HOMEOSTASIS

Many workers have pointed out that life on earth probably arose in the sea, and that the body water which is the environment of the cells, consisting of “salt water” is similar to the ancient ocean. The sea within us flows through blood and lymph vessels, bathes the cells as well as lies within the cells. However, water within body contains several salts that include sodium, chloride, potassium, calcium, magnesium, phosphate, and other electrolytes. Although it appears quite tempting to draw comparison between environment of the cell and the ancient oceans, it would be rather an oversimplification in considering the cellular environment to be wholly fluid ignoring the presence of cells, fibres and ground substance.

Claude Bernarde (1949) first coined the term internal environment or milieu interieur for the state in the body in which the interstitial fluid that bathes the cells and the plasma, together maintain the normal morphology and function of the cells and tissues of the body. The mechanism by which the constancy of the internal environment is maintained and ensured is called the homeostasis. For this purpose, living membranes with varying permeabilities such as vascular endothelium and the cell wall play important role in exchange of fluids, electrolytes, nutrients and metabolites across the compartments of body fluids.

The normal composition of internal environment consists of the following components (Fig. 4.1):

1. WATER Water is the principal and essential constituent of the body. The total body water in a normal adult male comprises 50-70% (average 60%) of the body weight and about 10% less in a normal adult female (average 50%). Thus, the body of a normal male weighing 65 kg contains approximately 40 litres of water. The total body water (assuming average of 60%) is distributed into 2 main compartments of body fluids separated from each other by membranes freely permeable to water. These are as under (Fig. 4.2):

   i) Intracellular fluid compartment This comprises about 33% of the body weight, the bulk of which is contained in the muscles.

   ii) Extracellular fluid compartment This constitutes the remaining 27% of body weight containing water. Included in this are the following 4 subdivisions of extracellular fluid (ECF):

   a) Interstitial fluid including lymph fluid constitutes the major proportion of ECF (12% of body weight).

   b) Intravascular fluid or blood plasma comprises about 5% of the body weight. Plasma content is about 3 litres of fluid out of 5 litres of total blood volume.

   c) Mesenchymal tissues such as dense connective tissue, cartilage and bone contain body water that comprises about 9% of the body weight.

   d) Transcellular fluid constitutes 1% of body weight. This is the fluid contained in the secretions of secretory cells of the body e.g. skin, salivary glands, mucous membranes of alimentary and respiratory tracts, pancreas, liver and biliary tract, kidneys, gonads, thyroid, lacrimal gland and CSF.

2. ELECTROLYTES The concentration of cations (positively charged) and anions (negatively charged) is different in intracellular and extracellular fluids:

   - In the intracellular fluid, the main cations are potassium and magnesium and the main anions are phosphates and proteins. It has low concentration of sodium and chloride.

   - In the extracellular fluid, the predominant cation is sodium and the principal anions are chloride and bicarbonate. Besides these, a small proportion of non-
diffusible nutrients and metabolites such as glucose and urea are present in the ECF.

The essential difference between the two main subdivisions of ECF is the higher protein content in the plasma than in the interstitial fluid which plays an important role in maintaining fluid balance.

The major functions of electrolytes are as follows:

i) Electrolytes are the main solutes in the body fluids for maintenance of acid-base equilibrium.

ii) Electrolytes maintain the proper osmolality and volume of body fluids (Osmolarity is the solute concentration per kg water, compared from osmolality which is the solute concentration per litre solution).

iii) The concentration of certain electrolytes determines their specific physiologic functions e.g. the effect of calcium ions on neuromuscular excitability. The concentration of the major electrolytes is expressed in milliequivalent (mEq) per litre so as to compare the values directly with each other. In order to convert mg per dl into mEq per litre the following formula is used:

\[
\text{mEq/L} = \frac{\text{mg/dl}}{\text{Eq weight of element}} \times 10
\]

NORMAL WATER AND ELECTROLYTE BALANCE (GIBBS-DONNAN EQUILIBRIUM)

Normally, a state of balance exists between the amount of water absorbed into the body and the amount eliminated from the body. The water and electrolytes are distributed nearly constantly in different body fluid compartments:

1. Water is normally absorbed into the body from the bowel or is introduced parenterally; average intake being 2800 ml per day.

2. Water is eliminated from the body via:
   i) kidneys in the urine (average 1500 ml per day);
   ii) via the skin as insensible loss in perspiration or as sweat (average 800 ml per day), though there is wide variation in loss via sweat depending upon weather, temperature, fever and exercise;
   iii) via the lungs in exhaled air (average 400 ml per day); and
   iv) minor losses via the faeces (average 100 ml per day) and lacrimal, nasal, oral, sexual and mammary (milk) secretions.

The cell wall as well as capillary endothelium are entirely permeable to water but they differ in their permeability to electrolytes. Capillary wall is completely impermeable to electrolytes while the cell membrane is somewhat impermeable. As mentioned earlier, concentration of potassium and phosphate are high in the intracellular fluid whereas concentration of sodium and chloride are high in the ECF. The osmotic equilibrium between the two major body fluid compartments is maintained by the passage of water from or into the intracellular compartment. The 2 main subdivisions of ECF—blood plasma and interstitial fluid, are separated from each other by capillary wall which is freely permeable to water but does not allow free passage of macro-molecules of plasma proteins resulting in higher protein content in the plasma.

ACID-BASE BALANCE

Besides changes in the volume of fluids in the compartments, changes in ionic equilibrium affecting the acid-base balance of fluids occur. In terms of body fluids,

- an acid is a molecule or ion which is capable of giving off a hydrogen ion (H+ ion donor); and
- a base is a molecule or ion which is capable of taking up hydrogen ion (H+ ion acceptor).

A number of acids such as carbonic, phosphoric, sulfuric, lactic, hydrochloric and ketoacids are formed during normal metabolic activity. However, carbonic acid is produced in largest amount as it is the end-product of aerobic tissue activity. In spite of these acids, the pH of the blood is kept constant at 7.4 ± 0.05 in health.

The pH of blood and acid-base balance are regulated in the body as follows:

1. BUFFER SYSTEM Buffers are substances which have weak acids and strong bases and limit the change in H+ ions concentration to the normal range. They are the first line of defense for maintaining acid-base balance and do so by taking up H+ ions when the pH rises. The most important buffer which regulates the pH of blood is bicarbonate-carbonic acid system followed by intracellular buffering action of haemoglobin and carbonic anhydrase in the red cells.

2. PULMONARY MECHANISM During respiration, CO2 is removed by the lungs depending upon the partial pressure of CO2 in the arterial blood. With ingestion of high quantity of acid-forming salts, ventilation is increased as seen in acidosis in diabetic ketosis and uraemia.

3. RENAL MECHANISM The other route by which H+ ions can be excreted from the body is in the urine. Here, H+ ions secreted by the renal tubular cells are buffered in the glomerular filtrate by:
   i) combining with phosphates to form phosphoric acid;
   ii) combining with ammonia to form ammonium ions; and
   iii) combining with filtered bicarbonate ions to form carbonic acid.

However, carbonic acid formed is dissociated to form CO2 which diffuses back into the blood to reform bicarbonate ions.

PRESSURE GRADIENTS AND FLUID EXCHANGES

Besides water and electrolytes (or crystalloids), both of which are freely interchangeable between the interstitial fluid and plasma, the ECF contains colloids (i.e. proteins) which minimally cross the capillary wall. These substances exert pressures responsible for exchange between the interstitial fluid and plasma.

Normal Fluid Pressures

1. OSMOTIC PRESSURE This is the pressure exerted by the chemical constituents of the body fluids. Accordingly, osmotic pressure may be of the following types (Fig. 4.3.A):

   a) Crystalloid osmotic pressure exerted by electrolytes present in the ECF and comprises the major portion of the total osmotic pressure.

   b) Colloid osmotic pressure (Oncotic pressure) exerted by proteins present in the ECF and constitutes a small part of the total osmotic pressure but is more significant physiologically. Since the protein content of the plasma is higher than that of interstitial fluid, oncotic pressure of plasma is higher (average 25 mmHg) than that of interstitial fluid (average 8 mmHg).

   c) Effective oncotic pressure is the difference between the higher oncotic pressure of plasma and the lower oncotic
The mechanism by which constancy of the internal environment is maintained and ensured is called the **homeostasis**. Living membranes such as cell wall and vascular endothelium play important role in exchanges of fluid, electrolytes, nutrients and metabolites.

**Total body water** is about 60% of the body weight and is divided into intracellular (33%) and extracellular compartments (27%). Intracellular fluid has low concentration of sodium and chloride while extracellular compartment has high sodium, chloride and bicarbonate; plasma has high protein content compared from interstitial fluid.

**Effective oncotic pressure** is the difference between the higher oncotic pressure of plasma and the lower oncotic pressure of interstitial fluid and is the force that tends to draw fluid into the vessels.

**Effective hydrostatic pressure** is the difference between the higher hydrostatic pressure in the capillary and the lower tissue tension; it is the force that drives fluid through the capillary wall into the interstitial space.

### DISTURBANCES OF BODY WATER

The common derangements of body water are as follows:
1. Oedema
2. Dehydration
3. Overhydration

These are discussed below.

### EDEMA

#### DEFINITION AND TYPES

The Greek word *oedema* means swelling. Oedema is defined as abnormal and excessive accumulation of “free fluid” in the interstitial tissue spaces and serous cavities. The presence of abnormal collection of fluid within the cell is sometimes called intracellular oedema but should more appropriately be called hydropic degeneration (page 17).

**Free fluid in body cavities**: Commonly called as effusion, it is named according to the body cavity in which the fluid accumulates. For example, ascites (if in the peritoneal cavity), hydrothorax or pleural effusion (if in the pleural cavity), and hydropericardium or pericardial effusion (if in the pericardial cavity).

**Free fluid in interstitial space**: Commonly termed as oedema, the fluid lies free in the interstitial space between the cells and can be displaced from one place to another. In the case of oedema in the subcutaneous tissues, momentary pressure of finger produces a depression known as pitting oedema. The other variety is non-pitting or solid oedema in which no pitting is produced on pressure e.g. in myxoedema, elephantiasis.

Oedema may be of 2 main types:
1. **Localised** when limited to an organ or limb e.g. lymphatic oedema, inflammatory oedema, allergic oedema, pulmonary oedema, cerebral oedema etc.
2. **Generalised (anasarca or dropsy)** when it is systemic in distribution, particularly noticeable in the subcutaneous tissues e.g. renal oedema, cardiac oedema, nutritional oedema.

Depending upon fluid composition, oedema fluid may be:
- **transude** which is more often the case, such as in oedema of cardiac and renal disease; or
- **exudate** such as in inflammatory oedema.

The differences between transude and exudate are tabulated in **Table 4.1**.

### PATHOGENESIS OF OEDEMA

Oedema is caused by mechanisms that interfere with normal fluid balance of plasma, interstitial fluid and lymph flow. The following mechanisms may be operating singly or in combination to produce oedema:
1. Decreased plasma oncotic pressure
2. Increased capillary hydrostatic pressure
3. Lymphatic obstruction
4. Tissue factors (increased oncotic pressure of interstitial fluid, and decreased tissue tension)
5. Increased capillary permeability
6. Sodium and water retention.

These mechanisms are discussed below and illustrated in **Fig. 4.3**.

1. **DECREASED PLASMA ONCOTIC PRESSURE** The plasma oncotic pressure exerted by the total amount of plasma...
proteins tends to draw fluid into the vessels normally. A fall in the total plasma protein level (hypoproteinaemia of less than 5 g/dl, mainly hypoalbuminaemia), results in lowering of plasma oncotic pressure in a way that it can no longer counteract the effect of hydrostatic pressure of blood. This results in increased outward movement of fluid from the capillary wall and decreased inward movement of fluid from the interstitial space causing oedema (Fig. 4.3,B). Hypoproteinaemia usually produces generalised oedema (anasarca). Out of the various plasma proteins, albumin has four times higher plasma oncotic pressure than globulin; thus it is mainly hypoproteinaemia (albumin below 2.5 g/dl) that generally results in oedema.

The examples of oedema by this mechanism are seen in the following conditions:

i) Oedema of renal disease e.g. in nephrotic and nephritic syndrome.
ii) Ascites of liver disease e.g. in cirrhosis of the liver.
iii) Oedema due to other causes of hypoproteinaemia e.g. in protein-losing enteropathy.

2. INCREASED CAPILLARY HYDROSTATIC PRESSURE

The hydrostatic pressure of the capillary is the force that normally tends to drive fluid through the capillary wall into the interstitial space by counteracting the force of plasma oncotic pressure. A rise in the hydrostatic pressure at the venular end of the capillary which is normally low (average 12 mmHg) to a level more than the plasma oncotic pressure results in minimal or no reabsorption of fluid at the venular end, consequently leading to oedema (Fig. 4.3,C).

The examples of oedema by this mechanism are seen in the following disorders:

i) Oedema of cardiac disease e.g. in congestive cardiac failure, constrictive pericarditis.
ii) Ascites of liver disease e.g. in cirrhosis of the liver.
iii) Passive congestion e.g. in mechanical obstruction due to thrombosis of veins of the lower legs, varicosities, pressure by pregnant uterus, tumours etc.
iv) Postural oedema e.g. transient oedema of feet and ankles due to increased venous pressure seen in individuals whose job involves standing for long hours such as traffic constables and nurses.

3. LYMPHATIC OBSTRUCTION Normally, the interstitial fluid in the tissue spaces escapes by way of lymphatics. Obstruction to outflow of these channels causes localised oedema, known as lymphoedema (Fig. 4.3,D).

The examples of lymphoedema include the following:

i) Removal of axillary lymph nodes in radical mastectomy for carcinoma of the breast causing lymphoedema of the affected arm.
ii) Pressure from outside on the main abdominal or thoracic duct such as due to tumours, effusions in serous cavities etc may produce lymphoedema. At times, the main lymphatic channel may rupture and discharge chyle into the pleural cavity (chylothorax) or into peritoneal cavity (chylos ascites).
iii) Inflammation of the lymphatics as seen in filariasis (infection with Wuchereria bancrofti) results in chronic lymphoedema of scrotum and legs known as elephantiasis, a form of non-pitting oedema.
iv) Occlusion of lymphatic channels by malignant cells may result in lymphoedema.
v) Milroy’s disease or hereditary lymphoedema is due to abnormal development of lymphatic channels. It is seen in families and the oedema is mainly confined to one or both the lower limbs (page 391).

4. TISSUE FACTORS The two forces acting in the interstitial space—oedema of the interstitial space and tissue tension, are normally quite small and insignificant to counteract the effects of plasma oncotic pressure and capillary hydrostatic pressure respectively. However, in some situations, the tissue factors in combination with other mechanisms play a role in causation of oedema (Fig. 4.3,E). These are as under:

i) Elevation of oncotic pressure of interstitial fluid as occurs due to increased vascular permeability and inadequate removal of proteins by lymphatics.
ii) Lowered tissue tension as seen in loose subcutaneous tissues of eyelids and external genitalia.
5. **INCREASED CAPILLARY PERMEABILITY** An intact capillary endothelium is a semipermeable membrane which permits the free flow of water and crystalloids but allows minimal passage of plasma proteins normally. However, when the capillary endothelium is injured by various 'capillary poisons' such as toxins and their products (e.g. histamine, anoxia, venoms, certain drugs and chemicals), the capillary permeability to plasma proteins is enhanced due to development of gaps between the endothelial cells, causing leakage of plasma proteins into interstitial fluid. This, in turn, causes reduced plasma oncotic pressure and elevated oncotic pressure of interstitial fluid, consequently producing oedema (Fig. 4.3,F).

The examples of oedema due to increased vascular permeability are seen in the following conditions:

i) **Generalised oedema** occurring in systemic infections, poisonings, certain drugs and chemicals, anaphylactic reactions and anoxia.

ii) **Localised oedema** A few examples are as under:

  ◆ **Inflammatory oedema** as seen in infections, allergic reactions, insect-bite, irritant drugs and chemicals. It is generally exudate in nature.

  ◆ **Angioneurotic oedema** is an acute attack of localised oedema occurring on the skin of face and trunk and may involve lips, larynx, pharynx and lungs. It is possibly neurogenic or allergic in origin.

6. **SODIUM AND WATER RETENTION** The mechanism of oedema by sodium and water retention in extravascular compartment is best described in relation to derangement in normal regulatory mechanism of sodium and water balance.

  *Natrium* (Na) is the Latin term for sodium. Normally, about 80% of sodium is reabsorbed by the proximal convoluted tubule under the influence of either intrinsic renal mechanism or extra-renal mechanism while retention of water is affected by release of antidiuretic hormone (Fig. 4.4):

  ◆ **Intrinsic renal mechanism** is activated in response to sudden reduction in the effective arterial blood volume (hypovolaemia) e.g. in severe haemorrhage. Hypovolaemia stimulates the arterial baroreceptors present in the carotid sinus and aortic arch which, in turn, send the sympathetic outflow via the vasomotor centre in the brain. As a result of this, renal ischaemia occurs which causes reduction in the glomerular filtration rate, decreased excretion of sodium in the urine and consequent retention of sodium.
**Extra-renal mechanism** involves the secretion of aldosterone, a sodium-retaining hormone, by the renin-angiotensin-aldosterone system. Renin is an enzyme secreted by the granular cells in the juxta-glomerular apparatus. Its release is stimulated in response to low concentration of sodium in the tubules. Its main action is stimulation of the angiotensinogen which is $\alpha_2$-globulin or renin substrate present in the plasma. On stimulation, angiotensin I, a decapetide, is formed in the plasma which is subsequently converted into angiotensin II, an octapeptide, in the lungs and kidneys by angiotensin converting enzyme (ACE). Angiotensin II stimulates the adrenal cortex to secrete aldosterone hormone. Aldosterone increases sodium reabsorption in the renal tubules and sometimes causes a rise in the blood pressure.

