Lymphedema

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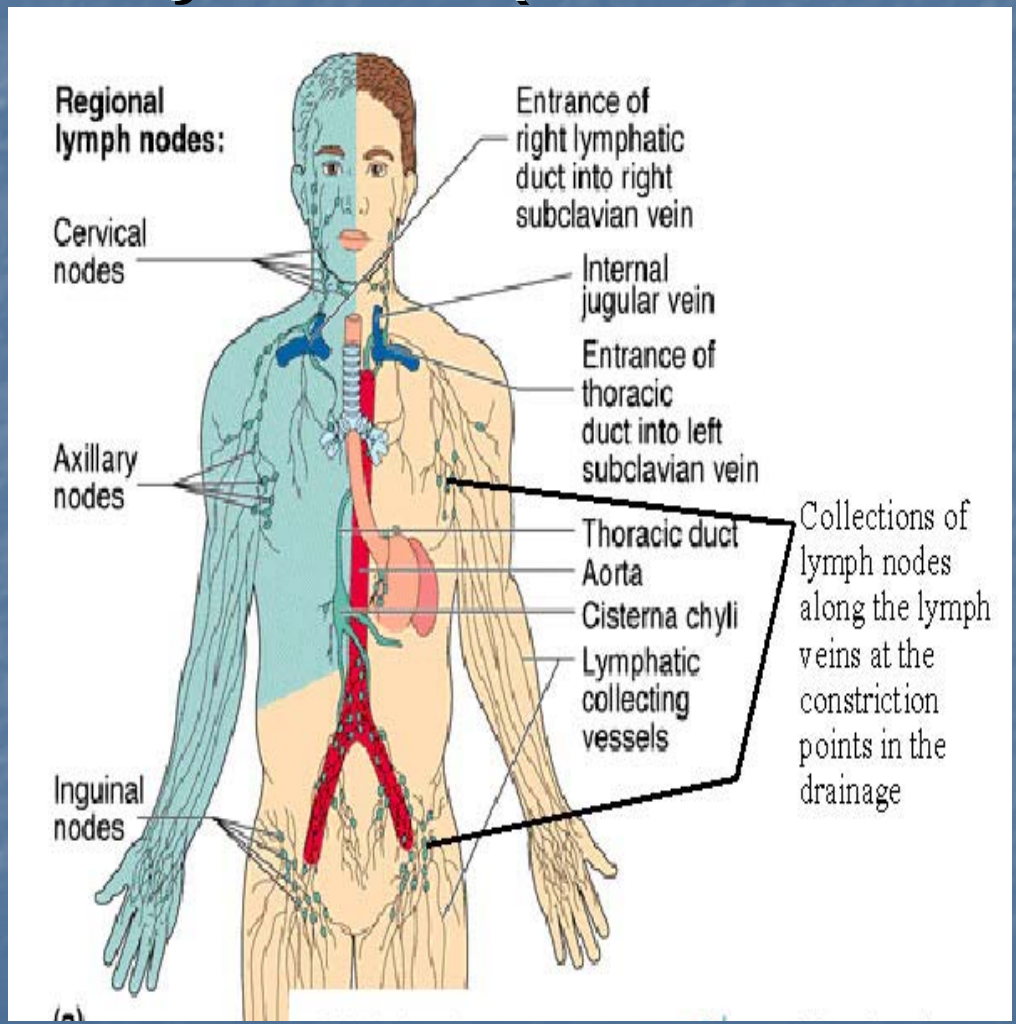
Lymphatic System = "Sanitation system" (Homeostatic Fluid-Balance)



- Discovered by Gasparo Asselli (1581-1626)
- Gained recent importance among the medical community

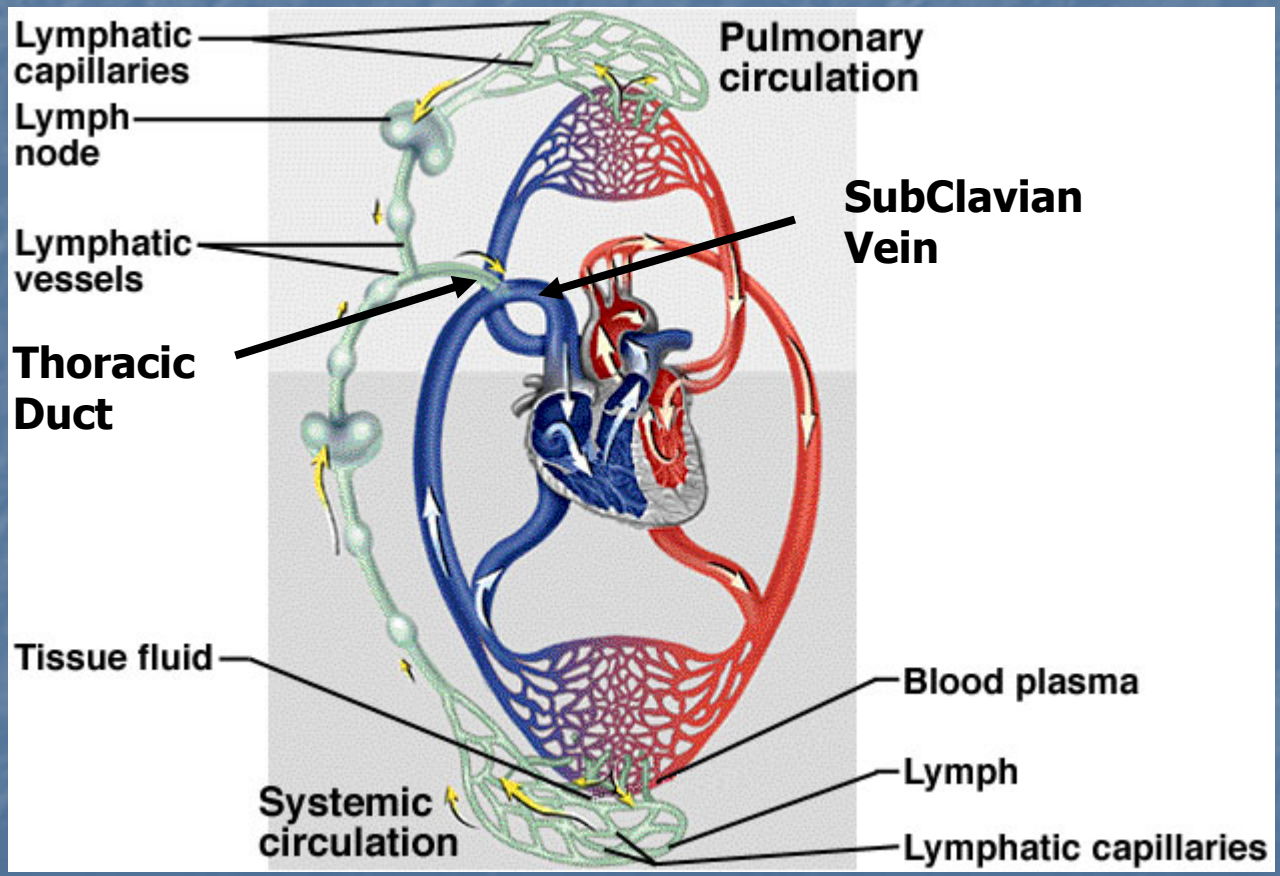
"Unlocking the Drains: After centuries of playing second fiddle to the blood system, our lymphatic circulation is coming into its own as a key player in diseases ranging from cancer to asthma."
July 28, 2005 Nature.

