Disturbances of Circulation

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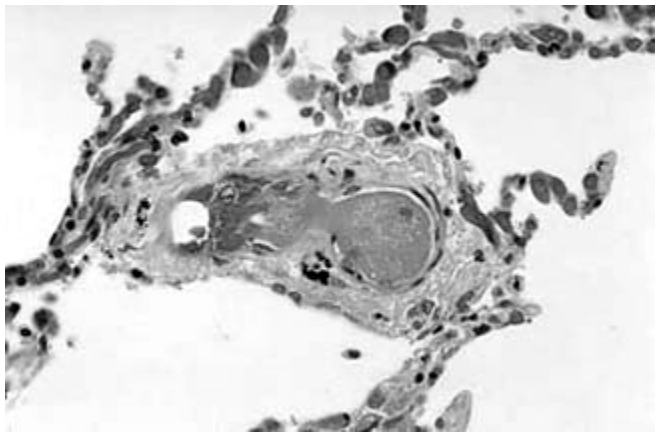


HYPEREMIA AND CONGESTION

This lesson corresponds to the web lesson of the same name

Both hyperemia and congestion are the result of excessive blood in a part of the body. They differ from hemorrhage in that with hyperemia and congestion, the blood is still confined within the vasculature. In hemorrhage, the blood has escaped from the blood vessels.

LEARNING OBJECTIVES FOR THIS LESSON

1. Be able to visually identify tissues that are hyperemic.
2. Hypothesize whether the increased blood in a part is hyperemia or congestion.
3. Outline the pathogenesis of the hyperemia or congestion seen.
4. Relate the lesions of hyperemia or congestion to the clinical signs.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

HYPEREMIA

Definition:

- An excess of blood contained within blood vessels in a part of the body due to an active process

Gross appearance:

- bright red
- warmer than usual
- swollen
- pulse may be felt readily
- due to the elastic recoil of arterioles, hyperemia is dissipated after death in skin and mucous membranes and is usually not apparent post-mortem

Microscopic:

- capillaries and occasionally arterioles are dilated and engorged with blood

Causes:

- physiologic: in response to increased demands for nutrients because of work being done
- pathologic: in response to certain vasodilator chemicals and neurogenic stimuli associated with irritation of tissue

Effect:

- hastens movements of metabolites into area and flushing of catabolites from the area

CONGESTION

Definition:

- An excess of blood contained within blood vessels in a part of the body due to a passive process

Gross appearance:

- dark blue-red tinge
- swollen
- cooler than normal
- after death the color becomes even more dark blue and the cut surface of such tissues oozes blood freely
- if chronic, the tissue may have a brown color

Microscopic:

- capillaries and veins are engorged with blood
- may see excessive hemosiderin in tissues (especially lungs)
- even later will see fibrosis in the walls of veins and the parenchyma

Causes:

- **peripheral -**
  obstructive - e.g., thrombus or embolus
  constrictive - e.g., organ twists, collapsing veins
- **central -** due to heart failure, which may be caused by:
  conditions associated with weakened ventricular muscle
  conditions causing ventricles to pump against increased resistance (e.g., valvular stenoses, hypertension)
  conditions that increase volume of blood delivered to ventricles (leaky valves, septal defects)
- **hypostatic -**
  When animals lie in a recumbent position for long periods of time, the blood tends to gravitate to the dependent portions. The same phenomenon occurs at death until clotting prevents further settling.

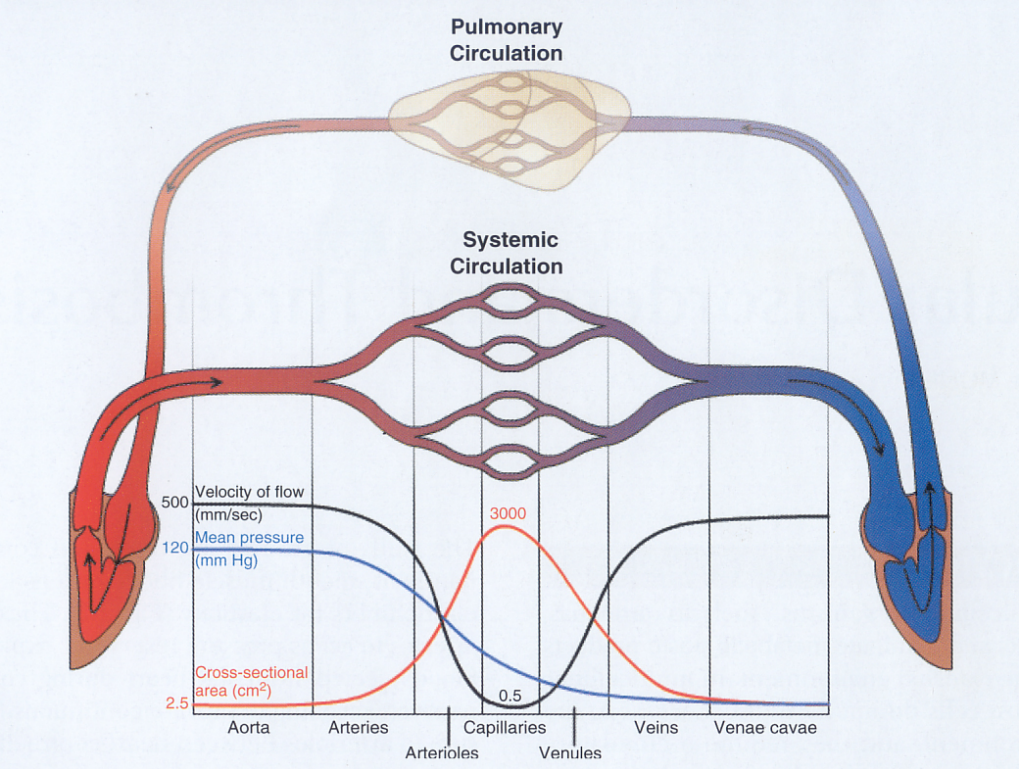
Effects:

- leads to hypoxia and accumulation of catabolites in the tissues → edema → interferes with normal function of involved tissue
- may see necrosis if the condition is severe enough
- thrombosis occurs readily in the veins where blood is moving sluggishly
- proliferation of connective tissue if the condition is prolonged

QUICK REVIEW OF THE CIRCULATORY SYSTEM (Anatomy, Histology, Physiology…):

This includes:

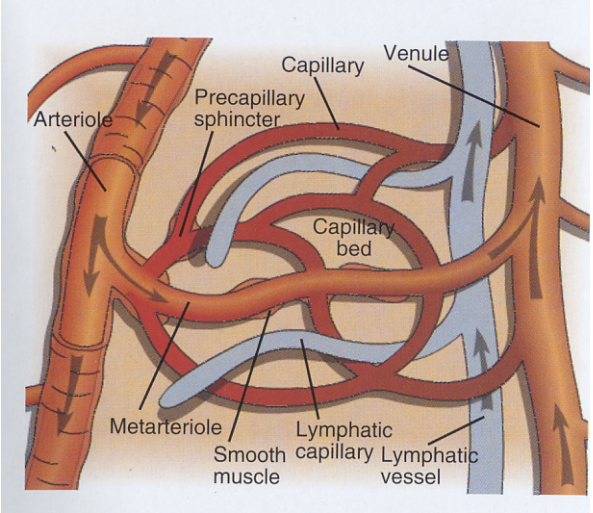
- ♥ Blood, the fluid
- ♥ Heart, the pump
- ♥ Arteries, the distribution network
- ♥ Veins, the collection network
- ♥ Capillaries, the connections between the two capillaries
- ♥ Lymphatics, network of vessels to drain fluid from tissues



Here is how it happens, the nutshell version:

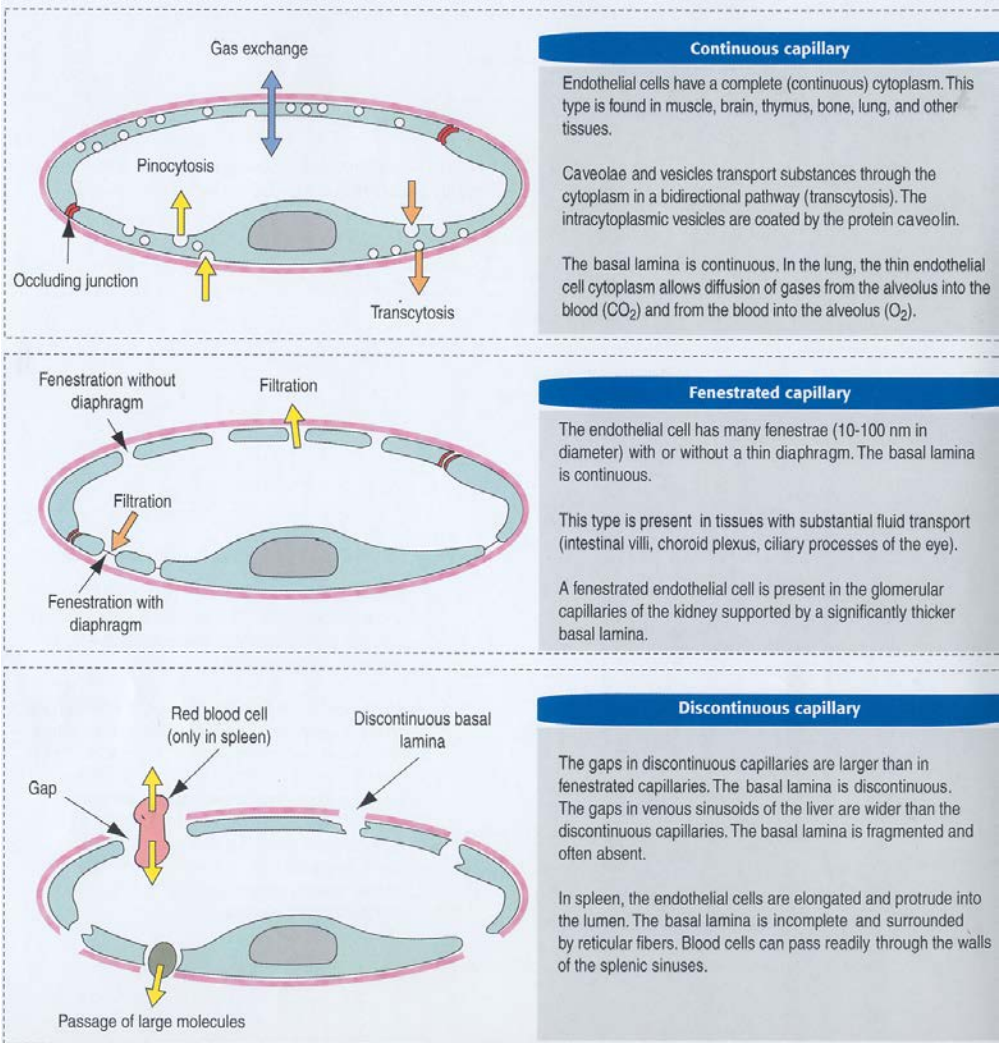
The heart contracts, moving blood into the large arteries that have thick walls and can expand and contract using their elastic fibers. This is important because they need to maintain continuous pressure regardless of any period in the heartbeat cycle. Blood then moves into the arterioles which are the major site of vascular resistance in the body. They can dilate and constrict according to needs. Capillaries are where the exchange of nutrients and oxygen takes place. Capillaries have very narrow lumens - blood moves through them slowly and the red cells usually have to go single file. Collection system starts with the venules and then on to the veins. These are both low resistance pathways and blood can easily collect here. During normal conditions, the venous system holds 65% of all the blood in the body. Veins have valves in them because without the valves, blood might just slip backwards too much. Valves help to ensure that blood continues to move toward the heart.

But of course there are **lymphatics** too. These originate as blind ends out in the capillary beds. The endothelium of lymphatics has pretty big gaps that can accommodate larger particles, which they pick up and move on toward the larger lymphatic vessels which eventually dump into the vena cavae. Lymphatics are very low pressure and don't work very well without some muscle contractions happening around them.



At the right is a view of the microcirculation, including lymphatics →

We'll focus on the microvasculature. Important to remember that not all endothelium here is created equal:



HYPEREMIA

Hyperemia is from the Greek “hyper” meaning *excess* and "emia" meaning *pertaining to blood*. Basically, it is excessive blood in a part when blood is confined **within** the vasculature. If there is excess blood **outside** the vasculature, that is hemorrhage. (Hemorrhage is the next lesson.)

Hyperemia can be broken down into active hyperemia or passive hyperemia. However, most people refer to passive hyperemia as "congestion." So, for all practical purposes, hyperemia is an active process and congestion is passive.

Hyperemia is an important concept to understand *because it is one of the four cardinal signs of inflammation.* These four cardinal signs were outlined by Celsus a long, long time ago. He was a Latin scholar who noted that inflammatory processes were characterized by **"rubor et tumor cum calor et dolor,"** which is Latin for “redness and swelling with heat and pain." A few centuries later, **functio laesa** (loss of function) was added to these cardinal signs of inflammation, so there are officially five cardinal signs of inflammation.

The **rubor**, or redness, is a result of hyperemia.

