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# Lymphatics: Future Perspectives Unrealized Potential

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**Abstract:** Proposed fundamental laws of biology and a model of health and disease underscore the importance of the lymphatic system. The lymphatics are responsible for two of the laws of biology and the fulcrum of health and disease balancing regeneration with degeneration through the immune system. It is responsible for protection from the environment and repair of senile and damaged tissue. Life is constantly bombarded by forces that increase entropy. Lymphatics provide negative entropy to maintain health. Lymphatics help maintain cellular homeostasis removing products of metabolism. Using these principles, the role of lymphatics is investigated in salt sensitivity hypertension, cardiorenal system, the new pillar of heart failure and kidney disease—Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors, and brain diseases. The realization of organ lymphatics in maintenance of health and disease opens the avenue to new therapeutics. This is the unrealized potential of lymphatic study.

**Keywords:** lymphangiontrope; salt sensitivity; cardiorenal syndrome; SGLT2 inhibitors; Down's syndrome; depression; schizophrenia; C Reactive Protein

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**Citation:** Houck, P.D.; Dandapantula, H.K.; Massey, J.M. Lymphatics: Future Perspectives Unrealized Potential. *Lymphatics* **2023**, *1*, 87–96. https://doi.org/10.3390/lymphatics1020009

Academic Editor: Varsha Gandhi

Received: 30 April 2023
Revised: 25 May 2023
Accepted: 23 June 2023
Published: 3 July 2023



## 1. Introduction

Science is a collection of fundamental laws of nature and models incorporating these laws. Models predict outcomes such as the loading conditions on a bridge. These same laws determine the reason for failure. Biology lacks the organization of science; restricted to observation. Without fundamental laws, disease states representing the failure of health are often a mystery. The lymphatic system is difficult to observe, and thus little information is available on how this system can affect disease. Therapeutic manipulation of extremities by massage and lymphedema pumps is successful in relieving pain and loss of function. Enhancing lymphatic function in individual organs to compensate for disease is lacking. Knowledge gained in this area has unrealized potential, opening new avenues of disease management.

The lymphatic system is an open vascular system communicating with the environment. Protection from the environment is one of its many functions. The immune system with all of its complexities is a derivative of lymphatic system and must be considered as part of unrealized therapeutic targets of the lymphatic system. The author has proposed fundamental laws of biology and a model of health and disease [1]. The laws and model of health and disease is still subject to debate. To date, no exceptions to this model have been proposed. The laws and models identify the lymphatic system as a kingpin in the science of life processes. Inflammation serves as the fulcrum balancing degeneration and regeneration, Figure 1. The importance of the lymphatic system is demonstrated by having a dedicated fundamental law of nature, law 5 Table 1: "5. There must be a distinction between self and the environment. (Immunity and inflammation are defenses against invaders from the environment and are responsible for repair of damaged and senile cells.)". The filtering of the interstitial space maintaining homeostasis is implicated in Law 4 Table 1 "4. The cell must be in homeostasis with its environment". Removal of cellular debris, products of metabolism and reparative ability also implicates the role of

lymphatics in maintaining low entropy Law 2 Table 1: "Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos (The energy to support negative entropy is yet to be defined.)".