Relevant Anatomy (Lymphatic System)

The fluid = Lymph

- 10% net ultra-filtrate i.e. protein, lipids, metabolic waste and water (Starling fluid mechanism)
- Macrophages, migrating dendritic cells, lymphocytes (components of the immune system)
- Clear up penetrating micro-organism, cell debris, foreign antigens and self antigens.
- Carries immune memory – distinguish between self & foreign antigens.
- Lymph is not part of CNS, CSF replaces the lymph.

Lymph – “semi-circulation”



Relevant Anatomy (Lymphatic System)

Vessels – 4 Systems

Blind-ended lymphatic capillaries from dermal papillae drain lymph from skin and subcutaneous tissue into *epifascial* valved vessels

Deep valved *subfascial* system drains lymph from fascia muscles joints, and bones etc.

The *visceral* system which is wrapped around vital organs such as liver, lungs and lymphoid tissues

Anastomoses branches connect adjacent lymph collectors such as epifascial and subfascial vessels

- These vessels are irregular shaped and more permeable compared to their blood vessel counterparts

Relevant Anatomy (lymphatic system)

- Lymphatic vessels entering nodes are called afferent and leaving called efferent

Nodal regions

Cervical

Axillary

Inguinal

Pelvic

Abdominal

Thoraic

Organs

Liver

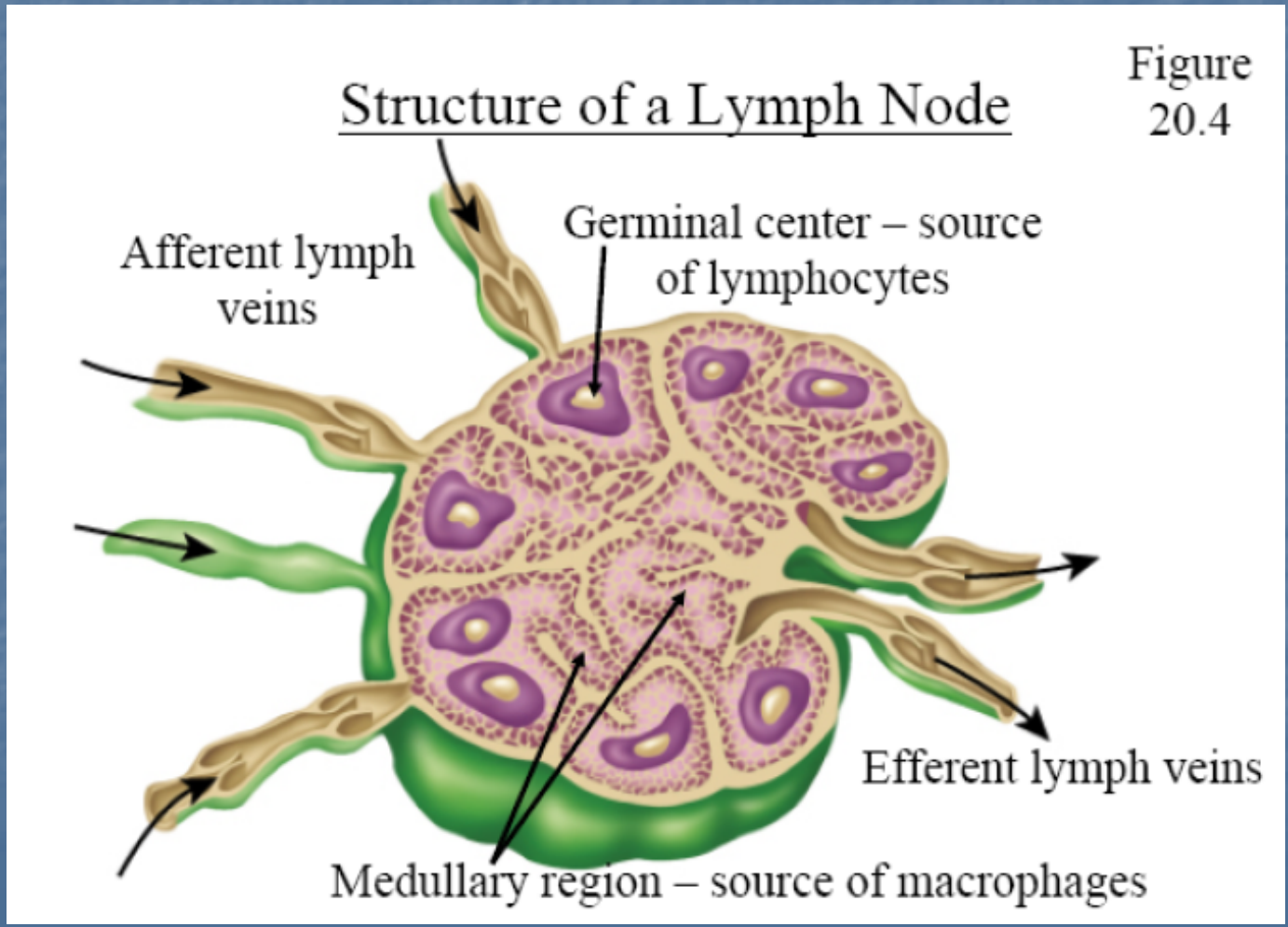
Spleen

Tonsils

Thymus

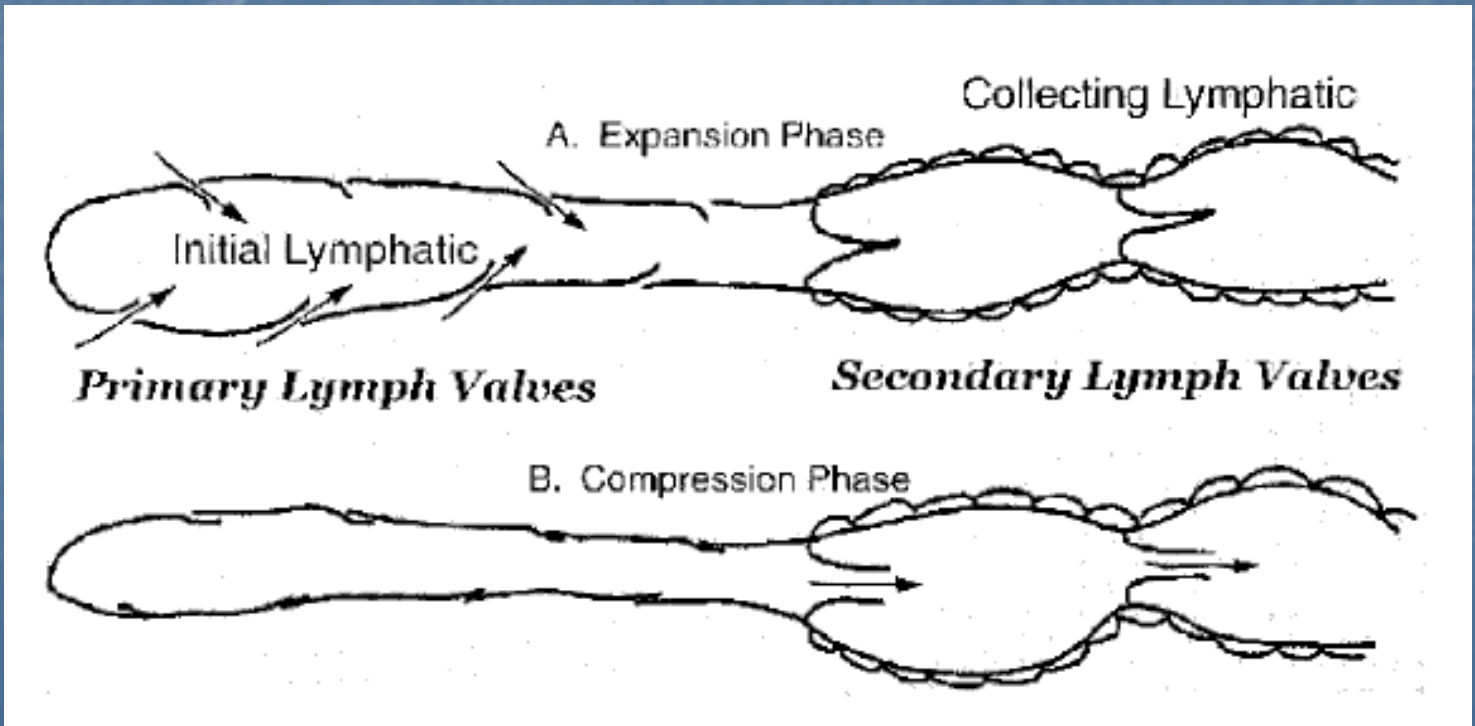
•The efferent ducts from the nodal regions empty the fluid into subclavian veins via thoracic duct.

