PERTURBATIONS OF FLOW 1

HYPERAEMIA AND CONGESTION

- **hyperaemia** = literally, "too much blood"
  = increased blood volume within the vasculature of a tissue or organ

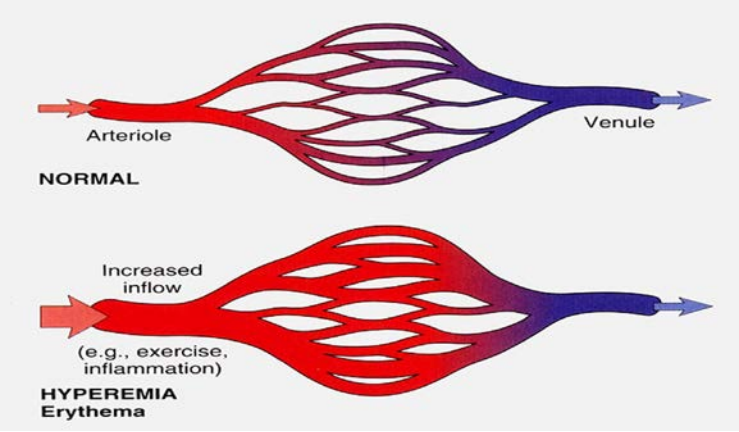
- differs from tissue haemorrhage in that the increased blood volume is still within blood vessels
- results from either **increased entry of arterial blood** or from **decreased venous outflow**
- may be active or passive, localised or generalised, and physiological or pathological

ACTIVE HYPERAEMIA

- **active hyperaemia** = increased blood volume due to arteriolar dilation and expansion of the perfused capillary bed (Figure 1)

- during normal tissue perfusion, blood may be shunted past many capillaries
- during active hyperaemia, all capillaries in the affected area are distended and perfused

Figure 1



Reference: "Robbins and Cotran Pathologic Basis of Disease" – V Kumar, AK Abbas and N Fausto, 7th ed., Saunders, 2005

- active hyperaemia is usually a **localised phenomenon**; there is insufficient blood volume to permit generalised active hyperaemia whilst maintaining adequate systemic blood pressure

- active hyperaemia is mediated by vasoactive molecules (e.g. histamine, bradykinin, vasodilatory prostaglandins and lactic acid) and neurogenic mechanisms (e.g. the axon reflex)

- active hyperaemia is associated with an increase in tissue metabolism and oxygen consumption

Examples of Active Hyperaemia

- e.g. increased blood flow to gastrointestinal tract following ingestion of food
- e.g. increased blood flow to skeletal muscles during exercise
- e.g. increased blood flow to skin during exercise or hot weather to augment heat loss
- e.g. blushing due to embarrassment or nervousness ("neurovascular hyperaemia")
- e.g. **inflammation** - local active hyperaemia is responsible for the redness (rubor, erythema) and heat (calor) of acute inflammation

Gross Appearance of Active Hyperaemia

- tissues affected by active hyperaemia appear red (erythematous), swollen, warm and turgid
- the capillary beds are engorged with bright red oxygenated blood
- the cut surface appears wet, with red blood oozing from it
- if active hyperaemia is due to inflammation, there will be concurrent localised oedema and inflammatory exudate may also be visible
- a pulse is sometimes palpable in sites of acute inflammatory hyperaemia (e.g. at the coronary band in horses with acute laminitis) due to arteriolar dilation and increased afferent blood flow

Microscopic Appearance of Active Hyperaemia

- microscopically, the arterioles and capillaries are distended by blood
- if the cause is inflammatory, other morphological features of inflammation will also be present (e.g. oedema, intravascular margination of leukocytes and extravasation of leukocytes)

NOTE: If the term "hyperaemia" is used without qualification as to whether it is "active" or "passive", it refers to <u>active</u> hyperaemia.

CONGESTION (PASSIVE HYPERAEMIA)

- **congestion = passive congestion = passive hyperaemia**(Figure 2)
  = a passive process in which increased blood volume within the vasculature of a tissue is due to impairment of venous outflow

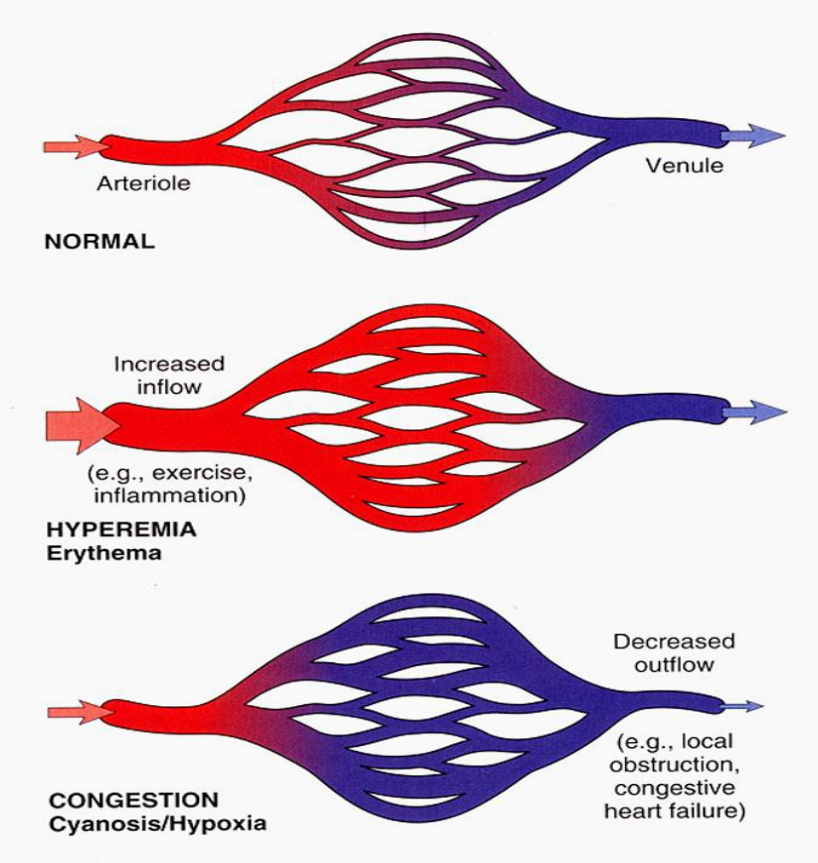
- venous blood pools within veins, venules and capillaries **upstream** from the causal lesion

