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SPECIAL ARTICLE:

Physiology 301 (Clinical Correlation Lectures): Lymph Formation > Lymph Absorption: The Formula of Edema

A Second Experiment in the Teaching of Lymphology to Medical Students

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In a previous issue of Lymphology (Lymphology 3 (1970), 59-61) we presented the syllabus of an elective course on the Lymphvascular System for senior medical students. In the new curriculum of the University of Arizona College of Medicine in Tucson, we are beginning even earlier by "injecting" lymph into the thinking of our freshman medical students in their first encounter with the vast array of clinical problems manifesting as edema. In the following lecture, given during the freshman physiology course, we have elaborated Starling's views, as developed and refined by lymphologists *Rusznyak, Foldi and Szabo,* into a unified concept of the pathophysiology, diagnosis, and treatment of edema. While much of this material is very familiar to lymphologists, we have been surprised at how unfamiliar it is to the vast majority of medical students and practicing physicians. Further details on the structure and function of the lymph circulation are provided throughout the medical curriculum and in great depth in the elective course on the Lymphvascular System for interested senior medical students.

Lymph formation > lymph absorption: The formula of edema

As tissue fluid resembles lymph in appearance and composition, tissue swelling and serous effusions were originally viewed as disturbances in the drainage of lymph. However, after *Starling* elucidated the forces governing the exchange of fluid across blood capillaries, attention turned to the blood circulation and away from the lymph circulation. Yet, *Starling* himself emphasized that transcapillary forces regulated primarily the rate of formation of lymph whereas "edema in all conditions represents an imbalance between lymph formation and lymph absorption. "Dropsy", he explained, denoted an abnormal accumulation of lymph in connective tissue spaces including serous cavities. These spaces normally contained a small amount of tissue fluid derived from plasma filtering through capillaries, and this fluid returned to the bloodstream through an elaborate network of lymphatics. In health, lymph production and lymph absorption were exactly in equilibrium. In dropsy, the balance between these two processes was upset.

Despite the simplicity and soundness of *Starling*'s reasoning, subsequent investigators striving to elucidate the phenomenon of edema have narrowed their focus to single forces (capillary hydrostatic or plasma oncotic pressure) or else endowed primary

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*Dr. M. Witte is currently recipient of a U.S.P.H.S. Career Research Development Award and has just completed tenure as an Established Investigator of the American Heart Association.

causative roles to organs such as the kidney or liver, remote from the edematous site. In the process, the general principle has been forgotten – that edema per se signifies a *local* imbalance between formation and absorption of lymph.

"Plasma" circulates throughout the extracellular space, rapidly in blood and sluggishly in tissues and lymphatics. The net flux of fluid out of blood capillaries into tissues (the volume of lymph formed) depends upon hydrostatic and oncotic forces on both sides of the capillary membrane and upon a filtration coefficient reflecting the "leakiness" and surface area of the filtering capillaries (Fig. 1).

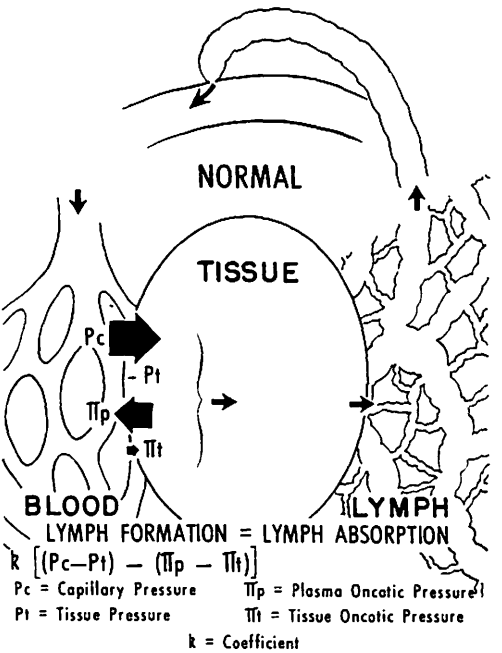

Fig. 1. Schematic diagram illustrating the normal balance between the processes of lymph formation and lymph absorption. The amount of lymph formed depends upon the gradient of hydrostatic pressure (Pc-Pt) and oncotic pressure (πp-πt) between blood (p) and tissues (t) and upon the filtration coefficient (k). An equivalent volume of lymph is absorbed into the lymphatic system and returns to the bloodstream.

