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CONTRASTING PATTERNS OF LYMPHATIC AND BLOOD CIRCULATORY DISORDERS

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La fixte du milieu interieur est la condition de la vie libre

--C. Bernard (1)

In comparing disorders of blood and lymph flow, it is advantageous to consider first the respective role of each vascular system in maintaining body fluid homeostasis, and then to examine the general and special manifestations of each during disease or dysfunction. On an evolutionary scale, the low-pressure "open" exchange or simple diffusion of tissue fluid with sea water, embryologically and phylogenetically long antedates development of a high-pressure, rapidly circulating "closed" bloodstream. Yet, whether as a solitary contractile vacuole in single-cell protozoa, simple water canals in the roundworm, an intricate network of thin-walled channels boosted by strategically placed pulsating "lymph hearts" in amphibia, or barely perceptible, irregularly contracting truncal segments interrupted by immunoreactive lymph nodes in mammals, a stable microenvironment ultimately depends on the constant renewal of tissue fluid that surrounds and bathes all cellular elements.

Quantitatively, total body lymph flow in man amounts to a paltry 1-1/2 to 2-1/2 liters per day as compared to blood which circulates at several liters per minute! Whereas blood flows continuously in a circular pattern, propelled forward by a powerful muscular pump (the heart) and plasma volume is carefully regulated by the kidneys under neuroendocrine influences including atrial natriuretic factor and the renin-aldosterone axis, lymph flow is sporadic, in a unicentral direction, and interstitial fluid-lymph volume homeostasis is linked directly to hydrostatic and oncotic pressure operating across the microvasculature and within tissue spaces. Lymph propulsion, moreover, derives from spontaneous segmental contractions of larger and probably smaller lymph trunks as well as from a host of extraneous, haphazard forces including respiration, skeletal muscle "squeezing," piston-like action of intestinal villi, peristalsis, and transmitted arterial pulsation.

Some lymphatic functions are highly specialized such as absorption of triglycerides as chylomicra and cholesterol via mesenteric lacteals, and the highly intricate intercommunicating immunologic network connecting widely dispersed lymphoid aggregates and nodes. The lymphatic system thereby helps to maintain optimal nutrition and natural immunity, but can become deranged as in "chylous syndromes" associated with intestinal lymphorrhea or protein-losing enteropathy, or as in generalized immunodeficiency where the host becomes extremely susceptible to opportunistic infection and malignant lymphoma.

Although the blood and lymph circulations are closely integrated, primary disturbances in blood flow are often

sudden and characteristically threaten life or limb. For example, acute occlusion of the common femoral artery produces agonizing pain from ischemic neuropathy, muscular paresis, extreme pallor, and coolness to touch--in short, a cadaveric leg. With near total ischemia, distal capillary perfusion and pressure is very low, edema is uncommon, and tissue necrosis rapidly ensues if blood inflow is not promptly restored. Paradoxically, return of arterial flow as after thromboembolectomy commonly produces severe edema as an expanded microvascular surface area from "reactive hyperemia" combines with capillary damage from oxygen-derived free radicals to augment extravasation of plasma which temporarily overwhelms a dormant lymphatic system. Indeed, if more than 8 hours elapse before arterial continuity is reestablished, edema may be so intense as to compromise neurologic and muscular function and require prompt fasciotomy for "compartment decompression." Similar but even more dire sequelae are seen in the viscera where prolonged intestinal ischemia culminates in turgid or frankly infarcted bowel, or in the brain where extraordinary microvascular sensitivity to anoxemia