Hyperemia is noted as an increased redness in a part. In order to understand how it works, we need to examine the peripheral circulation. In the terminal circulatory bed under normal circumstances, blood may be flowing through a few of the capillaries in a tissue and may be shunted past many capillaries. Therefore, the amount of blood flow usually corresponds to the amount of work being carried out and so will vary in different areas at different times. If, however, more blood is needed in an area, then all the capillaries and shunts open, the vessels dilate, and a much greater amount of blood is present. The tissue visibly becomes quite red because of the increased amount of blood there. The area is red because the blood present is arterial blood and therefore well oxygenated.

Hyperemia is always localized. If it occurred all over the body, there wouldn't be enough blood in the major vessels and shock would ensue.

Hyperemia is a change that is usually noted clinically rather than at postmortem. Because of the elastic recoil in the arterioles postmortem, blood is forced to the venous side and hyperemia is not so easy to determine after death.

REVIEW OF HYPEREMIA

Hyperemia is defined as excess blood (especially in the capillaries) in a part. The part is red, swollen, warmer than normal, and there may be a pulse. It is mediated actively by purposeful dilation of arterioles to increase blood flow in response to some stimulus.

CONGESTION

Congestion has many of the same features as hyperemia. The big difference is that congestion is due to **obstruction** of venous return and therefore is a *passive* process. Whereas hyperemia is an active process, associated with the body's response to an insult, congestion may or may not be associated with inflammation. It is simply due to obstruction of venous return and can happen for a number of reasons.

In congestion, blood accumulates in dilated capillaries and venules. Because the blood is poorly oxygenated venous blood, the area appears as dark red or sometimes blue. When it is quite dark, the term "cyanotic" is used, from "cyanos" which is Greek for blue substance. The blood accumulates in the peripheral vasculature because the outflow is impeded. Because normal arteriolar flow continues, the capillary beds, venules, and maybe even the veins become distended with blood. Because of the sluggish flow, the oxygen content in the capillary and venous blood diminishes and that is what produces the dark red to blue color. Congestion is often accompanied by edema. (Edema is covered later in the unit on Disturbances of Circulation.)

Localized vs. generalized congestion:

Congestion can be in a localized area of the body or it can be cardiac in origin in which case it is generalized.

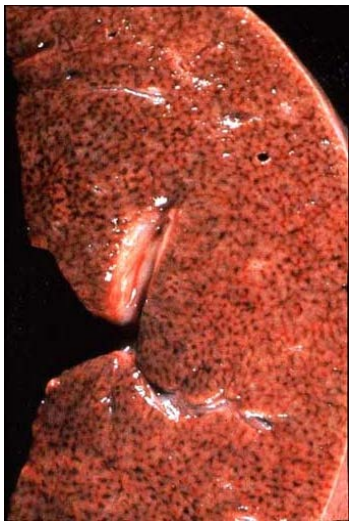
- **Localized** constrictive forces would include external pressure such as a plug in the vessel caused by a thrombus, embolus, tourniquet, or tumor, chemical mediators like ergot, or, commonly, a twisting or turning of a part that "kinks off" its own easily collapsed veins.

- If the blood flow is impeded **centrally**, such as occurs in heart failure, with backup of blood in the systemic vasculature, the congestion can be **generalized.**

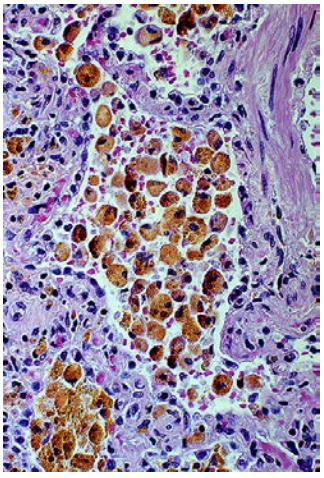
  Basically, there are three reasons for backup of blood in the heart.
  - One or both of the ventricles is weakened and cannot pump the blood volume adequately.
  - One of the atrioventricular valves is leaking, resulting in increased volume load on the ventricle and resulting backup.
  - One of the outflow valves is stenotic, creating an increased pressure load on the ventricle.

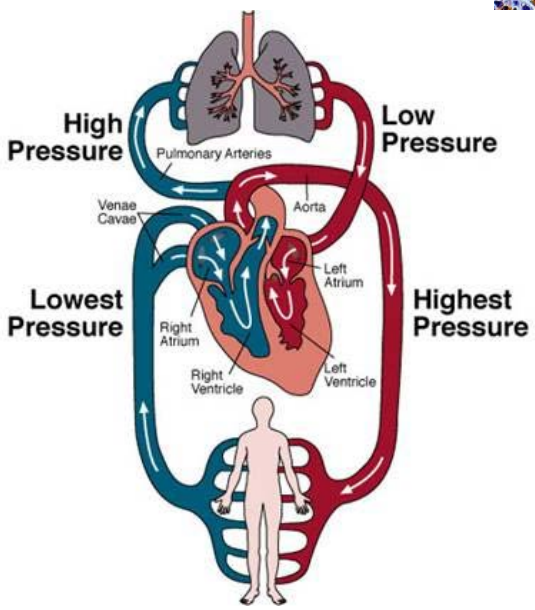
  The primary body organs affected by congestion due to heart failure depend on the part of the heart affected.

➔ **If the problem is primarily in the <u>right side of the heart</u>**, the blood will back up causing congestion throughout the body but especially in the **liver.** As the blood sludges in the central vein areas of the liver, hypoxia or anoxia occurs. If the anoxia persists, the hepatocytes in this area become necrotic. As the hepatocytes die and leave, the red blood cells pool in the dilated sinusoids that remain and may eventually occupy much of the space formerly occupied by hepatocytes. These areas appear red or reddish-blue grossly and give the enlarged liver in chronic passive congestion its characteristic appearance. The mottled pattern resembles that of the spice nutmeg, and the term *nutmeg liver* has become synonymous with *chronic passive congestion of the liver*.



➔ **If the blockage originates due to backup on the <u>left side of the heart</u>**, the hydrostatic pressure is first noticeable in the **lung**. Red blood cells fill the capillaries in the lung, giving the lungs that dark red color. Acellular fluid leaks out of the packed blood vessels, creating excess fluid in the lungs (pulmonary edema). If congestion continues for long enough, red blood cells also leak through alveoli and are picked up by alveolar macrophages. When this condition persists, the breakdown products of the red blood cells appear in the alveolar macrophages in the form of hemosiderin.





Hypostatic congestion

Hypostatic congestion is a specialized form of congestion and is the pooling of blood in capillaries and veins in a dependent part *due to the effect of gravity*. This is most commonly seen in sick animals that are in a recumbent position for a long time. Hypostatic congestion of the "down" lung is often seen in animals that were in prolonged lateral recumbency prior to death. Hypostatic pooling of blood can also happen postmortem.

REVIEW OF CONGESTION

In congestion, the part is dark red to blue, swollen, and cooler than normal. It occurs secondary to some other problem that is inhibiting venous return. Peripheral congestion may be due to obstructions inside or constrictions outside the vein. Central congestion is due to problems involving the heart or large vessels. In general, right heart problems are manifested in the general venous system of the body but especially the liver, and left heart problems are manifested in the lungs. However, failure of one side of the heart can/will eventually lead to failure of the opposite side so that both pulmonary and generalized venous congestion occur. Hypostatic congestion is simply pooling of blood due to gravity in the face of weakened or absent heart action.

HEMORRHAGE

This lesson corresponds to the web lesson of the same name

Hemorrhage means that blood has escaped from where it is supposed to be, which is inside the blood vessels.

LEARNING OBJECTIVES FOR THIS LESSON
1. Recognize and describe the hemorrhage as to its size and form.
2. Outline the pathogenesis of the hemorrhage.
3. Relate the hemorrhage to other clinical signs.
4. Predict the fate of the hemorrhagic lesion if the animal is alive or if it had lived.

SUMMARY OF IMPORTANT CONCEPTS FROM THIS LESSON

HEMORRHAGE

Definition: the escape of blood from any part of the blood vascular system
Classification:

- by degree of vascular injury
  - **hemorrhage per diapedesis** - Hemorrhage resulting from loss of functional continuity of a vessel wall despite maintenance of perceptible morphologic continuity usually results in focal hemorrhage.
  - **hemorrhage per rhexis** - hemorrhage resulting from loss of perceptible morphologic and functional continuity of a vessel wall, often results in extensive hemorrhage
- by size and form
  - hemorrhage usually associated with *hemorrhage per diapedesis*:
    - **petechiae** - less than 2mm
    - **ecchymoses** - 2-20mm
    - **paint-brush hemorrhage** - extensive streaking with hemorrhage
  - hemorrhage usually associated with *hemorrhage per rhexis*:
    - **massive** or **submassive** hemorrhage - hemorrhage involving all (massive) or most (submassive) of a particular anatomic site
    - **hematoma** - a collection of blood in the tissue which produces a tumor-like swelling. Hematomas are three-dimensional.
- by location

  pulmonary hemorrhage, gastric hemorrhage, hemosalpinx, hemothorax, hemoptysis, hematemesis

Causes:

- ❖ *hemorrhage per diapedesis* -
  hypoxia, anoxia, toxic injury, vasculitis, nutritional deficiency, abnormal coagulation of blood
- ❖ *hemorrhage per rhexis* -
  trauma, vessel wall necrosis, vessel wall invasion by neoplasia, primary vascular disease

Effect and significance of hemorrhage:

- ☞ according to amount and rate of blood loss
  - o if rapid blood loss occurs (1/4 to 1/3 of the total blood volume over a period of less than a few hours), hypovolemic shock and perhaps death will occur
  - o if slower blood loss occurs (as much as 1/2 total blood volume over weeks or months), no serious consequences may occur because the body compensates
- ☞ according to site of hemorrhage
  - o severity of consequences exceeds what is normally seen with amount of blood loss, for instance, intracranial hemorrhage or hemopericardium
  - o severity of consequences is generally proportional to the amount of blood loss

Fate of hemorrhage:

- ➢ arrest of hemorrhage (will be covered in detail in module on hemostasis), decreased blood pressure in massive hemorrhage, pressure of surrounding tissue, coagulation
- ➢ disposal of escaped blood
  - o small hemorrhages - serum is readily absorbed, red blood cells are phagocytized by macrophages
  - o large hemorrhages - the clot contracts, squeezing out serum which is reabsorbed. Solid portions of the clot are phagocytized or organized by connective tissue.
  - o large hematomas - may be walled off by connective tissue and the center remains liquid for long periods of time (aural hematoma)

Hemorrhage – Definition:

Hemorrhage is defined as the presence of blood, specifically red blood cells, outside of the blood vessel. Hemorrhage can be used as a noun or a verb. The etymology is from the Greek "haima" meaning *blood* and "rhegnymi" meaning *to burst forth*.

Hemorrhage per diapedesis vs. hemorrhage per rhexis:

Blood can exit a blood vessel very slowly by squeezing through functionally damaged vessel walls or it can pour out due to a big tear. The former is referred to as hemorrhage per diapedesis. The latter is hemorrhage per rhexis. Why the distinction? Hemorrhage per diapedesis occurs when the endothelium cannot function properly. Vessels that are not visibly broken but perhaps somewhat anoxic and not functioning properly.

Hemorrhage per rhexis, on the other hand, is due to a big tear, causing much larger accumulations of blood (naturally).

Hemorrhage per diapedesis:

Causes of hemorrhage per diapedesis include:

- *Hypoxia and anoxia* – If the endothelial cells themselves aren't getting enough oxygen to maintain themselves, they break down and the vessel walls become a little leaky. RBCs diapedese out through these tiny leaks.
- *Abnormal coagulation of blood* – In general, we get small holes in our blood vessels all the time. These are promptly plugged by an intact clotting mechanism. However, if the clotting mechanism don't work so good, RBCs slip out through the holes.
- *Toxic injury* – Endothelial cells can be affected by circulating toxins and when the metabolism of the endothelial cell is negatively impacted, presto, little leaks.
- *Inflammation of vessel wall* (vasculitis) – When endothelial cells are affected by inflammation and/or infection, once again, they don't work too well, and small holes develop.
- *Nutritional deficiency* – Some nutrients are absolutely essential to maintain endothelial cell function. If these nutrients are blocked in some way, endothelial cells lose their integrity and then RBCs can diapedese out.

Hemorrhage per diapedesis is often classified according to the size.

- *Petechial hemorrhage* (petechiae) is derived from Latin for "freckle"; petechiae are spots of hemorrhage that are pinpoint or less than 2mm in diameter.
- *Ecchymotic hemorrhage* (ecchymoses) is from the "ek" for out and "chymos" for juice, so think of it as squeezing juice out! These are hemorrhages 2 to 20mm in diameter.

- *"Paint-brush" hemorrhage* refers to when the purpuric hemorrhage forms streaks.

All of these described forms of hemorrhage (petechiae, ecchymoses, purpura, and paint-brush hemorrhages) tend to occur most often on mucosal, serosal, or skin surfaces. They are visible but cannot be palpated (i.e. not thick enough to be palpably three-dimensional).

Hemorrhage per rhexis

Hemorrhage per rhexis is usually associated with larger areas of hemorrhage than hemorrhage per diapedesis.

