The Lymphatic System and Lymph Nodes

Functions:
(1) Removes water, electrolytes, low-molecular-weight moieties (polypeptides, cytokines, growth factors) and macromolecules (fibrinogen, albumin, globulins, coagulation and fibrinolytic factors) from the interstitial fluid (ISF) and returns them to the circulation.
(2) Permits the circulation of lymphocytes and other immune cells.
(3) Intestinal lymph (chyle) transports cholesterol, long-chain fatty acids, triglycerides and the fat-soluble vitamins (A, D, E and K) directly to the circulation, bypassing the liver.

Mechanisms of lymph transport:
Resting ISF is negative (—2 to —6 mmH2O), whereas lymphatic pressures are positive, indicating that lymph flows against a small pressure gradient. It is believed that prograde lymphatic flow depends upon three mechanisms:
1. Transient increases in interstitial pressure secondary to muscular contraction and external compression.
2. The sequential contraction and relaxation of lymphangions. (Valves partition the lymphatics into segments).
3. The prevention of reflux due to valves.

Lymphangions are believed to respond to increased lymph flow in much the same way as the heart responds to increased venous return in that they increase their contractility and stroke volume. Contractility is also enhanced by noradrenaline, serotonin, certain prostaglandins and thromboxanes, and endothelin-1. Lymphatics may also modulate their own contractility through the production of nitric oxide and other local mediators. Transport in the thoracic and right lymph ducts also depends upon intrathoracic (respiration) and central venous (cardiac cycle) pressures. Therefore, cardiorespiratory disease may have an adverse effect on lymphatic function.

In summary, in the healthy limb, lymph flow is largely due to intrinsic lymphatic contractility, although this is augmented by exercise, limb movement and external compression. However, in lymphoedema, when the lymphatics are constantly distended with lymph, these external forces assume a much more important functional role.
**Acute Lymphangitis**

**Definition:** It is infection spreading from a skin (wound, abrasion, laceration) through the draining superficial lymphatic vessels to the draining lymph nodes. It is usually seen in the extremities (upper and lower limbs).

**Causative Microorganisms:** 1) Group A B-haemolytic streptococci (streptococcus pyogenes), 2) Staphylococcus aureus.

**Clinical Presentation:**
(1) **Red bluses or streaks in the skin** (correspond to inflamed lymphatics) extending from the source of infection to the regional LNs.

(2) **Regional LNs** are enlarged and tender and may suppurate with abscess formation, occasionally the infection bypasses one group to affect another at a higher level (e.g, if the point of infection is the foot, an abscess may form in the external iliac group of LNs rather than the superficial (lower) and deep inguinal groups and because the point of infection may have healed and been forgotten, by the time the mass appears it may be mistaken for an (appendix abscess).

**Treatment:**
(1) **Bed rest** (to reduce lymphatic drainage) with elevation of the affected limb (to reduce swelling).

(2) **Antibiotics.** Failure to improve within 48 hours suggests inappropriate antibiotic therapy, or the presence of undrained pus, or the presence of an underlying systemic disorder (malignancy, immunodeficiency).

(3) **Drainage of an abscess** if it has formed.

**Complications:**
(1) **Post-lymphatic oedema.** due to permanent lymphatic obstruction after resolution of acute lymphangitis leading to persistent oedema. These patients are prone to so-called acute inflammatory episodes (AlEs).

(2) **Chronic lymphangitis.** Follows repeated attacks of acute lymphangitis.

(3) **Bacteraemia or Septicaemia.**
**LYMPHOEDEMA**

**Definition:** It is abnormal limb swelling due to the accumulation of increased amounts of high protein ISF secondary to defective lymphatic drainage in the presence of (near) normal net capillary filtration. So it is accumulation of fluid in the interstitial spaces (extracellular fluid compartment), in the limbs it accumulates mainly in the subcutaneous tissues.

**Clinical Presentation:**

1) Gradually increasing circumference of the affected limb (huge enlargement) with multifolding of the skin.

