) and predisposes to incarceration and strangulation.

Although many patients and clinicians believe that hemorrhoids are caused by chronic constipation, prolonged sitting, and vigorous straining, little evidence to support a causative link exists.

Decreased venous return

Most authors agree that **low-fiber diets** cause small-caliber stools, which result in straining during defecation. This **increased pressure** causes engorgement of the hemorrhoids, possibly by interfering with **venous return**. Pregnancy and abnormally high tension of the internal sphincter muscle can also cause hemorrhoidal problems. Prolonged sitting on a toilet is believed to cause a relative venous return problem in the perianal area (a tourniquet effect), resulting in enlarged hemorrhoids. Aging causes weakening of the support structures, which facilitates prolapse.

Straining and constipation

Straining and constipation have long been thought of as culprits in the formation of hemorrhoids. This may or may not be true. Patients who report hemorrhoids have a canal resting tone that is higher than normal.

Pregnancy

Pregnancy clearly predisposes women to symptoms from hemorrhoids, although the etiology is unknown. The relationship between pregnancy and hemorrhoids lends credence to hormonal changes or direct pressure as the culprit.

Portal hypertension

Portal hypertension has often been mentioned in conjunction with hemorrhoids. However, hemorrhoidal symptoms do not occur more frequently in patients with portal hypertension than in those without it. Bleeding is very often complicated by **coagulopathy**.

Anorectal varices are common in patients with portal hypertension. Varices occur in the midrectum, at connections between the portal

system and the middle and inferior rectal veins. Varices occur more frequently in patients who are noncirrhotic, and they rarely bleed.

Other risk factors

Other risk factors historically associated with the development of hemorrhoids include the following:

- Familial tendency
- Higher socioeconomic status
- Chronic diarrhea
- Colon malignancy
- Hepatic disease
- Obesity
- Spinal cord injury
- Loss of rectal muscle tone
- Rectal surgery
- Inflammatory bowel disease, including ulcerative colitis, and Crohn disease

Pathophysiology of symptoms of internal hemorrhoids

Internal hemorrhoids cannot cause cutaneous pain, because they are above the dentate line and are not innervated by cutaneous nerves. However, they can **bleed, prolapse**, and, as a result of the deposition of an irritant onto the sensitive perianal skin, cause perianal itching and irritation. Internal hemorrhoids can produce **perianal pain** by prolapsing and causing **spasm of the sphincter** complex around the hemorrhoids. This spasm results in discomfort while the prolapsed hemorrhoids are exposed.

Internal hemorrhoids can also cause acute pain when **incarcerated** and strangulated. Again, the pain is related to the sphincter complex spasm. Strangulation with necrosis may cause more deep discomfort. When these catastrophic events occur, the sphincter spasm often causes concomitant external thrombosis. External thrombosis causes acute cutaneous pain.

Internal hemorrhoids most commonly cause **painless bleeding** with bowel movements. The covering epithelium is damaged by the hard bowel movement, and the underlying veins bleed. With spasm of the sphincter complex elevating pressure, the internal hemorrhoidal veins can spurt.

Internal hemorrhoids can deposit mucus onto the perianal tissue with prolapse. This mucus with microscopic stool contents can cause a **localized dermatitis**, which is called pruritus ani.

Pathophysiology of symptoms of external hemorrhoids

External hemorrhoids cause symptoms in 2 ways. First, **acute thrombosis** of the underlying external hemorrhoidal vein can occur. Acute thrombosis is usually related to a specific event, such as physical exertion, straining with constipation, a bout of diarrhea, or a change in diet. These are acute, painful events.

Pain results from rapid **distention of innervated skin** by the clot and surrounding edema. The pain lasts 7-14 days and resolves with resolution of the thrombosis. External thromboses occasionally erode the overlying skin and cause **bleeding**.

Anal Fissure

An anal fissure is a painful linear tear or crack in the distal anal canal, which, in the short term, usually involves only the epithelium and, in the long term, involves the full thickness of the anal mucosa.

The exact etiology of anal fissures is unknown, but the initiating factor is thought to be **trauma** from the passage of a particularly hard or painful bowel movement. **Low-fiber diets** are associated with the development of anal fissures. No occupations are associated with a higher risk for the development of anal fissures.

Initial minor tears in the anal mucosa due to a hard bowel movement probably occur often, and, in most people, these heal rapidly without long-term sequelae. In patients with underlying abnormalities of the

internal sphincter, these injuries progress to acute and chronic anal fissures.

The most commonly observed abnormalities are **hypertonicity and hypertrophy of the internal anal sphincter**, leading to elevated anal canal and sphincter resting pressures. The internal sphincter maintains the resting pressure of the anal canal; anal-rectal manometry can be used to measure this pressure.

The posterior anal commissure is the most poorly perfused part of the anal canal. In patients with hypertrophied internal anal sphincters, this delicate blood supply is further compromised, thus rendering the posterior midline of the anal canal **relatively ischemic**. This is thought to account for why many fissures do not heal spontaneously and may last for several months.

Pain accompanies each bowel movement as this raw area is stretched and the injured mucosa is abraded by the stool. The internal sphincter also begins to spasm when a bowel movement is passed, which has 2 effects. First, the spasm itself is painful; second, the spasm further reduces the blood flow to the posterior midline and the anal fissure, contributing to the poor healing rate.

Fistula-in-Ano

A fistula-in-ano is a hollow tract lined with **granulation tissue**, connecting a primary opening inside the anal canal to a secondary opening in the perianal skin. Secondary tracts may be multiple and can extend from the same primary opening.

Perianal Abscess

A perianal abscess represents an infection of the soft tissues surrounding the anal canal, with formation of a discrete abscess cavity.

The severity and depth of the abscess are quite variable, and the abscess cavity is often associated with formation of a fistulous tract.

Perirectal abscesses and fistulas represent anorectal disorders that arise predominately from the **obstruction of anal crypts**. Normal anatomy demonstrates anywhere from 4-10 anal glands drained by respective crypts at the level of the dentate line. Anal glands normally function to lubricate the anal canal. Obstruction of anal crypts results in **stasis** of glandular secretions and, when subsequently infected, suppuration and abscess formation within the anal gland results. The abscess typically forms in the intersphincteric space and can spread along various potential spaces.

Less common causes of anorectal abscess that must be considered in the differential diagnosis include tuberculosis, squamous cell carcinoma, adenocarcinoma, actinomycosis, lymphogranuloma venereum, Crohn's disease, trauma, leukemia, and lymphoma. These may result in the development of atypical fistula-in-ano or complicated fistulas.

Rectal Prolaps

Three different clinical entities are often combined under the umbrella term rectal prolapse:

- Full-thickness rectal prolapse
- Mucosal prolapse
- Internal prolapse (internal intussusception)

Full-thickness rectal prolapse is defined as protrusion of the full thickness of the rectal wall through the anus; it is the most commonly recognized type. Mucosal prolapse, in contrast, is defined as protrusion of only the rectal mucosa from the anus. Internal intussusception may be a full-thickness or a partial rectal wall disorder, but the prolapsed tissue does not pass beyond the anal canal and does not pass out of the anus.

The pathophysiology of rectal prolapse is not completely understood or agreed upon. There are 2 main theories, which essentially are different ways of expressing the same idea.

The first theory postulates that rectal prolapse is a **sliding hernia through a defect in the pelvic fascia**. The second theory holds that rectal prolapse starts as a **circumferential internal intussusception of the rectum** beginning 6-8 cm proximal to the anal verge. With time and straining, this progresses to full-thickness rectal prolapse, although some patients never progress beyond this stage.

The pathophysiology and etiology of mucosal prolapse most likely differ from those of full-thickness rectal prolapse and internal intussusception. Mucosal prolapse occurs when the connective tissue attachments of the rectal mucosa are loosened and stretched, thus allowing the tissue to prolapse through the anus. This often occurs as a continuation of long-standing **hemorrhoidal disease**.

Cholangitis

- Cholecystitis
- Gallbladder empyema

Cholelithiasis

- Biliary obstruction
- Postcholecystectomy syndrome

Acute liver failure

Cirrhosis

- Hepatic encephalopathy
- Portal hypertension
- Ascites
- Esophageal varices
- Hepatorenal syndrome

Bilirubin impaired conjugation

Conjugated hyperbilirubinemia

Acute pancreatitis

Chronic pancreatitis

Pancreatic necrosis and abscess

Pancreatic pseudocysts

Cholangitis

Cholangitis is an infection of the biliary tract with the potential to cause significant morbidity and mortality.

Historically, **choledocholithiasis** was the most common cause of biliary tract obstruction resulting in cholangitis. Over the past 20 years,

biliary tract manipulations/interventions and stents have reportedly become more common causes of cholangitis.

Cholecystitis

Cholecystitis is defined as inflammation of the gallbladder that occurs most commonly because of an **obstruction of the cystic duct** from cholelithiasis. Acalculous cholecystitis is related to conditions associated with biliary stasis, including debilitation, major surgery, severe trauma, sepsis, and prolonged fasting. Ninety percent of cases of cholecystitis involve stones in the cystic duct (ie, **calculous cholecystitis**), with the other 10% of cases representing acalculous cholecystitis.

Acute calculous cholecystitis is caused by obstruction of the cystic duct, leading to **distention** of the gallbladder. As the gallbladder becomes distended, blood flow and lymphatic drainage are compromised, leading to **mucosal ischemia and necrosis**.

Although the exact mechanism of acalculous cholecystitis is unclear. Injury may be the result of **retained concentrated bile**, an extremely noxious substance. In the presence of prolonged fasting, the gallbladder never receives a cholecystokinin stimulus to empty; thus, the concentrated bile remains stagnant in the lumen.

Endotoxin is able to cause necrosis, hemorrhage, areas of fibrin deposition, and extensive mucosal loss, consistent with an **acute ischemic insult**. Endotoxin also abolished the contractile response to CCK, leading to gallbladder stasis.

Gallbladder Empyema

Acute cholecystitis in the presence of bacteria-containing bile may progress to suppurative infection in which the gallbladder fills with purulent material, a condition referred to as empyema of the gallbladder. In the bacterially contaminated gallbladder, the stagnation and marked inflammation associated with acute cholecystitis fills the gallbladder lumen with exudative material principally comprised of **frank pus**. This

process may be associated with calculous cholecystitis, acalculous cholecystitis, or carcinoma of the gallbladder. Left untreated, generalized **sepsis** ensues, with progression in the gallbladder to patchy **gangrene**, microperforation, macroperforation, or, rarely, cholecystoduodenal fistula.

Cholelithiasis

Gallstones are concretions that form in the biliary tract, usually in the gallbladder. Gallstones develop insidiously, and they may remain asymptomatic for decades. Migration of a gallstone into the opening of the cystic duct may block the outflow of bile during gallbladder contraction. The resulting **increase in gallbladder wall tension** produces a characteristic type of pain (**biliary colic**). Cystic duct obstruction, if it persists for more than a few hours, may lead to acute gallbladder inflammation (**acute cholecystitis**).

Choledocholithiasis refers to the presence of one or more gallstones in the common bile duct. Usually, this occurs when a gallstone passes from the gallbladder into the common bile duct. A gallstone in the common bile duct may impact distally in the **ampulla of Vater**, the point where the common bile duct and pancreatic duct join before opening into the duodenum. Obstruction of bile flow by a stone at this critical point may lead to abdominal **pain and jaundice**. Stagnant bile above an obstructing bile duct stone often becomes infected, and bacteria can spread rapidly back up the ductal system into the liver to produce a life-threatening infection called **ascending cholangitis**. Obstruction of the pancreatic duct by a gallstone in the ampulla of Vater also can trigger activation of pancreatic digestive enzymes within the pancreas itself, leading to **acute pancreatitis**.

Chronically, gallstones in the gallbladder may cause progressive fibrosis and loss of function of the gallbladder, a condition known as

chronic cholecystitis. Chronic cholecystitis predisposes to gallbladder cancer.

Gallstone formation occurs because certain substances in bile are present in concentrations that approach the limits of their solubility. When bile is concentrated in the gallbladder, it can become **supersaturated** with these substances, which then precipitate from solution as microscopic crystals. The crystals are trapped in gallbladder mucus, producing gallbladder sludge. Over time, the crystals grow, aggregate, and fuse to form macroscopic stones. The 2 main substances involved in gallstone formation are **cholesterol and calcium bilirubinate**.

Cholesterol gallstones

Liver cells secrete cholesterol into bile along with phospholipid (lecithin) in the form of small spherical membranous bubbles, termed unilamellar vesicles. Liver cells also secrete bile salts, which are powerful detergents required for digestion and absorption of dietary fats.

Bile salts in bile dissolve the unilamellar vesicles to form soluble aggregates called mixed **micelles**. This happens mainly in the gallbladder, where bile is concentrated by reabsorption of electrolytes and water.

Compared with vesicles (which can hold up to 1 molecule of cholesterol for every molecule of lecithin), mixed micelles have a lower carrying capacity for cholesterol (about 1 molecule of cholesterol for every 3 molecules of lecithin). If bile contains a relatively high proportion of cholesterol to begin with, then as bile is concentrated, progressive dissolution of vesicles may lead to a state in which the cholesterol-carrying capacity of the micelles and residual vesicles is exceeded. At this point, bile is supersaturated with cholesterol, and **cholesterol monohydrate crystals** may form.

Thus, the main factors that determine whether cholesterol gallstones will form are:

- The amount of cholesterol secreted by liver cells, relative to lecithin and bile salts,

- The degree of concentration and extent of stasis of bile in the gallbladder.

Calcium, bilirubin, and pigment gallstones

Bilirubin, a yellow pigment derived from the breakdown of heme, is actively secreted into bile by liver cells. Most of the bilirubin in bile is in the form of glucuronide conjugates, which are quite water soluble and stable, but a small proportion consists of unconjugated bilirubin. **Unconjugated bilirubin**, like fatty acids, phosphate, carbonate, and other anions, tends to form insoluble precipitates with calcium. Calcium enters bile passively along with other electrolytes.

In situations of high heme turnover, such as chronic hemolysis or cirrhosis, unconjugated bilirubin may be present in bile at higher than normal concentrations. **Calcium bilirubinate** may then crystallize from solution and eventually form stones.

Bile is normally sterile, but in some unusual circumstances (eg, above a biliary stricture), it may become colonized with bacteria. The **bacteria hydrolyze conjugated bilirubin**, and the resulting increase in unconjugated bilirubin may lead to precipitation of calcium bilirubinate crystals. Bacteria also hydrolyze lecithin to release fatty acids, which also may bind calcium and precipitate from solution.

Mixed gallstones

Cholesterol gallstones may become colonized with bacteria and can elicit gallbladder mucosal inflammation. Lytic enzymes from bacteria and leukocytes hydrolyze bilirubin conjugates and fatty acids. As a result, over time**, cholesterol stones may accumulate a substantial proportion of calcium bilirubinate** and other calcium salts, producing mixed gallstones.

Biliary Obstruction

Half the bile produced runs directly from the liver into the duodenum via a system of ducts, ultimately draining into the common bile duct. The remaining **50% is stored in the gallbladder**. In response to

a meal, this bile is released from the gallbladder via the cystic duct. The common biliary tract courses through the head of the pancreas for approximately 2 cm before passing through the ampulla of Vater into the duodenum.

Biliary obstruction refers to the **blockage of any duct** that carries bile from the liver to the gallbladder or from the gallbladder to the small intestine. This can occur at various levels within the biliary system. The major signs and symptoms of biliary obstruction result directly from the failure of bile to reach its proper destination.

The clinical setting of cholestasis or failure of biliary flow may be due to biliary obstruction by mechanical means or by metabolic factors in the hepatic cells. **Intrahepatic cholestasis generally occurs at the level of the hepatocyte or biliary canalicular membrane**. Causes include hepatocellular disease (eg, viral hepatitis, drug-induced hepatitis), drug-induced cholestasis, biliary cirrhosis, and alcoholic liver disease. In hepatocellular disease, interference in the 3 major steps of bilirubin metabolism, ie, uptake, conjugation, and excretion, usually occurs. **Excretion is the rate-limiting step** and is usually impaired to the greatest extent. As a result, **conjugated bilirubin predominates in the serum**.

Extrahepatic obstruction to the flow of bile may occur within the ducts or secondary to external compression. Overall, gallstones are the most common cause of biliary obstruction. Other causes of **blockage within the ducts** include **malignancy, infection, and biliary cirrhosis**. **External compression** of the ducts may occur secondary to inflammation (eg, pancreatitis) and **malignancy**. Regardless of the cause, the physical obstruction causes a predominantly conjugated hyperbilirubinemia.

Accumulation of bilirubin in the bloodstream and subsequent deposition in the skin causes **jaundice** (icterus). Conjunctival icterus is generally a more sensitive sign of hyperbilirubinemia than generalized jaundice. Urine bilirubin is normally absent. When it is present, **only conjugated bilirubin is passed into the urine**. This may be evidenced by

dark-colored urine seen in patients with obstructive jaundice or jaundice due to hepatocellular injury.

The lack of bilirubin in the intestinal tract is responsible for the **pale stools** typically associated with biliary obstruction. The cause of **itching** (pruritus) associated with biliary obstruction is not clear. Some believe it may be related to the accumulation of bile acids in the skin.

Postcholecystectomy Syndrome

The term postcholecystectomy syndrome describes the presence of symptoms after cholecystectomy.

Postcholecystectomy syndrome is caused by **alterations in bile flow** due to the loss of the reservoir function of the gallbladder. Two types of problems may arise. The first problem is **continuously increased bile flow** into the upper GI tract, which may contribute to **esophagitis and gastritis**. The second consequence is related to the lower GI tract, where **diarrhea and colicky lower abdominal pain** may result.

The pathophysiology of postcholecystectomy syndrome is related to alterations in bile flow and remains poorly understood.

Acute Liver Failure

Acute liver failure is a condition in which the **rapid deterioration of liver function** results in **coagulopathy** and **alteration in the mental status** of a previously healthy individual.

Fulminant hepatic failure is generally used to describe the development of **encephalopathy** within 8 weeks of the onset of symptoms in a patient with a previously healthy liver. **Subfulminant** hepatic failure is reserved for patients with liver disease for up to 26 weeks before the development of hepatic encephalopathy.

The development of **cerebral edema** is the major cause of morbidity and mortality in patients with acute liver failure. The etiology of this intracranial hypertension is not fully understood, but it is considered to

be multifactorial. **Hyperammonemia** may be involved in the development of cerebral edema. Brain edema is thought to be both **cytotoxic and vasogenic in origin**.

Cytokine profiles are also deranged. Elevated serum concentrations of **bacterial endotoxin, tumor necrosis factor–alpha, and interleukin–1 and IL-6** have been found in fulminant hepatic failure.

Cytotoxic edema

Cytotoxic edema is the consequence of **impaired cellular osmoregulation in the brain**, resulting in astrocyte edema. In the brain, ammonia is detoxified to glutamine via amidation of glutamate by glutamine synthetase. The **accumulation of glutamine in astrocytes** results in astrocyte swelling and brain edema.

Vasogenic factors

An **increase of intracranial blood volume and cerebral blood flow** is a factor in acute liver failure. The increased cerebral blood flow results because of **disruption of cerebral autoregulation**. This is mediated by **elevated systemic concentrations of nitric oxide**, a potent vasodilator.

Multisystem organ failure

Another consequence of fulminant hepatic failure is multisystem organ failure, which is often observed in the context of a hyperdynamic circulatory state that mimics sepsis (**low systemic vascular resistance**); therefore, circulatory insufficiency and poor organ perfusion possibly either initiate or promote complications of fulminant hepatic failure.

Cirrhosis

Cirrhosis represents the final common histologic pathway for a wide variety of chronic liver diseases. **Many forms of liver injury are marked by fibrosis**. Fibrosis is defined as an excess deposition of the components of extracellular matrix (ie, collagens, glycoproteins, proteoglycans) within the liver.

Cirrhosis is defined histologically as a diffuse hepatic process characterized by **fibrosis** and the conversion of normal liver architecture into **structurally abnormal nodules**. The progression of liver injury to cirrhosis may occur over weeks to years.

Common signs and symptoms may stem from **decreased hepatic synthetic function** (eg, coagulopathy), **decreased detoxification** capabilities of the liver (eg, hepatic encephalopathy), or **portal hypertension** (eg, variceal bleeding).

Alcoholic liver disease once was considered to be the predominant cause of cirrhosis. **Hepatitis C** has emerged as the leading cause of both chronic hepatitis and cirrhosis. Many cases of cryptogenic cirrhosis appear to have resulted from nonalcoholic **fatty liver disease**.

The development of hepatic fibrosis reflects an alteration in the normally balanced processes of **extracellular matrix production and degradation**. Extracellular matrix, the normal scaffolding for hepatocytes, is composed of collagens (especially types I, III, and V), glycoproteins, and proteoglycans. Stellate cells, located in the perisinusoidal space, are essential for the production of extracellular matrix. **Stellate cells** may become activated into collagen-forming cells by a variety of paracrine factors. Such factors may be released by hepatocytes, Kupffer cells, and sinusoidal endothelium following liver injury. As an example, increased levels of the cytokine transforming growth factor beta1 are observed in patients with chronic hepatitis C and those with cirrhosis.

Increased collagen deposition in the space of Disse (the space between hepatocytes and sinusoids) and the diminution of the size of endothelial fenestrae lead to the capillarization of sinusoids. Activated stellate cells also have contractile properties. Both **capillarization and constriction of sinusoids by stellate cells** contribute to the development of **portal hypertension**.

Hepatic Encephalopathy

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain disease. Hepatic encephalopathy is characterized by **personality changes, intellectual impairment, and a depressed level of consciousness**.

An important prerequisite for the syndrome is diversion of portal blood into the systemic circulation through **portosystemic collateral vessels**. Hepatic encephalopathy is also described in patients without cirrhosis with either spontaneous or surgically created portosystemic shunts. The development of hepatic encephalopathy is explained, to some extent, by the effect of **neurotoxic substances**, which occurs in the setting of cirrhosis and **portal hypertension**.

The encephalopathy of cirrhosis and fulminant hepatic failure share many of the same pathogenic mechanisms. However, **brain edema plays a much more prominent role in fulminant hepatic failure** than in cirrhosis. The brain edema of fulminant hepatic failure is attributed to increased permeability of the blood-brain barrier, impaired osmoregulation within the brain, and increased cerebral blood flow. In contrast, **brain edema is rarely reported in patients with cirrhosis**.

Type A hepatic encephalopathy describes encephalopathy associated with ***a*cute liver failure**. **Type C** hepatic encephalopathy describes encephalopathy associated with ***c*irrhosis and portal hypertension**.

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte function. **Astrocytes** account for about one third of cortical volume. They play a key role in the **regulation of the blood-brain barrier**. They are involved in maintaining **electrolyte homeostasis** and in **providing nutrients and neurotransmitter precursors to neurons**. They also play a role in the detoxification of a number of chemicals, including ammonia.

Ammonia and manganese, may gain entry into the brain in the setting of liver failure. These neurotoxic substances may then contribute to morphologic changes in astrocytes. Here, **astrocytes become swollen**. This may lead to **increased intracranial pressure** and, potentially, brain herniation.

Work focused on changes in gene expression in the brain has been conducted. The genes coding for a wide array of transport proteins may be upregulated or downregulated in cirrhosis and fulminant hepatic failure. As an example, the **gene coding for the peripheral-type benzodiazepine receptor is upregulated**. It may result in **impaired neurotransmission**.

Hepatic encephalopathy may also be thought of as a disorder that is the end result of **accumulated neurotoxic substances in the brain**. Putative neurotoxins include **short-chain fatty acids; mercaptans; false neurotransmitters**, such as tyramine, octopamine, and beta-phenylethanolamines; **manganese; ammonia; and gamma-aminobutyric acid** (GABA).

Ammonia hypothesis

Ammonia is produced in the gastrointestinal tract by **bacterial degradation of amines, amino acids, purines, and urea**. Enterocytes also convert glutamine to glutamate and ammonia.

Normally, ammonia is detoxified in the liver by conversion to **urea** by the Krebs-Henseleit cycle. Ammonia is also consumed in the conversion of glutamate to glutamine. Two factors contribute to the **hyperammonemia** that is seen in cirrhosis. First, there is a **decreased mass of functioning hepatocytes**, resulting in fewer opportunities for ammonia to be. Secondly, **portosystemic shunting** may divert ammonia-containing blood away from the liver to the systemic circulation.

The kidneys express glutaminase and, to some extent, play a role in ammonia production. However, the kidneys also express glutamine synthetase and play a key role in ammonia metabolism and excretion.

Brain astrocytes also possess glutamine synthetase. However, the **brain is not able to increase glutamine synthetase activity in the setting of hyperammonemia**. Thus, the brain remains vulnerable to the effects of hyperammonemia.

Ammonia has multiple neurotoxic effects. It can **alter the transit of amino acids, water, and electrolytes across astrocytes and neurons**. It can **impair amino acid metabolism and energy utilization in the brain**. Ammonia can also inhibit the generation of excitatory and inhibitory postsynaptic potentials.

GABA hypothesis

GABA is a neuroinhibitory substance produced in the gastrointestinal tract. Of all brain nerve endings, 24-45% may be GABAergic. **The GABA receptor complex contains binding sites for GABA, benzodiazepines, and barbiturates**.

It was believed that there were increased levels of GABA and endogenous benzodiazepines in plasma. These chemicals would then cross an extrapermeable blood-brain barrier. Binding of GABA and benzodiazepines to a supersensitive neuronal GABA receptor complex permitted the influx of chloride ions into the postsynaptic neuron, leading to generation of an **inhibitory postsynaptic potential**.

The neuronal GABA receptor complex contains a binding site for neurosteroids. Today, some investigators contend that **neurosteroids** play a key role in hepatic encephalopathy.

Neurotoxins, like ammonia and manganese, increase the production of the peripheral-type benzodiazepine receptor in astrocytes. They **stimulate the conversion of cholesterol to pregnenolone to neurosteroids**. Neurosteroids are then released from the astrocyte. They are capable of binding to their receptor within the neuronal **GABA receptor complex and can increase inhibitory neurotransmission**.

Portal Hypertension

Normal portal pressure is generally defined between 5 and 10 mm Hg. However, once the portal pressure rises to 12 mm Hg or greater, complications can arise, such as varices and ascites. The portal vein drains blood from the small and large intestines, stomach, spleen, pancreas, and gallbladder. Two important factors exist in the pathophysiology of portal hypertension, vascular resistance and blood flow.