**ADH mechanism** Retention of sodium leads to retention of water secondarily under the influence of anti-diuretic hormone (ADH) or vasopressin. This hormone is secreted by the cells of the supraoptic and paraventricular nuclei in the hypothalamus and is stored in the neurohypophysis (posterior pituitary). The release of ADH is stimulated by increased concentration of sodium in the plasma and hypovolaemia. Large amounts of ADH produce highly concentrated urine.

Thus, the possible factors responsible for causing oedema by excessive retention of sodium and water in the extravascular compartment via stimulation of intrinsic renal and extra-renal mechanisms as well as via release of ADH are as under:

i) Reduced glomerular filtration rate in response to hypovolaemia.

ii) Enhanced tubular reabsorption of sodium and consequently its decreased renal excretion.

iii) Increased filtration factor i.e. increased filtration of plasma from the glomerulus.

iv) Decreased capillary hydrostatic pressure associated with increased renal vascular resistance.

The examples of oedema by these mechanisms are as under:

i) **Oedema of cardiac disease** e.g. in congestive cardiac failure.

ii) **Ascites of liver disease** e.g. in cirrhosis of liver.

iii) **Oedema of renal disease** e.g. in nephrotic and nephritic syndrome.

**IMPORTANT TYPES OF OEDEMA**

As observed from the pathogenesis of oedema just described, more than one mechanism may be involved in many examples.
of localised and generalised oedema. Some of the important examples are described below.

**Renal Oedema**

Generalised oedema occurs in certain diseases of renal origin such as in nephrotic syndrome, nephritic syndrome, and in renal failure due to acute tubular injury.

1. **Oedema in nephrotic syndrome** Since there is persistent and heavy proteinuria (albuminuria) in nephrotic syndrome, there is hypoalbuminaemia causing decreased plasma oncotic pressure resulting in severe generalised oedema (nephrotic oedema). The hypoalbuminaemia also causes fall in the plasma volume activating renin-angiotensin-aldosterone mechanism which results in retention of sodium and water, thus setting in a vicious cycle which persists till the albuminuria continues. Similar type of mechanism operates in the pathogenesis of oedema in protein-losing enteropathy, adding further support to the role of protein loss in the causation of oedema.

   The **nephrotic oedema** is classically more severe, generalised and marked and is present in the subcutaneous tissues as well as in the visceral organs.

   **Grossly,** the affected organ is enlarged and heavy with tense capsule.

   **Microscopically,** the oedema fluid separates the connective tissue fibres of subcutaneous tissues. Depending upon the protein content, the oedema fluid may appear homogeneous, pale, eosinophilic, or may be deeply eosinophilic and granular.

2. **Oedema in nephritic syndrome** Oedema occurring in conditions with diffuse glomerular disease such as in acute diffuse glomerulonephritis and rapidly progressive glomerulonephritis is termed **nephritic oedema.** In contrast to nephrotic oedema, nephritic oedema is primarily not due to hypoproteinaemia because of low albuminuria but is largely due to excessive reabsorption of sodium and water in the renal tubules via renin-angiotensin-aldosterone mechanism. The protein content of oedema fluid in glomerulonephritis is quite low (less than 0.5 g/dl).

   The **nephritic oedema** is usually mild as compared to nephrotic oedema and begins in the loose tissues such as on the face around eyes, ankles and genitalia. Oedema in these conditions is usually not affected by gravity (unlike cardiac oedema).

   The salient differences between the nephrotic and nephritic oedema are outlined in **Table 4.2.**

3. **Oedema in acute tubular injury** Acute tubular injury following shock or toxic chemicals results in gross oedema of the body. The damaged tubules lose their capacity for selective reabsorption and concentration of the glomerular filtrate, resulting in excessive retention of water and electrolytes, and consequent oliguria. Besides, there is rise in blood urea.

**Cardiac Oedema**

Generalised oedema develops in right-sided and congestive cardiac failure. Pathogenesis of cardiac oedema is explained on the basis of the following mechanisms (Fig. 4.5):

1. Reduced cardiac output causes hypovolaemia which stimulates intrinsic-renal and extra-renal hormonal (renin-angiotensin-aldosterone) mechanisms as well as ADH secretion resulting in sodium and water retention (as discussed above) and consequent oedema.

2. Due to heart failure, there is elevated central venous pressure which is transmitted backward to the venous end of the capillaries, raising the capillary hydrostatic pressure and consequent transudation; this is known as **back pressure hypothesis.**

3. Chronic hypoxia may injure the capillary endothelium causing increased capillary permeability and result in oedema; this is called **forward pressure hypothesis.** However, this theory lacks support since the oedema by this mechanism is exudate whereas the cardiac oedema is typically transudate.

   In left heart failure, the changes are, however, different. There is venous congestion, particularly in the lungs, causing pulmonary oedema rather than generalised oedema.

   Cardiac oedema is influenced by gravity and is thus characteristically **dependent oedema** i.e. in an ambulatory patient it is on the lower extremities, while in a bed-ridden patient oedema appears on the sacral and genital areas. The accumulation of fluid may also occur in serous cavities.

**Pulmonary Oedema**

Acute pulmonary oedema is the most important form of local oedema as it causes serious functional impairment. However, it has special features and differs from oedema elsewhere in that the fluid accumulation is not only in the tissue space but also in the pulmonary alveoli.

**Etiopathogenesis** The hydrostatic pressure in the pulmonary capillaries is much lower (average 10 mmHg). Normally, the plasma oncotic pressure is adequate to prevent the escape of fluid into the interstitial space and hence lungs are normally free of oedema. Pulmonary oedema can result from either the elevation of pulmonary hydrostatic pressure or the increased capillary permeability (Fig. 4.6).

1. **Elevation in pulmonary hydrostatic pressure** (Haemodynamic oedema) In heart failure, there is increase in the

| **Table 4.2 Differences between nephrotic and nephritic oedema.** |
|------------------------|---------------------------|---------------------------|
| FEATURE                | NEPHROTIC OEDEMA          | NPHRITIC OEDEMA           |
| 1. Cause               | Nephrotic syndrome        | Glomerulonephritis (acute, rapidly progressive) |
| 2. Proteinuria         | Heavy                     | Moderate                  |
| 3. Protein content     | High (>1 g/dl)            | Low (<0.5 g/dl)           |
| 4. Mechanism           | ↓ Plasma oncotic pressure, Na⁺ and water retention | Na⁺ and water retention |
| 5. Degree of oedema    | Severe, generalised       | Mild                      |
| 6. Distribution        | Subcutaneous tissues as well as visceral organs | Loose tissues mainly (face, eyes, ankles, genitalia) |
pressure in pulmonary veins which is transmitted to pulmonary capillaries. This results in imbalance between pulmonary hydrostatic pressure and the plasma oncotic pressure so that excessive fluid moves out of pulmonary capillaries into the interstitium of the lungs. Simultaneously, the endothelium of the pulmonary capillaries develops fenestrations permitting passage of plasma proteins and fluid into the interstitium. The interstitial fluid so collected is cleared by the lymphatics present around the bronchioles, small muscular arteries and veins. As the capacity of the lymphatics to drain the fluid is exceeded (about ten-fold increase in fluid), the excess fluid starts accumulating in the interstitium (interstitial oedema) i.e. in the loose tissues around bronchioles, arteries and in the lobular septa. This causes thickening of the alveolar walls. Up to this stage, no significant impairment of gaseous exchange occurs. However, prolonged elevation of hydrostatic pressure and due to high pressure of interstitial oedema, the alveolar lining cells break and the alveolar air spaces are flooded with fluid (alveolar oedema) driving the air out of alveoli, thus seriously hampering the lung function.

Examples of pulmonary oedema by this mechanism are seen in left heart failure, mitral stenosis, pulmonary...
vein obstruction, thyrotoxicosis, cardiac surgery, nephrotic syndrome and obstruction to the lymphatic outflow by tumour or inflammation.

2. Increased vascular permeability (Irritant oedema) The vascular endothelium as well as the alveolar epithelial cells (alveolo-capillary membrane) may be damaged causing increased vascular permeability so that excessive fluid and plasma proteins leak out, initially into the interstitium and subsequently into the alveoli.

This mechanism explains pulmonary oedema in conditions such as in fulminant pulmonary and extrapulmonary infections, inhalation of toxic substances, aspiration, shock, radiation injury, hypersensitivity to drugs or antisera, uraemia and adult respiratory distress syndrome (ARDS).

2. Increased vascular permeability (Irritant oedema) The vascular endothelium as well as the alveolar epithelial cells (alveolo-capillary membrane) may be damaged causing increased vascular permeability so that excessive fluid and plasma proteins leak out, initially into the interstitium and subsequently into the alveoli.

This mechanism explains pulmonary oedema in conditions such as in fulminant pulmonary and extrapulmonary infections, inhalation of toxic substances, aspiration, shock, radiation injury, hypersensitivity to drugs or antisera, uraemia and adult respiratory distress syndrome (ARDS).

3. Acute high altitude oedema Individuals climbing to high altitude suddenly without halts and without waiting for acclimatisation to set in, suffer from serious circulatory and respiratory ill-effects. Commonly, the deleterious effects begin to appear after an altitude of 2500 metres is reached. These changes include appearance of oedema fluid in the lungs, congestion and widespread minute haemorrhages. These changes can cause death within a few days. The underlying mechanism is due to anoxic damage to the pulmonary vessels. However, if acclimatisation to high altitude is allowed to take place, the individual develops polycythaemia, raised pulmonary arterial pressure, increased pulmonary ventilation and a rise in heart rate and increased cardiac output, and thus the ill-effects do not appear.

MORPHOLOGIC FEATURES Irrespective of the underlying mechanism in the pathogenesis of pulmonary oedema, the fluid accumulates more in the basal regions of lungs. The thickened interlobular septa along with their dilated lymphatics may be seen in chest X-ray as linear lines perpendicular to the pleura and are known as Kerley’s lines. Grossly, the lungs in pulmonary oedema are heavy, moist and subcrepitant. Cut surface exudes frothy fluid (mixture of air and fluid). Microscopically, the alveolar capillaries are congested. Initially, the excess fluid collects in the interstitial lung spaces in the septal walls (interstitial oedema). Later, the fluid fills the alveolar spaces (alveolar oedema). Oedema fluid in the interstitium as well as the alveolar spaces appears as eosinophilic, granular and pink proteinaceous material, often admixed with some RBCs and alveolar macrophages, also called heart failure cells (Fig. 4.7). Organisation of alveolar oedema may be seen as brightly eosinophilic pink lines along the alveolar margin called hyaline membrane.

Long-standing pulmonary oedema is prone to get infected by bacteria producing hypostatic pneumonia which may be fatal.

Cerebral Oedema

Cerebral oedema or swelling of the brain is the most life-threatening example of oedema. The mechanism of fluid exchange in the brain differs from elsewhere in the body since there are no draining lymphatics in the brain but instead, the function of fluid-electrolyte exchange is performed by the blood-brain barrier located at the endothelial cells of the capillaries.

Cerebral oedema can be of 3 types: vasogenic, cytotoxic and interstitial.

1. Vasogenic Oedema This is the most common type and its mechanism is similar to oedema in other body sites from increased filtration pressure or increased capillary permeability. Vasogenic oedema is prominent around cerebral contusions, infarcts, brain abscess and some tumours.

Grossly, the white matter is swollen, soft, with flattened gyri and narrowed sulci. Sectioned surface is soft and gelatinous. Microscopically, there is separation of tissue elements by the oedema fluid and swelling of astrocytes. The perivascular (Virchow-Robin) space is widened and clear halos are seen around the small blood vessels.

2. Cytotoxic Oedema In this type, the blood-brain barrier is intact and the fluid accumulation is intracellular. The underlying mechanism is disturbance in the cellular osmoregulation as occurs in some metabolic derangements, acute hypoxia and with some toxic chemicals.

Figure 4.7 Pulmonary oedema. The alveolar capillaries are congested. The alveolar spaces as well as interstitium contain eosinophilic, granular, homogeneous and pink proteinaceous oedema fluid along with some RBCs and inflammatory cells.
Microscopically, the cells are swollen and vacuolated. In some situations, both vasogenic as well as cytotoxic cerebral oedema results e.g. in purulent meningitis.

3. INTERSTITIAL OEDEMA This type of cerebral oedema occurs when the excessive fluid crosses the ependymal lining of the ventricles and accumulates in the periventricular white matter. This mechanism is responsible for oedema in non-communicating hydrocephalus.

Hepatic Oedema

While oedema in chronic liver disease is discussed in detail in Chapter 19 (page 616), briefly the mechanisms involved in causation of oedema of the legs and ascites in cirrhosis of the liver is as under:

i) There is hypoproteinaemia due to impaired synthesis of proteins by the diseased liver.
ii) Due to portal hypertension, there is increased venous pressure in the abdomen, and hence raised hydrostatic pressure.
iii) Failure of inactivation of aldosterone in the diseased liver and hence hyperaldosteronism.
iv) Secondary stimulation of renin-angiotensin mechanism promoting sodium and water retention.

Nutritional Oedema

Oedema due to nutritional deficiency of proteins (kwashiorkor, prolonged starvation, famine, fasting), vitamins (beri-beri due to vitamin B12 deficiency) and chronic alcoholism occurs on legs but sometimes may be more generalised. The main contributing factors are hypoproteinaemia and sodium-water retention related to metabolic abnormalities. In kwashiorkor occurring in children in economically deprived communities in Africa and Asia, oedema is associated with characteristic mucocutaneous ulceration and depigmentation of the hair, all of which reverts back to normal on adequate nutrition.

Myxoedema

Myxoedema from hypothyroidism (page 794) is a form of non-pitting oedema occurring on skin of face and other parts of the body as also in the internal organs due to excessive deposition of glycosaminoglycans in the interstitium. Microscopically, it appears as basophilic mucopolysaccharides.

DEHYDRATION

Dehydration is a state of pure deprivation of water leading to sodium retention and hence a state of hyperatraemia. In other words, there is only loss of water without loss of sodium. Clinically, the patients present with intense thirst, mental confusion, fever, and oliguria.

ETIOLOGY Pure water deficiency is less common than salt depletion but can occur in the following conditions:

1. GI excretion:
   i) Severe vomitings
   ii) Diarrhoea
   iii) Cholera

2. Renal excretion:
   i) Acute renal failure in diuretic phase
   ii) Extensive use of diuretics
   iii) Endocrine diseases e.g. diabetes insipidus, Addison’s disease

3. Loss of blood and plasma:
   i) Severe injuries, severe burns
   ii) During childbirth

4. Loss through skin:
   i) Excessive perspiration
   ii) Hyperthermia

5. Accumulation in third space:
   i) Sudden development of ascites
   ii) Acute intestinal obstruction with accumulation of fluid in the bowel.

OVERHYDRATION

Overhydration is increased extracellular fluid volume due to pure water excess or water intoxication. Clinically, the patients present with disordered cerebral function e.g. nausea, vomiting, headache, confusion and in severe cases convulsions, coma, and even death.

ETIOLOGY Overhydration is generally an induced condition and is encountered in the following situations:

1. Excessive unmonitored intravascular infusion:
   i) Normal saline (0.9% sodium chloride)
   ii) Ringer lactate

2. Renal retention of sodium and water:
   i) Congestive heart failure
   ii) Acute glomerulonephritis
   iii) Cirrhosis
   iv) Cushing’s syndrome
   v) Chronic renal failure

MORPHOLOGICAL FEATURES There are no particular pathological changes in organs, except in advanced cases when the organs are dark and shrunken. However, there are haematological and biochemical changes.

- There is haemoconcentration as seen by increased PCV and raised haemoglobin.
- In late stage, there is rise in blood urea and serum sodium.
- Renal shutdown and a state of shock may develop.

MORPHOLOGICAL FEATURES Sudden weight gain is a significant parameter of excess of fluid accumulation. Haematological and biochemical changes include the following:

- Reduced PCV.
- Reduced plasma electrolytes and lowered plasma proteins.
**DISTURBANCES OF ELECTROLYTES AND pH OF BLOOD**

**ELECTROLYTE IMBALANCE**

It may be recalled here that normally the concentration of electrolytes within the cell and in the plasma is different. Intracellular compartment has higher concentration of potassium, calcium, magnesium and phosphate ions than the blood, while extracellular fluid (including serum) has higher concentration of sodium, chloride, and bicarbonate ions. In health, for *electrolyte homeostasis*, the concentration of electrolytes in both these compartments should be within normal limits. Normal serum levels of electrolytes are maintained in the body by a careful balance of 4 processes: their intake, absorption, distribution and excretion. Disturbance in any of these processes in diverse pathophysiologic states may cause *electrolyte imbalance*.

Among the important components in electrolyte imbalance, abnormalities in serum levels of sodium (hypotonic haemorrhage), potassium (hypokalaemia), calcium (hypocalcaemia) and magnesium (hypomagnesaemia) are clinically more important. A list of important clinical conditions producing abnormalities in sodium and potassium are given in Table 4.3, while calcium and phosphate imbalances are discussed in Chapter 26.

