REPAIR

Overview: The process of repair begins very early. Repair involves regeneration of the parenchyma or replacement of damaged tissue with a scar if regeneration is not possible. The process of complete regeneration (i.e., resolution of acute inflammation) requires an organ that is composed of cells that can divide and an intact basement membrane and connective tissue scaffolding.

Definitions: Healing versus regeneration

- **Regeneration** is complete replacement of damaged cells, with no scar formation.
  - ~ Can occur in renewing tissues (e.g., gastrointestinal tract and skin).
  - ~ Can occur in stable tissues (e.g., compensatory growth in the liver and kidney).
    - ~ Regeneration requires an intact connective tissue scaffold.

- **Healing** is regeneration of cells combined with scarring and fibrosis

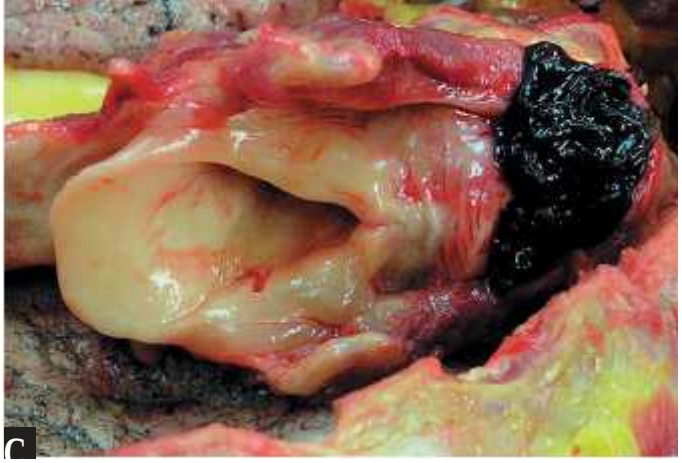

Figure 2-4. Aortoduodenal fistula. This patient had an abdominal aortic aneurysm, which was repaired with a graft. The graft became infected and was surgically replaced with a neointimal saphenous vein graft, which also became infected. A tract devel- oped between the neointimal graft and the duodenum. There is a defect in the neointimal aortic graft (**A**) (center of the photograph), which communicated with the duodenum (**B**) through a fistula, resulting in a massive amount of blood entering the gastrointestinal tract, which is visible in the esophagus of the patient (C).

Important mediators in repair

- **Epidermal growth factor (EGF):** Stimulates granulation tissue formation.
- **Vascular endothelial growth factor (VEGF):** Induces blood vessel formation.
- **PDGF:** Promotes migration and proliferation of fibroblasts, smooth muscle cells, and monocytes.
- **FGF:** Stimulates blood vessel formation and wound repair through macrophages, fibroblasts, and endothelial cell migration.
- **TGF-β:** Acts as growth inhibitor for epithelium.

Components of healing

- Induction of inflammatory process to deal with the source of injury (cell injury is prequel to healing). The inflammatory process acts to contain damage, remove injuring substance, remove dead tissue, and start deposition of extracellular matrix.
- Formation of new blood vessels.
- Production of extracellular matrix, including collagen.
- Tissue remodeling.
- Wound contracture.
- Increasing wound strength.

Replacement by scar: The following four processes occur.

1. Formation of new blood vessels (i.e., **angiogenesis**).
2. Migration and proliferation of fibroblasts.
3. Deposition of extracellular matrix.
4. Maturation and reorganization of fibrous tissue. Tissue remodeling is a balance between extracellular matrix synthe- sis and degradation. Extracellular matrix is degraded by matrix metalloproteinases (e.g., collagenases, gelatinases).

Time frame of scarring

- Within 24 hours of onset of acute inflammation, the process of scarring begins.
- At 3–5 days, **granulation tissue** is formed. The term granula- tion tissue indicates a proliferation of fibroblasts, new thin- walled vessels, and loose extracellular matrix.
- During week 2, collagen continues to be deposited and edema and inflammatory cells are almost entirely absent.
- By 1 month, the inflammatory infiltrate is absent and the scar consists of collagen. The collagen strengthens over the next few months.
- **Important point:** Formation of the scar occurs via either first or second intention.

HEALING BY FIRST INTENTION

Basic description: Healing of a wound that has clean edges, close reapproximation of margins, and minimal tissue disruption.

Example: Healing of surgical incision.

Result: Small to nonexistent scar.