Lymph Node Structure



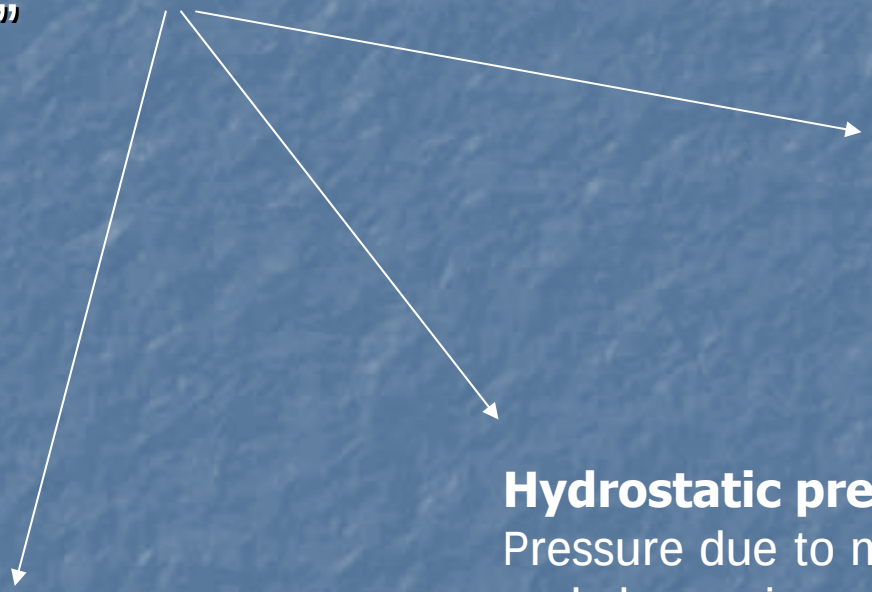
Homeostatic Physiology

- Main function of lymphatic system is to maintain tissue fluid homeostasis
- Lymphatics – 2 valved series of lymphangions
- Each lymphangion- 2 valves = 1 at entry / 1 at exit



Homeostatic Physiology

- Total tissue pressure gradient → lymphatics into "force pumps"



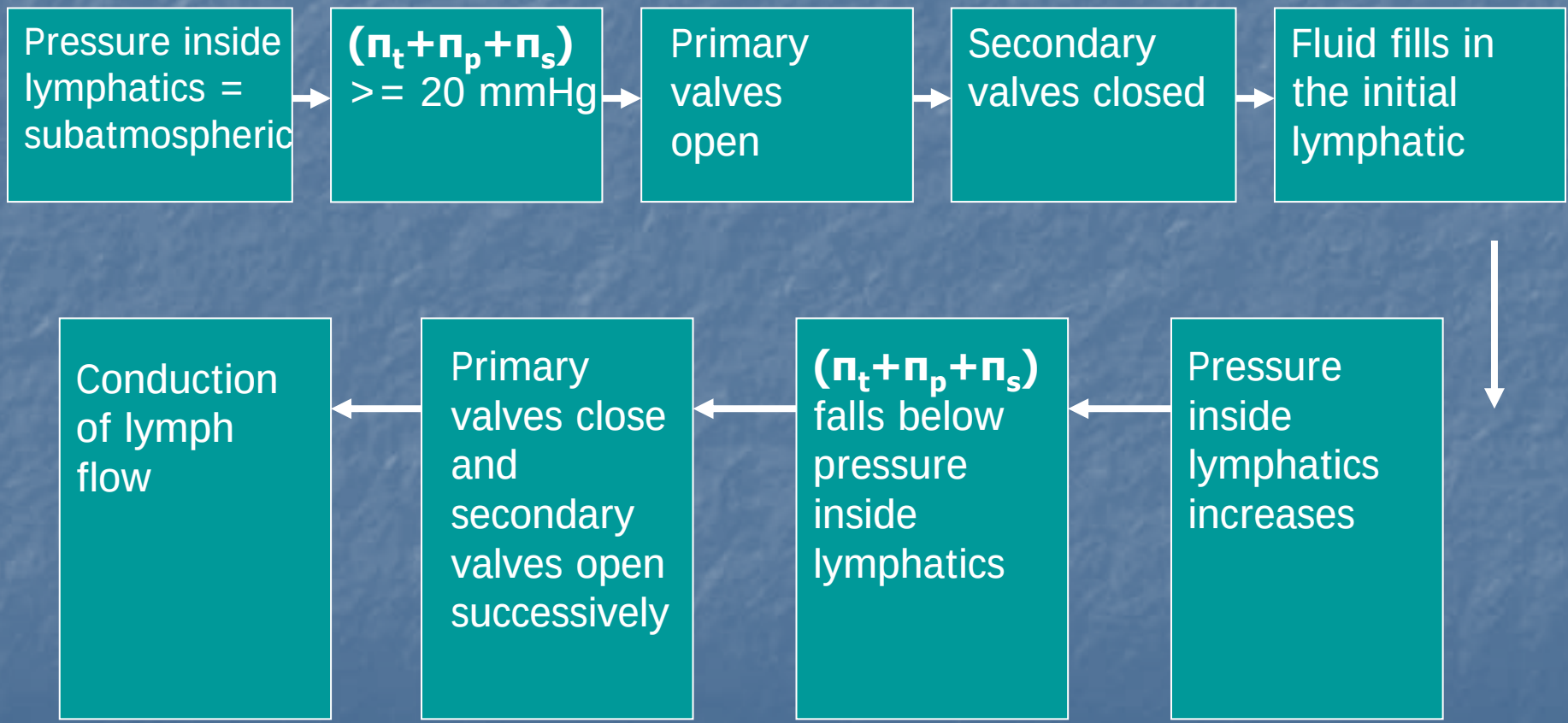
Oncotic pressure(π_T)= Osmotic pressure due to high M.W. protein associated with water in the interstitial space

