INFLAMMATION

Objectives -

1. Recognize and describe lesions of inflammation
2. Outline the pathogenesis of inflammatory processes
3. Relate the various mediators to the vascular and cellular events in the inflammatory process
4. Be able to give a morphologic diagnosis

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Introduction to Inflammation

This lesson corresponds to the web lesson of the same name.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

DEFINITION AND CARDINAL FEATURES

Definition:
- Inflammation is the response of living tissue to injury. It involves a well-organized cascade of fluid and cellular changes within living tissue.

Cardinal features:
- Rubor (redness); Tumor (swelling); Calor (heat); Dolor (pain); Functio laesa (loss of function)

CAUSES
- Etiologic agents – viruses, bacteria, fungi, parasites
- Hypersensitivity – body reacts against itself, there are four types of reactions
- Physical and chemical agents - trauma, sunburn, acid
- Necrosis - anoxia, trauma

EFFECTS
What’s good about inflammation? Drugs, antibodies, mediators can get in; fibrin and then fibrosis can wall it off
What’s bad about inflammation? Cytokines can make you sick, tissue can get destroyed, swelling won’t quit
Introduction to Inflammation

What is inflammation?
Inflammation is the response of living tissue to injury. It involves a well-organized cascade of fluidic and cellular changes. It is recognizable grossly and histologically and has both beneficial and detrimental effects locally and systemically.

Some form of an inflammatory response is seen in virtually all living organisms, but the higher life forms have the unique ability to use the blood vascular system to transport and deposit fluid and cells in the extravascular space.

Some general characteristics of inflammation are as follows:

1. The inflammatory process is redundant and complex. This makes it a challenging subject to study. You will see that many mediators of inflammation have the same functions and many mediators have multiple functions. Also, the same mediator may have different effects on different tissues.
2. The process is continuous over a period of time. Peracute, acute, subacute, and chronic are terms used to describe different stages of inflammation.
3. Inflammation is caused by a stimulus and removal of the stimulus should result in abatement of inflammation. If it doesn’t get fixed in the acute period, it becomes chronic.
4. Blood is the primary delivery system for inflammatory components.
5. Inflammation is on a continuum with the healing process.
The four principal effects of inflammation (rubor, tumor, calor et dolor) were described nearly 2,000 years ago by the Roman Aulus Cornelius Celsus, more commonly known as Celsus. (He wasn’t actually a practitioner of medicine. Rather, he wrote an encyclopedia that had many volumes about all kinds of subjects. Only the volume concerning medicine survived.)

**Redness (rubor)**
An acutely inflamed tissue appears red, due to dilatation of small blood vessels within the damaged area (hyperemia).

**Swelling (tumor)**
Swelling results from edema, the accumulation of fluid in the extravascular space as part of the inflammatory fluid exudate, and to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area.

**Heat (calor)**
Increase in temperature is readily detected in the skin. It is due to increased blood flow (hyperemia) through the region, resulting in vascular dilation and the delivery of warm blood to the area.

**Pain (dolor)**
Pain results partly from the stretching and distortion of tissues due to inflammatory edema and, in part from some of the chemical mediators of acute inflammation, especially bradykinin and some of the prostaglandins.

**Loss of function (functor laesa)**
Loss of function, a well-known consequence of inflammation, was added by Virchow (1821-1902) to the list of features described in Celsus’ written work. Movement of an inflamed area is inhibited by pain, either consciously or by reflexes, while severe swelling may physically immobilize the affected area.

**Causes of Inflammation**

**Microbial infections**
One of the most common causes of inflammation is microbial infection. Microbes include viruses, bacteria, protozoa, fungi and various parasites. Viruses lead to death of individual cells by intracellular multiplication, and either cause the cell to stop functioning and die, or cause explosion of the cell (cytolytic), in which case it also dies. Bacteria release specific toxins – either exotoxins or endotoxins. What’s the difference? Exotoxins are produced specifically for export (like anthrax toxins or tetanus toxins) whereas endotoxins are just part of the cell walls of Gram negative bacteria and they do terrible things to the body too but they aren’t as specific in their actions as the exotoxins.
**Hypersensitivity reactions**
A hypersensitivity reaction occurs when an altered state of immunologic responsiveness causes an inappropriate or excessive immune reaction that damages the tissues. The types of reaction will be discussed in more detail later (In the lesson on Immune Mediated Inflammation).

**Physical agents, irritant and corrosive chemicals**
Tissue damage leading to inflammation may occur through physical trauma, ultraviolet or other ionizing radiation, burns or excessive cooling ('frostbite'). Corrosive chemicals (acids, alkalis, oxidizing agents) provoke inflammation through direct tissue damage. These chemical irritants cause tissue damage that leads directly to inflammation.

**Tissue necrosis**
Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow (infarction) is a potent inflammatory stimulus. The edge of a recent infarct often shows an acute inflammatory response.

**Effects of Inflammation**
The effects of inflammation can be both local and systemic. The systemic effects of acute inflammation include fever, malaise, and leukocytosis. The local effects are usually clearly beneficial, for example the destruction of invading microorganisms, but at other times they appear to serve no obvious function, or may even be harmful.

<table>
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<td>Persistent cytokine release</td>
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**Systemic Effects of Inflammation**
Both acute and chronic inflammation, even if well localized, can have effects on the whole body. The main ones are:

**Leukocytosis**
*Leukocytosis* is a common feature of inflammatory reactions. Leukocytosis means that there is an abnormally high number of circulating white blood cells. A general rule is that increased neutrophils indicate a bacterial infection whereas increased lymphocytes are most likely to occur in viral infections. This is one reason why we often do a CBC when an animal is sick – gives us more clues.

**Fever**
*Fever* is a common systemic response to inflammation. Fever is most often associated with inflammation that has an infectious cause, although there are some non-infectious
febrile diseases. Fever is coordinated by the hypothalamus and involves a wide range of factors. Here are some of the contributors to fever:

What is the function of fever? The elevation of body temperature is thought to improve the efficiency of leukocyte killing and may also impair the replication of many invading organisms.