While it is beyond the scope of this book to delve into the subject of electrolyte imbalances in detail, a few general principles are as under:

i) Electrolyte imbalance in a given case may result from one or more conditions.

ii) Resultant abnormal serum level of more than one electrolyte may be linked to each other e.g. abnormality in serum levels of sodium and potassium; calcium and phosphate.

iii) Generally, the reflection of biochemical serum electrolyte levels is in the form of metabolic syndrome and clinical features rather than morphological findings in organs.

<table>
<thead>
<tr>
<th>Table 4.3 Electrolyte imbalances of sodium and potassium.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPONATRAEMIA</strong></td>
</tr>
<tr>
<td>A. Gain of Relatively More Water Than Loss of Sodium</td>
</tr>
<tr>
<td>i. Excessive use of diuretics</td>
</tr>
<tr>
<td>ii. Hypotonic irrigating fluid administration</td>
</tr>
<tr>
<td>iii. Excessive IV infusion of 5% dextrose</td>
</tr>
<tr>
<td>iv. Psychogenic polydipsia</td>
</tr>
<tr>
<td>v. Large volume of beer consumption</td>
</tr>
<tr>
<td>vi. Addison’s disease</td>
</tr>
<tr>
<td><strong>B. Loss of Relatively More Salt Than Water</strong></td>
</tr>
<tr>
<td>i. Excessive use of diuretics</td>
</tr>
<tr>
<td>ii. Renal failure (ARF, CRF)</td>
</tr>
<tr>
<td>iii. Replacement of water without simultaneous salt replacement in conditions causing combined salt and water deficiency</td>
</tr>
</tbody>
</table>

| **HYPERNATRAEMIA**                                         |
| A. Gain of Relatively More Salt Than Loss Of Water        |
| i. IV infusion of hypertonic solution                      |
| ii. Survivors from sea-drowning                            |
| iii. Difficulty in swallowing e.g. oesophageal obstruction |
| iv. Excessive sweating (in deserts, heat stroke)          |
| **B. Loss of Relatively More Water Than Salt**            |
| i. Diabetes insipidus                                     |
| ii. Induced water deprivation (non-availability of water, total fasting) |
| iii. Replacement of salt without simultaneous water replacement in conditions causing combined salt and water deficiency |

| **HYPOKALAEMIA**                                          |
| A. Decreased Potassium Intake                             |
| i. Anorexia                                               |
| ii. IV infusions without potassium                        |
| iii. Fasting                                             |
| iv. Diet low in potassium                                 |
| B. Excessive Potassium Excretion                          |
| i. Loss from GI tract (e.g. vomitings, diarrhoea, laxatives) |
| ii. Loss from kidneys (e.g. excessive use of diuretics, corticosteroid therapy, hyperaldosteronism, Cushing’s syndrome) |
| iii. Loss through skin (e.g. profuse perspiration)        |
| iv. Loss from abnormal routes (e.g. mucinous tumours, drainage of fistula, gastric suction) |

| **HYPERKALAEMIA**                                         |
| A. Excessive Potassium Intake                             |
| i. Excessive or rapid infusion containing potassium        |
| ii. Large volume of transfusion of stored blood           |
| B. Decreased Potassium Excretion                          |
| i. Oliguric phase of acute renal failure                  |
| ii. Adrenal cortical insufficiency (e.g. Addison’s disease) |
| iii. Drugs such as ACE (angiotensin-converting enzyme) inhibitors |
| iv. Renal tubular disorders                               |
| C. Excessive Mobilisation from Intracellular into Extracellular Compartment |
| i. Excess insulin therapy                                 |
| ii. Alkalosis                                             |

**GENERAL PATHOLOGY**

- Various mechanisms operating singly or in combination to produce oedema are: decreased plasma oncotic pressure, increased capillary hydrostatic pressure, lymphatic obstruction, tissue factors (increased oncotic pressure of interstitial fluid, and decreased tissue tension), increased capillary permeability, and sodium and water retention.
- Generalised oedema of renal origin occurs in nephrotic syndrome, nephritic syndrome, and in renal failure due to acute tubular injury.
- Cardiac oedema is generalised and dependent type and develops in right-sided and congestive cardiac failure.
- Acute pulmonary oedema results from either the elevation of pulmonary hydrostatic pressure or the increased capillary permeability from various causes.
- In cerebral oedema, fluid-electrolyte exchange occurs at the blood-brain barrier because there are no lymphatics. Cerebral oedema can be vasogenic, cytotoxic and interstitial.
- Dehydration is pure deprivation of water leading to sodium retention and a state of hypernatraemia.
- Overhydration is increased extracellular fluid volume due to pure water excess or water intoxication.

**Table 4.3 Electrolyte imbalances of sodium and potassium.**

<table>
<thead>
<tr>
<th><strong>HYPONATRAEMIA</strong></th>
<th><strong>Gain of Relatively More Water Than Loss of Sodium</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Excessive use of diuretics</td>
</tr>
<tr>
<td>ii.</td>
<td>Hypotonic irrigating fluid administration</td>
</tr>
<tr>
<td>iii.</td>
<td>Excessive IV infusion of 5% dextrose</td>
</tr>
<tr>
<td>iv.</td>
<td>Psychogenic polydipsia</td>
</tr>
<tr>
<td>v.</td>
<td>Large volume of beer consumption</td>
</tr>
<tr>
<td>vi.</td>
<td>Addison’s disease</td>
</tr>
<tr>
<td><strong>B. Loss of Relatively More Salt Than Water</strong></td>
<td>i. Excessive use of diuretics</td>
</tr>
<tr>
<td>ii.</td>
<td>Renal failure (ARF, CRF)</td>
</tr>
<tr>
<td>iii.</td>
<td>Replacement of water without simultaneous salt replacement in conditions causing combined salt and water deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HYPERNATRAEMIA</strong></th>
<th><strong>Gain of Relatively More Salt Than Loss Of Water</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>IV infusion of hypertonic solution</td>
</tr>
<tr>
<td>ii.</td>
<td>Survivors from sea-drowning</td>
</tr>
<tr>
<td>iii.</td>
<td>Difficulty in swallowing e.g. oesophageal obstruction</td>
</tr>
<tr>
<td>iv.</td>
<td>Excessive sweating (in deserts, heat stroke)</td>
</tr>
<tr>
<td><strong>B. Loss of Relatively More Water Than Salt</strong></td>
<td>i. Diabetes insipidus</td>
</tr>
<tr>
<td>ii.</td>
<td>Induced water deprivation (non-availability of water, total fasting)</td>
</tr>
<tr>
<td>iii.</td>
<td>Replacement of salt without simultaneous water replacement in conditions causing combined salt and water deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HYPOKALAEMIA</strong></th>
<th><strong>Decreased Potassium Intake</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Anorexia</td>
</tr>
<tr>
<td>ii.</td>
<td>IV infusions without potassium</td>
</tr>
<tr>
<td>iii.</td>
<td>Fasting</td>
</tr>
<tr>
<td>iv.</td>
<td>Diet low in potassium</td>
</tr>
<tr>
<td><strong>B. Excessive Potassium Excretion</strong></td>
<td>i. Loss from GI tract (e.g. vomitings, diarrhoea, laxatives)</td>
</tr>
<tr>
<td>ii.</td>
<td>Loss from kidneys (e.g. excessive use of diuretics, corticosteroid therapy, hyperaldosteronism, Cushing’s syndrome)</td>
</tr>
<tr>
<td>iii.</td>
<td>Loss through skin (e.g. profuse perspiration)</td>
</tr>
<tr>
<td>iv.</td>
<td>Loss from abnormal routes (e.g. mucinous tumours, drainage of fistula, gastric suction)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HYPERKALAEMIA</strong></th>
<th><strong>Excessive Potassium Intake</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Excessive or rapid infusion containing potassium</td>
</tr>
<tr>
<td>ii.</td>
<td>Large volume of transfusion of stored blood</td>
</tr>
<tr>
<td><strong>B. Decreased Potassium Excretion</strong></td>
<td>i. Oliguric phase of acute renal failure</td>
</tr>
<tr>
<td>ii.</td>
<td>Adrenal cortical insufficiency (e.g. Addison’s disease)</td>
</tr>
<tr>
<td>iii.</td>
<td>Drugs such as ACE (angiotensin-converting enzyme) inhibitors</td>
</tr>
<tr>
<td>iv.</td>
<td>Renal tubular disorders</td>
</tr>
<tr>
<td><strong>C. Excessive Mobilisation from Intracellular into Extracellular Compartment</strong></td>
<td>i. Muscle necrosis (e.g. in crush injuries, haemolysis)</td>
</tr>
<tr>
<td>ii.</td>
<td>Diabetic acidosis</td>
</tr>
<tr>
<td>iii.</td>
<td>Use of drugs such as beta-blockers, cytotoxic drugs</td>
</tr>
<tr>
<td>iv.</td>
<td>Insufficient insulin</td>
</tr>
</tbody>
</table>
iv) Clinical manifestations of a particular electrolyte imbalance are related to its pathophysiologic role in that organ or tissue.

**PH OF BLOOD**

During metabolism of cells, carbon dioxide and metabolic acids are produced. CO₂ combines with water to form carbonic acid. The role of bicarbonate buffering system in the extracellular compartment has already been stated above. In order to have acid-base homeostasis to maintain blood pH of 7.4, both carbonic acid and metabolic acids must be excreted from the body via lungs (for CO₂) and kidneys (for metabolic acids). Thus, the pH of blood depends upon 2 principal factors: 
- serum concentration of bicarbonate; and
- partial pressure of CO₂ that determines the concentration of carbonic acid.

Accordingly, the disorders of the pH of the blood, termed as acidosis (blood pH below 7.4) and alkalosis (blood pH above 7.4), can be of 2 types:
1. Alternations in the blood bicarbonate levels: These are metabolic acidosis and alkalosis.
2. Alteration in Pco₂ (which depends upon the ventilatory function of the lungs): These are respiratory acidosis and alkalosis.

**ACID BASE IMBALANCE**

Abnormalities in acid-base homeostasis produce following 4 principal metabolic states which have diverse clinical manifestations due to pathophysiologic derangements:

**Metabolic Acidosis**

A fall in the blood pH due to metabolic component is brought about by fall of bicarbonate level and excess of H⁺ ions in the blood. This occurs in the following situations:
- Production of large amounts of lactic acid (lactic acidosis) e.g. in vigorous exercise, shock.
- Uncontrolled diabetes mellitus (diabetic ketoacidosis).
- Starvation.
- Chronic renal failure.
- Therapeutic administration of ammonium chloride or acetazolamide (diamox).

High blood levels of H⁺ ions in metabolic acidosis stimulate the respiratory centre so that the breathing is deep and rapid (*air hunger or Kussmaul's respiration*). There is fall in the plasma bicarbonate levels.

**Metabolic Alkalosis**

A rise in the blood pH due to rise in the bicarbonate levels of plasma and loss of H⁺ ions is called metabolic alkalosis. This is seen in the following conditions:
- Severe and prolonged vomitings.
- Administration of alkaline salts like sodium bicarbonate.
- Hypokalaemia such as in Cushing’s syndrome, increased secretion of aldosterone.

Clinically, metabolic alkalosis is characterised by depression of respiration, depressed renal function with uraemia and increased bicarbonate excretion in the urine. The blood level of bicarbonate is elevated.

**Respiratory Acidosis**

A fall in the blood pH occurring due to raised Pco₂ consequent to hypoventilation of lungs (CO₂ retention) causes respiratory acidosis. This can occur in the following circumstances:
- Air obstruction as occurs in chronic bronchitis, emphysema, asthma.
- Restricted thoracic movement e.g. in pleural effusion, ascites, pregnancy, kyphoscoliosis.
- Impaired neuromuscular function e.g. in poliomyelitis, polyneuritis.

Clinically, there is peripheral vasodilatation and raised intracranial pressure. If there is severe CO₂ retention, patients may develop confusion, drowsiness and coma. The arterial Pco₂ level is raised.

**Respiratory Alkalosis**

A rise in the blood pH occurring due to lowered Pco₂ consequent to hyperventilation of the lungs (excess removal of CO₂) is called respiratory alkalosis. This occurs in the following conditions:
- Hysterical overbreathing.
- Working at high temperature.
- At high altitude.
- Meningitis, encephalitis.
- Salicylate intoxication.

Clinically, the patients with respiratory alkalosis are characterised by peripheral vasoconstriction and consequent pallor, lightheadedness and tetany. The arterial Pco₂ is lowered.

---

**GIST BOX 4.3 Disturbances of Electrolytes and pH of Blood**

- Normal serum levels of electrolytes are maintained in the body by a careful balance of 4 processes: their intake, absorption, distribution and excretion.
- The pH of blood depends upon serum concentration of bicarbonate and partial pressure of CO₂.
- Metabolic acidosis is a fall in the blood pH due to fall of bicarbonate level and excess of H⁺ ions in the blood, while a rise in the blood pH due to rise in bicarbonate levels of plasma and loss of H⁺ ions is called metabolic alkalosis.
- Raised Pco₂ consequent to hyperventilation of lungs (CO₂ retention) causes respiratory acidosis, while a lowered Pco₂ consequent to hyperventilation of the lungs (excess removal of CO₂) is called respiratory alkalosis.

---

**HAEMODYNAMIC DERANGEMENTS**

The principles of blood flow are called haemodynamics. Normal circulatory function requires uninterrupted flow of blood from the left ventricle to the farthest capillaries in the body; return of blood from systemic capillary network into the right ventricle; and from the right ventricle to the farthest pulmonary capillaries and back to the left atrium (*Fig. 4.8*). There are three essential requirements to maintain normal blood flow and perfusion of tissues: normal anatomic features, normal physiologic controls for blood flow, and normal biochemical composition of the blood.
Derangements of blood flow or haemodynamic disturbances are considered under 2 broad headings:
I. **Disturbances in the volume of the circulating blood** These include: hyperaemia and congestion, haemorrhage and shock.
II. **Circulatory disturbances of obstructive nature** These are: thrombosis, embolism, ischaemia and infarction.

**DISTURBANCES IN THE VOLUME OF CIRCULATING BLOOD**

**HYPERAEMIA AND CONGESTION**

Hyphaemia and congestion are the terms used for localised increase in the volume of blood within dilated vessels of an organ or tissue.

- Increased volume of blood from arterial and arteriolar dilatation (i.e. increased inflow) is referred to as hyperaemia or active hyperaemia.
- Impaired venous drainage (i.e. diminished outflow) is called venous congestion or passive hyperaemia (Fig. 4.9).

If the condition develops rapidly it is called acute, while more prolonged and gradual response is known as chronic.

**Active Hyperaemia**

The dilatation of arteries, arterioles and capillaries is effected either through sympathetic neurogenic mechanism or via the release of vasoactive substances. The affected tissue or organ is pink or red in appearance (erythema).

The examples of active hyperaemia are seen in the following conditions:
- Inflammation e.g. congested vessels in the walls of alveoli in pneumonia
- Blushing i.e. flushing of the skin of face in response to emotions
- Menopausal flush
- Muscular exercise
- High grade fever
- Goitre
- Arteriovenous malformations

Clinically, hyperaemia is characterised by redness and raised temperature in the affected part.

**Passive Hyperaemia (Venous Congestion)**

The dilatation of veins and capillaries due to impaired venous drainage results in passive hyperaemia or venous congestion, commonly referred to as passive congestion. Congestion may be acute or chronic, the latter being more common and is called chronic venous congestion (CVC). The affected tissue or organ is bluish in colour due to accumulation of venous blood (cyanosis). Obstruction to the venous outflow may be local or systemic. Accordingly, venous congestion is of 2 types:

- **Local venous congestion** results from obstruction to the venous outflow from an organ or part of the body e.g. portal venous obstruction in cirrhosis of the liver, outside pressure on the vessel wall as occurs in tight bandage, plasters, tumours, pregnancy, hernia etc, or intraluminal occlusion by thrombosis.
- **Systemic (General) venous congestion** is engorgement of veins e.g. in left-sided and right-sided heart failure and diseases of the lungs which interfere with pulmonary blood flow like pulmonary fibrosis, emphysema etc. Usually the fluid accumulates upstream to the specific chamber of the heart which is initially affected (page 399). For example, in left-sided heart failure (such as due to mechanical overload in aortic stenosis, or due to weakened left ventricular wall...
as in myocardial infarction) pulmonary congestion (or CVC of lungs) results, whereas in right-sided heart failure (such as due to pulmonary stenosis or pulmonary hypertension) systemic venous congestion (i.e. CVC of systemic organs) results. Fig. 4.10 illustrates the mechanisms involved in passive or venous congestion of different organs.

**MORPHOLOGY OF CVC OF ORGANS**

**CVC Lung**

Chronic venous congestion of the lung occurs in left heart failure (Chapter 14) (e.g. in rheumatic mitral stenosis) resulting in rise in pulmonary venous pressure.

*Grossly,* the lungs are heavy and firm in consistency. The sectioned surface is dark and rusty brown in colour, referred to as *brown induration* of the lungs.

*Histologically,* the features are as under:

i) The alveolar septa are widened due to presence of interstitial oedema and dilated and congested capillaries in the septal wall. There is also slight increase in fibrous connective tissue in the alveolar septa.

ii) Rupture of dilated and congested capillaries may result in minute intra-alveolar haemorrhages. The breakdown of erythrocytes liberates haemosiderin pigment which is taken up by alveolar macrophages, called as *heart failure cells,* seen in the alveolar lumina. The brown induration observed on the cut surface of the lungs is due to the pigmentation and fibrosis (Fig. 4.11).