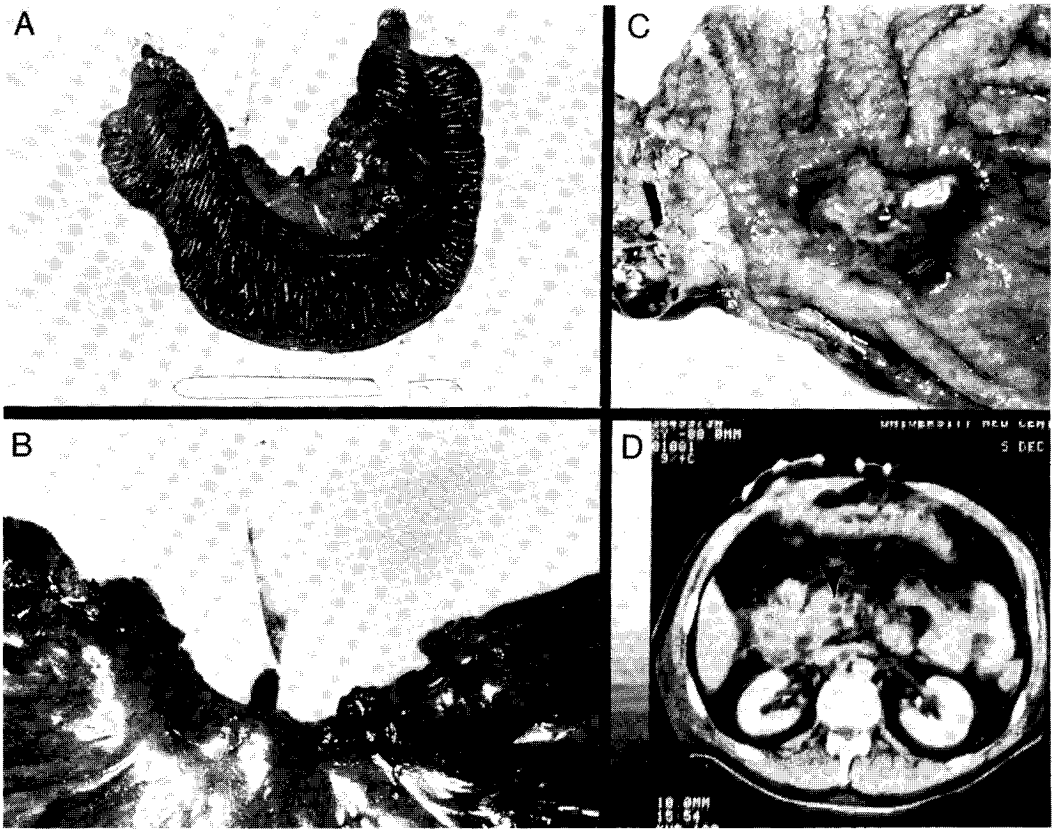

Fig. 1. Acute pylethrombosis in a 62-year-old man with 2 weeks of abdominal pain. Despite resection of an ischemic jejunal segment (A) and distal gastric resection of an ulcerating antral carcinoma (C), progressive small intestinal infarction led to death 25 days after operation. Close-up (B) of resected jejunum shows large venous clot and abdominal computed tomography (6 days after laparotomy) shows circumferential contrast within the portal vein consistent with portal vein thrombosis (D-black arrowhead) and numerous adjacent venous collaterals (D). Acute phlebothrombosis associated with visceral carcinoma is known as Trousseau's syndrome. Reprinted with permission of the Ann. Surg. *(2).*

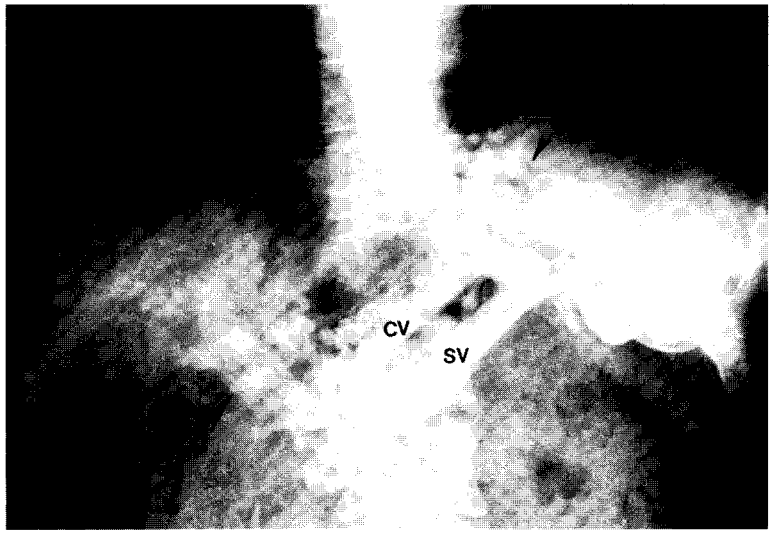

Fig. 2. Splenoportogram in a 25-year-old man with chronic extrahepatic portal block (arrow) associated with large eosphagogastric varices (arrowheads). The thrombosed and recanalized portal vein with numerous bridging collateral channels represents cavernous transformation. SV-splenic vein; CV-coronary vein (modified from Ann. Surg.*) (2).*

and a limited ancillary tissue fluid drainage system produces galloping edema associated with severe intracranial hypertension. Unless promptly relieved, brain herniation is rapidly lethal, or irreversible destruction of the cortical gray matter ensues.