**Endotoxemia**

Sepsis is the term used for disease due to toxic bacterial products circulating in the blood. Endotoxemia specifically refers to circulating gram-negative bacterial toxic products (LPS). There are some cell wall products released from gram-positive bacteria that can have a similar toxic effect.
Acute Inflammation

This lesson corresponds to the web lesson of the same name.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

Inflammation has VASCULAR and CELLULAR events:

1. VASCULAR EVENTS
   
   Vasodilation
   
   And then increased Vascular permeability

2. CELLULAR EVENTS
   
   Cells move out of the vessels into the area of inflammation using chemotaxis
   
   Inflammatory cells become activated and then can phagocytose offending materials
ACUTE INFLAMMATION

In the early stages of inflammation, the affected tissue becomes reddened, due to increased blood flow, and swollen, due to edema fluid. These changes are the result of vascular response to inflammation. The vascular events of the acute inflammatory response involve three main processes:

1. changes in vessel caliber and, consequently, blood flow (hemodynamics)
2. increased vascular permeability and
3. formation of the fluid exudate

1. Changes in Vessel Caliber

The microcirculation consists of the network of small capillaries lying between arterioles, which have a thick muscular wall, and thin-walled venules. Capillaries have no smooth muscle in their walls to control their caliber, and are so narrow that red blood cells must pass through them in single file. The smooth muscle of arteriolar walls forms pre-capillary sphincters that regulate blood flow through the capillary bed. Flow through the capillaries is intermittent, and some form preferential channels for flow while others are usually shut down. In other words, there is not blood flowing through all capillaries all the time. They take turns. When inflammation happens, none of them gets to take their scheduled tea break. They are all open.

Experimental evidence indicates that blood flow to the injured area may increase up to ten-fold as vessels dilate. What causes this to happen? MEDIATORS - including nitric oxide, histamine and prostaglandins (PGI₂) and LTB₄.

2. Increased vascular permeability

In acute inflammation, the capillary hydrostatic pressure increases, and there is also escape of plasma proteins into the extravascular space due to increased vascular permeability (endothelial contraction allowing proteins to escape between cells). Consequently, much more fluid leaves the vessels than is returned to them. The net escape of protein-rich fluid is called exudation; hence, the fluid is called an exudate.
What causes the increase in vascular permeability in acute inflammation?

There are two mechanisms –

- Chemical mediators of acute inflammation may cause retraction of endothelial cells, leaving intercellular gaps (chemical mediated vascular leakage).
- Toxins and physical agents may cause necrosis of vascular endothelium, leading to abnormal leakage (injury induced vascular leakage).

3. Formation of the Cellular Exudate

How do white blood cells get out of the circulation and into the area where they are needed?

Cells are called out to the area of inflammation in a process called CHEMOTAXIS.
Chemotaxis of leukocytes

The movement of leukocytes from the vessel lumen in a directional fashion to the site of tissue damage is called chemotaxis. All granulocytes and monocytes respond to chemotactic factors and move along a concentration gradient (from an area of lesser concentration of the factor to an area of greater concentration of the factor).

**Important neutrophil chemotactic factors**

**Bacteria are strongly chemotactic for neutrophils**
- C5a, C3a
- Fibrin, fibrinopeptides
- Leukotriene B₄ (LTB₄)
- IL-8 (a chemokine, from macrophages)

**Important eosinophil chemotactic factors**
- Histamine
- IL-5 (also known as eotaxin, a chemokine, from mast cells)

**Important monocyte chemotactic factors**
- Complement factors
- Fibrinopeptides

Okay, now the WBCs are where they were meant to be. What’s next? Now they attack the offender.
Microbicidal Activity of Leukocytes

Leukocytes play a very important role in microbial killing. In any inflammatory response, leukocyte activation is a prerequisite to their full participation in the process. Leukocytes become activated during inflammation.

Leukocytes and phagocytosis

The process whereby cells ingest solid particles is termed phagocytosis. The first step in phagocytosis is adhesion of the particle to be phagocytosed to the cell surface. The phagocyte ingests the attached particle by sending out pseudopodia around it. These meet and fuse so that the particle lies in a phagocytic vacuole (also called a phagosome) bounded by cell membrane. Lysosomes, membrane-bound packets containing the toxic compounds, then fuse with phagosomes to form phagolysosomes. It is within these that intracellular killing of microorganisms occurs.

Intracellular killing of micro-organisms by leukocytes

Neutrophils and macrophages are specialized cells, containing noxious antimicrobial agents. Neutrophils produce hydrogen peroxide (bactericidal by itself) which reacts with myeloperoxidase in the cytoplasmic granules to create oxygen radicals which are wickedly damaging. Antibacterial cationic proteins, lysozyme, and defensins all affect bacterial permeability so the bacteria leak to death.

- Release of lysosomal products from the cell damages local tissues and can kill microorganisms outside of the cell. Enzymes such as elastase and collagenase will chew through tissue. Some of the compounds are pyrogens, producing fever by acting on the hypothalamus. Acid hydrolases degrade tissue matrixes.
Chronic Inflammation

This lesson corresponds to the web lesson of the same name.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

**Definition:**
Host response to an inciting stimulus that goes on for weeks or months

**Characteristics:**
- Not usually red or hot (unlike acute inflammation)
- Do not “ooze”
- Productive or proliferative
- Often present in infections with higher order organisms (mycobacteria, fungi, metazoan parasites) and in many autoimmune diseases

**Histologic appearance:**
- Primarily mononuclear cells involved
- Fibroblasts and new blood vessels, together called “granulation tissue”

**Granulomatous inflammation**
- Is always chronic
- Is composed predominantly of macrophages
- May have multinucleate giant cells – macrophages fuse
Chronic Inflammation

Chronic inflammation, like its acute cousin, is a host response to an inciting stimulus. There are, however, some distinct differences. First and foremost is the time factor. Chronic inflammation is considered to be inflammation of prolonged duration - weeks to months. Second, rather than being just exudative, chronic inflammation usually is productive or proliferative. Chronic inflammation is rarely gooey. Cells in the chronic inflammatory process tend to produce substances that add new tissue, such as collagen and new blood vessels. Many of these changes also represent the repair process and there is a blurry continuum between chronic inflammation and the whole repair process. In general, chronic inflammation is characterized by inflammation, tissue destruction, and attempts at repair all happening at once.

