BOOK REVIEW: *Lymphedema: Complete Medical and Surgical Management*, Neligan PC, Masia J and Piller NB Eds., CRC Press, Boca Raton, FL (2016). 634 pages with DVD.

This profusely-illustrated compendium provides a snapshot of our current knowledge of lymphedema nature, burden, and treatment, with an emphasis on surgical protocols currently practiced throughout the world. The 48 chapters by 76 authors from around the globe document the state of current conservative practice as well as the surgical and microsurgical protocols being performed at various centers. A complementary DVD is included which includes videos of a variety of microsurgical techniques.

This volume is a worthwhile addition to the library of all medical students and practicing physicians and surgeons, especially those whose formal education has not included topics in lymphology, lymphatic pathology, diagnosis, physical and psychosocial burden, and treatment of lymphedema. It presents, in one volume, a collection of current topics relating to lymphedema diagnosis and treatment that can only be found by tediously combing the current medical literature. Therapists and medically-versed advocates will also find a wealth of usable information in its pages.

The volume is organized in 6 parts discussed below. My view is that of a lymphedema patient and lymphedema therapist advocate, and not a medical professional. My function is to translate medical information into terms understandable by and made useful to the patient and lymphedema therapist. My viewpoint may not coincide with those of the editors and writers, who may have a different audience in mind. As a lymphedema patient and therapist advocate my focus is on patient-centered issues that relate to lymphedema patients' receiving timely and optimal care.

There are a number of key themes I perceive throughout this book. Some of these are as follows:

- Lymphedema is a chronic inflammatory process associated with:
  - continuous inflammation;
  - collagen deposition (fibrosis or hardening of tissue);
  - lipid cell production (fatty tissue replacing tissue fluid swelling);
  - impaired infection control (increased risk of cellulitis).
- Early intervention may prevent or reduce the impact of lymphedema on quality of life (QoL):
  - There is a need for broader use of diagnosis and measurement of Stage 0 LE;
  - There is a need for lymphedema-sensitive QoL instruments -- midline as well as extremity.
- Treatment must match the patient's diagnosis and needs as well as the disease status:
  - Differential diagnosis to determine cause and stage is vital;
  - Current ICD-10-CM codes are not adequate to describe cause and severity of LE;
  - There is no "best" protocol for lymphedema treatment;
  - There is an individual genetic component to lymphedema.
- Greater use is being made for methods for lymphatic visualization;
  - Used for diagnosis, clinical investigation, and to support therapeutical and microsurgical protocols;
  - Radionuclide lymphoscintigraphy, Indocyanine lymphography, Magnetic resonance lymphangiography
- A variety of surgical protocols are becoming available for prevention, cure and palliation;

Most chapters are preceded with a summary of the "Key Points" of the chapter, and end with a "Clinical Pearls" summary.

The 48 chapters are somewhat overlapping and therefore much of the information is repetitive in order to achieve self-standing chapters. Sometimes this is good since the essence of pedagogy is repetition. But once learned, much time is lost in reading the same material over again—sometimes word-for-word as in Chapters 4 and 10, or when the information is contradictory such as in Chapters 4 and 14.

Part I Current Concepts in Lymphedema. The three chapters in this part introduce lymphedema from the clinical view, its burden on patient quality of life (QoL), and related QoL measurement instruments—both general and lymphedema-specific. Chapter 1 is a concise introduction to the book, discussing current non-surgical and surgical management techniques. It summarizes, in few pages, the wisdom of 141 references. Most of the QoL instruments in current use, including those used to evaluate efficacy of physical therapy to manage lymphedema, are evaluations of functional disability secondary to lymphedema, and not the severity of lymphedema, i.e. general QoL instruments are mainly insensitive to lymphedema. This has given impetus to a number of lymphedema-specific instruments that are more suitable to measurement of functional impact of lymphedema in its later stages, in spite of the fact that "early physiotherapy intervention may reduce the risk of developing lymphedema and of progressive lymphedema." It is a regrettable fact that the instruments being used to evaluate efficacy of lymphedema treatment for the purpose of therapist reimbursement and insurance coverage are insensitive to early manifestations of lymphedema when the disease is most amenable to prevention, and instead require progression to functional disability to be usable.