In contrast to femoral arterial occlusion, deep femoral venous obstruction as in phlegmasia cerulea dolens is accompanied early on by massive, unremitting peripheral edema. As blood flow slows from a combination of outflow resistance and down regulation of arterial inflow, blood stagnates in the small vessels. Like arterial insufficiency there is intense "ischemic" pain but as microvascular pressure skyrockets (>40mmHg) and oxyhemoglobin desaturates, fluid extravasation becomes prodigious and the leg takes on a deeply cyanotic hue. Without prompt compartment decompression, muscular and neural damage are permanent.

Other sites of venous blockade have variant but equally dire complications. Thus, propagating pylethrombosis from appendicitis, diverticulitis, pancreatitis, or Trousseau's syndrome *(Fig. 1)* produces extensive bowel infarction whereas more gradual obstruction to portal venous flow as with hepatic cirrhosis or cavernous transformation *(Fig. 2)*, is characteristically complicated by variceal disruption and life-threatening hematemesis (2). Varix hemorrhage may be accompanied by ascites, a special form of celomic edema where an imbalance of hydrodynamic forces in the liver and extrahepatic portal bed from splanchnic venous hypertension overwhelms accelerated lymphatic transport. Other noteworthy complications of inadequate blood flow include cardiac and intestinal angina, limb claudication, rest pain, and focal tissue necrosis such as "ischemic" and "stasis" ulcers. These are just a few examples of the disabling aftermaths of deranged blood flow often in conjunction with normal or even excess lymph flow. Especially intense edema occurs when venous obstruction is combined with lymphatic blockade. Thus, bilateral radical neck dissection or occlusion of the superior vena cava by thrombus or tumor encroachment impedes drainage from

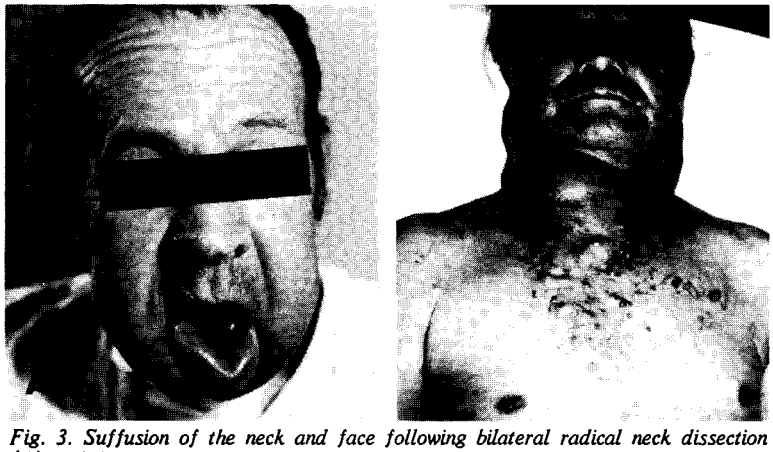

Fig. 3. Suffusion of the neck and face following bilateral radical neck dissection (A) and from superior vena caval encroachment by a rapidly enlarging anaplastic thyroid cancer (B). Concomitant ablation or obstruction of both venous and lymphatic drainage promotes intense edema. Note in (A) that sky blue dye placed just beneath the tongue mucosa 3 weeks earlier remains undrained, whereas in (B) the gradual development of a rich collateral venous network on the chest wall and along the esophagous (the latter not shown) has facilitated partial decompression and amelioration of facial swelling.

both vascular systems and intense suffusion of the head and neck ensues *(Fig. 3)*.