Increase in vascular resistance

The initial factor in the pathophysiology of portal hypertension is the increase in vascular resistance to the portal blood flow. Changes in portal vascular resistance are determined primarily by blood vessel radius. Because portal vascular resistance is indirectly proportional to the fourth power of the vessel radius, **small decreases in the vessel radius cause large increases in portal vascular resistance**.

Liver disease is responsible for a decrease in portal vascular radius, producing a dramatic increase in portal vascular resistance. In cirrhosis, the increase occurs at the hepatic microcirculation (sinusoidal portal hypertension). Increased hepatic vascular resistance in cirrhosis is **not only a mechanical consequence of the hepatic architectural disorder**, but a dynamic component also exists due to the **active contraction of myofibroblasts, activated stellate cells, and vascular smooth-muscle cells of the intrahepatic veins**.

Factors that increase hepatic vascular resistance include **endothelin, alpha-adrenergic stimulus, and angiotensin II**. Factors that decrease hepatic vascular resistance include nitric oxide, prostacyclin.

Increase in portal blood flow

The increase in blood flow in the portal veins is established through **splanchnic arteriolar vasodilatation** caused by an excessive release of **endogenous vasodilators** (eg, endothelial, neural, humoral). The increase in portal blood flow aggravates the increase in portal pressure and contributes to why portal hypertension exists despite the formation of an

extensive network of portosystemic collaterals that may divert as much as 80% of portal blood flow. Manifestations of splanchnic vasodilatation include **increased cardiac output, arterial hypotension**.

Formation of varices

The hypertensive portal vein is decompressed by diverting up to 90% of the portal flow through portasystemic collaterals back to the heart resulting in enlargement of these vessels. These vessels are commonly located at the **gastroesophageal junction** where they lie subjacent to the mucosa and present as **gastric and esophageal varices**. Varices form when the portal pressure exceeds 10 mm Hg and usually do not bleed unless the hepatic venous pressure gradient exceeds 12 mm Hg.

Mechanism of variceal hemorrhage

Increased portal pressure contributes to increased varix size and **decreased varix wall thickness**, thus leading to increased variceal wall tension. Rupture occurs when the wall tension exceeds the elastic limits of the variceal wall. Varices are most superficial at the gastroesophageal junction and have the thinnest wall in that region.

Ascites

Ascites describes the condition of pathologic fluid collection within the abdominal cavity. Healthy men have little or no intraperitoneal fluid, but women may normally have as much as 20 ml, depending on the phase of their menstrual cycle.

The accumulation of ascitic fluid represents a state of **total-body sodium and water excess**, but the event that initiates the unbalance is unclear. Three theories of ascites formation have been proposed: underfilling, overflow, and peripheral arterial vasodilation.

The underfilling theory suggests that the primary abnormality is inappropriate **sequestration of fluid within the splanchnic vascular bed** due to portal hypertension and a consequent **decrease in effective circulating blood volume.** This activates the plasma renin, aldosterone,

and sympathetic nervous system, resulting in **renal sodium and water retention**.

The overflow theory suggests that the primary abnormality is **inappropriate renal retention of sodium and water in the absence of volume depletion**. This theory was developed in accordance with the observation that patients with cirrhosis have **intravascular hypervolemia** rather than hypovolemia.

The most recent theory, **the peripheral arterial vasodilation hypothesi*s***, includes components of both of the other theories. It suggests that **portal hypertension leads to vasodilation, which causes decreased effective arterial blood volume**. As the natural history of the disease progresses, neurohumoral excitation increases, **more renal sodium is retained, and plasma volume expands**. This leads to **overflow of fluid into the peritoneal cavity**. The vasodilation theory proposes that underfilling is operative early and overflow is operative late in the natural history of cirrhosis.

Nitric oxide mediates splanchnic and peripheral vasodilation.

Regardless of the initiating event, a number of factors contribute to the accumulation of fluid in the abdominal cavity. **Elevated levels of epinephrine and norepinephrine** are well-documented factors. **Hypoalbuminemia** and reduced plasma oncotic pressure favor the extravasation of fluid from the plasma to the peritoneal fluid, and, thus, ascites is infrequent in patients with cirrhosis unless both portal hypertension and hypoalbuminemia are present.

Esophageal Varices

The portal vein carries approximately 1500 mL/min of blood from the small and large bowel, the spleen, and the stomach to the liver. Obstruction of portal venous flow, whatever the etiology, results in a rise in portal venous pressure. The response to increased venous pressure is the development of a collateral circulation diverting the obstructed blood flow to the systemic veins. These **portosystemic collaterals** form by the

opening and dilatation of preexisting vascular channels connecting the portal venous system and the superior and inferior vena cava.

High portal pressure is the main cause of the development of portosystemic collaterals; however, other factors such as **active angiogenesis** may also be involved. The most important portosystemic anastomoses are the gastroesophageal collaterals. Draining into the azygos vein, these collaterals include esophageal varices, which are responsible for the main complication of portal hypertension -- massive **upper gastrointestinal hemorrhage**.

An elevated portal venous pressure (>10 mm Hg) distends the veins proximal to the site of the block and increases capillary pressure in organs drained by the obstructed veins.

Because the portal venous system lacks valves, resistance at any level between the right side of the heart and the splanchnic vessels results in retrograde flow of blood and transmission of elevated pressure. The anastomoses connecting the portal and systemic circulation **may enlarge** to allow blood to bypass the obstruction and pass directly into the systemic circulation.

The role of endothelin-1 and nitric oxide in the pathogenesis of portal hypertension and esophageal varices has been demonstrated. **ET-1** is a powerful vasoconstrictor synthesized by sinusoidal endothelial cells that has been implicated in the **increased hepatic vascular resistance** of cirrhosis and in the development of liver fibrosis. NO is a vasodilator substance that is synthesized by sinusoidal endothelial cells. In the cirrhotic liver, the production of **NO is decreased**.

Gastroesophageal varices have 2 main inflows, the first is the left gastric or coronary vein. The other major route of inflow is the splenic hilus, through the short gastric veins. The gastroesophageal varices are important because of their propensity to bleed.

Studies of hepatic microcirculation have identified several mechanisms that may explain the **increased intrahepatic vascular resistance**. These mechanisms may be summarized as follows:

- A reduction of sinusoidal caliber due to hepatocyte enlargement
- An alteration in the elastic properties of the sinusoidal wall due to collagen deposition in the space of Disse
- Compression of hepatic venules by regeneration nodules
- Central vein lesions caused by perivenous fibrosis
- Venoocclusive changes

The following are **risk factors for variceal hemorrhage**:

- Variceal size: The larger the varix, the higher the risk of rupture and bleeding.
- The presence of endoscopic red color signs (eg, red whale markings, cherry red spots)
- The presence of ascites, increases the risk of hemorrhage.

A well-documented association exists between variceal hemorrhage and bacterial infections, and this may represent a causal relationship. **Infection could trigger variceal bleeding** by a number of mechanisms, including the following:

- The release of endotoxin into the systemic circulation
- Worsening of hemostasis
- Vasoconstriction induced by contraction of stellate cells

Hepatorenal Syndrome

Hepatorenal syndrome is the development of **renal failure** in patients with advanced chronic liver disease, who have **portal hypertension and ascites**. **Oliguria** is present in patients with chronic liver disease in the **absence of proteinuria** and linked the abnormalities in renal function to disturbances present in the systemic circulation.

The hallmark of hepatorenal syndrome is **renal vasoconstriction**, although the pathogenesis is not fully understood. Multiple mechanisms are probably involved and include interplay between **disturbances in systemic hemodynamics, activation of vasoconstrictor systems, and a reduction in activity of the vasodilator systems**. The hemodynamic

pattern of patients with hepatorenal syndrome is characterized by **increased cardiac output, low arterial pressure, and reduced systemic vascular resistance**. Renal vasoconstriction occurs in the absence of reduced cardiac output and blood volume, which is in contrast to most clinical conditions associated with renal hypoperfusion.

Increased renal vascular resistance and decreased peripheral resistance is characteristic of hepatorenal syndrome, it also occurs in other conditions, such as anaphylaxis and sepsis. Splanchnic circulation is responsible for arterial vasodilatation and reduced total systemic vascular resistance.

The renin-angiotensine-aldosteron system and sympathetic nervous system are the predominant systems responsible for renal vasoconstriction. The activity of both systems is **increased in patients with cirrhosis and ascites**, and this effect is magnified in hepatorenal syndrome. **Adenosine** is well known for its vasodilator properties, although it acts as a **vasoconstrictor in the lungs and kidneys**. Elevated levels of adenosine are more common in patients with heightened activity of the RAAS and may work **synergistically with angiotensin II to produce renal vasoconstriction**.

The vasoconstricting effect of these various systems is antagonized by local renal vasodilatory factors, the most important of which are the PGs. Nitric oxide is another vasodilator believed to play an important role in renal perfusion. When both **NO and PG production are inhibited**, marked renal vasoconstriction develops.

Various theories have been proposed to explain the development of hepatorenal syndrome in cirrhosis. The 2 main theories are the **arterial vasodilation theory and the hepatorenal reflex theory**. The former theory not only describes sodium and water retention in cirrhosis, but also may be the most rational hypothesis for the development of HRS. **Splanchnic arteriolar vasodilatation** may be mediated by NO. Underfilling of the systemic arterial bed causes a decrease in the effective arterial

blood volume and results in **homeostatic/reflex activation of the endogenous vasoconstrictor systems**.

Activation of the RAAS and SNS results in vasoconstriction not only of the renal vessels, but also in vascular beds of the brain, muscle, spleen, and extremities. The **splanchnic circulation is resistant to these effects because of the continuous production of local vasodilators such as NO**.

As liver disease progresses in severity, a critical level of vascular underfilling is achieved. Renal vasodilatory systems are unable to counteract the maximal activation of the endogenous vasoconstrictors and/or intrarenal vasoconstrictors, which leads to uncontrolled renal vasoconstriction.

Bilirubin Impaired Conjugation

Bilirubin is a tetrapyrrole created by the normal breakdown of heme. Accumulation of bilirubin or its conjugates in body tissues produces **jaundice** (ie, icterus), which is characterized by high plasma bilirubin levels and deposition of yellow bilirubin pigments in skin, sclerae, mucous membranes, and other less visible tissues.

Unconjugated bilirubin is transported in the plasma **bound to albumin**. At the sinusoidal surface of the liver, unconjugated bilirubin detaches from albumin and is transported through the hepatocyte membrane by facilitated diffusion. Within the hepatocyte, bilirubin is bound to 2 major intracellular proteins, cytosolic Y protein (ie, ligandin or glutathione S-transferase B) and cytosolic Z protein (also known as fatty acid–binding protein).

In order for bilirubin to be excreted into bile and, therefore, eliminated from the body, it must be made more soluble. This **water-soluble or conjugated form of bilirubin** is produced when glucuronic acid enzymatically is attached to one or both of the propionic side chains of bilirubin. This is catalyzed by the microsomal enzyme bilirubin uridine-diphosphate glucuronosyltransferase, which is located in the endoplasmic

reticulum of the hepatocyte. Bilirubin glucuronidation can be inhibited by certain **antibiotics** (eg, novobiocin or gentamicin at serum concentrations exceeding therapeutic levels) and by chronic hepatitis, and advanced cirrhosis.

The kidneys do not filter unconjugated bilirubin because of its avid binding to albumin. For this reason, the presence of **bilirubin in the urine** indicates the presence of conjugated hyperbilirubinemia.

Diseases that reduce the rate of secretion of conjugated bilirubin into the bile or the flow of bile into the intestine produce a mixed or predominantly conjugated hyperbilirubinemia due to the reflux of conjugates back into the plasma. Elevated conjugated bilirubin levels usually indicate hepatobiliary disease.

Conjugated hyperbilirubinemia results from reduced secretion of conjugated bilirubin into the bile, such as occurs in patients with **hepatitis**, or it results from impaired flow of bile into the intestine, such as occurs in patients with **biliary obstruction**. Bile formation is sensitive to various hepatic insults, including high levels of inflammatory cytokines, such as may occur in patients with septic shock.

High levels of conjugated bilirubin may secondarily **elevate the level of unconjugated bilirubin**. Although the mechanism of this effect is not fully defined, one likely cause is reduced hepatic clearance of unconjugated bilirubin that results from **competition with conjugated bilirubin** for uptake or excretion.

Acute Pancreatitis

Pancreatitis is an inflammatory process in which **pancreatic enzymes autodigest the gland**. The gland sometimes heals without any impairment of function or any morphologic changes; this process is known as **acute pancreatitis**. Pancreatitis can also recur intermittently, contributing to the functional and morphologic loss of the gland; recurrent attacks are referred to as **chronic pancreatitis**.

The pancreas is a gland located in the upper posterior abdomen. It is responsible for insulin production (endocrine pancreas) and the manufacture and secretion of digestive enzymes (exocrine pancreas) leading to **carbohydrate, fat, and protein metabolism**. When a meal is ingested, the vagal nerves, vasoactive intestinal polypeptide, gastrin-releasing peptide, secretin, cholecystokinin, and encephalins stimulate release of these proenzymes into the pancreatic duct.

A feedback mechanism exists to limit pancreatic enzyme activation after appropriate metabolism has occurred. It is hypothesized that elevated levels of trypsin, having become unbound from digesting food, lead to decreased cholecystokinin and secretin levels, thus limiting further pancreatic secretion.

Because **premature activation** of pancreatic enzymes within the pancreas leads to organ injury and pancreatitis, several mechanisms exist to limit this occurrence. First, proteins are translated into the inactive proenzymes. The **proenzymes** are packaged in a paracrystalline arrangement with protease inhibitors. Zymogen granules have an acidic pH and a low calcium concentration, which are **factors that guard against premature activation** until after secretion has occurred and extracellular factors have triggered the activation cascade. Under various conditions, disruption of these protective mechanisms may occur, resulting in intracellular enzyme activation and **pancreatic autodigestion**.

Acute pancreatitis may occur when factors involved in maintaining cellular homeostasis are out of balance. The initiating event may be anything that **injures the acinar cell** and impairs the secretion of zymogen granules; examples include **alcohol** use, **gallstones**, and certain **drugs**.

At present, it is unclear exactly what pathophysiologic event triggers the onset of acute pancreatitis. It is believed, however, that both extracellular factors (eg, neural and vascular response) and intracellular factors (eg, intracellular digestive enzyme activation, increased calcium signaling, and heat shock protein activation) play a role. Once a cellular

injury pattern has been initiated, **cellular membrane trafficking becomes chaotic**, with the following deleterious effects:

- Lysosomal and zymogen granule compartments fuse, enabling activation of trypsinogen to trypsin,
- Intracellular trypsin triggers the entire zymogen activation cascade,
- Secretory vesicles are extruded across the basolateral membrane into the interstitium, where molecular fragments act as chemoattractants for inflammatory cells.

Activated neutrophils then exacerbate the problem by releasing superoxide or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, **macrophages release cytokines** that further mediate local (and, in severe cases, systemic) inflammatory responses. The early mediators defined to date are **tumor necrosis factor-alpha, interleukin-6, and IL-8**.

These mediators of inflammation cause an increased pancreatic vascular permeability, leading to **hemorrhage, edema, and eventually pancreatic necrosis**. As the mediators are excreted into the circulation, **systemic complications** can arise, such as bacteremia due to gut flora translocation, acute respiratory distress syndrome, pleural effusions, gastrointestinal hemorrhage, and renal failure.

The **systemic inflammatory response syndrome** can also develop, leading to the development of systemic shock. Eventually, the mediators of inflammation can become so overwhelming to the body that hemodynamic instability and death ensue.

In acute pancreatitis, parenchymal edema and peripancreatic fat necrosis occur first; this is known as acute edematous pancreatitis. When necrosis involves the parenchyma, accompanied by hemorrhage and dysfunction of the gland, the inflammation evolves into hemorrhagic or necrotizing pancreatitis**. Pseudocysts and pancreatic abscesses** can result from necrotizing pancreatitis because enzymes can be walled off by granulation tissue (pseudocyst formation) or via bacterial seeding of pancreatic or peripancreatic tissue (pancreatic abscess formation).

The history of renal disease, hypoxemia, and abdominal compartment syndrome are significant risk factors for **acute renal failure** in patients with severe acute pancreatitis.

Chronic Pancreatitis

Chronic pancreatitis is commonly defined as a continuing, chronic, inflammatory process of the pancreas, characterized by **irreversible morphologic changes**. This chronic inflammation can lead to chronic abdominal pain and/or impairment of endocrine and exocrine function of the pancreas. Chronic pancreatitis usually is envisioned as an **atrophic fibrotic gland with dilated ducts and calcifications**.

By definition, chronic pancreatitis is a completely different process from acute pancreatitis. In acute pancreatitis, the patient presents with acute and severe abdominal pain, nausea, and vomiting. The pancreas is acutely inflamed (neutrophils and edema), and the serum levels of pancreatic enzymes (amylase and lipase) are elevated. Full recovery is observed in most patients with acute pancreatitis, whereas in chronic pancreatitis, the primary process is a chronic, irreversible inflammation (monocyte and lymphocyte) that leads to **fibrosis with calcification**.

Whatever the etiology of chronic pancreatitis, pancreatic fibrogenesis appears to be a typical response to injury. This involves a complex interplay of **growth factors, cytokines, and chemokines**, leading to deposition of extracellular matrix and fibroblast proliferation. Evidence indicates involvement of distinct chemokines in the initiation and perpetuation of chronic pancreatitis.

Pancreatic Necrosis and Abscess

Although there can be overlap in the characterization of infections in the pancreas, recognizing the different terms used in describing this **complication of acute pancreatitis** is important. A pancreatic abscess (PA) is a collection of pus resulting from tissue necrosis, liquefaction, and infection. **Infected necrosis** refers to bacterial contamination of necrotic

pancreatic tissue in the absence of abscess formation. A **pseudocyst** is a peripancreatic fluid collection containing high concentrations of pancreatic enzymes within a defined fibrous wall and lacking an epithelial lining.

Pancreatic abscess is a late complication of acute necrotizing pancreatitis (ANP), occurring more than 4 weeks after the initial attack.

Pancreatic abscesses form through various mechanisms, including fibrous wall formation around fluid collections, penetrating peptic ulcers, and secondary infection of pseudocysts.

Pancreatic Pseudocysts

Single or multiple fluid collections that look like cysts on pancreatic imaging are often observed during acute pancreatitis. Pseudocysts are best defined as a localized **fluid collection** that is rich in **amylase and other pancreatic enzymes**, that has a **nonepithelialized wall** consisting of fibrous and granulation tissue, and that usually appears several weeks after the onset of pancreatitis.

These characteristics contrast with those of acute fluid collections, which are more evanescent and are serosanguinous inflammatory reactions to acute pancreatitis. Pancreatic pseudocysts can be single or multiple. Multiple cysts are more frequently observed in patients with alcoholism.

The pathogenesis of pseudocysts seems to stem from disruptions of the pancreatic duct due to **pancreatitis and extravasation of enzymatic material**.

VASCULAR SYSTEM

Aterosclerosis

- Abdominal aorta aneurysm
- Thoracic aortic aneurysm
- Aortic dissection
- Carotid artery disease
- Subclavian steal syndrome
- Myocardial rupture, cardiac tamponade
- Aortoiliac occlusive disease
- Peripheral vascular disease
- Mesenteric ischemia
- Abdominal angina

Superficial trombophlebitis

Deep venous thrombosis

- Phlegmasia alba and cerulea solens

Superior vena cava syndrome

Arteriovenous fistula

Ischemic ulcers

Diabetic foot

Disseminated intravascular coagulation

Syncope

Aterosclerosis

Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by the following:

- Endothelial dysfunction
- Vascular inflammation

- Buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall

Atherosclerotic buildup results in the following:

- Plaque formation
- Vascular remodeling
- Acute and chronic luminal obstruction
- Abnormalities of blood flow
- Diminished oxygen supply to target organs

These so-called **vulnerable plaques**, as compared with stable plaques, consist of a large lipid core, inflammatory cells, and thin, fibrous caps that are subjected to greater biomechanical stress, thus leading to **rupture that perpetuates thrombosis**.

Initially thought to be a chronic, slowly progressive. Although a systemic disease, atherosclerosis manifests in a focal manner and affects different organ systems in different patients for reasons that remain unclear.

Plaque growth and vascular remodeling

Hemodynamic factors interact with the **activated vascular endothelium**. Fluid shear stresses generated by blood flow influence the phenotype of the endothelial cells by modulation of gene expression and regulation of the activity of flow-sensitive proteins.

Atherosclerotic plaques (or atheromas), which may require 10-15 years for full development, characteristically occur in regions of branching and marked curvature at areas of geometric irregularity. **Shear stress and turbulence** may promote atherogenesis at these important sites within the coronary arteries, the major branches of the thoracic and abdominal aorta, and the large conduit vessels of the lower extremities.

The earliest pathologic lesion of atherosclerosis is the **fatty streak**, which is observed in most individuals by age 20 years. The fatty streak is the result of focal accumulation of serum lipoproteins within the intima of the vessel wall. Microscopy reveals **lipid-laden macrophages**, T lymphocytes, and smooth muscle cells in varying proportions. The fatty

streak may progress to form a **fibrous plaque**, the result of progressive lipid accumulation and the **migration and proliferation of smooth muscle cells**.

Platelet-derived growth factor, insulinlike growth factor, thrombin, and angiotensin II (A-II) are **potent mitogens** that are produced by activated platelets, macrophages, and dysfunctional endothelial cells that characterize early atherogenesis, vascular inflammation, and platelet-rich thrombosis at sites of **endothelial disruption**. The relative deficiency of endothelium-derived **nitric oxide** further potentiates this proliferative stage of **plaque maturation**.

The smooth muscle cells are responsible for the deposition of extracellular connective tissue matrix and form a fibrous cap that overlies a core of lipid-laden foam cells, extracellular lipid, and necrotic cellular debris. Growth of the fibrous plaque results in **vascular remodeling**, progressive luminal narrowing, blood-flow abnormalities, and compromised oxygen supply to the target organ. Developing atherosclerotic plaques acquire their own microvascular network, the **vasa vasorum**, which are prone to **hemorrhage** and contribute to **progression of atherosclerosis**.

As endothelial injury and inflammation progress, fibroatheromas grow and form the plaque. As the plaque grows, 2 types of remodeling occur. **Positive remodeling** is an outward compensatory remodeling in which the **arterial wall bulges** outward and the lumen remains uncompromised. Such plaques grow further; however, they do not become hemodynamically significant for a long time. In fact, the plaque does not begin to encroach on the lumen until it occupies 40% of the cross-sectional area. The **encroachment must be at least 50-70% to cause flow limitation**. Many fewer lesions exhibit almost no compensatory vascular dilation, and the atheroma steadily grows inward, causing gradual luminal narrowing. Many of the plaques with initial positive remodeling eventually progress to the **negative remodeling stage**, causing **narrowing**

of the vascular lumen. They are also vulnerable to plaque rupture and thrombosis.

Plaque rupture

Denudation of the overlying endothelium or rupture of the protective fibrous cap may result in exposure of the **thrombogenic contents** of the core of the plaque to the circulating blood. This exposure constitutes an advanced or complicated lesion. The plaque rupture occurs due to weakening of the fibrous cap. Inflammatory cells localize to the shoulder region of the vulnerable plaque. T lymphocytes elaborate interferon gamma, an important cytokine that **impairs vascular smooth muscle cell proliferation and collagen synthesis**. Furthermore, activated macrophages produce **matrix metalloproteinases** that degrade collagen.

A plaque rupture may result in **thrombus formation, partial or complete occlusion** of the blood vessel, and progression of the atherosclerotic lesion due to organization of the thrombus and incorporation within the plaque. Plaque rupture is the main event that causes acute presentations.

Most plaque ruptures occur because of disruption of the fibrous cap, which allows contact between the highly thrombogenic lipid core and the blood. These modestly obstructive plaques, which have a greater burden of soft lipid core and thinner fibrous caps with chemoactive cellular infiltration near the shoulder region, are called **vulnerable plaques**. The amount of collagen in the fibrous cap depends on the balance between synthesis and destruction of intercellular matrix and inflammatory cell activation.

Abdominal Aorta Aneurysm

The aortic wall contains smooth muscle, elastin, and collagen arranged in concentric layers in order to withstand arterial pressure. The **number of medial elastin layers from the proximal thoracic aorta to the infrarenal aorta is markedly reduced**, with medial thinning and intimal thickening. Elastin is the principal load-bearing element in the aorta. The

decrease in content coupled with the histological changes of this matrix protein in aneurysms may explain the propensity for aneurysm formation in the infrarenal aorta. Genetic predisposition clearly exists.

The aortic media appear to degrade by means of a proteolytic process. This implies **an increase in the concentration of proteolytic enzymes relative to their inhibitors** in the abdominal aorta as the individual ages. Reports have documented increased expression and activity of **matrix metalloproteinases**. A **chronic adventitial and medial inflammatory infiltrate** is demonstrated.

Most abdominal aortic aneurysms occur in persons with **advanced atherosclerosis**. Atherosclerosis may induce abdominal aortic aneurysm formation by causing **mechanical weakening of the aortic wall with loss of elastic recoil, along with degenerative ischemic changes, through obstruction of the vasa vasorum**.

The combination of proteolytic degradation of aortic wall connective tissue, inflammation and immune responses, biomechanical wall stress, and molecular genetics represents a dynamic process that leads to **aneurysmal deterioration** of aortic tissue.

Thoracic Aortic Aneurysm

The occurrence and expansion of an aneurysm in a given segment of the arterial tree probably involves local hemodynamic factors and factors intrinsic to the arterial segment itself. **Elastic fiber fragmentation** and loss with **degeneration of the media** result in weakening of the aortic wall, loss of elasticity, and consequent dilation.

The human aorta is a relatively low-resistance circuit for circulating blood. **Systemic hypertension** compounds the injury, accelerates the expansion of known aneurysms, and may contribute to their formation. Hemodynamically, the coupling of **aneurysmal dilation and increased wall stress** is present. As diameter increases, wall tension increases, which contributes to increasing diameter. As tension increases, risk of rupture increases.

When symptomatic by **rupture or dissection**, they may involve the pericardium, aortic valve, or coronary arteries. They may rupture into the pericardium, causing tamponade. They may dissect into the aortic valve, causing aortic insufficiency, or into the coronary arteries, causing myocardial infarction.