Causes of hemorrhage per rhexis include:

- *Trauma* – If there is enough damage to cause a big hole, plenty of ample (sic) blood will pour out.
- *Vessel wall necrosis* (local tissue death) – When a patch of endothelial cells die, a big hole results.
- *Vessel wall invasion by neoplasm* (tumor) – Tumors growing into a blood vessel can cause sufficient physical disruption of the wall that significant hemorrhage happens.
- *Primary vascular disease* – There are some diseases that specifically target endothelial cells. Some of these diseases just cause hemorrhage per diapedesis but if damage is bad enough, hemorrhage per rhexis occurs.

Hemorrhage per rhexis is classified according to the amount and area in which it occurs.

- *Massive* or *submassive* hemorrhage is hemorrhage involving all or most of a particular anatomic site. This hemorrhage is hefty - tends to be thicker than ecchymoses.
- A *hematoma* is a collection of blood in the tissue that produces a tumor-like swelling. Hematomas are three-dimensional.

Hemorrhage vocabulary:

Hemorrhage is also classified according to the area of the body in which it occurs. You will need to know the following definitions of hemorrhage classified by site:

Epistaxis – blood from nares
Hematuria – blood in the urine
Hemarthrosis – blood in a joint
Hemothorax – blood in the thorax
Hemopericardium – blood in the pericardial sac
Hemoperitoneum – blood in the abdominal cavity
Hemosalpinx – blood in a tube, usually refers to oviduct
Hyphema – blood in the anterior chamber of the eye
Hemoptysis – coughing up blood

Hematemesis – vomiting blood
Hematochezia – presence of blood in the stool
Melena – presence of tarry blood in the stool

Agonal hemorrhage is hemorrhage that happens immediately prior to death, as a result of tissue anoxia. This hemorrhage can be very dramatic; it is important to remember that it occurred as a result of dying and not the other way around. Agonal hemorrhage is most commonly seen in cattle where it appears as petechial or ecchymotic hemorrhages in the endocardium.

Hemorrhage – outcomes:

What are some outcomes of hemorrhage? This depends on the amount of hemorrhage, the rate of hemorrhage, and the location of the hemorrhage.

If rapid severe blood loss occurs such that *one-fourth to one-third of the total blood volume is lost within a matter of minutes* or hours, serious consequences may occur. For one, the animal becomes anemic and therefore may not have adequate hemoglobin to transport oxygen to her tissues. Anemia is defined as a condition in which blood is deficient in either quantity or quality. The tissues become pale and depleted of blood. The animal may also become sluggish and breathe more rapidly to try to get more oxygen. If hemorrhage occurs slowly, as much as one-half of the total blood volume can be lost over a period of weeks to months and no serious consequences may occur. The body is able to replace some of the lost red blood cells by increasing production of these cells (hematopoiesis). In addition, the affected animal will learn to limit its exercise so that slight listlessness and loss of stamina may be the only clinical signs he experiences.

If *more than one-third of the total blood volume is lost in a matter of minutes or hours,* hypovolemic shock may ensue. Shock is defined as an acute syndrome characterized by a progressive failure of the circulation resulting in ineffective capillary perfusion and tissue anoxia leading to cellular dysfunction and ultimately cell death. Shock can be classified into hypovolemic, cardiogenic, or vasogenic (distributive). When it occurs due to rapid blood loss, it is hypovolemic shock. Lesson 4 in this unit covers shock in detail.

What stops hemorrhage? And how are the red blood cells removed? A number of factors contribute to the arrest of hemorrhage. As hemorrhage occurs, the blood pressure drops. This helps to decrease blood loss. Also, clotting occurs. We will cover this also in a later lesson.

What happens to the blood that has accumulated and clotted outside the vessel? With small hemorrhages, the serum is readily absorbed by lymphatics in the area. The red blood cells and hemoglobin degradation products are phagocytized by macrophages either at the site or in the sinus of a regional lymph node. With a larger hemorrhage, the clot may be organized by fibrous tissue, and result in scarring.

EDEMA

This lesson corresponds to the web lesson of the same name

LEARNING OBJECTIVES FOR THIS UNIT:
1. Recognize edema, describe its distribution (localized or generalized), and know the proper terminology for edema appearing in various tissues or regions of the body.
2. Know the general causes and the pathogenesis of edematous lesions.
3. Relate the lesion of edema to the clinical signs and to other lesions that may be present.

SUMMARY OF IMPORTANT CONCEPTS RELATING TO EDEMA:

Definition:

Edema is accumulation of abnormal quantities of water in interstitial tissues and/or body cavities.

Appearance:

- *Grossly*, edema is recognized as fluid within body cavities and/or by soft, doughy, usually cool and non-painful tissue distention that pits on pressure.
- *Microscopically*, edema is recognized by separation of normal tissue elements by clear or pink material, and by dilation of lymphatics.

Transudates vs. exudates:

Transudates occur when fluid accumulates without increased vascular permeability and are characterized by clear fluid, low specific gravity, and low protein. **Exudates** occur when vessels are damaged and leaky and are characterized by turbid fluid, high specific gravity, high protein concentrations, and high cell counts.

The four major causes of edema (which are not mutually exclusive) are

(i) increased hydrostatic pressure
(ii) increased vascular permeability
*(iii)*decreased intravascular oncotic pressure (hypoproteinemia)
(iv) lymphatic obstruction

A common cause in human medicine but rare cause in veterinary medicine is excessive retention of sodium.

The inciting cause of edema is often more clinically significant than the edema itself. However, presence of edema may be life-threatening in sites such as brain, larynx, and lung.

Edema fluid and excessive interstitial proteins are normally removed via lymphatic drainage. Persistent edema may cause tissue fibrosis.

Edema – Definition:

Edema is accumulation of excessive water in body cavities or interstitial tissues.

Recognition and Classification of Edema

Gross characteristics of edema:
Tissues affected by edema are usually soft and doughy. Distended tissue tends to accumulate the most fluid ventrally simply because of gravity. The edematous tissue pits on pressure and the indentations remain after pressure is removed. Some people refer to "pitting edema", but in fact, all edema is "pitting." Edematous tissue is cool to the touch rather than warm, unless inflammation is also present, in which case there is some heat (rubor tumor **calor** et dolor). The edematous tissue is not reddened (i.e., unless also hyperemic), and not painful, unless, once again, inflammation is present. Distended lymphatics are often visible in edematous lesions. At postmortem examination, edema is recognized by the presence of clear yellow-tinged fluid that distends loose connective tissues or accumulates in body cavities such as the peritoneal, pleural, or pericardial spaces. The fluid may flow upon cutting through the tissue or if the vessels were damaged sufficiently that clotting proteins accompanied the fluid, it may form a jelly-like clot.

Generalized vs. localized edema

- Edema is usually localized to one area. Infrequently it affects most or all of the body. This is referred to as "generalized edema". *Anasarca* is a term that means general edema (like of the whole body!) but in common usage, this term is really only used for fetuses.

- Edema usually occurs localized to one anatomic site. Terminology for edema involves inserting the prefix "hydro" before the body part. Consequently –
  Hydroperitoneum (ascites) – edema fluid in the peritoneal cavity
  Hydrothorax – edema fluid in the thoracic cavity
  Hydropericardium – edema fluid in the pericardial sac
  Hydrocephalus – edema fluid in the ventricles of the brain
  The term "hydrops" is sometimes used in a manner similar to the prefix "hydro", e.g. "<u>hydrops</u> of the gall bladder" or "<u>hydrops</u> amnion".

Composition of Edema Fluid (Transudate versus Exudate)

Edema can also be classified based on the composition of the fluid. Edema fluid consists primarily of water but also contains variable amounts of protein, leukocytes and erythrocytes. The relative concentrations of protein and cells within edema fluid and its

specific gravity are often used to classify types of edema as either a **transudate** or an **exudate**.

Edema may be either a transudate or an exudate.

TRANSUDATE = accumulation of fluid due to a hydrostatic imbalance between the intravascular and extravascular compartments despite normal vascular permeability

What are characteristics of a transudate? Since vascular permeability is normal, there will be little protein or blood cells accompanying the fluid (leakage of materials as large as proteins and cells from vessels requires some degree of vascular damage). Therefore, the specific gravity of the fluid will be relatively low. **Transudates are generally clear and colorless** due to the relative absence of protein and cells.

EXUDATE = accumulation of fluid due to increased vascular permeability

In situations of increased vascular permeability, protein and blood cells escape through the vessel wall and are present in the extravascular edema fluid. As a result, exudates have higher specific gravity, are generally opaque, and are often amber.

What are causes of exudates? Usually, exudates occur when infectious agents or toxins either directly damage vessels or cause tissues to produce chemical signals that alter vascular permeability (i.e., bigger holes in the vessels).

Causes of Edema

- **Normal Body Water Distribution**

To understand the pathogenesis of edema, we must know a few things about normal body water composition. Water makes up two-thirds (2/3) of the total body weight. About eight twelfths (8/12) is intracellular, three twelfths (3/12) is interstitial and one twelfth (1/12) intravascular.

- **Forces Regulating Movement of Body Water**

  Factors that regulate movement of body water between these compartments are as follows:

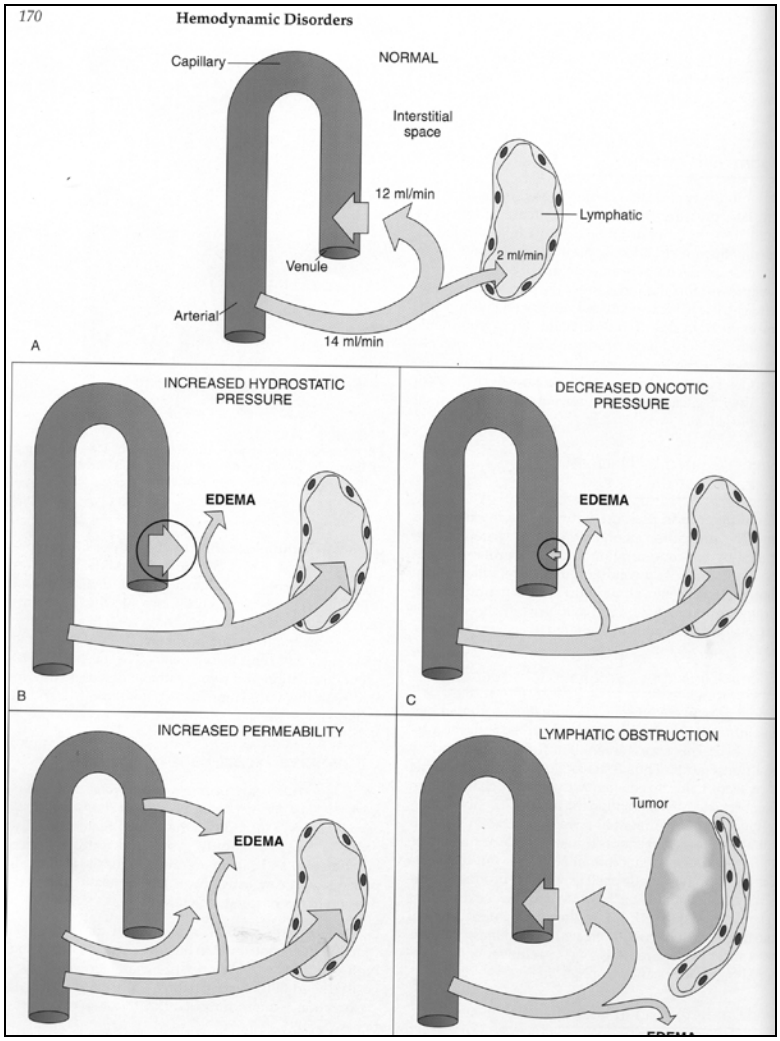
  - Forces Driving Fluid Out of Blood Vessels
    - ✓ Hydrostatic pressure (blood pressure) within the vessel is the chief factor that tends to drive fluid from vessels. This amounts to about 30 mm Hg at the arterial end of the capillary and 12 mm Hg at the venous end.
    - ✓ Interstitial fluid colloidal osmotic pressure (interstitial oncotic pressure) is a less important factor. Since the vessel wall is normally permeable to both water and crystalloids, tissue osmotic pressure is due almost entirely

to colloids (chiefly proteins). Since the interstitium is typically low in proteins, this normally does not contribute significantly to edema formation.

- ❖ Forces Drawing Fluid Into Blood Vessels
  - ✓ Intravascular colloidal osmotic pressure (oncotic pressure) is a very important factor. This is due largely to plasma protein content and amounts to about 25 mm Hg.
  - ✓ Tissue tension (tissue hydrostatic pressure) totals only 4 to 8 mm Hg and is important only in relation to the distribution of edema. Lax areas of the body are much more prone to accumulation of edema fluid than tense areas.

These forces are normally kept in a delicate balance so that normal body fluid movement occurs without edema happening. When this balance is lost edema results.