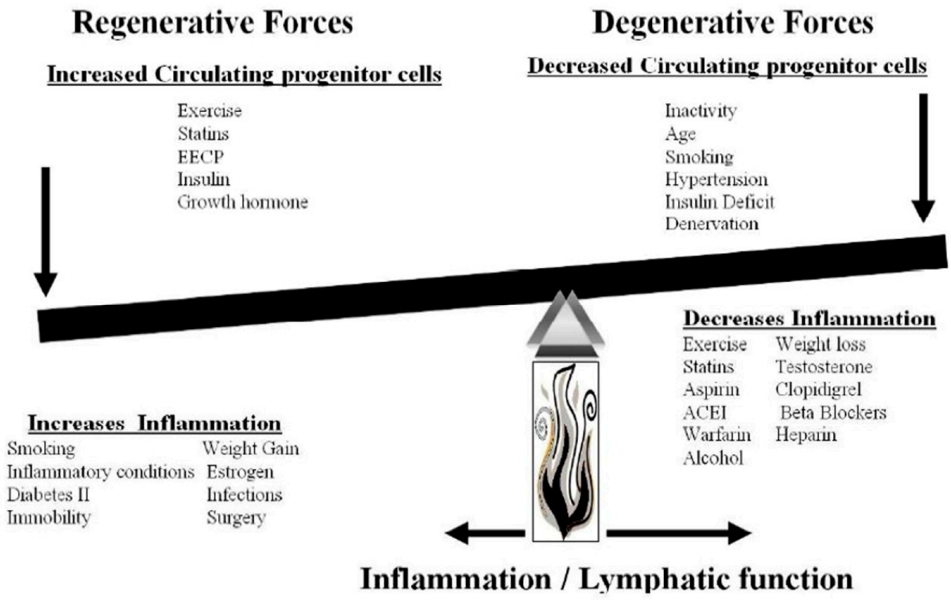


**Figure 1.** Model of Health and Disease. Adapted from [1], with the permission from Elsevier.

**Table 1.** Fundamental Laws of Nature [1].

| **Fundamental Laws of Nature** |
|---|
| 1. Biology must be consistent with the fundamental laws of physics and chemistry. |
| 2. Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos. (The energy to support negative entropy is yet to be defined.) |
| 3. The cell is the fundamental unit of biology. |
| 4. The cell must be in homeostasis with its environment. (This property allows evolution. The environment changes life.) |
| 5. There must be a distinction between self and the environment. (Immunity and inflammation are defenses against invaders from the environment and are responsible for repair of damaged and senile cells.) |
| 6. Electromagnetic information transfer is necessary for development and regeneration. (Life, with regeneration of tissue, cannot exist in a non-electromagnetic environment, hence denervation) |

Evolution into multicellular creatures required circulation and protection from microbial environment. Four hundred eighty million years ago, insects evolved with an open system. The open circulation system predated the dinosaurs 200 million years and humans who have only been around for 200 to 300,000 years. Larger animals now have a closed circulatory system and an open system that protects them from the microenvironment. The insect gift of open circulation must still be inscribed in our DNA. It has not been identified. The sequence needs to be identified.

Lymphatics is the disregarded circulatory system that is responsible for 12 L of interstitial fluid movement in the central circulation every 24 h [2]. The lymphangion is a valved pumping chamber similar to a single ventricle. The pump reacts to electrical, hormonal and loading condition adjusting the flow of lymph by changing the frequency and amplitude of contraction. The tone of the collecting ducts also affects flow as does the central venous pressure. Hormonal receptors abound in this system making it an integral in circulation homeostasis. One purpose of the lymphatic system is to return tissue fluid

that has exited the capillaries back to the central circulation. Cellular debris, immune cells, reparative stem cells, proteins, dietary fats are just a few of the passengers that ride with the interstitial fluid traveling the lymphatic highway to the central circulation. Protection from the environment, immunity, aiding repair, managing senescent cells are biologic activities of the underrated lymphatic vascular system.

The study of this system is limited to animal models, usually the mesenteric system, thoracic duct, and skin where video microscopy reveals change in function to various stimuli. Tables from the following article demonstrate "lymphangiontrope", an invented term, to illustrate that lymphatic function can be increased or decreased [3].

The table illustrates positive and negative Lymphangiontrope. It should be noted that age is the greatest risk factor for heart failure and is associated with negative lymphangiontrope. The medications used to treat heart failure have positive lymphangiontrope. Heart failure medications are used to improve cardiac hemodynamics and blood vessel properties. These same medications have a dual role in improving lymphangiontrope. The patient with a failing closed circulation can be compensated by enhancing the lymphatic open circulation.

Lymphedema is primarily a failure of the lymphatic system, usually a structural or obstructive lesion. In cardiogenic edema the lymphatic system is overwhelmed and fails to compensate for the closed circulatory system. Both conditions can be enhanced by improving the function of structurally sound lymphangion. Cell therapy and pharmacotherapy are on the horizon [4].

Lymphatics function is not considered a target of intervention. Medications, enhancing lymphatic function, along with mechanical unloading, electrical stimulation all could be new therapeutic targets. Possible lymphatic role in salt sensitivity, cardio-renal syndrome, sodium dependent glucose transporter, and brain disease, will be proposed.