2) In the early stages the lymphoedema is pitting on pressure thus it simulates ordinary oedema, but with time lymphoedema characteristically becomes Non-pitting lymphoedema due to subcutaneous thickening with fibrous tissue being worsened by recurring low grade lymphangitis and cellulitis. (Recurrent acute infective episodes). In the early stages, lymphoedema will ‘pit’ and the patient will report that the swelling is down in the morning. This represents a reversible component to the swelling, which can be controlled. Failure to do so allows fibrosis, dermal thickening and hyperkeratosis to occur.

3) Unlike other types of oedema, lymphoedema characteristically involves the foot. The contour of the ankle is lost through infilling of the submalleolar depressions, a ‘buffalo hump’ forms on the dorsum of the foot, the toes appear ‘square’ due to confinement of footwear, and the skin on the dorsum of the toes cannot be pinched due to subcutaneous fibrosis (Stemmer’s sign) Lymphoedema usually spreads proximally to knee level and less commonly affects the whole leg.

4) Lymphangiomas are dilated dermal lymphatics that ‘blister’ onto the skin surface. The fluid is usually clear but may be bloodstained and, in the long term, they thrombose and fibrose, forming hard nodules and raising concerns about malignancy. If lymphangiomas are < 5 cm across, they are termed **lymphangioma circumscriptum**, and if they are more widespread, they are termed **lymphangioma diffusum**. If they form a reticulate pattern of ridges then it has been termed **lymphoedema ab igne**. Lymphangiomias frequently weep (lymphorrhoea, chylorrhoea), causing skin maceration and they act as a portal for infection.

5) Lymphangiosarcoma was originally described in post-mastectomy oedema (Stewart—Treves syndrome) and affects around 0.5% of patients at a mean onset of 10 years. However, lymphangiosarcoma can develop in any longstanding lymphoedema, but usually takes longer to manifest (20 years). It presents as
single or multiple bluish/red skin and subcutaneous nodules that spread to form satellite lesions that may then become confluent.

6) Ulceration, non-healing bruises, and raised purple-red nodules should lead to suspicion of malignancy.

7) Constant dull ache, even severe pain or Burning and bursting sensations or Pins and needles.

8) Sensitivity to heat.

9) General tiredness and debility.

10) Skin problems, including dehydration, flakiness, weeping, excoriation and breakdown. Chronic eczema, fissuring, verrucae and papillae (warts) are frequently seen in advanced disease. Ulceration is unusual, except in the presence of chronic venous insufficiency.

11) Immobility, leading to obesity and muscle wasting.

12) Backache and joint problems.

13) Fungal infection of the skin (dermatophytosis) and nails (onychomycosis) Athlete’s foot.

**Pathophysiology:**

The ISF compartment (10-12 litres in a 70-kg man) constitutes 50% of the wet weight of skin and subcutaneous tissues and, in order for oedema to be clinically detectable, its volume has to double. About 8 litres (protein concentration approximately 20-30g/L, similar to ISF) of lymph is produced each day and travels in afferent lymphatics to lymph nodes. There, the volume is halved and the protein concentration doubled, resulting in 4 litres of lymph re-entering the venous circulation each day via efferent lymphatics. In one sense, all oedema is lymphoedema in that it results from an inability of the lymphatic system to clear the ISF compartment. However, in most types of oedema this is because capillary filtration rate is pathologically high and overwhelms a normal lymphatic system, resulting in the accumulation of low-protein oedema fluid. In contrast, in true lymphoedema, when the primary problem is in the lymphatics, capillary filtration is normal and the oedema fluid is relatively high in protein. Of course, in a significant number of patients with oedema there is both abnormal capillary filtration and abnormal lymphatic drainage. Lymphoedema results from lymphatic 1-aplasia, 2-hypoplasia, 3-dysmotility (reduced contractility with or without valvular insufficiency), 4-obliteration by inflammatory, infective or neoplastic processes, or 5-surgical extirpation. Whatever the primary abnormality, the resultant physical and/or functional obstruction leads to lymphatic hypertension and distension, with further secondary impairment of contractility and valvular competence. Lymphostasis and lymphotension lead to the accumulation in the ISF of fluid,
proteins, growth factors and other active peptide moieties, glycosaminoglycans and particulate matter, including bacteria. As a consequence, there is increased collagen production by fibroblasts, an accumulation of inflammatory cells (predominantly macrophages and lymphocytes) and activation of keratinocytes. The end result is protein-rich oedema fluid, increased deposition of ground substance, subdermal fibrosis and dermal thickening and proliferation. Lymphoedema, unlike all other types of oedema, is confined to the epifascial space. Although muscle compartments may be hypertrophied owing to the increased work involved in limb movement, they are characteristically free of oedema.