Part II Anatomy, Physiology, and Lymphangiogenesis. The 120 pages in the eight chapters of this part constitute a primer on lymphology. But more than being just a primer, it documents the recent advances in our knowledge of the lymphatic system, and should be required reading for practicing physicians and therapists who received their medical education more than ten years ago. But even in this 2016 publication, the old, now discredited classical theory about the return of tissue fluid being 90% through resorption by the venous capillaries and 10% by the lymphatics creeps into Chapter 4 on embriology and doesn't get corrected until ten chapters later in Chapter 14.

Chapters 5 and 6 on lymphatic pathways are a "must read" for lymphedema therapists. The lymphatic pathways of the human body, based on cadaver studies, are meticulously diagrammed and can be of great use to the therapist in visualizing patterns of lymphatic flow. For those patients, therapists and physicians who cannot understand how removal of just one sentinel lymph node can be responsible for upper limb or breast lymphedema, FIG 5-17 shows how "an axillary node can drain the entire breast and a large part of the upper limb". Building on the knowledge of lymphatic pathways, Chapter 6 applies this anatomical information to discuss lymphatic drainage pathways.

Chapter 7 summarizes our knowledge of lymphangiogenesis (the formation of lymphatic vessels), a subject of intense research for only 10-15 years, and which is already the basis of development of new treatments for lymphedema, both pharmaceutical and surgical. Another aspect of lymphangiogenesis, how genetics may influence prenatal or postnatal lymphangiogenesis, is discussed in Chapter 8. A classification system for primary lymphedema based on genetics is proposed. This classification system should be learned by practicing physicians, and should become the basis for diagnosing primary lymphedema. Lymphologists might consider pressing for use of this classification system as the basis for an expansion of the diagnostic code set **Q82.0 Hereditary or Primary Lymphedema** in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).

Continuing the discussion of lymphangiogenesis, Chapter 9 outlines what we know of the interrelationship between lymphangiogenesis, inflammation, and adipogenesis (the formation of fatty tissue), the relationship between lymphedema and obesity, and how this preliminary knowledge might lead to clinical changes. Chapter 11 discusses the role of the peripheral lymphatics in immune regulation. In the last 10 years lymphedema has been elevated from its previous role of a drain blockage in the body's waste system to a complex body system interrelated with immune, metabolic, wound repair, and circulatory functions.

Chapter 10 on lymphatic malformations must have presented problems in placement for the Editors. Its initial discussion of vascular embryology is repeated from Chapter 4 and its classification of vascular and lymphatic malformations takes a different viewpoint from those in Chapters 8 and 45. Its discussion of the genetics of vascular receptors duplicates much of the content of Chapter 8, and its discussion of diagnostics and diagnostic imaging and treatment anticipate these subjects that are dealt with in much greater detail in later chapters. Chapter 10 would read better as a closing to Part II and an introduction to the later parts.

Part III Pathophysiology and Clinical Presentation. The 8 chapters in the next 100 pages introduce a variety of clinical presentations of lymphedema and the pathophysiology for these differing presentations. The points of view of many different medical specialties are represented in this Part, e.g., Lymphologist, Dermatologist, Pathologist, General Surgeon, Plastic Surgeon, Pediatrician, Phlebologist, Internist, Nurse, Oncologist, Epidemiologist. This Part gives the flavor of the many manifestations of lymphedema.

Chapter 12 continues the discussion of primary lymphedema started in Chapters 4 and 8 with a description of the normal functions of the lymphatic system and a discussion of how development irregularities may lead to lymphedema. This short chapter is augmented with a list of 99 references. An even shorter Chapter 13 discusses the pathophysiology of secondary lymphedema in terms of degree of damage, stage of disease, and presence of comorbidities after summarizing the role of the lymphatic drainage system.