## 2. Salt Sensitivity and Hypertension

Sodium is a major driver of hypertension and epidemiologic studies demonstrate that with the greater ingestion of salt the higher the population's blood pressure [5,6]. Hypertension is a major contributor to cardiovascular events. The events increase above a systolic pressure of 115 mmHg. Treatment is recommended above 120 mmHg systolic with lifestyle measures and drug therapy above 130 mmHg systolic [7]. Current Dietary studies involving precise measurements of intake and output of sodium were never equivalent with some individuals, over the three days of the study, accumulating more salt than excreted or vice versa [8]. Individuals demonstrate a wide range of responsiveness to salt loaded hypertension or hypotension due to failure to retain sodium. Some patients have their blood pressure controlled with diuretic management. Other patients experience hypotension, reactive hypertension, hypovolemic, hyponatremic or have orthostatic syncope with diuretic therapy. The term salt sensitivity was coined to explain the differences between individuals. Unfortunately, patients are not characterized in this important determinant before initiating therapy. The measure of sodium balance is a difficult undertaking. There is no simple test to determine sodium sensitivity. Therefore, patients are not characterized by the type of hypertension relative to sodium sensitivity.

Two recent studies [9,10] report an explanation for individual differences in salt balance implicating tissue storage of sodium. The previous two compartment model of intracellular and extracellular sodium storage and kidney dominance is incorrect with three compartments now explaining salt sensitivity, response to diuretic therapy and hyponatremia.

Endothelium is the largest collection of cells in the body. The lymphatic system composed of endothelial cells is exposed to the environment of salt ingestion and certainly must be specialized in sodium storage. As life crawled out of the oceans with previously free access to sodium and water; adaptation to conserve salt and water was necessary. Survival in an environment without salt and water requires conservation. This ability to store sodium was shown in the skin of rats [11]. The lymphatic system's unique position modifying dietary salt and water homeostasis makes it a target to develop new therapies

for hypertension. Perhaps imaging the sodium storage in the skin could select individuals for diuretic therapy and more importantly select individuals who would be harmed by diuretics.

## 3. Cardio-Renal Syndrome

Until recently, cardio-renal syndrome has been unexplained. The notion is heart failure and the kidney ware connected with the failure of one causing failure in the other. The reason for this evil synergy was not known. Salah [12] demonstrated the physiology can be explained by overtasked renal lymphatics causing a kidney tamponade. The actual cause of the dysregulation of the renal cortical lymphatics was not elucidated. Central venous pressure elevation is a primary determinant and reduces the flow from the thoracic duct putting back pressure on the lymph circulation.

Patients typically present with heart failure and may have normal or mildly elevated creatinine. Attempt at diuresis with loop diuretics to decongest the patient is either successful or results in in a rise in creatinine and diuretic resistance. The cardio-renal patient has the diuretic discontinued and inotropic support is initiated with dobutamine, milrinone, or dopamine. In several days the creatinine is improved and the patient successfully has diuresis with the re-introduced loop diuretics. Heart failure specialists use these inotropic agents in the belief that increasing heart contractility will improve renal function. These agents help restore lymphatic function by increasing the amplitude and frequency of the lymphangion. This restores the compensatory function of the lymphatic system for a volume overloaded systemic system. The hypothesis is loop diuretics produce negative lymphangiotrope causing lymphatic stress with interstitial kidney edema and renal tamponade.

The concept of positive and negative lymphangiotrope involves a medication, mechanical, electrical, molecular, cellular stimuli to enhance or hinder the performance of the lymphangion. The lymphangion is pivotal; having a role of producing edema in the early stages of infection to keep the offenders from spreading to other parts of the body and then has to switch to removing the excess tissue edema. The Tables in Figure 2 of lymphangiotrope illustrate some interventions in animal models. The medication most promising was Nesiritide an analogue of brain natriuretic peptide. Giving this medication prior to loop diuretics could prevent cardio-renal syndrome increasing the function of renal cortical lymphatics. Sadly, the medication is no longer available. The medication was studied for acute decompensated heart failure. The doses utilized resulted in excess preload reduction and renal insufficiency. Using one-half the recommended dose without the bolus allows renal decongestion due to stimulation of the lymphangion and improved diuresis compensating heart failure. This same dose may be advantageous in other diseases of lymphatic insufficiency such as adult respiratory distress syndrome ARDS, edema removal after an inflammatory process, brain edema, depression, schizophrenia, and other disease entities that reflect reduced lymphatic function.

### *A Blind Squirrel Finds a Nut—Sodium Dependent Glucose Transporter*

Receptors for sodium-dependent glucose transporters are found in the small intestine and in the kidney [20]. Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors are the newest pillar for heart failure therapy [21]. The drug was not sought; but, serendipitously discovered due to the requirement that all new diabetic medications have to have cardiovascular safety evidence. The drug in the diabetic population had reduced incidence of heart failure. Initially the drug was felt to improve heart failure by glucose-mediated diuresis. This mechanism is not the likely reason for benefit since trials have been performed in non-diabetics with equally good results without the requirement of elevated glucose. The drug is renal protective and reduces proteinuria. The receptors are in the gut and kidney.