- congestion may be **localised** or **generalised** and may develop rapidly or slowly

Gross Appearance of Congestion

- congested tissues appear swollen and turgid, with a wet cut surface from which excess blood oozes
- congested tissues appear red-purple to blue-black (**cyanosis**) (c.f. red in active hyperaemia) due to engorgement of veins, venules and capillary beds with poorly oxygenated venous blood
- there is no associated increase in tissue temperature (c.f. active hyperaemia) and, in living animals, the affected area may actually feel cooler than normal
- oedema commonly contributes to the tissue swelling and the wet cut surface appearance

Figure 2



Reference: "Robbins and Cotran Pathologic Basis of Disease" – V Kumar, AK Abbas and N Fausto, 7th ed., Saunders, 2005

Consequences of Congestion

- passive congestion → **venous hypertension** (increased hydrostatic pressure within the engorged veins, and hence the upstream venules and capillaries) → oedema, diapedesis of erythrocytes from blood vessels into tissues, +/- capillary rupture with haemorrhage
- stagnation of poorly oxygenated venous blood → local tissue hypoxia → degeneration, atrophy or necrosis of parenchymal cells +/- reparative fibrosis

- if venous outflow obstruction develops slowly, existing **collateral venous channels** may open or new ones may develop to provide alternative routes of venous drainage
- e.g. in chronic portal hypertension due to hepatic cirrhosis, extensive collateral venous channels develop to shunt mesenteric blood away from portal vein branches into the caudal vena cava or right renal or gonadal vein (= **acquired portosystemic shunting**); development of these shunts relieves the portal hypertension, the congestion of the splanchnic viscera and the associated ascites

Examples of Localised Congestion

- e.g. luminal obstruction of a vein (e.g. by a thrombus) or external compression of a vein (e.g. by a tumour or abscess or by a too tight bandage or torniquet) → passive congestion of tissues upstream
- e.g. intestinal strangulation due to torsion or volvulus → compression of mesenteric veins → obstruction of venous outflow → passive congestion of the bowel segment and its mesentery

- e.g. **hypostatic** or **dependent congestion** = gravitational pooling of venous blood in dependent (down-side) areas in recumbent or inactive animals (especially large animals) or as a post-mortem change

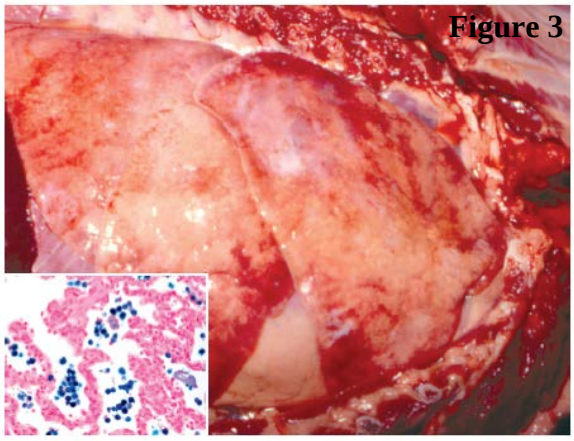
Examples of Generalised Congestion

- generalised congestion almost always refers to **congestive heart failure** but may also develop in **shock**

Left-sided Congestive Heart Failure

- in left-sided congestive heart failure, venous return to the left heart is impaired and **venous blood pools upstream in the lungs** (**pulmonary veins** and **venules** and **alveolar septal capillaries**)
- increased hydrostatic pressure within the alveolar capillaries → accumulation of low protein oedema fluid in the pulmonary interstitial connective tissues (starting at the hilus of the lungs) and thence in the lumina of the alveoli → impaired gaseous exchange +/- cyanosis
- irritation of airway mucosa by oedema fluid → a wheezing bronchial cough

- in the **acute stage of pulmonary congestion**, the lungs appear diffusely dark red to red-purple
- the lungs are heavy, wet and rubbery and do not fully collapse when the chest is opened during a post-mortem examination
- the subpleural and interstitial tissues are distended by oedema fluid and, in species with well-developed interlobular septa (e.g. cattle and pigs), the septa are expanded by oedema
- oedema fluid pours from the cut surface of the lungs and stable white or pink (blood-stained) foam is present in the lumina of the bronchioles +/- bronchi and trachea
- the foam is due to admixture of oedema fluid with surfactant and air bubbles



Chronic Pulmonary Congestion and Edema Because of Chronic Heart Failure (Dilative Cardiomyopathy), Lungs, 5-Year-Old Dog. The lungs have failed to collapse (fibrosis) and have a mottled and yellow-brown appearance (hemosiderosis). *Inset*, Microscopic view of alveoli. Large numbers of macrophages containing hemosiderin (heart failure cells *[blue color]*) are present in alveoli. During heart failure, red blood cells gain access to alveoli where they are rapidly phagocytosed by pulmonary macrophages and the iron of the hemoglobin molecule is converted to hemosiderin. Hemosiderin gives a positive reaction for iron with the Prussian blue reaction. Prussian blue (iron) reaction with nuclear fast red counter-stain. (Courtesy Dr. A. López, Atlantic Veterinary College.)

