

POSITIONED

- **Cardiovascular disease is a chronic degenerative immune system disorder (CDD) caused by inflammation.**
- **The lymphatics play a major role in the clearance of pro- inflammatory substances.**
- **Exit of high density lipoprotein, as well as macrophage and dendritic cell migration is dependent on the lymphatic system.**
- **Other CDD may have immune and lymphatic dysfunction**



LIFE

AUSTRALIA

IN COLOR First pictures
of a heart transplant

Continuing
LIFE's series:

Egypt, II The kings and gods

U.S. Politics

A guide to the
conventions
and the
candidates

Dr. Norman Shumway
performs a
heart transplant



LIFE

A new report on an era
of medical failure

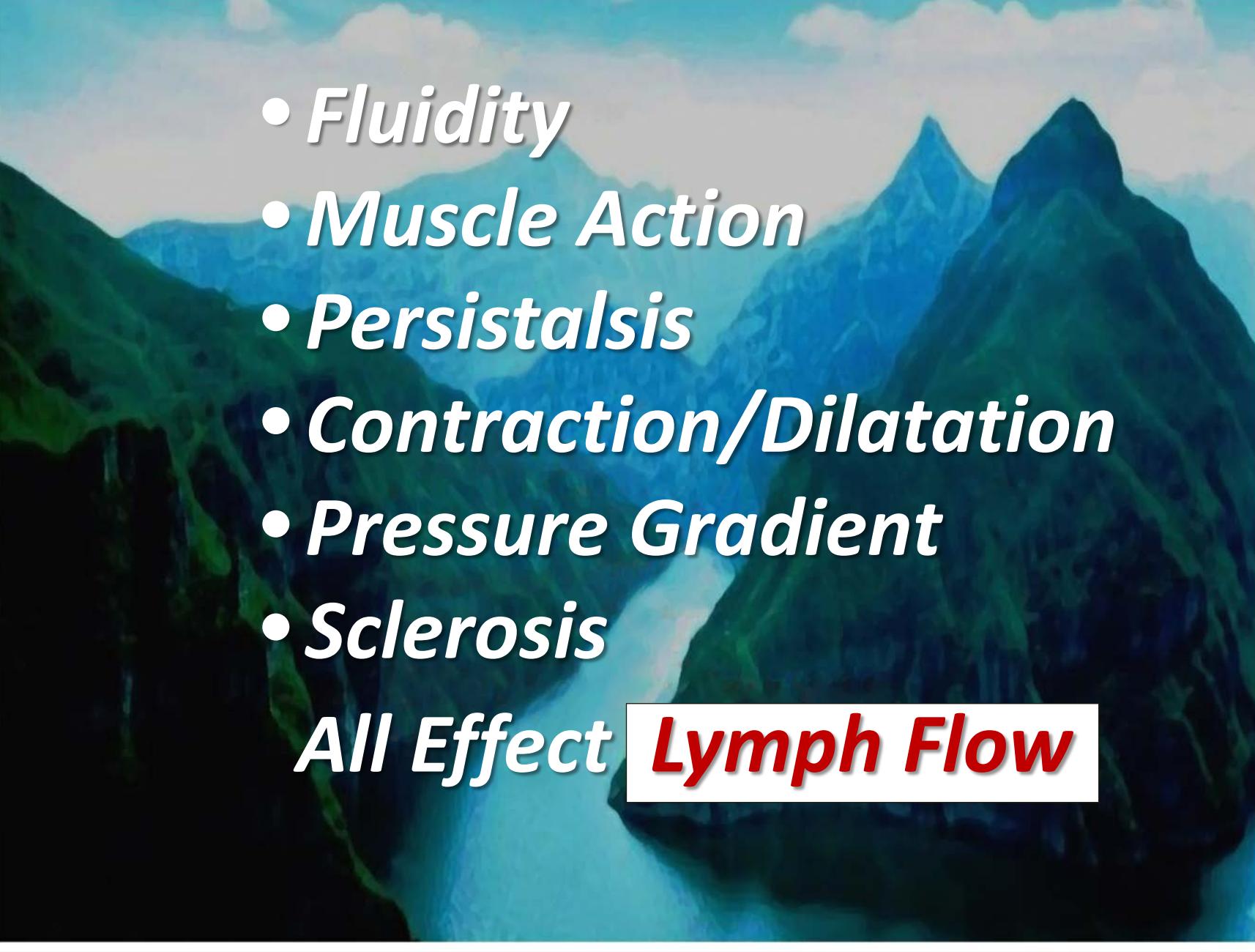
The Tragic Record of Heart Transplants

Six recipients of transplants,
shown here against a picture of the heart,
were all dead within eight months
of being photographed together.



LYMPHATICS

- *Fluid Exchange*
- *Protein Exchange*
- *Immune Domain*
- *Fatty Acid (Lipid) Transport*

- 
- *Fluidity*
 - *Muscle Action*
 - *Persistalsis*
 - *Contraction/Dilatation*
 - *Pressure Gradient*
 - *Sclerosis*

All Effect **Lymph Flow**

⇒ Forms of Fluid as It Moves from Capillary Blood to Lymph

Capillary Vesicles, Interstitial Lymph



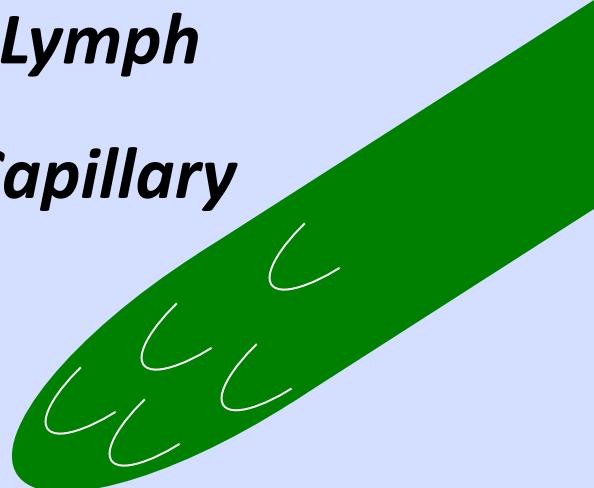
Rivulets



Gel



Capillary



Free

(sol)