The magnitude of these mechanical forces and the value of the filtration coefficient vary widely throughout the body. For example, in hepatic sinusoids, the discontinuous endothelial lining is almost freely permeable to plasma protein and perfusion derives mainly from portal venous blood entering under low pressure. Unrestrained by significant oncotic pressure gradient in the direction of the capillary lumen, fluid flux is exquisitely sensitive to changes in capillary hydrostatic pressure and hepatic lymph production sharply increases with small increments in sinusoidal pressure. This unique feature of the hepatic microcirculation is dramatically portrayed during right heart failure as the rapidly enlarging liver siphons off fluid from the venous circulation. For the moment, the failing heart and the rest of the body are protected from the dangers of acute congestion.

In contrast, peripheral capillaries exhibit higher hydrostatic pressure and are relatively impermeable to plasma protein. Tissue oncotic pressure, accordingly, is low and oncotic gradient between plasma and tissues high. A moderate rise in capillary pressure (as during assumption of the erect position) enhances salt and water filtration, and thereby widens the oncotic gradient and offsets the capillary hypertension. In addition, a reduction in arterial inflow (Bayliss phenomenon) with compensatory rise in peripheral vascular resistance takes place, correspondingly reducing the surface area of filtering capillaries. Further sustained restriction to venous flow, however, eventually increases capillary transudation and lymph flow rises.

Excess capillary filtrate not reabsorbed into veins enters lymphatic channels. Lymph

is propelled onwards from the initial lymphatics into major lymphatic trunks and slowly empties into veins thereby offsetting continued loss of plasma from blood capillaries.

The process of lymph formation can be roughly assessed by measurements of venous pressure (as an approximation to capillary pressure) and tissue hydrostatic pressure (Guyton capsule or needle) and colloid osmotic pressure of plasma and regional lymph, tissue or edema fluid (direct osmometry or calculated from protein composition of the fluids). The filtration coefficient is estimated from experimentally determined normal values for the organ; changes in the coefficient are generally reflected in shifts in organ blood flow (measured by extraction techniques or flowmeters) and varying levels of capillary "leakiness" by alterations in tissue and lymph protein levels. Capillary filtration can be estimated directly in accessible regions such as the limbs by plethysmography.

Lymph absorption, on the other hand, can be studied directly by uptake and transport of protein-bound materials (radiolabeled or colored) and by introduction of opaque media into tissues (indirect lymphography) or directly into lymphatic channels (direct lymphangiography). Cannulation of regional lymph trunks or large lymphatic collecting channels such as the thoracic duct permits direct measurement of lymph flow rate. As lymph formation and lymph absorption normally are precisely balanced measurements of lymph flow accurately reflect the amount of lymph formed. In fact, *Starling* acknowledged that the strongest argument favoring his Filtration Hypothesis was the predictable effects on thoracic duct lymph flow after altering capillary hydrostatic and plasma oncotic pressures.