**CVC Liver**

Chronic venous congestion of the liver occurs in right heart failure and sometimes due to occlusion of inferior vena cava and hepatic vein.

*Grossly,* the liver is enlarged and tender and the capsule is tense. Cut surface shows characteristic *nutmeg* appearance due to red and yellow mottled appearance, corresponding to congested centre of lobules and fatty peripheral zone respectively (Fig. 4.12).

*Microscopically,* the changes of passive congestion are more marked in the centrilobular zone (zone 3) which is farthest from blood supply (periportal zone, zone 1) and thus bears the brunt of hypoxia the most.

---

*Nutmeg* (vernacular name *jaiphal*) is the seed of a spice tree that grows in India, and is used in cooking as spice for giving flavours.
**CVC Spleen**

Chronic venous congestion of the spleen occurs in right heart failure and in portal hypertension from cirrhosis of liver.

***CVC Lung***

The alveolar septa are widened and thickened due to congestion, oedema and mild fibrosis. The alveolar lumina contain heart failure cells (alveolar macrophages containing haemosiderin pigment).

**Grossly,** the spleen in early stage is slightly to moderately enlarged (up to 250 g as compared to normal 150 g), while in long-standing cases there is progressive enlargement and may weigh up to 500 to 1000 g. The organ is deeply congested, tense and cyanotic. Sectioned surface is gray tan (Fig. 4.14).

**Microscopically,** the features are as under (Fig. 4.15):

i) Red pulp is enlarged due to congestion and marked sinusoidal dilatation and there are areas of recent and old haemorrhages. Sinusoids may get converted into capillaries (capillarisation of sinusoids).

ii) There is hyperplasia of reticuloendothelial cells in the red pulp of the spleen (splenic macrophages).

iii) There is fibrous thickening of the capsule and of the trabeculae.
iv) Some of haemorrhages overlying fibrous tissue get deposits of haemosiderin pigment and calcium salts; these organised structures are termed as Gamma-Gandy bodies or siderofibrotic nodules.
v) Firmness of the spleen in advanced stage is seen more commonly in hepatic cirrhosis (congestive splenomegaly) and is the commonest cause of hypersplenism (Chapter 12).

CVC Kidney

**Grossly**, the kidneys are slightly enlarged and the medulla is congested.

**Microscopically**, the changes are rather mild. The tubules may show degenerative changes like cloudy swelling and fatty change. The glomeruli may show mesangial proliferation.

HAEMORRHAGE

Haemorrhage is the escape of blood from a blood vessel. The bleeding may occur *externally, or internally* into the serous cavities (e.g. haemothorax, haemoperitoneum, haemopericardium), or into a hollow viscus. Extravasation of blood into the tissues with resultant swelling is known as *haematoma*. Large extravasations of blood into the skin and mucous membranes are called *echymoses*. *Purpuras* are small areas of haemorrhages (upto 1 cm) into the skin and mucous membrane, whereas *petechiae* are minute pinhead-sized haemorrhages. Microscopic escape of erythrocytes into loose tissues may occur following marked congestion and is known as *diapedesis*.

**ETIOLOGY** The blood loss may be large and sudden (*acute*), or small repeated bleeds may occur over a period of time (*chronic*). The various causes of haemorrhage are as under:

1. **Trauma** to the vessel wall e.g. penetrating wound in the heart or great vessels, during labour etc.
2. **Spontaneous haemorrhage** e.g. rupture of an aneurysm, septicaemia, bleeding diathesis (such as purpura), acute leukaemias, pernicious anaemia, scurvy.
3. **Inflammatory lesions of the vessel wall** e.g. bleeding from chronic peptic ulcer, typhoid ulcers, blood vessels traversing a tuberculous cavity in the lung, syphilitic involvement of the aorta, polyarteritis nodosa.
4. **Neoplastic invasion** e.g. haemorrhage following vascular invasion in carcinoma of the tongue.
5. **Vascular diseases** e.g. atherosclerosis.
6. **Elevated pressure within the vessels** e.g. cerebral and retinal haemorrhage in systemic hypertension, severe haemorrhage from varicose veins due to high pressure in the veins of legs or oesophagus.

**Figure 4.13** CVC liver. The centrilobular zone shows marked degeneration and necrosis of hepatocytes accompanied by haemorrhage while the peripheral zone shows mild fatty change of liver cells.

**Figure 4.14** CVC spleen (Congestive splenomegaly). Sectioned surface shows that the spleen is heavy and enlarged in size. The colour of sectioned surface is grey-tan.
The effects of blood loss depend upon 3 main factors:
i) the amount of blood loss;  
ii) the speed of blood loss; and  
iii) the site of haemorrhage.

The loss up to 20% of blood volume suddenly or slowly generally has little clinical effects because of compensatory mechanisms. A sudden loss of 33% of blood volume may cause death, while loss of up to 50% of blood volume gradually over a period of 24 hours may not be necessarily fatal. However, chronic blood loss generally produces iron deficiency anaemia, whereas acute haemorrhage may lead to serious immediate consequences such as hypovolaemic shock.

**GIST BOX 4.4**

**Hyperaemia, Congestion and Haemorrhage**
- Increased volume of blood from arterial and arteriolar dilatation (i.e. increased inflow) is referred to as hyperaemia or active hyperaemia, while impaired venous drainage (i.e. diminished outflow) is called venous congestion or passive hyperaemia.
- Congestion may be acute or chronic, the latter being more common and is called chronic venous congestion (CVC).
- Systemic venous congestion is engorgement of veins e.g. in left-sided heart failure (CVC lungs), right-sided heart failure (CVC liver, spleen, kidneys, other sites).
- Haemorrhage is the escape of blood from a blood vessel. The bleeding may occur externally, or internally into the serous cavities, into a hollow viscus, or in to skin and mucous membranes.
- Rapid loss of above 33% of blood volume is more serious than gradual blood loss of 50% in 24 hours.

**SHOCK**

**Definition**

Shock is a life-threatening clinical syndrome of cardiovascular collapse characterised by:

- an acute reduction of effective circulating blood volume (hypotension); and  
- an inadequate perfusion of cells and tissues (hypoperfusion).

If uncompensated, these mechanisms may lead to impaired cellular metabolism and death.

Thus, by definition "true (or secondary) shock" is a circulatory imbalance between oxygen supply and oxygen requirements at the cellular level, and is also called as circulatory shock and is the type which is commonly referred to as ‘shock’ if not specified.

The term “initial (or primary) shock” is used for transient and usually a benign vasovagal attack resulting from sudden reduction of venous return to the heart caused by neurogenic vasodilatation and consequent peripheral pooling of blood e.g. immediately following trauma, severe pain or emotional overreaction such as due to fear, sorrow or surprise. Clinically, patients of primary shock suffer from the attack lasting for a few seconds or minutes and develop brief unconsciousness, weakness, sinking sensation, pale and clammy limbs, weak and rapid pulse, and low blood pressure. Another type of shock which is not due to circulatory derangement is anaphylactic shock from type 1 immunologic (anaphylactic) reaction (page 60).

**Classification and Etiology**

Although in a given clinical case, two or more factors may be involved in causation of true shock, a simple etiologic classification of shock syndrome divides it into following 3 major types and a few other variants (Table 4.4):

1. **Hypovolaemic shock** This form of shock results from inadequate circulatory blood volume by various etiologic factors that may be either from the loss of red cell mass and plasma due to haemorrhage, or from the loss of plasma volume alone.

2. **Cardiogenic shock** Acute circulatory failure with sudden fall in cardiac output from acute diseases of the heart without
In general, all forms of shock involve following 3 derangements:

i) Reduced effective circulating blood volume.

ii) Reduced supply of oxygen to the cells and tissues with resultant anoxia.

iii) Inflammatory mediators and toxins released from shock-induced cellular injury.

These derangements initially set in compensatory mechanisms (discussed below) but eventually a vicious cycle of cell injury and severe cellular dysfunction lead to breakdown of organ function (Fig. 4.16).

1. **Reduced effective circulating blood volume** It may result by either of the following mechanisms:

   i) by actural loss of blood volume as occurs in hypovolaemic shock; or

   ii) by decreased cardiac output without actual loss of blood (normovolaemia) as occurs in cardiogenic shock and septic shock.

2. **Impaired tissue oxygenation** Following reduction in the effective circulating blood volume from either of the above two mechanisms and from any of the etiologic agents, there is decreased venous return to the heart resulting in decreased cardiac output. This consequently causes reduced supply of oxygen to the organs and tissues and hence tissue anoxia occurs, which sets in cellular injury.

3. **Release of inflammatory mediators** In response to cellular injury, innate immunity of the body gets activated as a body defense mechanism and causes release of inflammatory mediators but eventually these agents themselves become the cause of cell injury. Endotoxins in bacterial wall in septic shock stimulate massive release of pro-inflammatory mediators (cytokines) but a similar process of release of these agents takes place in late stages of shock from other causes. Several pro-inflammatory mediators are released from monocytess, macrophages, other leucocytes and other body cells, the most important being the tumour necrosis factor-(TNF)-α and interleukin-1 (IL-1) cytokines (Fig. 4.17).

   After these general comments on mechanisms in shock, features specific to pathogenesis of three major forms of shock are given below:

**PATHOGENESIS OF HYPOVOLAEMIC SHOCK** Hypovolaemic shock occurs from inadequate circulating blood volume due to various causes, most often from loss of red cell mass due to haemorrhage and, therefore, also called as haemorrhagic shock. The major effects in this are due to decreased cardiac output and low intracardiac pressure. The severity of clinical features depends upon degree of blood volume lost; accordingly haemorrhagic shock is divided into 4 types:

i) \( \leq 1000 \text{ ml} \): Compensated

ii) 1000-1500 ml: Mild

iii) 1500-2000 ml: Moderate

iv) \( >2000 \text{ ml} \): Severe

   Major clinical features are increased heart rate (tachycardia), low blood pressure (hypotension), low urinary output (oliguria to anuria) and alteration in mental state (agitated to confused to lethargic).

**PATHOGENESIS OF CARDIOGENIC SHOCK** Cardiogenic shock results from a severe left ventricular dysfunction from various causes such as acute myocardial infarction. The

---

**Table 4.4** Classification and etiology of shock.

<table>
<thead>
<tr>
<th>1. HYPOVOLAEMIC SHOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Acute haemorrhage</td>
</tr>
<tr>
<td>ii) Dehydration from vomitings, diarrhoea</td>
</tr>
<tr>
<td>iii) Burns</td>
</tr>
<tr>
<td>iv) Excessive use of diuretics</td>
</tr>
<tr>
<td>v) Acute pancreatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. CARDIOGENIC SHOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Deficient emptying e.g.</td>
</tr>
<tr>
<td>a) Myocardial infarction</td>
</tr>
<tr>
<td>b) Cardiomyopathies</td>
</tr>
<tr>
<td>c) Rupture of the heart, ventricle or papillary muscle</td>
</tr>
<tr>
<td>d) Cardiac arrhythmias</td>
</tr>
<tr>
<td>ii) Deficient filling e.g.</td>
</tr>
<tr>
<td>a) Pulmonary embolism</td>
</tr>
<tr>
<td>b) Pulmonary embolism</td>
</tr>
<tr>
<td>c) Tension pneumothorax</td>
</tr>
<tr>
<td>d) Dissecting aortic aneurysm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. SEPTIC SHOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Gram-negative septicemia (endotoxic shock) e.g.</td>
</tr>
<tr>
<td>Infection with E. coli, Proteus, Klebsiella, Pseudomonas and Bacteroides</td>
</tr>
<tr>
<td>ii) Gram-positive septicemia (exotoxic shock) e.g. Infection with streptococci, pneumococci</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. OTHER TYPES</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Traumatic shock</td>
</tr>
<tr>
<td>a) Severe injuries</td>
</tr>
<tr>
<td>b) Surgery with marked blood loss</td>
</tr>
<tr>
<td>c) Obstetrical trauma</td>
</tr>
<tr>
<td>ii) Neurogenic shock</td>
</tr>
<tr>
<td>a) High cervical spinal cord injury</td>
</tr>
<tr>
<td>b) Accidental high spinal anaesthesia</td>
</tr>
<tr>
<td>c) Severe head injury</td>
</tr>
<tr>
<td>iii) Hypoadrenal shock</td>
</tr>
<tr>
<td>a) Administration of high doses of glucocorticoids</td>
</tr>
<tr>
<td>b) Secondary adrenal insufficiency (e.g. in tuberculosis, metastatic disease, bilateral adrenal haemorrhage, idiopathic adrenal atrophy)</td>
</tr>
</tbody>
</table>

---

actual reduction of blood volume (normovolaemia) results in cardiogenic shock.

3. **Septic (Toxaemic) shock** Severe bacterial infections or septicaemia induce septic shock. It may be the result of Gram-negative septicaemia (endotoxic shock) which is more common, or less often from Gram-positive septicaemia (exotoxic shock).

4. **Other types** These include following types:

i) **Traumatic shock** Shock resulting from trauma is initially due to hypovolaemia, but even after haemorrhage has been controlled, these patients continue to suffer loss of plasma volume into the interstitium of injured tissue and hence is considered separately in some descriptions.

ii) **Neurogenic shock** Neurogenic shock results from causes of interruption of sympathetic vasomotor supply.

iii) **Hypoadrenal shock** Hypoadrenal shock occurs from unknown adrenal insufficiency in which the patient fails to respond normally to the stress of trauma, surgery or illness.
resultant decreased cardiac output has its effects in the form of decreased tissue perfusion and movement of fluid from pulmonary vascular bed into pulmonary interstitial space initially (interstitial pulmonary oedema) and later into alveolar spaces (alveolar pulmonary oedema).

**PATHOGENESIS OF SEPTIC SHOCK** Septic shock results most often from Gram-negative bacteria entering the body from genitourinary tract, alimentary tract, respiratory tract or skin, and less often from Gram-positive bacteria. In septic shock, there is immune system activation and severe systemic inflammatory response to infection as follows:

i) **Activation of macrophage-monocytes** Lysis of Gram-negative bacteria releases endotoxin, a lipopolysaccharide (LPS), into circulation where it binds to lipopolysaccharide-binding protein (LBP). The complex of LPS-LBP binds to CD14 molecule on the surface of the monocyte/macrophages which are stimulated to elaborate proinflammatory cytokines, the most important ones being TNF-α and IL-1. The effects of these cytokines are as under:
   a) **By altering endothelial cell adhesiveness**: This results in recruitment of more neutrophils which liberate free radicals that cause vascular injury.
   b) **Promoting nitric oxide synthase**: This stimulates increased synthesis of nitric oxide which is responsible for vasodilatation and hypotension.

ii) **Activation of other inflammatory responses** Microbial infection activates other inflammatory cascades which have profound effects in triggering septic shock. These are as under:
   a) **Activation of complement pathway**: End-products C5a and C3a induce microemboli and endothelial damage.
b) Activation of mast cells: Histamine is released which increases capillary permeability.

c) Activation of coagulation system: Enhances development of thrombi.

d) Activation of kinin system: Released bradykinin causes vasodilatation and increased capillary permeability. The net result of above mechanisms is vasodilatation and increased vascular permeability in septic shock. Profound peripheral vasodilatation and pooling of blood causes hyperdynamic circulation in septic shock, in contrast to hypovolaemic and cardiogenic shock. Increased vascular permeability causes development of inflammatory oedema. Disseminated intravascular coagulation (DIC) is prone to develop in septic shock due to endothelial cell injury by toxins. Reduced blood flow produces hypotension, inadequate perfusion of cells and tissues, finally leading to organ dysfunction.

Pathophysiology (Stages of Shock)

Although deterioration of the circulation in shock is a progressive and continuous phenomenon and compensatory mechanisms become progressively less effective, historically shock has been divided arbitrarily into 3 stages (Fig. 4.18):

1. Compensated (non-progressive, initial, reversible) shock
2. Progressive decompensated shock
3. Irreversible decompensated shock

COMPENSATED (NON-PROGRESSIVE, INITIAL, REVERSIBLE) SHOCK
In the early stage of shock, an attempt is made to maintain adequate cerebral and coronary blood supply by redistribution of blood so that the vital organs (brain and heart) are adequately perfused and oxygenated. This is achieved by activation of various neurohormonal mechanisms causing widespread vasoconstriction and by fluid conservation by the kidney. If the condition that caused the shock is adequately treated, the compensatory mechanism may be able to bring about recovery and re-establish the normal circulation; this is called compensated or reversible shock. These compensatory mechanisms are as under:

i) Widespread vasoconstriction
In response to reduced blood flow (hypotension) and tissue anoxia, the neural and humoral factors (e.g. baroreceptors, chemoreceptors, catecholamines, renin, and angiotensin-II) are activated. All these bring about vasoconstriction, particularly in the vessels of the skin and abdominal viscera. Widespread vasoconstriction is a protective mechanism as it causes increased peripheral resistance, increased heart rate (tachycardia) and increased blood pressure. However, in septic shock, there is initial vasodilatation followed by vasoconstriction. Besides, in severe septic shock there is elevated level of thromboxane A2 which is a potent vasoconstrictor and may augment the cardiac output along with other sympathetic mechanisms. Clinically, cutaneous vasoconstriction is responsible for cool and pale skin in initial stage of shock.

ii) Fluid conservation by the kidney
In order to compensate the actual loss of blood volume in hypovolaemic shock, the following factors may assist in restoring the blood volume and improve venous return to the heart:

a) Release of aldosterone from hypoxic kidney by activation of renin-angiotensin-aldosterone mechanism.

b) Release of ADH due to decreased effective circulating blood volume.

c) Reduced glomerular filtration rate (GFR) due to arteriolar constriction.

d) Shifting of tissue fluids into the plasma due to lowered capillary hydrostatic pressure (hypotension).

iii) Stimulation of adrenal medulla
In response to low cardiac output, adrenal medulla is stimulated to release excess of catecholamines (epinephrine and non-epinephrine) which increase heart rate and try to increase cardiac output.