- ➢ **Four Major Causes of Edema exist (which are NOT mutually exclusive)**



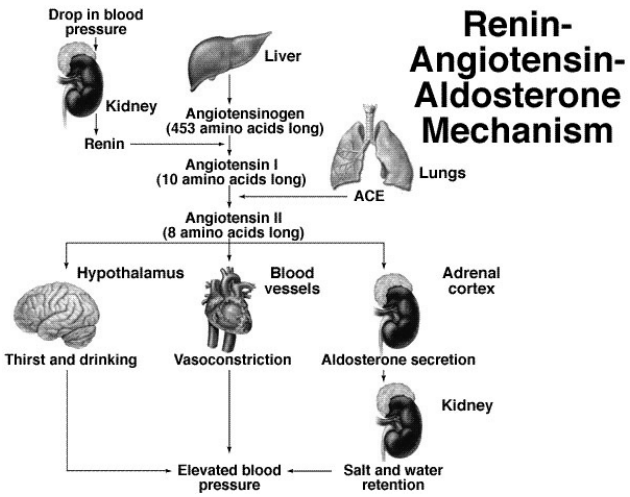
❶Increased Intravascular Hydrostatic Pressure

Increased intravascular hydrostatic pressure causes edema. Venous obstruction results in increased hydrostatic pressure as blood backs up in the venous system, with leakage of crystalloids and fluid into the interstitial tissues. Capillary permeability is not altered, so significant leakage of colloids (proteins) does not occur unless the pressure increases significantly. Primary hypertension is also a reason for increased intravascular hydrostatic pressure but this is quite rare in animals.

Right sided heart failure results in pooling of blood in the right atrium and vena cava. The resultant impedance of venous return to the heart increases hydrostatic pressure within the general body vasculature and results in edema. Depending on the species of animal, the edema fluid tends to accumulate within the peritoneal cavity (ascites; dog), the pleural cavity (hydrothorax) or in the subcutaneous tissues of the ventral body (e.g., "brisket edema"; cattle) and intermandibular area ("bottle jaw"; sheep).

In left sided heart failure blood pools in the left atrium, impeding venous return from the lungs and causing pulmonary congestion. The increased hydrostatic pressure within the pulmonary vasculature causes pulmonary edema.

Reduced cardiac output due to left sided heart failure also decreases blood supplied to the kidneys, creating a situation that is critically involved in the progression of congestive heart failure. Reduced renal blood flow induces secretion of renin by cells within the juxtaglomerular complex. Renin converts the protein alpha2-globulin to angiotensin I, which is in turn converted to angiotensin II by a serum enzyme. Angiotensin II is a potent vasoconstrictor and also stimulates secretion of aldosterone by the adrenal gland. Aldosterone stimulates renal **sodium retention**, which expands the total fluid volume and worsens the edema. The increased serum and interstitial sodium concentration is sensed by osmoreceptors in the hypothalamus, which respond by inducing secretion of antidiuretic hormone (ADH) by the posterior pituitary. ADH increases reabsorption of water from the distal tubules and collecting ducts of the kidney. This, of course, even further expands the fluid volume and worsens the edema.



❷ Decreased Intravascular Osmotic Pressure (hypoproteinemia)

Reduction in serum albumin decreases intravascular oncotic pressure and causes edema. Capillary blood contains a decreased quantity of colloids (protein) due to either decreased hepatic synthesis of these proteins or increased protein loss through the kidney or gastrointestinal tract. As a result of the hypoproteinemia, fluid and crystalloids fail to be reabsorbed at the venous end of the capillary and accumulate in the interstitium as edema.

In liver disease, there is decreased production of albumin and so the plasma colloidal osmotic pressure decreases and edema occurs. More commonly occurring conditions that may cause hypoproteinemia are renal and gastrointestinal disease. In these diseases, hypoproteinemia occurs due to loss of protein through urine (protein-losing nephropathy such as amyloidosis) or feces (protein-losing enteropathy such as intestinal lymphosarcoma).

❸ Increased Vascular Permeability

Injury to vascular walls allows leakage of fluid, protein, and cells, and causes edema. Endothelial cell damage results in increased capillary permeability to fluid, crystalloids, and colloids. The increase in colloids within the interstitium reduces reabsorption of fluid at the venous end of the capillary. These colloids are eventually drained away by the lymphatics.

Vascular inflammation causes increased vessel permeability so that proteins move into body cavities and/or the tissue interstitial space.

Two additional conditions that may cause direct injury to vessel walls are trauma and anoxia. It's easy to see how trauma alters vascular permeability, but how does anoxia do the same thing? Endothelial cells, like all other cells, require oxygen to function normally. When adequate oxygen is not present, they fail to create a tight seal and colloids leak between endothelial cells and into and through the vessel wall.

❹ Lymphatic Obstruction (lymphangiectasia)

Blockage of lymph vessels causes edema. Normally, small quantities of fluid, crystalloids, and colloids escape from the capillary and are drained from the interstitium by lymphatics. In lymphatic obstruction, these materials accumulate in the interstitium as edema. **Lymphangiectasia** means "lymph-vessel-dilation". It may be **primary lymphangiectasia** if the lymph obstruction is due to maldevelopment of the lymphatics. Or it may be **secondary lymphangiectasia** if the obstruction is acquired. Examples of secondary lymphangiectasia include lymphatic obstruction by tumor cells or lymphatic compression by a bandage wrapped too tightly around a leg.

To summarize the four major causes of edema:

1. increased hydrostatic pressure
2. increased vascular permeability
3. decreased colloidal osmotic pressure of plasma
4. lymphatic obstruction

For each of these four causes of edema, would you expect the fluid to be a transudate or an exudate; localized or generalized? The answers are summarized below.

↑ hydrostatic pressure → transudate; edema may be localized or generalized

↑ vascular permeability → exudate; edema may be localized or generalized

↓ plasma osmotic pressure → transudate; generalized edema

lymphatic obstruction → transudate; edema may be localized or generalized

Clinical Significance of Edema

Edema may cause clinical signs and death by exerting pressure on vital structures.

One example is brain edema. When the brain swells there is little room for outward expansion of tissue because the brain is enclosed within the dura mater and the bony skull. Significant intracranial edema, then, may cause herniation of brain tissue through the foramen magnum or beneath the tentorium (transtentorial herniation). Recall that the tentorium is an osseous structure that separates the cerebral cortex from the cerebellar

cortex and under which the brainstem passes. Either type of herniation can cause severe neurologic signs and death.

Another example is larynx, where edema can cause upper airway occlusion and death from asphyxia.

Severe pulmonary edema would have a similar detrimental influence on oxygen availability.

Fate of Edema

Edema fluid is removed via veins and/or lymphatic vessels. Chronic edema may be organized by fibrous connective tissue.

What happens to edema? If the cause is remedied, most of the edema is drained from the tissues through lymphatics. If the cause is unresolved, as with congestive heart failure, the edema will continue to accumulate and generalized edema will result. In some cases, it's difficult to completely control edema even when diuretics are used.

Persistent edema can stimulate fibrosis.

SHOCK

This lesson corresponds to the web lesson of the same name

LEARNING OBJECTIVES FOR THIS LESSON:

1. Based on the inciting cause, be able to classify shock as cardiogenic, hypovolemic, or distributive, and know the pathogenesis of each type.
2. Know the mediators involved in septic shock and anaphylactic shock.
3. Know how the decreased tissue perfusion associated with shock causes cell injury and recognize the gross and/or histologic changes in tissues that may result from shock.
4. Know the compensatory changes that may occur in response to a state of shock.

SUMMARY OF IMPORTANT CONCEPTS RELATED TO SHOCK

Definition: failure of the circulatory system to adequately perfuse vital organs.

Causes:

- Cardiac pump failure (cardiogenic shock)
  myocarditis, acute myocardial degeneration, cardiac tamponade
- Loss of blood volume (hypovolemic shock)
  hemorrhage, diarrhea, water deprivation, vasculitis, burns
- Venous pooling of blood that causes functional hypovolemia (distributive or vasogenic shock)
  sepsis, anaphylaxis

Pathogenesis of endotoxic or septic shock:

Endotoxin binds to serum protein → resulting complex binds to macrophage/monocyte → TNFalpha secreted into circulation → marked capillary dilation → severe pooling of venocapillary blood → decreased cardiac venous return and cardiovascular collapse

Pathogenesis of anaphylactic shock:

Exposure to allergens → activation of mast cells or other effector cells → release of histamine and other chemical mediators → marked venocapillary dilation

Effect of shock: anoxic cell injury

Body response to shock:

- ✓ increased cardiac output by increasing heart rate and contractility
- ✓ increased blood pressure through vasoconstriction
- ✓ conserve body water

Lesions of shock: congestion, edema, anoxic necrosis of certain tissues

✹ ✹ ✹ ✹ ✹ ✹ ✹ ✹ ✹ ✹ ✹ ✹

Shock – definition:

Shock is failure of the circulatory system to adequately perfuse vital organs.

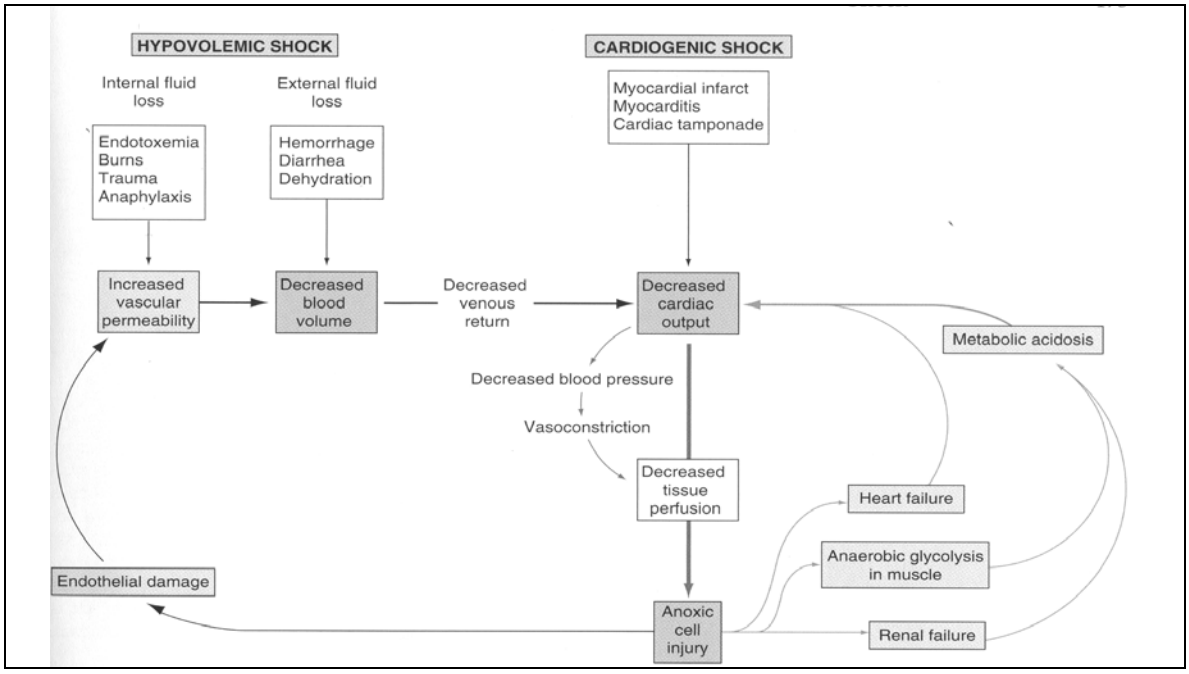
In shock, tissue perfusion and oxygen delivery are insufficient to meet the basal metabolic demands of tissues. Whatever the inciting cause, shock is characterized by **low blood flow** that is usually accompanied by low blood pressure (**hypotension**). Situations of inadequate tissue perfusion result in a variety of adjustments to the circulatory system that are directed toward maintaining normal arterial blood pressure and conserving body water. These compensatory mechanisms may maintain viability of vital organs and sustain the life of the patient, a situation termed "compensated shock". When the adjustments fail to reestablish and maintain perfusion sufficient to sustain vital tissues, a condition of "uncompensated shock" ensues where progressive circulatory collapse leads to increasingly severe disruption of critical cellular metabolic pathways and death. Clinically, the primary goal of therapy for shock is the rapid restoration of systemic blood flow by replacement of intravascular fluid and the use of drugs that increase vascular tone and support cardiac function.

Causes, Types, and Pathogeneses of Shock

Shock is initiated by anything that severely and usually relatively suddenly decreases cardiac output, blood volume, and/or peripheral vascular resistance. The types of shock can be classified on the basis of the primary general cause:

- **Cardiogenic shock** is caused by insults that negatively affect cardiac output (inhibit the heart's ability to pump blood). Cardiac output = heart rate x stroke volume, so anything affecting heart rate or contractility can decrease cardiac output. Examples include:
  - ✓ myocarditis, such as might occur with a septicemia or viral infection
  - ✓ myocardial degeneration such as might occur with vitamin E/selenium deficiency in pigs (mulberry heart disease), monensin toxicity in horses, or myocardial infarcts (which occur much more commonly in humans than in domestic animals)
  - ✓ cardiac tamponade, which occurs when fluid (usually blood) accumulates rapidly in the pericardial space and impinges on the ability of the cardiac ventricles to dilate and fill with blood
  - ✓ electrolyte imbalances (such as hyperkalemia in uremic animals) that negatively affect heart rate
  - ✓ valvular insufficiency (endocardiosis in dogs) leading to stretching and failure of heart muscle

- **Hypovolemic shock** is caused by a sudden severe loss of blood volume. Causes include:
  - ✓ <u>acute hemorrhage</u> involving loss of greater than ¼ - ⅓ of total blood volume. The blood may be lost externally or into internal spaces such as the peritoneal cavity or the alimentary tract.
  - ✓ <u>loss of fluid</u> (intravascular and extravascular), which may occur with water deprivation, vomiting, diarrhea, etc.
  - ✓ <u>increased vascular permeability</u> leading to loss of intravascular fluid, proteins, and sometimes blood cells. These insults include infections, toxicities, and immune reactions that injure vessels. Specific examples include equine viral arteritis, African horse sickness, canine herpesvirus, and the hemorrhagic fevers (e.g., Rift Valley fever, simian hemorrhagic fever, Ebola virus infection)



- **Distributive (vasogenic) shock** is caused by a sudden severe decrease in peripheral vascular resistance that causes extensive pooling of blood within the venous system and subsequent decreased venous return to the heart. *Some authors classify these types of shock as varieties of hypovolemic shock* (the hypovolemia would be relative in these cases). **There are some important examples of distributive shock**:

  - ❑ **Septic shock** (endotoxic shock, toxic shock) results from a bacterial infection (localized or systemic) in which large quantities of endotoxin are released into circulation. **Endotoxins** are complex components of the cell wall of gram-negative bacteria (e.g., *Escherichia coli*, *Klebsiella*, *Salmonella* sp.) and are released only upon death of the bacteria and degradation of the cell wall. Endotoxin is sometimes referred to as "lipopolysaccharide" because the most

toxic part of the complex is this type of molecule. Less commonly, other types of toxins from Gram-positive bacteria can cause shock by a similar pathogenesis.