The clinical appearance of edema signifies that lymph formation has exceeded lymph absorption at the edematous site. This situation may arise either from a "high-output" or "low-output failure" of the lymph system. When lymph formation increases and lymph drainage although enhanced fails to keep pace, a "high-output failure" exists (Fig. 2). Elevated hydrostatic pressure, decreased plasma oncotic pressure, enhanced surface area of filtering capillaries and increased capillary permeability associated with high tissue oncotic pressure each enhance the formation of lymph. Elevated capillary pressure may be generalized, as in congestive heart failure, or regional, as in the splanchnic bed in portal hypertension of hepatic cirrhosis or in the lower extremity in phlegmasia cerulea dolens. Hypoproteinemia with reduced plasma colloid pressure follows profound albumin loss into the digestive tract (protein-losing enteropathy) or urine (nephrotic syndrome) or decreased hepatic synthesis of albumin (kwashiorkor). Breakdown of capillary permeability associated with enlarged capillary surface area and raised tissue oncotic pressure is characteristic of thermal burns, peritonitis, trauma, and histamine-like drugs. Although these disturbances greatly increase lymph formation, they are not invariably accompanied by edema. Regional or thoracic duct lymph flow is stimulated by experimental plasmapheresis, ligation of the femoral vein or pampiniform plexus, constriction of the portal vein or supradiaphragmatic inferior vena cava. Yet, anasarca, peripheral edema, scrotal swelling or ascites do not necessarily follow. Similarly, patients with hepatic cirrhosis and portal hypertension, often associated with lower plasma albumin levels, uniformly manifest abnormally high flows of thoracic duct lymph but do not invariably exhibit ascites or peripheral edema. As *Starling* recognized, "the organism has various powers of accomodating itself to changed conditions in the lymphatic apparatus so that it is in most situations difficult to upset the normal balance,

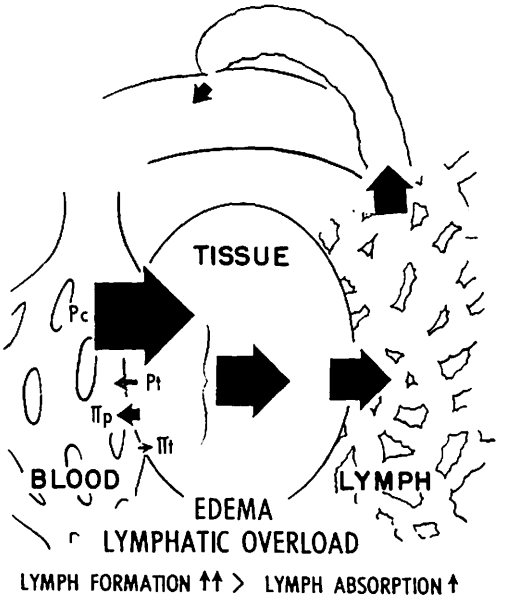

Fig. 2. Schematic diagram illustrating the situation when edema derives from lymphatic overload or "high output failure" of the lymph circulation. Increased amounts of lymph are formed most commonly from increased capillary hydrostatic pressure but also occasionally from reduced plasma oncotic pressure, altered filtration coefficient with greater surface area for filtration, enhanced capillary permeability and increased tissue oncotic pressure. Lymph absorption also rises but does not keep pace with the rate of lymph formation. See text for detailed explanation and Fig. 1 for meaning of symbols.

that is to cause 'dropsy' by altering only one of the factors unless the alterations be of a very extreme degree. In nearly all cases we shall find that dropsy is due to the simultaneous alteration of two or more of these factors and finally, to a failure of the lymph circulation to continue to handle the tremendous volume of fluid."

Edema may also arise during "low-output failure" of the lymph circulation and is then referred to as "lymphedema" (Fig. 3). In this situation, transcapillary fluid exchange and lymph formation are essentially undisturbed. It is the process of lymph absorption that is defective. Although complete obstruction to lymphatic drainage is difficult to reproduce in animals because of the extraordinary capacity for lymphatic regeneration and collateral pathways, extensive neoplasia, chronic inflammation or congenital hypoplasia or aplasia of the lymphatics commonly manifest as edema or effusion. Defective lymphatic drainage (typified in the "milk leg" of *Milroy*'s disease and the elephantine extremity of African filariasis) can be demonstrated on lymphangiogram. Obliteration of abdominal lymphatics (as in widespread cancer, tuberculosis and *Whipple*'s disease) is reflected in reduced flow of lymph from the cannulated thoracic duct.