PROGRESSIVE DECOMPENSATED SHOCK
This is a stage when the patient suffers from some other stress or risk factors (e.g. pre-existing cardiovascular and lung disease) besides persistence of the shock condition; this causes progressive deterioration. The effects of resultant tissue hypoperfusion in progressive decompensated shock are as under:

i) Pulmonary hypoperfusion
Decompensated shock worsens pulmonary perfusion and increases vascular permeability resulting in tachypnoea and adult respiratory distress syndrome (ARDS).

<table>
<thead>
<tr>
<th>STAGE</th>
<th>PATHOGENESIS</th>
<th>EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPENSATED (INITIAL) SHOCK</td>
<td>i) Widespread vasoconstriction</td>
<td>• Tachycardia</td>
</tr>
<tr>
<td></td>
<td>ii) Fluid conservation by kidney</td>
<td>• Cool clammy skin</td>
</tr>
<tr>
<td></td>
<td>iii) Stimulation of adrenal medulla</td>
<td></td>
</tr>
<tr>
<td>PROGRESSIVE DECOMPENSATED SHOCK</td>
<td>i) Pulmonary hypoperfusion</td>
<td>• ↓ Cardiac output</td>
</tr>
<tr>
<td></td>
<td>ii) Tissue ischaemia</td>
<td>• Mental confusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Urinary output</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tachypnoea</td>
</tr>
<tr>
<td>IRREVERSIBLE DECOMPENSATED SHOCK</td>
<td>i) Progressive vasodilatation</td>
<td>• Brain: Hypoxic encephalopathy</td>
</tr>
<tr>
<td></td>
<td>ii) ↑ Vascular permeability</td>
<td>• Heart: Focal myocardial necrosis</td>
</tr>
<tr>
<td></td>
<td>iii) Myocardial depressant factor (MDF)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>iv) Pulmonary hypoperfusion</td>
<td>• Lungs: ARDS</td>
</tr>
<tr>
<td></td>
<td>v) Anoxic damage</td>
<td>• Kidney: ATN</td>
</tr>
<tr>
<td></td>
<td>vi) Hypercoagulability</td>
<td>• Adrenals: Necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GI: Haemorrhagic gastroenteropathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Liver: Necrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood: DIC</td>
</tr>
</tbody>
</table>
ii) **Tissue ischaemia** Impaired tissue perfusion causes switch from aerobic to anaerobic glycolysis resulting in *metabolic lactic acidosis*. Lactic acidosis lowers the tissue pH which in turn makes the vasomotor response ineffective. This results in vasodilatation and peripheral pooling of blood.

Clinically, at this stage the patient develops confusion and worsening of renal function.

**IRREVERSIBLE DECOMPENSATED SHOCK** When the shock is so severe that in spite of compensatory mechanisms and despite therapy and control of etiologic agent which caused the shock, no recovery takes place, it is called decompensated or irreversible shock. Its effects due to widespread cell injury are as follows:

i) **Progressive vasodilatation** During later stages of shock, anoxia damages the capillary and venular wall while arterioles become unresponsive to vasoconstrictors listed above and begin to dilate. Vasodilatation results in peripheral pooling of blood which further deteriorates the effective circulating blood volume.

ii) **Increased vascular permeability** Anoxic damage to tissues releases proinflammatory mediators which cause increased vascular permeability. This results in escape of fluid from circulation into the interstitial tissues thus deteriorating effective circulating blood volume.

iii) **Myocardial depressant factor (MDF)** Progressive fall in the blood pressure and persistently reduced blood flow to myocardium causes coronary insufficiency and myocardial ischaemia due to release of myocardial depressant factor (MDF). This results in further depression of cardiac function, reduced cardiac output and decreased blood flow.

iv) **Worsening pulmonary hypoperfusion** Further pulmonary hypoperfusion causes respiratory distress due to pulmonary oedema, tachypnoea and adult respiratory distress syndrome (ARDS).

v) **Anoxic damage to heart, kidney and brain** Progressive tissue anoxia causes severe metabolic acidosis due to anaerobic glycolysis. There is release of proinflammatory cytokines and other inflammatory mediators and generation of free radicals. Since highly specialised cells of the myocardium, proximal tubular cells of the kidney, and neurons of the CNS are dependent solely on aerobic respiration for ATP generation, there is ischaemic cell death in these tissues.

vi) **Hypercoagulability of blood** Tissue damage in shock activates coagulation cascade with release of clot promoting factor, thromboplastin and release of platelet aggregator, ADP, which contributes to slowing of blood-stream and vascular thrombosis. In this way, hypercoagulability of blood with consequent microthrombi impair the blood flow and cause further tissue necrosis.

Clinically, at this stage the patient has features of coma, worsened heart function and progressive renal failure due to acute tubular necrosis.

---

**MORPHOLOGIC FEATURES**

Eventually, shock is characterised by multisystem failure. The morphologic changes in shock are due to hypoxia resulting in degeneration and necrosis in various organs. The major organs affected are the brain, heart, lungs and kidneys. Morphologic changes are also noted in the adrenals, gastrointestinal tract, liver and other organs. The predominant morphologic changes and their incidence are shown in **Fig. 4.19** and described below.

1. **HYPOXIC ENCEPHALOPATHY** Cerebral ischaemia in compensated shock may produce altered state of consciousness. However, if the blood pressure falls below 50 mmHg as occurs in systemic hypotension in prolonged shock and cardiac arrest, brain suffers from serious ischaemic damage with loss of cortical functions, coma, and a vegetative state. **Grossly,** the area supplied by the most distal branches of the cerebral arteries suffers from severe ischaemic necrosis which is usually the border zone between the anterior and middle cerebral arteries (page 874).

   **Microscopically,** the changes are noticeable if ischaemia is prolonged for 12 to 24 hours. Neurons, particularly Purkinje cells, are more prone to develop the effects of ischaemia. The cytoplasm of the affected neurons is intensely eosinophilic and the nucleus is small pyknotic. Dead and dying nerve cells are replaced by gliosis.

2. **HEART IN SHOCK** The heart is more vulnerable to the effects of hypoxia than any other organ. Heart is affected in cardiogenic as well as in other forms of shock. There are 2 types of morphologic changes in heart in all types of shock:
   i) **Haemorrhages and necrosis** There may be small or large ischaemic areas or infarcts, particularly located in the subepicardial and subendocardial region.
   ii) **Zonal lesions** These are opaque transverse contraction bands in the myocytes near the intercalated disc.

3. **SHOCK LUNG** Lungs due to dual blood supply are generally not affected by hypovolaemic shock but in septic shock the morphologic changes in lungs are quite prominent termed ‘shock lung.’

   **Grossly,** the lungs are heavy and wet.
Clinical Features and Complications

The classical features of decompensated shock are characterised by depression of 4 vital processes:

i) Very low blood pressure
ii) Subnormal temperature
iii) Feeble and irregular pulse
iv) Shallow and sighing respiration

In addition, the patients in shock have pale face, sunken eyes, weakness, cold and clammy skin.

Life-threatening complications in shock are due to hypoxic cell injury resulting in immuno-inflammatory responses and activation of various cascades (clotting, complement, kinin). These include the following*:

1. Acute respiratory distress syndrome (ARDS)
2. Disseminated intravascular coagulation (DIC)
3. Acute renal failure (ARF)
4. Multiple organ dysfunction syndrome (MODS)

With progression of the condition, the patient may develop stupor, coma and death.

GIST BOX 4.5 | Shock

- Shock is a clinical syndrome of cardiovascular collapse characterised by an acute reduction of effective circulating blood volume (hypotension) and an inadequate perfusion of cells and tissues (hypoperfusion).
- There are 3 major forms of shock: hypovolaemic, cardiogenic and septic.
- All forms of shock involve 3 mechanisms: reduced effective circulating blood volume, impaired tissue oxygenation and release of proinflammatory mediators.
- Shock is divided into 3 stages: initial reversible stage (compensated shock), progressive decompensated shock and finally the stage of irreversible decompensated shock.
- Shock causes morphologic changes in different organ systems, notably in the brain (hypoxic encephalopathy), heart (haemorrhage and necrosis), lungs (ARDS), kidneys (tubular necrosis), adrenals (haemorrhage and necrosis), liver (focal necrosis), gut (haemorrhagic gastro-enteropathy) and other organs.
- Clinically, shock is characterised by low blood pressure, low body temperature, feeble pulse, shallow respiration, pale face and cold clammy skin.

CIRCUITARY DISTURBANCES OF OBSTRUCTIVE NATURE

THROMBOSIS

Definition and Effects

Thrombosis is the process of formation of solid mass in circulation from the constituents of flowing blood; the mass itself is called a thrombus. A term commonly used erroneously synonymous with thrombosis is blood clotting. While thrombosis is characterised by events that essentially involve activation of platelets, the process of clotting involves only

*Major complications of shock can be remembered from acronym ADAM: A = ARDS; D = DIC; A = ARF; M = MODS.
conversion of soluble fibrinogen to insoluble polymerised fibrin. Besides, clotting is also used to denote coagulation of blood in vitro e.g. in a test tube. Haematoma is the extravascular accumulation of blood e.g. into the tissues. Haemostatic plugs are the blood clots formed in healthy individuals at the site of bleeding e.g. in injury to the blood vessel. In other words, haemostatic plug at the cut end of a blood vessel may be considered the simplest form of thrombosis. Haemostatic plugs are useful as they stop escape of blood and plasma, whereas thrombi developing in the unruptured cardiovascular system may be life-threatening by causing one of the following harmful effects:

1. Ischaemic injury  Thrombi may decrease or stop the blood supply to part of an organ or tissue and cause ischaemia which may subsequently result in infarction.
2. Thromboembolism  Thrombus or its part may get dislodged and be carried along in the bloodstream as embolus to lodge in a distant vessel.

Pathophysiology

Since the protective haemostatic plug formed as a result of normal haemostasis is an example of thrombosis, it is essential to describe thrombogenesis in relation to the normal haemostatic mechanism.

Human beings possess inbuilt system by which the blood remains in fluid state normally and guards against the hazards of thrombosis and haemorrhage. However, injury to the blood vessel initiates haemostatic repair mechanism or thrombogenesis.

Virchow described three primary events which predispose to thrombus formation (Virchow’s triad): endothelial injury, altered blood flow, and hypercoagulability of blood. To this are added the activation processes that follow these primary events: activation of platelets and of clotting system (Fig. 4.20). These events are discussed below:

1. ENDOTHELIAL INJURY  The integrity of blood vessel wall is important for maintaining normal blood flow. An intact endothelium has the following functions:
   
i) It protects the flowing blood from thrombogenic influence of subendothelium.
   
ii) It elaborates a few anti-thrombotic factors (thrombosis inhibitory factors) as follows:
   
a) Heparin-like substance which accelerates the action of antithrombin III and inactivates some other clotting factors.
   
b) Thrombomodulin which converts thrombin into activator of protein C, an anticoagulant.
   
c) Inhibitors of platelet aggregation such as ADPase, PGI₂ (or prostacyclin).
   
d) Tissue plasminogen activator which accelerates fibrinolytic activity.

   iii) It releases a few prothrombotic factors which have procoagulant properties (thrombosis favouring factors) as under:
   
a) Thromboplastin or tissue factor released from endothelial cells.
   
b) von Willebrand factor that causes adherence of platelets to the subendothelium.
   
c) Platelet activating factor which is activator and aggregator of platelets.
   
d) Inhibitor of plasminogen activator that suppresses fibrinolysis.

Vascular injury exposes the subendothelial extracellular matrix or ECM (e.g. collagen, elastin, fibronectin, laminin and glycosaminoglycans) which is thrombogenic and thus plays an important role in initiating haemostasis as well as thrombosis (Fig. 4.21). Injury to vessel wall also causes vasoconstriction of small blood vessels briefly so as to reduce the blood loss. Endothelial injury is of major significance in the formation of arterial thrombi and thrombi of the heart, especially of the left ventricle. A number of factors and conditions may cause vascular injury and predispose to the formation of thrombi. These are as under:

![Figure 4.20](image)

**Figure 4.20** Major factors in pathophysiology of thrombus formation.

![Figure 4.21](image)

**Figure 4.21** Role of endothelial injury and platelet activation in thrombosis. A, Endothelial injury exposes subendothelial matrix to circulating blood. B, This triggers three platelet steps involving platelet activation: adhesion, release and aggregation. Platelet release is associated with release of granules (alpha granules and dense bodies). C, Concurrent activation of coagulation cascade generates fibrin strands and thrombin forming a tight meshwork called thrombus.
i) Endocardial injury in myocardial infarction, myocarditis, cardiac surgery, prosthetic valves.
ii) Ulcerated plaques in advanced atherosclerosis.
iii) Haemodynamic stress in hypertension.
iv) Arterial diseases.
v) Diabetes mellitus.
vi) Endogenous chemical agents such as hypercholesterolaemia, endotoxins.
vii) Exogenous chemical agents such as cigarette smoke.

2. ROLE OF PLATELETS Following endothelial cell injury, platelets come to play a central role in normal haemostasis as well as in thrombosis. The sequence of events is as under (Fig. 4.21):

i) Platelet adhesion Glycoprotein Ib (GpIb) receptor on the platelets recognises the site of endothelial injury and the circulating platelets adhere to exposed subendothelial ECM (primary aggregation). von Willebrand’s factor (vWF), synthesised by the endothelial cells binds to GpIb and forms a firm adhesion of platelets with ECM. Thus, deficiency of vWF (as happens in von Willebrand’s disease) or absence of GpIb (as is seen in Bernard-Soulier disease) would result in defective platelet adhesion and cause abnormal bleeding.

ii) Platelet release reaction Activated platelets then undergo release reaction by which the platelet granules are released to the exterior. Two main types of platelet granules are released:
   a) Dense bodies Their release liberates ADP (adenosine diphosphate), ionic calcium, 5-HT (serotonin), histamine and epinephrine. Release of contents of dense bodies are more important since ADP is further an activator of platelets, and calcium is required in the coagulation cascade.
   b) Alpha granules Their release produces fibrinogen, fibronectin, platelet-derived growth factor (PDGF), platelet factor 4 (an antiheparin) and thrombospondin.

As a sequel to platelet activation and release reaction, the phospholipid complex-platelet factor 3 gets activated which plays important role in the intrinsic pathway of coagulation.

iii) Platelet aggregation Following release of ADP, a potent platelet aggregating agent, aggregation of additional platelets takes place (secondary aggregation). This results in formation of temporary haemostatic plug. However, stable haemostatic plug is formed by the action of fibrin, thrombin and thromboxane A2.

3. ROLE OF COAGULATION SYSTEM Coagulation mechanism is the conversion of the plasma fibrinogen into solid mass of fibrin. The coagulation system is involved in both haemostatic process and thrombus formation. Fig. 4.22 shows schematic representation of the cascade of intrinsic (blood) pathway, the extrinsic (tissue) pathway, and the common pathway leading to formation of fibrin polymers.

i) In the intrinsic pathway, contact with abnormal surface (e.g. ECM in the subendothelium) leads to activation of factor XII and the sequential interactions of factors XI, IX, VIII and finally factor X, along with calcium ions (factor IV) and platelet factor 3.
ii) In the extrinsic pathway, tissue damage results in release of tissue factor or thromboplastin. Tissue factor on interaction with factor VII activates factor X.

iii) The common pathway begins where both intrinsic and extrinsic pathways converge to activate factor X which forms a complex with factor Va and platelet factor 3, in the presence of calcium ions. This complex activates prothrombin (factor II) to thrombin (factor IIa) which, in turn, converts fibrinogen to fibrin. Initial monomeric fibrin is polymerised to form insoluble fibrin by activation of factor XIII.

Regulation of coagulation system Normally, the blood is kept in fluid state and the coagulation system is kept in check by controlling mechanisms. These are as under:

i) Protease inhibitors These act on coagulation factors so as to oppose the formation of thrombin e.g. antithrombin III, protein C, C1 inactivator, α1-antitrypsin, α2-macroglobulin.

ii) Fibrinolytic system Plasmin, a potent fibrinolytic enzyme, is formed by the action of plasminogen activator on plasminogen present in the normal plasma. Two types of plasminogen activators (PA) are identified:

   a) Tissue-type PA derived from endothelial cells and leucocytes.

   b) Urokinase-like PA present in the plasma.

Plasmin so formed acts on fibrin to destroy the clot and produces fibrin split products (FSP).