- histologically, pulmonary veins and venules and alveolar capillaries are engorged with blood
- there is also interstitial +/- intra-alveolar oedema and multifocal diapedesis of erythrocytes from the alveolar capillaries into the alveolar lumina

- in the **chronic stage of pulmonary congestion**, diffuse interstitial fibrosis may result in palpable stiffness of the lungs
- may also see diffuse tan-brown discolouration ("bronzing" or haemosiderosis) of the lungs
- histologically, alveolar septa are thickened by fibrous connective tissue
- macrophages that have phagocytosed free erythrocytes and contain haemosiderin pigment ("**heart failure cells**") are present within the alveoli and in the interstitial tissues (Figure 3)

Right-sided Congestive Heart Failure

- in right-sided congestive heart failure, venous return to the right heart is impaired and **venous**

blood pools upstream in the **cranial** and **caudal venae cavae** and their **venous tributaries**, and in the **veins and capillary beds of the splanchnic viscera** and **dependent areas**

- **passive congestion is most obvious in the liver**

- in the **acute stage of hepatic congestion**, the liver is swollen and dark red-purple, and venous blood oozes from the cut surface
- a film of coagulated fibrin may be present over the capsule and between apposed liver lobes
- hilar lymphatics are distended and the hilar connective tissues are oedematous
- histologically, the central veins and periacinar (zone 3) sinusoids are distended with blood
- the hypoxic periacinar hepatocytes may undergo hydropic or fatty degeneration or necrosis
- periportal (zone 1) and midzonal (zone 2) hepatocytes are better oxygenated because of their proximity to portal vein and hepatic artery branches and are therefore less susceptible to the hypoxia of congestion but they may undergo hydropic or fatty degeneration

- in the **chronic stage of hepatic congestion**, the liver is enlarged with rounding of lobe borders
- the parenchyma may feel firmer than normal due to fibrosis
- +/- irregular milky opacity of the capsule due to subcapsular fibrosis ("sugar-frosting")
- there may be a grossly obvious zonal pattern ("**nutmeg liver**"), with the congested periacinar zones appearing red and depressed below surviving tan-yellow, degenerate periportal and mid zones (Figure 4)
- histologically, the periacinar hepatocytes are atrophic and the central veins and periacinar sinusoids are dilated and engorged with blood
- lymphatics of the capsule and portal areas are dilated
- +/- mild periacinar haemorrhage with accumulation of siderophages
- in severe and chronic cases, fibrosis may develop around the central veins ("**cardiac fibrosis**")

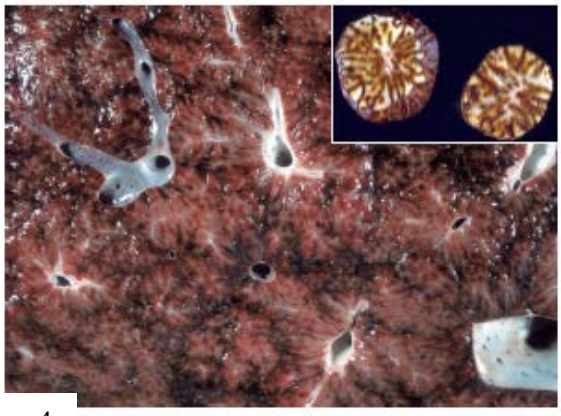


Figure 4 **Chronic Passive Congestion (Nutmeg Liver), Liver, Cut Surface, Cow.** The congestion in the centrilobular areas and the peripheral lipid accumulation give the liver a characteristic appearance that has been likened to that of the cut surface of a nutmeg, hence the term nutmeg liver. *Inset*, Cut surface of a nutmeg for comparison. (Figure courtesy Dr. D.A. Mosier, College of Veterinary Medicine, Kansas State University. Inset courtesy Dr. M.O. Howard, College of Veterinary Medicine, Iowa State University; and Noah's Arkive, College of Veterinary Medicine, The University of Georgia.)

- increased hydrostatic pressure in the hepatic sinusoids → **formation of excess hepatic lymph**
  within the space of Disse (perisinusoidal space)
- hepatic lymph is rich in proteins (including fibrinogen) normally synthesised by hepatocytes
- the excess lymph pours off the surface of the liver → **ascites** (a modified transudate containing coagulated fibrin)
- ascites is particularly prominent in dogs in right-sided congestive heart failure

other consequences of generalised congestion in right-sided heart failure include:

- **hydrothorax** = accumulation of non-inflammatory oedema fluid in the thoracic cavity
  - often prominent in cats

(**NOTE** – Hydrothorax may also develop in some cats and dogs with left-sided congestive heart failure)

- **hydropericardium** = accumulation of non-inflammatory oedema fluid in the pericardial sac

- **congestion of the spleen**

- **congestion of the kidneys**

- **congestion of the stomach, intestines, pancreas and their mesenteries**
  - the increased hydrostatic pressure in the gastrointestinal capillary beds can cause diarrhoea or (infrequently) intra-luminal bleeding or formation of rectal haemorrhoids

- **distension of jugular +/- other superficial veins**

- **ventral (dependent) subcutaneous oedema** - especially in horses and ruminants
  - ruminants often develop prominent ventral subcutaneous oedema over the brisket ("brisket disease") and in the intermandibular space ("bottle jaw")