It is readily appreciated that obliterated or congenitally deficient lymphatics cannot transport lymph effectively, but it is unclear what factors limit maximal lymphatic absorption when there is an excessive production of lymph. Propulsion of lymph is a poorly understood phenomenon dependent upon intrinsic lymphatic contractility as well as respiratory movement and other muscular activity, transmitted arterial pulsations, and cyclic changes in intrathoracic and intraabdominal pressure. Yet the lymphatic apparatus can nonetheless keep pace with enormous increases in lymph formation. For example, the flow of lymph from the cannulated thoracic duct in patients with hepatic cirrhosis without ascites may exceed 15 liters per day, a figure closely approximating estimates of normal whole body capillary filtration, all but one liter of which is normally reabsorbed directly into the venous system. On the other hand, different patients with cirrhosis manifest massive ascites with thoracic duct lymph flow rates of 4 liters per day or less.

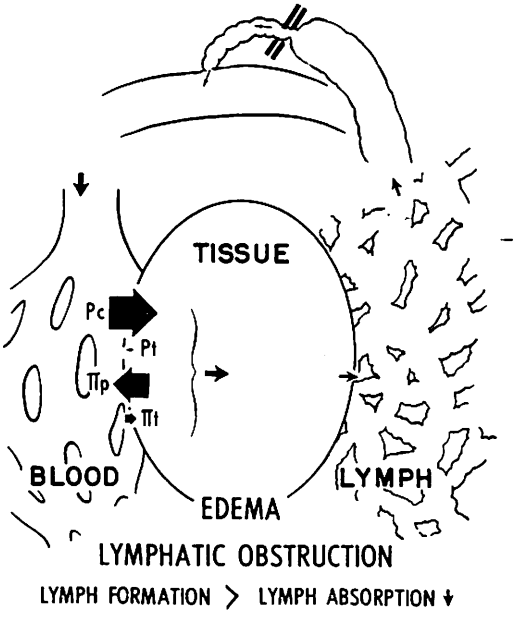

Fig. 3. Schematic diagram illustrating the situation when edema derives from lymphatic obstruction or "low-output failure" of the lymph circulation. Here, the process of lymph formation is essentially undisturbed but a reduced amount of lymph is absorbed into the lymphatic apparatus and returned via this route to the venous system. The defect may lie anywhere in the lymphatic system from the tissues to the main lymphatic trunks. See text for detailed explanation and Fig. 1 for meaning of symbols.

Lymph also flows rapidly from the cannulated thoracic duct in patients with advanced cardiac failure, but lymph flow in situ may be stagnant when the disease reaches this stage. *McMaster* observed that colored vital dyes injected subcutaneously into edematous legs of patients with heart failure entered widely dilated, richly intercommunicating lymphatic channels but failed to show "streamer" formation or forward flow. Instead, coloring matter pooled in lymphatics, extravasated into tissues and even flowed retrograde. Great dilatation of the thoracic duct and its tributaries, ballooning of the duct as it approaches the venous junction, equilibration of thoracic duct lymph pressure and central venous pressure, and sluggish to and from motion of venous blood refluxing through the cervical lymph-venous junction further attest to generalized impairment to lymph flow in severe heart failure.

At least two major factors limit flow of thoracic duct lymph into the venous system – local resistance at the lymphatic-venous junction in the neck and systemic venous pressure itself. In patients and dogs with right heart failure, high systemic venous pressure impedes thoracic duct lymph flow even though lymph flow may be greater than normal for a given venous pressure. There is also an increase in thoracic duct "end pressure" (the highest level lymph can rise in an indwelling cannula), a value that probably represents the maximum force capable of propelling lymph onward. As lymph end pressure occasionally does not exceed the elevated subclavian venous pressure, the differential gradient for lymph flow may be almost nil. In contrast to patients with heart failure, systemic venous pressure is usually normal in patients with cirrhosis. However, the thoracic duct is similarly dilated proximal to the lymphatic-venous junction suggesting a pinchcock or sphincter impeding lymph drainage at this site. It is also reasonable to suspect that in both cirrhosis and heart failure overstretching of engorged lymphatic vessels impairs intrinsic contractility and thereby weakens propulsion of lymph. Lymph nodes and prelymphatic pathways are other suggested sites of resistance to increased flow of lymph. The passage of time allows the lymphatic system to adapt to increased volumes of lymph which might not be handled efficiently in the acute situation.