Grossly, chronic inflammation does not have as much rubor (redness) or calor (heat) as in the acute reaction. Also, exudates aren’t so grossly apparent as they are in acute inflammation. Because of the fibroplasia and neovascularization, areas affected by chronic inflammation tend to be slightly swollen and firm. If fibrosis is extensive the lesions can be large and disfiguring. Fibrosis (granulation tissue) is the best indicator that the inflammatory response is chronic.
Chronic inflammation tends to occur under the following conditions:

Infections by *organisms which are resistant to killing and clearing* by the body tend to cause chronic inflammation. Such persistent organisms include some of the higher bacteria (including mycobacteria), fungi, and quite a few metazoan parasites. *Repeated bouts of acute inflammation* can result in a chronic reaction. *Prolonged exposure to toxins* can cause chronic inflammation. Chronic inflammation is a common component in many of the *autoimmune diseases*. Because the reaction is against a host epitope, which is always present, the inflammation is by definition chronic and persistent.

Because chronic inflammation doesn’t ooze, rather its exudates tends to be kind of solid and white or grayish and it looks the same no matter what the cell types, the only way to add an exudative moniker is to see the histology. Here are the cell types:

1. The simplest type of chronic inflammation has mostly lymphocytes with lesser numbers of macrophages. This will occur mostly in viral infections where the virus survives longer than the acute phase. This is called “lymphohistiocytic”.
2. **Chronic active** inflammation is the same but in this one there are still some neutrophils present, so there are acute things going on inside of the chronicity. This happens in many bacterial infections that are not due to very pus-producing bacteria.
3. Next is **granulomatous** - here the cell types are almost all macrophages. Good examples here are fungal infections or mycobacteria.
4. Some people use a term **pyogranulomatous** - which means granulomatous but within the macrophages are pockets of neutrophils. The most common disease causing this is FIP.
5. **Granulomas** occur when the inciting cause stimulates macrophages but the agents are distributed discretely within an organ. Think TB. Think *Blastomyces*. Think foreign body.

**But with all of these types, there is evidence of fibroblasts moving in and some new blood vessels.**

If plasma cells are present in the inflammation, you know two things. First, it is a chronic problem because it takes a good 2-4 weeks to generate plasma cells. Second, there must be some persistent antigen in there, because plasma cells indicate the body needs plenty of antibody at the site.
Granulomatous inflammation

There is one specific subset of chronic inflammation that deserves special attention, and that is granulomatous inflammation. Histologically, it is very characteristic and is described below.

Granulomatous inflammation is any inflammatory response consisting predominantly of macrophages
Macrophages often differentiate into cells called epithelioid macrophages and these cells are found within granulomatous infiltrates. Their cytoplasm is abundant and finely granular, with indistinct cell boundaries, so that they resemble epithelial cells more than macrophages (hence the name - epitheliOID). Ultrastructurally, these cells contain abundant rough endoplasmic reticulum and a prominent Golgi apparatus but are poor at phagocytosis. Consequently, their role is believed to be biosynthesis and protein secretion.

A granuloma is a focally discrete chronic inflammatory reaction comprised predominantly of epithelioid macrophages that are organized or aggregated in closely packed collections. There is often a central core of caseous debris at the center of the granuloma surrounded by macrophages that in turn are encircled by a ring of lymphocytes and organizing fibroblasts.

Other cell types unique to granulomatous inflammation include the multinucleate giant cells, sometimes called Langhans cells. These are cells formed by the fusion of macrophages and they can look pretty spectacular under the microscope. But they are poorly phagocytic. Seeing giant cells means – hey, our regular old standard issue macrophages couldn’t take care of this problem, so we had to band together. Very often it is a big old problem, too large to phagocytose, like a foreign body, or a fungus.
Morphologic diagnosis in inflammation

This lesson corresponds to the web lesson of the same name.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

MORPHOLOGIC DIAGNOSIS

COMPONENTS OF A MORPHOLOGIC DIAGNOSIS FOR INFLAMMATION:

1. Severity
   Mild, moderate, severe

2. Time course
   Peracute, acute, subacute, chronic

3. Distribution of lesion
   Focal?
   Multifocal?
   Locally extensive?
   Diffuse?

4. Type of Exudate
   Difference between exudates and transudate
   Serous
   Fibrinous
   Catarrhal
   Purulent
   Abscess
   Hemorrhagic
   Mixed

5. Inflammatory name associated with the organ - usually it is just -itis, but there are exceptions.
Morphologic diagnosis in inflammation

A morphologic diagnosis is the way we describe and communicate about lesions. A morphologic diagnosis consists of a series of terms that serve to paint a picture with words. The important categories of words to include in your morphologic diagnosis include –

**KNOW THIS TABLE:**

| S | SEVERITY | How bad is it? Mild or moderate or marked/severe? |
| T | TIME COURSE | Is it peracute, acute, subacute or chronic? |
| D | DISTRIBUTION | Is it focal, multifocal or diffuse? |
| E | EXUDATE | What is the character of the inflammatory material - serous, catarrhal, purulent, fibrinous, granulomatous, fibrosing? |
| T | TISSUE | Where the heck is it? (plus -itis) |

So, every inflammatory lesion *could* consist of FIVE WORDS.

1. **Severity**

The terms we usually use to describe severity are subjective – mild, moderate, severe. Some people use “marked” instead of “severe.” Is the problem causing serious compromise (marked)? Or is it just a little thing that is an annoyance (mild)? You’ll get used to figuring out which word to use here.

2. **Time course designation for inflammation**

*Peracute* happens so fast you hardly even know it has happened. A good example would be a serious myocardial problem where the animal dies before there is even any evidence, clinically, grossly, or histologically, that the heart was damaged. *Acute inflammation* is short-lived, lasting only a few hours to a few days. If it persists for an extended period, like more than two weeks or so, then it is referred to as chronic inflammation. The hallmark of *chronic inflammation* is the formation of *fibrous connective* tissue (starts as granulation tissue) in the area of inflammation. An abundance of *macrophages* also may be a feature. This fibrous connective tissue formation results in organization or scarring.

You may have noticed there is a little bit of a time gap between acute and chronic - the term *subacute* can be used here.
Peracute \(\rightarrow\) Acute \(\rightarrow\) Subacute \(\rightarrow\) Chronic

3. **Extent of Lesion**

![Diagram of lesion extent](image)

This may be the easiest part of the morphologic diagnosis. If just one small part of the organ is affected, it is FOCAL. If there are several small parts affected, it is MULTIFOCAL. If the whole organ is affected, it is DIFFUSE. But what if it is diffuse, but just in one part of the organ? Then it is FOCALLY (or LOCALLY) EXTENSIVE.