- **nasal congestion** and **epistaxis** - especially in horses

OEDEMA

- **oedema = accumulation of excess body fluid**

- the excess fluid may accumulate **intracellularly** or **extracellularly**

- **intracellular oedema** (= **hydropic degeneration** or **acute cell swelling**) is the most common manifestation of cell injury (see Cells to Systems)
- the oedema usually results from physical damage to the cell membrane or from failure of cell ATP production and hence failure of the membrane Na^+-K^+-ATPase pump → movement of sodium ions and water into the cell

- the focus in this lecture is on **extracellular oedema**, in which the excess fluid accumulates within the **interstititial tissues** and/or within **body cavities**
- organs or tissues affected by extracellular oedema are described as being **oedematous**

- the following terms are used to describe extracellular oedema in specific locations:

- **ascites (hydroperitoneum)** = accumulation of non-inflammatory oedema fluid within the peritoneal cavity

- **hydrothorax** = accumulation of non-inflammatory oedema fluid within the pleural cavity

- **hydropericardium** = accumulation of non-inflammatory oedema fluid within the pericardial sac

- **hydrocoele** = accumulation of non-inflammatory oedema fluid within the cavity of the tunica vaginalis of the scrotum

- **anasarca** = severe generalised oedema (often most prominent in the subcutis but with accompanying body cavity effusions)

CAUSES OF EXTRACELLULAR OEDEMA

- all forms of extracellular oedema involve a disturbance of the forces involved in Starling's equilibrium hypothesis (Appendix 1)

- there are only **five major mechanisms that can cause extracellular oedema**:

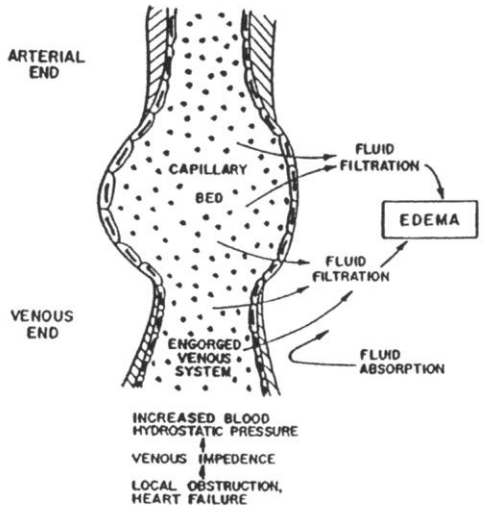
- **increased plasma hydrostatic pressure**
- **decreased plasma colloid osmotic pressure**
- **lymphatic obstruction**
- **increased vascular permeability**
- **sodium retention**

- some of these mechanisms may act in concert
- the distribution and severity of the oedema depend in part on the underlying mechanism

Increased Plasma Hydrostatic Pressure

- the **plasma hydrostatic pressure within the capillary bed is largely a reflection of the pressure at the <u>venular end</u> of the bed**
- oedema caused by increased plasma hydrostatic pressure is therefore usually a consequence of **<u>venous</u> hypertension** (e.g. in tissues undergoing **passive congestion**)
- increased venous pressure is relayed upstream into the capillary bed and negates the net absorptive pressure at the venular end of the bed so that the fluid filtered out at the arteriolar end of the bed fails to return to the circulation → oedema (Figure 5)

Figure 5



<u>Reference</u>: "Mechanisms of Disease – A Textbook of Comparative General Pathology" – D.O. Slauson and B.J. Cooper, 2nd edition, Williams and Wilkins, Baltimore, 1990

- dilation of the engorged veins, venules and capillaries may also increase their permeability by expanding the gaps between adjacent endothelial cells

IMPORTANT NOTE
- increased **arterial** pressure (e.g. systemic hypertension) does **NOT** usually cause oedema formation
- this is because increased arteriolar blood pressure (and/or increased blood volume) causes reflex vasoconstriction of the pre-capillary arteriolar sphincter in order to protect the delicate capillary bed downstream

- **localised oedema due to increased plasma hydrostatic pressure** is most commonly due to **local obstruction of venous outflow**, with congestion and oedema developing upstream from the obstruction
- e.g. occlusion of a vein by a luminal thrombus or by external compression
- e.g. intestinal mesenteric torsion
- e.g. compression of iliac veins by a gravid uterus → oedema of the hindlimbs
- localised venous hypertension and oedema may also develop in sites of **arteriovenous anastomoses**

- **more generalised oedema due to increased plasma hydrostatic pressure** may develop in

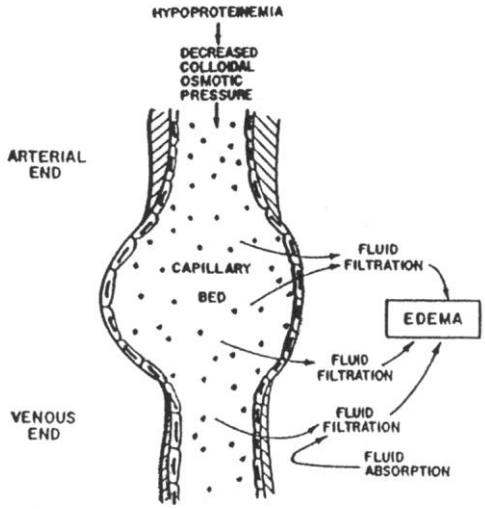
conditions in which there is impaired venous return to the heart
- e.g. right-sided congestive heart failure
- e.g. cirrhosis with portal hypertension and ascites
- in these conditions, decreased venous return to the right heart → decreased cardiac output → decreased effective circulating blood volume → **activation of the renin-angiotensin-aldosterone system** → renal retention of sodium and water → increased plasma hydrostatic pressure and decreased plasma osmotic pressure (via dilution of circulating albumin) → exacerbation of the oedema