4. ALTERATION OF BLOOD FLOW Turbulence means unequal flow while stasis means slowing.

i) Normally, there is axial flow of blood in which the most rapidly-moving central stream consists of leucocytes and red cells. The platelets are present in the slow-moving laminar stream adjacent to the central stream while the peripheral stream consists of most slow-moving cell-free plasma close to endothelial layer (Fig. 4.23,A).

ii) Turbulence and stasis occur in thrombosis in which the normal axial flow of blood is disturbed. When blood slows down, the blood cells including platelets marginate to the periphery and form a kind of pavement close to endothelium (margination and pavematting) (Fig. 4.23,B). While stasis allows a higher release of oxygen from the blood, turbulence may actually injure the endothelium resulting in deposition of platelets and fibrin. Formation of arterial and cardiac thrombi is facilitated by turbulence in the blood flow, while stasis initiates the venous thrombi even without evidence of endothelial injury.

5. HYPERCOAGULABLE STATES (THROMBOPHILIA) Thrombophilia or hypercoagulable states are a group of conditions having increased risk or predisposition to develop venous thrombosis. These conditions may be hereditary (or primary) or acquired (or secondary) causes (Table 4.5). However, in a given case of thrombosis, several factors are generally present simultaneously.

Hereditary (Primary) factors These include deficiency or mutation of some factors as under:

i) Deficiency of antithrombin III It is inherited as autosomal dominant disorder having less than 50% antithrombin III. The condition is associated with recurrent episodes of venous thrombosis.

ii) Deficiency of protein C and S Both these are autosomal dominant disorders having either reduced amount of protein C or S, or both, or their functional defect. Clinically, both the conditions are associated with lifelong risk of thrombosis of deep leg veins.

iii) Mutation in factor V Leiden This is also a autosomal dominant disorder in which the mutation lies in replacement of arginine by glycine at position 506. It is the most common cause of thrombophilia.

iv) Defects in fibrinolysis These include a few rare inherited disorders such as dysfibrinogenaemia and plasminogen disorders.

### Table 4.5 Causes of thrombophilia (hypercoagulable states).

<table>
<thead>
<tr>
<th>INHERITED (PRIMARY) FACTORS</th>
<th>ACQUIRED (SECONDARY) FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Deficiency of antithrombin III</td>
<td>a) Risk factors:</td>
</tr>
<tr>
<td>ii) Deficiency of protein C</td>
<td>i) Advancing age, ii) Prolonged bed-rest, iii) Prolonged immobilisation (e.g. in plaster cast, long distance travel), iv) Cigarette smoking, v) Obesity</td>
</tr>
<tr>
<td>iii) Deficiency of protein S</td>
<td>b) Predisposing clinical conditions:</td>
</tr>
<tr>
<td>iv) Mutation in factor V Leiden</td>
<td>i) Heart diseases (e.g. myocardial infarction, CHF, rheumatic mitral stenosis, cardiomyopathy)</td>
</tr>
<tr>
<td>v) Defects in fibrinolysis (dysfibrinogenaemia, plasminogen disorders)</td>
<td>ii) Vascular diseases (e.g. atherosclerosis, aneurysms of the aorta and other vessels, varicosities of leg veins)</td>
</tr>
<tr>
<td>vi) Increased levels of coagulations factors (II and VIII)</td>
<td>iii) Hypercoagulable conditions (e.g. polycythaemia, myeloproliferative disorders, dehydration, nephrotic syndrome, disseminated cancers)</td>
</tr>
<tr>
<td></td>
<td>iv) Shock</td>
</tr>
<tr>
<td></td>
<td>v) Tissue damage e.g. trauma, fractures, burns, major surgery on bones, abdomen or brain.</td>
</tr>
<tr>
<td></td>
<td>vi) Late pregnancy and puerperium</td>
</tr>
<tr>
<td></td>
<td>vii) Certain drugs (e.g. anaesthetic agents, oral contraceptives, hormonal replacement therapy).</td>
</tr>
<tr>
<td></td>
<td>c) Antiphospholipid antibody (APLA) syndrome:</td>
</tr>
<tr>
<td></td>
<td>i) Lupus anticoagulant antibody</td>
</tr>
<tr>
<td></td>
<td>ii) Anti-cardiolipin antibody</td>
</tr>
</tbody>
</table>
v) Increased levels of coagulation factors (II and VIII). Elevated level of prothrombin and factor VIII due to genetic mutation may predispose to thrombosis.

**Secondary (acquired) factors** As listed in Table 4.5, thrombosis is favoured by certain risk factors, some predisposing clinical conditions and antiphospholipid antibody (APLA) syndrome. There are 2 types of APLA: lupus anticoagulant antibody and anti-cardiolipin antibody. Presence of either of the two APLA predisposes an individual to recurrent thrombosis: venous in the former and arterial in the latter type. Other features include spontaneous abortions, transient ischaemic attacks, thrombocytopenia, elevation of activated partial thromboplastin time and multi-organ involvement. Patients of SLE may often coexpress lupus anticoagulant.

**Origin of Thrombi at Different Sites**

Thrombi may arise from the heart, arteries, veins or in microcirculation by different mechanisms.

**CARDIAC THROMBI** Thrombi may form in any of the chambers of the heart and on the valve cusps. They are more common in the atrial appendages, especially of the right atrium, and on mitral and aortic valves such as vegetations seen in infective endocarditis and non-bacterial thrombotic endocarditis (page 425). Cardiac thrombi are mural (non-occlusive) as are the mural thrombi encountered in large vessels such as the aorta in atherosclerosis and in aneurysmal dilatations. Rarely, large round thrombus may form and obstruct the mitral valve and is called ball-valve thrombus. Agonal thrombi are formed shortly before death and may occur in either or both the ventricles. They are composed mainly of fibrin.

**ARTERIAL THROMBI** The examples of major forms of thrombi formed in the arteries are as under:

i) **Aorta:** aneurysms, arteritis.

ii) **Coronary arteries:** atherosclerosis.

iii) **Mesenteric arteries:** atherosclerosis, arteritis.

iv) **Arteries of limbs:** atherosclerosis, diabetes mellitus, Buerger’s disease, Raynaud’s disease.

v) **Renal artery:** atherosclerosis, arteritis.

vi) **Cerebral artery:** atherosclerosis, vasculitis.

**VENOUS THROMBI** A few common examples of these are as under:

i) **Veins of lower limbs:** deep veins of legs, varicose veins.

ii) **Popliteal, femoral and iliac veins:** postoperative stage, postpartum.

iii) **Pulmonary veins:** CHF; pulmonary hypertension.

iv) **Hepatic and portal vein:** portal hypertension.

v) **Superior vena cava:** infections in head and neck.

vi) **Inferior vena cava:** extension of thrombus from hepatic vein.

vii) **Mesenteric veins:** volvulus, intestinal obstruction.

viii) **Renal vein:** renal amyloidosis.

Distinguishing features between thrombi formed in rapidly-flowing arterial circulation and slow-moving venous blood are given in Table 4.6.

**CAPILLARY THROMBI** Minute thrombi composed mainly of packed red cells are formed in the capillaries in acute inflammatory lesions, vasculitis and in disseminated intravascular coagulation (DIC).

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ARTERIAL THROMBI</th>
<th>VENOUS THROMBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blood flow</td>
<td>Formed in rapidly-flowing blood of arteries and heart</td>
<td>Formed in slow-moving blood in veins</td>
</tr>
<tr>
<td>2. Sites</td>
<td>Common in aorta, coronary, cerebral, iliac, femoral, renal and mesenteric arteries</td>
<td>Common in superficial varicoso veins, deep leg veins, popliteal, femoral and iliac veins</td>
</tr>
<tr>
<td>3. Thrombogenesis</td>
<td>Formed following endotheial cell injury e.g. in atherosclerosis</td>
<td>Formed following venous stasis e.g. in abdominal operations, childbirth</td>
</tr>
<tr>
<td>4. Development</td>
<td>Usually mural, not occluding the lumen completely, may propagate</td>
<td>Usually occlusive, take the cast of the vessel in which formed, may propagate in both directions</td>
</tr>
<tr>
<td>5. Macroscopy</td>
<td>Grey-white, friable with lines of Zahn on surface</td>
<td>Red-blue with fibrin strands and lines of Zahn</td>
</tr>
<tr>
<td>6. Microscopy</td>
<td>Distinct lines of Zahn composed of platelets, fibrin with entangled red and white blood cells</td>
<td>Lines of Zahn with more abundant red cells</td>
</tr>
<tr>
<td>7. Effects</td>
<td>Ischaemia leading to infarcts e.g. in the heart, brain etc</td>
<td>Thromboembolism, oedema, skin ulcers, poor wound healing</td>
</tr>
</tbody>
</table>

**Morphologic Features**

The general morphologic features of thrombi formed in various locations are as under:

**Grossly,** thrombi may be of various shapes, sizes and composition depending upon the site of origin. Arterial thrombi tend to be white and mural while the venous thrombi are red and occlusive. Mixed or laminated thrombi are also common and consist of alternate white and red layers called lines of Zahn. Red thrombi are soft, red and gelatinous whereas white thrombi are firm and pale.

**Microscopically,** the composition of thrombus is determined by the rate of flow of blood i.e. whether it is formed in the rapid arterial and cardiac circulation, or in the slow moving flow in veins. The lines of Zahn are formed by alternate layers of light-staining aggregated platelets admixed with fibrin meshwork and dark-staining layer of red cells. Red (venous) thrombi have more abundant red cells, leucocytes and platelets entrapped in fibrin meshwork. Thus, red thrombi closely resemble blood clots in vitro (Fig. 4.24).

Red thrombi (antemortem) have to be distinguished from postmortem clots (Table 4.7).
Fate of Thrombus

The outcome of thrombi can be as under (Fig. 4.25):

1. **RESOLUTION** Thrombus activates the fibrinolytic system with consequent release of plasmin which may dissolve the thrombus completely resulting in resolution. Usually, lysis is complete in small venous thrombi while large thrombi may not be dissolved. Fibrinolytic activity can be accentuated by administration of thrombolytic substances (e.g. urokinase, streptokinase), especially in the early stage when fibrin is in monomeric form e.g. thrombolytic therapy in early stage acute myocardial infarction.

2. **ORGANISATION** If the thrombus is not removed, it starts getting organised. Phagocytic cells (neutrophils and macrophages) appear and begin to phagocytose fibrin and cell debris. The proteolytic enzymes liberated by leucocytes and endothelial cells start digesting coagulum. Capillaries grow into the thrombus from the site of its attachment and fibroblasts start invading the thrombus. Thus, fibrovascular granulation tissue is formed which subsequently becomes dense and less vascular and is covered over by endothelial cells. The thrombus in this way is excluded from the vascular lumen and becomes part of vessel wall. The new vascular channels in it may be able to re-establish the blood flow, called recanalisation. The fibrosed thrombus may undergo hyalinisation and calcification e.g. phleboliths in the pelvic veins.

3. **PROGRESSION** The thrombus may enlarge in size due to more and more deposition from the constituents of flowing blood. In this way, it may ultimately cause obstruction of some important vessel.

4. **THROMBOEMBOLISM** The thrombi in early stage and infected thrombi are quite friable and may get detached from the vessel wall. These are released in part or completely in blood-stream as emboli which produce ill-effects at the site of their lodgement (page 105).

Clinical Effects

Besides differences in mechanism of thrombosis at different sites, clinical effects depend upon not only the site but also on rapidity of formation and nature of thrombi.

1. **Cardiac thrombi** Large thrombi in the heart may cause sudden death by mechanical obstruction of blood flow or through thromboembolism to vital organs.

2. **Arterial thrombi** These cause ischaemic necrosis of the deprived part (infarct) which may lead to gangrene. Sudden death may occur following thrombosis of coronary artery.

3. **Venous thrombi (Phlebothrombosis)** These may cause following effects:
   
i) Thromboembolism
   
ii) Oedema of area drained
   
iii) Poor wound healing
   
iv) Skin ulcer
   
vi) Painful thrombosed veins (thrombophlebitis)
   
vii) Painful white leg (phlegmasia alba dolens) due to ileofemoral venous thrombosis in postpartum cases
   
iiii) Thrombophlebitis migrans in cancer.

4. **Capillary thrombi** Microthrombi in microcirculation may give rise to disseminated intravascular coagulation (DIC).
Figure 4.25 Fate of thrombus.

**GIST BOX 4.6 Thrombosis**

- Thrombosis is the process of formation of solid mass in circulation from the constituents of flowing blood; the mass itself is called a thrombus.
- Thrombogenesis involves interplay of 5 events: endothelial injury, platelets and their release reaction, coagulation system, alterations in the flow of blood and role of certain predisposing conditions and factors causing hypercoagulable states (or thrombophilia).
- Thrombi may originate in the chambers of the heart, lumina of arteries, veins and microcirculation.
- The effects of thrombi depend upon their anatomic location, rapidity of formation and nature of thrombi. In general, thrombi produce life-threatening harmful effects by ischaemia and by thromboembolism.
- Grossly, thrombi are of various shapes, size, consistency and colour. Microscopically, all types of thrombi show lines of Zahn formed by alternate layers of light-staining aggregated platelets and dark-staining red cells.
- The possible fates of thrombi are resolution, organisation, propagation and thromboembolism.

**EMBOLISM**

**Definition and Types**

*Embolism* is the process of partial or complete obstruction of some part of the cardiovascular system by any mass carried in the circulation; the transported intravascular mass detached from its site of origin is called an *embolus*. Most usual forms of emboli (90%) are thromboemboli i.e. originating from thrombi or their parts detached from the vessel wall.

Emboli may be of various types:

A. **Depending upon the matter in the emboli:**
   i) *Solid* e.g. detached thrombi (thromboemboli), atheromatous material, tumour cell clumps, tissue fragments, parasites, bacterial clumps, foreign bodies.
   ii) *Liquid* e.g. fat globules, amniotic fluid, bone marrow.
   iii) *Gaseous* e.g. air, other gases.

B. **Depending upon whether infected or not:**
   i) *Bland*, when sterile.
   ii) *Septic*, when infected.

C. **Depending upon the source of the emboli:**
   i) *Cardiac emboli* from left side of the heart e.g. emboli originating in the atrium and atrial appendages, infarct in the left ventricle, vegetations of endocarditis.
   ii) *Arterial emboli* e.g. in systemic arteries in the brain, spleen, kidney, intestine.
   iii) *Venous emboli* e.g. in pulmonary arteries.
   iv) *Lymphatic emboli* can also sometimes occur.

D. **Depending upon the flow of blood**, two special types of emboli are mentioned:
   i) *Paradoxical embolus* An embolus which is carried from the venous side of circulation to the arterial side or vice versa, is called paradoxical or crossed embolus e.g. through arteriovenous communication such as in patent foramen ovale, septal defect of the heart, and arteriovenous shunts in the lungs.
   ii) *Retrograde embolus* An embolus which travels against the flow of blood is called retrograde embolus. For example, metastatic deposits in the spine from carcinoma prostate in which case the spread occurs by retrograde embolism through intraspinal veins (which normally do not carry the blood from the prostate) which carry tumour emboli from large thoracic and abdominal veins because of increased pressure in body cavities such as during coughing or straining.

Some of the important types of embolism are listed in Table 4.8 and are described below:

<table>
<thead>
<tr>
<th>TABLE 4.8 Important types of embolism.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>1. Pulmonary embolism</td>
</tr>
<tr>
<td>2. Systemic embolism</td>
</tr>
<tr>
<td>3. Fat embolism</td>
</tr>
<tr>
<td>4. Air embolism</td>
</tr>
<tr>
<td>5. Decompression sickness</td>
</tr>
<tr>
<td>6. Amniotic fluid embolism</td>
</tr>
<tr>
<td>7. Atheroembolism</td>
</tr>
<tr>
<td>8. Tumour embolism</td>
</tr>
</tbody>
</table>
Thromboembolism

A detached thrombus or part of thrombus constitutes the most common type of embolism. These may arise in the arterial or venous circulation (Fig. 4.26):

**Arterial (systemic) thromboembolism** Arterial emboli may be derived from the following sources:

A. *Causes within the heart* (80-85%): These are mural thrombi in the left atrium or left ventricle, vegetations on the mitral or aortic valves, prostatic heart valves and cardiomyopathy.

B. *Causes within the arteries*: These include emboli developing in relation to atherosclerotic plaques, aortic aneurysms, pulmonary veins and paradoxical arterial emboli from the systemic venous circulation.

The *effects of arterial emboli* depend upon their size, site of lodgement, and adequacy of collateral circulation. If the vascular occlusion occurs, the following ill-effects may result:

i) *Infarction* of the organ or its affected part e.g. ischaemic necrosis in the lower limbs (70-75%), spleen, kidneys, brain, intestine.

ii) *Gangrene* following infarction in the lower limbs if the collateral circulation is inadequate.

iii) *Arteritis and mycotic aneurysm* formation from bacterial endocarditis.

iv) *Myocardial infarction* may occur following coronary embolism.

v) *Sudden death* may result from coronary embolism or embolism in the middle cerebral artery.

**Venous thromboembolism** Venous emboli may arise from the following sources:

i) Deep vein thrombosis (DVT) of the lower legs, the most common cause of venous thrombi.

ii) Thrombi in the pelvic veins.

iii) Thrombi in the veins of the upper limbs.

iv) Thrombosis in cavernous sinus of the brain.

v) Thrombi in the right side of heart.

The most significant *effect* of venous embolism is obstruction of pulmonary arterial circulation leading to pulmonary embolism described below.

**Pulmonary Thromboembolism**

**DEFINITION** Pulmonary embolism is the most common and fatal form of venous thromboembolism in which there is occlusion of pulmonary arterial tree by thromboemboli. In contrast, pulmonary thrombosis is uncommon and may occur in pulmonary atherosclerosis and pulmonary hypertension.