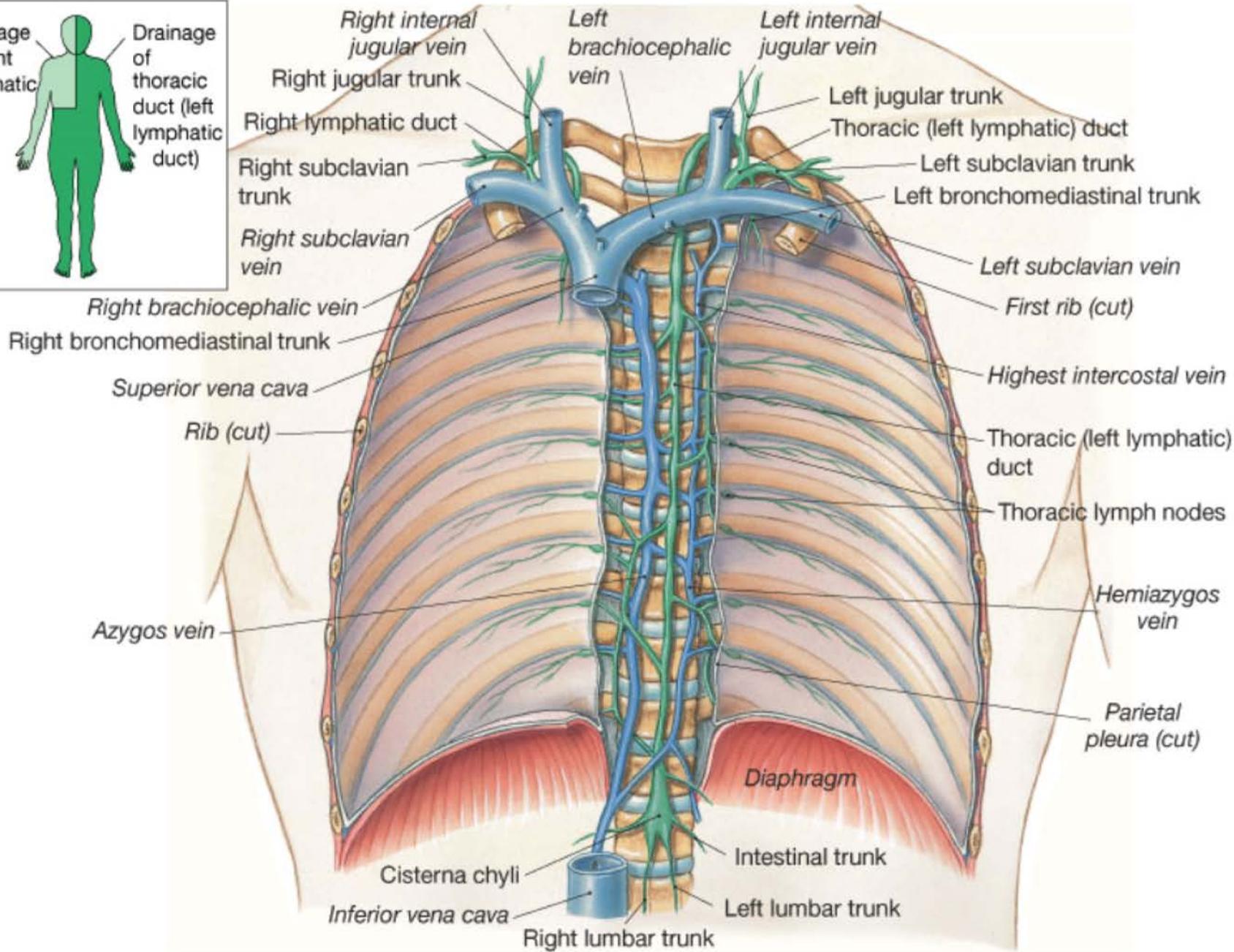
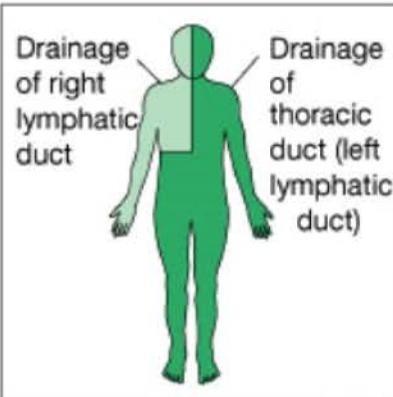
Free

(sol)

Gel

Free

(sol)



LYMPH COLLECTS
IN DUCTS BEFORE
EMPTYING INTO
THE RIGHT AND
LEFT SUBCLAVIAN
VEINS AND
REJOINING
CIRCULATION

LYMPH NODES
FILTER TISSUE
FLUID (LYMPH)