After lymph formation and lymph absorption are assessed, attempts are made to restore the balance between these two processes. Treatment of edema from "low-output failure"

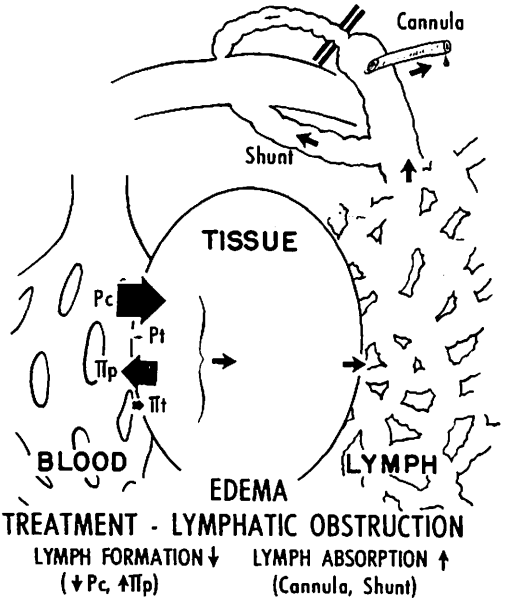

Fig. 4. Schematic diagram illustrating the approach to treatment of lymphatic obstruction or "low-output failure" of the lymph circulation. Usually efforts are directed to improve lymph absorption by removing or bypassing the obstruction or else providing more lymphatic channel pathways. Occasionally reduction of lymph formation to subnormal levels is also helpful. See text for detailed explanation and Fig. 1 for meaning of symbols.

of the lymph circulation (Fig. 4) is aimed at the difficult and often unsuccessful task of facilitating lymph drainage. Lymphatics are transposed into the local area and edematous tissue is shifted to sites where lymphatics are more plentiful. Lymph is propelled more vigorously through the use of mechanical compression or else evacuated periodically to the outside. Obstruction is relieved or bypassed by diverting sequestered lymph directly into the venous system through lymphatic-venous or lymph nodal-venous anastomoses. Efforts to reduce lymph formation below normal with the use of elastic stockings (increased tissue pressure), diuretic drugs, or dietary salt restriction (contraction of plasma volume and reduction in capillary pressure) only occasionally ameliorate "lymphedema".

In "high-output failure" of the lymph circulation, treatment usually aims to reduce lymph formation by decreasing capillary pressure, increasing plasma oncotic pressure, or restoring normal capillary flow and permeability, thereby decreasing the area of filtering capillaries (Fig. 5) and lowering tissue oncotic pressure. The inotropic action of digitalis, corrective cardiac surgery, contraction of plasma volume by dietary salt and water restriction and diuretic drugs work together to lower venous pressure in patients with heart failure. As a result, lymph formation falls and edema fluid is reabsorbed. Similarly, in patients or dogs with ascites from hepatic venous outflow block, thoracic duct lymph formation falls sharply after splanchnic capillary pressure is reduced either by administration of diuretic drugs or operative portal decompression, and ascites diminishes or disappears. In patients with protein-losing enteropathy, nephropathy or kwashiorkor, appropriate administration of antibiotics, steroid drugs, or essential amino acids restores plasma protein levels and hence effective plasma oncotic pressure. When disruption of capillary integrity is the primary problem, "noxious stimuli" are counteracted (anti-histaminic agents) or eliminated (debridement) to facilitate removal by lymphatics of excess tissue proteins, thereby restoring the normal oncotic pressure gradient between plasma and tissues. In turn, therapy of edema can be gauged by its ability to reduce the abnormal forces promoting excess lymph or, alternatively, to diminish lymph flow. If the imbalance between lymph formation and lymph absorption is unaffected, treatment is not likely to succeed.