In contrast to these acute manifestations of abnormal blood flow, impaired tissue fluid or lymph flow is a more insidious process, often accompanied by a latent or prodromal period of many months or years before symptoms become clinically apparent. Even acute ligation of the thoracic duct, the chief pathway for most body lymph, as in treatment of traumatic chylous fistula, is rarely associated with significant short- or long-term complications. Perhaps the prototype disorder, however, for appreciating the dynamics of impaired lymph flow is peripheral lymphedema *(Fig. 4)*. Although the partition of extracellular fluid has long been recognized to depend primarily on transcapillary hydrostatic and oncotic pressure gradients and regional lymph flow, initial attempts to reproduce lymphedema solely by obliterating lymph trunks were unsuccessful as the extraordinary regenerative capacity of lymphatics and opening of auxiliary lymphatic-venous connections seemingly precluded sustained tissue swelling (3). Indeed, this failure supported for many years a long-held but now recognized as erroneous notion that recurrent or smoldering infection was essential for the development of clinical lymphedema. Either overt or indolent low-grade lymphangitis, it was surmised, superimposed lymphatic fibrosis on extant truncal disease. This sequence seemed to explain the unpredictable occurrence of arm edema following radical mastectomy (4), the late appearance of leg edema after radical groin dissection, and the exaggerated form of tropical lymphedema or elephantiasis in which natives afflicted with filariasis often walk barefooted and suffer frequent febrile episodes or mumu attacks (5) *(Fig. 5)*.

Beginning with Danese (6) in the United States, however, and culminating with the brilliant expositions of Olszewski (7) of Poland and Clodius (8) of Switzerland and their respective associates, it was determined that after experimental lymphatic ablation an interval of many months or years typically elapsed before peripheral edema became intractable *(Fig. 6)*. During this latent period, lymphangiography *(Fig. 6)* showed gradual dilation of blocked lymphatic trunks, progressive destruction of

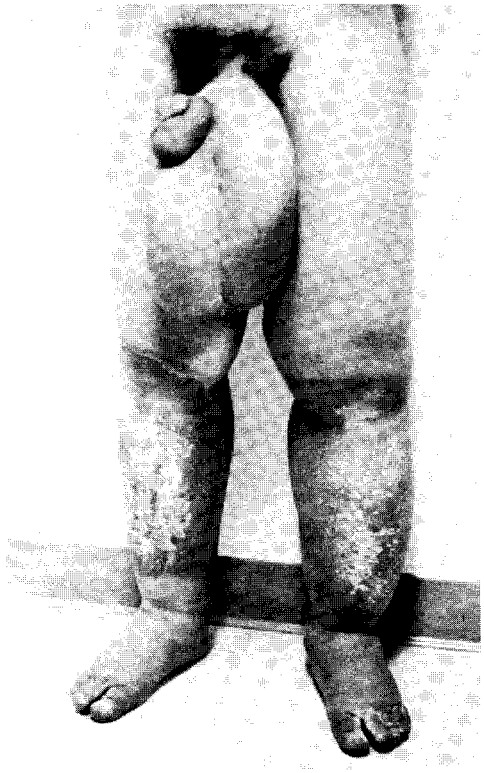

Fig. 4. Massive peripheral and genital edema in a 27-year-old man with familial lymphatic aplasia (Milroy's Disease). His father, sister, and younger brother are similarly afflicted. The extensive scrotal edema recurred within 6 years after excisional therapy (note the healed medial raphe scar).

intralymphatic valves, dermal backflow, and retention of contrast media in abnormal vessels for several days. Once lymphedema was firmly established the x-ray pattern showed extreme truncal ectasia with retrograde filling, frank valvular incompetence and pooling of contrast in the affected extremity. In other words, the lymphangiographic appearance of the "occult" and "overt" phases of lymphedema differed only in degree. These studies confirmed that unrelieved lymphatic obstruction or hypoplasia was itself sufficient to produce chronic lymphedema and that superimposed injury, infection, and nodal or tissue matrix immunoreactivity were aggravating factors, and probably responsible for the grotesque changes associated with elephantiasis.

Besides edema, perhaps the most serious sequelae to disturbed lymph flow are heightened susceptibility to infection and diffuse interstitial fibrosis. Although a close connection has been forged between protein-rich edema and deposition of collagen, the biochemical link between the two is unclear. It seems reasonable to speculate, however, that fibrin or other cell-binders such as fibronectin (α-surface macroglobulin) dispersed within the tissue matrix provides the scaffolding for migration of fibroblasts and deposition of fibroconnective tissue. In this context, the pathogenesis of a variety of visceral disorders characterized by intense fibrosis may also be rooted in defective tissue fluid-lymph flow. Thus, the pathophysiology of diseases as diverse as regional enteritis, pneumoconiosis, hepatic cirrhosis, chronic pancreatitis, and sclerosing cholangitis may each be traceable to impaired tissue fluid drainage, subclinical organ edema, an indolent course with a long prodome, sporadic episodes of lymphangitis, and ultimately, intense scar formation (9).