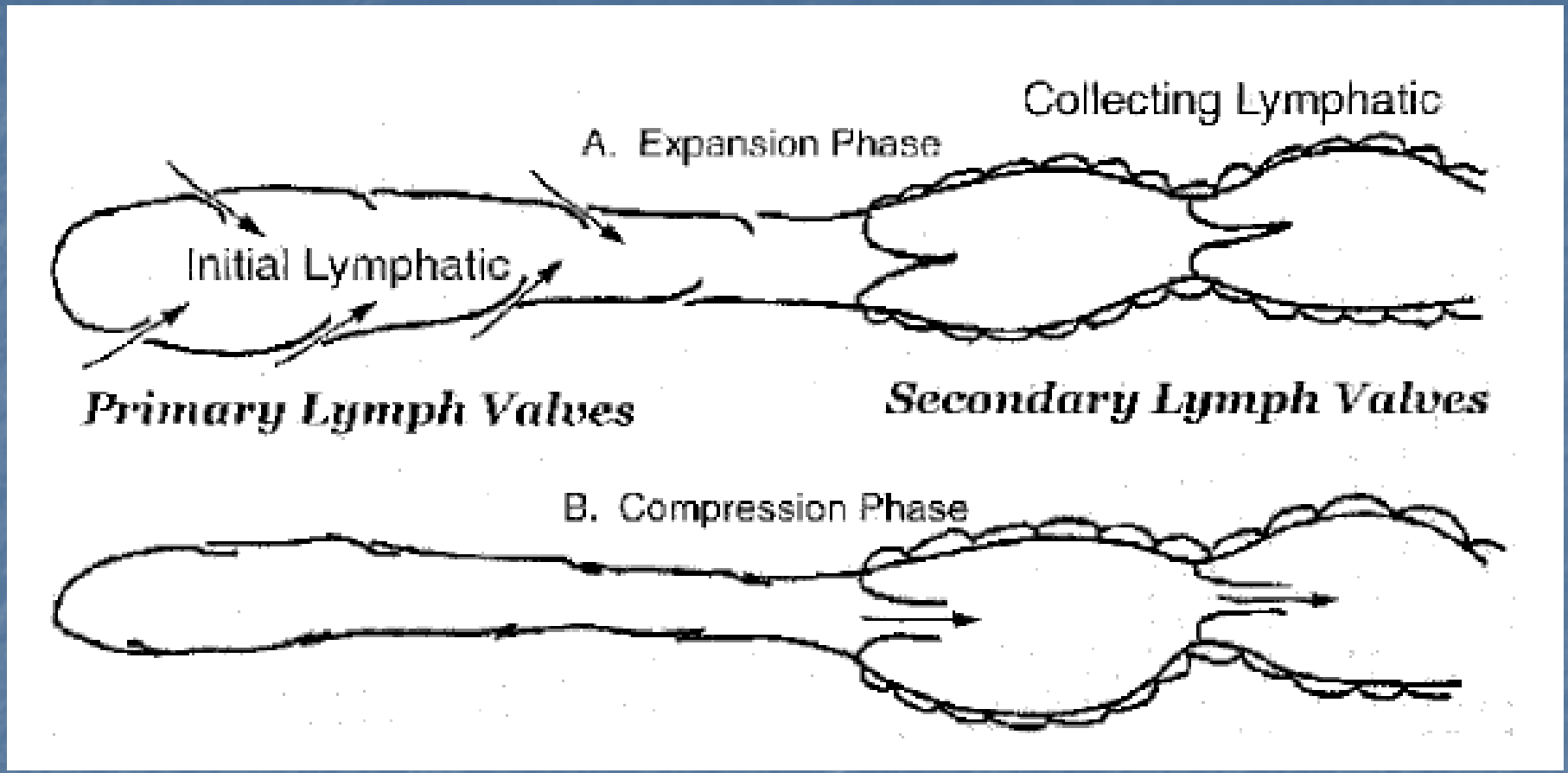
Hydrostatic pressure (π_p) = ρgh
Pressure due to movement, exercise and change in position

Surrounding pressure (π_s) = pressure due to contraction and expansion of adjoining blood vascular walls and skeletal muscles