The **pathogenesis** of these types of shock involves the release of large quantities of toxin into the circulation that ultimately cause marked arteriolar dilation and pooling of blood in capillaries and veins. The large volume of blood is maintained in the peripheral circulation and the circulating blood volume is thus markedly decreased. More specifically, the endotoxins released into circulation bind to a serum protein known as lipopolysaccharide-binding protein (LPS-BP) and this complex then binds to receptors on the surfaces of macrophages and other monocytes. After binding of the LPS-BP complexes, the monocyte/macrophages are stimulated to secrete large quantities of chemical signals, the most important of which are tumor necrosis factor-alpha (**TNFα**) and interleukin-1β (**IL-1β**). In such large quantities as are involved in these situations, **these chemical mediators stimulate vasodilation** to cause the functional hypovolemia characteristic of this type of shock.

In addition to vasodilation, the mediators also activate complement and initiate coagulation (the important condition known as "disseminated intravascular coagulation" or "DIC" occurs in septic shock). The bottom line is that many effects are involved in septic shock, including functional hypovolemia, DIC, endothelial cell damage, anoxia, and metabolic acidosis.

- **Anaphylactic shock** is a systemic manifestation of an acute hypersensitivity (allergic) response. This is an idiosyncratic reaction that occurs in certain predisposed individuals upon exposure to certain antigens (substances, usually proteins, to which the individual is allergic) such as insect stings, foods, medicines, etc. We will discuss hypersensitivity reactions in more detail in another section of this course, but for the present discussion just remember that upon exposure to these allergens, **histamine** and other chemicals are released from cells such as mast cells. Histamine and the other substances bind to receptors, **causing vasodilation and increased vascular permeability with loss of intravascular fluid**.

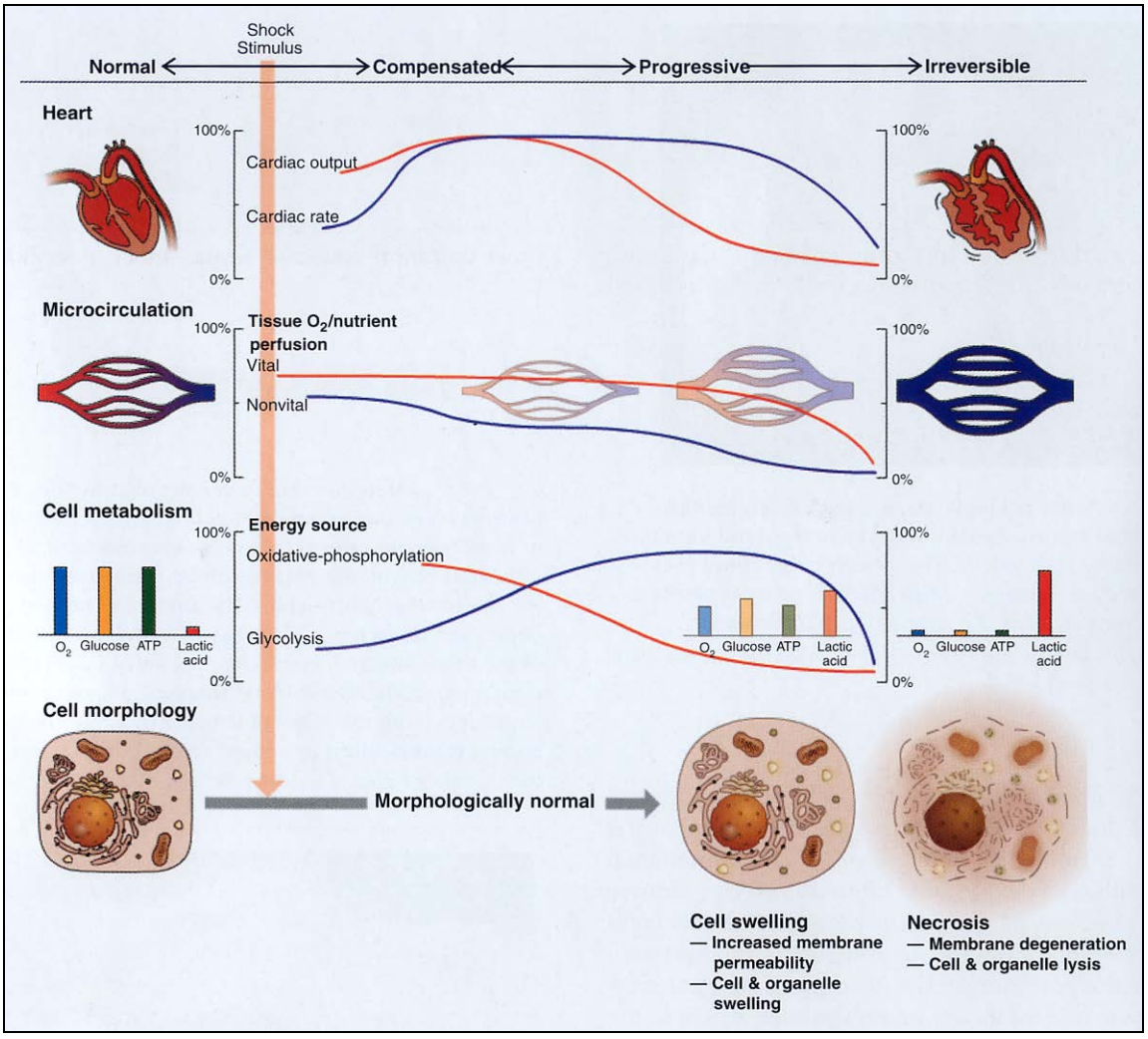
- **Neurogenic shock** can occur following severe emotional stress, severe pain, or electrical shock (e.g., lightning strike, biting through the electrical cord). This type of shock is not related to cytokine release, but rather is a result of massive autonomic discharges that cause extensive peripheral vasodilation, venous pooling, and tissue hypoperfusion.

Consequences of Shock

Shock, no matter what the cause, is bad. It often leads to death. There are some compensatory mechanisms (see below). But if the compensatory mechanisms can't

overcome the shock (and often they can't), shock progresses from reversible to irreversible. The end result is inadequate tissue perfusion and here are some of the augmenting mechanisms that help shock progress from reversible to irreversible (and death).

- ✓ Anoxic injury to endothelial cells leads to increased vascular permeability and further loss of intravascular fluid, aggravating the hypovolemia and anoxia.
- ✓ Insufficient renal and muscular perfusion results in metabolic acidosis, which further suppresses cardiac output.
- ✓ Insufficient myocardial perfusion causes anoxic injury to myocytes, further decreasing cardiac output.



Cardiovascular and Systemic Responses to shock

The body responds to shock by attempting to increase cardiac output and by shunting blood flow to vital organs such as brain, heart and kidneys and away from tissues such as the gastrointestinal tract, skeletal muscle, and skin. Vasopressive signals have less effect

on the vasculature of "vital" tissues than on the "less vital" tissues. Thus, brain, heart, and kidney are preferentially perfused in the initial stages of shock.

- Support of cardiac function:
  - Secretion of norepinephrine and epinephrine by the adrenal medulla increases heart rate.
  - Production of aldosterone by the adrenal cortex stimulates retention of sodium and water, thus increasing blood volume.

- Vascular changes:
  - Secretion of norepinephrine and epinephrine by adrenal medulla stimulates vasoconstriction.
  - The renin-angiotensin system results in the eventual production of angiotensin II, which is a potent vasoconstrictor.

If the inciting cause is not relieved, these compensatory responses will eventually fail (a state of uncompensated shock exists) and the animal will die.

Gross and histologic lesions of shock

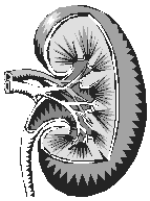
The lesions of shock are those of

a. the various initiating causes (e.g., hemorrhages, burns, cardiac tamponade, etc.)
b. changes that reflect edema and venocapillary pooling of blood, and
c. degenerative changes in tissues subjected to anoxia.

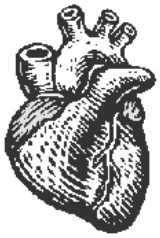
Unless the precipitating event is severe hemorrhage, there will be severe organ congestion that is especially prominent in the visceral tissues of liver, gastrointestinal tract, kidneys, and adrenal glands. Frequently, hemorrhage into the lumen of the gastrointestinal tract follows congestion and anoxic necrosis of the superficial mucosa. In some tissues the congestive, edematous, and degenerative changes are only evident microscopically. Keep in mind that the adjustments discussed in the previous section shunt blood flow to and protect (at least temporarily) organs such as brain, heart, and kidneys while sacrificing tissues such as intestine, skeletal muscle, and skin.

There are some interesting species differences in the organs that are particularly severely affected in shock; these are often referred to as the "shock organs". In most species the lung is considered the "shock organ" because of the frequent occurrence of severe edema, thrombosis, and degenerative changes associated with shock. In horses, the large colon is often considered the "shock organ" because of the tremendous submucosal colonic edema that occurs with endotoxemia. Liver is considered the shock organ in the dog. In spite of these species differences, however, it is wise to remember that shock is a systemic response, involving generalized cardiovascular collapse.

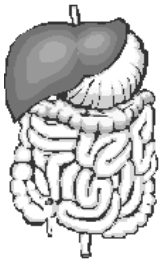
Typical tissue changes that may occur in animals subjected to shock include:



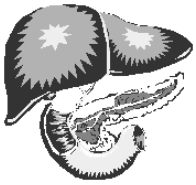
Kidney: proximal tubular necrosis. The changes may be severe, though often are not grossly obvious. Animals that survive long enough in shock often develop oliguric renal failure.



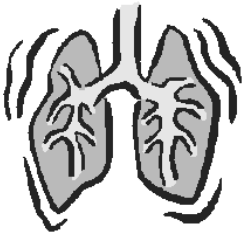
Heart: multifocal epicardial/endocardial hemorrhages (grossly visible) and multifocal myofiber necrosis (usually not grossly visible). In spite of the protective adjustments, progressive deterioration of cardiac function occurs with uncompensated shock.



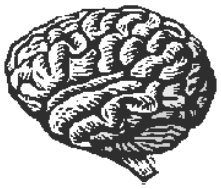
Stomach and intestines: congestion, edema (particularly severe in the equine colon), and mucosal necrosis with hemorrhage (all of these changes are grossly visible)



Liver: centrilobular sinusoidal congestion (grossly visible) with hepatocellular vacuolar degeneration and necrosis (may be grossly apparent)



Lungs: congestion, edema (both grossly visible) and, in septic shock, capillary thrombosis and necrosis



Brain: edema and anoxic cerebral laminar necrosis (both changes grossly visible if severe)

HEMOSTASIS

This lesson corresponds to the web lesson of the same name

LEARNING OBJECTIVES FOR THIS LESSON:

1. Outline the pathogenesis of the formation of temporary and permanent hemostatic plugs including the following structures and substances in the outline: *platelets, endothelium, Factor XIIa, Factor X, final common pathway, fibrin*
2. Describe the resolution of a permanent hemostatic plug using the following terms: *Factor XIIa, plasmin, fibroblasts, endothelium*

Endothelial damage results in:

- Loss of PGI_2 → no longer suppresses thromboxane A_2 (TXA_2) → platelets aggregate, vessel constricts
- Platelet adherence to defect → degranulation → attract more platelets and participate in clothing cascade
- Exposed collagen (basement membrane, thrombin, etc.) provides surface for activation of coagulation factor XII and release of tissue thromboplastin

Temporary hemostatic plug: made by **platelets**
Adhesion, activation, aggregation

Permanent hemostatic plug: formation of **fibrin clot** added to platelets

Coagulation cascade

- **Intrinsic system**: XII → XIIa → XI→ XIa → IX → IXa → + VIII + Ca++ X→ Xa → + V + Ca++ → Prothrombin→ thrombin → Fibrinogen → fibrin → + XIIIa + platelets → stable clot (= permanent hemostatic plug)
- **Extrinsic system**: Tissue factor (also known as thromboplastin), from damaged tissue + Ca++ + VII → X → Xa → + V + Ca++ → Prothrombin → thrombin → Fibrinogen → fibrin → + XIIIa + platelets → stable clot.

