membrane integrity. *Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with pathologic cell injury. Furthermore, in keeping with its role in certain physiologic processes, apoptosis does not elicit an inflammatory response.* The morphologic features, mechanisms, and significance of these two death pathways are discussed in more detail later in this chapter.

Histologic Signs of Reversible Cell Injury

i. **Cellular swelling:** The first sign of almost all forms of injury to cells, is a reversible alteration called cellular swelling (Fig. 1.14B). Microscopic examination may reveal small, clear vacuoles within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum (ER). This pattern of nonlethal injury is sometimes called **vacuolar degeneration.** The intracellular changes associated with reversible injury include:
   (1) plasma membrane alterations such as blunting, or distortion of microvilli, and loosening of intercellular attachments;
   (2) mitochondrial swelling
   (3) dilation of the ER with detachment of ribosomes and
   (4) minimal nuclear alterations (clumping of chromatin).

   Cellular swelling is the result of failure of energy-dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis.

ii. **Fatty change:** Fatty change occurs in hypoxic injury and in various forms of toxic or metabolic injury. It is manifested by the appearance of small or large lipid vacuoles in the cytoplasm (Fig. 1.15). It is principally encountered in cells participating in fat metabolism (e.g. hepatocytes). Like cellular swelling, fatty change is also reversible stage of tissue injury.

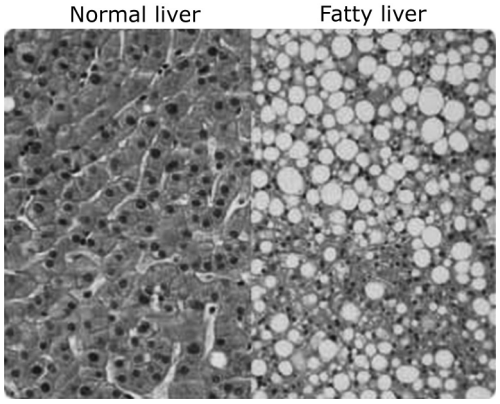

Fig. 1.15: Fatty change in the liver

Histologic Signs of Necrosis

Necrosis is the type of cell death that is associated with loss of membrane integrity and leakage of cellular contents culminating in dissolution of cells, largely resulting from the degradative action of enzymes on lethally injured cells (Fig. 1.14C). The leaked cellular contents often elicit a local host reaction, called *inflammation,* that attempts to eliminate the dead cells and start the subsequent repair process (Chapter 2). The

delicate control is made possible by the fact that ventilation is controlled by both CO_2 as well as H^+ concentration through central and peripheral chemoreceptors.

a. *Effect of CO_2:* CO_2 is a highly diffusible gas. It can easily cross the blood–brain and blood–CSF barriers, and stimulate the medullary central chemoreceptors. In contrast, H^+ cannot cross these barriers easily. Therefore, central chemoreceptors are most sensitive to changes in arterial pCO_2 and less so to changes in H^+ concentration.
b. *Effect of pH:* An increase in H^+ concentration of arterial blood also stimulates pulmonary ventilation, chiefly through the peripheral (sino-aortic) chemoreceptors. Therefore, the respiratory system helps in regulation of acid–base balance of the body even when the increase in H^+ concentration is not due to CO_2 but due to non-volatile acids like sulphuric acid, phosphoric acid or lactic acid.

ROLE OF KIDNEYS

The kidneys regulate pH by either acidification or alkalinization of the urine. The renal response occurs over hours/days, and is capable of nearly complete restoration of acid–base balance.

As mentioned above, about 60 mEq of H^+ is added to the blood every day as non-volatile acids. They cannot be excreted by the lungs. They are excreted by the kidneys in an indirect manner. In the kidneys, most of the excretory products are initially filtered into the glomerular filtrate. All that is necessary for their excretion is that renal tubules reabsorb them partially or not all. In contrast, the concentration of H^+ in the blood is so small, that they cannot be excreted in this manner. Actually, most of the H^+ produced in the body do not remain as such. They are immediately buffered by HCO_3^- and other buffers. The kidney generates new hydrogen ions equivalent to the amount metabolically produced and actively secretes them into the urinary tubules, where they are buffered by phosphate and ammonium ions.

The generation of H^+ in the renal tubules is accompanied by production of HCO_3^- which diffuses into the blood circulation and replenishes the amount of HCO_3^- lost during initial buffering of the acids. In case excess of base ($NaHCO_3$) is ingested, it is excreted by the kidney by filtration followed by partial or complete non-reabsorption.

In primary pulmonary diseases such as emphysema, pulmonary excretion of CO_2 is diminished and therefore arterial pCO_2 and H^+ concentration tend to rise (respiratory acidosis). In such circumstances, renal excretion of H^+ is the only means of maintaining body pH near normal (renal compensation). Similarly in chronic renal failure, renal excretion of H^+ is diminished leading to metabolic acidosis. In such a condition, excessive loss of CO_2 by hyperventilation is the only means of maintaining body pH near normal (respiratory compensation).