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<tr>
<th>Ordinary Oedema</th>
<th>Lymphoedema</th>
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<tr>
<td>Pitting.</td>
<td>Nonpitting (due to excessive collagen deposition).</td>
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<tr>
<td>Involves epifascial, subfascial and muscle compartments.</td>
<td>Is confined to the epifascial space only.</td>
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<tr>
<td>Capillary filtration rate is pathologically high and overwhelms a normal lymphatic system, resulting in the accumulation of low-protein oedema fluid.</td>
<td>Capillary filtration is normal but there is an abnormal lymphatic drainage system and the oedema fluid is relatively high in protein.</td>
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**Classification**

In general, primary lymphoedema progresses more slowly than secondary lymphoedema. Two main types of lymphoedema are recognised:

1- **Primary lymphoedema**, in which the cause is unknown (or at least uncertain and unproved), but often presumed to be due to (congenital lymphatic dysplasia). Primary lymphoedema is usually further subdivided on the basis the presence of family, age of onset and lymphangiographic findings:
   a - **Congenital** (onset < 2 years old).
      • Sporadic.
      • Familial (Milroy’s disease).
   b - **Praecox** (onset 2 - 35 years old).
      • Sporadic.
      • Familial (Meige’s disease).
   c - **Tarda** (onset after 35 years old).
2- **Secondary lymphoedema**, in which there is a clear underlying cause, such as inflammation, malignancy or surgery.

1- **Infection**.
   - a - Parasitic infection (filariasis).
   - b - Fungal infection (tinea pedis).

2- **Exposure to foreign body material** (silica particles).

3- **Malignancy**.
   - a - Primary lymphatic malignancy.
   - b - Metastatic spread to lymph nodes.

4- **Surgery**. Excision of LNs.

5- **Radiotherapy**. to groups of lymph nodes.

6- **Trauma**. (particularly degloving injuries).

7- **Venous complications**.
   - a - Superficial thrombophlebitis.
   - b - Deep venous thrombosis.

**Clinical classification of lymphoedema**

<table>
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<tr>
<th>Grade (Brunner)</th>
<th>Clinical features</th>
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<tr>
<td>Subclinical (latent) I</td>
<td>Oedema <strong>pits</strong> on pressure and the swelling largely, or completely disappears on elevation and bed rest.</td>
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<tr>
<td>II</td>
<td>Oedema does <strong>not pit</strong> and does not significantly reduce upon elevation.</td>
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<tr>
<td>III</td>
<td>Oedema is associated with <strong>irreversible skin changes</strong>, i.e. fibrosis, papillae.</td>
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**Differential diagnosis of the swollen limb**

*1) Non-vascular or lymphatic*

1) **General disease states**.

   1- Cardiac failure from any cause.
2- Liver failure.
3- Hypoproteinaemia due to nephrotic syndrome, malabsorption, protein- losing enteropathy.
4- Hypothyroidism (myxoedema).
5- Allergic disorders, including angioedema and idiopathic cyclic oedema.
6- Prolonged immobility and lower limb dependency.

2) **Local disease processes.** (Ruptured Baker’s cyst, Myositis ossificans, Bony or soft-tissue tumours, Arthritis, Haemarthrosis, Calf muscle haematoma, Achilles tendon rupture).