The lymph processes the gut nutrition, water, electrolytes, sodium, and glucose. Assigning the benefit of SGLT2 inhibitors as having positive lymphangiotrope is a theory that can be tested by lymphatic researchers. The blind squirrel should look to the lymphatic

system to find other new agents reflecting positive lymphangiotrope. These agents will improve the care of decompensated heart failure.

**Table 1 Lymphaniontrope under various stimuli**

| Medication/ Intervention | Amplitude | Frequency | Tone | Model |
|---|---|---|---|---|
| Prostanoids | | | | |
| PGF2a | ↑ | ↑ | ↑ | Bovine, Ovine |
| PGH2/TXA2 | ↑ | ↑ | | Canine, Porcine |
| PGE1 and PGE2 | ↑→ | ↓ | | Rat, Guinea Pig |
| PGI2 | ↑→ | | | Pig mesentery |
| Histamine H1 H2 | | ↑ | | Bovine |
| Nitric Oxide | ↓ | ↓ | ↓ | Bovine, Mouse, and Rat (mesentery and thoracic |
| LDL | ↑ | ↑ | ↓ | |
| Aging | ↓ | ↓ | ↓ | Rat mesentery |
| Neuropeptide substance P Gastrin releasing peptide | ↑ | ↑ | | Rat (mesentery, thoracic duct, cervical |
| Aspirin | ↓ | ↓ | | Bovine Messentery |
| Electrical stimulation | ↑ | ↑ | | Bovine Messentery |
| Pentobarbitone Halothane | ↓ | ↓ | | Bovine Messentery |
| Ether | → | → | | Bovine Messentery |
| Endothelin | ↑ | ↑ | | Bovine Messentery |
| BNP ANP | ↑↑↑ | ↑↑↑ | | Unpublished data in rat mesentery |
| Furosemide | | | | |
| Spironolactone | | | | |
| ACEI / ARB | | | | |
| Beta Blockers | | | | |

**Figure 2.** *Cont.*

| | | | | |
|---|---|---|---|---|
| Acetylcholine | ↓↓↓ | ↓↓↓ | | Isolated canine thoracic duct |
| Isoproterenol | ↓↓ | ↓↓ | | Isolated canine thoracic duct |
| Adenosine | ↓ | ↓ | | Isolated canine thoracic duct |
| ATP | ↓ | ↓ | | Isolated canine thoracic duct |
| Epinephrine | ↑↑↑ | ↑↑↑ | | Isolated canine thoracic duct |
| Norepinephrine | ↑↑ | ↑↑ | | Isolated canine thoracic duct |
| 5 Hydroxy Tryptamine Serotonin | ↑ | ↑ | | Isolated canine thoracic duct |
| Acetylcholine | ↓↓↓ | ↓↓↓ | | Isolated canine thoracic duct |
| Isoproterenol | ↓↓ | ↓↓ | | Isolated canine thoracic duct |
| Adenosine | ↓ | ↓ | | Isolated canine thoracic duct |
| ATP | ↓ | ↓ | | Isolated canine thoracic duct |
| Epinephrine | ↑↑↑ | ↑↑↑ | | Isolated canine thoracic duct |
| Norepinephrine | ↑↑ | ↑↑ | | Isolated canine thoracic duct |
| 5 Hydroxy Tryptamine Serotonin | ↑ | ↑ | | Isolated canine thoracic duct |

**Figure 2.** Table of Lymphangiotrope [13–19]. Adapted from [3].

## 4. The Brain

The metabolism and structural function of the kidney is relatively simple as compared to the brain. The brain has a high blood flow requirement and is the more metabolically active. The preferred energy is simple glucose metabolism as opposed to ketones except when glucose is unavailable. Processing and storing information without introducing errors requires energy. Law 2 would label this energy as negative entropy. Generally, 20% of the blood flow and metabolism are devoted to the brain. As a result, metabolic byproducts have to be removed.

The glymphatic system recently recognized; and the well-known cerebral spinal fluid flushing the interstitial space has the role of garbage collector of all the metabolic leftovers. Ascribing brain diseases to the structural malfunction of this system is also an unrealized theory. Over the last 50 years, the most popular theory of mental disease, depression, and anxiety is an imbalance of neurotransmitters. Serotonin uptake inhibitors are the products of this model. Outside of this direction of drug development little progress has been made in brain diseases. Figure 2 is a table demonstrating serotonin and dopamine are both stimulants of lymphatic function. Perhaps there is no imbalance of neurotransmitters. The imbalance may be a failure to remove metabolic debris, so neurotransmitters fail. Thinking clearly is no longer possible due to the collection of metabolic garbage. Failure to remove metabolic byproducts increases the entropy of the brain. Failure to maintain order results in mental diseases.