Homeostatic Physiology

Lymphatic flow → No back flow



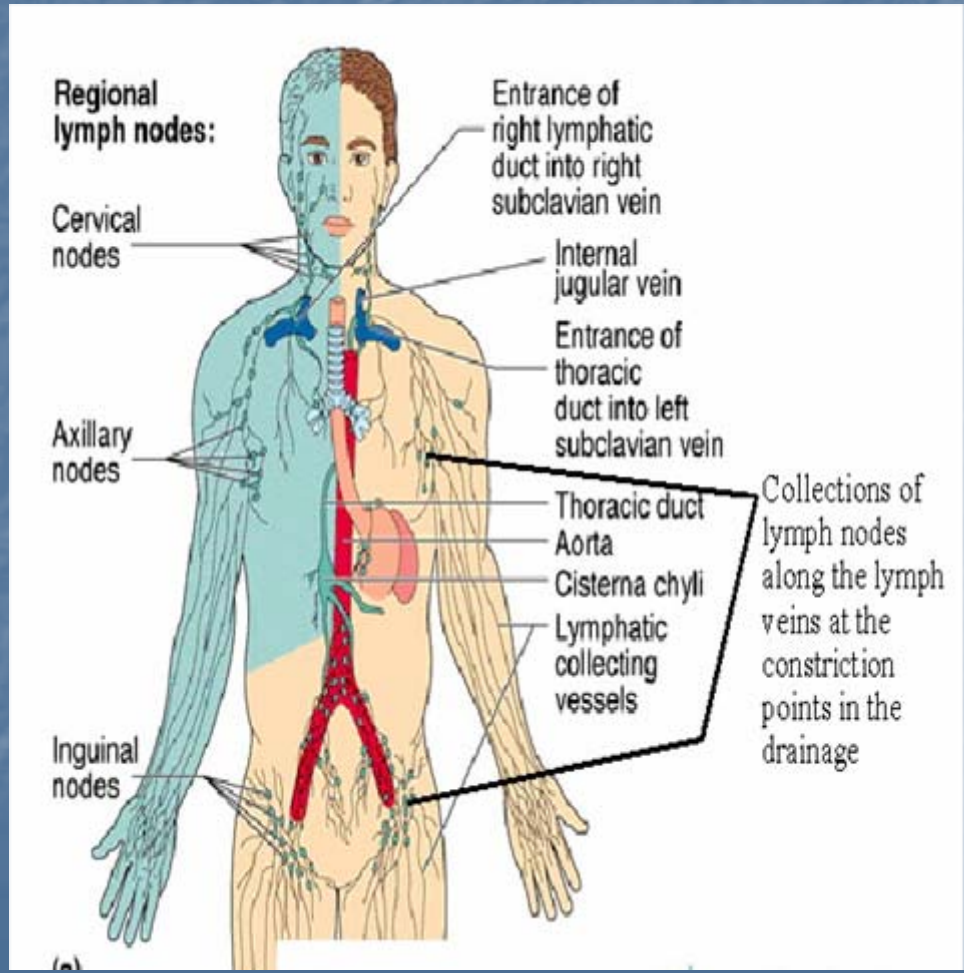


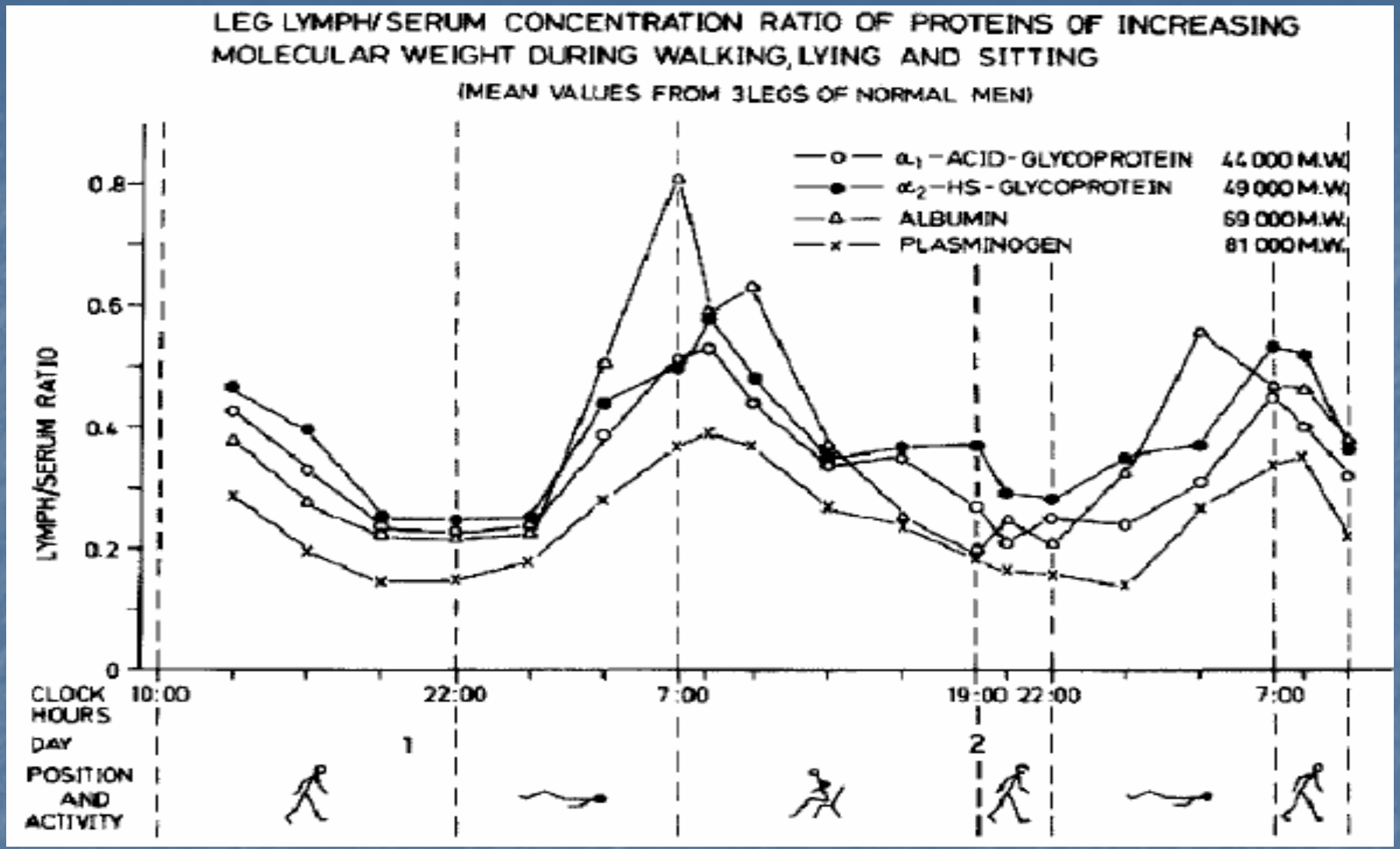
Lumen Structure

Homeostatic physiology

Conduction of fluid through lymphangions

- Inside Lymphtic main propelling force for flow = rhythmic contractions of lymphangions
- Lymphangion has motor control. Generates 5–7 action potentials per minute.
- Valves at graduated intervals facilitating transport of lymph centripetally in proximal direction towards nodes.
- Unilateral flow from the periphery to the great veins of the neck, avoiding retroflow.





A 24-hour pattern of lymph protein concentration during various activities

Edema→ hemorrhage of homeostasis

- **Edema** (**oedema**, formerly known as **dropsy**) is the swelling of any organ or tissue due to accumulation of excess fluid.
- Different types of edema: -
  1) Generalized edema
  2) Pulmonary edema
  3) Lymphedema

Lymphedema is the accumulation of excessive proteins, edema, chronic inflammation, and fibrosis as a result of impairment of the lymph vessels.