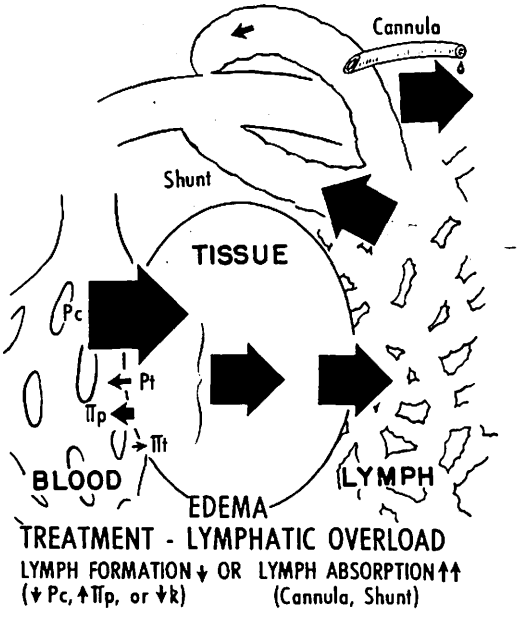

Fig. 5. Schematic diagram illustrating the approach to treatment of lymphatic overload or "high-output failure" of the lymph circulation. Usually, treatment is designed to reduce excessive lymph formation by correcting abnormal transcapillary forces. Alternatively, lymph absorption can be enhanced to keep pace with the imcreased lymph formation. See text for detailed explanation and Fig. 1 for meaning of symbols.

Although conventional treatment of "high-output failure" of the lymph circulation usually aims to reduce lymph formation, efforts may also be directed at enhancing lymph absorption to match the high rate of lymph formation (Fig. 5). Insertion of Southey tubes into the swollen legs of a patient with the postphlebitic syndrome, abdominal paracentesis with or without ascitic fluid reinfusion in hepatic cirrhosis, and external drainage of the thoracic duct in anasarca from cardiac failure, effectively augment the capacity of the patient's own lymphatic apparatus. In dogs with constriction of the thoracic inferior vena cava, ascites disappears when splanchnic lymph flow is enhanced by several liters per day after diversion of the thoracic duct into low pressure intrathoracic veins. In patients with hepatic cirrhosis and in dogs with thoracic inferior vena caval constriction, massive ascites may also be relieved by enlargement of the cervical thoracic duct-venous junction. In dogs with isolated right heart failure from pulmonic stenosis and tricuspid insufficiency, diversion of the thoracic duct beyond the high pressure central veins into low pressure pulmonary veins or the left atrium greatly facilitates lymph flow. Salt and water excretion by the kidney rises and ascites diminishes.

Therefore, the chain of events promoting edema during "high-output failure" of the lymph circulation can be interrupted by further enhancing lymph drainage. Renal salt and water retention, the phenomenon responsible for the development of progressive massive edema, results only indirectly from the damaged heart valve or the cirrhotic liver. The immediate stimulus arises and persists from the discrepancy between the volume of plasma leaving the circulation and the volume returning via the lymphatic apparatus. While positive balance of salt and water transiently replenishes the circulating plasma volume, the mechanical imbalance promoting the initial increase in lymph formation is reinforced. A vicious cycle ensues and edema progresses.

Thus, the patient with edema is the victim of a disturbance in the circulation of extracellular fluid. In some instances, the physician may recognize the nature of this disturbance – whether a high- or low-output failure of the lymph circulation – by a simple bedside examination. Or it may require highly sophisticated measurements of the forces on both sides of the capillary membrane, analysis of the properties of the capil-

lary membrane itself, or examination of the dynamics of lymph absorption. Once the nature of the imbalance between lymph formation and lymph absorption is understood, appropriate treatment can be sought and then evaluated by its ability to return these processes into balance. Until this information is available, it is misleading to invoke hypothetical and illusory factors to explain the peculiar anatomic distribution, spontaneous remission, or failure of therapy in edematous states. As *Starling* reproached the secretagogue exponents of his day, "I would point out at the onset that we are not justified in assuming an unknown cause so long as the phenomenon can be explained by a cause which is familiar to us. To call in vital activities as a sort of irresponsible deity to explain irregularities in our experimental results is an unscientific and I might say cowardly device."

Illustrative Material

Photographs of patients and experimental animals are presented to illustrate the varied appearance and distribution of edema. Edema fluid samples are examined for gross appearance and total protein content determined on the refractometer (American Optical T/S Meter) by students.