Differentiation of pulmonary thrombosis from pulmonary thromboembolism is tabulated in *Table 4.9*.

**ETIOLOGY** Pulmonary emboli are more common in hospitalised or bed-ridden patients, though they can occur in ambulatory patients as well. The causes are as follows:

i) Thrombi originating from large veins of lower legs (such as popliteal, femoral and iliac) are the cause in 95% of pulmonary emboli.

ii) Less common sources include thrombi in varicosities of superficial veins of the legs, and pelvic veins such as periprostatic, periovian, uterine and broad ligament veins.

**PATHOGENESIS** The risk factors for pulmonary thromboembolism are stasis of venous blood and hypercoagulable states. Detachment of thrombi from any of the above-mentioned sites produces a thromboembolus that flows through venous drainage into the larger veins draining into right side of the heart.

---

**Figure 4.26** Sources of arterial and venous emboli.

- If the thrombus is large, it is impacted at the bifurcation of the main pulmonary artery (*saddle embolus*), or may be found in the right ventricle or its outflow tract.

- More commonly, there are *multiple emboli*, or a large embolus may be fragmented into many smaller emboli which are then impacted in a number of vessels, particularly affecting the lower lobes of lungs.

- Rarely, *paradoxical embolism* may occur by passage of an embolus from right heart into the left heart through atrial or ventricular septal defect. In this way, pulmonary emboli may reach systemic circulation.

**CONSEQUENCES OF PULMONARY EMBOLISM** Pulmonary embolism occurs more commonly as a complication in patients of acute or chronic debilitating diseases who are immobilised for a long duration. Women in their reproductive period are at higher risk such as in late pregnancy, following delivery and with use of contraceptive pills. The effects of pulmonary embolism depend mainly on the size of the occluded vessel, the number of emboli, and on the cardiovascular status of the patient. Natural history of pulmonary embolism may have following consequences (Fig. 4.27):

i) *Sudden death* Massive pulmonary embolism results in instantaneous death, without occurrence of chest pain or
dyspnoea. However, if the death is somewhat delayed, the clinical features resemble myocardial infarction i.e. severe chest pain, dyspnoea and shock.

ii) Acute cor pulmonale Numerous small emboli may obstruct most of the pulmonary circulation resulting in acute right heart failure. Another mechanism is by release of vasoconstrictor substances from platelets or by reflex vasoconstriction of pulmonary vessels.

iii) Pulmonary infarction Obstruction of relatively small-sized pulmonary arterial branches may result in pulmonary infarction (page 112). The clinical features include chest pain due to fibrinous pleuritis, haemoptysis and dyspnoea due to reduced functioning pulmonary parenchyma.

iv) Pulmonary haemorrhage Obstruction of terminal branches (endarteries) leads to central pulmonary haemorrhage. The clinical features are haemoptysis, dyspnoea, and less commonly, chest pain due to central location of pulmonary haemorrhage. Sometimes, there may be concomitant pulmonary infarction.

v) Resolution Vast majority of small pulmonary emboli (60-80%) are resolved by fibrinolytic activity. These patients are clinically silent owing to bronchial circulation so that lung parenchyma is adequately perfused.

vi) Pulmonary hypertension, chronic cor pulmonale and pulmonary arteriosclerosis These are the sequelae of multiple small thromboemboli undergoing organisation rather than resolution.

Systemic Embolism

This is the type of arterial embolism that originates commonly from thrombi in the diseased heart, especially in the left ventricle. These heart diseases include myocardial infarction, cardiomyopathy, RHD, congenital heart disease, infective endocarditis, and prosthetic cardiac valves. The emboli are arterial and invariably cause infarction at the sites of lodgement. These sites, in descending order of frequency, are: lower extremity, brain, and internal visceral organs (spleen, kidneys, intestines). Thus, the effects and sites of arterial emboli are in striking contrast to venous emboli which are often lodged in the lungs.

Fat Embolism

Obstruction of arterioles and capillaries by fat globules constitutes fat embolism. If the obstruction in the circulation is by fragments of adipose tissue, it is called fat-tissue embolism.

ETIOLOGY Causes of fat embolism may be traumatic and non-traumatic:

Traumatic causes:
i) Trauma to bones is the most common cause of fat embolism e.g. in fractures of long bones leading to passage of fatty marrow in circulation, concussions of bones, after orthopaedic surgical procedures etc.

ii) Trauma to soft tissue e.g. laceration of adipose tissue and in puerperium due to injury to pelvic fatty tissue.

Non-traumatic causes:
i) Extensive burns
ii) Diabetes mellitus
iii) Fatty liver
iv) Pancreatitis
v) Sickle cell anaemia
vi) Decompression sickness
vii) Inflammation of bones and soft tissues
viii) Extrinsic fat or oils introduced into the body
ix) Hyperlipidaemia
x) Cardiopulmonary bypass surgery

PATHOGENESIS Pathogenesis of fat embolism is explained by following mechanisms which may be acting singly or in combination:

i) Mechanical theory Mobilisation of fluid fat may occur following trauma to the bone or soft tissues. Fat globules released from the injured area may enter venous circulation and finally most of the fat is arrested in the small vessels in the lungs. Some of the fat globules may further pass through lungs and enter into the systemic circulation to lodge in other organs.

ii) Emulsion instability theory This theory explains the pathogenesis of fat embolism in non-traumatic cases. According to this theory, fat emboli are formed by aggregation of plasma lipids (chylomicrons and fatty acids) due to disturbance in natural emulsification of fat.

iii) Intravascular coagulation theory In stress, release of some factor activates disseminated intravascular coagulation (DIC) and aggregation of fat emboli.

iv) Toxic injury theory According to this theory, the small blood vessels of lungs are chemically injured by high plasma levels of free fatty acid, resulting in increased vascular permeability and consequent pulmonary oedema.

CONSEQUENCES OF FAT EMBOLISM The effects of fat embolism depend upon the size and quantity of fat globules, and whether or not the emboli pass through the lungs into the systemic circulation.

i) Pulmonary fat embolism In patients dying after fractures of bones, presence of numerous fat emboli in the capillaries of the lung is a frequent autopsy finding because the
small fat globules are not likely to appreciably obstruct the vast pulmonary vascular bed. However, widespread obstruction of pulmonary circulation due to extensive pulmonary embolism can occur and result in sudden death.

**Microscopically**, the lungs show hyperaemia, oedema, petechial haemorrhages and changes of adult respiratory distress syndrome (ARDS). Pulmonary infarction is usually not a feature of fat embolism because of the small size of globules. In routine stains, the fat globules in the pulmonary arteries, capillaries and alveolar spaces appear as vacuoles. Frozen section is essential for confirmation of globules by fat stains such as Sudan dyes (Sudan black, Sudan III and IV), oil red O and osmic acid.

ii) Systemic fat embolism Some of the fat globules may pass through the pulmonary circulation such as via patent foramen ovale, arteriovenous shunts in the lungs and vertebral venous plexuses, and get lodged in the capillaries of organs like the brain, kidney, skin etc.

ดร Brain The pathologic findings in the brain are petechial haemorrhages on the leptomeninges and minute haemorrhages in the parenchyma.

**Microscopically**, microinfarcts of brain, oedema and haemorrhages are seen. The CNS manifestations include delirium, convulsions, stupor, coma and sudden death.

ดร Kidney Renal fat embolism present in the glomerular capillaries, may cause decreased glomerular filtration. Other effects include tubular damage and renal insufficiency.

ดร Other organs Besides the brain and kidneys, other findings in systemic fat embolism are petechiae in the skin, conjunctivae, serosal surfaces, fat globules in the urine and sputum.

**Gas Embolism**

Air, nitrogen and other gases can produce bubbles within the circulation and obstruct the blood vessels causing damage to tissue. Two main forms of gas embolism—air embolism and decompression sickness are described below.

**Air Embolism**

Air embolism occurs when air is introduced into venous or arterial circulation.

**VENOUS AIR EMBOLISM** Air may be sucked into systemic veins under the following circumstances:

i) **Operations on the head and neck, and trauma** The accidental opening of a major vein of the neck like jugular, or neck wounds involving the major neck veins, may allow air to be drawn into venous circulation.

ii) **Obstetrical operations and trauma** During childbirth by normal vaginal delivery, caesarean section, abortions and other procedures, fatal air embolism may result from the entrance of air into the opened-up uterine venous sinuses and endometrial veins.

iii) **Intravenous infusion of blood and fluid** Air embolism may occur during intravenous blood or fluid infusions if only positive pressure is employed.

iv) **Angiography** During venous angiographic procedures, air may be entrapped into a large vein causing air embolism.

The effects of venous air embolism depend upon the following factors:

i) **Amount of air** introduced into the circulation. The volume of air necessary to cause death is variable but usually 100-150 ml of air entry is considered fatal.

ii) **Rapidity** of entry of a smaller volume of air is important determinant of a fatal outcome.

iii) **Position of the patient** during or soon after entry of air is another factor. The air bubbles may ascend into the superior vena cava if the position of head is higher than the trunk (e.g. in upright position) and reach the brain.

iv) **General condition** of the patient e.g. in severely ill patients, as little as 40 ml of air may have serious results.

The mechanism of death is by entrapment of air emboli in the pulmonary arterial trunk in the right heart. If bubbles of air in the form of froth pass further out into pulmonary arterioles, they cause widespread vascular occlusions. If death from pulmonary air embolism is suspected, the heart and pulmonary artery should be opened **in situ** under water so that escaping froth or foam formed by mixture of air and blood can be detected.

**ARTERIAL AIR EMBOLISM** Entry of air into pulmonary vein or its tributaries may occur in the following conditions:

i) **Cardiothoracic surgery and trauma** Arterial air embolism may occur following thoracic operations, thoracocentesis, rupture of the lung, penetrating wounds of the lung, artificial pneumothorax etc.

ii) **Paradoxical air embolism** This may occur due to passage of venous air emboli to the arterial side of circulation through a patent foramen ovale or via pulmonary arteriovenous shunts.

iii) **Arteriography** During arteriographic procedures, air embolism may occur.

The effects of arterial air embolism are in the form of certain characteristic features:

i) Marble skin due to blockage of cutaneous vessels.

ii) Air bubbles in the retinal vessels seen ophthalmoscopically.

iii) Pallor of the tongue due to occlusion of a branch of lingual artery.

iv) Coronary or cerebral arterial air embolism may cause sudden death by much smaller amounts of air than in the venous air embolism.

**Decompression Sickness**

This is a specialised form of gas embolism known by various names such as caisson’s disease, divers’ palsy or aeroembolism.

**PATHOGENESIS** Decompression sickness is produced when the individual decompresses suddenly, either from high atmospheric pressure to normal level, or from normal pressure to low atmospheric pressure.

ดร In divers, workers in caissons (diving-bells), offshore drilling and tunnels, who descend to high atmospheric pressure, increased amount of atmospheric gases (mainly nitrogen; others are O₂, CO₂) are dissolved in blood and tissue fluids. When such an individual ascends too rapidly i.e. comes to normal level suddenly from high atmospheric pressure, the gases come out of the solution as minute bubbles, particularly
in fatty tissues which have affinity for nitrogen. These bubbles may coalesce together to form large emboli.

- In aeroembolism, seen in those who ascend to high altitudes or air flight in unpressurised cabins, the individuals are exposed to sudden decompression from low atmospheric pressure to normal levels. This results in similar effects as in divers and workers in caissons.

**EFFECTS** The effects of decompression sickness depend upon the following:

1. **Depth or altitude reached**
2. **Duration of exposure to altered pressure**
3. **Rate of ascent or descent**
4. **General condition of the individual**

Pathologic changes are more pronounced in sudden decompression from high pressure to normal levels than in those who decompress from low pressure to normal levels. The changes are more serious in obese persons as nitrogen gas is more soluble in fat than in body fluids.

Clinical effects of decompression sickness are of 2 types—acute and chronic.

- **Acute form** occurs due to acute obstruction of small blood vessels in the vicinity of joints and skeletal muscles. The condition is clinically characterised by the following:
  i) *The bends*, as the patient doubles up in bed due to acute pain in joints, ligaments and tendons.
  ii) *The chokes* occur due to accumulation of bubbles in the lungs, resulting in acute respiratory distress.
  iii) **Cerebral effects** may manifest in the form of vertigo, coma, and sometimes death.

- **Chronic form** is due to foci of ischaemic necrosis throughout body, especially the skeletal system. Ischaemic necrosis may be due to embolism per se, but other factors such as platelet activation, intravascular coagulation and hypoxia might contribute. The features of chronic form are as under:
  i) **Avascular necrosis of bones** e.g. head of femur, tibia, humerus.
  ii) **Neurological symptoms** may occur due to ischaemic necrosis in the central nervous system. These include paraesthesia and paraplegia.
  iii) **Lung involvement** in the form of haemorrhage, oedema, emphysema and atelactasis may be seen. These result in dyspnoea, nonproductive cough and chest pain.
  iv) **Skin manifestations** include itching, patchy erythema, cyanosis and oedema.
  v) **Other organs** like parenchymal cells of the liver and pancreas may show lipid vacuoles.

**Amniotic Fluid Embolism**

This is the most serious, unpredictable and unpreventable cause of maternal mortality. During labour and in the immediate postpartum period, the contents of amniotic fluid may enter the uterine veins and reach right side of the heart resulting in fatal complications. The amniotic fluid components which may be found in uterine veins, pulmonary artery and vessels of other organs are: epithelial squames, vernix caseosa, lanugo hair, bile from meconium, and mucus. The mechanism by which these amniotic fluid contents enter the maternal circulation is not clear. Possibly, they gain entry either through tears in the myometrium and endocervix, or the amniotic fluid is forced into uterine sinusoids by vigorous uterine contractions.

**MORPHOLOGIC FEATURES** Notable changes are seen in the lungs such as haemorrhages, congestion, oedema and changes of ARDS, and dilatation of right side of the heart. These changes are associated with identifiable amniotic fluid contents within the pulmonary microcirculation.

The **clinical syndrome** of amniotic fluid embolism is characterised by the following features:

1. Sudden respiratory distress and dyspnoea
2. Deep cyanosis
3. Cardiovascular shock
4. Convulsions
5. Coma
6. Unexpected death

The **cause of death** may not be obvious but can occur as a result of the following mechanisms:

1. Mechanical blockage of the pulmonary circulation in extensive embolism.
2. Anaphylactoid reaction to amniotic fluid components.
3. Disseminated intravascular coagulation (DIC) due to liberation of thromboplastin by amniotic fluid.
4. Haemorrhagic manifestations due to thrombocytopenia and afibrinogenemia.

**Ateroembolism**

Atheromatous plaques, especially from aorta, may get eroded to form atherosclerotic emboli which are then lodged in medium-sized and small arteries. These emboli consist of cholesterol crystals, hyaline debris and calcified material, and may evoke foreign body reaction at the site of lodgement.

**MORPHOLOGIC FEATURES** Pathologic changes and their effects in ateroembolism are as under:

1. Ischaemia, atrophy and necrosis of tissue distal to the occluded vessel.
2. Infarcts in the organs affected such as the kidneys, spleen, brain and heart.
4. Hypertension, if widespread renal vascular lesions are present.

**Tumour Embolism**

Malignant tumour cells invade the local blood vessels and may form tumour emboli to be lodged elsewhere, producing metastatic tumour deposits. Notable examples are clear cell carcinoma of kidney, carcinoma of the lung, malignant melanoma etc (Chapter 7).

**Miscellaneous Emboli**

Various other endogenous and exogenous substances may act as emboli. These may include the following:

1. Fragments of tissue
2. Placental fragments
3. Red cell aggregates (sludging)
4. Bacteria
5. Parasites
6. Barium emboli following enema
7. Foreign bodies e.g. needles, talc, sutures, bullets, catheters etc.
Embolism is the process of partial or complete obstruction of some part of the cardiovascular system by any mass carried in the circulation.

Most common forms of emboli (90%) are thromboemboli originating from thrombi or their detached parts within the heart, arteries or veins.

Pulmonary thromboembolism is common and fatal form of venous thromboembolism, most often originating from deep vein thrombosis of the lower legs.

Most common form of arterial embolism arises in the thrombi from the left ventricle due to heart diseases.

Fat embolism may be traumatic (most often from surgical or accidental trauma to the bones) or from several non-traumatic causes.

Gas embolism may be air embolism (arterial or venous) or decompression sickness (in divers or in high altitude).

Amniotic fluid embolism is the most serious, unpredictable and unpreventable cause of maternal mortality occurring during labour and in the immediate postpartum period.

Other forms of embolism include atheroembolism, tumour embolism etc.

**ISCHAEMIA**

**DEFINITION**  
Ischaemia is defined as deficient blood supply to part of a tissue relative to its metabolic needs. The cessation of blood supply may be complete (complete ischaemia) or partial (partial ischaemia). The adverse effects of ischaemia may result from 3 ways:

1. **Hypoxia** due to deprivation of oxygen to tissues relative to its needs; this is the most important and common cause. It may be of 4 types:
   i) **Hypoxic hypoxia:** due to low oxygen in arterial blood.
   ii) **Anaemic hypoxia:** due to low level of haemoglobin in blood.
   iii) **Stagnant hypoxia:** due to inadequate blood supply.
   iv) **Histotoxic hypoxia:** low oxygen uptake due to cellular toxicity.

2. **Malnourishment of cells** due to inadequate supply of nutrients to the tissue (i.e. glucose, amino acids); this is less important.