4. **Types of Exudates**

**Serous exudate**

Serous inflammation is characterized by the outpouring of a translucent, thin fluid that may accumulate on a mucosal surface, skin, or in the peritoneal, pleural, and pericardial cavities. Serous inflammation is a common manifestation of the acute inflammatory reaction and usually indicates the insult is mild. What does it look like? Think of a mild skin wound - the clear to yellowish fluid that oozes out is serous exudate. Other examples would include the fluid that
accumulates in a blister or a runny nose in hay fever. Serous exudates are usually the result of a mild, often transient irritant.

*What is the significance of a serous exudate?* It may just be the early phase of a more intense exudate and a warning of a more serious problem to follow.

![Serous exudate on an ulcerated sarcoptic mange site. Just oozing clear fluid – this is serous exudate.](image1)

![Serous fluid accumulating within the pericardial sac. Hydropericardium is really serous exudate.](image2)

*What is the outcome of a serous exudate?* If it doesn’t progress to something worse, the fluid is reabsorbed as the inflammation resolves.

**Fibrinous exudate**

Fibrinous exudation occurs in more severe conditions that allow the escape of larger fibrinogen molecules from the vascular system. As the vascular damage becomes more marked, instead of just serous fluid seeping out, fibrinogen gets out as well. When fibrinogen reaches the tissue it is converted to fibrin, which is the chief component of this type of inflammation.

*What is the gross appearance of fibrinous exudation?* Fibrinous inflammation occurs chiefly on mucous and serous membranes. Prime locations include the entire respiratory and digestive tracts, pleura, peritoneum, and pericardium.
Fibrin in the opened thorax of a horse. Very YELLOW (typically very yellow in horses) and STRINGY.

Fibrin on the mucosal surface of the intestines in a cow with salmonellosis. String-like.

In the earliest phases, the surface with a fibrinous exudate has a slightly roughened appearance, and will be slightly dull and granular. Think buttered bread, dropped butter side down on the floor. Pick it up – fibrin deposition looks like this. As the deposition of fibrin increases, there will be yellowish strands present. These can be peeled off. If the insults are repeated, these yellowish strands can accumulate into a carpet of fibrin. This thick layering of fibrin that can be peeled away is termed a pseudomembrane. If there is extensive necrosis of underlying areas so that the fibrin is tightly adhered to the tissue and is harder to peel away, it is called a diphtheritic membrane. This term diphtheritic membrane came from human diphtheria, caused by Corynebacterium diphtheriae. If there is so much fibrin that it gushes out and forms a large accumulation mimicking the shape of the tubular organ, then it is termed a fibrin cast. This happens in very severe intestinal infections, such as parvovirus in dogs or salmonellosis in cattle.

What is the outcome of fibrinous inflammation? If it is not too severe, it may resolve without any sequelae. If it is extensive, fibroblasts may migrate in and begin organizing the exudate through the generation of fibrous connective tissue. Sometimes this can be harmful. For instance, with fibrinous inflammation in the peritoneal cavity, two fibrin-covered serosal surfaces of gut may stick to each other. If fibroblasts come in and make permanent connections, then two loops of intestine are stuck to each other forever. This will impede gut motility! Other places this can be bad is in the pericardium or pleura. Fibrous adhesions will impede function as heart or lungs need to be able to slip around freely inside those spaces and not be anchored by fibrous adhesions. As this connective tissue formation process begins, we refer to it as “organizing.” Once it is fully organized, it is “fibrous tissue.” Please remember that fibrosis or fibrous tissue is NOT a type of inflammation, it is growth of new cells and laying down of collagen leading to repair. The two terms FIBROUS and FIBRINOUS are just way too similar SOUNING. It is unfortunate because the processes they represent are HUGELY DIFFERENT.

Fibrin = acute. Fibrous = chronic. BIG DIFFERENCE
**Catarrhal exudate**

Catarrhal exudate is a term that is not used very often. It represents excessive mucus production and so can only be used for inflammation in organs where mucus is already being produced. It is most often associated with the mucosal surfaces of the intestinal, reproductive, and respiratory tracts. It is seen in mild or persistent infections of these areas. Sometimes the word “mucous” used synonymously with catarrhal.

What does catarrhal exudate look like grossly? Catarrhal inflammation appears as a thin gray-yellow blanket of excess mucus. Think snot.

So far, we have covered non-cellular exudates. Now we’ll move into those exudates that contain cells as a primary component.

**Purulent exudate**

Purulent exudate is PUS. Pus is an accumulation of dead neutrophils. Neutrophils have enzymes that help to liquefy the surrounding tissue, and so the result is a homogenous mass of creamy pus. Think humus. Think vanilla pudding. Another term for purulent inflammation is suppurative. The two can be used interchangeably. Pyo- is the prefix for anything with pus - pyothorax, pyometra. Pyogenic bacteria are, by definition, bacteria that promote the body’s production of pus. They are strongly chemotactic for neutrophils which accumulate and turn into…pus.
Abscess in a vertebral body. Pus can look sort of dry like this. Or, it can be very fluid, as in this pyometra.

*What does purulent exudate look like grossly?* The consistency may vary somewhat, depending on the host species, the inciting agent, and duration. If pus is present for a while and the inciting agent is removed, the pus becomes dry, or “inspissated”. Also, the color may vary due to the inciting agent. Almost all cases of pus formation are due to bacteria. If the purulent inflammation is well circumscribed and surrounded by a fibrous wall or capsule, it is called an *abscess* (see box below).

*What is the significance of purulent inflammation?* This is a prompt and violent reaction against irritants and pathogens. The neutrophils are moving in to neutralize the offending agent. In 99% of cases, bacteria will be in there, or HAD been in there.

*What are the outcomes?* One consequence is that localized purulent inflammation can break loose and spread to other areas. This may result in septicemia if infection spreads to the blood stream. If it does not spread, the resorption of pus is not without ill effects, including fever and general signs of illness. If purulent inflammation is close to a body surface, it often discharges to the outside, which is much better. Sometimes it does this through the formation of a fistulous tract.
An **abscess** represents a subset of purulent inflammation. An abscess is defined as a discrete accumulation of pus surrounded by a fibrous capsule. They are usually formed in response to a focal bacterial infection. The neutrophils are unable to fully overcome the infection and if they accumulate in large enough numbers, the body responds by walling off the focus of infection with a circumferential band of collagen. Although the inciting cause is now effectively separated from spreading to other parts of the body, the fibrous wall also prevents delivery of antibiotics to the site.