(*Note – From factor X on, the cascade is the same for both systems; called the final common pathway*)

Resolution of permanent hemostatic plug:

- Fibrinolytic system: XIIa → plasminogen → plasmin → hydrolyzes fibrin and fibrinogen (also certain other clotting factors and plasma proteins) → hemostatic plug dissolves.
- Repair
  - mitogenic factors from platelets stimulate fibroblasts to breach the gap
  - macrophages phagocytose platelet debris
  - endothelial cells proliferate and grow over the fibroblasts and restore the normal continuity of the endothelial lining.

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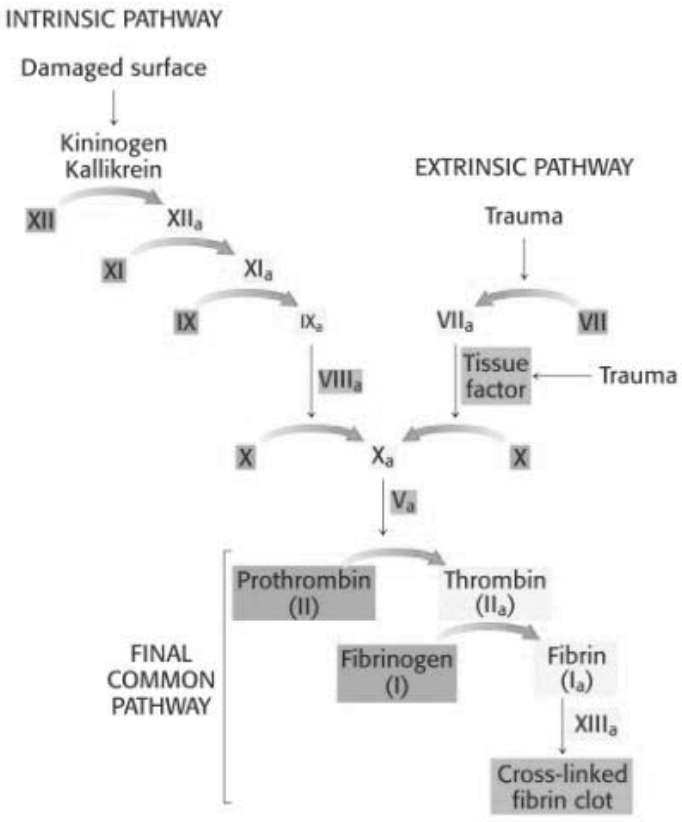

INTRINSIC PATHWAY
Damaged surface
Kininogen
Kallikrein
XII
XIIa
XI
XIa
IX
IXa
VIIIa
X
Xa
Va
EXTRINSIC PATHWAY
Trauma
VIIa
VII
Tissue factor
Trauma
X
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
XIIIa
Cross-linked fibrin clot
FINAL COMMON PATHWAY

Under normal circumstances the circulating blood is maintained in a fluid state to keep it moving, allowing transport of oxygen and other nutrients to body tissues. At the same time, the blood must be able to thicken (coagulate) rapidly in response to minute tears that constantly occur, especially in smaller blood vessels. Keeping these two systems in balance is called *hemostasis*. Failure to maintain normal hemostasis results in *thrombosis* or *hemorrhage*.

TEMPORARY HEMOSTATIC PLUG

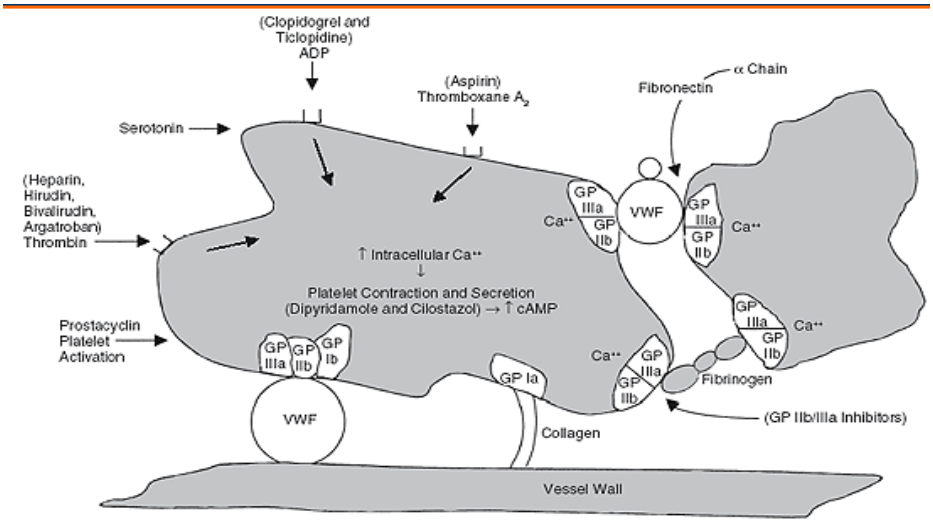
The temporary hemostatic plug is made by *platelets*. The series of events is as follows:

platelet adhesion ⇨ platelet activation ⇨ platelet aggregation

Platelets are tiny bi-concave discs (~2.5 x 1μm in diameter) that originate from bone marrow megakaryocytes.

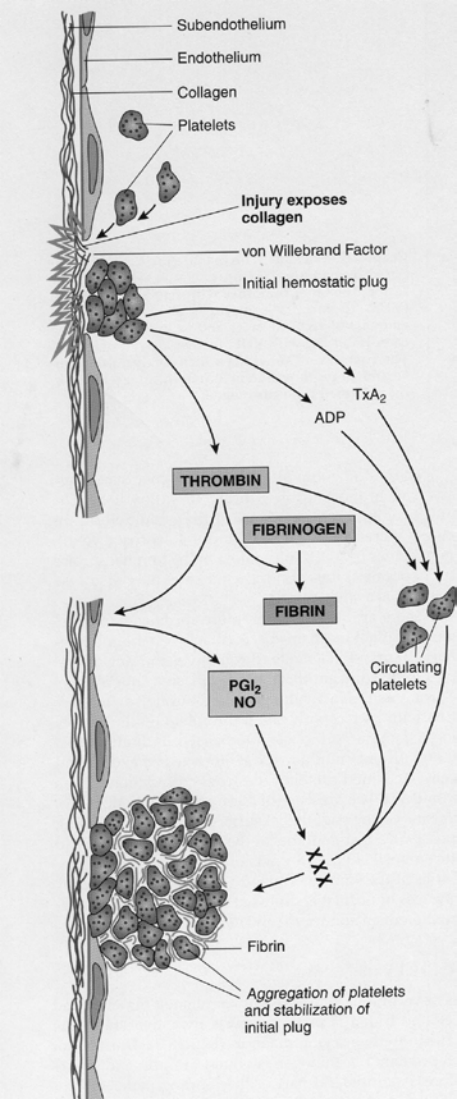
*Platelet **adhesion** is the first step in the formation of temporary hemostatic plugs:*

Circulating platelets do not adhere to normal endothelium or to each other until a vessel endothelial lining is broken to expose **subendothelial collagen**. Adhesion requires secretion of the protein called vonWillebrand factor (vWF), found in the vessel wall, plasma, and on the surface of platelets. In the diagram below, vWF is shown adhered to the vessel wall in an area of broken endothelial lining. vWF binds to platelets.



*After platelets are adhered, then they can become **activated** and **aggregated**, which means they go on to secrete certain substances and form a nice PLUG in the vessel well.*

But the plug is not stable and has to be held together by FIBRIN, which is what happens next.



PERMANENT HEMOSTATIC PLUG

Sometimes, all that is necessary at the site of blood vessel damage is the temporary platelet plug. In more severe cases though, the more stable and stronger permanent plug is needed. For this, a clot must be formed, i.e., intravascular blood coagulation.

Remember that "permanent" is really a misnomer because of the third step in the procedure, fibrinolysis, which dissolves the plug. If it were REALLY permanent, it would be very bad news because every clot that ever formed would stay there and blood couldn't circulate too good.

Blood coagulation reactions form a second key element of the hemostatic seal --the fibrin clot. Spreading outward from and anchoring the platelet plugs, the fibrin clot contributes needed bulk. A rather complicated nomenclature of Roman numerals, letters, and eponyms designates the components of what is fondly (?) known as The Coagulation Cascade.

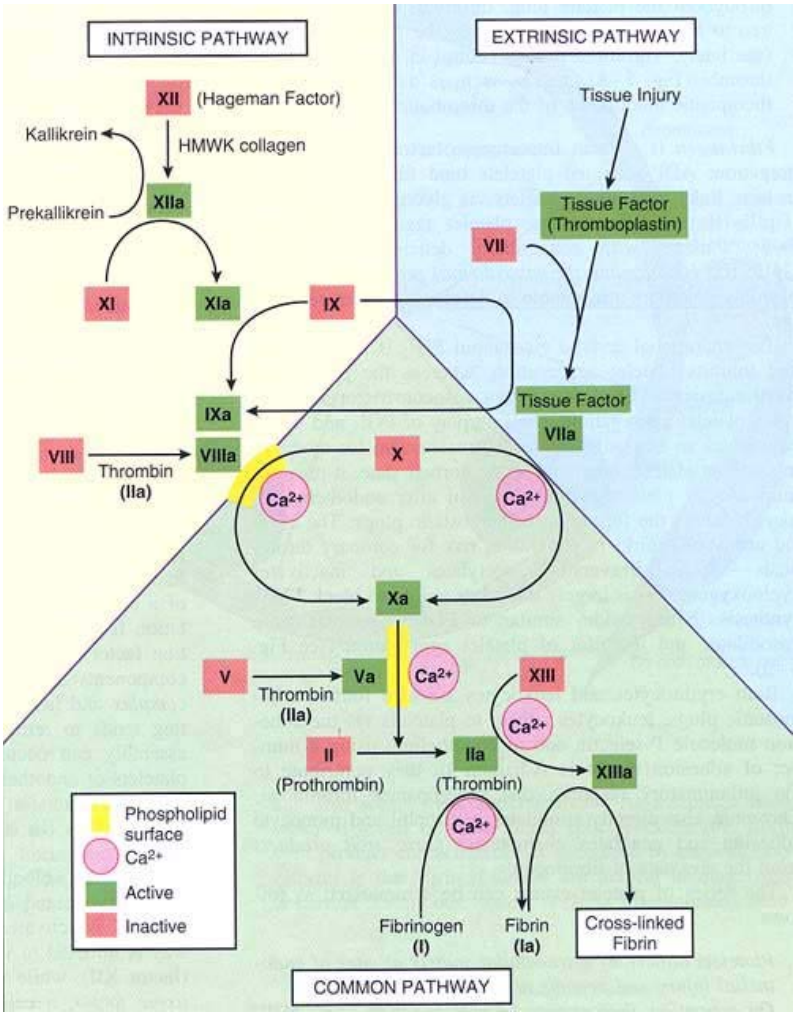
(*NOTE: The coagulation cascade has been divided into an intrinsic and an extrinsic pathway for convenience and to help memorization. It should be noted however, that these two pathways intermix extensively in real life.)*

The Roman numerals range from Factor I to Factor XIII. There are no Factors IV or VI. They are activated in a CASCADE which results in fibrin forming and holding the clot in place.

All of the coagulation factors are present in the blood in an inactive form. ***The coagulation factors in each step of the coagulation cascade are activated by factors from the preceding step.*** *The end result is FIBRIN formation.*

The Coagulation Cascade

Although we now know that these three pathways are quite intermixed, it is easier to learn the cascade using the traditional pathways. They are described in detail with diagram and descriptions on the next pages.

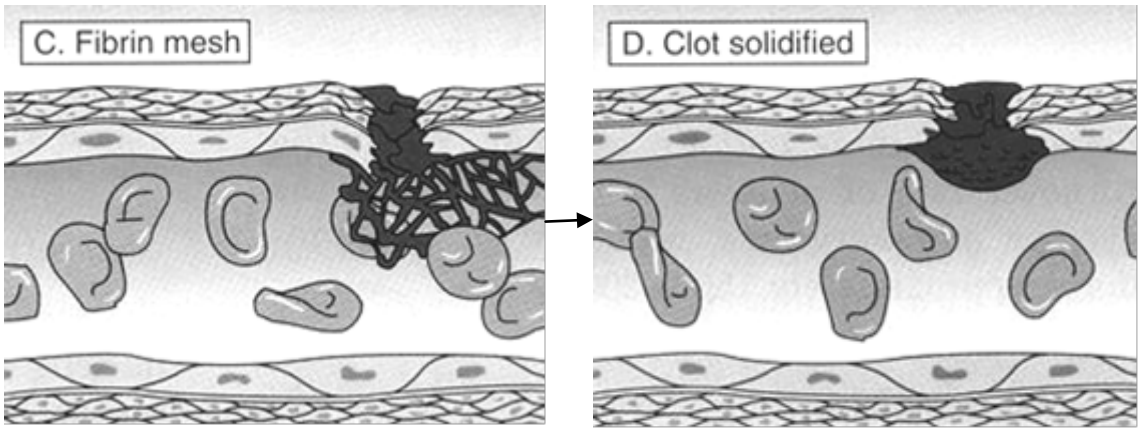


The end result of the clotting pathway is the production of thrombin for the conversion of fibrinogen to fibrin. Fibrinogen is a soluble protein in plasma. When exposed to thrombin, fibrinogen undergoes a complex series of reactions, with the end result being polymerization to fibrin, an insoluble gel.