Aortic Dissection

The aortic wall is exposed to high pulsatile pressure and shear stress, making the aorta particularly prone to injury and disease from **mechanical trauma**. The aorta is more prone to rupture than any other vessel, especially with the development of aneurysmal dilatation, because its wall tension.

An intimal tear **connects the media with the aortic lumen**, and an exit tear creates a true lumen and a false lumen. The **true lumen** is lined by intima, and the **false lumen** is lined by media. The true lumen is frequently smaller than the false lumen. Typically, **flow in the false lumen is slower than flow in the true lumen**, and the false lumen often becomes aneurysmal when subjected to systemic pressure.

Ascending aortic involvement may result in **death** from wall rupture, hemopericardium and tamponade, occlusion of the coronary ostia with myocardial infarction, or severe aortic insufficiency.

Carotid Artery Disease

Symptomatic carotid artery disease is conventionally defined as the **sudden onset of focal neurologic symptoms** and attributable to a carotid artery vascular distribution. Carotid artery disease is typically the result of **atherosclerosis at the bifurcation of the common carotid artery** or in the origins of either the internal or the external carotid artery. Cholesterol deposits in the endothelium and underlying smooth muscle of the artery are accompanied by cellular proliferation of the surrounding fibrous and smooth muscle tissues to form atheromatous plaque. Large

plaque that extends into the lumen of the artery not only reduces blood flow but also presents an irregular surface prone to thrombus formation. Proposed mechanisms of **stroke or transient ischemic attack** include embolism of plaque associated thrombus or other atheromatous debris, acute thrombotic carotid artery occlusion from plaque erosion or rupture, or reduced cerebral perfusion from progressive plaque growth and expansion.

During periods prone to ischaemia **collateral flow** is critical for cerebral blood flow compensation and a major determinant of the severity of the ischaemic insult. Other factors include plaque morphology, duration of hypoperfusion, characteristics of the embolus, and cerebral vasoreactivity (cerebrovascular reserve, or the capacity for vasodilation). The principal pathways of collateral flow are the Circle of Willis, extracranial anastomotic channels, and leptomeningeal communications that bridge watershed areas between major arteries.

Subclavian Steal Syndrome

The term subclavian steal has been used to describe **retrograde blood flow in the vertebral artery** associated with proximal **ipsilateral subclavian artery stenosis or occlusio**n. This phenomenon may occur when the subclavian artery is occluded proximal to the origin of the vertebral artery. The term subclavian steal syndrome should really be reserved for those patients who develop **neurological symptoms** as a consequence of brain ischemia that occurs **during or immediately following exercise of the ipsilateral arm**.

Subclavian steal produces symptoms by **flow-related phenomena** rather than embolic. When an atherosclerotic lesion in the proximal subclavian artery progresses to cause hemodynamically significant stenosis, **collateral vessels** from the subclavian artery gradually enlarge. The upper extremity becomes dependent on these large collateral blood vessels that originate from the subclavian artery distal to the obstruction.

The collateral vessels serve as points of re-entry for **blood flowing retrograde into the arm from the head, shoulder, and neck**, thereby providing the extremity with adequate perfusion. When the arm is exercised, the blood vessels dilate to enhance perfusion to the ischemic muscle, thus lowering the resistance in the outflow vessels. Blood is siphoned from the head, neck, and shoulder through collateral vessels to supply this low-resistance vascular bed, satisfying increased oxygen demand by the exercising muscles of the upper extremity.

Myocardial Rupture

Myocardial rupture occurs in the setting of acute myocardial infarction, blunt and penetrating cardiac trauma, primary cardiac infection, primary and secondary cardiac tumors, infiltrative diseases of the heart, and aortic dissection.

The **consequences** of myocardial rupture can include pericardial tamponade, ventricular septal defect with left-to-right shunt, acute mitral regurgitation, or formation of a pseudoaneurysm. Both hemodynamic factors (increased intracavitary pressure) and regional myocardial structural weakness (myocyte necrosis, collagen matrix resolution, intense inflammation) are important contributory factors.

Blunt cardiac trauma, most commonly in the setting of an automobile accident, may cause myocardial rupture as a result of cardiac compression between the sternum and the spine, direct impact (sternal trauma), or from deceleration injury. It may result in rupture of the papillary muscles, cardiac free wall, or the ventricular septum.

Cardiac tamponade

Cardiac tamponade is a clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in **reduced ventricular filling** and subsequent hemodynamic compromise.

The pericardial space normally contains 20-50 ml of fluid. Pericardial effusions can be serous, serosanguineous, hemorrhagic, or chylous.

3 phases of hemodynamic changes in tamponade:

- *Phase I*: The accumulation of pericardial fluid causes increased stiffness of the ventricle, requiring a higher filling pressure. During this phase, the **left and right ventricular filling pressures are higher than the intrapericardial pressure**.
- *Phase II*: With further fluid accumulation, the **pericardial pressure increases above the ventricular filling pressure**, resulting in **reduced cardiac output**.
- *Phase III*: A **further decrease in cardiac output** occurs, which is due to **equilibration of pericardial and left ventricular filling pressures**.

The underlying pathophysiologic process for the development of tamponade is **markedly diminished diastolic filling** because transmural distending pressures are insufficient to overcome the increased intrapericardial pressures. Tachycardia is the initial cardiac response to maintain the cardiac output.

Systemic venous return is also altered during tamponade. Because the heart is compressed throughout the cardiac cycle due to the increased intrapericardial pressure, systemic venous return is impaired and right atrial and right ventricular collapse occurs. Because the pulmonary vascular bed is a vast and compliant circuit, blood preferentially accumulates in the venous circulation, at the expense of left venricle filling. This results in **reduced cardiac output and venous return**.

The amount of pericardial fluid needed to impair the diastolic filling of the heart depends on the rate of fluid accumulation and the compliance of the pericardium. **Rapid accumulation** of as little as **150 m**l of fluid can result in a **marked increase in pericardial pressure** and can severely impede cardiac output, whereas **1000 ml of fluid may accumulate over a longer period without any significant effect on diastolic filling** of the heart. This is due to adaptive stretching of the pericardium over time.

Aortoiliac Occlusive Disease

In patients with peripheral arterial disease, obstructing plaques caused by atherosclerotic occlusive disease commonly occur in the **infrarenal aorta and iliac arteries**. Atherosclerotic plaques may induce symptoms either by obstructing blood flow or by embolizing atherosclerotic and/or thrombotic debris to more distal blood vessels. If the plaques are large enough to impinge on the arterial lumen, reduction of blood flow to the extremities occurs.

One theory emphasizes that atherosclerosis occurs as a response to arterial injury. Factors that are known to be injurious to the arterial wall include mechanical factors such as **hypertension** and low wall shear stress, as well as chemical factors such as **nicotine, hyperlipidemia, hyperglycemia, and homocysteine**.

Some plaques are unstable, and fissures occur on the surface of the plaque that expose the circulating platelets to the inner elements of the atheroma. **Platelet aggregation** then is stimulated. Platelets bind to fibrin and a fresh blood clot forms in the area of plaque breakdown.

If the atheroma enlarges enough to occupy at least 50% of the arterial lumen, the flow velocity of blood through that stenosis can significantly increase. The oxygen requirements of the lower extremity at rest are low enough that even with a moderate proximal stenosis, no increase in blood flow velocity occurs. During exercise, however, the oxygen debt that occurs in ischemic muscle cannot be relieved because of the proximal obstruction of blood flow; this results in **claudication symptoms**. In more advanced cases, critical tissue ischemia occurs, and **neuropathic rest pain or tissue loss ensues**. Commonly, in patients with critical limb ischemia, multiple arterial segments are involved in the occlusive atherosclerotic process.

Peripheral Vascular Disease

Peripheral vascular disease is a nearly pandemic condition that has the potential to cause loss of limb or even loss of life. Peripheral vascular

disease manifests as **insufficient tissue perfusion caused by existing atherosclerosis** that may be acutely compounded by either emboli or thrombi.

Peripheral vascular disease, also known as **arteriosclerosis obliterans**, is primarily the result of atherosclerosis. The atherosclerotic process may gradually progress to complete occlusion of **medium and large arteries**. Vascular disease may manifest acutely when thrombi, emboli, or acute trauma compromises perfusion. Thromboses are often of an atheromatous nature and occur in the lower extremities more frequently than in the upper extremities. **Multiple factors predispose patients for thrombosis**. These factors include sepsis, hypotension, low cardiac output, aneurysms, aortic dissection, bypass grafts, and underlying atherosclerotic narrowing of the arterial lumen.

Emboli, the most common cause of sudden ischemia, usually are of cardiac origin (80%); they also can originate from proximal atheroma, or tumor. Emboli tend to lodge at artery bifurcations or in areas where vessels abruptly narrow. The femoral artery bifurcation is the most common site (43%), followed by the iliac arteries (18%), the aorta (15%), and the popliteal arteries (15%).

The site of occlusion, presence of collateral circulation, and nature of the occlusion (thrombus or embolus) determine the severity of the acute manifestation. Emboli tend to carry higher morbidity because the **extremity has not had time to develop collateral circulation**. Whether caused by embolus or thrombus, occlusion results in both proximal and distal thrombus formation due to flow stagnation.

Peripheral arterial occlusive disease

Claudication, which is defined as **reproducible ischemic muscle pain**, is one of the most common manifestations of peripheral vascular disease caused by atherosclerosis. Claudication occurs during **physical activity** and is relieved after a short rest. Pain develops because of **inadequate blood flow**.

Under resting conditions, normal blood flow to extremity muscle groups averages 300-400 ml/min. Once exercise begins, blood flow increases up to 10-fold owing to the **increase in cardiac output and compensatory vasodilation** at the tissue level. When exercise ceases, blood flow returns to normal within minutes.

In patients resting blood flow is similar to that of a healthy person. However, during exercise, blood flow cannot maximally increase in muscle tissue because of **proximal arterial stenoses**. When the metabolic demands of the muscle exceed blood flow, claudication symptoms ensue. At the same time, a longer recovery period is required for blood flow to return to baseline once exercise is terminated.

Mesenteric Ischemia

Patients with mesenteric ischemia have a rare, potentially life-threatening disease. Acute and chronic forms of mesenteric ischemia share many similarities and have many differences. This article discusses mesenteric artery ischemia in general.

The splanchnic blood flow normally ranges from 10-40% of the cardiac output depending on the state of the patient. This wide variation in flow through the mesenteric system is caused by **local and regional control mechanisms**. **Adenosine**, a metabolic byproduct of ischemia, causes dilation of the splanchnic vessels, as does nitric oxide. The **sympathetic system** antagonizes these vasodilatory effects and causes redirection of the blood from the gut to the more vital brain and heart during times of stress. Activation of the **renin-angiotensin** pathway is also known to cause vasoconstriction of the splanchnic bed. During times of **hypovolemia**, a patient may experience nonobstructive mesenteric ischemia because of the low-flow state.

The consequences of vascular occlusion depend on the vessels involved. A patient with **chronic mesenteric ischemia** with atrial fibrillation who has an embolism to a branch of the superior mesenteric artery may experience mild or no symptoms because of adequate

collateral flow. The patient with **acute thrombosis** loses perfusion from the origin of the superior mesenteric artery, resulting in a greater amount of **dead bowel**. Tissue injury can result from one of 2 mechanisms:

- **ischemic injury** to the bowel or
- **reperfusion injury**.

Within 4 hours after ischemia begins, the **mucosal villi** become necrotic. As early as 6 hours, **full-thickness infarction** can be observed. If left untreated, patients can **hemorrhage** into their bowel, experience **perforation**, and, ultimately, become **septic** and die.

Reperfusion injury occurs when ischemic bowel regains its blood flow. The result is a release of **oxygen free radicals** by leukocytes.

Acute mesenteric ischemia

Insufficient perfusion of the small bowel and colon may result from arterial occlusion by **embolus or thrombosis**, thrombosis of the venous system, or **nonocclusive processes** such as vasospasm or low cardiac output.

Injury severity is inversely proportional to the mesenteric blood flow and is influenced by the number of vessels involved, systemic mean blood pressure, duration of ischemia, and collateral circulation. The **superior mesenteric vessels** are involved more frequently than the inferior mesenteric vessels, with blockage of the latter often being silent because of better collateral circulation.

Damage to the affected bowel portion may range from reversible ischemia to transmural infarction with necrosis and perforation. The injury is complicated by reactive vasospasm in the superior mesenteric artery region after the initial occlusion. Arterial insufficiency causes **tissue hypoxia**, leading to initial **bowel wall spasm**. This leads to gut emptying by **vomiting or diarrhea**. Mucosal sloughing may cause **bleeding** into the gastrointestinal tract.

At this stage, **little abdominal tenderness** is present, producing the classic **intense visceral pain that is disproportionate to physical examination findings**.

As the ischemia persists, the **mucosal barrier** becomes **disrupted**, and bacteria, toxins, and vasoactive substances are released into the systemic circulation. This can cause death from **septic shock**, cardiac failure, or **multisystem organ failure** before bowel necrosis actually occurs.

As hypoxic damage worsens, the bowel wall becomes edematous and cyanotic. **Fluid is released into the peritoneal cavity**. Bowel necrosis can occur in 8-12 hours from the onset of symptoms. Transmural necrosis leads to peritoneal signs and heralds a much worse prognosis.

Embolic acute mesenteric ischemia is usually caused by an **embolus of cardiac origin**. Typical causes include mural thrombi after myocardial infarction, atrial thrombi associated with mitral stenosis and atrial fibrillation, vegetative endocarditis.

The vascular occlusion is sudden, so the patients have not developed a compensatory increase in collateral flow. As a result, they experience worse ischemia than patients with thrombotic acute mesenteric ischemia. The superior mesenteric artery is the visceral vessel most susceptible to emboli because of its small take-off angle from the aorta and higher flow.

Thrombotic acute mesenteric ischemia is a late complication of preexisting **visceral atherosclerosis**. Symptoms do not develop until 2 of the 3 arteries (usually the celiac and superior mesenteric arteries) are stenosed or completely blocked. Progressive worsening of the atherosclerotic stenosis before the acute occlusion allows time for development of additional **collateral circulation**.

A drop in cardiac output from myocardial infarction or congestive heart failure may cause acute mesenteric ischemia in a patient with visceral atherosclerosis.

Non-occlusive mesenteric ischemia is precipitated by a **severe reduction in mesenteric perfusion**, with secondary arterial spasm from such causes as cardiac failure, septic shock, hypovolemia, or the use of

potent **vasopressors** in patients in critical condition. Because bowel perfusion, similar to cerebral perfusion, is preserved in the setting of hypotension, ischemia represents a **failure of autoregulation**.

Mesenteric venous trombosis often (ie, >80% of the time) is the result of some processes that make the patient more likely to form a clot in the mesenteric circulation (ie, secondary trombosis). Other associated causes include **pancreatitis, sickle cell disease, and hypercoagulability caused by malignancy**. Symptoms may be present longer than in the typical cases of acute mesenteric ischemia, sometimes exceeding 30 days. Infarction from trombosis is rarely observed with isolated superior mesenteric vein thrombosis, unless collateral flow in the peripheral arcades or vasa recta is compromised as well. **Fluid sequestration** and **bowel wall edema** are more pronounced than in arterial occlusion.

Chronic mesenteric ischemia

In more than 95% of patients, the cause of mesenteric ischemia is **diffuse atherosclerotic disease**, which decreases the flow of blood to the bowel. As the atherosclerotic disease progresses, symptoms worsen. Usually, all 3 major mesenteric arteries are occluded or narrowed.

Although the pathophysiologic mechanism by which ischemia produces **pain** is still not completely understood, current physiologic understanding of splanchnic perfusion suggests a key role for the splanchnic circulation in the regulation of cardiovascular homeostasis. **Gastrointestinal perfusion is often compromised early relative to other vascular beds** in situations including critical illness, major surgery, and exercise, all of which are characterized by increased demands on the circulation to maintain tissue oxygen delivery. Perhaps more importantly, this relative hypoperfusion often outlasts the period of the hypovolemic insult or low-flow state.

Mesenteric artery trombosis

The atherosclerotic plaque, usually at the origin of the superior mesenteric artery or celiac artery, grows over time. It is the most common visceral branch to thrombose.

A thrombus forms during a state of **low flow**, resulting in acute cessation of flow to the gut. **Bloody stools** develop as the more sensitive mucosa dies first.

The bowel gradually becomes necrotic; subsequently, **bacterial overgrowth** develops, and the resulting **bowel perforation** causes sepsis and finally death.

Mesenteric venous thrombosis

Mesenteric venous thrombosis (also known as visceral venous thrombosis) is a rare but lethal form of mesenteric ischemia.

While the mesenteric arterial system may carry 25-40% of the cardiac output at one time, the venous system typically carries 30%. The mechanism that causes ischemia is a **massive influx of fluid into the bowel wall and lumen**, resulting in systemic hypovolemia and hemoconcentration. Resulting bowel edema and decreased outflow of blood secondary to venous thrombosis impede the inflow of arterial blood, which leads to bowel ischemia. While bowel ischemia is detrimental to the patient, the resulting **multiple organ system failure** actually accounts for the increased mortality rate.

Abdominal Angina

Abdominal angina is defined as the **postprandial pain** that occurs in individuals with sufficient mesenteric vascular occlusive disease such that **blood flow cannot increase enough to meet visceral demands**. The mechanism is believed to be similar to the angina pectoris or the intermittent claudication.

Intestinal ischemia results from the **mismatch of oxygen supply to and oxygen consumption** by the gastrointestinal tract owing to reduced blood flow. The decreased blood flow results from narrowing of the mesenteric vessels, which can be secondary to a thrombus or embolus. The most common cause of abdominal angina is **atherosclerotic vascular disease**.

Unless significant stenoses or actual occlusion of 2 of the 3 vessels is present, efficient collateral circulation between the celiac and superior

mesenteric arteries (ie, the pancreaticoduodenal arcades) and the superior and inferior mesenteric arteries (ie, the meandering mesenteric artery) ensures that blood flow to the gut generally is adequate. Because the superior mesenteric artery provides vascularity to the foregut, midgut, and hindgut, collaterals cannot sufficiently compensate for occlusion of this central artery.

Within 15 minutes of eating increased blood flow in the celiac and superior mesenteric vessels can be shown in healthy volunteers. Patients with abdominal angina are **unable to sufficiently increase flow** in the mesenteric vessels, and ischemic pain results. Affected individuals learn to associate food with pain, and thus, they develop a fear of eating. Weight loss may be significant.

Superficial Trombophlebitis

Thrombosis or thrombophlebitis of the superficial venous system receives little attention in textbooks of surgery and medicine. It is usually a benign self-limiting disease, but it can be recurrent and tenaciously persistent. At times, when affecting the greater saphenous vein, **thrombophlebitis can progress into the deep venous system**, which may lead to pulmonary embolism. Superficial thrombophlebitis is an **inflammatory reaction with thrombus** of a vein under the skin.

Although the etiology is frequently obscure, superficial venous thrombosis is most often associated with one of the components of the **Virchow triad**, ie, intimal damage (which can result from trauma, infection, or inflammation), stasis, or changes in the blood constituents (presumably causing changes in coagulability). Superficial thrombophlebitis usually occurs in the lower extremities, it also occurs anywhere medical interventions occur, such as in the arm or neck (external jugular vein) from intravenous catheters.

Deep Venous Thrombosis

Deep venous thrombosis and pulmonary embolism are manifestations of a single disease entity, namely, venous thromboembolism.

Deep venous thrombosis is the presence of coagulated blood, a thrombus, in one of the deep venous conduits that return blood to the heart. The clinical conundrum is that symptoms (pain and swelling) are often nonspecific or absent. However, if left untreated, the thrombus may become fragmented or dislodged and migrate to obstruct the arterial supply to the lung.

Rudolf Virchow described 3 factors that are critically important in the development of venous thrombosis:

- venous stasis,
- activation of blood coagulation, and
- vein damage.

Venous stasis can occur as a result of anything that slows or obstructs the flow of venous blood. This results in an increase in viscosity and the formation of microthrombi, which are not washed away by fluid movement; the thrombus that forms may then grow and propagate.

Endothelial (intimal) damage in the blood vessel may be intrinsic or secondary to external trauma. It may result from accidental injury or surgical insult.

A **hypercoagulable state** can occur due to a biochemical imbalance between circulating factors. This may result from an increase in circulating tissue activation factor, combined with a decrease in circulating plasma antithrombin and fibrinolysins.

The origin of venous thrombosis is frequently multifactorial, with components of the Virchow triad assuming variable importance in individual patients, but the end result is early thrombus interaction with the endothelium. This interaction stimulates **local cytokine production**

and facilitates leukocyte adhesion to the endothelium, both of which promote venous thrombosis.

Decreased vein wall contractility and **vein valve dysfunction** contribute to the development of **chronic venous insufficiency**.

Development of thrombosis

It may be initiated via several pathways, usually consisting of cascading activation of enzymes that magnify the effect of an initial trigger event. A similar complex of events results in fibrinolysis, or the dissolution of thrombi. The **balance of trigger factors and enzymes** is complex. Microscopic thrombus formation and thrombolysis (dissolution) are continuous events, but with increased stasis, procoagulant factors, or endothelial injury, the **coagulation-fibrinolysis balance** may favor the pathologic formation of an obstructive thrombus. Clinically relevant deep venous thrombosis is the persistent formation of macroscopic thrombus in the deep proximal veins.

The coagulation mechanism consists of a series of self-regulating steps that result in the production of a **fibrin clot**. These steps are controlled by a number of relatively inactive cofactors or zymogens, which, when activated, promote or accelerate the clotting process. These reactions usually occur at the **phospholipid surface** of platelets, endothelial cells, or macrophages. Generally, the initiation of the coagulation process can be divided into 2 distinct pathways, an intrinsic system and an extrinsic.

The extrinsic system operates as the result of activation by **tissue lipoprotein**, usually released as the result of some mechanical injury or trauma. **The intrinsic system** usually involves circulating **plasma factors**. Both of these pathways come together at the level of **factor X**. This in turn promotes the conversion of prothrombin to thrombin (factor II).

Once a fibrin clot is formed and has performed its function of hemostasis, mechanisms exist in the body to restore the normal blood flow by lysing the fibrin deposit. **Circulating fibrinolysins** perform this function. **Plasmin** digests fibrin and also inactivates clotting factors V and VIII and fibrinogen.

Three naturally occurring anticoagulant mechanisms exist to prevent inadvertent activation of the clotting process. These include **the heparin-antithrombin III (ATIII), protein C and thrombomodulin protein S**, and the tissue factor inhibition pathways.

Thrombus usually forms behind valve cusps or at venous branch points, most of which begin in the calf. Venodilation may disrupt the endothelial cell barrier and expose the subendothelium. **Platelets adhere to the subendothelial surface** by means of von Willebrand factor or fibrinogen in the vessel wall. **Neutrophils** and platelets are activated, releasing procoagulant and inflammatory mediators. Neutrophils also adhere to the basement membrane and migrate into the subendothelium. Complexes form of the surface of platelets and increase the rate of thrombin generation and fibrin formation. Stimulated leukocytes irreversibly bind to endothelial receptors and extravasate into the vein wall by means of mural chemotaxis. An active inflammatory response occurs in the wall of the vein.

Patients that are **immobilized for long periods** of time seem to be at high risk for the development of venous thrombosis, an additional stimulus is required to develop deep venous thrombosis.

Oral contraceptive use and estrogen replacement therapy

The mechanism for thromboembolic disease in women who use oral contraceptives is multifactorial. Both **estrogens and progestogens** are implicated in promoting thrombosis, even with low-dose therapy. Hypercoagulable state alterations include **hyperaggregable platelets**, decreased endothelial fibrinolysis, elevated levels of procoagulants, increased blood viscosity secondary to elevated red blood cells volume.

Pregnancy

During pregnancy, an increase in most **procoagulant factors** and a **reduction in fibrinolytic activity** occur. Plasma fibrinogen levels gradually increase after the third month of pregnancy, to double those of the nonpregnant state. In the second half of pregnancy, levels of **factors VII,**

VIII, IX, and X also increase. Decreased fibrinolytic activity is probably related to a decrease in the level of circulating plasminogen activator.

Malignancy and illness

Hypercoagulability occurs in association with a number of malignancies. The pathophysiology is poorly understood, but tissue factor, **tumor-associated cysteine proteinase**, **circulating mucin molecules**, and **tumor hypoxemia** have all been implicated as causative factors.

Other factors

Other disease states are associated with venous thromboembolism. Paroxysmal nocturnal **hemoglobinuria, nephritic syndrome, and inflammatory bowel disease** all are associated with increased risks of thromboembolism.

Evolution of venous insufficiency

Over time, **thrombus organization** begins with the infiltration of inflammatory cells into the clot. This results in a fibroelastic intimal thickening at the site of thrombus attachment. In many patients, this interaction between vessel wall and thrombus leads to **valvular dysfunction** and overall vein wall fibrosis. **Vein wall remodeling** after venous thrombosis leads to an imbalance in connective tissue matrix regulation and a loss of regulatory venous contractility that contributes to the development of **chronic venous insufficiency**.

Over a few months, most acute deep venous thrombosis evolve to complete or partial **recanalization**, and **collaterals** develop. Furthermore, the **damage to the underlying valves** and those compromised by **peripheral dilation** and insufficiency usually persists and may progress. **Venous stasis, venous reflux, and chronic edema** are common in patients who have had a large deep venous thrombosis.

The acute effect of an occluded outflow vein may be minimal if adequate collateral pathways exist. As an alternative, it may produce **marked pain and swelling** if flow is forced retrograde. In the presence of deep vein outflow obstruction, contraction of the calf muscle produces

dilation of the feeding perforating veins, it renders the valves nonfunctional (because the leaflets no longer coapt), and it forces the **blood retrograde** through the perforator branches into the **superficial system**. This high-pressure flow may cause dilation of the superficial (usually low-pressure) system and produce superficial venous incompetence. This chain of events (ie, obstruction to antegrade flow producing dilation, stasis, further valve dysfunction, with upstream increased pressure, dilation, and other processes) may produce hemodynamic findings of **venous insufficiency**.

Another mechanism that contributes to venous incompetence is the **natural healing process** of the thrombotic vein. The thrombotic mass is broken down over weeks to months by inflammatory reaction and fibrinolysis, and the **valves and venous wall are altered by organization** and **ingrowth of smooth muscle cells and production of neointima**. This process leaves damaged, incompetent, underlying valves, predisposing them to venous reflux. The mural inflammatory reaction breaks down collagen and elastin, leaving a noncompliant venous wall.