I. "Low-output failure" of the lymph circulation
   A. Congenital
      1. Dog – Lymphedema of the hindlimbs
      2. Patients – Lymphedema praecox (lymphangiogram of involved lower extremity)
   B. Acquired
      1. Dogs
         a. Lymphedema of hindlimb from lymphatic sclerosis and lymphadenectomy
         b. Lymphedema of hindlimb following amputation and reimplantation
      2. Patients
         a. Lymphedema of face and tongue following bilateral radical neck dissection and radiotherapy for carcinoma of the pharynx (injection of tongue with patent blue)
         b. Elephantiasis of scrotum and lower extremities from filariasis

II. "High-output failure" of the lymph circulation
   A. Increased capillary hydrostatic pressure ($\uparrow P_c$) with and without reduced plasma oncotic pressure ($\downarrow \pi p$)
      1. Dogs
         a. Ascites secondary to supradiaphragmatic inferior vena cava constriction
         b. Ascites secondary to dimethylnitrosamine-induced hepatic cirrhosis
      2. Patients
         a. Ascites secondary to Budd-Chiari syndrome (thrombosis of hepatic veins)
         b. Ascites secondary to alcoholic cirrhosis
         c. Upper extremity edema from axillary vein thrombosis
         d. Lower extremity edema from congestive heart failure
   B. Increased filtration coefficient ($\uparrow k$) (increased capillary surface area and permeability with increased tissue oncotic pressure) ($\uparrow \pi t$)
      1. Rabbit – paraphenylenediamine-induced oropharyngeal glottic edema
      2. Patients
         a. Thermal burn of hand
         b. Facial edema from trauma
         c. Laryngeal edema from hereditary angioneurotic edema

III. "*Unknown*" for student analysis:
   Case history: Male infant was born two months premature with massive ascites, scrotal and bilateral lower extremity edema. A sample of edema fluid aspirated from the leg was pale yellow and crystal clear; protein content was 2.5 mg%. Protein content of ascitic fluid was 3.0 mg% and that of blood plasma 4.5 gm%. Central venous pressure was normal.
   Analysis: High protein peripheral edema fluid in the absence of inflammation strongly suggests inadequate lymphatic drainage ("low output failure") of the lymph circulation.

Further studies: Injection of patent blue into dorsum of both feet failed to reveal any lymphatic channels. Dye persisted without streamer formation for 48 hours although a similar injection into the dorsum of the hand led to rapid streamer formation and visualization of axillary lymph nodes. Post-mortem examination revealed congenital lymphedema of the lower extremities in addition to widespread abdominal visceral lymphangiectasia involving the intestine, pancreas, and liver.

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BOOK REVIEW

Micu, D.: Cellular Pathology of the Lymphoid Organs. 1972. 223 pp., 122 figs. (Idelson Publ. House, Naples.) Cloth

The great and complex activity of the lymphocyte and particularly the important role played by this cell in the defense reactions of the organism have been gradually demonstrated and in the last two decades the medical literature regarding the physiology and pathology of the lymphoid organs has been considerably enriched by numerous papers and some monographs. Among the latter Dr. Micu's book, recently published by the Idelson Publishing House, Naples, is a valuable contribution to progress in this field.

As it is said in the introduction the first concern of the author "was to prune the existing knowledge of most of the older data overgrown with luxuriant morphologic descriptions that have gradually proved to be but partly useful". In this respect it should be emphasized that based on his wide personal experience the author has succeeded to blend harmoniously the still valid older data with the new ones of cytochemistry, cytoenzymology, cytoimmunology, cytogenetics and tissue cultures. Among the latter Dr. Micu's personal investigations as well as those carried out in collaboration with other authors over a period of more than twenty years of activity in this field, hold an important place.

Some of the diseases of the lymphoid organs whose cytology is studied by the author are: acute and chronic inflammations, giant follicular lymphoma, reactive or malignant reticulosis, reticulum cell sarcoma and lymphosarcoma, acute and chronic leukemias, Hodgkin's disease, Waldenström's