In contrast to lymph stasis or low-output failure of lymph flow, other edemas arise from an imbalance in capillary dynamics accompanied by overflow of lymph where the lymphatic system acts as a "safety valve" to minimize tissue swelling. These syndromes include elevated microvascular pressure most often from venous blockade, intense hypoproteinemia as with nephrosis, and disruption of the blood capillary endothelial barrier as with burns, sepsis, or toxins. Lymph flow is accelerated, and when the rate of tissue fluid turnover exceeds the transport capacity of the expanded lymphatic system, clinical edema supervenes (so-called high-output failure or dynamic insufficiency of the lymph circulation) (10). Because capillary permeation to plasma protein varies widely (e.g., the tight microvascular junctions of the choroid of the eye and brain compared with the discontinuous endothelium of the hepatic sinusoid or fenestrated capillaries of the bowel), the protein content of

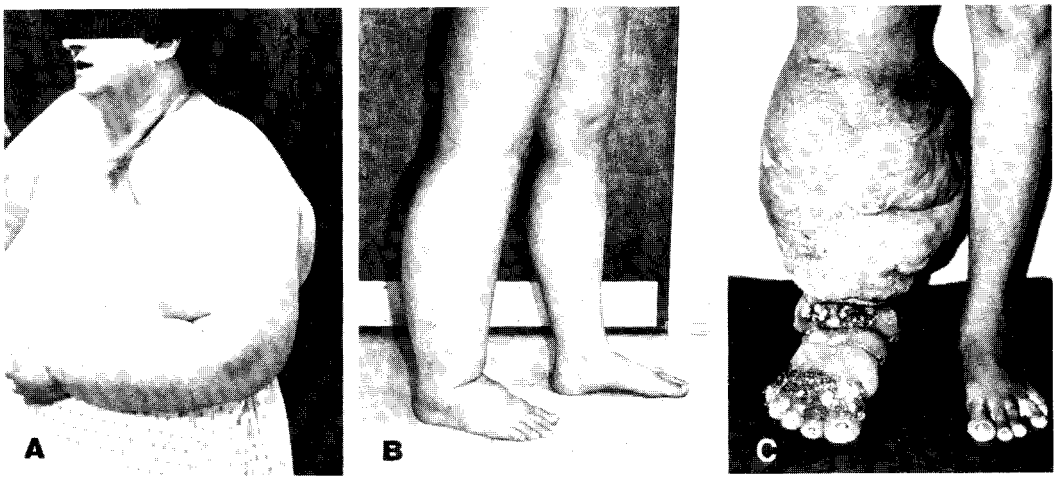

Fig. 5. Extensive arm edema 3 years after radical mastectomy and axillary irradiation for management of breast carcinoma (A), progressive, refractory leg edema 8 years after radical groin dissection for treatment of malignant melanoma (B), and grotesque appearance of filarial lymphedema (C, courtesy of S. Jamal, M.D.).