Persistent obstructive thrombus, coupled with valvular damage, ensures continuation of this cycle. Over time, the venous damage may become irreversible. Hemodynamic venous insufficiency is the underlying pathology of postthrombotic syndrome, also referred to as **postphlebitic syndrome**. If numerous valves are affected, flow does not occur centrally unless the leg is elevated. Inadequate expulsion of venous blood results in **stasis** and a persistently elevated venous pressure or **venous hypertension**. As fibrin extravasates and inflammation occurs, the superficial tissues become **edematous and hyperpigmented**. With progression, **fibrosis** compromises tissue oxygenation, and **ulceration** may result.

Venous hypertension in diseased veins is thought to cause **chronic venous insufficiency** by the following sequence of events. Increased venous pressure transcends the venules to the capillaries, impeding flow. Low-flow states within the capillaries cause leukocyte trapping. Trapped

leukocytes release proteolytic enzymes and oxygen free radicals, which damage capillary basement membranes. Plasma proteins, such as fibrinogen, leak into the surrounding tissues, forming a **fibrin cuff**. Interstitial fibrin and resultant **edema** decrease oxygen delivery to the tissues, resulting in local **hypoxia**. Inflammation and tissue loss result.

Pulmonary embolism (Thorax chapter)

Phlegmasia Alba and Cerulea Dolens

Pulmonary embolism complicates approximately 50% of cases of untreated proximal deep venous thrombosis. Less frequent manifestations of venous thrombosis include phlegmasia alba dolens, phlegmasia cerulea dolens, and venous gangrene. These form a clinical spectrum of the same disorder. All 3 manifestations result from **acute massive venous thrombosis and obstruction of the venous drainage of an extremity**.

In ***phlegmasia alba dolens***, the thrombosis involves only **major deep venous channels of the extremity**, therefore sparing collateral veins. The **venous drainage is decreased** but still present; the **lack of venous congestion** differentiates this entity from plegmasia cerulea dolens.

In ***plegmasia cerulea dolens***, the **thrombosis extends to collateral veins**, resulting in **venous congestions** with massive **fluid sequestration** and **more significant edema**. Without established gangrene, these phases are reversible if proper measures are taken.

Of plegmasia cerulea dolens cases, 40-60% also have capillary involvement, which results in ***irreversible venous gangrene*** that involves the skin, subcutaneous tissue, or muscle. Under these conditions, the hydrostatic pressure in arterial and venous capillaries exceeds the oncotic pressure, causing fluid sequestration in the interstitium. **Venous pressure may increase rapidly**, as much as 16- to 17-fold within 6 hours. Fluid sequestration may reach 6-10 l in the affected extremity within days. **Circulatory shock**, which is present in about one third of patients, and **arterial insufficiency may ensue**.

The exact mechanism may involve shock, increased venous outflow resistance, and **collapse of arterioles** due to increased interstitial pressure.

Superior Vena Cava Syndrome

Superior vena cava syndrome is obstruction of blood flow through the superior vena cava. It is a medical emergency and most often manifests in **patients with a malignant disease process within the thorax**.

The superior vena cava is the major drainage vessel for venous blood from the head, neck, upper extremities, and upper thorax. It is located in the middle mediastinum and is **surrounded by relatively rigid structures** such as the sternum, trachea, right bronchus, aorta, pulmonary artery, and the perihilar and paratracheal lymph nodes. It is a thin-walled, low-pressure, vascular structure. This wall is easily compressed as it traverses the right side of the mediastinum.

Obstruction of the superior vena cava may be caused by neoplastic invasion of the venous wall associated with intravascular thrombosis or, more simply, by extrinsic pressure of a tumor mass against the relatively fixed thin-walled superior vena cava. Incomplete superior vena cava obstruction is more often secondary to extrinsic compression without thrombosis.

An obstructed superior vena cava initiates **collateral venous return** to the heart from the upper half of the body. The first and most important pathway is the **azygous venous system**.

Despite these collateral pathways, **venous pressure** is almost always elevated in the upper compartment if obstruction of the superior vena cava is present. Venous pressure is as high as 200-500 cm H_2 O.

Arteriovenous Fistula

Arteriovenous fistula describes an abnormal communication between an artery and a vein and can occur at any point in the vascular system. Classification of vascular anomalies has been recently revised, resulting in a division being made between tumors and malformations.

Vascular tumors

The most common vascular tumor is **infantile hemangioma**. It is seen shortly after birth. These tumors are usually solitary but not infrequently they may be multiple and involving the liver, GI tract, and CNS. They are characterized by 3 phases of growth-proliferation, involution, and involuted phase.

The first phase is characterized by **rapid growth of the tumor**, bright red or bluish in color. They may develop **surface ulcerations** and episodes of **bleeding**.

The involuting phase usually begins at the end of first year of life and is characterized by decreased tempo of the tumor growth, with the gradual color fading from the center of the mass and less tense consistency.

Transition to the involuted phase occurs during the second half of the first decade of life. Normal skin is restored in half of patients, and persistent skin changes such as **telangiectasias**, skin thinning and scarring may occur.

Vascular malformations

Generally, congenital vascular malformations are in-born errors in embryologic development.

Venous malformations are the most common vascular malformations. They are usually sporadic and may be present at birth but are not always clinically obvious and predominantly occur in the skin and soft tissue.

Arteriovenous malformations have the presence of arteriovenous shunts in multiple capillary beds both on the skin but also involving

internal organs. They are usually accompanied by a bruit and hyperemia with prominent venous outflow.

An abnormal communication causes shunting of blood from the high-pressure arterial side to the low-pressure venous side. Blood follows the path of least resistance. Flow in the afferent artery and efferent vein increases, causing dilatation, thickening, and tortuosity of the vessels.

If the resistance in the fistula is low enough, the fistulous tract steals from the distal arterial supply, actually causing a reversal of arterial flow in the segment distal to the arteriovenous fistula. This is known as a **parasitic circulation**. The parasitic circulation causes decreased arterial pressures in the distal capillary beds and can cause **tissue ischemia**.

The heart responds to the decreased peripheral vascular resistance by **increasing stroke volume and cardiac output**. This leads to tachycardia, left ventricular dilatation, and, eventually, heart failure.

Ischemic Ulcers

Arterial (or ischemic) ulceration can be caused by either progressive **atherosclerosis** or **arterial embolization**. Both lead to ischemia of the skin and ulceration.

Venous (or stasis) ulceration is initiated by **venous hypertension** that develops because of inadequate calf muscle pump action and after the onset of either primary (with no obvious underlying etiology) or secondary (as seen after deep venous thrombosis) **valvular incompetence**. Two hypotheses have been proposed to explain venous ulceration once venous hypertension develops.

The first states that distension of the capillary beds occurs because of **increased stasis**. This leads to **leakage of fibrinogen** into the surrounding dermis. Over time, a fibrinous pericapillary cuff is formed, impeding the delivery of oxygen and other nutrients or growth factors to the affected tissue. The resulting hypoxic injury leads to **fibrosis and then ulceration**.

The other hypothesis suggests that the **endothelium is damaged** by increased venous pressure and **leukocyte activation**. **Proteolytic enzymes** and free radicals are released, escape through the leaky vessel walls, and damage the surrounding tissue, leading to **injury and ulceration**.

Diabetic Foot

The term 'Diabetic Foot' consists of a mix of pathologies including **diabetic neuropathy, peripheral vascular disease, Charcot's neuroarthropathy, foot ulceration, and osteomyelitis**.

Diabetic neuropathy can affect the sensory, motor and autonomic functions to varying degrees. **Motor neuropathy** leads to muscle atrophy, foot deformity, altered foot biomechanics, and redistribution of foot pressures which eventually predispose the foot to ulcerate. **Sensory neuropathy** renders the foot '*deaf and blind*' to stimuli, which would normally elicit pain or discomfort. This predisposes the foot to repetitive trauma, which may go unnoticed until ulceration ensues. **Autonomic neuropathy** results in loss of sweating, with the resultant dry skin being predisposed to cracks and fissures. The altered autonomic regulation of cutaneous blood flow also contributes.

Charcot neuroarthropathy is a non-infective process occurring in a well-perfused and insensitive foot. It is characterized by bone and joint destruction, fragmentation and remodelling. The *neurotraumatic theory* attributes bony destruction to the **loss of pain and proprioception**, combined with repetitive mechanical trauma to the foot, which is largely unperceived by the patient who continues to weight bear.

Diabetes is associated with an increased risk of **accelerated atherosclerosis**. Subjects with peripheral vascular disease are predisposed to **poor wound healing**. Poor glycaemic control also impairs polymorphonuclear leucocyte function and predisposes to onychomycosis and toe-web tinea infections, all of which may lead to skin disruption.

Dissemanated Intravascular Coagulation

Disseminated intravascular coagulation is not a specific diagnosis, and its presence always indicates another underlying disease. It is characterized by a **systemic activation of the blood coagulation system**, which results in the generation and **deposition of fibrin**, leading to microvascular thrombi in various organs and contributing to the development of **multiorgan failure**. Consumption and subsequent exhaustion of coagulation proteins and platelets, due to the ongoing activation of the coagulation system, may induce **severe bleeding** complications.

The main pathways leading to fibrin deposition are:

- **tissue factor**-mediated thrombin generation and
- **dysfunctional physiologic anticoagulant mechanisms**, such as the antithrombin system and the protein C system, which insufficiently balance this thrombin generation.

A third pathway in addition to enhanced fibrin formation is impaired fibrin removal due to **depression of the fibrinolytic system**. This impairment of endogenous thrombolysis is mainly caused by high circulating levels of the fibrinolytic inhibitor PAI-1.

Thrombin generation and tissue factor

Thrombin generation is detectable at 3-5 hours after the occurrence of bacteremia or endotoxemia. Ample evidence exists for a pivotal role of the tissue factor/factor VIIa system in the initiation of thrombin generation.

Tissue factor expression on circulating monocytes of patients with severe infection has been demonstrated. Another source of tissue factor may be its localization on polymorphonuclear cells.

Impaired coagulation inhibitor systems

An impaired function of various natural regulating pathways of coagulation activation may amplify the further thrombin generation and contribute to fibrin formation. Plasma levels of the most important

inhibitor of thrombin, **antithrombin III**, are usually markedly reduced in patients with disseminated intravascular coagulation. This reduction is caused by a **combination of consumption**, due to ongoing thrombin generation; **degradation by elastase**, that is released from activated neutrophils; and **impaired synthesis**.

In addition to the decrease in antithrombin III, a significant depression of the protein C system may occur. This impaired function of the **protein C pathway** is mainly due to **downregulation of thrombomodulin** expression on endothelial cells by **proinflammatory cyto**kines, like tumor necrosis factor-alpha and interleukin-1b.

Defective fibrinolysis

There is a rapidly occurring increase in fibrinolytic activity, most probably due to the release of **plasminogen activators** from endothelial cells. However, this **profibrinolytic response is almost immediately followed by a suppression of fibrinolytic activity** due to a sustained increase in plasma levels of **plasminogen activator inhibitor**, type 1.

In general, patients with disseminated intravascular coagulation should not be treated with antifibrinolytic agents, because this may increase the fibrinolytic deficit and may result in increased thrombosis.

Syncope

Syncope is defined as a transient, self-limited loss of consciousness with an **inability to maintain postural tone** that is followed by spontaneous recovery. The term syncope excludes seizures, coma, shock, or other states of altered consciousness.

Syncope occurs due to **global cerebral hypoperfusion**. Brain parenchyma depends on adequate blood flow to provide a constant supply of glucose, the primary metabolic substrate. Brain tissue cannot store energy in the form of high-energy phosphates found elsewhere in the body; therefore, a cessation of cerebral perfusion lasting only 3-5 seconds can result in syncope.

Cerebral perfusion is maintained relatively constant by an intricate and complex feedback system involving cardiac output, systemic vascular resistance, arterial pressure, intravascular volume status, cerebrovascular resistance with intrinsic autoregulation, and metabolic regulation. A clinically significant defect in any one of these or subclinical defects in several of these systems may cause syncope.

Cardiac output can be diminished secondary to mechanical outflow obstruction, pump failure, hemodynamically significant arrhythmias, or conduction defects. **Systemic vascular resistance** can drop secondary to vasomotor instability, autonomic failure, or vasodepressor/vasovagal response. Mean arterial pressure decreases with all causes of hypovolemia.

Syncope can occur without reduction in cerebral blood flow in patients who have severe metabolic derangements (eg, **hypoglycemia**, **hyponatremia**, **hypoxemia, hypercarbia**).

Foreign Body Aspiration

Near-total obstruction of the larynx or trachea can cause immediate **asphyxia** and death. Should the object pass beyond the carina, its location would depend on the patient's age and physical position at the time of the aspiration. Because the angles made by the mainstem bronchi with the trachea are identical until age 15 years, foreign bodies are found on either side with equal frequency. With normal growth and

development, the adult right and left mainstem bronchi diverge from the trachea with very different angles, with the right mainstem bronchus being more acute. **Objects that descend beyond the trachea are more often found in the right endobronchial tree** than in the left.

Once aspirated, objects may subsequently change position or migrate distally. The object itself might cause **obstruction**. Vegetable material may swell over hours or days, worsening the obstruction. Cough, wheeze, stridor, dyspnea, cyanosis, and even asphyxia might ensue. Organic foreign bodies, such as oily nuts (commonly peanuts), induce inflammation and edema.

Local inflammation, edema, cellular infiltration, ulceration, and granulation tissue formation may contribute to airway obstruction. The airway becomes more likely to bleed with manipulation; the object is more likely to be obscured and becomes more difficult to dislodge. **Mediastinitis or tracheoesophageal fistulas** may result. Distal to the obstruction, air trapping may occur, leading to local emphysema, atelectasis, hypoxic vasoconstriction, postobstructive pneumonia, and the possibility of volume loss, necrotizing pneumonia or abscess, suppurative pneumonia, or bronchiectasis.

Bronchiectasis

Bronchiectasis is an uncommon disease, most often secondary to an infectious process, that results in the **abnormal and permanent distortion of one or more of the conducting bronchi or airways**. Bronchiectasis can be categorized as a chronic obstructive pulmonary disease manifested by airways that are inflamed and easily collapsible, resulting in **air flow obstruction** with shortness of breath, **impaired clearance of secretions** (often with disabling cough), and occasionally hemoptysis. Severe cases can result in progressive impairment with respiratory failure.

Bronchiectasis most commonly presents as a focal process involving a lobe, segment, or subsegment of the lung. Far less commonly, it may be a diffuse process involving both lungs (**cystic fibrosis**).

Bronchiectasis is an abnormal dilation of the proximal and medium-sized bronchi (>2 mm in diameter) caused by **weakening or destruction of the muscular and elastic components of the bronchial walls**. Affected areas may show a variety of changes, including transmural inflammation, edema, scarring, and ulceration. Distal lung parenchyma may also be damaged secondary to persistent microbial infection and frequent postobstructive pneumonia.

The tissue is also damaged in part by the host response of neutrophilic proteases, inflammatory cytokines, nitric oxide, and oxygen radicals. Peribronchial alveolar tissue may be damaged, resulting in **diffuse peribronchial fibrosis**.

Atelectasis

Atelectasis is defined as diminished volume affecting all or part of a lung. Atelectasis is divided physiologically into obstructive and nonobstructive causes.

Obstructive atelectasis

Obstructive atelectasis is the most common type and results from **reabsorption of gas from the alveoli** when the obstruction occurs at the level of the larger or smaller bronchus. Causes of obstructive atelectasis include foreign body, tumor, and mucous plugging. The rate at which atelectasis develops and the extent of atelectasis depend on several factors, including the extent of collateral ventilation which is provided by the pores of Kohn and the canals of Lambert and the composition of inspired gas.

Nonobstructive atelectasis

Nonobstructive atelectasis can be caused by loss of contact between the parietal and visceral pleurae, **compression, loss of surfactant**, and **replacement of parenchymal tissue by scarring or infiltrative disease**.

Relaxation or passive atelectasis results from a **pleural effusion** or a **pneumothorax**. Generally, the uniform elasticity of a normal lung leads to preservation of shape even when volume is decreased. The different lobes also function differently, eg, the middle and lower lobes collapse more than the upper lobe in the presence of pleural effusion, while the upper lobe may be affected more by pneumothorax.

Compression atelectasis occurs from any **space-occupying lesion** of the thorax compressing the lung and forcing air out of the alveoli. The mechanism is similar to relaxation atelectasis.

Adhesive atelectasis results from **surfactant deficiency**. Surfactant normally reduces the surface tension of the alveoli, thereby decreasing the tendency of these structures to collapse. Decreased production or inactivation of surfactant leads to alveolar instability and collapse. This is observed particularly in **ARDS** and similar disorders.

Cicatrization atelectasis results from diminution of volume as a sequela of **severe parenchymal scarring** and is usually caused by granulomatous disease or necrotizing pneumonia.

Replacement atelectasis occurs when the alveoli of an entire lobe are **filled by tumor** (eg, bronchioalveolar cell carcinoma), resulting in loss of volume.

Pulmonary Embolism

Pulmonary embolism is a common and potentially lethal condition. Most patients who succumb to pulmonary embolism do so within the first few hours of the event.

The diagnosis is often missed because patients with pulmonary embolism present with **nonspecific signs and symptoms** (unexplained dyspnea, tachypnea, or chest pain).

When a pulmonary embolism is identified, it is characterized as acute or chronic. An embolus is **acute** if it is **situated centrally** within the vascular lumen or if it occludes a vessel (vessel cutoff sign). Acute pulmonary embolism commonly causes **distention of the involved vessel**. An embolus is **chronic** if it is **eccentric** and **contiguous with the vessel wall**, it reduces the arterial diameter by more than 50%, evidence of **recanalization within the thrombus** is present, and an arterial web is present.

A pulmonary embolism is also characterized as central or peripheral, depending on the location or the arterial branch involved. Central vascular zones include the main pulmonary artery, the left and right main pulmonary arteries, the anterior trunk, the right and left interlobar arteries, the left upper lobe trunk, the right middle lobe artery, and the right and left lower lobe arteries. A pulmonary embolus is characterized as **massive** when it involves **both pulmonary arteries or when it results in hemodynamic compromise**. Peripheral vascular zones include the segmental and subsegmental arteries of the individual lobes.

There are both respiratory and hemodynamic consequences associated with pulmonary embolism.

Respiratory consequences

Acute respiratory consequences of pulmonary embolism include the following:

- Increased alveolar dead space
- Hypoxemia
- Hyperventilation

Additional consequences that may occur include regional loss of surfactant and pulmonary infarction. The mechanisms of **hypoxemia** include **ventilation-perfusion mismatch, intrapulmonary shunts, and**

reduced cardiac output. **Pulmonary infarction is an uncommon consequence** because of the bronchial arterial collateral circulation.

Hemodynamic consequences

Pulmonary embolism reduces the cross-sectional area of the pulmonary vascular bed, resulting in an increment in **pulmonary vascular resistance**, which, in turn, increases the right ventricular afterload. If the afterload is increased severely, **right ventricular failure** may ensue. In addition, the humoral and reflex mechanisms contribute to the pulmonary arterial constriction.

Chronic pulmonary hypertension may occur with failure of the initial embolus to undergo lyses or in the setting of recurrent thromboemboli.

Aspiration Pneumonia

Aspiration is defined as the inhalation of either **oropharyngeal or gastric contents** into the lower airways.

Three types of material cause 3 different pneumonic syndromes. Aspiration of gastric acid causes **chemical pneumonia**. Aspiration of bacteria from oral and pharyngeal areas causes **bacterial pneumonia**, and aspiration of oil (eg, mineral oil or vegetable oil) causes exogenous **lipoid pneumonia**, a rare form of pneumonia.

The risk of aspiration is indirectly related to the level of consciousness of the patient. Aspiration of small amounts of material from the buccal cavity, particularly during sleep, is not an uncommon event. No disease ensues in healthy persons, because the aspirated material is cleared by mucociliary action and alveolar macrophages. **The nature of the aspirated material, volume of the aspirated material, and state of the host defenses are 3 important determinants of the extent and severity of aspiration pneumonia.**

Chemical pneumonia

Chemical pneumonia is due to the parenchymal inflammatory reaction caused by a large volume of gastric contents independent of infection. In

fact, aspiration of a massive amount of gastric contents can produce **acute respiratory distress within 1 hour**. This disease occurs in people with altered levels of consciousness resulting from seizures, cerebrovascular accident, central nervous system mass lesions, drug intoxication or overdose, and head trauma.

The acidity of gastric contents results in chemical burns to the tracheobronchial tree involved in the aspiration. If the pH of the aspirated fluid is less than 2.5 and the volume of aspirate is greater than 0.3 ml/kg of body weight (20-25 mL in adults), it has a greater potential for causing chemical pneumonia. The initial **chemical burn** is followed by an **inflammatory cellular reaction** fueled by the release of potent cytokines, particularly tumor necrosis factor–alpha and interleukin–8.

Bacterial pneumonia

Bacterial pneumonia most commonly occurs in individuals with **chronically impaired airway defense mechanisms**, such as gag reflex, coughing, ciliary movement, and immune mechanisms, all of which aid in removing infectious material from the lower airways. This syndrome caused by aspiration can occur in the community or in the hospital (ie, nosocomial). In anaerobic pneumonia, the pathogenesis is related to the large volume of aspirated anaerobes (eg, as in persons with poor dentition, poor oral care, and periodontal disease) and to host factors (eg, as in alcoholism) that suppress cough, mucociliary clearance, and phagocytic efficiency, both of which increase the bacterial burden of oropharyngeal secretions.

Restrictive Lung Disease

Restrictive lung diseases are characterized by reduced lung volume, either because of an alteration in lung parenchyma or because of a disease of the pleura, chest wall, or neuromuscular apparatus. In physiological terms, restrictive lung diseases are characterized by **reduced total lung capacity (TLC), vital capacity, or resting lung volume**.

Accompanying characteristics are preserved airflow and **normal airway resistance**, which are measured as the functional residual capacity (FRC). If caused by parenchymal lung disease, restrictive lung disorders are accompanied by **reduced gas transfer**, which may be marked clinically by **desaturation after exercise**.

The many disorders that cause reduction or restriction of lung volumes may be divided into 2 groups based on anatomical structures.
The first is intrinsic lung diseases or **diseases of the lung parenchyma**. The diseases cause inflammation or scarring of the lung tissue (interstitial lung disease) or result in filling of the air spaces with exudate and debris (pneumonitis). They include idiopathic fibrotic diseases, connective-tissue diseases, drug-induced lung disease, and primary diseases of the lungs (including sarcoidosis).

The second is extrinsic disorders or **extraparenchymal diseases**. The **chest wall, pleura, and respiratory muscles** are the components of the respiratory pump, and they need to function normally for effective ventilation. Diseases of these structures result in lung restriction, impaired ventilatory function, and respiratory failure (eg, nonmuscular diseases of the chest wall, neuromuscular disorders).

Arterial hypoxemia in these disorders is primarily caused by **ventilation-perfusion mismatching**, with further contribution from an intrapulmonary shunt. The diffusion of oxygen is impaired, which contributes a little towards hypoxemia at rest but is primarily the mechanism of **exercise-induced desaturation**. As a result of atelectasis, gas distribution becomes nonuniform, resulting in ventilation-perfusion mismatch and hypoxemia.

Respiratory Failure

Respiratory failure is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon

dioxide elimination. In practice, it may be classified as either hypoxemic or hypercapnic.

Hypoxemic respiratory failure (type I) is characterized by an arterial oxygen tension (**P_a O_2) lower than 60 mm Hg** with a normal or low arterial carbon dioxide tension (P_a CO_2). This is the most common form of respiratory failure, and it can be associated with virtually all acute diseases of the lung, which generally involve fluid filling or collapse of alveolar units. Some examples of type I respiratory failure are cardiogenic or noncardiogenic pulmonary edema, pneumonia, and pulmonary hemorrhage.

Hypercapnic respiratory failure (type II) is characterized by a **$PaCO_2$ higher than 50 mm Hg**. Hypoxemia is common in patients with hypercapnic respiratory failure who are breathing room air. The pH depends on the level of bicarbonate, which, in turn, is dependent on the duration of hypercapnia. Common etiologies include **drug overdose, neuromuscular disease, chest wall abnormalities, and severe airway disorders (eg, asthma and chronic obstructive pulmonary disease)**.

Respiratory failure may be further classified as either **acute or chronic**. Although acute respiratory failure is characterized by life-threatening derangements in arterial blood gases and acid-base status, the manifestations of chronic respiratory failure are less dramatic and may not be as readily apparent.

Acute hypercapnic respiratory failure develops over minutes to hours; therefore, **pH is less than 7.3**. **Chronic respiratory failure** develops over several days or longer, allowing time for **renal compensation** and an increase in bicarbonate concentration. Therefore, the pH usually is only slightly decreased. The clinical markers of chronic hypoxemia, such as **polycythemia or cor pulmonale**, suggest a long-standing disorder.

Hypoxemia is the major immediate threat to organ function. After the patient's hypoxemia is corrected and the ventilatory and hemodynamic status have stabilized, every attempt should be made to identify and

correct the underlying pathophysiologic process that led to respiratory failure in the first place.

Respiratory failure can arise from an **abnormality in any of the components of the respiratory system**, including the airways, alveoli, central nervous system, peripheral nervous system, respiratory muscles, and chest wall. Patients who have **hypoperfusion secondary to cardiogenic, hypovolemic, or septic shock** often present with respiratory failure.

Ventilatory capacity is the maximal spontaneous ventilation that can be maintained without development of respiratory muscle fatigue. Ventilatory demand is the spontaneous minute ventilation that results in a stable $P_a CO_2$. Normally, ventilatory capacity greatly exceeds ventilatory demand. Respiratory failure may result from either a **reduction in ventilatory capacity or an increase in ventilatory demand (or both)**. Ventilatory capacity can be decreased by a disease process involving any of the functional components of the respiratory system and its controller.

Ventilatory demand is augmented by an increase in minute ventilation and/or an increase in the work of breathing.

Gas exchange

Respiration primarily occurs at the alveolar capillary units of the lungs, where exchange of oxygen and carbon dioxide between alveolar gas and blood takes place. After diffusing into the blood, the oxygen molecules reversibly bind to the hemoglobin. The quantity of oxygen combined with hemoglobin depends on the level of blood $P_a O_2$. This relationship, expressed as the **oxygen hemoglobin dissociation curve**, is not linear but has a sigmoid-shaped curve with a steep slope between a $P_a O_2$ of 10 and 50 mm Hg and a flat portion above a $P_a O_2$ of 70 mm Hg.