The brain is excluded from the body by the blood brain barrier. This is another example of biology utilizing negative entropy, Law 2 "Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos. (The energy to support negative entropy is yet to be defined.)" The brain is sensitive to circulating organic molecules, un-authorized ions, or un-welcomed microbiomes. Foreign invaders will increase the

entropic state of the brain. The inflammatory system can cause breakdown of the blood brain barrier and predispose the brain to increased entropy. Delirium, ICU psychosis [22], depression [23], anxiety [24] schizophrenia [25], Down's syndrome [26], dementia [27], all have reduced intellectual potential with a common thread—elevated C Reactive Protein CRP. Elevated CRP is associated with inflammation and a generalized increased entropic state. Other common threads of increased entropy include age, sleep disorders, and metabolic syndrome [28].

With age, there is a decline in mental function and age is the greatest risk factor for dementia. Potential etiology has been demonstrated in a rat model. The amplitude and frequency of the lymphangion is reduced with age [29]. Furthermore, with age there is a disturbance of sleep. Obesity associated obstructive sleep apnea, metabolic syndrome, and many psycho-neurological diseases disturb sleep. Without sleep, the glymphatic system is unable to cleanse the metabolic products increasing the brain's entropic state. Dysfunction of the glymphatic system appears to be an etiologic agent linking mental diseases and reduction in intelligence in Down's syndrome [30]. The role of chronically elevated C Reactive Protein in mental disease is predictably complex. CRP has been given to rats and the mesenteric lymphangion demonstrates increased amplitude and frequency [31]. This finding is counter to the above theory and relates to the complexity of CRP.

Tissue injury is a potent stimulant to produce C reactive protein. Clinically there is a bi-modal response with an initial decrease in lymphatic function followed by edema of the tissues injured. Eventually to heal the injury the tissue edema must resolve, and progenitor cells delivered to replace apoptotic cells. CRP remains elevated for about a month after the insult. CRP exists in two forms native CRP (nCRP) which can dissociate into monomeric (mCRP). These isoforms have different biologic functions with nCRP isoform activating the classical complement pathway, inducing phagocytosis, and promoting apoptosis. Native CRP fulfills the role of initial response to injury. Monomeric CRP fulfills the healing phase by promoting the chemotaxis and recruitment of circulating leukocytes to areas of inflammation and can delay apoptosis promoting healing [32]. CRP is part of the fulcrum balancing regeneration with degeneration. CRP is a fulcrum itself promoting shifts from edema to healing.

Chronically elevated CRP has cardiovascular risk. It is implicated in mental health diseases, dementia, and predicts greater intellectual deficits in Down's syndrome. Chronic elevation of CRP can be seen in some races. The reason for chronic elevation is unknown and could be a normal function of ongoing tissue injury or could be an adverse response promoting tissue injury. Chronic CRP elevation may represent a biologic resistance similar to insulin resistance. The elevated CRP may have adverse effects on lymphatic function due to native CRP as opposed to monomeric CRP. More study into the type of CRP, disease states and the stimulation of the lymphangion is needed. The concept of resistance is emerging in multiple hormonal systems. Perhaps CRP elevation in disease states also represents a form of resistance.

Other links increasing C Reactive Protein include saturated fatty acids, bone metabolism including vitamin D deficiency and Parathyroid excess. Obesity through Leptin mediated pathways and other immune diseases contributes to elevations of C Reactive Protein and is associated with depression [33–35].

Lowering chronically elevated CRP levels with weight loss, exercise, statin medications, colchicine is clinically beneficial. Exercise, improved sleep, and weight loss are beneficial in both cardiovascular disease and mental health. These factors enhance lymphangion function. New therapies for mental health should be sought that enhance glymphatic function cleansing the central nervous system of adverse metabolic byproducts and reducing the entropic state of the brain [36].

## 5. Future Perspectives

Lymphatic function is pivotal in understanding disease processes. It is the fulcrum in the model of health and disease and the workhorse of Law 5 "There must be a distinction

between self and the environment. (Immunity and inflammation are defenses against invaders from the environment and are responsible for repair of damaged and senile cells.)" Lymphatics help maintain low entropy and cellular homeostasis by reparative function and filtering of metabolic and biologic debris deposited in the interstitial spaces. Law "Life, as opposed to non-living, exhibits negative entropy, developing order out of chaos. (The energy to support negative entropy is yet to be defined.)" Law 4. "The cell must be in homeostasis with its environment."