Decreased Plasma Colloid Osmotic Pressure

- plasma colloid osmotic (oncotic) pressure is due to the effect of colloidal solutes
- the largest and most important colloids in plasma are the **plasma proteins**; these exert their full osmotic effect across the capillary wall to oppose fluid movement into the interstitium in response to plasma hydrostatic pressure
- **albumin** is the most abundant plasma protein and exerts most of the colloid osmotic pressure of plasma
- oedema due to decreased plasma colloid osmotic pressure is usually referable to **hypoalbuminaemia** (Figure 6)
- the **serum (plasma) albumin concentration must be ≤ 10-15 g/L before fluid transudation from vessels will occur** (transudation may occur at an albumin concentration ≥ 15 g/L if there is a concurrent increase in plasma hydrostatic pressure)

- hypoalbuminaemia can result from either decreased hepatic synthesis or increased loss (Table 1)

Figure 6



Reference: "Mechanisms of Disease – A Textbook of Comparative General Pathology" – D.O. Slauson and B.J. Cooper, 2nd edition, Williams and Wilkins, Baltimore, 1990

Table 1 - Major Causes of Hypoalbuminaemia

Decreased Hepatic Synthesis
- chronic hepatic insufficiency (with loss of 75-80% of liver function) - starvation/chronic low protein intake (weeks to months) - protein maldigestion - protein malabsorption

Increased Loss
- protein-losing enteropathy (e.g. Jöhne's disease, trichostrongylosis, intestinal lymphangiectasia) - protein-losing nephropathy (e.g. glomerulonephritis, glomerular amyloidosis) - severe exudative dermatoses (e.g. burns) - chronic external haemorrhage (e.g. gastrointestinal parasitism, heavy flea burden) - high protein effusions - vasculopathies with increased vascular permeability (e.g. generalised vasculitis)

- only **chronic hepatic insufficiency**, **protein malnutrition/starvation**, **protein-losing nephropathy** and **protein-losing enteropathy** are common causes of hypoalbuminaemia < 20 g/L in domestic animals

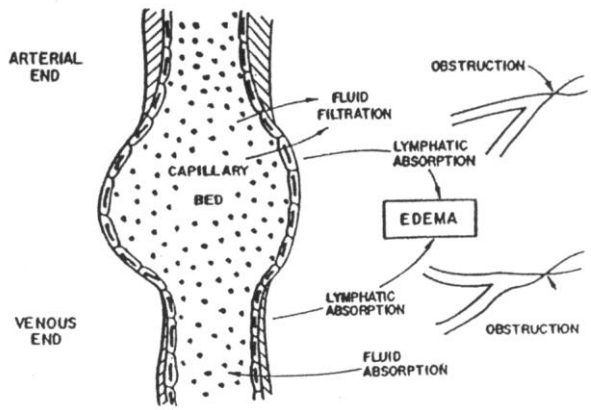
- oedema due to decreased plasma colloid osmotic pressure is expected to be **generalised** because all capillary beds of the body will be affected

- decreased plasma colloid osmotic pressure → net movement of fluid into the interstitium and body cavities → decreased effective circulating blood volume → renal hypoperfusion/hypotension → **activation of the renin-angiotensin-aldosterone system** → renal retention of sodium and water → further dilution of plasma albumin and increased plasma hydrostatic pressure → exacerbation of the oedema

Lymphatic Obstruction

- impairment of lymphatic drainage → oedema (**lymphoedema**) upstream (Figure 7)

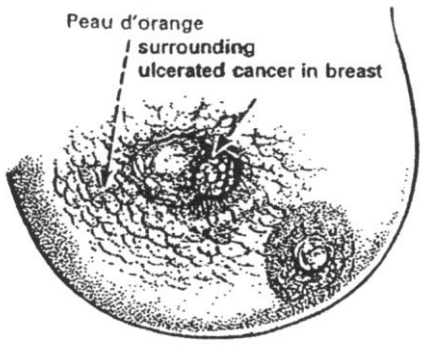
Figure 7



Reference: "Mechanisms of Disease – A Textbook of Comparative General Pathology" – D.O. Slauson and B.J. Cooper, 2nd edition, Williams and Wilkins, Baltimore, 1990

- lymphoedema is usually **localised** to the drainage field of the obstructed lymphatic(s)
- e.g. lymphatic damage caused by trauma/inflammation/infection
- e.g. lymphatic obstruction caused by lymphangitis, lymphadenitis or soft tissue scarring
- e.g. lymphoedema of the external genitalia and legs of humans with parasitism of the lymphatic system by *Brugia* and *Wuchereria* species of filariid nematodes (elephantiasis)
- e.g. obstruction of efferent lymphatics or lymph nodes by malignant tumour metastases (Figure 8)

Figure 8



Reference: "Pathology Illustrated" – A.D.T. Govan, P.S. Macfarlane, R. Callander, 4th edition, Churchill Livingstone, Edinburgh, 1995

- **generalised lymphoedema** is rare and due to severe congenital malformation of the lymphatic system