The carbon dioxide is transported in 3 main forms:

- in simple solution,
- as bicarbonate, and
- combined with protein of hemoglobin as a carbamino compound.

During ideal gas exchange, **blood flow and ventilation would perfectly match each other**, resulting in no alveolar-arterial oxygen tension (PO_2) gradient. However, even in normal lungs, not all alveoli are ventilated and perfused perfectly. For a given perfusion, some alveoli are underventilated, while others are overventilated. Similarly, for known alveolar ventilation, some units are underperfused, while others are overperfused.

The optimally ventilated alveoli that are not perfused well have a large ventilation-to-perfusion ratio (V/Q) and are called **high-V/Q units** (which act like dead space). Alveoli that are optimally perfused but not adequately ventilated are called **low-V/Q units** (which act like a shunt).

Alveolar ventilation

At steady state, the rate of carbon dioxide production by the tissues is constant and equals the rate of carbon dioxide elimination by the lung.
Even normal lungs have some degree of V/Q mismatching and a small quantity of right-to-left shunt, with $P_A\ O_2$ slightly higher than $P_a\ O_2$. However, **an increase in the alveolar-arterial PO_2 gradient above 15-20 mm Hg indicates pulmonary disease as the cause of hypoxemia**.

Hypoxemic respiratory failure

The pathophysiologic mechanisms that account for the hypoxemia observed in a wide variety of diseases are **V/Q mismatch and shunt**. These 2 mechanisms lead to widening of the alveolar-arterial PO_2 gradient, which normally is less than 15 mm Hg.

***V/Q mismatch* is the most common cause of hypoxemia**. Alveolar units may vary from low-V/Q to high-V/Q in the presence of a disease process. The low-V/Q units contribute to hypoxemia and hypercapnia, whereas the high-V/Q units waste ventilation but do not affect gas exchange unless the abnormality is quite severe.

The **low V/Q ratio** may occur either from a decrease in ventilation secondary to airway or interstitial lung disease or from overperfusion in the presence of normal ventilation. The overperfusion may occur in case of **pulmonary embolism**, where the blood is diverted to normally

ventilated units from regions of lungs that have blood flow obstruction secondary to embolism.

Administration of 100% oxygen eliminates all of the low-V/Q units, thus **leading to correction of hypoxemia**. Hypoxemia increases minute ventilation by chemoreceptor stimulation, but the $P_a CO_2$ generally is not affected.

***Shunt* is defined as the persistence of hypoxemia despite 100% oxygen inhalation**. The deoxygenated blood (mixed venous blood) bypasses the ventilated alveoli and mixes with oxygenated blood that has flowed through the ventilated alveoli, consequently leading to a reduction in arterial blood content.

Anatomic shunt exists in normal lungs because of the bronchial and thebesian circulations, which account for 2-3% of shunt. A normal right-to-left shunt may occur from atrial septal defect, ventricular septal defect, patent ductus arteriosus, or arteriovenous malformation in the lung.

Shunt as a cause of hypoxemia is observed primarily in **pneumonia, atelectasis, and severe pulmonary edema** of either cardiac or noncardiac origin. Hypercapnia generally does not develop unless the shunt is excessive (> 60%). Compared with V/Q mismatch, hypoxemia produced by shunt is difficult to correct by means of oxygen administration.

Hypercapnic respiratory failure

At a constant rate of carbon dioxide production, P_aCO_2 is determined by the level of alveolar ventilation. The relation between P_aCO_2 and alveolar ventilation is hyperbolic. As ventilation decreases below 4-6 l/min, P_aCO_2 rises precipitously. A **decrease in alveolar ventilation** can result from a reduction in overall (minute) ventilation or an **increase in the proportion of dead space ventilation**. A reduction in minute ventilation is observed primarily in the setting of neuromuscular disorders and CNS depression. In pure hypercapnic respiratory failure, the hypoxemia is easily corrected with oxygen therapy. Hypoventilation

can be differentiated from other causes of hypoxemia by the presence of a normal alveolar-arterial PO_2 gradient.

Cyanosis

Cyanosis is a bluish or purplish tinge to the skin and mucous membranes.

Before the era of rapid blood gas analysis, clinicians often assessed hypoxemia on clinical grounds alone, primarily by looking for cyanosis in the perioral area and fingers. Clinical assessment of hypoxemia is now known to be notoriously unreliable for the following reasons:

- Physicians may diagnose cyanosis as an indicator of hypoxemia when the patient has normal oxygen saturation; alternatively, physicians may miss cyanosis when it should be present (the patient has very low oxygen saturation with normal hemoglobin).
- Approximately **50 g/l of unoxygenated hemoglobin** in the capillaries generates the dark blue color appreciated clinically as cyanosis. For this reason, patients who are **anemic may be hypoxemic without showing any cyanosis**.
- **Ancillary signs and symptoms of hypoxemia** (eg, tachycardia, tachypnea, mental status changes) are nonspecific and of **no value** in reliably detecting hypoxemia. For example, patients may be dyspneic at rest for reasons other than hypoxemia (ie, they have normal PaO_2 and SaO_2). Conversely, many patients who are chronically hypoxemic (low PaO_2 and/or low SaO_2) are perfectly lucid and without any obvious physical signs of their low oxygen state (at least while at rest).

The requirement of **50 g/l of reduced (ie, deoxygenated) hemoglobin in the capillaries** translates into a reduced hemoglobin content of 34 g/l in arterial blood. For this reason, patients with normal hemoglobin manifest cyanosis at higher SaO_2 values than patients with anemia.

Acute Respiratory Distress Syndrome

Some patients with nonthoracic injuries, **severe pancreatitis, massive transfusion, sepsis**, and other conditions develop respiratory distress, diffuse lung infiltrates, and respiratory failure. The term "acute respiratory distress syndrome" was used instead of "adult respiratory distress syndrome" because the syndrome occurs in both adults and children.

ARDS was recognized as the most severe form of acute lung injury, a form of diffuse alveolar injury. ARDS is defined as an acute condition characterized by **bilateral pulmonary infiltrates and severe hypoxemia in the absence of evidence for cardiogenic pulmonary edema**.

The severity of hypoxemia necessary to make the diagnosis of ARDS is defined by the ratio of the partial pressure of oxygen in the patient's arterial blood (PaO_2) to the fraction of oxygen in the inspired air (FIO_2). In ARDS, the **PaO_2/FIO_2 ratio is less than 200**, and in acute lung injury, it is less than 300.

ARDS is associated with **diffuse alveolar damage and lung capillary endothelial injury**. The early phase is described as being exudative, whereas the later phase is fibroproliferative in character. Early ARDS is characterized by an increase in the permeability of the alveolar-capillary barrier, leading to an **influx of fluid into the alveoli**.

The main site of injury may be focused on either the vascular endothelium (eg, sepsis) or the alveolar epithelium (eg, aspiration of gastric contents). **Injury to the endothelium results in increased capillary permeability and the influx of protein-rich fluid into the alveolar space**. **Injury to the alveolar lining cells also promotes pulmonary edema formation**. Two types of alveolar epithelial cells exist. Type I cells, which make up 90% of the alveolar epithelium, are injured easily. **Damage to type I cells** allows both increased entry of fluid into the alveoli and decreased clearance of fluid from the alveolar space. Type II alveolar epithelial cells are relatively more resistant to injury. However, type II

cells have several important functions, including the production of surfactant, ion transport, and proliferation and differentiation into type l cells after cellular injury. **Damage to type II cells** results in decreased production of **surfactant** with resultant decreased compliance and **alveolar collapse**. Interference with the normal repair processes in the lung may lead to the development of **fibrosis**.

Neutrophils are thought to play a key role in the pathogenesis of ARDS, as suggested by studies of bronchoalveolar lavage and lung biopsy specimens in early ARDS. Despite the apparent importance of neutrophils in this syndrome, ARDS may develop in profoundly neutropenic patients. The neutrophils observed in ARDS may be reactive rather than causative.

Cytokines (tumor necrosis factor, leukotrienes, macrophage inhibitory factor, and numerous others), along with **platelet** sequestration and activation, are also important in the development of ARDS. An imbalance of proinflammatory and anti-inflammatory cytokines is thought to occur after an inciting event, such as sepsis.

ARDS causes a marked **increase in intrapulmonary shunting**, leading to severe hypoxemia. Although a high FIO_2 is required to maintain adequate tissue oxygenation and additional measures, like lung recruitment with **PEEP**, are often required. Theoretically, high FIO_2 levels may cause alveolar damage via oxygen free radical and related oxidative stresses, collectively called oxygen toxicity. Generally, **oxygen concentrations higher than 65% for prolonged periods (days) can result in hyaline membrane formation, and, eventually, fibrosis**.

ARDS is uniformly associated with **pulmonary hypertension**. Pulmonary artery vasoconstriction likely contributes to ventilation-perfusion mismatch and is one of the mechanisms of hypoxemia in ARDS.

The acute phase of ARDS usually resolves completely. Less commonly, residual pulmonary fibrosis occurs, in which the alveolar spaces are filled with mesenchymal cells and new blood vessels. This process seems to be facilitated by interleukin-1. The findings of fibrosis on biopsy correlate with an increased mortality rate.

Pediatric ARDS

Although originally described in adults, this syndrome occurs in children of all ages. It is a clinical entity of dyspnea, cyanosis resistant to supplemental oxygen, and bilateral chest infiltrates on chest radiography with noncardiogenic pulmonary edema.

The ratio of the partial pressure of oxygen in arterial blood to the fraction of inspired oxygen (PaO_2/FiO_2 or PF ratio) of less than 200 for ARDS.

Several diseases can cause ARDS, more commonly following **pneumonia, aspiration, and sepsis**. The net effect at a cellular level is **massive cell damage, alveolar denudation, and sloughing of cell debris into the lumen of the alveolus**. Furthermore, **surfactant is markedly inactivated**.

Meanwhile, in the pulmonary capillary bed, endothelial cells swell, platelets aggregate, and a procoagulant cascade arises, leading to **small-vessel thrombosis**.

The net effect is impairment in oxygenation. A widened interstitial space between the alveolus and the vascular endothelium decreases oxygen-diffusing capacity. **Collapsed alveoli** result in either low ventilation-perfusion (V/Q) units or a right-to-left pulmonary shunt. The end result is **marked venous admixture**, the process whereby deoxygenated blood passing through the lungs does not absorb sufficient oxygen and causes a relative desaturation of arterial blood when it mixes with blood that is already oxygenated.

Hypoxia, hypercarbia, and small-vessel thrombosis combine to elevate pulmonary artery pressures. **Persistent pulmonary hypertension** can result in increased right ventricular work, right ventricular dilatation, and, ultimately, left ventricular outflow tract obstruction secondary to intraventricular septal shifting toward the left ventricle. These changes, in turn, may decrease cardiac output and further reduce oxygen delivery to vital organs.

Carcinoid lung tumors

Carcinoid lung tumors represent the most indolent form of a spectrum of bronchopulmonary neuroendocrine tumors that includes small cell carcinoma of the lung.

Central carcinoids can cause **bronchial obstruction**. All of the sequelae resulting from bronchial obstruction can follow, including persistent **atelectasis, recurrent pneumonia, pulmonary abscess, and bronchiectasis**. If large enough, it can create a ball-valve mechanism within the bronchus, producing hyperinflation in the pulmonary parenchyma distal to the tumor.

Carcinoids characteristically are vascular tumors and **can bleed secondary to bronchial irritation**.

As neuroendocrine tumors, carcinoids are capable of producing a variety of biologically active peptides and hormones, including **serotonin, adrenocorticotropin hormone (ACTH), antidiuretic hormone (ADH), melanocyte-stimulating hormone (MSH)**, and others.

Excess serotonin production has been implicated in the development of **carcinoid syndrome**. This syndrome is characterized by a constellation of symptoms, including **tachycardia, flushing, bronchoconstriction, hemodynamic instability, diarrhea, and acidosis**.

Ectopic production of ACTH and **Cushing syndrome** have been reported in association with carcinoid tumors.

The **syndrome of inappropriate vasopressin (ADH) secretion** can be produced by pulmonary carcinoid tumors, although it more commonly is associated with small cell lung carcinoma. The production of excess circulating AVP creates hyponatremia secondary to water retention. Patients present with weight gain, weakness, lethargy, and mental confusion and, in severe cases, can develop convulsions and coma.

Secondary lung tumors

Lung metastases can commonly cause no symptoms, or they can be the major cause of morbidity. Symptoms include hypoxemia, dyspnea, cough, and hemoptysis. **Hypoxemia and dyspnea are most commonly observed in patients with lymphangitic spread, and cough and hemoptysis are associated with endobronchial metastases**.

Small cell lung cancer

Production of various **peptide hormones** leads to a wide range of **paraneoplastic syndromes**; the most common of these is the syndrome of inappropriate secretion of antidiuretic hormone and the syndrome of ectopic adrenocorticotropic hormone (ACTH) production.

Lung Abscess

Lung abscess is defined as **necrosis of the pulmonary tissue** and formation of cavities containing necrotic debris or fluid caused by **microbial infection**. The formation of multiple small (< 2 cm) abscesses is occasionally referred to as **necrotizing pneumonia or lung gangrene**. Both lung abscess and necrotizing pneumonia are manifestations of a similar pathologic process.

Lung abscesses can be classified based on the duration and the likely etiology. **Acute abscesses** are less than 4-6 weeks old, whereas **chronic abscesses** are of longer duration. **Primary abscess** is infectious in origin, caused by aspiration or pneumonia in the healthy host; **secondary abscess** is caused by a preexisting condition (eg, obstruction), spread from an extrapulmonary site, bronchiectasis, and/or an immunocompromised state. Lung abscesses can be further characterized by the responsible pathogen, such as *Staphylococcus* lung abscess and anaerobic or *Aspergillus* lung abscess.

Most frequently, the lung abscess arises as a **complication of aspiration pneumonia caused by mouth anaerobes**. A bacterial inoculum from the gingival crevice reaches the lower airways, and infection is initiated because the bacteria are not cleared by the patient's host

defense mechanism. Other mechanisms for lung abscess formation include bacteremia or tricuspid valve endocarditis, causing **septic emboli** (usually multiple) to the lung.

Diaphragmatic Hernias

The pathophysiology of **congenital diaphragmatic hernia** involves pulmonary hypoplasia, pulmonary hypertension, pulmonary immaturity, and potential deficiencies in the surfactant and antioxidant enzyme system.

Because of bowel herniation into the chest during crucial stages of lung development, **airway divisions are limited to the 12th to 14th generation on the ipsilateral side** and to the 16th to 18th generation on the contralateral side. Normal airway development results in 23-35 divisions. Because airspace development follows airway development, alveolarization is similarly reduced.

Development of the pulmonary arterial system parallels development of the bronchial tree, and, therefore, **fewer arterial branches are observed in congenital diaphragmatic hernia**. Abnormal medial muscular hypertrophy is observed as far distally as the acinar arterioles, and the pulmonary vessels are more sensitive to stimuli of vasoconstriction. **Pulmonary hypertension** resulting from these arterial anomalies leads to right-to-left shunting at atrial and ductal levels. This persistent fetal circulation leads to **right-sided heart strain or failure** and to the vicious cycle of progressive hypoxemia, hypercarbia, acidosis, and pulmonary hypertension observed in the neonatal period.

Infants with congenital diaphragmatic hernias also have **impairment of the pulmonary antioxidant enzyme system** and are more susceptible to hyperoxia-induced injury.

In addition, a **left ventricular smallness and hypoplasia** are observed with congenital diaphragmatic hernia. This is believed to arise from decreased in utero blood flow to the left ventricle, the mechanical

compression of the herniated viscus similar to that observed in the lungs, and/or a primary yet unidentified developmental defect that simultaneously causes the diaphragmatic hernia and lung problems.

Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema is defined as pulmonary edema due to **increased capillary hydrostatic pressure secondary to elevated pulmonary venous pressure**. It reflects the **accumulation of fluid with a low-protein content in the lung interstitium and alveoli** as a result of cardiac dysfunction.

Pulmonary edema can be caused by the following major pathophysiologic mechanisms:

- Imbalance of **Starling forces** - increased pulmonary capillary pressure, decreased plasma oncotic pressure, increased negative interstitial pressure
- Damage to the alveolar-capillary barrier
- Lymphatic obstruction
- Idiopathic (unknown) mechanism

Increased hydrostatic pressure leading to pulmonary edema may result from many causes, including **excessive intravascular volume administration, pulmonary venous outflow obstruction and left ventricle (LV) failure** secondary to systolic or diastolic dysfunction. Cardiogenic pulmonary edema leads to progressive **deterioration of alveolar gas exchange and respiratory failure**.

Exchange of fluid normally occurs between the vascular bed and the interstitium. Pulmonary edema occurs when the net flux of fluid from the vasculature into the interstitial space is increased. The Starling relationship determines the fluid balance between the alveoli and the vascular bed.

For pulmonary edema to develop secondary to increased pulmonary capillary pressure, the **pulmonary capillary pressure must rise to a level**

higher than the plasma colloid osmotic pressure. Pulmonary capillary pressure is normally 8-12 mm Hg, and colloid osmotic pressure is 28 mm Hg.

The **lymphatics** play an important role in maintaining an adequate fluid balance in the lungs by removing solutes, colloid, and liquid from the interstitial space at a rate of approximately 10-20 ml/h. An acute rise in pulmonary arterial capillary pressure (ie, to >18 mm Hg) may increase filtration of fluid into the lung interstitium, but the lymphatic removal does not increase correspondingly. In contrast, in the presence of chronically elevated left atrium (LA) pressure, the rate of lymphatic removal can be as high as 200 ml/h, which protects the lungs from pulmonary edema.

The progression of fluid accumulation in cardiogenic pulmonary edema can be identified as 3 distinct physiologic stages.

Stage 1

Elevated LA pressure causes **distention and opening of small pulmonary vessels**. At this stage, blood gas exchange does not deteriorate, or it may even be slightly improved.

Stage 2

Fluid and colloid shift into the lung interstitium from the pulmonary capillaries, but an initial **increase in lymphatic outflow** efficiently removes the fluid. The continuing filtration of liquid and solutes may overpower the drainage capacity of the lymphatics. In this case, the **fluid initially collects in the relatively compliant interstitial compartment**.

The accumulation of liquid in the interstitium may compromise the small airways, leading to **mild hypoxemia**. Hypoxemia at this stage is rarely of sufficient magnitude to stimulate tachypnea. **Tachypnea** at this stage is mainly the result of the stimulation of juxtapulmonary capillary (J-type) receptors, which are nonmyelinated nerve endings located near the alveoli.

Stage 3

As fluid filtration continues to increase, **fluid accumulates in the relatively noncompliant interstitial space, which can contain up to 500ml of fluid**. With further accumulations, the **fluid crosses the alveolar epithelium in to the alveoli**, leading to alveolar flooding. At this stage, abnormalities in gas exchange are noticeable, vital capacity and other **respiratory volumes are substantially reduced**, and **hypoxemia becomes more severe**.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema develops within a few hours after a neurologic insult, and diagnosis requires exclusion of other causes of pulmonary edema.

The pathogenesis of neurogenic pulmonary edema is not completely understood. **Intracranial hypertension** is considered a key etiologic factor.

Hypothalamic lesions, stimulation of the vasomotor centers of the medulla, elevated intracranial pressure, and activation of the sympathetic system have potential roles. Neurogenic pulmonary edema trigger zones may exist in these structures, with specific neurologic foci or centers producing massive sympathetic discharges that lead to neurogenic pulmonary edema.

Alterations in pulmonary vascular pressures appear to be the most likely Starling force to influence the formation of neurogenic pulmonary edema. **An increase in left atrial pressure may occur because of increases in sympathetic tone and venous return**. **Left ventricular performance may deteriorate secondary to the direct effects of catecholamines and other mediators**, as well as transient systemic hypertension. **Pulmonary venoconstriction occurs with sympathetic stimulation**, which may increase the capillary hydrostatic pressure.

Epinephrine, norepinephrine, and even a release of secondary mediators may directly increase pulmonary vascular permeability and to

pulmonary microvascular injury. Consequently, an increase in vascular permeability results in edema formation, as suggested by the frequent observation of pulmonary hemorrhage in neurogenic pulmonary edema.

Pleural Effusion

A pleural effusion is an abnormal collection of fluid in the pleural space resulting from **excess fluid production or decreased absorption**. It is the most common manifestation of pleural disease, with etiologies ranging **from cardiopulmonary disorders to symptomatic inflammatory or malignant diseases**. Pleural effusions are a common finding in patients with pneumonia.

During the exudative stage, sterile pleural fluid rapidly accumulates in the pleural space. The pleural fluid originates in the interstitial spaces of the lung and in the capillaries of the visceral pleura because of increased permeability.

Empyema Thoracis

Empyema thoracis develops as **frank pus accumulates in the pleural space**. **Preexisting pleural fluid** is required for the development of an empyema because empyema is not seen after direct inoculation into a "dry" pleural space. The pus is seen after thoracentesis or any drainage procedure of the pleural space and is generally characterized as thick, viscous, and opaque. Empyema thoracis may arise without an associated pneumonic process, such as from **esophageal perforation, trauma, a surgical procedure on pleural space, or septicemia**. T

Bacterial invasion of the pleural space occurs, with accumulation of polymorphonuclear leukocytes, bacteria, and cellular debris. A tendency toward loculation and septation exists.

In the organization stage, fibroblasts grow into the exudates from both the visceral and parietal pleural surfaces, and they produce an inelastic membrane called **pleural peel**. Pleural fluid is thick. In an

untreated patient, pleural fluid may drain spontaneously through the chest wall.

Mechanical Ventilation

Complications of mechanical ventilation

With **ventilator-induced lung injury**, the alveolar epithelium is at risk for both barotrauma and volutrauma.

Barotrauma refers to rupture of the alveolus with subsequent entry of air into the pleural space (**pneumothorax**) and/or the tracking or air along the vascular bundle to the mediastinum (**pneumomediastinum**). Large tidal volumes and elevated peak inspiratory and plateau pressures are risk factors.

The inspiratory-to-expiratory ratio can be adjusted by increasing the inspiratory flow rate, by decreasing the tidal volume, and by decreasing the ventilatory rate. **Attention to the inspiratory-to-expiratory ratio is important to prevent barotrauma in patients with obstructive airway disease** (eg, asthma, chronic obstructive pulmonary disease).

Volutrauma refers to the **local overdistention of normal alveoli**. Volutrauma has gained recognition over the last 2 decades and is the impetus for the lung protection ventilation with low tidal volumes of 6–8 ml/kg. When a mechanical ventilation breath is forced into the patient, the positive pressure tends to follow the path of least resistance to the normal or relatively normal alveoli, potentially causing overdistention. This overdistention sets off an **inflammatory cascade** that augments or perpetuates the initial lung injury, causing additional damage to previously unaffected alveoli. The inflammatory cascade occurs locally and **may augment the systemic inflammatory response** as well.

Oxygen toxicity

Oxygen toxicity is a function of increased FIO_2 and its duration of use. Oxygen toxicity is due to the production of **oxygen free radicals**, such as superoxide anion, hydroxyl radical, and hydrogen peroxide. Oxygen

toxicity can cause a variety of complications ranging **from mild tracheobronchitis, absorptive atelectasis, and hypercarbia to diffuse alveolar damage that is indistinguishable from ARDS**.

No consensus has been established for the level of FIO_2 required to cause oxygen toxicity, but this complication has been reported in patients given a **maintenance FIO_2 of 50%.** The medical literature suggests that the clinician should attempt to attain an FIO_2 of 60% or less within the first 24 hours of mechanical ventilation. If necessary, PEEP should be considered a means to improve oxygenation while a safe FIO_2 is maintained. When PEEP is effective and not contraindicated because of hemodynamics, the patient can often be oxygenated while the risks of oxygen toxicity are limited.

Ventilator-associated pneumonia

The risk is highest immediately after intubation. Ventilator-associated pneumonia occurs more **frequently in trauma, neurosurgical, or burn units than in respiratory units**.

It is defined as a new infection of the lung parenchyma that develops **within 48 hours after intubation**. Microorganisms implicated in ventilator-associated pneumonia that occurs in the first 48 hours after intubation are **flora of the upper airway**, including *Haemophilus influenza* and *Streptococcus pneumonia.* After this early period, gram-negative bacilli such as *Pseudomonas aeruginosa; Escherichia coli;* and *Acinetobacter, Proteus,* and *Klebsiella* species predominate. *Staphylococcus aureus,* especially methicillin-resistant *S aureus* (MRSA), typically becomes a major infective agent after 7 days of intubation and mechanical ventilation.

Cardiovascular effects

Mechanical ventilation always has some effect on the cardiovascular system. **Positive-pressure ventilation can decrease preload, stroke volume, and cardiac output.** Positive-pressure ventilation also affects renal blood flow and function, resulting in gradual **fluid retention**. The incidence of stress ulcers and sedation-related ileus is increased when

patients receive mechanical ventilation. In fact, mechanical ventilation is a **primary indication for GI prophylaxis**. Positive pressure maintained in the chest may decrease venous return from the head, **increasing intracranial pressure** and worsening agitation, delirium, and sleep deprivation.

Pulmonary Function Testing

Spirometry

Spirometry assesses the **integrated mechanical function of the lung, chest wall, and respiratory muscles** by measuring the total volume of air exhaled from a full lung (total lung capacity [TLC]) to an empty lung (residual volume). This volume, the **forced vital capacity** (FVC) and the forced expiratory volume in the first second of the forceful exhalation (**FEV_1**) The patient is instructed to inhale as much as possible and then exhale rapidly and forcefully for as long as flow can be maintained.

Reduction in the amount of air exhaled forcefully in the first second of the forced exhalation (**FEV_1**) may reflect reduction in the maximum inflation of the lungs (TLC), **obstruction of the airways, or respiratory muscle weakness**. Airway obstruction is the most common cause of reduction in FEV_1. Airflow obstruction may be secondary to bronchospasm, airway inflammation, loss of lung elastic recoil, increased secretions in the airway or any combination of these causes. Response of FEV_1 to inhaled bronchodilators is used to assess the **reversibility of airway obstruction**.