Failure of lymphatic function promotes decompensation in heart failure, reduces function in specific organs promoting renal failure, brain diseases, peripheral edema, salt sensitivity hypertension. The role of lymphatic dysfunction should be considered in every disease process.

The role of lymphatic function in repair processes needs better definition and should be considered a new target of intervention.

Maintaining low entropy to maintain health is a new concept in medical therapy and is a major function of the lymphatics and immune system. Identifying causes of increased entropy and enhancing lymphatic function will hasten recovery and decrease decline attributable to age.

Age is a disease of increased entropy and reduced lymphatic function.

Imaging both the circulatory and immune function of the lymphatics system will hasten our knowledge of this system by viewing interventions.

All drugs should be tested for lymphangiontrope. Standarization of a specific pharmacologic model, such as, the effect of the pharmaceutical on rat mesentery lymphangion amplitude and frequency should be established. Correlation of these effects in animals should be correlated to expected results in human trials. Continued search and validation of other lymphatic models reflecting human disease needs to accelerate.

The genetic information associated with lymphedema is under investigation and nicely outlined by Rockson [37]. Interspeicies genetic similarities have not been investigated. The genesis and potential repair mechanisms of the lymphatic system may be found in these genetic similarities. Determining the DNA sequence and gene promoters in other creatures such as insects will find new therapeutics for humans.

Immunology is part of the lymphatic system with Th1 and Th2 balance of the innate and the immune system. The lymphatic system delivers all these cells to targets of infection and repair. This system needs to be mapped with biomarkers that can identify repair mechanisms and excess activity [37–40].

Consider using CRP or one of its isomers as a therapeutic drug to enhance lymphatic function or to modify diseases that have elevated CRP.

Nesiritide should be restudied in heart failure as a subcutaneous injection with the use of a neprilysin inhibitor. This same agent should be studied in chronic kidney disease and brain disease to prove enhancement of lymphatic function is a therapeutic target.

The study of brain diseases needs a new target, besides neurotransmitters, the glymphatic system. BNP discovered in the brains of sheep used in heart failure could make a full circle and be used in the treatment of brain diseases.

## 6. Conclusions

The ignored lymphatic vascular system is a prime target for new interventions with unrealized potential.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References