Contact activation of the coagulation pathway, in addition to promoting blood clotting, results in the generation of plasminogen activator activity, which is involved in fibrinolysis or clot removal. So, as soon as the clot starts forming, it has activated the mechanism for its resolution!

Some clinically relevant info on clotting:

- ☞ Animals lacking factor IX (hemophilia B) or factor VIII (hemophilia A) bleed severely; this means that the intrinsic system is essential for normal hemostasis.
- ☞ Calcium ions (Ca^{++}) are needed in most thrombin-generating reactions. Consequently, addition of EDTA, which binds calcium, will keep blood from clotting in the tube when you collect it.
- ☞ Clotting factors VII, IX, X and prothrombin all require carboxylation of glutamate residues for functional activity. Vitamin K is a necessary cofactor in this reaction. Warfarin works by inhibiting Vitamin K, so animals that ingest warfarin develop bleeding disorders due to deficiencies of functional factors VII, IX, X and prothrombin.



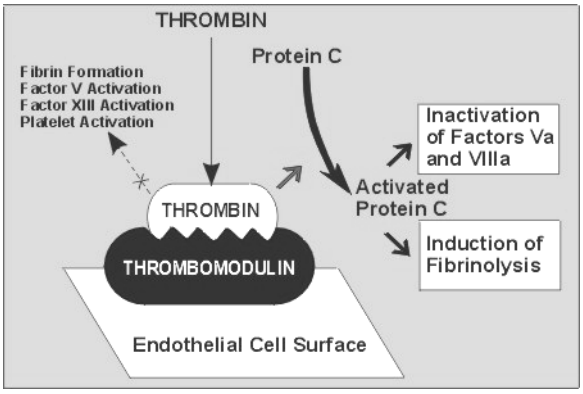
Inhibition of coagulation

So, with all of these clotting factors in the blood why aren't we all one big blood clot? Well, regulatory mechanisms normally prevent activated coagulation reactions from proceeding unchecked to cause either local thrombosis or disseminated intravascular coagulation (DIC). These include:

- ❑ Cellular clearance of activated clotting factors, especially during hepatic circulation, continually removes pro-clotting stuff from the circulation.
- ❑ There are a number of plasma protease inhibitors that neutralize coagulation enzymes.
  - ✓ For instance, the poorly characterized extrinsic pathway inhibitor (EPI), functions to inactivate Factors VIIa and Xa.

- ✓ Antithrombin III is an important plasma protease inhibitor that serves as the key inhibitor of the enzymes thrombin, factor Xa, and factor IXa. Adding heparin to blood in vitro converts antithrombin III from a slow to an instantaneous inhibitor of these enzymes (this is the mechanism for heparin's therapeutic effect). Simply stated, heparin keeps blood from clotting.

- ✓ Thrombin, when bound to a receptor on endothelial cells called thrombomodulin, acquires the ability to activate *protein C*. Activated protein C destroys factors Va and VIIIa.



If the fibrin clot is already formed, however, all is not lost!!! The body has mechanisms by which fibrin clots can be broken down. This process is called **fibrinolysis.**

FIBRINOLYSIS

The fibrinolytic system is activated by fibrin deposition. By dissolving fibrin, the fibrinolytic system helps keep the lumen of an injured blood vessel open. A balance between fibrin deposition and lysis maintains and remolds the hemostatic seal during the days required to repair an injured vessel wall.

The big player in the fibrinolysis system is **plasmin**. Plasmin breaks down both fibrin and fibrinogen (and also certain other clotting factors and plasma proteins) and causes dissolution of the hemostatic plug.

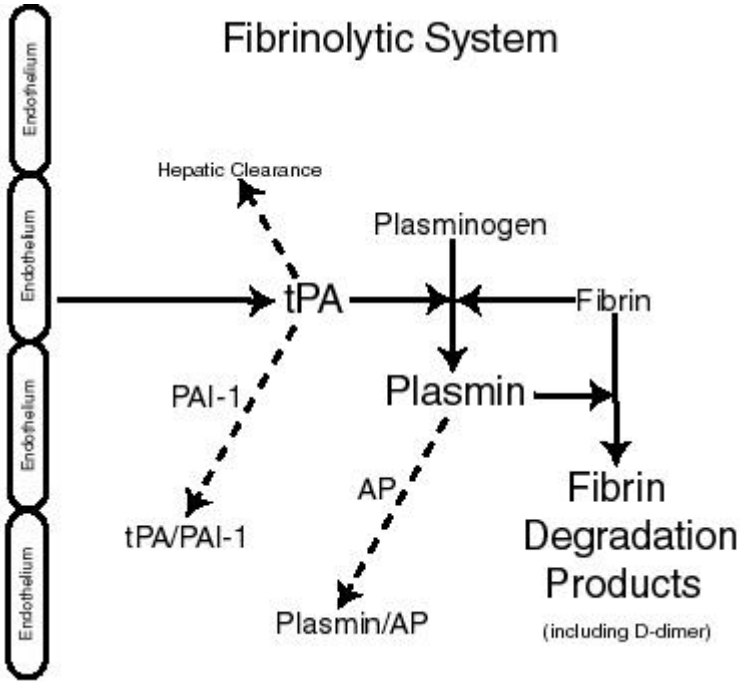
Depending on the size of the area involved, this may take a few days to a few weeks. During this time, mitogenic factors from platelets have promoted fibroplasia (in larger vessels - smooth muscle proliferation also) causing a scar to form in the defect. Shortly thereafter endothelial cells on either side of the defect proliferate and their progeny slide over the scar thus restoring the integrity of the vessel. The platelet plug is slowly removed by phagocytosis.

Plasmin is a powerful proteolytic enzyme that arises from an inert plasma precursor, plasminogen. Factor XIIa is an activator of plasminogen – so, as soon as the clot starts to form, mechanisms for its destruction also begin. Other plasminogen activators are released from vascular endothelial cells.

- ☞ Tissue *plasminogen activator (tPA)*, from endothelial cells, is a poor activator when free in solution, but becomes an efficient activator when it and plasminogen bind to fibrin in proximity to each other.

Streptokinase, a bacterial product not normally found in the body, is another potent plasminogen activator; it has been used to induce fibrinolysis therapeutically in patients with acute thrombotic disorders.

Fibrin is degraded first into large fragments (X and Y), and then into smaller fragments (D and E). These soluble fragments, referred to collectively as *fibrin degradation products*, are swept into the circulation.



HEMOSTATIC DISORDERS

The past few pages have discussed what happens when hemostasis proceeds in a nice orderly fashion. What happens when things go awry? Usually, there is thrombosis or excessive bleeding. We will discuss thrombosis is more detail later (next lesson).

INHERITED CONDITIONS

Inherited bleeding disorders are a wide variety of distinct diseases each caused by a separate defect in an inherited hemostatic protein or pathway. Inherited hemostatic disorders are broadly classified as either

- ➢ failure of primary hemostasis (formation of temporary plug) or

- failure of secondary hemostasis (permanent plug).

Primary hemostatic defects

These include platelet disorders and vonWillebrand's factor deficiency. Defective platelet function is most often due to structural abnormalities in the platelet plasma membrane or other cell structures.

vonWillebrand's disease is is caused by either lack or decreased function of an important protein (vWF) found on the surface of the platelet. This protein is essential for platelet adherence to sub-endothelial collagen. The disease is due to mutation in the gene for vWF and is inherited. There are many forms of this disease in people and in animals based on the concentration of active vWF, as well as the mode of inheritance. This can present as epistaxis, mucosal hemorrhage, or problems with post-surgical bleeding.

Secondary hemostatic defects

These are due to deficiencies in coagulation factors. Animal may present with bleeding into body cavities, joints, or intestine.
Hemophilia A and B are caused by deficiency in Factors VIII and IX respectively. These have been described in several species, including cats, sheep, horses, cows and many breeds of dog.
Others include relatively rare disorders:
Factor I deficiency - DOGS AND GOATS
Factor II deficiency - DOGS
Factor VII deficiency - DOGS
Factor X Deficiency - DOGS
Factor XII Deficiency - CATS
Factor XI Deficiency - CATTLE (common); DOGS

Inherited conditions have been identified with an essentially total deficiency of alpha2-antiplasmin. The severe tissue bleeding after trivial injury establishes that alpha2-antiplasmin is a key regulator of normal fibrinolytic activity.

Heterozygotes for hereditary antithrombin III deficiency with 50% of normal antithrombin III levels have an increased risk for thrombosis. Homozygotes have not been identified, presumably because the homozygous state is lethal in utero.

ACQUIRED CONDITIONS

- THE MOST COMMON ACQUIRED CONDITION is Disseminated Intravascular Coagulopathy (DIC). This is a multifactoral condition caused by a myriad of conditions ranging from bacterial septicemia to neoplasia. It is classified as a **consumptive coagulopathy** as it is characterized by the development of multiple thrombi in the microvasculature that use up (consume) clotting factors V, VII, VIII, and X as well as prothrombin and

fibrinogen faster than they can be produced. This eventually leads to widespread bleeding.

- Chronic liver disease can cause uncontrollable bleeding because of excessive fibrinolysis thought to stem from an acquired severe alpha2-antiplasmin deficiency (secondary to diminished hepatocellular synthesis plus increased consumption due to excessive plasminogen activator activity). In addition, there is decreased production of clotting factors.

- Renal disease can result in acquired anti-thrombin III deficiency. Glomerulopathies (problems with the glomerulus) can lead to loss of this small protein in the urine. Amyloidosis is a good example of renal disease resulting in loss of anti-thrombin III, one of the smaller molecules that slips through the damaged glomerular filtration apparatus. Anti-thrombin III is lost in the urine and widespread thrombosis, especially pulmonary, results.

- Vitamin K deficiency due to lack of production or decreased function (i.e., warfarin) results in bleeding because Vitamin K is necessary for several of the coagulation factors to work (Factors II, VII, IX, and X).

- Administration of corticosteroids may lead to a coagulopathy. There is decreased production of plasminogen activators from endothelium, resulting in decreased plasmin and therefore decreased clot lysis. So, thrombosis is a problem.

These examples are but a few of the ways that alterations in the coagulation cascade can have disastrous results, underscoring the importance of a functional hemostatic system. Against this background of normal hemostasis, the mechanisms of thrombosis can now be explored.

THROMBOSIS, EMBOLISM, ISCHEMIA AND INFARCTION

This lesson corresponds to the web lesson of the same name

LEARNING OBJECTIVES FOR THIS LESSON:

1. Outline the biological mechanisms that lead to thrombosis
2. List the possible outcomes of thrombus formation
3. Identify and classify thrombi based on gross or microscopic features
4. Describe the causes and consequences of embolism
5. Identify embolic lesions
6. Describe the pathogenesis of ischemia and infarction
7. Identify infarction and classify as arterial or venous

SUMMARY OF IMPORTANT CONCEPTS

Thrombosis

Definition: the formation of a blood clot within the vasculature of a living animal.

Causes and mechanisms:

- endothelial damage
- hemodynamic changes
- hypercoagulable states caused by abnormalities in the blood or elements within blood

Possible outcomes of thrombus formation:

- propagation
- dissolution
- organization and recanalization
- thromboembolism
- ischemia or infarction
- disseminated intravascular coagulopathy (DIC)

Morphology: Thrombi have a rough surface and are attached to the endothelial surface. This differs from postmortem clots that are glistening and unattached. Can be: occlusive; venous; arterial; mural or valvular; vegetative

Embolism

Definition: a detached intravascular solid that is carried by the blood to a site distant from its point of origin

Common sources:

- thrombi (thromboembolism)
- bacteria (septic)
- parasitic
- neoplastic

Consequences:

- ischemia
- infarction
- spread of infection
- metastasis

Morphology: embolic "showers"; thromboembolism

Ischemia

Definition: a localized reduction in blood flow due to a vascular obstruction. Infarction is necrosis of tissue due to vascular obstruction.

Causes and mechanisms:

- external pressure
- thrombi
- emboli
- vasoconstriction

Consequences:

- depend on location and duration
- collateral circulation and vulnerability of tissue to hypoxia influence outcome

Morphology:

- arterial
- venous
- white or red
- bland or septic

❋ ❋ ❋ ❋ ❋ ❋ ❋ ❋ ❋ ❋ ❋ ❋

Now that you have an understanding of normal hemostasis we will discuss diseased states as a result of abnormal hemostasis, and obstruction of blood flow: namely, thrombosis, embolism, ischemia and infarction.

THROMBOSIS

Thrombosis is the formation of a blood clot within the vasculature of a living animal.

Causes of thrombosis

Thrombosis can result from any one or any combination of the following three causes:

- *Endothelial damage*

  Damage to endothelial cells can result in release of tissue thromboplastin and exposure of the sub-endothelial vascular collagen to platelets and clotting factors. In addition, during inflammation, cytokines (i.e., IL1 and TNF-alpha) can induce endothelial cells to synthesize and release tissue factor.

  Platelets adhere to the exposed sub-endothelial collagen where the endothelium has been lost. Platelets adhere via von Willebrand's factor (vWF) and tissue factor is released by adjacent damaged endothelial cells activating the coagulation cascade.

