OEDEMA

• Definition and types
• The Greek word oedema means swelling. Oedema may be defined as abnormal and excessive accumulation of 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. The accumulation of fluid in the body cavities is correspondingly known as ascites (in the peritoneal cavity), hydrothorax or pleural effusion (in the pleural cavity) and hydropericardium or pericardial effusion (in the pericardial cavity).
• The oedema may be of 2 main types.
  • Localized in the organ and limb; and
  • Generalized (anasarca or dropsy) when it is systemic in distribution, particularly noticeable in the subcutaneous tissues.
• Besides, there are a few special forms of oedema. The oedema 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 tissue, 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 fluid may be:
1] transudate which is more often the case, such as in oedema of cardiac and renal disease; or
2] exudate such as in inflammatory oedema.

The differences between transudate and exudate are tabulated.
Pathogenesis of oedema
Oedema is caused by mechanisms that interfere with normal fluid balance of plasma, interstitial fluid and lymph flow. The following six mechanisms may be operating singly or in combination to produce oedema;
Types of oedema

- 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.
- Sodium and water retention.
These mechanisms are discussed below.

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), 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.
   - Hypoproteinaemia usually produced generalized oedema (anaasarca). Out of the various plasma proteins, albumin has four times higher plasma oncotic pressure than globulin so that it is hypoalbuminemia (albumin below 2.5 g/dl) that results in oedema more often.
The examples of oedema by this mechanisms are seen in the following conditions:

- Oedema of renal disease e.g. in nephrotic syndrome, acute glomerulonephritis.
- Ascites of liver disease e.g. in cirrhosis.
- 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 counter acting 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.
• The examples of oedema by this mechanisms are seen in the following disorders:
  • Oedema of cardiac disease e.g. in congestive cardiac failure, constrictive pericarditis.
  • Ascites of liver disease e.g. in cirrhosis of liver.
  • Passive congestion e.g. in mechanical obstruction due to thrombosis of veins of the lower legs, varicosities, pressure by pregnant uterus, tumors et.
  • Postural oedema e.g. transient oedema of feet and ankles due to increased venous pressure seen in individuals who remain standing erect for longtime such as traffic constables.
3. Lymphatic Obstruction:

- Normally the interstitial fluid in the tissue spaces escapes by way of lymphatics so that obstruction to outflow of these channels causes localized oedema, known as lymphoedema.
The examples of lymphoedema include the following:

- Removal of axillary lymph nodes in radical mastectomy for carcinoma of the breast produces lymphoedema of the affected arm.
- 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 (chylosus ascites).
- Inflammation of the lymphatics as seen in filariasis (infection with Wuchereria bancrofti) results in chronic lymphoedema of scrotum and legs known as elephantiasis.
- Occlusion of lymphatic channels by malignant cells may result in lymphoedema.
- 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.
4. Tissue Factors:

- The forces acting in the interstitial space – oncotic pressure of the interstitial space and tissue tension, are normally quite small and insignificant to counteract the effect 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. These are as under:
  - Elevation of oncotic pressure of interstitial fluid as occurs due to increased vascular permeability and inadequate removal of proteins by lymphatics.
  - Lowered tissue tension as seen in loose subcutaneous tissues of eyelids and external genitalia.
5. Increased capillary permeability:

- As described previously, 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, histamine, anoxia, venoms, certain drugs and chemicals, the capillary permeability to plasma proteins is enhanced due to development of gaps between the endothelial cells. This, in turn, causes reduced plasma oncotic pressure and elevated oncotic pressure of interstitial fluid which consequently produces oedema.
• The examples of oedema by this mechanism are seen in the following conditions:

• Generalized oedema due to increased vascular permeability may occur in systemic infections, poisonings, certain drugs and chemicals, anaphylactic reactions and anoxia.

• Localized oedema such as:

  • 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 localized 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.
• **Sodium and water retention:**

• Before describing the mechanism of oedema by sodium and water retention, it is essential to recollect the normal regulatory mechanism of sodium and water balance.

• Normally, about 80% of sodium is reabsorbed by the proximal convoluted tubule under the influence of intrinsic renal mechanism or extra-renal mechanism:
• **Intrinsic renal mechanism** is activated in response to sudden reduction in the effective arterial blood volume (hypovolaemia) as occurs in severe haemorrhage. Hypovolaemia stimulated 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 renninangiotensin-aldosterone system. Rennin in an enzyme secreted by the granular cells in the juxtaglomerular 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 α2-globulin or rennin substrate present in the plasma. On stimulation, angiotensin I, a decapeptide, is formed in the plasma which is subsequently converted into angiotensin II, an octapeptide, in the lungs and kidneys. 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.
**AHD 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 hormone is stimulated by increased concentration of sodium in the plasma and hypovolaemia. Large amounts of ADH produce highly concentrated urine.