1. Houck, P.D.; DeOliveria, J.M. Applying laws of biology to diabetes with emphasis on metabolic syndrome. *Med. Hypotheses* **2013**, *80*, 637–642. [CrossRef] [PubMed]
2. von der Weid, P.Y.; Muthuchamy, M. Regulatory mechanisms in lymphatic vessel contraction under normal and inflammatory conditions. *Pathophysiology* **2010**, *17*, 263–276. [CrossRef] [PubMed]
3. Houck, P.D. Alternative view of congestive heart failure exacerbations: Role of lymphatic function and inflammation. *OA Med. Hypothesis* **2013**, *1*, 6. [CrossRef]
4. Ogino, R.; Yokooji, T.; Hayashida, M.; Suda, S.; Yamakawa, S.; Hayashida, K. Emerging Anti-Inflammatory Pharmacotherapy and Cell-Based Therapy for Lymphedema. *Int. J. Mol. Sci.* **2022**, *23*, 7614. [CrossRef] [PubMed]
5. Weinsier, R.L. Overview: Salt and the Development of Essential Hypertension. *Prev. Med.* **1976**, *5*, 7–14. [CrossRef]
6. Filippini, T.; Malavolti, M.; Whelton, P.K.; Vinceti, M. Sodium Intake and Risk of Hypertension: A Systematic Review and Dose–Response Meta-analysis of Observational Cohort Studies. *Curr. Hypertens. Rep.* **2022**, *24*, 133–144. [CrossRef] [PubMed]
7. Jones, D.W.; Whelton, P.K.; Allen, N.; Clark, D., III; Gidding, S.S.; Muntner, P.; Nesbitt, S.; Mitchell, N.S.; Townsend, R.; Falkner, B. American Heart Association Council on Hypertension; Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Lifelong Congenital Heart Disease and Heart Health in the Young; and Stroke Council. Management of Stage 1 Hypertension in Adults With a Low 10-Year Risk for Cardiovascular Disease: Filling a Guidance Gap: A Scientific Statement From the American Heart Association. *Hypertension* **2021**, *77*, e58–e67. [CrossRef] [PubMed]
8. Schrauben, S.J.; Inamdar, A.; Yule, C.; Kwiecien, S.; Krekel, C.; Collins, C.; Anderson, C.; Bailey-Davis, L.; Chang, A.R. Effects of dietary app-Supported Tele-counseling on sodium intake, diet quality, and blood pressure in patients with diabetes and kidney disease. *J. Ren. Nutr.* **2022**, *32*, 39–50. [CrossRef]
9. Olde Engberink, R.H.G.; Selvarajah, V.; Vogt, L. Clinical impact of tissue sodium storage. *Pediatr. Nephrol.* **2020**, *35*, 1373–1380. [CrossRef]
10. Choi, H.Y.; Park, H.C.; Ha, S.K. Salt Sensitivity and Hypertension: A Paradigm Shift from Kidney Malfunction to Vascular Endothelial Dysfunction. *Electrolyte Blood Press* **2015**, *13*, 7–16. [CrossRef]
11. Karlsen, T.V.; Nikpey, E.; Han, J.; Reikvam, T.; Rakova, N.; Castorena-Gonzalez, J.A.; Davis, M.J.; Titze, J.M.; Tenstad, O.; Wiig, H. High-Salt Diet Causes Expansion of the Lymphatic Network and Increased Lymph Flow in Skin and Muscle of Rats. *Arterioscler. Thromb. Vasc. Biol.* **2018**, *38*, 2054–2064. [CrossRef]
12. Salah, H.M.; Biegus, J.; Fudim, M. Role of the Renal Lymphatic System in Heart Failure. *Curr. Heart Fail. Rep.* **2023**, *20*, 113–120. [CrossRef]
13. Thornbury, K.D. The effect of anesthetics on lymphatic contractility. *Microvasc. Res.* **1989**, *37*, 70–76.
14. Allen, J.M.; Burke, E.P.; Johnston, M.G.; McHale, N.G. The inhibitory effect of aspirin on lymphatic contractility. *Br. J. Pharmacol.* **1984**, *82*, 509–514. [CrossRef]
15. Sakai, H.; Ikomi, F.; Ohhashi, T. Effects of endothelin on spontaneous contractions in lymph vessels. *Am. J. Physiol.* **1999**, *277*, H459–H466. [CrossRef]
16. McHale, N.G.; Roddie, I.C.; Thornbury, K.D. Nervous modulation of spontaneous contractions in bovine mesenteric lymphatics. *J. Physiol.* **1980**, *309*, 46172. [CrossRef]
17. Foy, W.L.; Allen, J.M.; McKillop, J.M.; Goldsmith, J.P.; Johnston, C.F.; Buchanan, K.D. Substance P and gastrin releasing peptide in bovine mesenteric lymphatic vessels: Chemical characterization and action. *Peptides* **1989**, *10*, 533–537. [CrossRef]
18. Takahashi, N.; Kawai, Y.; Ohhashi, T. Effects of vasoconstrictive and vasodilative agents on lymphatic smooth muscles in isolated canine thoracic ducts. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 165–170. [PubMed]
19. Hashimoto, S.; Kawai, Y.; Ohhashi, T. Effects of vasoactive substances on the pig isolated hepatic lymph vessels. *J. Pharmacol. Exp. Ther.* **1994**, *269*, 482–488. [PubMed]
20. Wright, E.M.; Hirayama, B.A.; Loo, D.F. Active sugar transport in health and disease. *J. Intern. Med.* **2007**, *261*, 32–43. [CrossRef] [PubMed]
21. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **2022**, *145*, e876–e894. [CrossRef] [PubMed]
22. Macdonald, A.; Adamis, D.; Treloar, A.; Martin, F. C-reactive protein levels predict the incidence of delirium and recovery from it. *Age Ageing* **2007**, *36*, 222–225. [CrossRef] [PubMed]
23. Cepeda, M.S.; Stang, P.; Makadia, R. Depression Is Associated With High Levels of C-Reactive Protein and Low Levels of Fractional Exhaled Nitric Oxide: Results From the 2007-2012 National Health and Nutrition Examination Surveys. *J. Clin. Psychiatry* **2016**, *77*, 1666–1671. [CrossRef] [PubMed]
24. Liukkonen, T.; Räsänen, P.; Jokelainen, J.; Leinonen, M.; Järvelin, M.R.; Meyer-Rochow, V.B.; Timonen, M. The association between anxiety and C-reactive protein (CRP) levels: Results from the Northern Finland 1966 birth cohort study. *Eur. Psychiatry* **2011**, *26*, 363–369. [CrossRef]