Spirometry is used to establish baseline lung function, detect pulmonary disease, monitor effects of therapies used to treat respiratory disease, evaluate respiratory impairment, and evaluate operative risk.

Obstructive defects

Disproportionate reduction in the **FEV_1 as compared to the FVC** (and therefore the FEV_1 -to-FVC ratio) is the hallmark of obstructive lung diseases. This physiologic category of lung diseases includes but is not

limited to asthma, acute and chronic bronchitis, emphysema, bronchiectasis, cystic fibrosis, pneumonia, alpha1-antitrypsin deficiency, and bronchiolitis. **The expiratory flow at any given expiratory volume is reduced**. The mechanism responsible for the reduction in airflow can be bronchial spasm, airway inflammation, increased intraluminal secretions, and/or reduction in parenchymal support of the airways due to loss of lung elastic recoil.

Restrictive defects

Reduction in the FVC with a normal or elevated FEV_1 -to-FVC ratio should trigger further diagnostic workup to rule out restrictive lung disease. Because the FEV_1 is a fraction of the FVC, it also is reduced, but the FEV_1 -to-FVC ratio is preserved at a normal or elevated level. Measuring the TLC and residual volume (RV) can confirm restriction suggested by spirometry.

Causes of restriction on spirometry include obesity, ascites, pleural effusion, pleural tumors, kyphoscoliosis, pulmonary fibrosis, neuromuscular disease, diaphragm weakness or paralysis, space-occupying lesions, lung resection, inadequate inspiration or expiration secondary to pain, and severe obstructive lung disease.

Assessment of operative risk

The FEV_1 obtained from good quality spirometry is a useful tool. **When the FEV_1 is greater than 2 L or 50% of predicted, major complications are rare.**

Operative risk is heavily dependent on the surgical site, with chest surgery having the highest risk for postoperative complications, followed by upper and lower abdominal sites. **Patient-related factors associated with increased operative risk** for pulmonary complications include preexisting pulmonary disease, cardiovascular disease, pulmonary hypertension, dyspnea upon exertion, heavy smoking history, respiratory infection, cough (particularly productive cough), advanced age (>70 y), malnutrition, general debilitation, obesity, and prolonged surgery.

UROLOGY

Vesicoureteral reflux

Urinary tract infections

- Acute pyelonephritis
- Chronic pyelonephritis

Urinary tract obstruction

- Hydronephrosis and hydroureter
- Benign prostatic hypertrophy
- Nephrolihtiasis
- Bladder stones
- Nephrocalcinosis
- Uric acid nephropathy
- Ureteral strictures

Urinary incontinence

- Neurogenic bladder
- Overactive bladder

Acute renal failure

Chronic kidney disease (chronic renal failure)

- Azotemia
- Uremia

Phimosis

- Paraphimosis

Priapism

Cryptorchidism

Hydrocele

Spermatocele

Varicocele

Testicular torsion

Enterovesical fistula

- Vesicovaginal fistula

Vesicoureteral Reflux

Vesicoureteral reflux is characterized by the **retrograde flow of urine from the bladder to the kidneys**. It may be associated with urinary tract infection, hydronephrosis, and abnormal kidney development (renal dysplasia).

Unrecognized vesicoureteral reflux with **concomitant urinary tract infection** may lead to long-term effects on renal function. Some individuals are at an increased risk for pyelonephritis, hypertension, and progressive renal failure.

When the ureter inserts into the trigone, the distal end of the ureter courses through the intramural portion of the bladder wall at an oblique angle. **The intramural tunnel length–to–ureteral diameter ratio is 5:1 for a healthy nonrefluxing ureter**. As the bladder fills with urine and the bladder wall distends and thins, the intramural portion of the ureter also stretches, thins out, and becomes compressed against the detrusor backing. This process allows a continual antegrade flow of urine from the ureter into the bladder but prevents retrograde transmission of urine from the bladder back up to the kidney; thus, a healthy intramural tunnel, within the bladder wall, functions as a flap-valve mechanism for the intramural ureter and prevents urinary reflux.

An abnormal intramural tunnel (ie, **short tunnel**) results in a malfunctioning flap-valve mechanism and vesicoureteral reflux. When the intramural tunnel length is short, urine tends to reflux up the ureter and into the collecting system.

The human kidney contains two types of renal papillae: simple (convex) papilla and compound (concave) papilla. Compound papillae predominate at the polar regions of the kidney, whereas simple papillae are located at nonpolar regions. **Approximately 66% of human papillae are convex and 33% are concave**.

Intrarenal reflux or retrograde movement of urine from the renal pelvis into the renal parenchyma **is a function of intrarenal papillary**

anatomy. Simple papillae possess oblique, slitlike, ductal orifices that close upon increased intrarenal pressure. Thus, **simple papillae do not allow intrarenal reflux**. However, **compound papillae possess gaping orifices** that are perpendicular to the papillary surface that remain open upon increased intrarenal pressure. These **gaping orifices allow free intrarenal reflux**.

Patients with uncorrected vesicoureteral reflux may develop renal scarring and impaired renal growth. Persistent intrarenal reflux causes eventual **reflux nephropathy**.

Two types of urine may enter the renal papillae: infected urine or sterile urine. **Intrarenal reflux of infected urine** appears to be primarily responsible for the renal damage. The presence of bacterial endotoxins (lipopolysaccharides) activates the host's immune response and a release of **oxygen free radicals**. The release of oxygen free radicals and proteolytic enzymes results in **fibrosis and scarring** of the affected renal parenchyma during the healing phase.

Initial scar formation at the infected polar region distorts local anatomy of the neighboring papillae and **converts simple papillae into compound papillae**. **Compound papillae, in turn, perpetuate further intrarenal reflux and additional renal scarring**. Thus, a potentially vicious cycle of events may occur after initial intrarenal introduction of infected urine. Intrarenal reflux of sterile urine (under normal intrapelvic pressures) has not been shown to produce clinically significant renal scars. Thus, **renal lesions appear to develop only in the setting of intrarenal reflux in combination with urinary tract infection**. One exception to this may include intrarenal reflux of sterile urine in the setting of abnormally high detrusor pressures.

Renal lesions are associated with higher grades of reflux. Pyelonephritic scarring may, over time, cause serious hypertension due to activation of the renin-angiotensin system. Scarring related to vesicoureteral reflux is one of the most common causes of **childhood hypertension**.

Urinary Tract Infections

The causes of male urinary tract infections include prostatitis, epididymitis, orchitis, and pyelonephritis, cystitis, and urethritis. Urinary tract infections are common in females, and cystitis (bladder infection) represents the majority of these infections. Urinary tract infection is one of the most common pediatric infections. The 2 **broad clinical categories are pyelonephritis and cystitis**. Related terms include pyelonephritis, which refers to upper urinary tract infection; bacteriuria, and candiduria. Very ill patients may be referred to as having **urosepsis**.

Uropathogenic bacteria, derived from a subset of fecal flora, have traits that enable adherence, growth, and resistance of host defenses. These traits facilitate colonization and infection of the urinary tract. **Adhesins** are bacterial surface structures that enable attachment to host membranes. Other factors that may be important for *E coli* virulence in the urinary tract include capsular polysaccharides, hemolysins, and cytotoxic necrotizing factor protein.

Complications of acute bacterial prostatitis include bacteremia, septic shock, prostatic abscess, epididymitis, seminal vesiculitis, and pyelonephritis. Other complications from urinary tract infections include fistula formation, recurrent infection, bacteremia, hydronephrosis and pyonephrosis, and gram-negative sepsis. **Pyonephrosis** refers to infected hydronephrosis associated with suppurative destruction of the kidney parenchyma, which results in nearly total loss of renal function.

As with females, the usual route of inoculation in males is with gram-negative aerobic bacilli from the gut, with *Escherichia coli* being the most common offending organism. In the normal host, urinary tract infection may occur due to infection of other portions of the genitourinary tract, typically the prostate. Older males with prostatic hypertrophy have **incomplete bladder emptying, predisposing them to urinary tract infection on the basis of urinary stasis**. Entry of microorganisms into the

prostate gland almost always occurs via the urethra; with intraprostatic reflux of urine, bacteria migrate from the urethra or bladder through the prostatic ducts.

Chronic prostatitis may be caused by inflammatory or noninflammatory diseases. This condition may arise via dysfunctional voiding, intraprostatic reflux, chronic exposure to microorganisms, autoimmune mechanisms, irritative urinary metabolites, and as a variant of neuropathic pain. Chronic bacterial prostatitis is **the most common cause of relapsing urinary tract infection in men**.

Epididymitis is a clinical syndrome caused by infection or inflammation of the epididymis. This condition is **the most common cause of acute scrotum in adult male populations**. *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the most common pathogens in patients younger than 35 years, whereas Enterobacteriaceae and gram-positive cocci are frequent pathogens in older patients. In either case, infection results from retrograde ascent of infected urine from the prostatic urethra into the vas deferens and, finally, into the epididymis.

Most cases of ***bacterial cystitis*** occur by an **ascending mechanism**. Bacterial cystitis in the male is uncommon in the absence of anatomic abnormality, defect in bladder emptying mechanism, or urethral catheterization (eg, poor bladder emptying from prostatic obstruction or dysfunctional voiding). **The shorter length of the female urethra allows uropathogens easier access to the bladder**. Elevated postvoid residuals allow bacteria to multiply to critical levels. **High voiding pressures and poor bladder compliance diminish the natural uroepithelial resistance to infection**. Generally, urine is a good culture medium. Factors unfavorable to bacterial growth include a low pH (5.5 or less), a high concentration of urea, and the presence of organic acids derived from a diet that includes fruits and protein. Organic acids enhance acidification of the urine. **If the defense mechanisms of the lower urinary tract fail, upper tract or kidney involvement occurs and is termed pyelonephritis**.

Acute Pyelonephritis

Acute pyelonephritis is a potentially organ- and/or life-threatening infection that characteristically causes scarring of the kidney. An episode of acute pyelonephritis may lead to **significant renal damage**; kidney failure; sepsis, septic shock, and multiorgan system failure.

Patients present with **lower urinary tract infection symptoms** (eg, dysuria, frequency, urgency, gross hematuria, suprapubic pain) and classic **upper urinary tract infection symptoms** (eg, flank pain, back pain), with or without **systemic signs and symptoms** (eg, fever, chills, abdominal pain, nausea, vomiting, costovertebral angle tenderness) and with or without **leukocytosis**.

Acute pyelonephritis results from bacterial invasion of the renal parenchyma. **Bacteria usually reach the kidney by ascending from the lower urinary tract**. In all age groups, episodes of bacteriuria occur commonly, but most are asymptomatic and do not lead to infection. Hematogenous spread of gram-negative organisms to the kidney is less likely unless an underlying problem exists, such as an obstruction. The spectrum of microorganisms cultured in pyelonephritis is the same as cultured in cystitis. The development of infection is influenced by bacterial factors and host factors.

Adhesins have specific regions that attach to cell receptor epitopes in a lock-and-key fashion. Mannose-sensitive adhesins are present on essentially all *E coli*. They contribute to colonization and possibly pathogenesis of infection. Mannose-resistant adhesins permit the bacteria to attach to epithelial cells, thereby resisting the cleansing action of urine flow and bladder emptying. The P fimbriae family of adhesins is epidemiologically associated with prostatitis, pyelonephritis, and sepsis. Siderophores are involved in iron uptake, an essential element for bacteria, and possibly adhesion. Protectins resist phagocytosis and action of complement, and cleave host defense proteins (eg, immunoglobulins).

Evidence suggests that the pathogenesis of pyelonephritis takes a 2-step path. First**, microorganisms attach to the epithelium and triggers an inflammatory response**. Second, as a result of the inflammatory response, **chemokines allow polymorphonuclears to cross the epithelial barrier into the urine**. Several other host factors militate against symptomatic urinary tract infection. Phagocytosis of bacteria in urine is maximized at pH 6.5-7.5 and osmolality of 485 mOsm. Other important factors are the flushing action of urine flow in the ureter and bladder, the inhibition of attachment of type 1 fimbriae *E coli* to uroepithelial cells by tubular cell–secreted Tamm-Horsfall protein, and the inhibition of attachment by some surface mucopolysaccharides on the uroepithelial cells.

Complicated urinary tract infection is an infection of the urinary tract in which the **efficacy of antibiotics is reduced** because of the presence of one or more of the following:

- Structural abnormalities of the urinary tract
- Functional abnormalities of the urinary tract
- Metabolic abnormalities predisposing to urinary tract infections
- Recent antibiotic use
- Recent urinary tract instrumentation

Obstruction is the most important factor. It negates the flushing effect of urine flow; allows urine to pool (**urinary stasis**), providing bacteria a medium in which to multiply; and **changes intrarenal blood flow**, affecting neutrophil delivery. Obstruction may be extrinsic or intrinsic. **Extrinsic obstruction** occurs with chronic constipation (particularly in children), prostatic swelling/mass (eg, hypertrophy, infection, cancer), and retroperitoneal mass. **Intrinsic obstruction** occurs with bladder outlet obstruction. With increasing size of stone, the probability of stone passage decreases while the probability of obstruction increases.

Atrophic vaginal mucosa in postmenopausal women predisposes to the colonization of urinary tract pathogens and urinary tract infections because of the higher pH (5.5 vs 3.8) and the absence of lactobacilli.

Urea-splitting organisms produce urease, which hydrolyzes urea, yielding ammonia, bicarbonate, and carbonate; this leads to a more alkaline urine and allows **crystal formation** (staghorn calculus) from the supersaturation of carbonate apatite. Staghorn calculi continue to grow in size, leading to infection, obstruction, or both.

Pregnancy produces hormonal and mechanical changes that predispose the woman to upper urinary traction infections. **Hydroureter** of pregnancy, secondary to both hormonal and mechanical factors, manifests as dilatation of the renal pelvis and ureters (greater on the left than on the right), with the ureters containing up to 200 ml of urine. **Progesterone** decreases ureteral peristalsis and increases bladder capacity. The enlarging uterus displaces the bladder, contributing to urinary stasis.

Diabetes mellitus produces **autonomic bladder neuropathy, glucosuria**, leukocyte dysfunction, microangiopathy, and nephrosclerosis; additionally, it leads to recurrent bladder instrumentation secondary to the neuropathy.

Chronic Pyelonephritis

Chronic pyelonephritis is characterized by **renal inflammation and fibrosis** induced by recurrent or persistent renal infection, vesicoureteral reflux, or other causes of urinary tract obstruction. It occurs almost exclusively in patients with major anatomic anomalies, most commonly in young children with vesicoureteral reflux. It may also be acquired by patients with a flaccid bladder due to spinal cord injury.

Chronic pyelonephritis is associated with **progressive renal scarring**, which can lead to **end-stage renal disease**. For example, in reflux nephropathy, intrarenal reflux of infected urine is suggested to induce renal injury, which heals with scar formation. Infection without reflux is

less likely to produce injury. Dysplasia may also be acquired from obstruction.

Factors that may affect the pathogenesis of chronic pyelonephritis are as follows:

- the sex of the patient and his or her sexual activity;
- pregnancy, which may lead to progression of renal injury with loss of renal function;
- genetic factors;
- bacterial virulence factors; and
- neurogenic bladder dysfunction. In cases with obstruction, the kidney may become filled with abscess cavities.

Urinary Tract Obstruction

Urinary tract obstruction can occur **at any point in the urinary tract**, from the kidneys to the urethral meatus. It can develop secondary to **calculi, tumors, strictures, and anatomical abnormalities**. Obstructive uropathy can result in pain, urinary tract infection, loss in renal function, or, possibly, sepsis or death.

Chronic urinary tract obstruction can lead to **permanent damage to the urinary tract**. **Infravesical obstruction** can lead to changes in the bladder, such as **trabeculation, cellule formation, diverticula, bladder wall thickening, and, ultimately, detrusor muscle decompensation**. Progressive back pressure on the ureters and kidneys can occur and can cause **hydroureter and hydronephrosis**. The ureter can then become dilated and tortuous, with the inability to adequately propel urine forward. Hydronephrosis can cause permanent nephron damage and renal failure (when function of both kidneys is affected). Urinary stasis along any portion of the urinary tract increases the **risk of stone formation and infection**, and, ultimately, upper urinary tract injury. Urinary tract obstruction can cause long-lasting effects to the physiology of the kidney, including its **ability to concentrate urine**.

Hydronephrosis and Hydroureter

Hydronephrosis is defined as **distention of the renal calyces and pelvis with urine** as a result of **obstruction of the outflow of urine distal to the renal pelvis**. Analogously, hydroureter is defined as a dilation of the ureter.

Obstructive uropathy refers to the functional or anatomic obstruction of urinary flow at any level of the urinary tract. Obstructive nephropathy is present when the obstruction causes functional or anatomic renal damage. Thus, the terms hydronephrosis and obstruction should not be used interchangeably.

Hydronephrosis/hydroureter caused by obstruction anywhere in the urinary tract may be acute or chronic, unilateral or bilateral. The major causes range from **anatomic abnormalities** (including urethral valves or stricture, and stenosis at the ureterovesical or ureteropelvic junction), which account for the majority of cases in children. In comparison, **calculi** are most common in young adults, while **prostatic hypertrophy or carcinoma, retroperitoneal or pelvic neoplasms**, and calculi are the primary causes in older patients.

Hydronephrosis or hydroureter is a **normal finding in pregnant women**. The renal pelvises and caliceal systems may be dilated as a result of **progesterone effects and mechanical compression of the ureters** at the pelvic brim.

Hydronephrosis can result from anatomic or functional processes interrupting the flow of urine. The rise in ureteral pressure leads to marked changes in glomerular filtration, tubular function, and renal blood flow. The **glomerular filtration rate declines** significantly within hours following acute obstruction. This significant decline of GFR can persist for weeks after relief of obstruction. In addition, **renal tubular ability to transport sodium, potassium, and protons and concentrate and to dilute the urine is severely impaired**. The extent and persistence of these functional insults is directly related to the duration and extent of

the obstruction. **Brief disruptions are limited to reversible functional disturbance** with little associated anatomic changes. More chronic disruptions lead to **profound tubular atrophy and permanent nephron loss**.

To distinguish acute and chronic hydronephrosis, one may consider acute as hydronephrosis that, when corrected, allows full recovery of renal function. Conversely, chronic hydronephrosis is a situation in which the **loss of function is irreversible even with correction of the obstruction**.

Grossly, an acutely hydronephrotic system can be associated with little anatomic disturbance to renal parenchyma. On the other hand, a chronically dilated system may be associated with compression of the papillae, thinning of the parenchyma around the calyces, and coalescence of the septa between calyces. Eventually, **cortical atrophy progresses to the point at which only a thin rim of parenchyma is present**.

Benign Prostatic Hypertrophy

Benign prostatic hyperplasia, also known as benign prostatic hypertrophy, is a histologic diagnosis characterized by proliferation of the cellular elements of the prostate. **Cellular accumulation and gland enlargement may result from epithelial and stromal proliferation, impaired preprogrammed cell death (apoptosis), or both**.

The hyperplasia presumably results in enlargement of the prostate that may restrict the flow of urine from the bladder. The voiding dysfunction that results from prostate gland enlargement and bladder outlet obstruction is termed **lower urinary tract symptoms**.

Benign prostatic hyperplasia is considered a **normal part of the aging process in men and is hormonally dependent on testosterone and dihydrotestosterone** production. In the prostate gland, type II 5-alpha-reductase metabolizes circulating testosterone into dihydrotestosterone, which works locally, not systemically. Dihydrotestosterone binds to

androgen receptors in the cell nuclei, potentially resulting in hypertrophy.

Obstruction-induced bladder dysfunction contributes significantly to lower urinary tract symptoms. The **bladder wall becomes thickened**, trabeculated, and irritable when it is forced to hypertrophy and increase its own contractile force. This increased sensitivity (**detrusor overactivity**), even with small volumes of urine in the bladder, is believed to contribute to urinary frequency and lower urinary tract symptoms. The **bladder may gradually weaken and lose the ability to empty completely**, leading to increased residual urine volume and, possibly**, acute or chronic urinary retention**.

Nephrolihtiasis

Acute renal colic is probably the **most excruciatingly painful event** a person can endure. Although nephrolithiasis is not a common cause of renal failure, certain problems, such as preexisting azotemia and solitary functional kidneys, clearly present a higher risk of additional renal damage. **Recurrent obstruction, especially when associated with infection and tubular epithelial or renal interstitial cell damage from microcrystals, may activate the fibrogenic cascade**, which is mainly responsible for the actual loss of functional renal parenchyma.

Urinary tract stone disease is likely caused by two basic phenomena.

The first phenomenon is **supersaturation of the urine by stone-forming constituents**, including calcium, oxalate, and uric acid. **Crystals or foreign bodies can act as nidi**, upon which ions from the supersaturated urine form microscopic crystalline structures. The resulting calculi give rise to symptoms when they become impacted within the ureter as they pass toward the urinary bladder.

The overwhelming majority of renal calculi contain **calcium**. **Uric acid** calculi and crystals of uric acid, with or without other contaminating ions, comprise the bulk of the remaining minority. Other, less frequent stone types include **cystine, ammonium acid urate, xanthine,**

dihydroxyadenine, and various rare stones related to precipitation of medications in the urinary tract.

The second phenomenon, which is most likely responsible for calcium oxalate stones, is **deposition of stone material on a renal papillary calcium phosphate nidus**. Calcium phosphate precipitates in the basement membrane of the thin loops of Henle, erodes into the interstitium, and then accumulates in the subepithelial space of the renal papilla. The subepithelial deposits, which have long been known as Randall plaques, eventually erode through the papillary urothelium. Stone matrix, calcium phosphate, and calcium oxalate gradually deposit on the substrate to create a urinary calculus.

In the ureter, an **increase in proximal peristalsis through activation of intrinsic ureteral pacemakers** may contribute to the perception of pain. Muscle spasm, increased proximal peristalsis, local inflammation, irritation, and edema at the site of obstruction may contribute to the development of pain through chemoreceptor activation and stretching of submucosal free nerve endings.

A stone moving down the ureter and causing only intermittent obstruction actually may be more painful than a stone that is motionless. A constant obstruction, even if high grade, allows for various autoregulatory mechanisms and reflexes, interstitial renal edema, and pyelolymphatic and pyelovenous backflow to help diminish the renal pelvic hydrostatic pressure, which gradually helps reduce the pain.

Distention of the renal pelvis initially stimulates ureteral hyperperistalsis, but this diminishes after 24 hours, as does renal blood flow. Peak hydrostatic renal pelvis pressure is attained within 2-5 hours after a complete obstruction.

Within the first 90 minutes of a complete ureteral obstruction, afferent preglomerular arteriolar vasodilation occurs, which temporarily increases renal blood flow. Between 90 minutes and 5 hours after the obstruction, renal blood flow starts to decrease while intraureteral pressure continues to rise. By **5 hours after a complete obstruction, both**

renal blood flow and intraluminal ureteral pressure decrease on the affected side.

Renal blood flow decreases to approximately 50% of normal baseline levels after 72 hours, to 30% after 1 week, to 20% after 2 weeks, and to 12% after 8 weeks. By this point, intraureteral pressures have returned to normal, but the proximal ureteral dilation remains and ureteral peristalsis is minimal.

Interstitial edema of the affected kidney actually enhances fluid reabsorption, which helps to increase the renal lymphatic drainage to establish a new, relatively stable, equilibrium. **At the same time, renal blood flow increases in the contralateral kidney as renal function decreases in the obstructed unit.**

In summary, by 24 hours after a complete ureteral obstruction, the renal pelvic hydrostatic pressure has dropped because of (1) a reduction in ureteral peristalsis; (2) decreased renal arterial vascular flow, which causes a corresponding drop in urine production on the affected side; and (3) interstitial renal edema, which leads to **a marked increase in renal lymphatic drainage**.

Bladder Stones

Vesical calculi refer to the presence of stones or calcified materials in the bladder. These stones are **usually associated with urinary stasis**, but they can form in healthy individuals without evidence of anatomic defects, strictures, infections, or foreign bodies. **The presence of upper urinary tract calculi is not necessarily a predisposition to the formation of bladder stones.**

Prostatic enlargement, elevation of the bladder neck, and high **postvoid residual urine volume cause stasis, which leads to crystal nucleation and accretion**. This ultimately results in overt calculi. In addition, patients who have static urine and develop urinary tract infections are more likely to form bladder calculi.

Most vesical calculi are formed de novo within the bladder, but some may initially have formed within the kidneys as a dissociated Randall plaque or on a sloughed papilla and subsequently passed into the bladder, where additional deposition of crystals cause the stone to grow. However, most renal stones that are small enough to pass through the ureters are also small enough to pass through a normally functioning bladder and unobstructed urethra. In older men with bladder stones composed of uric acid, the stone most likely formed in the bladder. **Stones composed of calcium oxalate are usually initially formed in the kidney.** Patients with uric acid bladder calculi rarely ever have a documented history of **hyperuricemia**.

Cystinuria

Cystinuria is an autosomal-recessive **defect in reabsorptive transport** of cystine and the dibasic amino acids ornithine, arginine, and lysine from the luminal fluid of the renal proximal tubule and small intestine. The only phenotypic manifestation of cystinuria is cystine urolithiasis.

Amino acids are readily filtered by the glomerulus and undergo nearly complete reabsorption in the proximal convoluted tubule by a high-affinity luminal transmembrane channel. Defects in this channel cause **elevated levels of dibasic amino acid secretion in the urine**.

Cystine is relatively insoluble at physiologic urine pH levels of 5-7. Risk factors for cystine crystallization include (1) low pH level, (2) reduced ion strength, (3) the presence of cystine crystals, and (4) low levels of urinary macromolecules.

Two thirds of persons with cystinuria who form stones make pure cystine calculi, and one third have a mixture of cystine and calcium oxalate calculi.

Hypercalciuria

Hypercalciuria, or excessive urinary calcium excretion, occurs in about 5-10% of the population and is the most common identifiable cause of calcium kidney stone disease. (The other significant causes include hyperoxaluria, hyperuricosuria, low urinary volume, and hypocitraturia.)

Hypercalciuria is defined as **urinary excretion of more than 250 mg of calcium per day** in women or more than 275-300 mg of calcium per day in men while on a regular unrestricted diet.

The most common types of clinically significant hypercalciuria are absorptive, renal leak, resorptive, and renal phosphate leak. Other causes of hypercalciuria include hyperthyroidism, renal tubular acidosis, sarcoidosis and other granulomatous diseases, vitamin D intoxication, glucocorticoid excess, Paget disease, various paraneoplastic syndromes, prolonged immobilization, multiple myeloma, lymphoma, leukemia, metastatic tumors especially to bone, and Addison disease.