3) **Retroperitoneal fibrosis.** May lead to arterial, venous and lymphatic abnormalities.
4) **Gigantism.** (Rare, all tissues are uniformly enlarged).
5) **Drugs.** Corticosteroids (oestrogens, progestagens), Monoamine oxidase inhibitors (phenylbutazone, methyldopa, hydralazine, nifedipine).
6) **Trauma.** Painful swelling due to reflex sympathetic dystrophy
7) **Obesity.** (Lipodystrophy, Lipoidosis).

**2) Venous:**

1) **Deep venous thrombosis.** (There may be an obvious predisposing factor, such as recent surgery, The classical signs of pain and redness may be absent).
2) **Post-thrombotic syndrome.** (Swelling, usually of the whole leg, due to iliofemoral venous obstruction, Venous skin changes, secondary varicose veins on the leg and collateral veins on the lower abdominal wall, Venous claudication may be present).
3) **Varicose veins.** Simple primary varicose veins are rarely the cause of significant leg swelling.
4) **Klippel—Trenaunay syndrome and other malformations.** (Rare) Present at birth or develops in early childhood, Comprises an abnormal lateral venous complex, capillary naevus, bony abnormalities, hypo(a)plasia of deep veins and limb lengthening, Lymphatic abnormalities often coexist.
5) **External venous compression.** Pelvic or abdominal tumour including the gravid uterus, Retroperitoneal fibrosis.
6) **Ischaemia—Reperfusion.** Following lower limb revascularisation for chronic ischaemia.

**3) Arterial**

1) **Arteriovenous malformation.** May be associated with local or generalised swelling
2) **Aneurysm.** (Popliteal, Femoral, False aneurysm following (iatrogenic) trauma).

**Malignancies associated with lymphoedema**

1- Lymphangiosarcoma (Stewart—Treve’s syndrome).
2- Kaposi’s sarcoma (human immunodeficiency virus, HIV).
3- Squamous cell carcinoma.
4- Liposarcoma.
5- Malignant melanoma.
6- Malignant fibrous histiocytoma.
7- Basal cell carcinoma.
8- Lymphoma.

**INVESTIGATION OF LYMPHOEDEMA**

(1) **Routine tests:**
1- Full blood count, 2- Urea and electrolytes, creatinine. 3- Liver function tests. 4- Chest radiography. 5- Blood smear for microfilariae.

(2) **Lymphangiography:**
1- **Direct lymphangiography** involves the injection of contrast medium into a peripheral lymphatic vessel and subsequent radiographic visualisation of the vessels and nodes. It remains the ‘gold standard’ for showing structural abnormalities of larger lymphatics and nodes. However, it can be technically difficult, it is unpleasant for the patient, it may cause further lymphatic injury and, largely, it has become obsolete as a routine method of investigation. Few centres now perform this technique and those that do generally reserve it for preoperative evaluation of the rare patient with megalymphatics who is being considered for bypass or fistula ligation.

2- **Indirect lymphangiography** involves the intradermal injection of water-soluble, non-ionic contrast into a web space, from where it is taken up by lymphatics and then followed radiographically. It will show distal lymphatic but not normally proximal lymphatics and nodes.

(3) **Isotope Lymphoscintigraphy:**
This has largely replaced lymphangiography as the primary diagnostic technique in cases of clinical uncertainty. Radioactive technetium-labelled protein or colloid particles are injected into an interdigital web space and specifically taken up by lymphatics, and serial radiographs are taken with a gamma camera. The technique provides a qualitative measure of lymphatic function rather than quantitative
function or anatomical detail.

(4) Computerised Tomography
A single, axial computerised tomography (CT) slice through the midcalf has been proposed as a useful diagnostic test for lymphoedema (coarse, non-enhancing, reticular ‘honeycomb’ pattern in an enlarged subcutaneous compartment), venous oedema (increase volume of the muscular compartment), and lipoedema (increased subcutaneous fat). CT can also be used to exclude pelvic or abdominal mass lesions.

