Necrosis - cell death resulting from injury

cell lysis → releases contents into extracellular damaging other surrounding cells.

Results in death of groups of cells

Four types of necrosis

- Coagulative necrosis - typically seen in tissues with cells that lack an abundance of hydrolytic enzymes.
  - Ex. Muscle tissues.
  - Cells rupture & release lactic acid into ECF.
  - Damages other cells, causes proteins to denature.
Denatured proteins coagulate giving the tissue a whitish appearance.

- Liquefactive necrosis—seen in tissues with cells that have an abundance of hydrolytic enzymes. Ex. neural tissue

Lysis of cells → release of hydrolytic enzymes into ECF; these enzymes damage and digest surrounding cells. Tissue appears to liquify.

- Caseous necrosis—combination of liquefactive and coagulative necrosis

Ex. Lung tissue undergoing necrosis
Fat necrosis
seen in adipose (fat) tissue
release of lipases into ECF
when cells lyse, breakdown
triglycerides and other lipids
in the tissue giving the tissue
a soapy or foamy quality.
Tissues undergoing this type of
necrosis have a soapy, foamy, opaque
or whitish appearance.

Gangrene (gangrenous necrosis)—large
areas of

tissue undergoing

necrosis

3 Kinds of gangrene:
— Dry gangrene
usually results from disruption
of arterial blood flow to the
tissue
tissue has a dark brown or black color and is dry in appearance.

- Wet gangrene - usually results from interruption of venous blood flow out of the tissue.

- Gas gangrene - tissue becomes invaded by a Clostridium bacteria (typically present in soil). This bacteria is anaerobic and produces enzymes that destroy...
To stop the spread of the gangrene to other tissues, the gangrenous tissue is surgically removed, or it will cause the death of the individual.

Pg. 91-94 - Lifespan, Aging, + Death

Inflammation + Immunity

Body has two defensive systems that act cooperatively.
Non-Specific Defenses
(c.a.k. - "Inate Immune Defenses"
"Natural Immunity"
"Natile Immunity"

Specific Immune Defenses
(c.a.k. "Acquired Immunity"

Non-Specific Defenses

Two lines of defense:
- External defenses or Physical Barriers - prevent pathogens from entering the body

Include:
- Skin - physical barrier denying pathogens entrance
mucous lining of GI, urinary and respiratory tracts that traps pathogens before they can gain access to the body. These trapped pathogens are subsequently eliminated by sneezing, coughing, or urinating, or the mucous in the esophagus + resp. tract is swallowed and passes into the stomach where acid + enzymes kill the pathogens.

These mucous secretions also include antibodies, fatty acids, lactic acid, antimicrobial peptides, and lysozymes all act to kill the pathogens before they can enter.
If the pathogen makes it through the first line of defense, then it triggers a second line of defense called the inflammatory response or inflammation.

Inflammation is triggered by tissue damage caused by:
- bacterial toxins
- viral infection
- mechanical tissue damage

Inflammation is initiated within seconds of tissue damage and typically only lasts a week to 10 days, referred to as the "acute" inflammatory response ("AIR")
Characterized by:
- Redness of the inflamed tissue
- Swelling of the inflamed tissue
- Increased temperature of the inflamed tissue
- Pain in the inflamed tissue

Each is caused by inflammatory processes.

AIR is initiated by mast cells, mast cells are found in most tissues and release chemical signals when tissue damage occurs. i.e. the mast cells degranulate. Histamine is the most important of these chemical signals.
The released histamine has two effects:

- Overall, it causes vasodilation of the blood vessels in the damaged tissues. This increases blood flow to the damaged tissue, causing redness and increased temperature of the tissue.

- Increases the permeability of the capillaries in the damaged tissue. This allows plasma to leak out of the capillaries and into the damaged tissue (exudation). Accumulation of the fluid in the damaged tissue causes swelling (edema).
The increased permeability of the capillaries also makes it easier for WBCs, such as neutrophils and eosinophils, to pass out of the blood and into the damaged tissue.

Other chemical signals synthesized and released by the mast cells:
- Leukotrienes (lipid) reinforce vasodilation and increased permeability of capillaries caused by histamine. Also acts as a chemotactic agent for neutrophils and eosinophils.
Most cells also release neutrophil chemotactic factor and eosinophil chemotactic factor - A (ECF-A) that attract neutrophils and eosinophils to the site of inflammation.

Neutrophils and eosinophils are short lived WBCs that can be detected in inflamed tissue within 90 min of tissue damage.

These cells begin to phagocytose any invading pathogens and clearing up cell debris caused by tissue damage.

More importantly, the eosinophils release enzymes, such as histaminase, that helps limit the HTR.
Prostaglandins are another chemical signal that is synthesized by most cells when they degranulate.

Prostaglandins act to reinforce increased capillary permeability caused by histamine and leukotrienes and also have neutrophil chemotactic properties.

More importantly, prostaglandins stimulate pain receptors in the inflamed tissue.

Non-steroidal anti-inflammatory drugs (NSAIDs) - Aspirin, Ibuprofen, and naproxen act by inhibiting the COX1 and COX2 enzymes responsible for synthesis
of prostaglandins

Prostaglandins are also synthesized by cells in the stomach lining, where they stimulate the secretion of mucous. Overuse of NSAIDs causes stomach irritation and ulcer formation because it inhibits the synthesis of prostaglandins that normally stimulate mucous secretion.