Types of Lymphedema

Primary (developmental abnormality)

- Congenital 10-25%
- Lymphedema praecox 65-80%
- Lymphedema tarda 10%

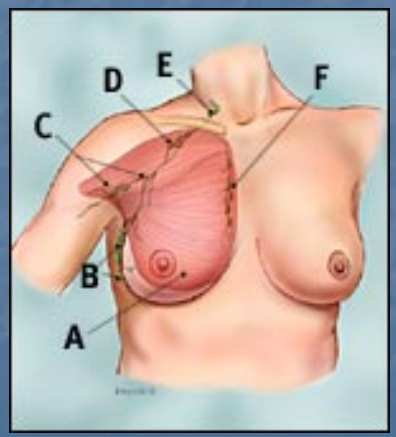
Secondary (acquired dysfunction)

- damage/removal of lymphregional lymph nodes through surgery, radiation, infection, or tumor invasion or compression
- *filariasis*, the direct infestation of lymph nodes by the parasite *Wuchereria bancrofti*.

- 3-5 million people are estimated to be affected with secondary lymphedema in the United States. The largest percentage of this group are breast cancer survivors.

Breast Cancer Related lymphedema

- Incidence: frequent complication of breast cancer therapy about 5 %– 30 %
- BCRL was first described by Halsted in 1921.
- Prevalent in upper extremity



Lymph nodes in and around the breast area
A pectoralis major muscle
B axillary lymph nodes: levels I
C axillary lymph nodes: levels II
D axillary lymph nodes: levels III
E supraclavicular lymph nodes
F internal mammary lymph nodes

Causes of BCRL

1. Surgery involving dissection and removal of Axillary nodes
   - This increases in resistance and obstruction to lymph drainage pathway.
   - Chronic work overload and high tissue pressure leads eventually to failure (reduced contractility) of some of the vessels.
   - Though some fluid escapes through collaterals and anastomoses, Fluid starts building up in interstitial space
   - Fluid build up and presence of microorganisms trigger inflammation of epidermal-dermal area.

Causes of BCRL

2. Another probable cause but currently under extensive research:

- Acute and chronic changes take place in body following metastasis, surgery, radiotherapy and pharmaceutical intervention.
- These changes can cause release of NO that induces hyperpolarization of lymphatic muscles →deactivation of pumps
- Many inflammatory mediators and humoral agents such as a-adrenergics, b-ardrenergics, prostaglandins, bradykins etc. may inhibit lymph pump
- Inhibition of lymph pump →obstruction to flow →fluid build up →edema

Location of the swelling

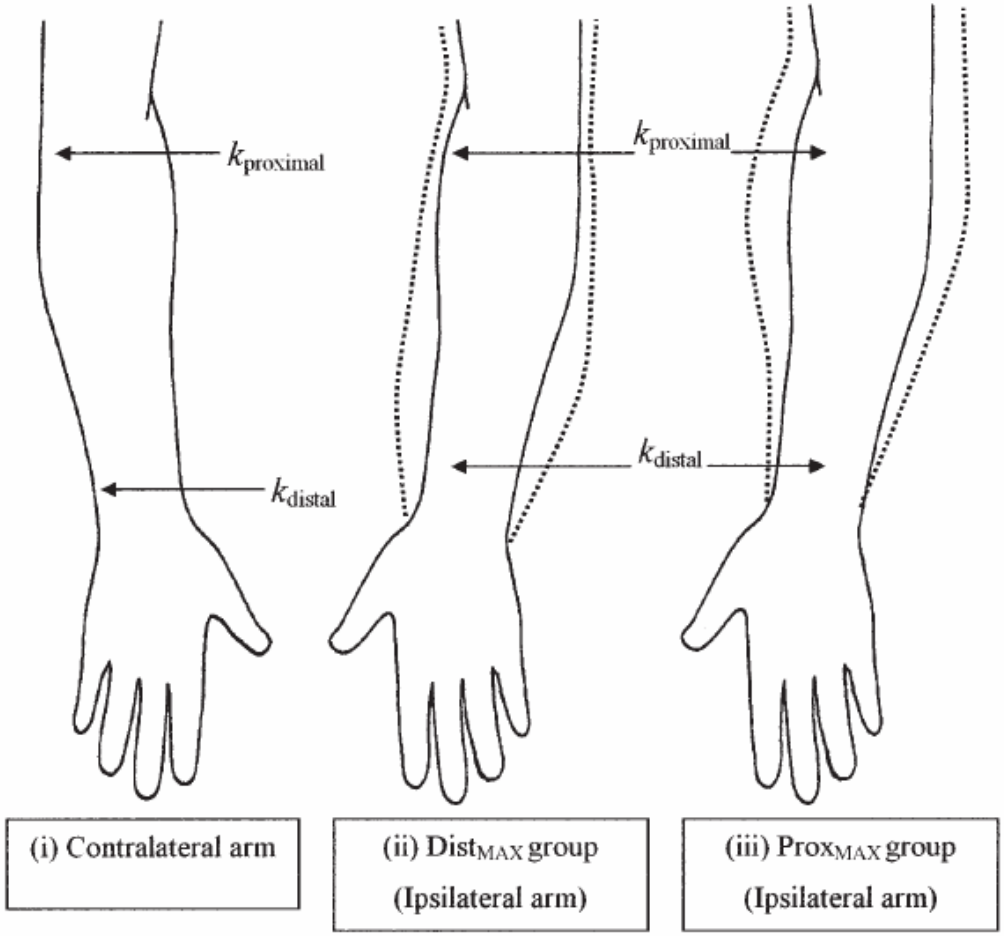
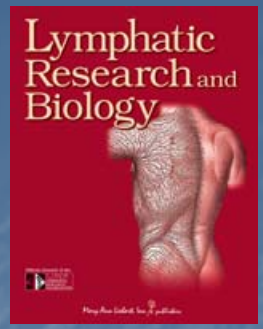


FIG. 1. Regional distribution of swelling in BCRL. (i) Nonswollen contralateral arm; (ii) $Dist_{MAX}$ group (distal swelling > proximal swelling); (iii) $Prox_{MAX}$ group (proximal swelling > distal swelling).