About 80% of all kidney stones contain calcium, and at least one third of all calcium stone formers are found to have hypercalciuria when tested. **Hypercalciuria contributes to kidney stone disease and osteoporosis**.

Hyperoxaluria

High levels of oxalate in the system can produce various health problems, particularly kidney stone formation.

Primary hyperoxaluria is a genetic defect that causes a loss of specific enzymatic activity.

Enteric hyperoxaluria is due to a gastrointestinal problem usually associated with chronic diarrhea. Malabsorption from any cause can result in enteric hyperoxaluria. Such causes include intestinal bacterial overgrowth syndromes, fat malabsorption, chronic biliary or pancreatic disease, various intestinal bypass surgical procedures, inflammatory bowel disease, or any medical condition that causes chronic diarrhea.

The basic mechanism is **competition for the available ingested calcium, the leading intestinal oxalate-binding agent**. Most of the bile acids produced during digestion are reabsorbed in the proximal intestinal tract. When this fails to occur, calcium and magnesium bind to these bile acids through saponification. This leaves very little free calcium available for absorption or binding with oxalate in the lower intestinal tract. Without

the calcium necessary to adequately bind oxalate in the intestinal tract, additional oxalate is absorbed and then excreted in the urinary tract.

Recent evidence suggests that dietary oxalate plays a much more important role and may be responsible for 50% of the total urinary oxalate. A **high intake of oxalate-rich foods** (eg, chocolate, nuts, spinach) and a diet rich in animal protein can result in hyperoxaluria. Low dietary calcium intake can also result in hyperoxaluria via decreased intestinal binding of oxalate and the resulting increased absorption. Ascorbic acid can be converted in oxalate, resulting in increased urinary oxalate levels.

Nephrocalcinosis

Nephrocalcinosis is a condition in which calcium levels in the kidneys are increased. Nephrocalcinosis has a **significant overlap with hypercalcemia, nephrolithiasis, renal parenchymal damage, and reduced renal function**. Patients with hypercalcemia develop renal function abnormalities. The used term is **hypercalcemic nephropathy**.

Calcium is a critical divalent cation that is transported, along with sodium, potassium, and water, in a complex and regulated manner along the renal tubular epithelium. The cytoplasmic concentration of calcium is tightly regulated and kept very low, being maintained by active extracellular extrusion of calcium and sequestration into the endoplasmic reticulum and mitochondria. Increased extracellular calcium leads to impairment of the calcium messenger system with gross tubular impairment.

Hypercalcemia results in **renal vasoconstriction and a reduced glomerular filtration rate.** It also interferes with renal tubular functions. **Impaired renal concentration ability and resistance to vasopressin** are the most common defects observed with hypercalcemia. This may be mediated by reduced sodium transport in the loop of Henle and by antidiuretic hormone antagonism via calcium-sensing receptors.

Cortical nephrocalcinosis is rare and usually occurs secondary to diffuse cortical disease injury. Medullary nephrocalcinosis assumes the form of small nodules of calcification clustered in each pyramid.

Uric Acid Nephropathy

Uric acid is the relatively water-insoluble and it poses a **special problem in the acidic environment of the distal nephron** of the kidney. Three forms of kidney disease have been attributed to excess uric acid: acute uric acid nephropathy, chronic urate nephropathy, and uric acid nephrolithiasis.

Uric acid, the product of the xanthine oxidase–catalyzed conversion of xanthine and hypoxanthine, is the final metabolite of endogenous and dietary purine nucleotide metabolism. In the collecting tubules of the kidneys, where the pH can fall to 5.0, uric acid formation is favored.

The critical physical property of uric acid in the clinical setting is solubility. Uric acid is less soluble than urate; thus, an acidic environment decreases solubility.

Urate is freely filtered at the glomerulus. An active anion-exchange process in the early proximal convoluted tubule reabsorbs most of it. Most urinary uric acid appears to be derived from tubular secretion, possibly from the the proximal tubule. Extracellular volume expansion or contraction, respectively, enhances or reduces uric acid excretion through the paired movement of sodium. Consequently, in cases of extracellular compartment depletion, urate excretion is diminished.

Acute uric acid nephropathy

Overproduction of uric acid occurs primarily when tissue breakdown is accelerated. Acute uric acid nephropathy is an **acute oligoanuric renal failure caused by renal tubular obstruction by urate and uric acid crystals**. This is observed almost exclusively in the setting of malignancy, especially leukemia and lymphoma, in which rapid cell turnover or cell lysis occurs from chemotherapeutic agents or radiation therapy.

When urate is filtered at exceedingly high concentrations from the plasma and is further concentrated through the course of the tubular system, with the pH becoming progressively more acidic, **uric acid precipitation and obstruction in the tubules, collecting ducts, and even pelves and ureters** may result.

Crystal deposition causes increased tubular pressure, increased intrarenal pressure, and extrinsic compression of the small-diameter renal venous network. This causes an increase in renal vascular resistance and a fall in renal blood flow. The elevated tubular pressure and decreased renal blood flow cause a decline in glomerular filtration and can result in **acute renal failure**.

Chronic urate nephropathy

A newer hypothesis proposes that **hyperuricemia may cause impairment of renal autoregulation, leading to hypertension, microalbuminuria and overt albuminuria, and progressive kidney failure**. The incidence of chronic kidney disease is high in these individuals, who have intratubular uric acid deposits and interstitial urate deposits.

Uric acid nephrolithiasis

Uric acid stones also result from uric acid precipitation in the collecting system. Urine oversaturation with uric acid and subsequent crystal formation is determined largely by urinary pH. Individuals who form uric acid stones tend to **excrete less ammonium**, which contributes directly to low urinary pH.

Ureteral Strictures

A ureteral stricture is characterized by a narrowing of the ureteral lumen, causing functional obstruction. The most common cause of ureteral stricture is **ureteropelvic junction obstruction**, which is characterized by a congenital or acquired narrowing.

Ureteral strictures are typically due to **ischemia, resulting in fibrosis**. Stricture is defined as ischemic when it follows open surgery or radiation

therapy, whereas the stricture is considered nonischemic if it is caused by spontaneous stone passage or a congenital abnormality. Less commonly, the etiology is mechanical, such as from a poorly placed permanent suture or surgical clip.

The stricture reveals disordered collagen deposition, fibrosis, and varying levels of inflammation, depending on factors such as etiology and interval since the causative insult.

The resulting ureteral obstruction may vary widely from mild, causing only asymptomatic proximal ureteral dilation and hydronephrosis, to severe, causing complete obstruction and subsequent loss of renal function.

Uretral strictures in males

Urethral strictures arise from various causes and can result in a range of manifestations, from an asymptomatic presentation to severe discomfort secondary to urinary retention.

Urethral strictures occur after an **injury to the urothelium or corpus spongiosum** causes scar tissue to form.

Urinary Incontinence

Urinary incontinence is defined as the **involuntary loss of urine** that represents a hygienic or social problem to the individual. Most individual cases are likely multifactorial in nature.

Four types of urinary incontinence are defined: **stress, urge, mixed, and overflow**. Some include functional incontinence as a fifth type of incontinence.

Other terms describing urinary incontinence are as follows:

- Enuresis - Involuntary loss of urine
- Nocturnal enuresis - Loss of urine occurring during sleep
- Continuous urinary incontinence - Continuous leakage

Micturition requires coordination of several physiological processes. Somatic and autonomic nerves carry bladder volume input to the spinal

cord, and motor output innervating the detrusor, sphincter, and bladder musculature is adjusted accordingly. The cerebral cortex exerts a predominantly inhibitory influence, whereas the brainstem facilitates urination by **coordinating urethral sphincter relaxation and detrusor muscle contraction**.

As the bladder fills, sympathetic tone contributes to closure of the bladder neck and relaxation of the dome of the bladder and inhibits parasympathetic tone. At the same time, somatic innervation maintains tone in the pelvic floor musculature as well as the striated periurethral muscles.

When urination occurs, sympathetic and somatic tones in the bladder and periurethral muscles diminish, resulting in decreased urethral resistance. **Cholinergic parasympathetic tone increases, resulting in bladder contraction**. Urine flow results when bladder pressure exceeds urethral resistance. Normal bladder capacity is 300-500 mL, and the first urge to void generally occurs between bladder volumes of 150 and 300 mL.

Incontinence occurs when micturition physiology, functional toileting ability, or both have been disrupted.

Stress incontinence

During episodes of stress incontinence, **an increase in intra-abdominal pressure** (eg, from laughing, sneezing, coughing, climbing stairs**) raises pressure within the bladder to the point where it exceeds the urethra's resistance to urinary flow**. Leakage ceases when bladder pressure again falls below urethral pressure.

The major cause of stress incontinence is **urethral hypermobility** due to **impaired support from pelvic floor**. A less common cause is an intrinsic sphincter deficiency, usually secondary to pelvic surgeries. In either case, **urethral sphincter function is impaired**, resulting in urine loss at lower than usual abdominal pressures.

In women with stress urinary incontinence, either or both mechanisms may be present, or stress incontinence does not develop with poor pelvic

support unless intrinsic sphincter deficiency is also present. Intrinsic sphincter deficiency, resulting from loss of function of both the internal and the external sphincter mechanism, is the only cause of stress incontinence in males.

Urethral hypermobility is related to impaired neuromuscular functioning of the pelvic floor coupled with injury to the connective tissue supports of the urethra and bladder neck. In women without urethral hypermobility, the urethra is stabilized during stress by three interrelated mechanisms:

1. reflex, or voluntary, closure of the pelvic floor,
2. intact connective tissue support the bladder neck and urethra,
3. the urethrovaginal sphincter and the compressor urethrae may aid in compressing the urethra shut during stress maneuvers.

Damage to the nerves, muscle, and connective tissue of the pelvic floor is important in the genesis of stress incontinence. **Injury during childbirth** probably is the most important mechanism. Aging, hypoestrogenism, chronic connective tissue strain due to primary loss of muscular support, activities or medical conditions resulting in long-term repetitive increases in intra-abdominal pressure. When the urethra is hypermobile, pressure transmission to the walls of the urethra may be diminished as it descends and rotates under the pubic bone. **Intraurethral pressure falls below bladder pressure**, resulting in urine loss.

Intrinsic sphincter deficiency is a condition in which the **urethral sphincter is unable to coapt and generate enough resting urethral closing pressure** to retain urine in the bladder. The anatomic support of the urethra may be normal.

Intrinsic sphincter deficiency is due to devascularization and/or denervation of the bladder neck and proximal urethra.

Female urethral function is influenced by estrogen. The **lack of estrogen at menopause** leads to atrophy and replacement of submucosa (ie, vascular plexus) by fibrous tissue.

Urge incontinence

Urge incontinence is **involuntary urine loss associated with a feeling of urgency**. The corresponding urodynamic term is **detrusor overactivity**. Findings may indicate a higher sensitivity to efferent neurologic activity or a lower threshold of acetylcholine release needed to initiate a detrusor contraction. Another finding with detrusor overactivity is local loss of inhibitory medullary neurologic activity (vasoactive intestinal peptide, a smooth muscle relaxant, is decreased markedly in the bladder).

Urge incontinence may be a result of **detrusor myopathy, neuropathy**, or a combination of both.

In males, early obstruction due to **benign prostatic hyperplasia** (BPH) may result in urge incontinence. The pathophysiology is poorly understood. Relative obstruction develops because of mechanical factors, dynamic factors, and detrusor alterations.

The presence of **inflammation** in the bladder is believed to result in bladder muscle irritability and urge incontinence in some instances. Foreign bodies, including permanent sutures, bladder stones, and neoplasms, also have been linked to bladder irritability and instability.

Mixed incontinence

Mixed incontinence is urinary incontinence resulting from a **combination of stress and urge incontinence**. Approximately 40-60% of females with incontinence have this combination. It is generally defined as **detrusor overactivity and impaired urethral function**. The bladder outlet is weak and the detrusor is overactive.

Mixed incontinence is a common finding in **older patients with urinary incontinence** disorders. Often, stress incontinence symptoms precede urge incontinence symptoms in these individuals.

Reflex incontinence

Reflex incontinence is due to **neurologic impairment of the central nervous system**. Common neurologic disorders associated with reflex incontinence include stroke, Parkinson disease, and brain tumors. The

extrapyramidal system is believed to have an inhibitory effect on the micturition center; theoretically, loss of dopaminergic activity in this area could result in loss of detrusor inhibition. Reflex incontinence also occurs in patients with **spinal cord injuries** and multiple sclerosis.

Spinal cord injuries interrupt the sacral reflex arc from the suprasacral spinal cord, cerebral cortex, and higher centers. These pathways are crucial for voluntary and involuntary inhibition. In the initial phase of spinal cord injury, the bladder is areflexic and overflow incontinence results. Later, **detrusor hyperreflexia** usually is found.

In patients with dementia, incontinence and urinary tract dysfunction may be due to specific involvement of the areas of the cerebral cortex involved in bladder control. Alternatively, incontinence may be related to **global deterioration of memory, intellectual capacity, and behavior**.

Overflow incontinence

The major contributing factor to overflow incontinence is **incomplete bladder emptying secondary to impaired detrusor contractility or bladder outlet obstruction**. Impaired detrusor contractility is typically neurogenic in nature; causes include diabetes mellitus, lumbosacral nerve disease from tumors, meningomyelocele, prolapsed intravertebral disks, and high spinal cord injuries.

In most cases, both **sensory and motor neuropathies** are present. The maximal storage capacity of the bladder is reached, oftentimes without the individual realizing that this has occurred. Incontinence occurs off the top of a **chronically over-filled bladder**. Effective emptying is not possible because of an **acontractile detrusor muscle**.

Common causes of bladder outlet obstruction in men include **benign prostatic hyperplasia**, vesical neck contracture, and **urethral strictures**. In women, urethral obstruction after anti-incontinence surgery can result in iatrogenically induced overflow incontinence.

Functional incontinence

Functional incontinence is seen in patients with **normal voiding systems but who have difficulty reaching the toilet** because of physical

or psychological impediments. In some cases, the cause is transient or reversible. In others, a permanent problem can be identified. The common functional contributors to incontinence: delirium, urinary infection, pharmacologic agents, psychiatric illness, reduced mobility, stool impaction.

Continuous incontinence

This severe type of incontinence is characterized by **constant or near constant leakage with no symptoms** other than wetness. Generally, this represents a significant breech in the storage capabilities of the bladder or urethra. **Urogenital fistulas** are a classic example.

A nonfunctioning urethra can result in continuous leakage. Scarring and fibrosis from previous surgery, partial urethral resection for vulvar cancer, and urethral sphincter paralysis due to lower motor neuron disease can cause the urethra to fail.

Pediatric urinary incontinence

Pediatric incontinence disorders are classified according to cause. Primary incontinence disorders generally are due to **congenital structural disorders**, including ectopic ureter, exstrophy, and epispadias. Secondary structural causes can result from obstruction from urethral valves, congenital urethral strictures, and large ectopic ureteroceles. **Neurogenic lesions** make up the next category of pediatric incontinence disorders. These include spinal dysraphism, tethered spinal cord, and spinal cord tumors.

Nonstructural causes account for most cases of pediatric incontinence. **Infection and inflammation** may be the source. Dysfunctional voiding habits can develop even at a young age. Some children may become so preoccupied with activities that voiding is delayed until capacity is reached and accidents result.

Nocturnal enuresis is the most common pediatric incontinence disorder.

Neurogenic Bladder

The coordinated activity to store and expel urine is regulated by the central and peripheral nervous systems. Neurogenic bladder is a term applied to a **malfunctioning urinary bladder due to neurologic dysfunction.**

Symptoms of neurogenic bladder range **from detrusor underactivity to overactivity**, depending on the site of neurologic insult. The urinary sphincter also may be affected resulting to the loss of coordination with bladder function.

Normal voiding essentially is a **spinal reflex that is modulated by the central nervous system**. The micturition control center is located in the frontal lobe of the brain, that is sending tonically inhibitory signals to the detrusor muscle to prevent the bladder from emptying (contracting) until a socially acceptable time and place to urinate is available. Certain lesions or diseases of the brain, including stroke, cancer, or dementia, result in **loss of voluntary control of the normal micturition reflex**. The pons synergically coordinates the urethral sphincter relaxation and detrusor contraction to facilitate urination. It is affected by emotions, which is why some people may experience incontinence when they are excited or scared. Usually the brain takes over the control of the pons at age 3-4 years. In the normal cycle of bladder filling and emptying, the spinal cord acts as an important intermediary between the pons and the sacral cord. The sacral reflex center is critical for normal micturition.

Under normal conditions, the **bladder and the internal urethral sphincter primarily are under sympathetic nervous system control**. It causes the bladder to increase its capacity without increasing detrusor resting pressure (accommodation) and stimulates the internal urinary sphincter to remain tightly closed. The **parasympathetic nerves stimulate the detrusor to contract and the internal sphincter relaxes and opens**. In addition, the activity of the pudendal nerve is inhibited to cause the external sphincter to open.

The pressure gradients within the bladder and urethra play an important functional role in normal micturition**. As long as the urethral pressure is higher than that of the bladder, patients will remain continent**. If the urethral pressure is abnormally low or if the intravesical pressure is abnormally high, urinary incontinence will result.

During coughing, sneezing, or laughing, the pressure within the abdomen rises sharply. This rise is transmitted to both the bladder and urethra. When the pressure transmitted to the bladder is greater than urethra, urine will leak out, resulting in stress incontinence.

If a problem occurs within the nervous system, the entire voiding cycle is affected. A **dysfunctional voiding** condition results in different symptoms, ranging **from acute urinary retention to an overactive bladder** or to a combination of both.

Lesions of the brain above the pons destroy the master control center, causing a complete **loss of voiding control**. The voiding reflexes of the lower urinary tract remain intact. Affected individuals show **signs of urge incontinence, or spastic bladder**. The bladder empties too quickly and too often, with relatively low quantities. Typical examples of a brain lesion are stroke, brain tumor, or Parkinson disease.

Diseases or injuries of the spinal cord between the pons and the sacral spinal cord also result in spastic bladder or **overactive bladder**. People who are paraplegic or quadriplegic have lower extremity spasticity and they experience **urge incontinence**.

Selected injuries of the sacral cord may prevent the bladder from emptying. If a **sensory neurogenic bladder** is present, the affected individual may **not be able to sense when the bladder is full**. In the case of a **motor neurogenic bladder**, the individual will sense the **bladder is full and the detrusor may not contract**. These individuals experience **overflow incontinence**; the bladder gradually overdistends until the urine spills out. Typical causes are a sacral cord tumor, herniated disc, and injuries that crush the pelvis.

Diabetes mellitus causes **peripheral neuropathy** resulting in **urinary retention**. These diseases destroy the nerves to the bladder and may lead to silent, painless distention of the bladder.

Overactive Bladder

Overactive bladder is a syndrome consisting of the **urinary urgency**, with or without urgency urinary incontinence, usually with **nocturia**, in the absence of causative infection or pathologic conditions and suggestive of underlying **detrusor overactivity**.

Urgency is defined as the sudden compelling desire to urinate, a sensation that is difficult to defer. Urgency urinary incontinence is urinary leakage associated with urgency.

Overactive bladder appears to be multifactorial in both etiology and pathophysiology.

Acute Renal Failure

Acute renal failure, or acute kidney injury is defined as an **abrupt or rapid decline in renal filtration function**. This condition is usually marked by a **rise in serum creatinine concentration or by azotemia** (a rise in blood urea nitrogen concentration).

Acute kidney injury may be classified into 3 general categories, as follows:

- ***Prerenal*** - as an adaptive response to **severe volume depletion and hypotension**, with **structurally intact nephrons**; essentially normal kidneys are responding to hypoperfusion by decreasing the glomerular filtration rate
- ***Intrinsic*** - in response to cytotoxic, ischemic, or inflammatory insults to the kidney, with **structural and functional damage**
- ***Postrenal*** - from obstruction to the passage of urine

Oliguric and nonoliguric patients with acute kidney injury

Patients who develop acute kidney injury can be oliguric or nonoliguric, have a rapid or slow rise in creatinine levels, and may have qualitative differences in urine solute concentrations and cellular content. If urinary output is preserved, it is called *nonoliguric* acute renal failure (approximately 50-60% of all causes are nonoliguric). **Oliguria** is defined as a daily urine volume of less than 400 ml/d and has a worse prognosis, except in prerenal failure. **Anuria** is defined as a urine output of less than 100 ml/d and, if abrupt in onset, suggests bilateral obstruction or catastrophic injury to both kidneys. A **vast array of fluid and electrolyte abnormalities can be seen with acute kidney injury**.

Tubular damage in nonoliguric acute renal failure is less severe than in oliguric. Patients with **nonoliguric acute renal failure may still make 1440 ml/d of urine even when the GFR falls to about 1 ml/min because of decreased tubular reabsorption**. Some studies indicate that nonoliguric forms of acute renal failure are associated with less morbidity and mortality than oliguric acute renal failure.

The pathophysiology of acute oliguric or nonoliguric acute renal failure depends on the anatomical location of the injury. In acute tubular necrosis, epithelial damage leads to **functional decline in the ability of the tubules to reabsorb salt, water, and other electrolytes. Excretion of acid and potassium also is impaired.** In more severe acute tubular necrosis, the tubular lumen is filled with epithelial casts, causing intraluminal obstruction, resulting in the decline of GFR.

Cardiovascular complications (eg, congestive heart failure], myocardial infarction, arrhythmias, cardiac arrest) are observed in patients with acute kidney injury. **Fluid overload secondary to oliguric acute kidney injury** is a particular risk for elderly patients with little cardiac reserve. **Acute kidney injury also can be a complication of cardiac diseases**, such as endocarditis, decompensated chronic heart failure, or atrial fibrillation with emboli. **Cardiac arrest** in a patient with acute kidney injury always should arouse **suspicion of hyperkalemia**.

Pulmonary complications have been reported in patients with acute kidney injury and are the single **most significant risk factor for death**. Several diseases exist that commonly present with simultaneous pulmonary and renal involvement, including pulmonary/renal syndromes. A dialysis-related hypoxia is thought to occur **secondary to white blood cell lung sequestration and alveolar hypoventilation**.

GI symptoms of nausea, vomiting, and anorexia are frequent complications of acute kidney injury and represent one of the cardinal signs of uremia.

Neurologic signs of uremia are a common complication of acute kidney injury. Neurologic sequelae include lethargy, somnolence, reversal of the sleep-wake cycle, and cognitive or memory deficits.

Acute tubular necrosis

Acute tubular necrosis is the most common cause of acute kidney injury in the renal category. Changes in serum creatinine levels and urine output over a 48-hour period are the most commonly applied and recognized biomarkers of kidney function.

The tubule cell damage and **cell death** that characterize acute tubular necrosis usually result from an **acute ischemic or toxic event**. Nephrotoxic mechanisms of acute tubular necrosis include direct drug toxicity, intrarenal vasoconstriction, and intratubular obstruction.

Acute tubular necrosis follows a well-defined 3-part sequence of initiation, maintenance, and recovery.

Initiation phase

Ischemic acute tubular necrosis is often described as a continuum of prerenal azotemia. It results when hypoperfusion overwhelms the kidney's autoregulatory defenses. Under these conditions, hypoperfusion initiates cell injury that often, but not always, leads to cell death.

Injury of tubular cells is most prominent in the straight portion of the **proximal tubules and in the thick ascending limb of the loop of Henle**, especially as it dips into the relatively hypoxic medulla. The reduction in the glomerular filtration rate that occurs from ischemic injury is a result

not only of reduced filtration due to **hypoperfusion** but also of **casts and debris obstructing the tubule lumen**, causing back-leak of filtrate through the damaged epithelium. Cell death occurs by both **necrosis and apoptosis**.

In addition, ischemia leads to decreased production of vasodilators (ie, nitric oxide, prostacyclin) by the tubular epithelial cells, leading to further vasoconstriction and hypoperfusion.

On a cellular level, ischemia causes depletion of adenosine triphosphate, an increase in cytosolic calcium, free radical formation, metabolism of membrane phospholipids, and abnormalities in cell volume regulation. With ineffective membrane transport, cell volume and electrolyte regulation are disrupted, leading to cell swelling and intracellular accumulation of sodium and calcium. In addition, free radical formation is increased, producing toxic effects. Damage inflicted by free radicals apparently is most severe during reperfusion.

Maintenance phase

The maintenance phase of acute tubular necrosis is characterized by a **stabilization of GFR at a very low level**, and it typically lasts 1-2 weeks. Complications typically develop during this phase.

The mechanisms of injury described above may contribute to continued nephron dysfunction, but **tubuloglomerular feedback** also plays a role. Tubuloglomerular feedback in this setting leads to **constriction of afferent arterioles by the macula densa cells, which detect an increased salt load in the distal tubules**.

Recovery phase

The recovery phase of acute tubular necrosis is characterized by **regeneration of tubular epithelial cells**. During recovery, an **abnormal diuresis sometimes occurs, causing salt and water loss and volume depletion**. The mechanism of the diuresis is not completely understood, but it may in part be due to the delayed recovery of tubular cell function in the setting of increased glomerular filtration.

Nephrotoxicity can result from various drugs, such as aminoglycosides, amphotericin, cisplatin, and crystal-forming drugs. Additionally, conditions such as multiple myeloma and rhabdomyolysis can cause nephrotoxicity.

Chronic Kidney Disease (Chronic Renal Failure)

Chronic kidney disease is defined as either kidney damage or a **decreased glomerular filtration rate of less than 60 ml/min/1.73 m^2 for 3 or more months**. Whatever the underlying etiology, the **destruction of renal mass with irreversible sclerosis and loss of nephrons** leads to a progressive decline in GFR.

Patients with chronic kidney disease stages 1-3 (GFR: 30-89 ml/min/1.73 m^2) are generally asymptomatic; **clinically manifestations typically appear in stages 4-5 (GFR < 29 ml/min/1.73 m^2 or dialysis).**

Approximately 1 million nephrons are present in each kidney, each contributing to the total GFR. In the face of renal injury (regardless of the etiology), the kidney has an innate ability to maintain GFR, despite progressive destruction of nephrons, by **hyperfiltration and compensatory hypertrophy of the remaining healthy nephrons**. This nephron adaptability allows for continued normal clearance of plasma solutes. **Plasma levels of substances such as urea and creatinine start to show significant increases only after total GFR has decreased to 50%,** when the renal reserve has been exhausted. The plasma creatinine value will approximately double (till in normal reference range) with a 50% reduction in GFR.