(5) Magnetic resonance imaging
Magnetic resonance imaging (MRI) can provide clear images of lymphatic channels and lymph nodes, and can be useful in the assessment of patients with lymphatic hyperplasia. MRI can also distinguish venous and lymphatic causes of a swollen limb.

(6) Ultrasound
Ultrasound can provide useful information about venous function.

MANAGEMENT OF LYMPHOEDEMA

(1) Relief of pain
On initial presentation, 50% of patients with lymphoedema complain of significant pain. The pain is usually multifactorial and its severity and underlying cause(s) will vary depending on the aetiology of the lymphoedema. For example, following treatment for breast cancer, pain may arise from the swelling itself, (radiation and surgery induced) nerve (brachial plexus and intercostobrachial nerve), bone (secondary deposits, radiation necrosis) and joint disease (arthritis, bursitis, capsulitis), and recurrent disease.

Use of (1) non-opioid (NSAIDs) and (2) opioid analgesics, (3) corticosteroids, (4) tricyclic antidepressants, (5) muscle relaxants, (6) anti-epileptics, (7) nerve blocks, (8) physiotherapy, (9) adjuvant anti-cancer therapies (chemo-, radio- and hormonal therapy).

(2) Control of swelling
Physical therapy for lymphoedema comprising 1-bed rest, 2-elevation, 3-bandaging, 4-compression garments, 5-massage and 6-exercises. The current preferred term is decongestive lymphoedema therapy (DLT) and comprises two phases. The first is a short intensive period of therapist-led care and the second is a maintenance phase in which the patient uses a self-care regimen with occasional professional intervention. The intensive phase comprises skin care, manual lymphatic drainage (MLD) and multi-layer lymphoedema bandaging (MLLB), and exercises.
(3) Skin care
1- Protect hands when washing up or gardening; wear a thimble when sewing.
2- Never walk barefoot and wear protective footwear outside.
3- Use an electric razor to depilate.
4- Never let the skin become macerated.
5- Treat cuts and grazes promptly (wash, dry, application of antiseptic and a plaster).
6- Use insect repellent sprays and treat bites promptly with antiseptics and antihistamines.
7- Seek medical attention as soon as limb becomes hot, painful or more swollen.
8- Do not allow blood to be taken from, or injections to be given into the affected arm (and avoid blood pressure measurement).
9- Protect the affected skin from sun (shade, high factor sun block).
10- Consider taking antibiotics if going on holiday.

(3) Manual lymphatic drainage
Aim to evacuate fluid and protein from the 1SF space, and stimulate lymphangion contraction. The therapist should perform MLD daily; they should also train the patient (and/or carer) to perform a simpler, modified form of massage, termed simple lymphatic drainage (SLD). In the intensive phase, SLD supplements MLD and, once the maintenance phase is entered, SLD will carry on as daily massage.

(4) Multilayer lymphoedema bandaging and compression garments
Elastic bandages provide compression, produce a sustained high resting pressure and ‘follow in’ as limb swelling reduces. However, the sub-bandage pressure does not alter greatly in response to changes in limb circumference consequent upon muscular activity and posture. By contrast, short-stretch bandages exert support through the production of a semi-rigid casing where the resting pressure is low but changes quite markedly in response to movement and posture. It is generally believed that non-elastic multilayer lymphoedema bandaging (MLLB) is preferable (and arguably safer) in patients with severe swelling during the intensive phase of DLT, whereas compression (hosiery, sleeves) is preferable in milder cases and during the maintenance phase. Whether the aim is to provide support or compression, the pressure exerted must be graduated (100% ankle/foot, 70% knee, 50% midthigh, 40% groin) and, of course, the adequacy of the arterial circulation must be assessed.