Oops – hard to treat!

**Hemorrhagic exudate**

Hemorrhagic exudates are characterized by large numbers of erythrocytes. The holes in the blood vessels are large enough that everything comes out so that the appearance of the exudate is very much like blood. Hemorrhagic exudates are usually mixed with serum, fibrin, and leukocytes. Distinguishing hemorrhagic exudates from simple hemorrhage can be problematic.
What is the significance of hemorrhagic inflammation? This type of inflammation is usually caused by highly virulent microorganisms or by acute poisoning by certain chemicals. It arises quickly and is often fatal. There is massive damage to endothelium.

What is the outcome of hemorrhagic inflammation? Often very serious.

- **Mixed exudates**

Mixed exudates are more common than simple ones because the inflammatory process frequently persists long enough to evoke the exudation of more than one type of exudate. Lots of word combinations - fibrinohemorrhagic, mucopurulent, etc.

- **Granulomatous “exudate”**

These represent exudates where the majority of cells are macrophages. However, these exudates don’t usually “ooze”. They are not usually WET.
Designation of organ or location

The location of inflammation is designated in the morphologic diagnosis by using a prefix that refers to the organ and the "itis" suffix. For example: inflammation of the skin = derma + titis; inflammation of the bone marrow = osteomyel + itis. Before moving to the next topic, review the more extensive list of prefixes in the table below. Practice adding “itis” to the end of each prefix to name an inflammatory process in the designated organ or tissue.

COMMONLY USED ANATOMIC PREFIXES FOR INFLAMMATION (-itis)

Arter .............................................. artery
Arthr ............................................. joint
Balan ............................................. glans penis
Blephar ........................................ eye lid
Bronch ......................................... bronchi
Burs .............................................. bursa
Cellul ........................................... connective tissue
Cheil ............................................... lip
Cholecyst ...................................... gall bladder
Col .................................................. colon
Conjunctiv ..................................... conjunctiva
Dermat .......................................... skin
Encephal ....................................... brain
Endocard ...................................... endocardium
Enter ........................................... intestine
Esophag ......................................... esophagus
Funicul ......................................... spermatic cord
Gastr ............................................. stomach
Gingiv ........................................... gum
Gloss ............................................. tongue
Hepat ............................................ liver
Kerat ............................................. cornea
Lamin ............................................. hoof
Laryng .......................................... larynx
Lymphaden ................................. lymph nodes
Mening ......................................... meninges
Metr ............................................... uterus
Myel ............................................. spinal cord
Myocard ....................................... myocardium
Myos ............................................. muscle
Nephr ............................................. kidney
Odont .......................................... tooth
Omphalo ....................................... umbilicus
Oophor ......................................... ovary
Ophthalm ..................................... eye
Orch ............................................. testicle
Oste ............................................. bone
Osteomyel ................................. bone marrow
Ot ............................................... ear
Pericard ........................................ pericardium
Splen ............................................ spleen
Trache ......................................... trachea
Periost ........................................ periosteum
Cellular Components of Inflammation

This lesson corresponds to the web lesson of the same name.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

GRANULOCYTES

*Neutrophils*
- Usually most abundant cell in the blood
- Important in acute inflammation (first cell to arrive)
- Nucleus is multilobed (starts out with only two lobes, kind of like a horseshoe, or "band")
- Very phagocytic
- Neutrophil-specific, or secondary granules, contain lysozyme, collagenase
- Short-lived once in tissue, from 6-72 hours
- End stage cell, don’t divide

*Eosinophils*
- Have big pink or red granules, with Major Basic Protein, which will help to kill parasites
- Live 8-12 days
- End stage cell, don’t divide

*Basophils and mast cells*
- Different origin of each of these cells but similar function
- Not very many anywhere, in blood or in tissue
- When you see them, it usually means allergy
- They are strongly chemotactic for eosinophils so the two cell types may occur together
- Can continue to divide, even when in tissue
- Can be powerful vasodilators (‘cause they got lots o’ histamine)

MONONUCLEAR CELLS

*Lymphocytes*
- Small round cells with large non-lobed nucleus
- Come in B cell and T cell varieties

*Mononuclear phagocytes*
- Big cells, lots of cytoplasm, big indented nucleus
- Monocytes in blood become macrophages when they go to the tissue
- Can live for as long as one month in tissue
- Heavy duty phagocytes
Cellular Components of Inflammation

In order to understand types of inflammation, it is essential to grasp the different categories of inflammatory cells, to be able to recognize them morphologically, and to understand the different situations in which they occur.

Granulocytes
Granulocytes consist of neutrophils, eosinophils, basophils, and heterophils in some species.

🌟 Neutrophils

Neutrophilic leukocytes are also known as polymorphs, “polys”, and polymorphonuclear cells. In some species, notably guinea pigs, birds and rabbits, the term heterophil is used to describe the functional counterpart. These cells are key cells involved in the earliest events associated with inflammation.

Neutrophils are formed in the bone marrow from granulocytic stem cells, the myeloblasts. What causes their release from the bone marrow when needed in inflammation? The nucleus of a very immature neutrophil is slightly indented; after that, it assumes a “band” shape. As the neutrophil
continues to mature, the nucleus becomes hyper-indented to take on a multilobed configuration with multiple constrictions (therefore called PolyMorphoNuclear cells, or PMNs). Even with the vast numbers of neutrophils in the body, there are severe infections in which tissue demand exceeds the vascular supply. The body responds by releasing neutrophils from the storage pool in the bone marrow to increase the number in the circulation. This increase is called a neutrophilic leukocytosis. If the tissue demand for neutrophils persists or increases, many of the immature forms, or “bands,” will be released as well. This is referred to as a “left shift.”

Neutrophils leave the blood in response to tissue damage. They migrate rapidly to areas where they are needed. Bacteria have factors that are very chemotactic for neutrophils.
Neutrophils have a short half-life. Depending on the severity of the lesion, they survive hours to a couple of days at a site of inflammation. They last less than a day in blood.