The hyperfiltration and hypertrophy of residual nephrons, although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction. This is believed to occur because of **increased glomerular capillary pressure**, which damages the capillaries and leads initially to secondary focal and segmental **glomerulosclerosis** and eventually to global glomerulosclerosis. Factors

other than the underlying disease process and glomerular hypertension that may cause progressive renal injury include the following:

- Systemic hypertension
- Proteinuria
- Hyperlipidemia
- Hyperphosphatemia with calcium phosphate deposition
- Decreased levels of nitrous oxide
- Uncontrolled diabetes

Hyperkalemia

The ability to maintain potassium excretion at near-normal levels is generally maintained in chronic kidney disease as long as both aldosterone secretion and distal flow are maintained. Another defense against potassium retention in patients with chronic kidney disease is **increased potassium excretion in the GI tract**, which also is under control of aldosterone.

Therefore, **hyperkalemia usually develops when the GFR falls to less than 20-25 ml/min** because of the decreased ability of the kidneys to excrete potassium. Hyperkalemia in chronic kidney disease can be **aggravated by an extracellular shift of potassium**, such as that occurs in the setting of acidemia or from lack of insulin.

Metabolic acidosis

Metabolic acidosis often is a **mixture of normal anion gap and increased anion gap**; the latter is observed generally with chronic kidney disease end-stage. In chronic kidney disease, **the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine** in the form of ammonium. In **end-stage** chronic kidney disease, **accumulation of phosphates, sulfates, and other organic anions** are the cause of the increase in anion gap.

Metabolic acidosis has been shown to have deleterious effects on protein balance, leading to the following:

- Negative nitrogen balance
- Increased protein degradation

- Increased essential amino acid oxidation
- Reduced albumin synthesis

Hence, metabolic acidosis is associated with protein-energy malnutrition, loss of lean body mass, and muscle weakness. **Metabolic acidosis causes an increase in ammoniagenesis to help excrete more hydrogen. However, this leads to an increase in fibrosis and rapid progression of kidney disease**.

Metabolic acidosis is a factor in the development of **renal osteodystrophy**, as bone acts as a buffer for excess acid, with resultant loss of mineral. Acidosis may interfere with **vitamin D metabolism**, and patients who are persistently more acidotic are more likely to have osteomalacia.

Salt and water handling abnormalities

Salt and water handling by the kidney is altered in chronic kidney disease. **Extracellular volume expansion** and total-body volume overload results from failure of sodium and free water excretion. This generally becomes clinically manifest **when the GFR falls to less than 10-15 mL/min**, when compensatory mechanisms have become exhausted. As kidney function declines further, sodium retention and extracellular volume expansion lead to **peripheral edema** and, not uncommonly, pulmonary edema and hypertension.

Anemia

Normochromic normocytic anemia principally develops from decreased renal synthesis of **erythropoietin**, the hormone responsible for bone marrow stimulation for red blood cell production. It starts early in the course of disease and becomes more severe as the GFR progressively decreases with the availability of less viable renal mass.

No reticulocyte response occurs. **Red blood cell survival is decreased**, and **tendency of bleeding is increased** from the uremia-induced platelet dysfunction. Other causes of anemia in chronic kidney disease include the following:

- Chronic blood loss

- Inflammation
- Nutritional deficiency

Bone disease

Renal bone disease is a common complication of chronic kidney disease. It results in both skeletal complications (eg, abnormality of bone turnover, mineralization, linear growth) and extraskeletal complications (eg, vascular or soft tissue calcification).

Chronic kidney disease–mineral and bone disorder involves biochemical abnormalities, (ie, **serum phosphorus, PTH, vitamin D levels,** and alkaline phosphatase) related to bone metabolism.

Secondary hyperparathyroidism develops in chronic kidney disease because of the following factors:

- Hyperphosphatemia
- Hypocalcemia
- Decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, or calcitriol)
- Intrinsic **alteration in the parathyroid gland**, which give rises to increased PTH secretion as well as increased parathyroid growth
- Skeletal resistance to PTH

Calcium and calcitriol are primary feedback inhibitors; **hyperphosphatemia is a stimulus to PTH synthesis and secretion**. Phosphate retention begins in early chronic kidney disease; when the GFR falls, less phosphate is filtered and excreted. Hyperphosphatemia **suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol**, so serum calcitriol levels are low when the GFR is less than 30 ml/min. Increased phosphate concentration also effects PTH concentration by its direct effect on parathyroid gland.

Hypocalcemia develops primarily from **decreased intestinal calcium absorption** because of low plasma calcitriol levels and possibly from **calcium binding to elevated serum levels of phosphate**.

Low serum calcitriol levels, hypocalcemia, and hyperphosphatemia have all been demonstrated to independently trigger PTH synthesis and

secretion. As these stimuli persist in chronic kidney disease, particularly in the more advanced stages, PTH secretion becomes maladaptive and the parathyroid glands, which initially hypertrophy, become hyperplastic. If serum levels of PTH remain elevated, a high bone turnover lesion, known as osteitis fibrosa, develops. This is one of several bone lesions, which as a group are commonly known as **renal osteodystrophy**.

Azotemia

Azotemia is an **elevation of blood urea nitrogen and serum creatinine levels**. In early renal disease, substantial decline in GFR may lead to only a slight elevation in serum creatinine. Elevation in serum creatinine is apparent only when the GFR falls to about 70 ml/min. This is due to compensatory hypertrophy and hyperfiltration of the remaining healthy nephrons.

Urine formation by each nephron involves 3 main processes, as follows: filtration at the glomerular level, selective reabsorption from the filtrate passing along the renal tubules, and secretion by the cells of the tubules into this filtrate. Perturbation of any of these processes impairs the kidney's excretory function, resulting in azotemia.

There are 3 pathophysiologic states in azotemia, as follows: prerenal azotemia, intrarenal azotemia, and postrenal azotemia.

Prerenal azotemia

Prerenal azotemia refers to elevation in urea and creatinine levels because of **problems in the systemic circulation that decrease flow to the kidneys**. In prerenal azotemia, decrease in renal flow stimulates salt and water retention to restore volume and pressure. When volume or pressure is decreased, the baroreceptor reflexes are activated. This leads to sympathetic nerve activation, resulting in **renal afferent arteriolar vasoconstriction and renin secretion** through β_1 -receptors. Constriction of the afferent arterioles causes a decrease in the intraglomerular pressure, reducing GFR proportionally. Renin converts angiotensin I to angiotensin II, which, in turn, stimulates aldosterone release. Increased

aldosterone levels results in salt and water absorption in the distal collecting tubule.

A decrease in volume or pressure is a nonosmotic stimulus for antidiuretic hormone production in the hypothalamus, which exerts its effect in the medullary collecting duct for water reabsorption. Through unknown mechanisms, activation of the sympathetic nervous system leads to **enhanced proximal tubular reabsorption of salt and water, as well as urea, creatinine, calcium, uric acid, and bicarbonate**.

Intrarenal azotemia

Intrarenal azotemia, also known as acute renal failure, and **acute kidney injury**, refers to elevation in urea and creatinine levels because of **problems in the kidney itself**. The most common causes of **nonoliguric acute renal failure** are acute tubular necrosis, **aminoglycoside nephrotoxicity, lithium toxicity, or cisplatin nephrotoxicity**.

Acute interstitial nephritis is characterized by inflammation and edema, resulting in azotemia, hematuria, sterile pyuria, white cell casts with variable eosinophiluria, proteinuria, and hyaline casts. The net effect is a **loss of urinary concentrating ability, with low osmolality (usually < 500 mOsm/l), high urinary sodium (>40 mmol/L), and occasionally, hyperkalemia and renal tubular acidosis**.

Glomerular diseases may reduce GFR due to changes in basement membrane permeability and because of stimulation of the renin-aldosterone axis. Glomerular diseases often manifest as **nephrotic or nephric syndrome**. In nephrotic syndrome, the urinary sediment is inactive, and there is gross proteinuria (>3.5 g/d), hypoalbuminemia, hyperlipidemia, and edema**. Azotemia and hypertension are uncommon initially, but their presence may indicate advanced disease**.

Postrenal azotemia

Postrenal azotemia refers to elevation in urea and creatinine levels because **of obstruction in the collecting system**. Obstruction to flow leads to a reversal of Starling forces responsible for glomerular filtration. **Progressive bilateral obstruction causes hydronephrosis** with an increase

in the Bowman capsular hydrostatic pressure and tubular blockage resulting in progressive decline and ultimate **cessation in glomerular filtration, azotemia, acidosis, fluid overload, and hyperkalemia**.

Unilateral obstruction rarely causes azotemia. With relief of complete ureteral obstruction within 48 hours of onset, there is evidence that relatively complete recovery of GFR can be achieved within a week. Complete or prolonged partial obstruction can lead to **tubular atrophy and irreversible renal fibrosis**.

Uremia

Uremia is a **clinical syndrome associated with fluid, electrolyte, and hormone imbalances and metabolic abnormalities, which develop in parallel with deterioration of renal function**. Uremia more commonly develops with **chronic renal failure**, but it also may occur with **acute renal failure** if loss of renal function is rapid. As yet, **no single uremic toxin** has been identified that accounts for all of the clinical manifestations of uremia. Toxins, such as parathyroid hormone, beta2-microglobulin, polyamines, advanced glycosylation end products, and other middle molecules, are thought to contribute to the clinical syndrome.

Normally, the kidney is the site of hormone production and secretion, acid-base homeostasis, fluid and electrolyte regulation, and waste-product elimination. In the presence of **renal failure**, these functions are not performed adequately and metabolic abnormalities, such as **anemia, acidemia, hyperkalemia, hyperparathyroidism, malnutrition, and hypertension**, can occur. The syndrome may be heralded by the clinical onset of **nausea, vomiting, fatigue, anorexia, weight loss, muscle cramps, pruritus, and change in mental status**.

Anemia-induced fatigue is thought to be one of the major contributors to the uremic syndrome. Erythropoietin is produced by peritubular cells in the kidney in response to hypoxia. Elevated PTH levels are thought to be associated with marrow calcification, which may

suppress red blood cell production and lead to a hypoproliferative anemia.

Bleeding diatheses are characteristic findings in patients with end-stage renal disease. The pathogenesis of uremic bleeding tendency is related to **multiple dysfunctions of the platelets**. The platelet numbers may be reduced slightly. Alterations of platelet adhesion and aggregation are caused by uremic toxins.

Acidosis is another major metabolic abnormality associated with uremia. **Failure to secrete hydrogen ions and impaired excretion of ammonium** may initially contribute to metabolic acidosis. As kidney disease continues to progress, **accumulation of phosphate and other organic acids, such as sulfuric acid, hippuric acid, and lactic acid**, creates an **increased anion-gap metabolic acidosis**. In uremia, metabolic acidemia may contribute to other clinical abnormalities, such as hyperventilation, anorexia, stupor, decreased cardiac response (congestive heart failure), and muscle weakness.

Hyperkalemia (potassium, >6.5 mmol/L) may be an acute or chronic manifestation of renal failure and it is a **clinical emergency**. As renal function declines, the nephron is unable to excrete a normal potassium load. In addition, other metabolic abnormalities, such as acidemia, may contribute to decreased potassium excretion.

In the setting of renal failure, there are a number of **abnormalities of the calcium-vitamin D metabolic** pathway, such as hypocalcemia, hyperphosphatemia, and increased PTH levels, that ultimately lead to renal bone disease (***osteodystrophy***). After exposure to the **sun**, **vitamin D-3** is produced in the skin and transported to the **liver** for hydroxylation (25[OH] vitamin D-3). Hydroxylated vitamin D-3 is then transported to the **kidney**, where a second hydroxylation occurs, and **1,25(OH)2 vitamin D-3** is formed. As the clinically active form of vitamin D, 1,25(OH)2 vitamin D-3 is responsible for GI absorption of calcium and phosphorus and suppression of PTH. During renal failure, 1,25(OH)2 vitamin D-3 levels are reduced secondary to decreased production in renal tissue as well as

hyperphosphatemia, which leads to decreased calcium absorption from the GI tract. Hypocalcemia stimulates the parathyroid gland to excrete PTH, a process termed secondary hyperparathyroidism. Hyperphosphatemia occurs as excretion of phosphate decreases with progressive renal failure. It stimulates parathyroid gland hypertrophy and stimulates increased production and secretion of PTH.

Cardiovascular abnormalities, including **uremic pericarditis**, pericardial effusions, and uremic suppression of myocardial contractility, are common in patients with CRF. **Left ventricular hypertrophy** is associated with increased ventricular thickness, arterial stiffening, coronary atherosclerosis, and/or coronary artery calcification. Patients are at increased risk for **cardiac arrhythmias** due to underlying electrolyte and acid-base abnormalities. Renal dysfunction may contribute to associated **fluid retention**, which may lead to uncontrolled hypertension and **congestive heart failure**.

Malnutrition usually occurs as renal failure progresses and is manifested by **anorexia, weight loss, loss of muscle mass, low cholesterol levels, and hypoalbuminemia**. Numerous epidemiologic studies have shown that a decreased serum albumin concentration is a very strong and independent predictor of mortality among dialysis patients.

Uremic encephalopathy is an organic brain disorder. It develops in patients with **acute or chronic renal failure**, usually when creatinine clearance remains below 15 ml/min. Manifestations of this syndrome vary from mild symptoms (eg, lassitude, fatigue) to severe symptoms (eg, seizures, coma). **Severity and progression depend on the rate of decline in renal function**; thus, symptoms are usually worse in patients with acute renal failure. Uremic encephalopathy has a **complex pathophysiology**, and many toxins that accumulate in kidney failure may be contributive. Secondary hyperparathyroidism causes an increase in **calcium content in the cerebral cortex**. The specific mechanism by which PTH causes disturbance in brain function is unclear, but it may be caused

by increases in intracellular concentration of calcium in brain cells. Another theory about the etiology of uremic encephalopathy suggests **imbalances of neurotransmitter amino acids** within the brain. During the early phase of uremic encephalopathy levels of glycine increase and levels of glutamine and GABA decrease; additionally, alterations occur in metabolism of dopamine and serotonin in the brain. As uremia progresses, it has been proposed that the accumulation of guanidino compounds results in activation of excitatory N-methyl-D-aspartate (NMDA) receptors and inhibition of inhibitory GABA receptors, which may cause myoclonus and seizures.

Phimosis

Phimosis is defined as the **inability of the prepuce (foreskin) to be retracted behind the glans penis** in uncircumcised males. **Nearly all males are born with congenital phimosis**, a benign condition that resolves in the overwhelming majority of infants as they transition into childhood.

The foreskin of an uncircumcised child **should not be forcefully retracted**. This may result in significant bleeding, as well as glanular excoriation and injury. Consequently, dense fibrous adhesions may form during the healing process, leading to true pathologic phimosis.

Adult phimosis may be caused by repeated episodes of balanitis or balanoposthitis. Such infections are commonly due to poor personal hygiene (failure to regularly clean under the foreskin).

Phimosis may be a presenting symptom of **early diabetes mellitus**. When the residual urine of a patient with diabetes mellitus becomes trapped under the foreskin, the combination of a moist environment and glucose in the urine may lead to a proliferation of bacteria, with subsequent infection, scarring, and eventual phimosis.

Paraphimosis

Paraphimosis is an uncommon condition in which the **foreskin, once pulled back behind the glans penis**, cannot be brought down to its original position, thus constituting one of the few urologic emergencies. Like phimosis, paraphimosis occurs only in uncircumcised or partially circumcised males.

When the foreskin becomes trapped behind the corona for a prolonged period, a tight band of tissue forms around the penis. This **constricting ring initially impairs venous blood and lymphatic flow from the glans penis and prepuce**, in turn causing edema of the glans. As the edema worsens, arterial blood flow becomes compromised. The ensuing tissue ischemia and vascular engorgement cause **painful swelling** of the glans and prepuce and may eventually lead to **gangrene or autoamputation of the distal penis**.

Priapism

Priapism is defined as an **abnormal persistent erection of the penis**. It is an **involuntary prolonged erection unrelated to sexual stimulation and unrelieved by ejaculation**. This condition is a true urologic emergency, and early intervention allows the best chance for functional recovery.

The penis is composed of 3 corporeal bodies: 2 corpora cavernosa and 1 corpus spongiosum. Erection is the result of smooth-muscle relaxation and increased arterial flow into the corpora cavernosa, causing engorgement and rigidity.

Engorgement of the corpora cavernosa compresses the venous outflow tracts (ie, subtunical venules), trapping blood within the corpora cavernosa. The major neurotransmitter that controls erection is **nitric oxide**, which is secreted by the endothelium that lines the corpora cavernosa. These events occur in both normal and pathologic erections.

The pathophysiology of priapism involves failure of detumescence and is the result of the **underregulation of arterial inflow** (ie, high flow) or, more commonly, the **failure of venous outflow** (ie, low flow). Priapism **typically involves engorgement of corpora cavernosa**. The corpus spongiosum is typically not engorged.

Priapism must be defined as either a low-flow (ischemic) or a high-flow (nonischemic) type. **Low-flow priapism**, which is by far the most common type, is a **failure of the detumescence mechanism** due to

1. an excessive release of neurotransmitters,
2. blockage of draining venules,
3. paralysis of the intrinsic detumescence mechanism, or
4. prolonged relaxation of the intracavernous smooth muscles.

Prolonged low-flow priapism leads to a **painful ischemic state**, which can cause **fibrosis of the corporeal smooth muscle and cavernosal artery thrombosis**. The degree of ischemia is a function of the number of emissary veins and the duration of occlusion. Trabecular interstitial edema is demonstrated after 12 hours of priapism and destruction of sinusoidal endothelium, exposure of the basement membrane, and thrombocyte adherence after 24 hours of priapism. At 48 hours, thrombi in the sinusoidal spaces and smooth-muscle cell histopathologic findings varied from necrosis to fibroblastlike cell transformation. **Priapism for longer than 24 hours is associated with the likelihood of permanent impotence.**

High-flow priapism, in contrast, is the result of uncontrolled arterial inflow from a **fistula between the cavernosal artery and the corpus cavernosum**. This is generally secondary to blunt or penetrating **injury to the penis or perineum**.

Cryptorchidism

Cryptorchidism is the most common genital problem encountered in pediatrics. Cryptorchidism literally means **hidden or obscure testis** and generally refers to an **undescended or maldescended testis**.

Normal testicular development begins at conception. The testis-determining factor is now identified as the *SRY* gene (**sex-determining region on Y chromosome**). The presence of this gene and an intact downstream pathway generally result in testicular formation. At 9 weeks' gestation, Leydig cells develop and secrete testosterone. Transinguinal migration, thought to be under **hormonal control**, occurs at 28-40 weeks' gestation, usually resulting in a scrotal testis by the end of a full term of gestation.

The etiology of cryptorchidism is **multifactorial**, but the exact mechanism of cryptorchidism has proven to be elusive. **Birth weight** is the principal determining factor for undescended testes at birth to age one year, independent of the length of gestation.

Transabdominal descent of the testis involves differential growth of vertebrae and pelvis until 23 weeks' gestation. Afterward, further descent is facilitated by the development of the **gubernaculum, processus vaginalis, spermatic vessels, and scrotum**. A normal **hypothalamic-pituitary-gonadal axis** is a prerequisite for testicular descent. Furthermore, testosterone and its conversion to **dihydrotestosterone** are also necessary for continued migration, especially during the inguinoscrotal phase.

In patients with cryptorchidism, the **gubernaculum is not firmly attached to the scrotum**, and the testis is not pulled into the scrotum. The genitofemoral nerve may also aid in descent and gubernacular differentiation, which may be mediated by calcitonin gene-related peptide.

Intra-abdominal pressure also appears to play a role in testicular descent. The effect of **decreased intra-abdominal pressure** is most

significant during transinguinal migration to the scrotum, probably in conjunction with androgens and a patent processus vaginalis.

Hydrocele

A hydrocele is a **fluid collection within the tunica vaginalis** of the scrotum or along the spermatic cord.

The pathophysiology of hydroceles requires an **imbalance of scrotal fluid production and absorption**.

Alternatively, hydroceles can be divided into those that represent a persistent communication with the abdominal cavity and those that do not. Fluid excesses are from **exogenous sources** (the abdomen) in communicating hydroceles, whereas noncommunicating hydroceles develop increased scrotal fluid from abnormal **intrinsic scrotal fluid shifts**.

Communicating hydroceles

With communicating hydroceles, simple **Valsalva** probably accounts for the classic variation in size during day-sleep cycles.

Noncommunicating hydroceles

In noncommunicating hydroceles, the pathophysiology may occur as a result of increased fluid production or as a consequence of impaired absorption. A sudden onset of scrotal hydrocele in older children has been noted after viral illnesses. In such cases, **viral-mediated serositis** may account for the net increased fluid production. **Posttraumatic** hydroceles likely occur secondary to increased serosal fluid production due to **underlying inflammation**.

Spermatocele

A spermatocele is **a benign cystic accumulation of sperm that arises from the head of the epididymis**. Spermatoceles can develop in varying

locations, ranging from the testicle itself to locations along the course of the vas deferens.

The specific pathophysiology remains to be elucidated. Although distal obstruction has been theorized as a potential mechanism, the presence of motile sperm in up to 80% of spermatoceles suggests maintenance of proximal patency.

Varicocele

A varicocele is a **dilatation of the pampiniform venous plexus and the internal spermatic vein**.

Several theories have been proposed to explain the harmful effect of varicoceles on sperm quality, including the possible effects of pressure, oxygen deprivation, heat injury, and toxins.

Despite considerable research, none of the theories has been proved unquestionably, although an **elevated heat effect caused by impaired circulation appears to be the most reproducible defect**. Regardless of the mechanism of action, a varicocele is indisputably a significant factor in **decreasing testicular function and in reducing semen quality** in a large percentage of men who seek infertility treatment.

Although unproved, a varicocele may represent a progressive lesion that can have detrimental effects on testicular function. An untreated varicocele, especially when large, may cause long-term deterioration in sperm production and even testosterone production.

Testicular Torsion

Testicular torsion is caused by **twisting of the spermatic cord and the blood supply to the testicle**. With mature attachments, the tunica vaginalis is attached securely to the posterior lateral aspect of the testicle, and, within it, the spermatic cord is not very mobile. If the **attachment of the tunica vaginalis to the testicle is inappropriately high**,

the spermatic cord can rotate within it, which can lead to intravaginal torsion.

Intravaginal torsion most commonly occurs in adolescents. It is thought that the **increased weight of the testicle after puberty**, as well as **sudden contraction of the cremasteric muscles** (which inserts in a spiral fashion into the spermatic cord), is the impetus for acute torsion.
In males who have an inappropriately high attachment of the tunica vaginalis, as well as abnormal fixation to the muscle and fascial coverings of the spermatic cord, the testicle can rotate freely on the spermatic cord within the tunica vaginalis (intravaginal testicular torsion).

By contrast, **neonates more often have extravaginal torsion**. This occurs because the tunica vaginalis is not yet secured to the gubernaculum and, therefore, the spermatic cord, as well as the tunica vaginalis, undergo torsion as a unit. In neonates, the testicle frequently has not yet descended into the scrotum, where it becomes attached within the tunica vaginalis. This **mobility of the testicle** predisposes it to torsion (extravaginal testicular torsion).

Testicular torsion is associated with **testicular malignancy**, especially in adults.

Torsion occurs as the testicle rotates between 90° and 180°, compromising blood flow to and from the testicle. Complete torsion usually occurs when the testicle twists 360° or more. The degree of torsion may extend to 720°.

The twisting of the testicle causes **venous occlusion and engorgement** as well as **arterial ischemia and infarction** of the testicle. In addition to the extent of torsion, the duration of torsion prominently influences the rates of both immediate salvage and late **testicular atrophy**.

Enterovesical Fistula

Normally, the urinary system is completely separated from the alimentary canal. Connections may result from:

1. incomplete separation of the two systems during embryonic development (eg, failure of the urorectal septum to divide the common cloaca),

2. infection,

3. inflammatory conditions,

4. cancer,

5. trauma or foreign body, or

6. iatrogenic causes.

Fistulae may be either congenital or acquired (eg, inflammatory, surgical, neoplastic). Congenital vesicoenteric fistulae are rare.

Inflammatory pathophysiology

A phlegmon or abscess in **diverticulitis** is a risk factor for fistula formation.

Crohn disease is the most common cause of an ileovesical fistula. The transmural nature of the inflammation characteristic of Crohn colitis often results in adherence to other organs. Subsequent erosion into adjacent organs can then give rise to a fistula.

Malignant pathophysiology

Rectovesical fistula is the most common presentation, as **rectal carcinoma** is the most common colonic malignancy. Transmural carcinomas of the colon and rectum may adhere to adjacent organs and may eventually invade directly, causing development of a fistula.

Iatrogenic pathophysiology

Iatrogenic fistulae are usually induced by surgical procedures, primary or adjunctive **radiotherapy**, and/or **postprocedural infection**. **Surgical procedures**, including prostatectomies, resections of benign or malignant rectal lesions, and laparoscopic inguinal hernia repair, are well-documented causes of rectovesical and rectourethral fistulae.

Fistulae develop spontaneously after perforation of the irradiated intestine, with the development of an abscess in the pelvis that subsequently drains into the adjacent bladder.

Traumatic pathophysiology

Urethral disruption caused by blunt trauma or a penetrating injury can result in fistulae, but these fistulae are typically rectourethral in nature.

Vesicovaginal Fistula

Vesicovaginal fistula is a subtype of female urogenital fistula. It is an abnormal fistulous tract extending between the bladder and the vagina that allows the continuous involuntary discharge of urine into the vaginal vault.

Vesicovaginal fistulas are attributed predominantly to inadvertent bladder injury during **pelvic surgery** (90%). Such injuries include unrecognized intraoperative laceration of the bladder, bladder wall injury from electrocautery or mechanical crushing, and the dissection of the bladder into an incorrect plane, causing avascular necrosis. **Gynecologic procedures** are the most common iatrogenic factor.

Risk factors include prior pelvic or vaginal surgery, ischemia, diabetes, arteriosclerosis, carcinoma, endometriosis, anatomic distortion by uterine myomas, cesarean delivery, and infection, particularly postoperative cuff abscess.

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