Chapters 14 and 15 detail lower-limb lymphedema in general, and specific to lymphatic filariasis. The latter chapter concerns the pathology of filariasis, its diagnosis, management, and the spectrum of its surgical treatments. Additional information on the prevalence and treatment of filariasis in India is found in Chapter 44. Chapter 17 deals with combined lymphatic and venous failure (phlebolymphedema), which represents a unique challenge for diagnosis and treatment.

Chapter 16 on pediatric lymphedema brings together aspects of primary and secondary lymphedema and the unique diagnostic and treatment issues for the pediatric patient.

Rounding out Part III, Chapter 18 summarizes risk factors for upper limb lymphedema development in breast cancer survivors, and Chapter 19 looks at extremity lymphedema outcomes after sentinel lymph node biopsy (SLNB). Neither of these chapters discusses truncal or breast lymphedema risk.

Part IV Diagnosis of Lymphedema. The nine chapters of Part IV cover the differential diagnosis of lymphedema, its staging and measurement, and details on current imaging methods. Included in this Part are chapters on the clinical diagnosis of lymphatic diseases sometimes grouped with lymphedema as part of a lymphatic syndrome (Chapter 20), and on the hydromechanics of intercellular fluid during sequential pneumatic compression (Chapter 25).

The congenital and acquired disorders of the lymphatic system discussed in Chapter 20 include infection, lipedema, lymphangiomatosis, vascular malformations, protein-losing enteropathy, intestinal lymphangiectasia, and lymphangioleiomatosis. The terse summary is accompanied by a list of 113 references that may be consulted for more detail.

Contained within the 5-page summary of differential diagnosis of lymphedema in Chapter 21 was the only mention of diagnostic tools I personally believe to be the future of diagnosis and measurement of early (Grade 0-1) lymphedema, i.e. tissue dielectric constant for measurement of tissue fluid, and ultrasonic measurement of skin thickness. Both of these techniques have considerable lab experience in the last 12 years and both can be implemented as inexpensive portable instruments for a physician's or therapist's office. And both can be used to diagnose and measure non-extremity, mid-line lymphedema.

The discovery in the last 20 years and current use of lymphatic molecular markers in lab investigations is the subject of Chapter 22, but the translation of these investigations into the clinical realm for benefit of lymphedema and cancer patients is only held out to be a "hope" by the authors. It is unfortunate that more detail was not given, e.g. work being performed in development of a lymphedema diagnostic array such as the six-protein biomarker panel announced by Stanford in 2012.

Different systems for the clinical staging of lymphedema are summarized in Chapter 23. In addition to contrasting the clinical staging systems proposed by the ISL with those used in Germany, Italy, Japan and Brazil, the points are made that: staging of lymphedema must be considered by the physician in determining treatment; early diagnosis and treatment provide the best quality of life for the patient and least cost for the individual and society, and; the International Classification of Functioning, Disability and Health (ICF) is gaining traction as a quantification tool to be used with staging for clinical evaluation and treatment planning.

Chapter 24 Measuring Methods summarizes current practice in the measurement of lymphedema, i.e. limb circumference, limb volume, lymph flow by lymphoscintigraphy, tissue fibrotic changes by mechanical tonometry, and tissue fluid content by bioimpedance spectroscopy. None of these measurements is ideal over all stages of lymphedema, and none are currently used to measure mid-line (non-extremity) lymphedema. No mention is made of the increasing use of ultrasound measurement of skin thickness and elasticity, tissue dielectric constant for measurement of tissue fluid content, and near-infrared fluoroscopy for measurement of lymph flow – techniques emerging from the lab for clinical measurement of pre-clinical and mid-line lymphedema.