Compression garments form the mainstay of management in most clinics. The control of lymphoedema requires higher pressures (30—40 mmHg arm, 40—60 mmHg leg) than are typically used to treat CVI. The patient should put the stocking
on first thing in the morning before rising. Donning and doffing lymphoedema grade stockings is difficult and many patients find them intolerably uncomfortable, especially in warm climates.

**Pneumatic compression devices**, Unless the device being used allows the sequential inflation of multiple chambers up to > 50 mmHg, it will probably be ineffective for lymphoedema.

(5) Exercise.
Lymph formation is directly proportional to arterial inflow and 40% of lymph is formed within skeletal muscle. Vigorous exercise, especially if it is anaerobic and isometric, will tend to exacerbate lymphoedema and patients should be advised to avoid prolonged static activities, for example carrying heavy shopping bags or prolonged standing. In contrast, slow, rhythmic, isotonic movements (e.g. swimming) and massage will increase venous and lymphatic return through the production of movement between skin and underlying tissues (essential to the filling of initial lymphatics) and augmentation of the muscle pumps. Exercise also helps to maintain joint mobility. Patients who are unable to move their limbs benefit from passive exercises.

(6) Limb Elevation.
When at rest, the lymphoedematous limb should be positioned with the foot/hand above the level of the heart. A pillow under the mattress or blocks under the bottom of the bed will encourage the swelling to go down overnight.

(7) Drugs.
The benzpyrones are a group of several thousand naturally occurring substances, (flavonoids) they reduce capillary permeability, improve microcirculatory perfusion, stimulate interstitial macrophage proteolysis, reduce erythrocyte and platelet aggregation, scavenge free radicals and exert an anti-inflammatory effect. Oxerutins (paroven).

Diuretics are of no value in pure lymphoedema. Their chronic use is associated with side-effects, including electrolyte disturbance, and should be avoided.

(8) Surgery
Only a small minority of patients with lymphoedema benefit from surgery.

1- Bypass procedures
The rare patient with proximal ilioinguinal lymphatic obstruction and normal distal lymphatic channels might benefit, from lymphatic bypass. Methods: 1-Omental pedicle.
2-Skin bridge (Gillies).
3-Anastomosing lymph nodes to veins (Neibulowitz).
4-Ileal mucosal patch (Kinmonth).
5-Direct lymphovenous anastomosis.

**2- Limb reduction procedures**
These are indicated when a limb is so swollen that it interferes with mobility and livelihood. These operations are not ‘cosmetic’ in the sense that they do not create a normally shaped leg and are usually associated with significant scarring.

1-**Sistrunk**. A wedge of skin and subcutaneous tissue is excised and the wound closed primarily. This is most commonly carried out to reduce the girth of the thigh.

2-**Homans**. First skin flaps are elevated, to allow the excision of a wedge of skin and a larger volume of subcutaneous tissue down to the deep fascia from beneath the flaps, which are then trimmed to size to accommodate the reduced girth of the limb and closed primarily. This is the most satisfactory operation for the calf. The main complication is skin flap necrosis. There must be at least 6 months between operations on the medial and lateral sides of the limb and the flaps must not pass the midline to avoid skin flap necrosis. This procedure has also been used on the upper limb, but is contraindicated in the presence of venous obstruction or active malignancy.

3-**Thompson** One denuded skin flap is sutured to the deep fascia and buried beneath the second skin flap (the so-called ‘buried dermal flap’). This procedure has become less popular as pilonidal sinus formation is common. The cosmetic result is no better than that obtained with the Homans’ procedure and there is no evidence that the buried flap establishes any new lymphatic connection with the deep tissues.

4-**Charles** This operation was initially designed for filariasis and involved circumferential excision of all the skin and subcutaneous tissues (lymphoedematous tissue) down to and including the deep fascia, with coverage using split-skin grafts. This leaves a very unsatisfactory cosmetic result and graft failure is not uncommon. However, it does enable the surgeon to reduce greatly the girth of a massively swollen limb (allows the surgeon to remove very large amounts of tissue and is particularly useful in patients with severe skin changes).