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EDITORIAL

RETURNING THE CENTRAL LYMPHATIC SYSTEM TO THE CENTER OF LYMPHOLOGY

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ABSTRACT

After the introduction of conventional oil contrast lymphography and the founding of the discipline of lymphology, great impetus was given to investigating central lymphatic system and its disorders along with lymphatic involvement and specifically lymphostasis in common diseases of major organs such as the liver (cirrhosis) and heart (heart failure). Gradually interest shifted to more peripheral disorders such as limb lymphedema and its treatment by physical and surgical measures. At the same time, basic lymphology turned to the study of isolated ex vivo and in vitro, including lymphatic endothelial models and more recently, molecular lymphology focusing on lymphatic growth and modulating factors, genes and proteins underlying primary lymphedema, and more potential biomarkers of lymphatic disease have gained prominence. However, it has been advances in lymphatic imaging, namely lymphoscintigraphy with SPECT-CT high resolution 3-D pictures and magnetic resonance imaging (contrast and non-contrast) of the peripheral and particularly central lymphatic system by more invasive means combined with endovascular interventional techniques to treat complex and life-threatening lymphatic disorders that has returned the central lymphatic system to the center of lymphology, where the journey began.

Keywords: central lymphatics, thoracic duct, multimodal lymphatic imaging, lymphatic malformations, endovascular intervention history

Lymphology — the study, specialty, and International Society focusing on lymphatics, lymph, lymph nodes and lymphocytes in health and disease — was founded in the mid-1960's by the first wave of "lymphologists" (nicknamed "lymphomaniacs"), as the normal and abnormal central lymphatic system — collectors and interposed nodes — was visualized for the first time in the living human. In the early International Society of Lymphology Congresses, most of the lectures and papers presented dealt with oil contrast lymphography, along with the anatomy (including electron microscopy) and physiology (including contractility of the intestinal lymphatics and thoracic duct under fluoroscopy) as well as the pathology and pathophysiology of the thoracic duct circulation along with regional liver, kidney, pancreatic, intestinal, cardiac, and pulmonary lymphatic systems (1-5). Peripheral lymphatics, lymphedema and chylous reflux were also featured along with innovative surgical approaches, including thoracic duct drainage and internal lymphatic-venous shunts in hepatic cirrhosis and right heart

failure (operations which have been rediscovered and applied clinically in recent years using refined surgical and endovascular interventional techniques), and physical treatments of these conditions. Publication of classic texts on Lymphology authored by ISL founding members just preceded or paralleled these early ISL Congresses (6-8).

Beginning in the 1980's, spurred by general interest in angiogenesis (more properly termed "hemangiogenesis") and endothelial cell isolation, lymphologists (9-12) isolated lymphatic endothelial cells in culture, and ISL Congresses turned their attention to more intricate processes of "lymphangiogenesis" and lymphatic vascular biology in general. Clinically, they also increased their attention to peripheral lymphedema and its treatment. Gradually, interest drifted away from the central lymphatics and related imaging techniques to focus on the pathophysiology of peripheral lymphedema and its treatment. In the late 1990s, molecular lymphology appeared on the ISL Congress programs (13,14), and with Alitalo's identification of a specific lymphatic growth factor (VEGFC) (15) in the VEGF family and the techniques of the Human Genome Project subsequently gene discovery spanning the entire genome and underlying familial primary lymphedema, captured the stage along with popularization of distal peripheral lymphatic-venous shunts and multimodality comprehensive physical therapy for limb lymphedema. Patient awareness and advocacy along with physician and other health provider education was brought to the fore in evolving partnership with National Lymphedema Network, beginning in 1987 under Saskia Thiadens, with a refocusing on more generalized central disturbances in primary lymphedema syndromes and expansion globally of lymphatic imaging for diagnosis and monitoring reaching into the endemic areas of filariasis in Southern India and northern Brazil. A variety of patient advocacy organizations and nonprofit foundations and organizations joined and expanded this international network.

However, until relatively recently, lymphology conferences did not once again prominently feature the central and regional lymphatics despite ever more powerful tools to image these structures. These tools, applicable even in critically ill neonates, included Magnetic Resonance Lymphography, without contrast, gamma ray (nuclear medicine,) with and without higher resolution Single Photon Emission (SPECT-CT) to pinpoint the centrality of abnormalities particularly in children with lymphedema syndromes (e.g., Noonan) and neonates with non-immune fetal hydrops as described by Carlo Bellini. Moreover, a specific complication was arising from advances in cardiothoracic surgery (e.g., single ventricle hearts corrected with Fontan shunts, which led commonly to lethal chylous reflux) and lymphatic malformations inside the body. At this point, the Children's Hospital of Philadelphia (CHOP) group (featured in this issue of *Lymphology*), based on the development of percutaneous and intranodal MRL by University of Pennsylvania radiologists Constantin Cope and Max Itkin, joined later by Yoav Dori at CHOP, revived interest in the central lymphatic system. This renewed focus on the central lymphatic system and how many of these complex syndromes – even their external physical features as well as the complications and demise were due to central lymphatic disturbance. This realization harkened back to work from more than a half-century earlier by surgeons John Kinmonth (8), ISL Presidents Jacques Gruwez (3), Allan Dumont (16), and other ISL founders (17). In 2019, CHOP initiated the annual Central Lymphatic Conference, bringing attention back to this important area, and at the 29th ICL, collaborated to feature a mini version of their symposium in Genoa and planned for subsequent ISL Congresses. In Genoa, CHOP organizers (Yoav Dori and Erin Pinto), named their inaugural symposium in Genoa the "Marlys Witte Symposium," recognizing my nearly lifelong standing interest and curiosity (nurtured by those surgeon-lymphologists who have passed away (the late Allan Dumont, Charles Witte, and William Cole) in the thoracic duct — the "beating heart" of the lymph circulation — and the liver and intestinal circulation (from which it arose) and related disturbances in cirrhosis and heart failure. Together, we

envisioned the potential of understanding "lymphodynamics" in our 1967-reported thoracic duct-pulmonary vein shunt in reversing the manifestations of experimental right failure, now repurposed to treat critically ill "Fontan children" (16). CHOP's Central Lymphatics symposium will be expanded and updated at CHOP in 2025 and in the 30th ISL International World Conference in Antalya, Turkey, as basic translational, and clinical research and implementation science explodes worldwide in this interesting, long neglected, and important area that spans "lymphology." Advances in lymphatic imaging — investigative, diagnostic, and interventional — led to the founding of the discipline of lymphology and continuing into the future is truly "making the invisible lymphatic system visible" and amenable to manipulation.

CONFLICT OF INTEREST

The author declares no financial conflict of interest exist.

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