Innovations and Promising Approaches Are we sometimes re-discovering what was done in the past?

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Lymphoedema still occurs – Our options are many

Revisit the past

Recognise and manage those who are genetically prone

Help lymphatics grow better or regrow after damage

Improve our surgical/radio-therapeutical practices

Veins and Lymphatics – recognise and use this partnership

Earlier detection Targeted treatments

More "Silver bullets and less of the "Shotgun" approaches

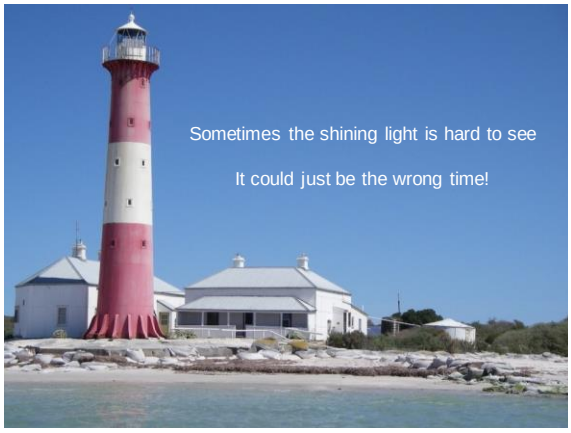
Improved teamwork

Involve the patient as a central focus and information source

Review sources of information other than RCT's

"Scientific progress sounds impressive when portrayed as a sudden beacon of light, even if the ideas have been around for ages."

- The Chronicle of Higher Education, March 05, 2017



But once seen things really get better !

Re-discovery of the lymphatic system

Oliver, G and Detmar, M Genes and Development (2002) 16: 773-783

From Gasparo Aselli (Asellius 1627) until the beginning of the last Century, the lymphatics and their embryonic development were widely studied but until recently the lack of specific lymphatic markers and the histo-genetic origin of the lymphatics has remained elusive and controversial

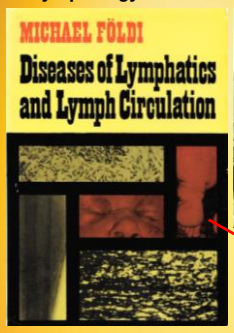
Advances have been possible due to the discovery and use of molecules which specifically control vessel growth and development and function

So we can link this to what those early pioneers (Milroy, 1892, Meige 1898)found about hereditary diseases linked to hypo/dysplasia and later about metastasis (Stacker, 2001)

The outcome ?

Improved diagnosis, targeted and sequenced treatment

Lymphology Discovered, Rediscovered and Forgotten



-Charles C Thompson, Budapest; **1969**

2016

On Brain Lymphatics

"According to prevailing textbook knowledge, the lymphvascular system has no role in fluid circulation of the brain substance and a functionally neligible one in cerebrospinal fluid drainage. ***Connections between the intracranal structures and the lymphatic system are nonetheless well known."***

Standing on the Shoulders of Giants
Blind Orion Searching for the Rising Sun by Nicolas Poussin 1658

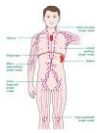
LANDMARKS

Giant Steps in Lymphology

1. Discovery of the chyliferous vessels and "lymphatic imaging" - Asellius, 1627 -
2. Lymph as the milieu interieur - Claude Bernard, 1878
3. Transcapillary exchange of liquid, lymph formation and edema - Starling, 1895
4. Embryology and phylogeny of lymphatic system - Sabin, Kampmeier-1903, 1909-
5. Transcapillary protein movement/lymph absorption– Krogh, Drinker, Mayerson, Courtice, 1925 -
6. Lymphangiogenesis in vivo, 1932- and in vitro,
7. Lymphocyte migrant streams - J Yoffey, B Morris, J Gowans, 1939 -
8. Lymphatic imaging/classification - J Kinmonth, M Servelle, F Kaindl, 1950 -
9. Intrinsic contractility and distinctive ultrastructure of lymphatics - J Hall, I Roddie, J Casley-Smith, L Leak 1962 –
10. Lymphostatic disorders /edematous states - I Rusznyak, G Szabo, M & E Foldi, W Olszewski, A Dumont, M & C Witte, 1960 –
11. Lymphscintigraphy including sentinel node mapping, 1970-
12. Highly specific molecular/histochemical markers- Lyve-1, Prox-1, Podoplanin, 5' nucleotidase, VEGFR-3, 1990-
13. Lymphatic growth factors/genetics - K. Alitalo, 1996 -/ teams U Pittsburgh, U Conn - St George, U Az - U Mich, 1998, U Leuven, 2003