LYMPHATIC
CAPILLARIES
COLLECT EXCESS
TISSUE FLUID

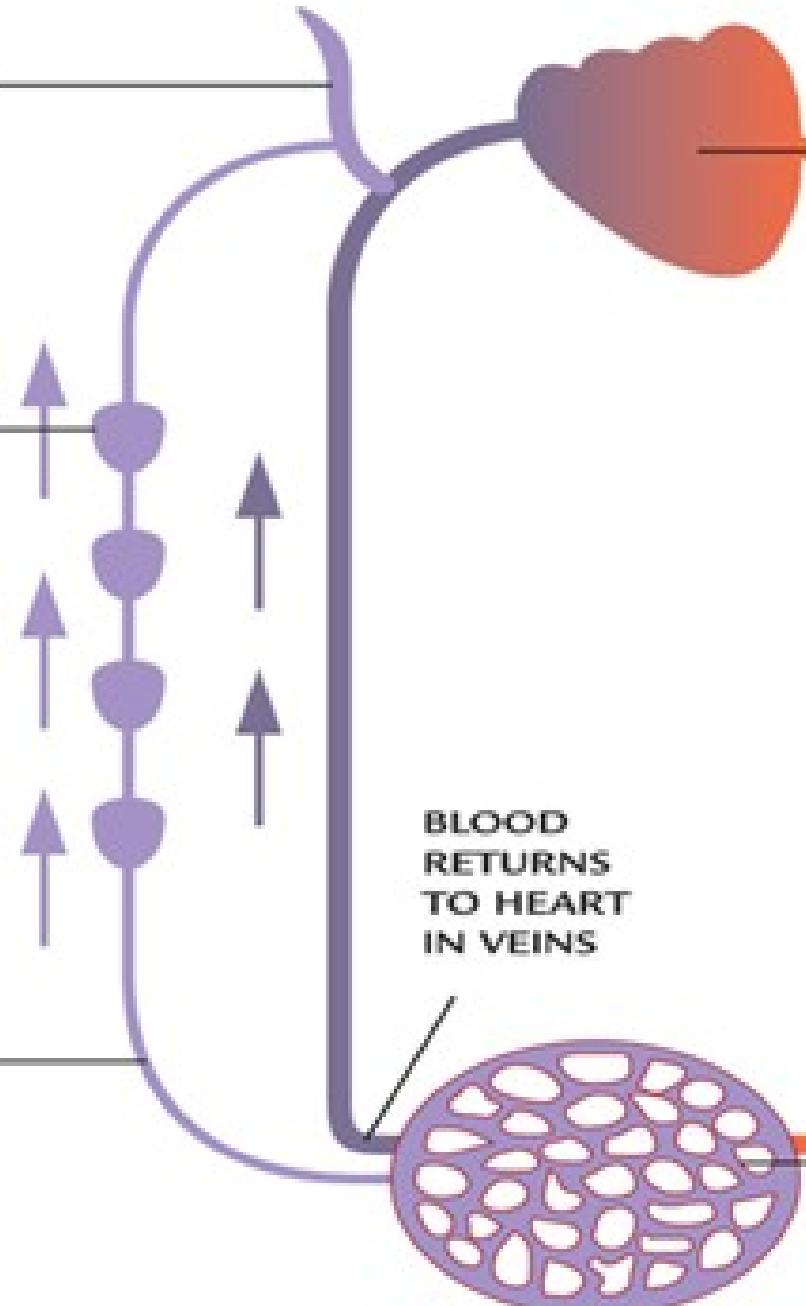
HEART

BLOOD LEAVES
HEART IN
ARTERIES AND
TRAVELS TO
TISSUES

BLOOD
RETURNS
TO HEART
IN VEINS

TISSUE

LYMPH CIRCUIT (SIMPLIFIED)