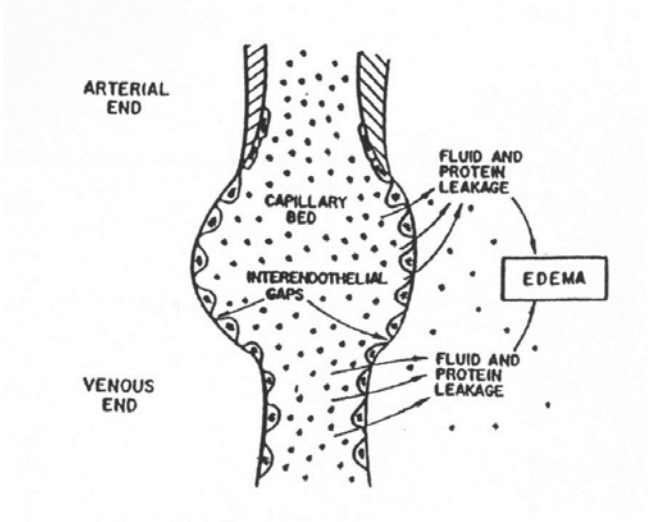
Increased Vascular Permeability

- normal fluid homeostasis depends on the structural integrity of blood vessel walls
- loss of endothelial integrity → increased vascular permeability → oedema
- oedema due to loss of endothelial integrity may be **generalised** (e.g. in hypoxaemic states, generalised vasculitis, oedema disease of pigs) but is more typically **localised** as **inflammatory oedema (**e.g. subcutaneous oedema in sites of trauma, burns, hives, arthropod bites/stings)

- in inflammation, inter-endothelial gaps open to permit escape of plasma proteins, fluid and leukocytes into tissues (Figure 9)
- initially, the gaps open due to mediators such as histamine, bradykinin, leukotrienes and substance P
- more persistent widening of the gaps is mediated by cytokines (e.g. interleukin-1, tumour necrosis factor and interferon-γ)

- inflammatory oedema leads to a rise in the interstitial hydrostatic pressure and interstitial colloid osmotic pressure → a new equilibrium point

Figure 9



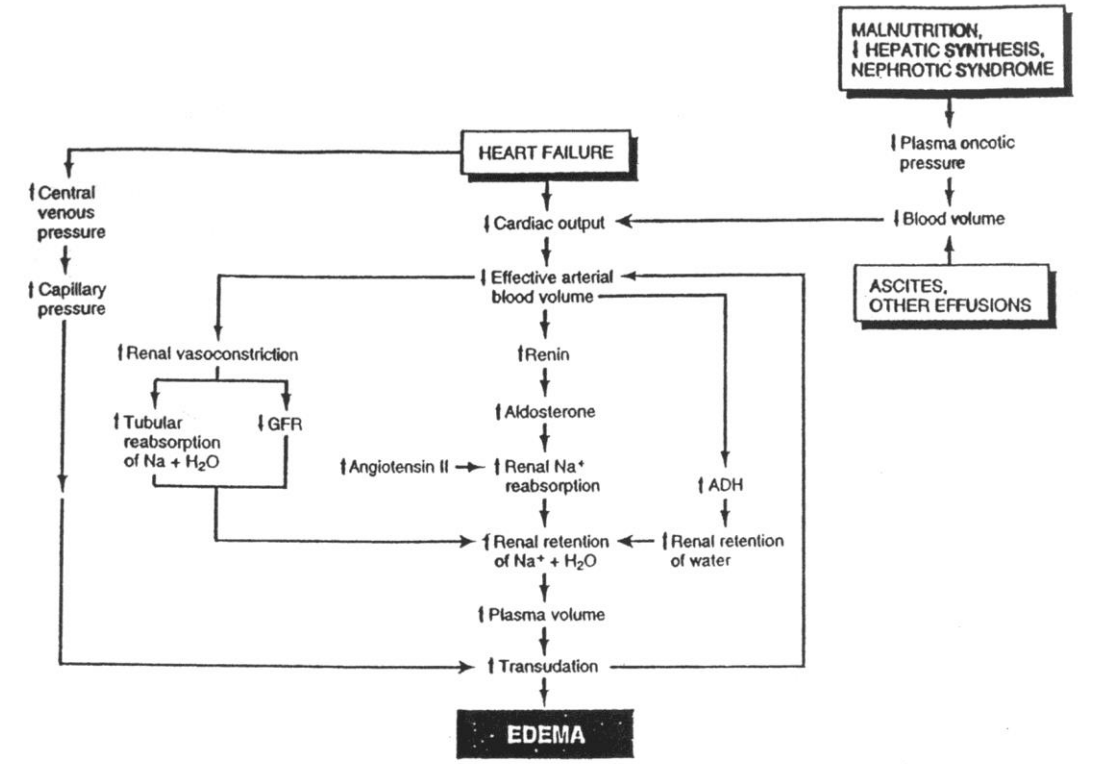
Reference: "Mechanisms of Disease – A Textbook of Comparative General Pathology" – D.O. Slauson and B.J. Cooper, 2nd edition, Williams and Wilkins, Baltimore, 1990

Sodium Retention

- activation of the renin-angiotensin-aldosterone system and renal retention of sodium and water contribute to generalised oedema development in such conditions as hypoalbuminaemia, right-sided congestive heart failure, and ascites caused by portal hypertension, by boosting the plasma hydrostatic pressure and lowering the plasma colloid osmotic pressure by dilution of albumin (Figure 10)

- **hypernatraemia** (increased blood sodium concentration) can arise if there is loss of body water in excess of electrolytes (e.g. loss of gastrointestinal fluids, heat stroke, diuretic use) or with high salt diets, saline fluid therapy, or primary hyperaldosteronism (caused by an aldosterone-secreting adrenocortical tumour)
- when the serum sodium concentration rises above 170 mmol/L, fluid shifts osmotically from the intracellular compartment to the interstitium and plasma, resulting in **cell shrinkage** and **systemic hypertension** and hence clinical signs
- osmotic brain shrinkage with tearing of meningeal vessels may provoke clinical signs such as lethargy, weakness, ataxia, seizures, stupor, muscle fasciculations and coma
- however, it is **rare for hypernatraemia alone to cause overt (clinically detectable) oedema of interstitial connective tissues**

Figure 10



Sequence of events leading to systemic edema in heart failure, or with reduced plasma osmotic pressure, as in the nephrotic syndrome. ADH, antidiuretic hormone; GFR, glomerular filtration rate.