Crystallization of Lymphology and birth of the **International Society for Lymphology** (ISL) in the 1960's

We often forget the Big Picture



Drainage pathways from lower body are long and against gravity

Acknowledge Individuality of patient :

Genetic check of high risk patients (where family history of Primary LO) (Ostergaard, et al 2011)

Knowing genetic picture can indicate risk and may indicate specific management

Primary Prevention

(Cheville, 2007)

Primary prevention remains under-emphasised

- Patient/Health Professional Education
- Timely diagnosis
- Identification of modifiable risk factors
- Early initiation of treatment

We should conduct a FULL Assessment

- Family review
  - Dysplasias of the lymph-vascular systems
  - Cardiovascular
- Medical History
  - Lifetime prior damage to lymphatic system paths or nodes
- Medication History
  - Current oedema causing medications
- Surgical/radio-therapeutical History
  - Lifetime removal or damage to nodes and vessels

We should

Invoke Pre-operative assessment in high risk cases

(Stout Gergich et al 2008)

- Pre Op and Base line allows early conservative treatment intervention. But what should it be?
  - Light compression
  - Breathing
  - Skin care
  - Diet
- Treatments appear more effective in early stage sub clinical lymphoedema (its just fluid)

We Can Undertake a Risk Assessment - Legs

EVENT/SITUATION		Score
More than 10 nodes removed from the groin		3
More than 2 but less than 10 nodes removed from groin		2
1 or 2 nodes removed from the groin		1
Radiotherapy to the groin/pelvic area		3
Fluids drained from wound more than 1 week		2
Infection at the wound site after surgery		2
Average of more than 2 infections (cellulitis) in the limb per year		3
Average of one infection (cellulitis) in the limb per year		2
Heaviness, tightness or tension in the limb at times		1
Limb feels worse as the day progresses		1
Frequent cuts/scratches to the limb		2
Dry or scaly skin on lower legs/feet		3
OTHER PROBLEMS WHICH MAY ADD TO RISK		
Family history of leg swelling		2
Frequent long distance air/bus/car traveler		2
Previous or current other injuries to legs, ankles or feet		1
Limb is most often in a dependant position (standing)		3
Generally experience high stress levels		2
Generally have high blood pressure		2
Thyroid gland activity is not normal and not medicated		1
Diabetic but controlled by diet or medication		1
Diabetic uncontrolled		3
Some varicose veins or spider veins		1
Many varicose veins or spider veins		2
Prior varicose vein stripping and scars		2
Smoking is currently part of my life		1
Body weight is a little high (overweight)		2
Body weight is very high (obese)		4
Diet is rich in animal (omega 6) fats		2
Swelling was present in limb prior to surgery/radiotherapy		1
	Total Score	_____

0-10 = LOW RISK 11-20 = Moderate Risk More than 20 = High Risk

We should acknowledge the impact of Medication induced oedema

- Three general areas/types determined by their mechanism of action
  - Sodium overload,
  - Renal dysfunction
  - Hyper-permeability/changes in permeability of blood vessels.

Keeley, V and Piller, N (2017) Edema causing Medications. Pathways

We must consider Proximity to veins

(Diseases/disorders/damage - reduce lymph transport capacity)

- Phlebitis - Lymphangitis, lymphadenitis
- Fragility - Excess leakage large molecules
- Thrombi - Blockage (external pressure)
- Stripping - Destruction of adventitial Lymph V's
- Ligation - Accidental ligation collectors
- Sclerotherapy - Accidental sclerosis of lymphatics
- Harvesting - Destruction/removal of collectors (CABG)

When we measure basic parameters we must be aware of their limitations and need to develop a concensus

Circumference
Tape measurement
Optoelectronic (Perometry etc)

Volume
Tape measurement
Immersion and reverse Plethysmography
Optoelectronic (Perometry etc)

These issues are the Core of the **Chronic Oedema Outcome Measures** project

Chronic oedema outcomes: Issues with tape and volumetric measures

volume and [illegible] to fluid only.

Fluid

Weight gain

Atrophy

A better method of assessment is needed because tape and volumetric measures indicate more than fluid changes ESPECIALLY OVER LONGER TIME PERIODS

We can detect subtle changes in Tissue Fluid and Tissue Composition

(Are these better than circumference and Volume Measures: Replace them or add these)

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Segmental/limb tissue fluid changes

Bioimpedance Spectroscopy

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Site specific fluids:

Electro-magnetic technique

Fluid levels in unique area (lymphatic territory/area under probe) to varying depths (to 5 mm) depending on head

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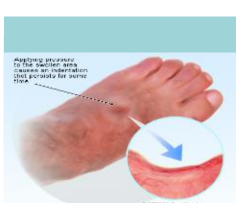
But if you don't have it try - Something Simple

The "pitting test"



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Detection of tissue composition changes

Tonometer, Indurometer and fibrometer

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But if you don't have them: Something simple

The Stemmer Sign

Positive Stemmer Sign – Skin fold cannot be picked up

You can use it in any lymphatic territory!