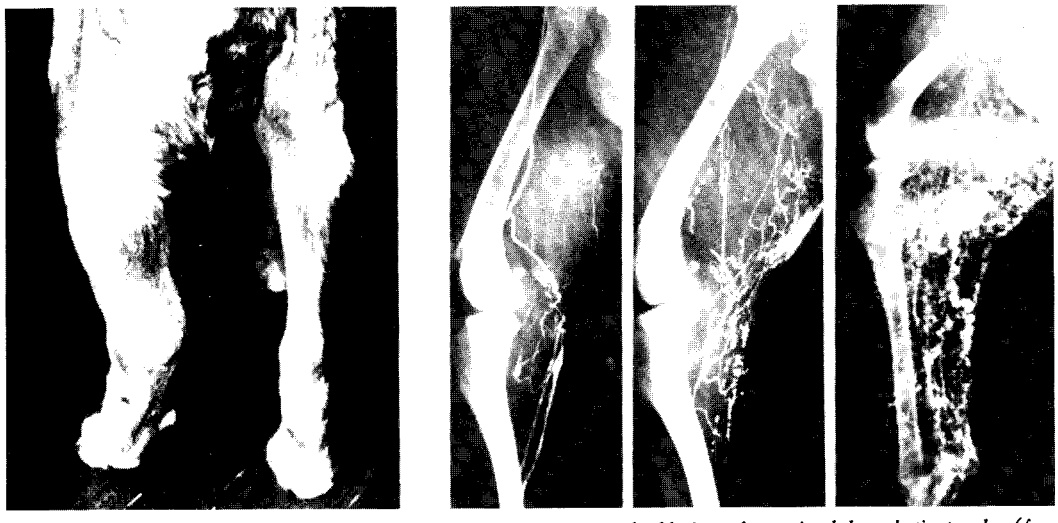

Fig. 6. Unremitting hindlimb edema of dog 2 years after surgical ablation of proximal lymphatic trunks (far left). Peripheral lymphangiography at 9, 14, and 48 months respectively (left to right--3 frames) shows progressive destruction of lymphatic network. Despite increasing dilatation and collateralization of lymphatics with dermal backflow and worsening valvular and truncal incompetence, overt edema was not apparent until profound lymphatic destruction was evident (far right) (modified from Lymphology) (7).

edema fluid or effusion often yields a clue to the underlying pathogenesis and the relative contribution by a deranged blood and/or lymph circulation. For example, the extremely low protein content of peripheral edema associated with femoral venous obstruction or congestive heart failure contrasts sharply with the high protein content of lymphatic hypoplasia or blockage (i.e., classic lymphedema) or that of burns or sepsis where the microcirculation is disrupted. Similarly, the very low protein ascitic fluid derived from weepage of bowel edema in "cirrhotic" portal hypertension contrasts sharply with protein-rich ascites emanating from the turgid liver in Budd-Chiari syndrome or in heart failure or

that originating from the extrahepatic portal bed in miliary cancer or tuberculosis where an expanded surface area for fluid exchange and concomitant lymphatic obstruction by tumor or obliterating lymphangitis predominate (11).

Certain features of lymphatic function such as the transport of triglycerides as chylomicra and aggregates of lymphatic tissue interspersed throughout the tissue-fluid-lymph circulation give rise when deranged to unique clinical findings. For example, mediastinal lymph nodal replacement by malignant lymphoma, luminal obstruction and paralysis of truncal contraction as in filariasis, lymphangiectasia, or lymphangiomyomatosis are associated with chylous edema or effusion, or promote severe hypoproteinemia as lymph seeps into the digestive tract (protein-losing enteropathy) or urine. Experimental reproduction of these syndromes by simple nodal and lymphatic obliteration has, however, been notoriously frustrating. Even though the pathogenesis is unquestionably rooted in failure of forward lymph propulsion, fluid and chyle extravasation probably arise from spontaneous disruption of chyle carrying lymphatic vessels in accordance with LaPlace's law much like rupture of esophageal varices, (another condition not readily reproducible experimentally) depends on vascular wall tension, intraluminal pressure, and thickness of the vessel wall (12).

Aside from extracellular fluid homeostasis and lipid absorption, other activities of the lymphatic system both unique and yet inseparable from the blood, bone marrow, and spleen are fundamental to immunosurveillance, and tumor cell dissemination both in terms of barrier function and growth-promotion in regional lymph nodes. The phenomena of "tolerance", allotransplantation rejection, autoimmunity, spread of infection and micrometastasis are ultimately traceable to the ability and limitations of cellular migrant streams such as lymphocytes, "fixed" and circulating macrophages and other white cell elements to distinguish "self" from "non-self". In conjunction with the bone marrow, thymus gland, spleen, and endothelium (both blood vascular and lymphatic) the lymphatic system both generates and regulates humoral and cellular immunity including the complex trafficking of T and B lymphocytes and innumerable related immune subtypes. Why cancer cells of epidermal origin tend early to lymphogenous dissemination and those of non-epidermal origin to hematogenous spread is largely unknown, but a key controlling factor may reside in distinct endothelial receptors lining arteries, veins, spleen sinuses, hepatic sinusoids and lymphatic vessels entering and leaving lymph nodes. Although the partial pressure of oxygen in lymph and tissue fluid approximates that of venous blood (13), without hemoglobin, lymph's oxygen carrying capacity is only a small fraction of that of blood. Perhaps this characteristic enables anerobic bacteria and carcinoma cells which preferentially derive energy from pathways of anerobic glycolysis to gain a foothold in the relatively "hypoxic" tissue fluid microenvironment. Lymph, too, is normally devoid of erythrocytes and platelets and thus its clotting consists of a weak coagulum of fibrin rather than a true organized thrombus. Lack of these blood elements in the tissue matrix probably limits particle entrapment and therefore interstitial phagocytosis and thus may contribute to spread of bacterial infection (i.e., lymphangitis and cellulitis) or to migration of cancer cells to regional lymph nodes.