Reference: "Robbins Pathologic Basis of Disease" – R.S. Cotran, V. Kumar, T. Collins. 6th edition, W.B. Saunders Company, Philadelphia, 1999

DIAGNOSTIC INVESTIGATION OF OEDEMA

- establishing whether oedema is of **localised or generalised distribution** provides an early important diagnostic clue to the likely underlying cause

- **localised oedema** (e.g. oedema restricted to one limb) is almost always referable to regional lymphatic obstruction, impaired regional venous drainage, or local inflammation with increased vascular permeability

- **generalised oedema** (e.g. anasarca or oedema in more than one limb) is usually referable to hypoalbuminaemia or a generalised increase in venous hydrostatic pressure (e.g. right-sided congestive heart failure), compounded by renal retention of sodium and water

- accompanying **colour changes** in oedematous tissues can also provide clues as to whether the oedema is referable to passive congestion and venous hypertension or to active inflammation (hyperaemia will be present in the latter case)

- **laboratory analysis of aspirated oedema fluid** allows subclassification into non-inflammatory and inflammatory types based on the protein concentration and total nucleated cell count of the fluid (Table 2)

Table 2 – Laboratory Evaluation of Oedema Fluid

	Protein concentration (g/L)	Total nucleated cell count (x 10^9/L)
Transudate	< 25	< 3.0
High protein transudate	>25	< 3.0
Exudate	> 25	> 3.0

- **non-inflammatory oedema fluid** is either a **transudate** (cell-poor, protein-poor) or a **modified transudate** (cell-poor but modified by addition of protein)

- **inflammatory oedema** results from increased vascular permeability and is an **exudate** (cell-rich and protein-rich)

GROSS APPEARANCE OF OEDEMA

- oedema is more easily detected with the naked eye than microscopically
- the gross appearance will vary with the severity of the oedema, speed of onset, duration, anatomic location and underlying cause

- oedema appears as excess watery, colourless to pale yellow, clear, non-viscous fluid within interstitial tissues and/or body cavities
- if oedema is accompanied by haemorrhage, the oedema fluid may be tinged red (serosanguineous)
- if the oedema fluid contains fibrinogen (e.g. when oedema results from increased vascular permeability), the fluid may form a gel on exposure to air due to polymerisation of fibrin

- oedema is most easily detected in loosely organised connective tissues (e.g. subcutis or submucosa of mucous membranes) and in organs with a distinct interstitium (e.g. lungs in cattle) because the oedema fluid physically distends the connective tissues
- oedema may be difficult to detect grossly in solid parenchymatous organs such as liver or kidney apart from an overall increase in size and weight and a bulging wet cut surface
- oedematous tissues are wet, shiny or glistening, swollen, heavy or rubbery, firm but doughy
- oedema fluid drips from the cut surface and, if pressure is applied, more fluid can be expressed
- oedematous tissue “pits” on pressure (i.e. finger pressure displaces the interstitial fluid into surrounding tissues to leave a transient indentation = “**pitting oedema**”)
- distended lymphatics may be visible over serosal surfaces of oedematous viscera and within adjacent mesenteries

- in the live animal, peripheral non-inflammatory oedema is usually non-painful (unless severe and pressing on sensory nerve endings) and the affected area may be cooler than the surrounding unaffected tissues
- if oedema is due to inflammation, the tissue may also be hyperaemic and warm
- if oedema is due to passive congestion, the tissue may also be congested and cool

- in **generalised subcutaneous oedema**, gravity tends to cause **dependent oedema** of **ventral areas** (especially in the preputial area in males)
- in "**brisket disease**" of cattle (e.g. right-sided congestive heart failure), oedema is most pronounced in the sternal subcutis
- in "**bottle jaw**" (e.g. cattle with right-sided congestive heart failure or sheep with hypoalbuminaemia due to gastrointestinal parasitism and protein loss), subcutaneous oedema is most prominent in the submandibular zone
- in horses, dependent oedema may chiefly involve the distal limbs ("stockings")

- with **corneal oedema**, the cornea thickens and appears opaque

MICROSCOPIC APPEARANCE OF OEDEMA

- oedema fluid varies in its microscopic appearance according to its protein content
- if the fluid is a pure transudate, it will be largely invisible microscopically but its presence can be inferred by the spreading apart of the interstitium and by the distension of lymphatics
- if the oedema fluid is a modified transudate or is inflammatory in origin, the fluid will stain pink with haematoxylin and eosin (H&E) stain due to its high protein content (in inflammatory oedema, there will also be other microscopic evidence of inflammation)

CLINICAL SIGNIFICANCE OF OEDEMA

- the significance of oedema depends on its severity, anatomic location, duration and underlying cause

- oedema → **impaired wound healing** and increased likelihood of **wound dehiscence** (breakdown) post-surgery
- oedematous tissues are susceptible to **secondary bacterial infection**, with enhanced spread of infectious agents and impaired clearance of infection
- chronic oedema (beyond 5-7 days) → **fibroplasia** and **permanent fibrosis**