* Excessive retention of sodium and water and their decreased renal excretion occur in response to hypovolaemia and lowered concentration of sodium in the renal tubules via stimulation of intrinsic renal and extra-renal mechanisms as well as via release of ADH.
• The examples of oedema by these mechanisms are as under:
• Oedema of cardiac disease e.g. in congestive cardiac failure.
• Ascites of liver disease e.g. in cirrhosis of liver.
• Oedema of renal disease e.g. in nephrotic syndrome, glomerulonephritis.
• **Pathogenesis and morphology of important types of oedema.**

• As observed from the pathogenesis of oedema just described, more than one mechanism may be involved in many examples of localized and generalized oedema. Some of the important examples are described below:
• **Renal oedema**
• General oedema occurs in certain disease of renal origin such as in nephrotic syndrome, some types of glomerulonephritis, 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 generalized oedema (nephrotic oedema). The hypoalbuminaemia causes fall in the plasma volume activating rennin-angiotensin-aldosterone mechanism which results in retention of sodium and water, thus setting in a vicious cycle which persists till the albuminuria continues. Similar types of mechanisms operates in the pathogenesis of oedema in protein-losing enteropathy, further confirming the role protein loss in the causation of oedema.
• The nephrotic oedema is classically more severe and marked and is present in the subcutaneous tissues as well as in the visceral organs. The affected organ is enlarged and heavy with tense capsule.

• **Microscopically**, the oedema fluid separates the connective tissue fibers of subcutaneous tissues. Depending upon the protein content, the oedema fluid may appear homogenous, pale, eosinophilic, or may be deeply eosinophilic and granular.
2. Oedema in glomerulonephritis. Oedema occurs in conditions with diffuse glomerular disease such as in acute diffuse glomerulonephritis and rapidly progressive glomerulonephritis (nephritic oedema). In contrast to nephrotic oedema, nephritic oedema is not due to hypoproteinaemia but is due to excessive reabsorption of sodium and water in the renal tubules via reninangiotensin-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 (unlikely cardiac oedema).

- The salient differences between the nephrotic and nephritic oedema are outlined.
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 increased reabsorption and oliguria. Besides, there is excessive retention of water and electrolytes and rise in blood urea.
• **Cardiac Oedema**

Generalized oedema develops in right-sided and congestive cardiac failure. Pathogenesis of cardiac oedema is explained on the basis of the following hypothesis.

• Reduced cardiac output causes hypovolaemia which stimulated intrinsic-renal and extra-renal hormonal (rennin-angiotensin-aldosterone) mechanisms as well as ADH secretion resulting in sodium and water retention and consequent oedema.

• 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.
• Chronic hypoxia may injure the capillary wall 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, so that pulmonary oedema develops rather than generalized 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 but has special features. It 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.
• **Elevation in pulmonary hydrostatic pressure (Haemodynamic oedema).** In heart failure, there is increased in the 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 tenfold 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.
Next follows the thickening of the alveolar walls because of the interstitial oedema. Upto 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 alveolus, thus seriously hampering the lung function.
Examples of pulmonary oedema by this mechanism are seen in the left heart failure, mitral stenosis, pulmonary vein obstruction, thyrotoxicosis, cardiac surgery, nephrotic syndrome and obstruction to the lymphatic outflow by tumor or inflammation.
• **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 examples 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).
• **Acute high altitude oedema.** Individuals climbing to high altitude suddenly without halts and without waiting for acclimatization to set in, suffer from serious circulatory and respiratory ill-effects. Commonly, the deleterious effects begin to appear after an altitude of 2500 meters is reached. These changes include: appearance of oedema fluid in the lungs, congestion and widespread minute hemorrhages. These changes can cause death within a few days. The underlying mechanism appears to be anoxic damage to the pulmonary vessels. However, if acclimatization 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.
• **Pathologic changes.** 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 lines perpendicular to the pleura and are known as Kerley' 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 (interstitial oedema) but later the fluid fills the alveolar spaces (alveolar oedema). The interstitium as well as the alveolar spaces thus contain an eosinophilic, granular and pink proteinaceous material, often admixed with some RBCs and macrophages. This 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.
• In chronically elevated venous pressure, known as chronic passive congestion of lung or brown induration, the lungs are firm and heavy. The sectioned surface is rusty brown in colour.

• Microscopically, the alveolar septa are widened and the alveolar spaces contain numerous haemosiderin laden macrophages (heart failure cells) and, in late stage, may show variable amount of fibrosis.
• **Cerebral oedema.**

• Cerebral oedema or swelling of brain is the most 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 oedema.** This is the most common type and corresponds to oedema elsewhere resulting 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 (Virchowrobin) space is widened and clear halos are seen around the small blood vessels.
• **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 osmorgulation as occurs in some metabolic derangements, acute hypoxia and with some toxic chemicals.

• **Microscopically,** the cells are swollen and vacuolated. In some situation, both vasogenic as well as Cytotoxic cerebral oedema results e.g. in purulent meningitis.
• **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.