  Remember from the unit on hemostasis that the endothelial cells have several anti-thrombotic properties. For example, endothelial cells secrete PGI_2 which inhibits platelet aggregation. Endothelial release of nitric oxide causes vasodilation and inhibits platelet adhesion and aggregation. Also, endothelial cells elaborate protein C and endothelial surfaces are covered with heparin-like molecules that promote the activity of anti-thrombin III.

  Loss or injury to endothelium results in decreased PGI_2 and nitric oxide (NO) which normally serve to inhibit platelet aggregation (PGI_2) and cause vasodilation (NO). TXA_2 from platelets causes vasoconstriction and in conjunction with ADP stimulates aggregation.

Examples of thrombosis due to endothelial damage:

- Inflammation of the vessel wall, such as might occur with bacterial localization, can generate thrombosis. Inflammation causes cytokine release that stimulates tissue factor release by endothelial cells. Activation of the coagulation system results in fibrin deposition and thrombi enlarge.

- Deposition of mineral, such as occurs in uremia, will result in sufficient endothelial damage that thrombosis can start.

- Physical trauma due to iatrogenic stimuli, such as repeated venipuncture, repeated injections, or caustic stimuli, can create thrombosis.

- Parasites that migrate through the vessels can damage them sufficiently to cause thrombosis.

❑ *Alteration in normal blood flow*

Abnormal blood flow resulting in eddy currents, turbulence or blood stasis disrupts the laminar flow of blood, bringing platelets in close contact with the vascular wall. If coagulation factors are activated, they may not be cleared as quickly if there is stasis or turbulence. Also, turbulence may cause endothelial injury resulting in release of tissue factor.

Examples of thrombosis due to abnormal blood flow:

♥ Adult canine heartworms can cause endothelial damage and at the same time cause turbulence when large numbers occupy the right heart and pulmonary arteries. Dogs with dirofilariasis develop pulmonary thrombosis due to turbulence from verminous obstruction of the pulmonary arteries and endothelial damage caused by the filarid nematodes in the right ventricle and pulmonary arteries. These thrombi can be fatal as they block the flow of non-oxygenated blood to the lungs.

♥ Venous stasis is a common cause of thrombosis, particularly in humans. Any partial or complete occlusion or compression of venous return can result in thrombosis.

♥ Cardiac anomalies or cardiac valvular dysfunction create turbulence that may result in thrombosis.

❑ *Hyper-coagulability of the blood*

Hyper-coagulability of the blood refers to those states in which thrombosis is favored due to a change in make-up of the formed elements of the blood. These are best described in human medicine, but a few examples in veterinary medicine are described. There may be an inherited deficiency of an anticoagulant component such as protein C in humans, or an imbalance in procoagulant and anticoagulant components in the blood. Patients with certain kinds of cancer and dogs with hyperadrenalcorticism are said to be in a hyper-coagulable state. Some prothrombotic states may result from imbalances in the normal fibrinolytic system.

Example of thrombosis due to hyper-coagulability of blood:

In dogs with glomerular disease such as renal amyloidosis, small blood borne proteins (i.e., anti-thrombin III) leak through the diseased glomerulus resulting in an imbalance in the prothrombotic and anti-thrombotic components in the blood favoring thrombosis.

Possible outcomes of thrombosis

- *Propagation*

  A small thrombus can become a large thrombus as more platelets and erythrocytes and fibrin accumulate. This can lead to complete obstruction of the vessel or extension of the thrombus into additional vessels. Venous thrombi have a tail that extends toward the heart (in the direction of blood flow) and propagation along this tail can lead to obstruction of the next largest vessel (Example: femoral vein to iliac to vena cava). Arterial thrombi have tails that build up against the flow of blood (again, propagating towards the heart).

- ***Dissolution***

  Alternatively, thrombi may have a more favorable outcome and undergo dissolution.

  The fibrinolytic system is mostly responsible for this process. Cleavage of plasminogen to plasmin by tissue plasminogen activator (tPA) begins the fibrinolytic pathway resulting in removal of the thrombus.

  Sometimes the central portion of the thrombus undergoes central softening as macrophages move in to digest the material and the periphery organizes resulting in a return of blood flow through a slightly narrowed lumen.

  In addition, the thrombus retracts. Retraction is mediated by actin-myosin proteins within platelets. A combination of fibrinolysis and retraction can result in a return to normal blood flow. Hooray.

- ***Organization and recanalization***

  Thrombi may be invaded by fibroblasts and endothelial cells. Granulation tissue develops and the endothelial cells line new, smaller vascular channels penetrating the thrombus.

  The thrombus is now converted to fibrous connective tissue. This scar tissue may shrink with time allowing for re-establishment of blood flow through the recanalized vessel.

- ***Thromboembolism***

  Parts of a thrombus may dislodge and form a new thrombus or obstruction at a distant location. Bad news. More detail on this very soon.

- ***Infarction and ischemia***

  Thrombi often result in reduced blood flow to tissue (ischemia) or complete obstruction of blood flow so that the tissue dies (infarction). More to follow about this also….

- ***Disseminated intravascular coagulopathy (DIC)***

  If numerous thrombi are forming simultaneously in a widespread manner (i.e., systemically, as occurs in some infectious and neoplastic diseases), coagulation factors and platelets can become depleted so that there is a deficiency of coagulation proteins and platelets resulting in uncontrollable hemorrhage. DIC is a syndrome characterized usually by wide-spread endothelial injury or activation resulting in platelets adhering and activation of the coagulation cascade at numerous sites. The fibrinolytic system is also continually activated and dissolves the small clots as they form. The net effect is consumption of platelets and coagulation factors so that fatal bleeding (often characterized by petechiae) occurs. DIC may be a complication of sepsis, endotoxemia, neoplasia, burns, heat stroke, shock, and endotheliotropic viral infections. Patients with DIC present with thrombocytopenia, prolonged clotting times due to consumption of factors V, VII, VIII, X, prothrombin and fibrinogen.

Morphology of thrombosis

During necropsy examinations, thrombi must be distinguished from postmortem clots. When an animal dies the blood clots within the vasculature, forming a mold in the shape of the vessel or heart chambers. These clots are shiny and gelatinous. They are usually red, but may have yellow plasma near the surface and be red at the base as the erythrocytes settle out before clotting. This type of clot is referred to as a "chicken fat" clot and red clots are described as "currant-jelly" clots.

In contrast to postmortem clots, thrombi can be distinguished because they usually have a rough surface, presumably due to more fibrin deposition. They may be red or pale tan depending on how many erythrocytes are incorporated in the thrombus. Also, thrombi should be attached to the vascular wall at some point whereas postmortem clots are not attached. However, note that postmortem clots in the cardiac chambers will be entangled in the chordae tendinae and may appear to be attached .

The following are some of the descriptive words we use to classify thrombi. You should use these modifiers when describing thrombi if they apply.

- *Occlusive thrombi* completely fill and obstruct the vessel.

- *Venous thrombi* are in veins.

- *Arterial thrombi* are in arteries. (Who's buried in Grant's tomb?!)

- *Mural thrombi* are thrombi attached to the endocardium (i.e., wall of the cardiac ventricle or atrium).

- *Valvular thrombi* are attached to any one of the heart valves.

- *Vegetative thrombi* are septic thrombi on the heart valves that have a "cauliflower" appearance. They are almost invariably septic (have bacteria in them) as well.

- *Septic thrombi* are thrombi that contain bacteria.

- *Verminous thrombi* are caused by nematodes, usually as a result of the worm's irritation of endothelial lining.

EMBOLISM

Embolism is the detachment of an intravascular solid that is then carried by the blood stream to a distant site from its point of origin. The common types of emboli in veterinary medicine are thromboembolism and bacterial (or septic) emboli. Air and fat can cause embolisms in special circumstances.

Causes and sources of embolism:

- *Thromboembolism* occurs when a piece of a previously formed thrombus breaks away and is carried to another site forming a new thrombus.

  A most serious example of thromboembolism is the breaking loose of a large venous thrombus from the peripheral venous system. The embolus is carried to the right heart and then pushed into the pulmonary arterial tree obstructing blood flow to the lungs and resulting in sudden death. This is a very real potential problem in people who get Deep Vein Thrombosis (DVT). Another example is embolism from a verminous thrombus in the mesenteric artery obstructing smaller arteries to the large colon of the horse resulting in acute infarction of the colon.

  A common example of thromboembolism in veterinary medicine is the saddle thrombus that lodges in the terminal aorta of cats with cardiomyopathy. Can you give the pathogenesis and consequences for this lesion in the cat?

- *Septic emboli* are clusters of bacteria and platelets that are carried by blood and lodge in very small vessels or capillaries. Often, these are found in the kidneys and lungs.

  The lung is a common site for emboli because it is the first capillary bed to be encountered by blood returning from the venous side. When septic thrombi shower the lung, the disease process is referred to as embolic pneumonia.

  The heart valves are frequent sites for bacteria to lodge following a bacteremia. This may be due to endothelial damage associated with turbulence around the valves. Once a septic thrombus forms on the heart valves, pieces can break off and lodge in kidney and spleen. These emboli are called septic thromboemboli.

- *Parasitic emboli* are pieces of intravascular nematodes that break off and lodge at a distant site. This is a common complication in dogs after therapy for heartworm disease. The emboli lodge in the lungs. Bad nooz.

- *Neoplastic emboli* are aggregates of tumor cells and sometimes platelets that get swept away from a primary tumor site only to lodge in another vessel. Once tumor cells invade a vessel, small aggregates of neoplastic cells combined with adherent platelets dislodge and form emboli at distant sites. This can result in blood-borne metastasis.

- *Fibrocartilaginous emboli* happen in dogs with disc disease. The degenerating disc material gets herniated into the circulation and whirls around until it plugs something somewhere.

Consequences of embolism

Emboli can obviously result in infarction or ischemia to the affected organ. The consequences of embolism depend on the type of emboli and the vessel and organ involved. Embolism to the brain can have fatal consequences. Septic emboli spread infections and neoplastic emboli can result in metastasis.

Morphology of embolism

Embolic disease is not always easy to diagnose by gross inspection. Septic emboli tend to "shower" organs with small emboli.

ISCHEMIA AND INFARCTION

Ischemia is reduced blood flow to a tissue and can be caused by pressure, vascular constriction, thrombi, or thromboembolism. Infarction is death of tissue due to an absence of blood flow, often due to obstruction of a blood vessel. Students are often confused about the difference in these two terms. Ischemia is the process of reduced blood flow, and infarction is the name given to the morphologic lesion that results.

Causes and mechanisms of ischemia

Ischemia can result from anything that impedes delivery of blood to tissue. External pressure or constriction can cause ischemia. Pressure from recumbency on a hard surface can impede venous return. As congestion worsens, the tissue swells and ischemia occurs. Another cause for ischemia can be congestive heart failure. Improperly applied bandages and casts can result in ischemia to the distal extremities of limbs if the venous return is compromised. Swelling and edema then compromise the arterial supply.

Constriction of venous flow to the intestines from volvulus, torsions, or entrapment results in ischemia of the bowel and infarction quickly follows, if the displacement is not corrected.

Arterial thrombi and emboli are more likely to result in infarction than ischemia because they can totally obstruct the end arteries in tissues such as brain, myocardium, kidney and spleen. Lungs and liver are less likely to be totally infarcted because of collateral circulation.

Consequences of infarction and ischemia

The consequences for the animal depend on the location of the damage. Infarcts to the heart and brain can be lethal, whereas a single small infarct to the kidney may have no clinical significance. Also, the consequences are less severe in organs that have good collateral circulation. For example, the skeletal musculature and liver are rarely infarcted by the obstruction of small vessels because collateral circulation compensates, whereas obstruction of end-arteries in the kidney and brain routinely results in infarction.

Morphology of infarction

Modifiers are used to describe different types of infarcts. Venous infarcts refer to infarctions that are due to obstructed veins. These result first in passive congestion that then leads to necrosis due to hypoxia. Venous infarcts are usually dark-red or black. A twisted intestine (volvulus or torsion) results in venous infarction because the tension created by the twist collapses the veins but the more muscular arteries continue to allow some blood to be pumped into the lesion.

Arterial infarcts result from obstructed arteries and are identified primarily by sharp lines of demarcation that delineate the vascular field of that particular artery. If the tissue is solid, the infarct may be pale with red edges. If the tissue is more spongy and has good collateral circulation, the lesion may be dark-red.

White infarcts refer to pale infarcts. This pallor is a result of dead tissue that is deprived of blood. White infarcts are always arterial infarcts.

Red infarcts are red due to accumulation of blood in the infarcted tissue. Venous infarcts are always red, or at least dark. Arterial infarcts may be white or red depending on the tissue and the duration of the infarct. White infarcts may become red after dead tissue breaks down and hemorrhage from the margins of the infarct leaks into the center.

Bland infarcts do not contain bacteria. *Septic infarcts* do contain bacteria. Septic infarcts cause inflammation and spread infections, whereas bland infarcts do not.

The pathogenesis of infarction at the cellular level will be covered in a future unit. For now, you should be able to recognize the lesion and realize how thrombosis, embolism, ischemia and infarction are related, as below:

thrombosis $\rightarrow$ embolism $\rightarrow$ ischemia $\rightarrow$ infarction