Once at the site, neutrophils’ main functions are to phagocytose small particles and kill microbes. There are three phases to phagocytosis. First, the particles must attach to the cell surface. Then the particle must be ingested. Third, the particle has to be digested within the cell. Attachment is greatly enhanced if the particle is coated, or opsonized, by specific IgG antibodies or non-specific C3b fragments from plasma.

Ingestion occurs after the particle has attached to the cell. Pseudopodia extend to surround and engulf the material, creating a phagosome, and internalizing the particle.

Digestion occurs when the lysosomes move toward the phagosome and eventually fuse, emptying their enzymes into the pocket, and inactivating the particle.

Neutrophils are the most common cell in purulent exudate. In fact, that’s what pus is - an accumulation of dead neutrophils. Most bacteria produce very strong chemotactic factors that attract neutrophils. Consequently, any accumulation of pus should make you think that bacteria are present.

How can you recognize neutrophils in tissue microscopically? The multilobed nucleus makes this cell an easy one to recognize.

As neutrophils die in large numbers within inflamed tissues, their contents are released into the extracellular fluids. Their enzymes cause local tissue digestion with liquefaction which mixes with the pus and makes it all more liquid.
**Eosinophils**

Eosinophilic granulocytes are so called because of the presence of big red-pink cytoplasmic granules. Eosin is the pink stain and because the granules pick up so much of the stain, the cells are “eosin-loving” or eosinophils. The eosinophilic granules vary in size in the different species, being large and prominent in the horse, and quite small and almost inconspicuous in the cat. The granules contain Major Basic Protein, which is toxic to parasites.

Eosinophils are similar to neutrophils in their maturation and release sequences, but there are not very many of them in the blood. Like neutrophils, eosinophils are also end cells that do not replicate after release. Extravascularly, they are slightly more long-lived than neutrophils, on the order of 8-12 days. Eosinophils are commonly found in mucous membranes.

What do they look like in tissue? Hooray, eosinophils are the easiest cell to recognize, especially in horses, where the granules are especially big and bright.

---

**Eosinophils**

- surrounding fungi and metazoan parasites in tissues
- hypersensitivity reactions, including allergy and anaphylaxis
- certain tumors, especially mast cell tumors (why? Because mast cells attract eosinophils!)
- in the brain of pigs and cattle poisoned by excess salt, or prolonged water deprivation (Why? No clue - nobody knows!)

Some of the strongest chemotactic factors for eosinophils include histamine and IL-5 (also known as eotaxin), both of which come from mast cells.

Eosinophils are very effective at killing metazoan parasites. They attach via antibody and then release their Major Basic Protein which causes parasites to disintegrate.
Basophils and Mast Cells

Both basophils and mast cells possess distinct spherical basophilic to metachromatic cytoplasmic granules.

**Basophils** are the third type of granulocytic leukocyte. Produced in the bone marrow, they occur in the circulation in very low numbers. They emigrate into extravascular tissues at sites of inflammation. They have a multilobed nucleus.

**Mast cells** are widely distributed in connective tissue and mucosal tissues throughout the body. They are particularly abundant in skin, gastrointestinal mucosa, and respiratory tract, all the host-environment interfaces. Nucleus is round to oval and contains a prominent nucleolus.

These cells are not phagocytic and are only sluggishly motile. Their main function is the degranulation of their cytoplasmic contents when stimulated. This degranulation releases a number of preformed proinflammatory products, including histamine, serotonin, eotaxin (IL-5), and heparin.

The degranulation of these cells usually is dependent on prior fixation of antibody (IgE) to the cell surface at Fc receptors and subsequent binding of antigen to these antibodies. This is the primary mechanism of degranulation in allergic responses. However, there are other mechanisms of mast cell degranulation including binding of C5a and C3a.

The end result is increased vascular permeability, vasodilation, anticoagulation, tissue destruction, and attraction of eosinophils. Basophils and mast cells are not end stage cells and both are capable of continued division at the site of inflammation.
**Mononuclear cells**

**Lymphocytes**

There are many types of lymphocytes but all appear similar morphologically. They are small round cells with a round, hyperchromatic nucleus and scant, light blue staining cytoplasm. Under the microscope, T and B cells look the same.

When B cells start to produce antibodies, they turn into…..

**Plasma cells** have a unique appearance. They have more cytoplasm than a lymphocyte and this is often basophilic, with a pale area or “halo” just next to the nucleus. This “halo” represents the Golgi apparatus. The nucleus is usually eccentrically placed and the chromatin often is clumped at the periphery, creating a “clock-face”. Takes a little imagination to see the clock, in my opinion.

Seeing numerous plasma cells in an organ or a lymph node is an indication of chronic antigenic stimulation.
Mononuclear phagocytes

The term *macrophage* means “big eater.” Macrophage is the term we use to describe a monocyte that has emigrated from the blood to the tissue. In addition, macrophages are routinely found in a number of organs, as fixed cells within the vasculature, sampling all the material that floats by. Some of these fixed macrophage cells include: Kupffer cells in the liver, pulmonary intravascular macrophages (PIMs) in the lung, sinusoidal lining cells in the spleen, and microglia in the CNS.

Macrophages do not divide at the site of inflammation. Compared to neutrophils, they are more long-lived, surviving at an inflammatory site for as long as a month. They are also slower to arrive at the site of inflammation, usually taking about 48 hours to get there.

They appear as large cells with bean shaped or oval nuclei with fine, diffusely scattered chromatin. The cytoplasm stains a pale pinkish-blue and may contain vacuoles or particulate debris.

The functions of macrophages are phagocytosis and destruction of foreign material and presentation of antigen to lymphocytes.

In addition to their phagocytic function, activated macrophages produce and secrete a wide variety of biologically active substances. Some of these include: cytokines, toxic oxygen metabolites, proteases, nitric oxide, growth factors that promote fibrosis, and angiogenesis factors. As such these cells are central figures in subacute and chronic inflammation.
When the inciting cause remains for a long time, often macrophages will fuse, creating an unusual cell, the multinucleated giant cell.