Chapter 25 Hydromechanics of Intercellular Fluid and Lymph is another chapter, like Chapter 10, which doesn't appear to fit into the organization of the book. The opening topics deal with the accumulation and flow of fluids in the lower limb under normal and lymphedematous state, a subject better fitting for inclusion in Part III on the pathophysiology and physical presentation of lymphedema. A brief section describes the lab methods used to measure fluid flow, not applicable for clinical measurement. The remainder of the section details the effects on fluid pressure and flow of manual massage, bandaging, and intermittent pneumatic compression on the lower limb. Of particular interest is the determination of optimum pressure and duration of pneumatic compression. This information better belongs in Part V in the section on current treatment of lymphedema.

The remaining three chapters of Part IV (Chapters 26-28) comprise an excellent description of the three major lymphedema imaging protocols: radionuclide lymphoscintigraphy; near-infrared

[indocyanine green (ICG)] fluorescent lymphography; and magnetic resonance lymphangiography. All three chapters are profusely illustrated, and contain interpretation criteria and guidelines for the diagnosis of lymphedema. Chapter 27 on ICG lymphography is one of the only places where we find discussion of non-extremity lymphedema, with illustration of how this technique may be used to diagnose facial and genital lymphedema.

Part V Current Treatment of Lymphedema. With the preliminaries out of the way, Part V gets into the meat of the subject of current surgical treatment of lymphedema. Many of the chapters in this part are accompanied by videos on an included DVD illustrating the procedure. Part V is rounded out with chapters on conventional treatment, pharmacologic treatment, filariasis treatment, related complications, and a separate chapter on the value of early diagnosis and treatment.

Chapter 29 summarizes conservative treatments for lymphedema, both traditional (manual lymphatic drainage and compression) and contemporary adjuvent (electrostimulation, pharmaceutical, low-level laser/light scanning, lymphatic draining massage, exercise, tissue manipulation, taping, diet, and placebo), with very little high-grade evidence to support any modality. Which treatment or combinations of treatments that will benefit a patient should be determined by the treating physician or therapist since "lymphedema is frequently a complicated pathophysiologic change to a variety of tissues and systems, and each patient is unique despite the common sign of swelling of a limb or other section of the body."

Pharmacologic treatment of lymphedema is covered in Chapter 30, which includes discussions of the potential beneficial effects and dangers of: benzopyrones (e.g. coumarins, flavonoids); herbal therapies (e.g. horse chestnut seed, butcher's broom, ginkgo, sweet clover, tonka beans); and vitamins and minerals. Excellent sections follow on the topics of drugs for lymphatic filariasis, antibiotics for lymphedema-related cellulitis, and drugs for lymphedema-related fibrosis. This chapter ends with a cautionary section on drugs that may worsen lymphedema, with a listing of pharmaceuticals that may cause peripheral edema. Lymphedema patients might do well to include this list in their medical record and discuss it with their physicians.

Chapters 31-41 detail the contemporary surgical approaches to lymphedema treatment. These 128 pages form the core of the book, and should be required reading for surgeons and medical students. This reviewer, however, is not qualified to evaluate them, and will merely indicate the variety of surgical techniques currently available to selected lymphedema patients. Which technique is appropriate to a particular patient can only be determined by the treating physician or surgeon based on the individual needs of the patient.

• Chapter 31 describes excisional approaches for debulking (e.g. radical excision, liposuction).

• Chapter 32 on liposuction starts with a discussion of the theories on how chronic lymphedema leads to adipose (fat) tissue deposition and how adipose tissue hypertrophy can be diagnosed. This is followed by a discussion of preoperative assessment and indications for liposuction. Finally the surgical technique, postoperative care and treatment outcomes are discussed.