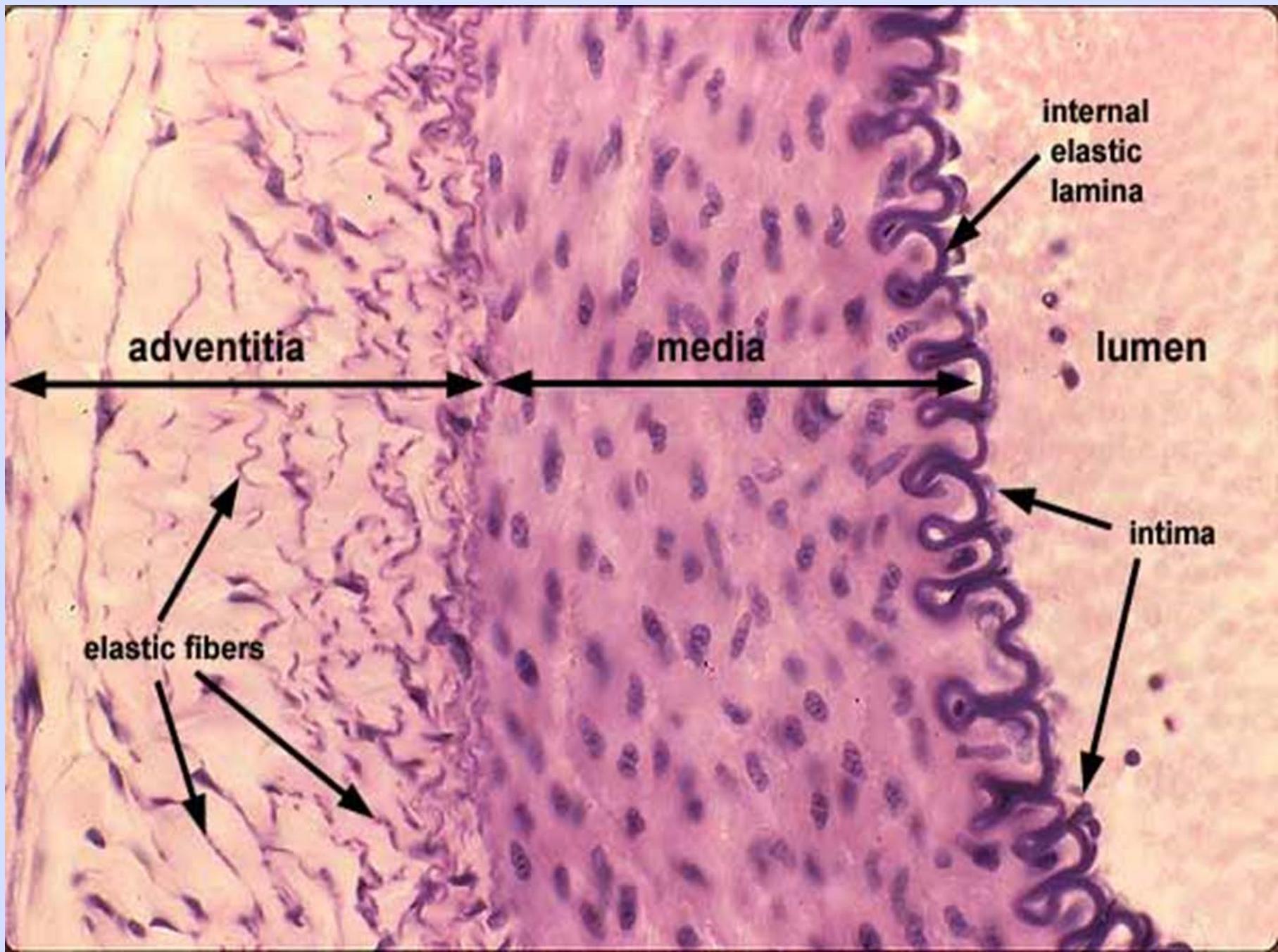
FACTORS IN ATHEROSCLEROSIS

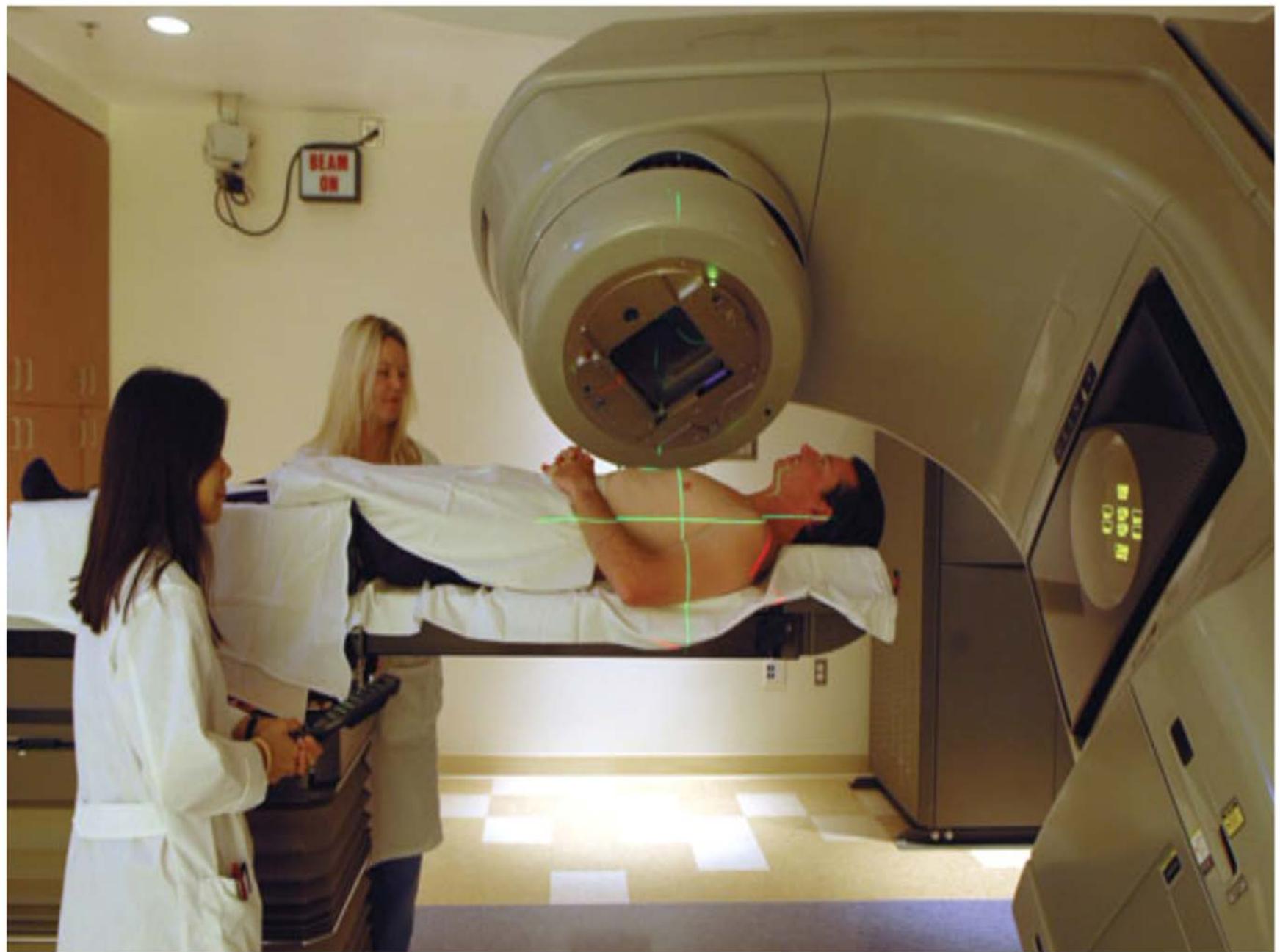
HARMFUL

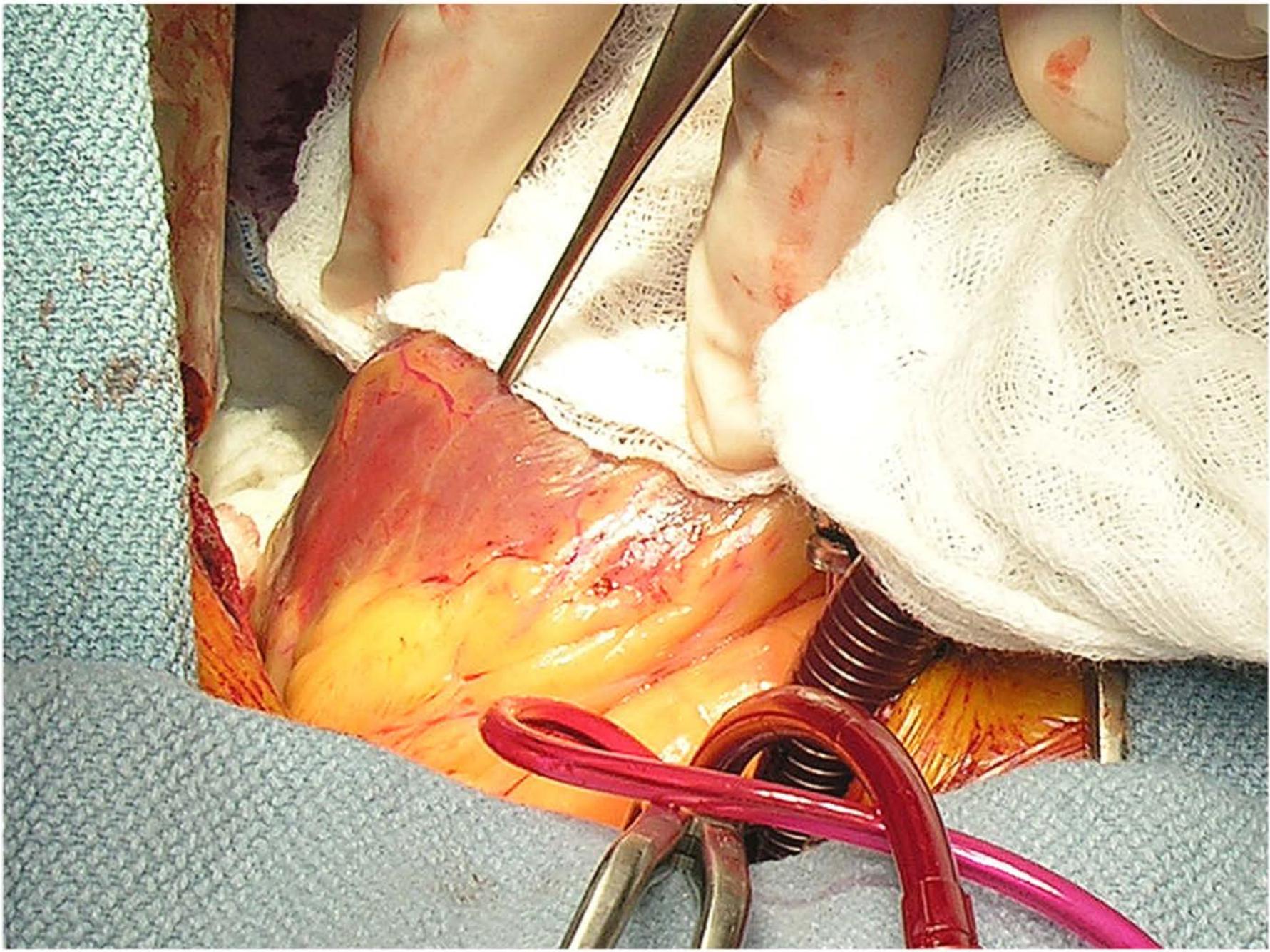
- Smoking
- Obesity
- Hypertension
- No exercise
- Diabetes
- Poor Diet
- Stress
- CRP, Homocystene
- Cholesterol
- Infection
- Trans & Saturated Fats
- Et Cetera

BENEFICIAL

- Exercise
- Good Diet (Vegetables)
- Stress Modifiers
- Deep Breathing
- Omega 3
- Massage
- Meditation, Yoga
- Positive attitude
- Prayer
- Green Tea
- Et Cetera







The Annals Of Thoracic Surgery, Vol 31, 290-293, 1981

The Role Of Lymphstasis In Atherogenesis

G.M . Lemole

The cardiac lymphatics are responsible for the transport of all the lipoproteins and cholesterol from the extravascular myocardial tissue, although little is known about the filtration and lymphatic clearance of the coronary artery wall.