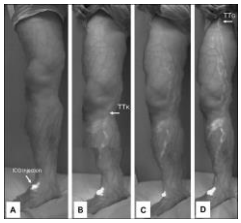
You may know the structural changes but what about functional ones

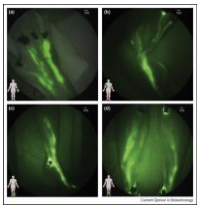
Assessing functional status of the lymphatic system

We should acknowledge patient and lymphatic individuality through improved awareness of individual drainage pathways

Wei Ren Pan et al , 2011

We can do that by using ICG

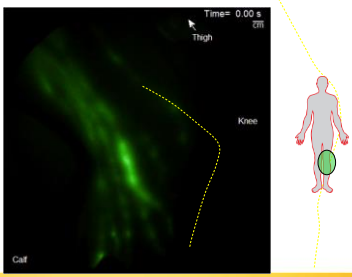




Flow and lympho-vaso-motricity can be determined

ICG lymphatic imaging

Normal Lymphatics in a normal Leg



NIRF Imaging, Inc.

Previously micro-surgery and super micro surgery were undertaken in the **late stages of lymphoedema:** Long term patency and success not always good

Now appropriate candidates are **selected in early stage of lymphoedemas- using ICG** imaging for functional collector location

Patients and therapists encouraged to ensure flow through the new anastomoses

We may have "lost the patient" in the quest for good science

What really is best for lymphoedema patients?
(Piller, Finnane, Partsch, Singh, Hayes and Woodman, Journal of Lymphoedema 2014, 9(1) 6-10)

Decisions, They are never Easy ! But this is what we would like to do and here are the reasons why
(Piller, Journal of Lymphoedema 2018, 13(1) 5-6

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We have some ideas about preventative measures - BUT

(Cernal, et al 2011 J Am Coll Surg, 213 (4)

- **Are recommendations fact or fiction?** (760 papers – selected 49)
  - Avoid needle sticks – **Variable – but sensible**
  - Avoid pressure (cuffs) – **Fiction?**
  - Limb precautions - **To be determined**
  - Travel Avoidance/wear garments if do – **Fiction?**
  - Weight maintenance - **Fact**
  - Avoid temp extremes, sun – **Fiction**
  - Avoid strong exercise - **Fiction**
- Uncertainty contributes to patient fear/anxiety
- Knowledge limitation means more research needed, defined outcomes, large sample sizes and prospective measures – H**ow can we make it happen?**

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Patients will see differing findings

Nickolaidis and Karlsson, "Evidence and Tradition in conflict, The Swedish Experience of lymphoedema treatment and care" JOL, 2013 8(2), 21-23,
Stated "Less emphasis should be placed on MLD and more on compression, exercise and weight reduction"

Huang, TW et al "Effects of MLD on BCRL: A systematic review and meta analysis World J Surg Oncol, 2013
Summarised " The current evidence from RCT's does not support the use of MLD in preventing or treating LO "

Godoy et al Lymphoscintigraphic evaluation of manual lymphatic therapy Phlebology (2015) 30 (1) 39-44
Stated: Manual lymphatic therapy improves the transport of radio tracers in lymph collectors

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What we and patients read should be questioned but how do we encourage and facilitate this

Just because it's a "systematic review" or "meta analysis" does not always mean it's got the answer for you or your patient

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OMG!

What should I do? (Patient)

What do I suggest? (Practitioner)

What really will make a difference? (Both)

Can we add research to add certainty?

Can we improve Modes of Communication Tele- Health?

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How do we consider and balance "Dr GOOGLE"?

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Nurse-Managed Technology to Enhance Cancer Care Outcomes for Survivors

- Mobile-device assessment of limb swelling
- Machine learning and touchscreen reporting
- Integration of assessment data into medical record

Melissa A. Stec, College of Nursing, University of Cincinnati, Cincinnati,

About Treatments

Can we shift the focus? Silver bullets vs Shotguns (Witte and Bernas, Lymphology, 2007)

- FDA/TGA and Ethics Cottee like : "Silver Bullets"
  - Carefully controlled evidence based focus on single therapeutic interventions/agents
- Reality is : "Shotguns"
  - Most treatments more "oriental" combination therapies with manual manouveres
- Major aim should be
  - Replicatible results with good safety margin
  - Can we ever dissect out active components?