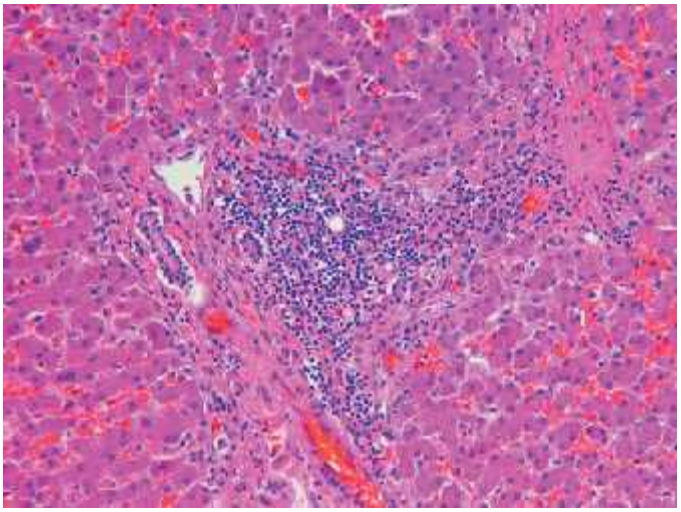

Figure 2-5. Chronic inflammation (chronic hepatitis). The portal tract in the center of the photomicrograph contains an increased number of lymphocytes. Lymphocytes and macrophages are the cell type most commonly present in chronic inflammation. Chronic inflammation is often due to an injurious stimulus that the body cannot remove from its tissue. In chronic hepatitis, that injurious stimulus is often an infection with hepatitis C virus. Hematoxylin and eosin, 200 .

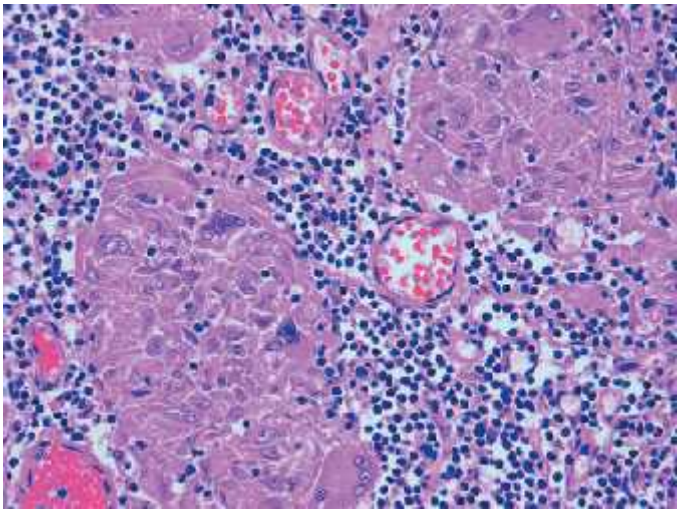

Figure 2-6. The photomicrograph shows granulomas in the left lower corner, left upper corner, and right upper corner. Granulo- mas are a collection of epithelioid histiocytes. Although multinucle- ated giant cells are often present, their presence is not required as a component of a granuloma. Granulomas are a specific form of chronic inflammation, most commonly associated with foreign bodies and some infections, including *Mycobacterium tuberculo- sis*. Hematoxylin and eosin, 200 .

HEALING BY SECOND INTENTION

Basic description: Healing of a wound that has unclean edges, extensive tissue disruption, and tissue necrosis.

Example: Healing of a cutaneous ulcer or a large laceration inflicted by a blow from a baseball bat.

Result: Larger, more prominent scar.

Important points

- The wound has much more necrotic debris and fibrin clot, which must be removed before the wound can be repaired. Normal removal of this tissue as part of the repair process can result in more damage by release of mediators from cells summoned to remove the debris.
- More granulation tissue is formed to bridge the gap between the edges of the wound. More granulation tissue results in a larger scar.
- **Wound contraction** occurs, reducing the wound by 5–10% of its full size. Wound contraction may occur due to contrac- tion of myofibroblasts.

GENERAL WOUND HEALING

Wound strength

- Is about 10% of that of normal skin at 1 week (with no sutures in place), increasing in amount of strength over the following month.
- After 2 or more months, the scar is fully healed, but still only has three fourths of the strength of normal skin.

Factors that may impair the process of wound healing

- **General factors:** Infections, nutritional deficiency (e.g., vita- min C deficiency), and glucocorticoid therapy, which results in decreased fibrosis.
- **Mechanical factors: Dehiscence** is unintentional reopening of the wound, often due to pressure or torsion.
- **Poor perfusion:** Decreases amount of blood available for healing.

Complications of cutaneous wound healing

- Inadequate healing, leading to dehiscence or ulceration.
- Excessive scar formation: **Hypertrophic scars** or **keloid scars.** Keloid scars involve tissue beyond the boundaries of the wound (Figure 2-7).
- Contractures.

Figure 2-7. Keloid scar. Keloid scars are a form of exuberant scar- ring in which the boundaries of the scar extend beyond the bound- aries of the wound. The ability to form keloid scars frequently occurs within certain demographic populations, such as African Americans.

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