3. **Inadequate clearance of metabolites** which results in accumulation of metabolic waste-products in the affected tissue; this is relevant in some conditions such as muscleache after ischaemia from heavy exercise.

**ETIOLOGY**  
A number of causes may produce ischaemia. These causes are discussed below with regard to different levels of blood vessels:

1. **Causes in the heart**  
   Inadequate cardiac output resulting from heart block, ventricular arrest and fibrillation from various causes may cause variable degree of hypoxic injury to the brain as under:
   i) If the arrest continues for 15 seconds, consciousness is lost.
   ii) If the condition lasts for more than 4 minutes, irreversible ischaemic damage to the brain occurs.
   iii) If it is prolonged for more than 8 minutes, death is inevitable.

2. **Causes in the arteries**  
The commonest and most important causes of ischaemia are due to obstruction in arterial blood supply as under:

   i) **Luminal occlusion of artery (intraluminal):**
      a) Thrombosis
      b) Embolism
   ii) **Causes in the arterial walls (intramural):**
      a) Vasospasm (e.g. in Raynaud’s disease)
      b) Hypothermia, ergotism
      c) Arteriosclerosis
      d) Polyarteritis nodosa
      e) Thromboangiitis obliterans (Buerger’s disease)
      f) Severed vessel wall
   iii) **Outside pressure on an artery (extramural):**
      a) Ligature
      b) Tourniquet
      c) Tight plaster, bandages
      d) Torsion.

3. **Causes in the veins**  
Blockage of venous drainage may lead to engorgement and obstruction to arterial blood supply resulting in ischaemia. The examples include the following:

   i) **Luminal occlusion of vein (intraluminal):**
      a) Thrombosis of mesenteric veins
      b) Cavernous sinus thrombosis
   ii) **Causes in the vessel wall of vein (intramural):**
      a) Varicose veins of the legs
   iii) **Outside pressure on vein (extramural):**
      a) Strangulated hernia
      b) Intussusception
      c) Volvulus

4. **Causes in the microcirculation**  
Ischaemia may result from occlusion of arterioles, capillaries and venules. The causes are as under:

   i) **Luminal occlusion in microvasculature (intraluminal):**
      a) By red cells e.g. in sickle cell anaemia, red cells parasitised by malaria, acquired haemolytic anaemia, sludging of the blood.
      b) By white cells e.g. in chronic myeloid leukaemia
      c) By fibrin e.g. defibrination syndrome
      d) By precipitated cryoglobulins
      e) By fat embolism
      f) In decompression sickness.
   ii) **Causes in the microvasculature wall (intramural):**
      a) Vasculitis e.g. in polyarteritis nodosa, Henoch-Schönlein purpura, Arthus reaction, septicaemia.
      b) Frost-bite injuring the wall of small blood vessels.
   iii) **Outside pressure on microvasculature (extramural):**
      a) Bedsores.

**FACTORS DETERMINING SEVERITY OF ISCHAEMIC INJURY**  
The extent of damage produced by ischaemia due to occlusion of arterial or venous blood vessels depends upon a number of factors as under:

1. **Anatomic pattern**  
The extent of injury by ischaemia depends upon the anatomic pattern of arterial blood supply of the organ or tissue affected. There are 4 different patterns of arterial blood supply:

   i) **Single arterial supply without anastomosis**  
      Some organs receive blood supply from arteries which do not have significant anastomosis and are thus functional end-arteries. Occlusion of such vessels invariably results in ischaemic necrosis. For example:
      a) Central artery of the retina
      b) Interlobular arteries of the kidneys.
Single arterial supply with rich anastomosis. Arterial supply to some organs has rich interarterial anastomoses so that blockage of one vessel can re-establish blood supply bypassing the blocked arterial branch, and hence infarction is less common in such circumstances. For example:

- Superior mesenteric artery supplying blood to the small intestine.
- Inferior mesenteric artery supplying blood to distal colon.
- Arterial supply to the stomach by 3 separate vessels derived from coeliac axis.
- Interarterial anastomoses in the 3 main trunks of the coronary arterial system.

Parallel arterial supply. Blood supply to some organs and tissues is such that vitality of the tissue is maintained by alternative blood supply in case of occlusion of one. For example:

- Blood supply to the brain in the region of circle of Willis.
- Arterial supply to forearm by radial and ulnar arteries.

Double blood supply. The effect of occlusion of one set of vessels is modified if an organ has dual blood supply. For example:

- Lungs are perfused by bronchial circulation as well as by pulmonary arterial branches.
- Liver is supplied by both portal circulation and hepatic arterial flow.

However, collateral circulation is of little value if the vessels are severely affected with spasm, atheroma or any other such condition.

2. General and cardiovascular status. The general status of an individual as regards cardiovascular function is an important determinant to assess the effect of ischaemia. Some of the factors which render the tissues more vulnerable to the effects of ischaemia are as under:

- Anaemias (sickle cell anaemia, in particular)
- Lowered oxygenation of blood (hypoxaemia)
- Senility with marked coronary atherosclerosis
- Cardiac failure
- Blood loss
- Shock.

3. Type of tissue affected. Vulnerability of the tissue of the body to the effect of ischaemia is variable. Mesenchymal tissues are quite resistant to the effect of ischaemia as compared to parenchymal cells of the organs. The following tissues are more vulnerable to ischaemia:

- Brain (cerebral cortical neurons, in particular).
- Heart (myocardial cells).
- Kidney (especially epithelial cells of proximal convoluted tubules).

4. Rapidity of development. Sudden vascular obstruction results in more severe effects of ischaemia than if it is gradual since there is less time for collaterals to develop.

5. Degree of vascular occlusion. Complete vascular obstruction results in more severe ischaemic injury than the partial occlusion.

EFFECTS. The effects of ischaemia are variable and range from ‘no change’ to ‘sudden death’.

1. No effects on the tissues. If the collateral channels develop adequately, the effect of ischaemia fails to occur.

2. Functional disturbances. These result when collateral channels are able to supply blood during normal activity but the supply is not adequate to withstand the effect of exertion. The examples are angina pectoris and intermittent claudication.

3. Cellular changes. Partial and gradual ischaemia may produce cellular changes such as cloudy swelling, fatty change, ischaemic atrophy and replacement fibrosis. Infarction results when the deprivation of blood supply is complete so as to cause necrosis of tissue affected.

4. Sudden death. The cause of sudden death from ischaemia is usually myocardial and cerebral infarction.

The most important and common outcome of ischaemia is infarction discussed below. Fig. 4.28 shows the organs most commonly affected by infarction.

INFARCTION

DEFINITION. Infarction is the process of tissue necrosis, usually coagulative type, resulting from ischaemia; the localised area of necrosis so developed is called an infarct.

ETIOLOGY. All the causes of ischaemia discussed above can cause infarction. However, there are a few other noteworthy features in infarction:

- Most commonly, infarcts are caused by interruption in arterial blood supply, called ischaemic necrosis.
- Less commonly, venous obstruction can produce infarcts termed stagnant hypoxia.
- Generally, sudden, complete, and continuous occlusion (e.g. thrombosis or embolism) produces infarcts.
iv) Infarcts may be produced by nonocclusive circulatory insufficiency as well e.g. incomplete atherosclerotic narrowing of coronary arteries may produce myocardial infarction due to acute coronary insufficiency.

**TYPES OF INFARCTS** Infarcts are classified depending upon different features:

1. According to their colour:
   i) Pale or anaemic, due to arterial occlusion and are seen in compact organs e.g. in the kidneys, heart, spleen.
   ii) Red or haemorrhagic, seen in soft loose tissues and are caused either by pulmonary arterial obstruction (e.g. in the lungs) or by arterial or venous occlusion (e.g. in the intestines).

2. According to their age:
   i) Recent or fresh
   ii) Old or healed

3. According to presence or absence of infection:
   i) Bland, when free of bacterial contamination
   ii) Septic, when infected.

**PATHOGENESIS** The process of infarction takes place as follows:

i) Localised hyperaemia due to local anoxaemia occurs immediately after obstruction of the blood supply.

ii) Within a few hours, the affected part becomes swollen due to oedema and haemorrhage. The amount of haemorrhage is variable, being more marked in the lungs and spleen, and less extensive in the kidneys and heart.

iii) Cellular changes such as cloudy swelling and degeneration appear early (reversible cell injury), while cell death (irreversible cell injury or necrosis) occurs in 12-48 hours.

iv) There is progressive proteolysis of the necrotic tissue and there is lysis of the red cells.

v) An acute inflammatory reaction and hyperaemia appear at the same time in the surrounding tissues in response to products of proteolysis.

vi) Blood pigments, haematoidin and haemosiderin, liberated by lysis of RBCs are deposited in the infarct. At this stage, most infarcts become pale-grey due to loss of red cells.

vii) Following this, there is progressive ingrowth of granulation tissue from the margin of the infarct so that eventually the infarct is replaced by a fibrous scar. Dystrophic calcification may occur sometimes.

**MORPHOLOGIC FEATURES** Some general morphological features of infarcts characterise infarcts of all organ sites.

**Grossly**, general features are as follows:

i) Infarcts of solid organs are usually wedge-shaped, the apex pointing towards the occluded artery and the wide base on the surface of the organ.

ii) Infarcts due to arterial occlusion are generally pale while those due to venous obstruction are haemorrhagic.

iii) Most infarcts become pale later as the red cells are lysed but pulmonary infarcts never become pale due to extensive amount of blood.

iv) Cerebral infarcts are poorly defined with central softening (encephalomalacia).

v) Recent infarcts are generally slightly elevated over the surface while the old infarcts are shrunken and depressed under the surface of the organ.

**Microscopically**, the general features are as under:

i) Pathognomonic cytologic change in all infarcts is coagulative (ischaemic) necrosis of the affected area of tissue or organ. In cerebral infarcts, however, there is characteristic liquefactive necrosis.

ii) Some amount of haemorrhage is generally present in any infarct.

iii) At the periphery of an infarct, inflammatory reaction is noted. Initially, neutrophils predominate but subsequently macrophages and fibroblasts appear.

iv) Eventually, the necrotic area is replaced by fibrous scar tissue, which at times may show dystrophic calcification.

v) In cerebral infarcts, the liquefactive necrosis is followed by gliosis i.e. replacement by microglial cells distended by fatty material (glitter cells).

**Infarct of Different Organs**

A few representative examples of infarction of some organs (lungs, kidney, liver and spleen) are discussed below. Myocardial infarction (page 409), cerebral infarction (page 872) and infarction of the small intestines (page 546) are covered in detail in respective chapters of Systemic Pathology.

**Table 4.10** sums up the gross appearance and the usual outcome of the common types of infarction.

**INFARCT LUNG** Embolism of the pulmonary arteries may produce pulmonary infarction, though not always. This is because lungs receive blood supply from bronchial arteries as well, and thus occlusion of pulmonary artery ordinarily does not produce infarcts. However, it may occur in patients who have inadequate circulation such as in chronic lung diseases and congestive heart failure.

**Grossly**, pulmonary infarcts are classically wedge-shaped with base on the pleura, haemorrhagic, variable in size, and most often in the lower lobes (Fig. 4.29). Fibrinous pleuritis usually covers the area of infarct. Cut surface is

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>GROSS APPEARANCE</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Myocardial infarction</td>
<td>Pale</td>
<td>Frequently lethal</td>
</tr>
<tr>
<td>2. Pulmonary infarction</td>
<td>Haemorrhagic</td>
<td>Less commonly fatal</td>
</tr>
<tr>
<td>3. Cerebral infarction</td>
<td>Haemorrhagic or pale</td>
<td>Fatal if massive</td>
</tr>
<tr>
<td>4. Intestinal infarction</td>
<td>Haemorrhagic</td>
<td>Frequently lethal</td>
</tr>
<tr>
<td>5. Renal infarction</td>
<td>Pale</td>
<td>Not lethal unless massive and bilateral</td>
</tr>
<tr>
<td>6. Infarct spleen</td>
<td>Pale</td>
<td>Not lethal</td>
</tr>
<tr>
<td>7. Infarct liver</td>
<td>Pale</td>
<td>Not lethal</td>
</tr>
<tr>
<td>8. Infarcts lower extremity</td>
<td>Pale</td>
<td>Not lethal</td>
</tr>
</tbody>
</table>
Derangements of Homeostasis and Haemodynamics

CHAPTER 4

Splenectomy, vascular injuries or invasion of splenic artery or its branches. Occlusion is caused most commonly by thromboemboli arising in the heart (e.g. in mural thrombi in the left atrium, vegetative endocarditis, myocardial infarction), and less frequently by obstruction of microcirculation (e.g. in myeloproliferative diseases, sickle cell anaemia, arteritis, Hodgkin’s disease, bacterial infections).

Grossly, splenic infarcts are often multiple. They are characteristically pale or anaemic and wedge-shaped with their base at the periphery and apex pointing towards hilum (Fig. 4.33).

INFARCT KIDNEY

Renal infarction is common, found in up to 5% of autopsies. Majority of them are caused by thromboemboli, most commonly originating from the heart such as in mural thrombi in the left atrium, myocardial infarction, vegetative endocarditis and from aortic aneurysm. Less commonly, renal infarcts may occur due to advanced renal artery atherosclerosis, arteritis and sickle cell anaemia.

Grossly, renal infarcts are often multiple and may be bilateral. Characteristically, they are pale or anaemic and wedge-shaped with base resting under the capsule and apex pointing towards the medulla. Generally, a narrow rim of preserved renal tissue under the capsule is spared because it draws its blood supply from the capsular vessels. Cut surface of renal infarct in the first 2 to 3 days is red and congested but by 4th day the centre becomes pale yellow. At the end of one week, the infarct is typically anaemic and depressed below the surface of the kidney (Fig. 4.31).

Microscopically, the affected area shows characteristic coagulative necrosis of renal parenchyma i.e. there are ghosts of renal tubules and glomeruli without intact nuclei and cytoplasmic content. The margin of the infarct shows inflammatory reaction—initially acute but later macrophages and fibrous tissue predominate (Fig. 4.32).

INFARCT SPLEEN

Spleen is one of the common sites for infarction. Splenic infarction results from occlusion of the splenic artery or its branches. Occlusion is caused most commonly by thromboemboli arising in the heart (e.g. in mural thrombi in the left atrium, vegetative endocarditis, myocardial infarction), and less frequently by obstruction of microcirculation (e.g. in myeloproliferative diseases, sickle cell anaemia, arteritis, Hodgkin’s disease, bacterial infections).

Grossly, splenic infarcts are often multiple. They are characteristically pale or anaemic and wedge-shaped with their base at the periphery and apex pointing towards hilum (Fig. 4.33).
General Pathology

SECTION I

Figure 4.33 Pale infarct spleen. A wedge-shaped shrunken area of pale colour is seen with base resting under the capsule, while the margin is congested.

Microscopically, the features are similar to those found in anaemic infarcts in kidney. Coagulative necrosis and inflammatory reaction are seen. Later, the necrotic tissue is replaced by shrunken fibrous scar (Fig. 4.34).

INFARCT LIVER Just as in lungs, infarcts in the liver are uncommon due to dual blood supply—from portal vein and from hepatic artery.

- Obstruction of the portal vein is usually secondary to other diseases such as hepatic cirrhosis, intravenous invasion of primary carcinoma of the liver, carcinoma of the pancreas and pylephlebitis. Occlusion of portal vein or its branches generally does not produce ischaemic infarction but instead reduced blood supply to hepatic parenchyma causes non-ischaemic infarct called infarct of Zahn.

Grossly, ischaemic infarcts of the liver are usually anaemic but sometimes may be haemorrhagic due to stuffing of the site by blood from the portal vein. Infarcts of Zahn (non-ischaemic infarcts) produce sharply defined red-blue area in liver parenchyma.

Microscopically, ischaemic infarcts show characteristics of pale or anaemic infarcts as in kidney or spleen. Infarcts of Zahn occurring due to reduced portal blood flow over a long duration result in chronic atrophy of hepatocytes and dilatation of sinusoids.

GIST BOX 4.8 Ischaemia andInfarction

- Ischaemia is defined as deficient blood supply to part of a tissue relative to its metabolic needs.
- Causes of ischaemia may lie in the heart, arteries, veins and microcirculation.
- Adverse effects of ischaemia may result in 3 ways: hypoxia, malnourishment of cells and inadequate clearance of metabolites.
- Severity of ischaemic injury depends upon anatomic pattern of blood supply, general and cardiovascular status, type of tissue affected, and speed of development of ischaemia.
- Most common effect of ischaemia is infarction, generally from coagulative necrosis in most organs, but in the brain it is liquefactive necrosis.
- Some of the common locations of infarcts are: brain, heart, kidneys, spleen, small intestines, and lower extremities. Infarction of lungs and liver is less frequent due to dual blood supply to both these organs.
A 35 years old female admitted with pain lower abdomen following abortion by village midwife 3 days back. She has been having high-grade fever and bleeding from gums for 2 days. Now, she has been unconsciousness for the last 3 hours.

On examination, she is moderately built and nourished and unconscious. Her blood pressure and pulse are not recordable; while respiration rate is 40/min. She has pallor +++, oral bleeding + but no jaundice, cyanosis or lymphadenopathy. Auscultation of chest showed bilateral crepts and wheezing.

1. **Discuss the clinical correlation with pathogenesis of the features.**
2. **What is the probable diagnosis?**
3. **How will you investigate and confirm the diagnosis?**

*Answers on page 906 (Appendix II)*