“Let’s join forces to fight the enemy.”
SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

There are 4 main types of immune-mediated disease, or hypersensitivity:

Type I – IMMEDIATE
- “allergic” or “anaphylactic” type
- Dependent on production of IgE (some individuals make more than they should)
- On re-exposure, IgE binds mast cells and basophils, releasing vasoactive amines and other mediators
- Result is local inflammation, edema
- Examples of local Type I: hay fever, urticaria
- Systemic Type I: anaphylaxis

Type II – CYTOTOXIC
- Production of IgG or IgM, they attach to target cells
- Then, one of three things happens, any of which kills the cell:
  1. Complement attaches, punching a hole in the cell or facilitating phagocytosis
  2. Killer cells attach to the antibody and kill the cell (ADCC)
  3. Antibody kills the cell by binding to a key molecule
- Examples: immune-mediated anemia, myasthenia gravis

Type III – IMMUNE COMPLEX
- Requires persistent antigenemia, to which host makes lots of antibody
- Many antigen-antibody complexes floating around
- Some IgE gets produced, increased vascular permeability
- Antigen-antibody complexes get lodged in the vessel wall, glomerulus
- Complement is activated, pulls neutrophils in, they chew up vessel wall
- Example: membranous glomerulonephritis

TYPE IV - DELAYED
- Is mediated by CELLS rather than antibodies
- Occurs 24-48 hours after antigen is presented
- Most cells in the reaction are mononuclear
- Example: tuberculin reaction
**IMMUNE MEDIATED INFLAMMATION**

**Introduction**

*Immune mediated inflammation* is simply inflammation that is **caused by** the immune response. All immune responses are directed by lymphocytes. Therefore, lymphocytes and their products drive immune mediated inflammation.

The immune response is not supposed to damage body tissues. Those immune-mediated reactions that DO damage normal tissues are called *Hypersensitivity Reactions*. There are four basic types. In reality, many reactions are combinations of two or more types with one type predominating.

**Type I - Anaphylactic or allergic hypersensitivity**

These reactions include allergic reactions, anaphylaxis, and atopy. Type I reactions can be localized allergy or generalized anaphylaxis. The reaction is mediated by production of IgE by plasma cells in response to certain antigens. IgE binds to mast cell and basophil Fc receptors. These cells are now specifically sensitized to a given antigen, and upon re-exposure to the antigen, IgE binds the antigen causing immediate degranulation and synthesis of inflammatory mediators by mast cell.

Histamine, heparin and serotonin are preformed in mast cell granules. Therefore, they are released immediately upon degranulation causing vasodilation and increased vascular permeability. Increased permeability of vessels means EDEMA.

**Examples of Type I hypersensitivity:**
- hay fever,
- urticaria,
- atopy,
- anaphylaxis
First exposure to antigen causes plasma cells to produce IgE that binds to Fc receptors on mast cells and basophils. You have to see it once in order to be RE-exposed, which is the time when the hypersensitivity reaction kicks in.

There are also some mediators released that cause smooth muscle contraction (bronchospasm - in asthma).

Why do some individuals develop allergies and others don’t? It’s simple. Those who are allergy-prone make more IgE that what is useful. Normal individuals synthesize only small amounts of IgE when exposed to the antigens and higher amounts of IgG and IgM.

**Anaphylaxis**
Systemic anaphylaxis occurs when antigen is systemically distributed in a highly sensitized individual. It is a generalized reaction mediated by mast cell and basophil granule release. Principal mediators include histamine and cytokines. The reaction is characterized by smooth muscle contraction in lungs and intestines, vasodilation, increased vascular permeability,
hypotension, vasomotor collapse, and pooling of blood in shock organs. Basically, death. Domestic animals are less susceptible to anaphylactic shock compared to humans.

**Special cases of type I reactions in veterinary medicine:**
- **Milk allergy in Jersey cattle** - Due to missed milking, milk proteins (alpha casein) get into circulation and act as antigens causing an allergic reaction. There is urticaria and sometimes life threatening anaphylaxis.
- **Allergies to vaccines and drugs** are not uncommon.
- **Chronic obstructive pulmonary disease** (COPD, also known as heaves) happens in horses that inhale fungal allergens from dusty hay.
- **Warble fly larvae in cattle - Hypoderma bovis** pupae develop under skin after larvae migrate from heel to back. If pupae rupture an anaphylactic response can occur.
- **Fly bite allergy** - Horses may also develop type I allergies to *Culicoides* and *Simulium* fly bites.

**Type II - Cytotoxic Hypersensitivity**

These reactions are also called cytotoxic or cytolytic because host cells are killed or undergo lysis after reacting with antibody. This Type II, or Cytotoxic, Hypersensitivity depends on the abnormal production of IgG or IgM directed against tissue antigens or a normal reaction to foreign antigens expressed on host cells, as shown in the diagram above.

An example of Type II hypersensitivity is neonatal isoerythrolysis in horses.
**Type III - Immune-complex hypersensitivity**

The third type of immunologic injury is also called *immune-complex mediated hypersensitivity*. At the center of the pathogenesis is an antigen that won’t go away or can’t be neutralized, so there are too many antigen-antibody complexes in the circulation. Immune complex disease is seen in persistent infectious diseases. There are too many antigen-antibody complexes, they settle out in blood vessels. Complement attacks them, causing increased permeability and inflammation of the vessel wall.

Rules of engagement for Type III:

1. Exposure to antigen causes plasma cells to produce IgG or IgM.
2. In conditions of persistent antigenemia and slight antigen excess, soluble antigen- antibody complexes form.
3. Deposition can be generalized (i.e. acute serum sickness) or localized (i.e., glomerulonephritis, Arthus reaction).
4. Examples include hypersensitivity pneumonia and immune complex glomerulonephritis. Organs with fenestrated endothelium are particularly susceptible. Examples include the glomerulus, synovium, and uvea.

Examples of Type III hypersensitivity: rheumatoid arthritis, membranous glomerulonephritis
When there are too many ag-ab complexes circulating, some get “stuck” in the glomerulus. This disrupts the membrane structure of the glomerulus and makes it leaky. Normally proteins don’t pass through the glomerulus into the urine but when the membrane is all disrupted, they can. So, animals with membranous glomerulonephritis often are losing much protein into the urine.

Type IV - Cell-mediated (or Delayed) Hypersensitivity

Also known as cell-mediated hypersensitivity (remember the other three are due to antibodies), this form is a common response to many intracellular pathogens and to large or complex infectious agents.

Type IV cell-mediated hypersensitivity is initiated by T lymphocytes specifically sensitized to locally deposited antigen. The two effector mechanisms are: (1) delayed type and (2) direct cytotoxicity.
Example - positive tuberculin skin test (DTH, type IV).