Other rare but sometimes highly lethal complications of lymphedema syndromes are vascular tumors. The exact origin of the endothelial malignancies (whether from lymphatics or blood vessels) is still uncertain, while a whole host of bizarre and poorly understood vascular hyperplasias, hamartomas, and "benign" tumors present variable and at times indistinguishable mixed components of blood and lymphatic vasculature (14).

In closing, it is appropriate to recognize that whereas Harvey of England "discovered" the blood circulation and Assellius of Italy the lymphatic circulation over 350 years ago, Nisimaru of Japan

(15) correctly emphasizes that the true circulation of the body is neither blood nor lymph but rather liquid or water, rapid in the bloodstream, and sluggishly in the tissue spaces and lymphatics. Throughout the animal kingdom, from the jelly-fish with its interstitium in direct equilibrium with surrounding ocean water, to man with highly compartmentalized extracellular fluid spaces, the constant replenishment of fresh water is paramount to survival. When blood flow fails, the manifestations are often immediate, self-evident, and potentially life-threatening. When the breakdown occurs in tissue fluid or lymph flow, on the other hand, the outcome though more subtle is no less inexorable, sometimes irreversible, and often equally devastating.

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REFERENCES

1. Bernard, C: *Readings in the History of Physiology*, Fulton, JF (Ed.), C.C. Thomas, Springfield, Illinois (1930), 307.
2. Witte, CL, M Brewer, MH Witte, et al: Protean manifestations of pylethrombosis. Ann. Surg. 202 (1985), 191.
3. Reichert, FL: The regeneration of the lymphatics. Arch. Surg. 13 (1926), 871.
4. Halsted, WS: The swelling of the arm after operations for cancer of the breast--elephantiasis chirurgica--its cause and prevention. Johns Hopkins Hosp. Bull. 32 (1921), 309.
5. Edwards, EA: Recurrent febrile episodes and lymphedema. J. Am. Med. Assoc. 184 (1963), 102.
6. Danese, CA, M Georgalas-Bertakis, LE Morales: A model of chronic postsurgical lymphedema in dogs' limbs. Surgery 64 (1968), 814.
7. Olszewski, W: On the pathomechanism of development of postsurgical lymphedema. Lymphology 6 (1973), 35.
8. Clodius, L, J Altofer: Experimental chronic lymphostasis of extremities. Folia. Angiol. 25 (1977), 137.
9. Witte, CL, MH Witte: Lymphatics in pathophysiology of edema. In *Experimental Biology of the Lymphatic Circulation*, Johnston, MG (Ed.), Elsevier, Amsterdam, New York (1985), 165.
10. Witte, CL, MH Witte, AE Dumont: High flow failure of the lymph circulation. Vasc. Surg. 11 (1977), 130.
11. Witte, CL, MH Witte, AE Dumont: Pathophysiology of chronic edema, lymphedema, and fibrosis. In *Edema*, Staub, NC and AE Taylor (Eds.), Raven Press, NY (1984), 521.
12. Witte, CL, MH Witte: Portal hypertension. In *Physiology of the Intestinal Circulation*, Shepherd, AP, DN Granger (Eds.), Raven Press, NY (1984), 335.
13. Farrell, KJ, CL Witte, MH Witte, et al: Oxygen exchange in the mesenteric microcirculation of the dog. Am. J. Physiol. 236 (1979), H846.
14. Witte, MH, CL Witte: Lymphangiogenesis and lymphologic syndromes. Lymphology 19 (1986), 21.
15. Nisimaru, Y: Concept of the body fluid circulation. Hiroshima J. Med. Sci. 18 (1969), 61.

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