• Chapter 33 starts the discussion of one of the many microsurgical techniques, i.e. multiple lymphaticovenous anastomoses and multiple lymphatic-venous-lymphatic anastomoses. This chapter proposes a staging of lymphedema based on immunohistologic criteria, lymphoscintrigraphic findings, clinical symptoms, and degree of physical disability that expands on the staging definitions discussed in Chapter 23. This chapter also presents a numerical index used to diagnose lymphedema based on lymphoscintigraphic results. Preventive as well as curative microsurgery is discussed and a combined microsurgery and liposuction technique is used in late-stage cases with significant fibrosis and excess adipose tissue.

• Chapter 34 defines lymphatic grafting as a means of bypassing lymphatic blockages or augmenting diminished lymphatic transport.

• Chapter 35 describes a supermicrosurgical technique for performing lymphaticovenular anastomoses for rerouting lymph directly to cutaneous venules by end-to-end anastomoses. Results are described for small numbers of patients who were treated with this procedure at early stage of lymphedema and others with lymphedema of longer duration.

• Chapter 36 describes the technique of autologous vascularized lymph node transfer (VLNT) for lymphedema that is refractive to conservative therapy. Application of this procedure is shown to treat upper and lower extremity iatrogenic lymphedema and lower limb congenital lymphedema. The procedure may be combined with lymphaticovenular anastomosis for improved results, or with localized liposculpture for cosmetic improvement. Physical therapy is used complementary to the surgical treatment.

• Chapter 37 details a lymphatic mapping technique developed to address the risk of lymphedema in the VLNT donor site. The axillary reverse mapping (ARM) technique was originally developed as a means of avoiding disruption of upper extremity lymphatic draining when performing axillary dissection as part of breast cancer surgical treatment. It was extended to use in vascularized lymph node transfer to avoid disruption of extremity drainage when harvesting donor lymph nodes from the groin, axillary or supraclavicular regions.

• Chapters 38 and 39 present case studies of the combination of VLNT with breast reconstruction using different donor sites.

• Chapter 40 details the so-called Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) concept that uses axillary reverse mapping to identify appropriate vessels for lymphovenous shunts to prevent lymphedema after axillary lymph node dissection. Use of this technique is proposed for prevention of lymphedema after treatment of melanoma.

• If I were to read only one chapter of this book it would be Chapter 41. After a brief history of surgical techniques, the author discusses the importance of preoperative assessment of the patient to determine the best therapeutic option to be offered. Clinical evaluation may be augmented by the diagnostic imaging previously detailed in Chapters 26-28, and followed by an appropriate combination of surgical and/or microsurgical procedures detailed in Chapters 31-37. A unique section in this chapter is a treatment algorithm (logical flow diagram) that leads the physician though the process of assessment, decision-making, and treatment.

Chapter 42 underscores the recurrent theme that "The sooner a diagnosis can be made, the more likely that we can develop a strategy and treatment plan before the condition becomes indolent and chronic." This chapter reviews in brief much of the preceding information on diagnosis and treatment of lymphedema. It would have made an appropriate closure for Part V.

Tacked at the end of Part V are chapters dealing with lymphedema complications, and the status of lymphedema treatment in India and China. I thought that Chapter 43, on the complications of lymphedema, belonged in Part III before or after Chapter 14. This chapter looked briefly at complications affecting specific body systems (cardiovascular, genitourinary, musculoskeletal, and integumentary), infection, malignant transformation, massive localized lymphedema, pain, progression, and the psychosocial consequences of lymphedema – material for the most part covered in detail in previous chapters.

Part VI Research and Future Directions. The last three chapters close out the book with discussions of lymphatic and lymphedema research being done on animal models (Chapter 46), stem cell – mediated lymphangiogenesis for lymphedema treatment (Chapter

47), and the work being done by the International Lymphoedema Framework (ILF) and national lymphedema frameworks in developing long-term strategies for furthering of lymphedema diagnosis and treatment worldwide (Chapter 48). The final part of the book would have greatly benefitted with a broader look at diagnosis and treatment of lymphedema with an identification of areas where knowledge, clinical techniques, and standards are lacking, and what can be done to fill these voids.

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