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV</th>
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<tbody>
<tr>
<td>Immune reactant</td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>T_{H1} cells</td>
</tr>
<tr>
<td></td>
<td>Soluble antigen</td>
<td>Cell- or matrix-associated antigen</td>
<td>Soluble antigen</td>
<td>T_{H2} cells</td>
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<tr>
<td></td>
<td>Mast-cell activation</td>
<td>FeR^{+} cells (macrophages, NK cells)</td>
<td>FeR^{+} cells Complement</td>
<td>Macrophage activation</td>
</tr>
<tr>
<td>Effector mechanism</td>
<td>Immunocomplex activation</td>
<td>Blood vessels</td>
<td>IFN-γ, T_{H1}</td>
<td>Eosinophil activation</td>
</tr>
<tr>
<td></td>
<td>Mastocytosis</td>
<td>Blood vessels</td>
<td>Cytokines, cytokines, cytotoxins</td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td>Example of hypersensitivity reaction</td>
<td>Meningoencephalitis, asthma, systemic anaphylaxis</td>
<td>Some drug allergies (e.g., penicillin)</td>
<td>Serum sickness, Arthus reaction</td>
<td>Contact dermatitis, tuberculin reaction</td>
</tr>
<tr>
<td></td>
<td>Chronic asthma, chronic allergic rhinitis</td>
<td>Contact dermatitis</td>
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![Diagram showing immune responses and effector mechanisms for Types I to IV immune reactions.](image)
Healing and Repair

This lesson corresponds to the web lesson of the same name.

SUMMARY OF IMPORTANT CONCEPTS FOR THIS LESSON

Repair by regeneration
This is when an organ can make new cells, like the liver!

Repair by replacement
This is when an organ can’t make new cells and the repair is through fibrous tissue (scar), like the heart.

Wound healing (all soft tissues):
Granulation tissue:
Composed of fibroblasts making collagen and endothelial cells making capillaries
Eventually becomes mature collagen (scar)

Special considerations in repair:
Bone has a system all its own.
Nervous tissue cannot regenerate
Heart myofiber regeneration is not possible. You only get a scar.
Healing and Repair

Inflammation and repair can be viewed as two parts of a single vital function, the physiologic response to tissue injury, the objective of which is restoration of normal structure and function. Up until now we have focused on the inflammation portion but it is good to remember that repair starts pretty soon after inflammation does and then continues during and beyond the inflammatory phase.

Perfect restoration of function is dependent upon the regeneration of lost cells by similar cells *(repair by regeneration)*, and the orderly arrangement of these new cells in relation to preexisting cells so that tissue functions are restored.

If the original cells cannot be replaced by their own kind then they are replaced by other cell types *(repair by replacement)*, usually by fibrous connective tissue. If necrosis is extensive, even tissues that are capable of regeneration are replaced by fibrous connective tissue.

---

There are three cell types based on ability to regenerate:

- **permanent cells** *(almost never divide)*:
  - nerve cell bodies, cardiac myocytes, cells of the lens

- **stable cells** *(will divide if stimulated)*:
  - fibroblasts, osteoblasts, parenchyma of liver, kidney, pancreas and endocrine glands, smooth muscle, vascular endothelium

- **labile cells** *(multiply through life)*:
  - epithelial cells of surfaces or linings of ducts and hollow visci, lymphoid and hematopoietic cells
Granulation tissue (= vascular fibrous connective tissue)

The term “granulation tissue” is derived from its pink soft granular appearance on the surface of wounds. Granulation tissue is recognized histologically by the presence of newly formed fibrous tissue and numerous small blood vessels. The fibrous connective tissue eventually may come to have the maturity of the loose fibrillar connective tissue of normal histology, but in the formative stages the fibroblasts are plump and only a few collagen fibrils have been produced.

Contraction occurs as a result of the action of myofibroblasts. These cells have features intermediate between those of fibroblasts and smooth muscle cells. They appear in the wound area 2 or 3 days after injury. Their origin is not entirely clear, but they probably derive either from perivascular cells or from other mesenchymal cells. Contraction may reduce the original defect by as much as 70% and greatly facilitate healing.

Fibroplasia begins early after injury, with existing fibroblasts adjacent to the wound being the source of new fibroblasts. The immature fibroblasts are characterized by their plumpness, basophilia, rich complement of rough endoplasmic reticulum, and prominent nucleoli, all evidence of active synthesis. They are active in synthesizing glycosaminoglycans and collagen fibers.

The new capillaries most commonly run in a perpendicular direction to the outer surface of the wound since their function is to carry supplies to the free surface, while fibroblasts tend to grow in from the side of the defect to bridge the gap. This often produces a histological picture of capillaries running at right angles to the direction of the fibroblasts. The formation of new capillaries is termed angiogenesis or neovascularization.
Remember, granulation tissue is part of the repair process and consists of inflamed, proliferating fibrous tissue and granulomatous refers to inflammatory infiltrates characterized by macrophages.

And sometimes granulation tissue doesn’t know when to quit growing and start turning into the permanent scar it is supposed to form. Think “exuberant granulation tissue” in horses, also known as “proud flesh.” A healing process that goes too far and too long.

All this healing takes energy and if an animal is in a compromised state, the repair will take a whole lot longer.

---

It is important to distinguish the term **granulation** from **granulomatous** inflammation. Although they sound similar, they are really quite different. As different as fibrinous is from fibrous (know that distinction too).
**Repair of bone**

Repair of bone is a specialized category of healing and repair and deserves individual attention. Immediately following fracture of bone, blood flows out of the broken vessels into the gap between the broken ends of bone and displaced or disrupted periosteum, and into the surrounding soft tissue. A big callus forms with fibrovascular tissue. The osteoprogenitor cells eventually invade into this callus and slowly new bone is formed and then remodeled.

**Repair of Nervous Tissue**

Repair in the central nervous system (CNS) is very limited because mature neurons do not divide. When damage occurs in the CNS, neurons and their processes are lost forever; they cannot be regenerated. Take care of your neurons! In the peripheral nervous system (PNS), injury to the nerves may be followed by regeneration if the nerve cell body remains alive.

**Repair of the Myocardium**

Myocardial cells do not have any regenerative capacity. When they die, as in a heart attack, they are gone forever and repair can only take place by fibrosis. This replacement by fibrosis decreases myocardial contractility.