Cox-2 inhibitors - Vioxx + Celebrex inhibit COX-2 enzyme specifically and not COX-1, so don't cause stomach irritation

Steroidal anti-inflammatory, e.g., cortisone
set to reduce the AIA by inhibiting the release of histamine, and by blocking the action of bradykinin that sets to stimulate pain receptors in inflamed tissue.

**Plasma Protein Systems**

- Coagulation system
- Kinin system
- Complement system

Activated when the plasma leaks out of the capillaries and into the damaged tissues.
Complement system
- Classical pathway
- Lectin pathway
- Alternative pathway

Clotting system
- Cellular injury
- Hageman factor
- Factor X
- Thrombin
- Fibrinogen
- Fibrin
- Blood clot
- Chemotactic factor
- Vascular permeability

Kinin system
- Prekallikrein
- Kininogen
- Bradykinin
- Pain, Histamine-like effects
- Plasmin

C3, C5b, 6-9
Membrane attack complex
- Promote cell degradation
- Chemotactic factor
- Anaphylatoxin
- Opsonin

Death of target

Cost surface of pathogens making them easier to phagocytose

Prevents bleeding and seals tissue
Prevents bacterial spread and further invasion by pathogens

Reinforces histamine effects on blood vessels

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As neutrophils become activated as they phagocytose pathogens & cell debris. Activated neutrophils secrete macrophage chemotactic factor (MCF) that attracts monocytes to the site of inflammation, that transform into large phagocytic cells called macrophages. Macrophages are long lived and are capable of phagocytosing large groups of bacteria and whole cell organelles.
Macrophages don't start arriving at the site of inflammation until a day or two after inflammation has begun.

Macrophages take over phagocytic role of the neutrophils as the neutrophils die.

Macrophages secrete chemical signals called cytokines.

Most important of these cytokines is interleukin-1 (IL-1).

IL-1 has 3 major systemic effects:
- Acts on the hypothalamus to induce fever
Fever is believed to help kill pathogens.

Stimulates the liver to synthesize and secrete "Acute Phase Reactants"—proteins that make up the plasma protein systems.

A sign of inflammation in the body is an increased red blood cell sedimentation rate.

Results from an increase in fibrinogen levels in the blood. That causes RBCs to clump and sediment more rapidly than normal in a blood sample.
Stimulates the production and release of neutrophils from the bone marrow. → increases # of circulating neutrophils.

In severe inflammation, IL-1 stimulates release of immature neutrophils (band cells). Presence of band cells is a cardinal sign of severe inflammation in the body.
Inflammation lasting longer than 2 weeks is called "chronic inflammation".

In chronically inflamed tissue:

- Dense infiltration of the inflammed tissue by macrophages and lymphocytes occurs.

- Macrophages differentiate into large epithelioid cells that don't phagocytose, and macrophages will fuse together to form giant macrophages that continue to phagocytose
Fibroblasts infiltrate the inflamed tissue and secrete collagen that forms a well ground the inflamed tissue isolating it.

This walled off, chronically inflamed tissue is called a granuloma.

The AER serves two additional functions:

- The macrophages involved in the AER are responsible for initiating the specific immune response.
The AIR is the first phase in wound healing.

Wounds involving little or no loss of tissue, e.g. paper cut, heal by "primary intention" i.e. they heal with little replacement of tissue.

Wounds involving significant tissue loss, e.g. a gouge, heal by "secondary intention" i.e. healing requires formation of a significant amount of scar tissue to replace lost tissue.
3 phases of wound healing:

- **Inflammatory phase** - Begins with tissue damage; the most important part is the movement of macrophages into the inflamed tissue.

Macrophages secrete growth factors that stimulate epithelial cell and blood vessel formation.

Macrophages also secrete fibroblast activating factor that attracts fibroblasts to the site of inflammation and activates them.
- Reconstructive Phase -

Most important cells in this phase are the fibroblasts.

It begins 3-4 days after initial damage and lasts 2 weeks or more depending on the extent of the injury.

The fibroblasts synthesize and secrete collagen that forms a framework replacing tissue that has been lost.

The fibroblasts and collagen together form "granulation" tissue or scar tissue.
At the same time epithelialization is occurring. Epithelial cells at the edge of the wound begin dividing and move under the blood clot covering the wound, reestablishing the epithelial covering over the deeper tissues. Some of the fibroblasts in the granulation tissue transform into myofibroblasts (can contract like muscle cells). Contraction of the myofibroblasts pull the edges of the wound together "wound contraction"
3rd phase - Maturation Phase; starts 2-3 wks after initial injury depending on severity of the injury and may last for years.

Two things happen:

- Remodeling of the collagen in the scar tissue to increase the strength of the scar tissue.
- Any capillaries in the scar tissue degenerate leaving an avascular scar. Leaves scar tissue with a whitish appearance.
Abnormal wound healing can occur as a result of an abnormal inflammatory response. e.g. granuloma formation

Keloid scar — a raised scar that extends beyond the boundaries of the original wound.
Keloids result from over production of collagen by fibroblasts during reconstructive phase.

Keloid scarring runs in families so believed to have a genetic component.

Keloid scarring is also more common in people of African descent, unknown why.