25. Orsolini, L.; Sarchione, F.; Vellante, F.; Fornaro, M.; Matarazzo, I.; Martinotti, G.; Valchera, A.; Di Nicola, M.; Carano, A.; Di Giannantonio, M.; et al. Protein-C Reactive as Biomarker Predictor of Schizophrenia Phases of Illness? A Systematic Review. *Curr. Neuropharmacol.* **2018**, *16*, 583–606. [CrossRef]
26. Manti, S.; Cutrupi, M.C.; Cuppari, C.; Ferro, E.; Dipasquale, V.; Di Rosa, G.; Chimenz, R.; La Rosa, M.A.; Valenti, A.; Salpietro, V. Inflammatory biomarkers and intellectual disability in patients with Down syndrome. *J. Intellect. Disabil. Res.* **2018**, *62*, 382–390. [CrossRef]
27. Lewis, N.A.; Knight, J.E. Longitudinal associations between C-reactive protein and cognitive performance in normative cognitive ageing and dementia. *Age Ageing* **2021**, *50*, 2199–2205. [CrossRef]
28. Del Giudice, M.; Gangestad, S.W. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain Behav. Immun.* **2018**, *70*, 61–75. [CrossRef]
29. Gashev, A.A.; Zawieja, D.C. Hydrodynamic regulation of lymphatic transport and the impact of aging. *Pathophysiology* **2010**, *17*, 277–287. [CrossRef]
30. Christensen, J.; Glenn, R.; Yamakawa, G.R.; Sandy, R.; Shultz, S.R.; Mychasiuk, R. Is the glymphatic system the missing link between sleep impairments and neurological disorders? Examining the implications and uncertainties. *Prog. Neurobiol.* **2021**, *198*, 101917. [CrossRef]
31. Nepiyushchikh, Z.V.; Gashev, A.A.; Zawieja, D.C.; Heuertz, R.M.; Ezekiel, U.; Muthuchamy, M. Effects of C-reactive protein on rat mesenteric lymphatic contractility. *FASEB J.* **2006**, *20*, LB10–LB11. [CrossRef]
32. Rajab, I.M.; Hart, P.C.; Potempa, L.A. How C-Reactive Protein Structural Isoforms With Distinctive Bioactivities Affect Disease Progression. *Front. Immunol.* **2020**, *11*, 2126. [CrossRef]
33. Santos, S.; Oliveira, A.; Casal, S.; Lopes, C. Saturated fatty acids intake in relation to C-reactive protein, adiponectin, and leptin: A population-based study. *Nutrition* **2013**, *29*, 892–897. [CrossRef]
34. Pasupuleti, P.; Suchitra, M.M.; Bitla, A.R.; Sachan, A. Attenuation of Oxidative Stress, Interleukin-6, High-Sensitivity C-Reactive Protein, Plasminogen Activator Inhibitor-1, and Fibrinogen with Oral Vitamin D Supplementation in Patients with T2DM having Vitamin D Deficiency. *J. Lab. Physicians* **2021**, *14*, 190–196. [CrossRef]
35. Hribal, M.L.; Fiorentino, T.V.; Sesti, G. Role of C reactive protein (CRP) in leptin resistance. *Curr. Pharm. Des.* **2014**, *20*, 609–615. [CrossRef]
36. Braun, M.; Iliff, J.J. The impact of neurovascular, blood-brain barrier, and glymphatic dysfunction in neurodegenerative and metabolic diseases. *Int. Rev. Neurobiol.* **2020**, *154*, 413–436. [CrossRef]
37. Kidd, P. Th1/Th2 balance: The hypothesis, its limitations, and implications for health and disease. *Altern. Med. Rev.* **2003**, *8*, 223–246.
38. Hunter, M.C.; Teijeira, A.; Halin, C. T Cell Trafficking through Lymphatic Vessels. *Front. Immunol.* **2016**, *7*, 613. [CrossRef] [PubMed]
39. Hampton, H.R.; Chtanova, T. Lymphatic Migration of Immune Cells. *Front. Immunol.* **2019**, *10*, 168. [CrossRef] [PubMed]
40. Devaraj, S.; Jialal, I. C-reactive protein polarizes human macrophages to an M1 phenotype and inhibits transformation to the M2 phenotype. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1397–13402. [CrossRef] [PubMed]