- **cerebral** and **pulmonary oedema** may be potentially fatal

- **cerebral oedema** → increased intra-cranial pressure and cerebral dysfunction (e.g. mental depression, seizures, coma), elongation of the brain with compression of the caudolateral cerebral hemispheres by the occipital bones, and potential for caudal herniation of the medulla oblongata and caudal cerebellar vermis through the foramen magnum, compression of drainage pathways for cerebrospinal fluid (→ internal hydrocephalus), stretching or compression of cerebral blood vessels (→ ischaemia or haemorrhage) etc

- **pulmonary oedema** may be fatal if severe and of rapid development ("drowning from within")
- oedema fluid flooding alveoli and within terminal bronchioles prevents ventilation and gas exchange
- stable foam formation within the airways further compromises ventilation
- pulmonary oedema also predisposes to secondary bacterial infection of the lungs

APPENDIX - STARLING'S EQUILIBRIUM HYPOTHESIS

- approximately 60% of lean body weight is water
- **two-thirds of body water is intracellular**; the remainder is mainly in extracellular compartments (mostly as interstitial fluid), with only approximately 5% in circulating plasma
- the **interstitium** (the extracellular spaces within and between tissues) is composed of an extracellular matrix synthesised and secreted by fibrocytes and fibroblasts suspended in it
- the extracellular matrix contains insoluble glycoproteins (e.g. fibronectin and laminin) and proteins (e.g. collagen and elastin fibres) and a soluble gel
- the soluble gel contains polysaccharide chains termed **glycosaminoglycans** (e.g. heparan sulphate, dermatan sulphate, chondroitin sulphate) that are covalently linked to proteins to form **proteoglycans**
- the fluid that is normally present in the interstitium is largely water that is attracted by the glycosaminoglycans
- the interstitial fluid is in constant exchange with intracellular fluid and with plasma

- in 1876, E.H. Starling proposed an hypothesis to explain the movement of fluid between cells, the interstitium and the plasma
- according to Starling's equilibrium hypothesis, two opposing forces control the movement of water, electrolytes and other small solutes across the walls of capillaries:

- **forces promoting fluid movement from the plasma into the interstitium:**

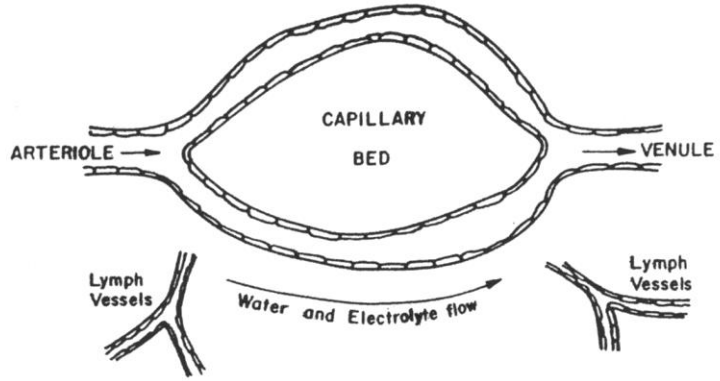
  (a) plasma hydrostatic pressure
  (b) interstitial colloid osmotic pressure

- **forces promoting fluid movement from the interstitium into the plasma:**

  (a) plasma colloid osmotic pressure
  (b) interstitial hydrostatic pressure

- the balance between these opposing forces dictates the direction of fluid movement
- in health, the plasma and interstitial osmotic pressures and the interstitial hydrostatic pressure remain relatively constant at the level of the microcirculation and favour retention of fluid in the bloodstream
- however, the high plasma hydrostatic pressure at the **arteriolar** end of each capillary bed results in a **net filtration pressure** promoting movement of fluid out of the circulation
- the drop in plasma hydrostatic pressure over the capillary bed results in a **net absorption pressure** at the **venular** end of the bed, favouring resorption of interstitial fluid back into the circulation (Figure 11)

Figure 11



	ARTERIOLAR	VENULAR
PLASMA HYDROSTATIC PRESSURE	30 mm Hg	17 mm Hg
TISSUE HYDROSTATIC PRESSURE	8 mm Hg	8 mm Hg
PLASMA COLLOIDAL-OSMOTIC PRESSURE	25 mm Hg	25 mm Hg
TISSUE COLLOIDAL-OSMOTIC PRESSURE	10 mm Hg	10 mm Hg
	(30−8) − (25−10) = 7 mm Hg Net Filtration Pressure	(17−8) − (25−10) = 6 mm Hg Net Absorption Pressure

Reference: "Mechanisms of Disease – A Textbook of Comparative General Pathology" – D.O. Slauson and B.J. Cooper, 2nd edition, Williams and Wilkins, Baltimore, 1990

NOTE: The exact pressure figures above should not be ascribed significance because they vary from species to species and between anatomic locations.

- in health, any outflow of plasma fluid into the interstitium from the arteriolar end of the capillary bed is almost matched by absorption at the venular end
- the slight excess of fluid that moves into the interstitium (due to the 1 mm Hg filtration pressure difference between the arteriolar and venular ends in the model above) is **lymph** that is usually drained away by low-pressure interstitial **lymphatics** and ultimately returned to the bloodstream via the thoracic duct

- the opposing effects of **plasma hydrostatic pressure** and **plasma colloid osmotic pressure** are the major factors governing movement of fluid between the circulation and the interstitium
- if capillary blood pressure increases or plasma colloid osmotic pressure decreases, excess interstitial fluid will accumulate (i.e. extracellular oedema develops)

- increased fluid movement into the interstitium → an increase in interstitial hydrostatic pressure and an increase in plasma colloid osmotic pressure → eventually, a new equilibrium will be reached that permits reabsorption of fluid into the plasma at the venular end of the capillary bed