Do we require balance between often expensive "silver bullet" and inexpensive "shotgun" treatment?

We know and use the core modalities

Manual Lymphatic Drainage
Skin Care
Activity/Exercise
Compression
Diet/Weight Management

BUT do we think Holistically enough? Are we and the patients aware of simple events proximal to the swelling may slow lymph flow

- Bloating
- Constipation
- Visceral Fat
- Shallow Breathing
- Constant external pressure in wrong place

We know compression delivered by:

- **Bandaging** – consider impact of
  - Short vs medium vs long stretch and how long pressure lasts
- **Garments** - consider impact of knit type
  - Round vs flat and how long the pressure lasts
- **Wraps** - can be adjusted by patient
- **Intermittent compression devices**- can be used at home

BUT – We need to better acknowledge common issues with pressures which lead to poor outcomes

- **Poor pressure gradient**
  - Fluids forced distally
- **Pressure too high** (general or local)
  - Lymph flow slowed or stopped
- **Garment difficult to Don or Doff**
  - Patient unable to wear
- **Older garments/bandages less elastic**
  - Less pressure variation with movement

We need to continue to explore new Therapies and Measurement

Shock wave therapy: Is the shock wave strong enough to break the fibrotic tissue? Other therapies will be more effective

Fat cavitation/ Fat freezing- controlled suction and freezing

Measurement strategies

Ultrasound elasto-graphy a special **ultrasound** technique normally used to test for **liver fibrosis**. Movement caused by **ultrasound** wave is **measured** and stiffness (or elasticity) is calculated. - use in measuring tissue fibrosis?

We should better assess/know patient compliance/adherence to our requirements of them!

(but accept what they can or can't do)

Compliance: You expect me to do what!!

We should recognise the two main patient groups

- **Current group** – With lymphoedema
  - Reactive health care and management
- **New group** – At risk of lymphoedema
  - Proactive health care (our and the patient's future lies here)

Surgical Interventions for Lymphoedema

Beltramino, Lymphology 36 2003 107-109

Avicenna – skin incisions with knife and cover with honey
Carnochen (1851)– ligation of femoral artery
Morton – (1878)Transection of the sciatic nerve
Handley – (1908) silk threads
Ransohoff and others –(1955) nylon threads/poly-ethylene tubing
Lanz – (1911) buried fascia (resurrected by Thompson (1966)
Olszewski – (1966) –lymph nodal- venous shunts - furthered by Campisi (1968)
Tosatti (1974), Clodius (1978)
Baumeister – (1981) lymph collector transplants

BUT results were underwhelming **UNTIL recently**.

Issues of lymphatic dysfunction are now specifically identified/visualised and early treatment begun before lymphatics in at risk patients become dysfunctional

What's in a name?

Lymphoedema or Chronic Oedema what is best?

What have we forgotten ?

- Sometimes we **aren't sure** or **don't know** !
- BUT it seems we have forgotten a range of possible **pharmacological** solutions
- Yes there were negatives to some but … is it time to re-explore them?

Future Research Priorities for Morbidity control of Lymphoedema

Narahari et al Journal of Dermatology 2017 62 33-40

Priorities

Simplification of integrated treatment for LO
Cellular changes and recommendations for their reversal
Eliminating bacterial entry lesions
Exploring evidence for therapies in traditional medicine
Improving patient concordance (to compression)
Epidemiology (of Filariasis)
Economic benefit of integrative treatments

The way out- Early Detection, Education, Advice and Action!

Priorities

- National/International Studies such as LIMPRINT to provide strong evidence about **Epidemiology** of Lymphoedemas
- National studies such as the ICF (International Classification of Functioning, Disability and Health) to report on the **Functional Status** of the Lymphoedema Patient
- Programs such as LYMPHA to better **prevent lymphoedema**
- **Concensus/Best practice/Templates for practice** documents at National and International Levels
- Improved **Funding for Research** and Evidence Provision
- Improved **Funding for Treatment** and Management

Our Priorities

- **Strategies and knowledge to minimise/prevent damage to the lymphatic system** in the first place
  - Particularly in
    - The treatment of Cancers when Surgery and/or Radiotherapy is required
    - Interventions involving the vascular/venous system
- **Improved communications** between Leading International and National Groups in the Venous and lymphatic areas

INTERNATIONAL LYMPHOEDEMA FRAMEWORK

BELONG TOGETHER as we have in this Congress!

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AMERICAN LYMPHEDEMA FRAMEWORK PROJECT ALFP