Anion Gap Concept

In the plasma, total cations (Na^+, K^+, Ca^{++}, Mg^{++}, etc.) are always counter-balanced by total anions (Cl^-, HCO_3^-, PO_4^-, SO_4^-, etc). Of these ions, only Na^+, K^+, Cl^-, and HCO_3^- are routinely measured. Therefore, the concentration of *measured anions* is always less than the concentration of *measured cations*. The difference is known as the anion gap:

$$\text{Anion gap} = \{ [Na^+] + [K^+] \} - \{ [Cl^-] + [HCO_3^-] \}$$

ACUTE INFLAMMATION

CARDINAL SIGNS

Acute inflammation is a short-term process, usually appearing in a few minutes or hours and ceasing once the injurious stimulus has been removed. It is characterized by five cardinal signs:

- Redness
- Warmth
- Swelling
- Pain
- Loss of function

The first four (classical signs) were described by Celsus about 2000 years ago, while *loss of function* was added to the list later by Virchow in 1870. Redness and warmth are due to increased blood flow at body core temperature to the areas such as skin, which normally are at a lower temperature; swelling is caused by accumulation of fluid and plasma proteins in the extravascular spaces; pain is due to release of chemicals that stimulate pain nerve endings or sensitize them to other stimuli. Loss of function has multiple causes, chiefly pain and local edema.

These five signs appear when acute inflammation occurs on the body's surface. In case of acute inflammation of internal organs all the five signs may not be apparent.

ACUTE INFLAMMATORY RESPONSE

The acute inflammatory response may be discussed under two headings: (1) The vascular response and (2) The cellular response.

1. The Vascular Response

Alterations in the microvasculature (arterioles, capillaries and venules) of the injured tissue are the earliest response to the injury. It consists of: (a) hemodynamic changes and (b) changes in vascular permeability.

(a) Haemodynamic changes

Transient vasoconstriction of the arterioles and reduced blood flow is the immediate response irrespective of the type of injury. It usually lasts only a few seconds but may be prolonged up to five minutes if the injury is very severe. It is followed by:

i. Persistent and progressive vasodilatation, which begins in the arterioles and spreads to the capillaries and venules as well. This change becomes prominent within an hour of injury. Vasodilatation results in increased blood flow to the microvasculature and accounts for the clinical signs of redness and warmth. Vasodilatation is brought about by the release of vasodilator mediators by the injured tissue cells as well as by the blood cells attracted by the injury.
ii. Transudation of fluid into the extracellular space (edema) is another consequence of vasodilatation. Starling forces, chiefly capillary hydrostatic pressure and plasma protein oncotic pressure, govern the tissue fluid exchange across the capillary wall. It involves tissue fluid formation at the proximal segment of the capillary followed by reabsorption in the distal segment. Vasodilatation, by increasing the

BASIC PRINCIPLES OF WOUND HEALING

If there is an injury to the skin, under normal circumstances, the wound heals in a few days. The process of wound healing consists of four overlapping phases:

1. **Haemostasis phase:** Injury to the skin or other tissues results in bleeding. The first step in wound healing involves stoppage of bleeding (haemostasis). Haemostasis starts when blood leaks out of the body. The circulating platelets collect at the site of injury, stick together, form platelet plug and seal the break in the wall of the blood vessel. This step is known as primary haemostasis. However, the platelet is soft and temporary. In the next step known as secondary haemostasis, the blood collected at the site of injury clots. Clotting of blood seals the leak in blood vessels permanently. The blood clot reinforces the platelet plug with threads of fibrin which are like a molecular binding agent. The hemostasis stage of wound healing happens within a few minutes.
2. **Inflammatory phase:** Inflammation is the second stage of wound healing and begins right after the injury when the injured blood vessels lose blood. Inflammation both controls bleeding and prevents infection. The acute inflammatory response has been described in detail earlier in this chapter. During the inflammatory phase, damaged cells are removed from the wound area. Swelling, heat, pain and redness commonly seen during this stage of wound healing are signs of acute inflammation. If some bacteria get into the wound, blood macrophages remove the pathogens. Inflammation is a natural part of the wound healing process and only problematic if prolonged or excessive, if infection cannot be controlled.
3. **Proliferative phase:** The proliferative phase features three distinct stages:
    1. Filling the wound
    2. Contraction of the wound margins
    3. Covering the wound by epithelialization

    The gap in the skin is filled by newly built tissue consisting of collagen fibres and extracellular matrix. In addition, a new network of blood vessels grows into the wound bed forming shiny, deep red granulation tissue. When tissues are injured, fibroblasts around the injured region differentiate into myofibroblasts, a type of highly contractile cells that produce abundant extracellular matrix proteins. It has become clear that both fibroblasts and myofibroblasts play a critical role in the wound healing process. Fibroblast cells lay down collagen fibers. Myofibroblasts cause the wound to contract by gripping the wound edges and pulling them together. In healthy stages of wound healing, granulation tissue is pink or red and uneven in texture. Moreover, healthy granulation tissue does not bleed easily. Dark granulation tissue can be a sign of infection, ischemia, or poor perfusion. In the final phase of the proliferative stage of wound healing, epithelial cells resurface the injury. It is important to remember that epithelialization happens faster when wounds are kept moist and hydrated (Fig. 2.6).
4. **Maturation phase:** When collagen is laid down during the proliferative phase, it is disorganized and the wound is thick. During the maturation phase, collagen is aligned along tension lines and water is reabsorbed so the collagen fibers can lie closer together and cross-link. Cross-linking of collagen reduces scar thickness and also makes the skin area of the wound stronger. When the wound fully closes, the cells that had been used to repair the wound but which are no longer