Earlier Studies on BCRL (Stanton & Gothard)

- Axillary Node removal → "Stopcock Mechanism"
  - Lymph drainage reduced globally
- Reduction in epifascial constant as the swelling is epifascial tissues.
- Used Gamma Cameras
- Not effective → does not explain regional swelling

Recent Studies



- Explains regional swelling
- 2 groups → Distmax and Proxmax
- k = rate of lymph drainage evaluated using radio protein 99M TC-HIG and scintillation detector → called Quantitative lymphoscintigraphy

Results

- $k_{prox} > k_{dist}$
- k of epifascial drainage is almost same in both arms
- highly positive correlation between subfascial k and severity of swelling in ipsilateral and contralateral arms ($k_{ipsi} < k_{contra}$)

Detection Lymphedema

- 90% detected on basis of observations, measurements and symptoms
- 10% require complex diagnostic measure.
  - Lymphoscintigraph: Safe and used extensively
  - MRI and CT: used in severe case but high cost

Treatment

Manual Lymphatic Drainage [MLD]

- Range of rythmic movements for facilitating lymph drainage
- Developed by Dr Vodder and perfected by Foldi

Pneumonic Pumps

Worn as a sleeve. 2 Features →

Gradient Pressure: Stronger pressure on hand than on upper arm (Pushes fluid in the upward direction)

Sequential Pressure: Pressure moves from the hand up the arm (“Milking technique”)

• upto 2 hours each day → plan and settings determined by therapist

• can be used while reading or watching T.V.

• Costs around $5000-$6000

Treatment

- To sustain the benefits procured from MLD and Pneumonic pumps, compressive garments and sleeves are worn

Compressive garments

- Made of stretchy elastic material
- Need practitioner for optimal pressure fitting of the garment
- Cost range from $50-$300
- Covered by most insurance companies
- Mostly worn during the day

Treatment

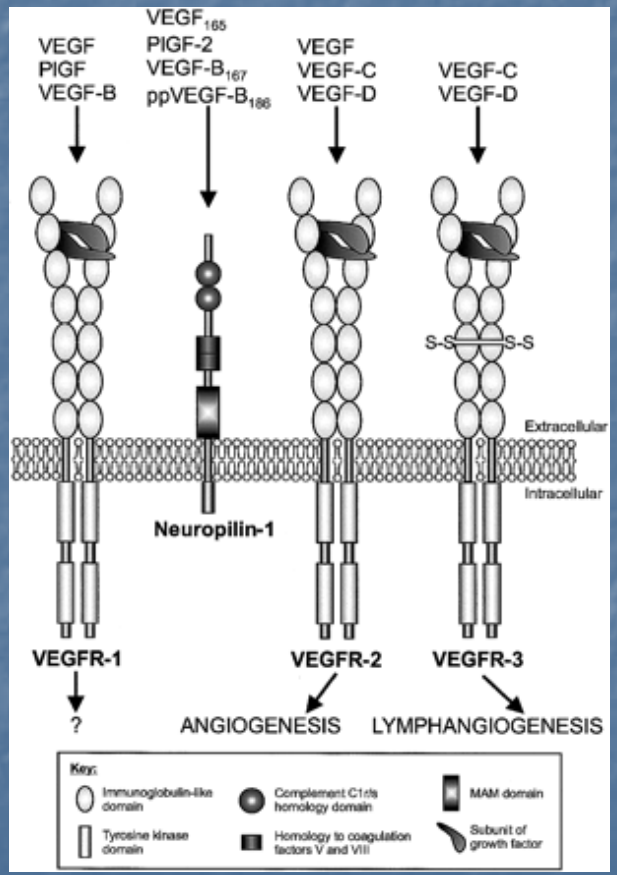
Compressive sleeves

- “Based on core principles of fluid dynamics and engineering. Using directional flow technology, Compressive Sleeves create pressure differentials and gradient compression to assist lymphatic function.”
- Examples such as Reid Sleeve and Tribute Sleeve

Meticulous hygiene is necessary to avoid cellulitis, bacterial and fungal infections and cracking of the skin

Lymphangiogenesis – *Innovation in Treatment*

- Growth of lymphatic vessels
- Proteins and growth factors discovery
  - In-vivo blood vessels and lymphatic are closely associated
  - Coordinated development
  - Indicates growth factors in angiogenesis and lymph angiogenesis is same
  - VEGF-C, VEGF-D are the ligands and VEGFR-3 is the receptor in lymphatic vessels growth



Lymphangiogenesis – *Innovation in Treatment*

- Therapeutic manipulation involves stimulation of lymphangiogenesis in region of excised lymph node by placing endothelial cells and providing growth factors.
- This will help in removal of accumulated fluid providing more escape routes.
- It can be done only when the tumor has been totally eradicated.
- Animal models → 'Chy' mouse model and Rodent model but clinical trials yet to be done.

Complications

- Patients with chronic lymphedema for 10 years have a 10% risk of developing lymphangiosarcoma
  - tumor is highly aggressive
  - most commonly observed in patients with post-mastectomy lymphedema
- Lymphangitis: Inflammation of the lymph vessels

Some of these complications can be fatal. Surgery and amputation maybe used for treating these complications.

Conclusion

- Recent upsurge in the field
- Everyday 3 research papers released on lymphatics
- Still a lot to be discovered about the structure and composition of lymphatics in contrast to already established vascular system
- Lymphedema → Painful and Degenerative
- New solutions required
- Pharmaceuticals looking for drug based cure
- Prospects in tissue culture in Lymphangiogenesis
- Lots of Research and career opportunities

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