It is postulated that a critical factor in the genesis of arteriosclerosis is lymphstasis, which adequately explains the positive correlation with the known risk factors for coronary artery disease and the negative correlation with high-density lipoproteins

Further research is necessary in this little-known area to better understand the etiology of atherosclerosis.

Atherosclerosis. 1984 Dec;53(3):297-308.

The Distribution Of Cholesterol And Apoprotein A-I Between The Lipoproteins In Plasma And Peripheral Lymph From Normal Human Subjects.

Rudra DN, Myant NB, Pflug JJ, Reichl D.

Gel electrophoresis showed (1) a higher proportion of large to small HDL particles in lymph than in plasma andwe suggest that the higher ratio of large to small HDL particles in lymph than in plasma is due to the conversion of small to large HDL by incorporation of cholesterol into the smaller particles.

Arteriosclerosis. 1990 May-June;10(3):477-85.

Different efflux pathways for high and low density lipoproteins from porcine aortic intima.

Nordestgaard BG, Hjelms E, Stender S, Kjeldsen K.

Department of Clinical Chemistry, University of Copenhagen, Denmark.

- **As much as 95%, of the HDL cholesteryl ester that entered the arterial intima during a period of 4 hours penetrated the arterial wall beyond the internal elastic lamina.**
- **The most important efflux route for HDL esterified cholesterol is through the vasa vasorum and lymphatics**

Arkh Patol. 1990;52(5):11-6

**The Morphogenesis Of Chronic Failure Of The Lymph Outflow From
The Heart In Dyslipoproteinemia And Recurrent Myocardial
Ischemia.**

[Article in Russian]

Gavrish AS.

**The results indicate that the
chronic lymphostasis and
lymphogenic cardiosclerosis
represent an essential factor in
the progression of a chronic
ischemic heart disease.**

Curr Atheroscler Rep. 2013 Sep;15(9):354. doi: 10.1007/s11883-013-0354-4.

Atherosclerosis And Transit Of HDL Through The Lymphatic Vasculature.

Martel C, Randolph GJ.

Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO

Here, we focus on recent evidence that the Lymphatic vasculature is critical for the removal of cholesterol, likely as a component of HDL, from tissues including skin and the artery wall.

Clin Invest. 2013 Apr;123(4):1571-9. doi: 10.1172/JCI63685. Epub 2013 Mar 25.

Lymphatic Vasculature Mediates Macrophage Reverse Cholesterol Transport In Mice.

Martel C¹, Li W, Fulp B, Platt AM, Gautier EL, Westerterp M, Bittman R, Tall AR, Chen SH, Thomas MJ, Kreisel D, Swartz MA, Sorci-Thomas MG, Randolph GJ.

¹Department Of Gene And Cell Medicine, Mount Sinai School Of Medicine, New York, New York,

Reverse Cholesterol Transport (RCT) refers to the mobilization of cholesterol on HDL particles (HDL-C) from extravascular tissues to plasma, ultimately for fecal excretion. Little is known about how HDL-C leaves peripheral tissues to reach plasma. We first used 2 models of disrupted lymphatic drainage from skin--1 surgical and the other genetic--to quantitatively track RCT following injection of [3h]-cholesterol-loaded macrophages upstream of blocked or absent lymphatic vessels. Macrophage RCT was markedly impaired in both models, even at sites with a leaky vasculature. Inhibited RCT was downstream of cholesterol efflux from macrophages, since macrophage efflux of a fluorescent cholesterol analog (bodipy-cholesterol) was not altered by impaired lymphatic drainage. We next addressed whether RCT was mediated by lymphatic vessels from the aortic wall by loading the aortae of donor atherosclerotic apo-e-deficient mice with [2h]6-labeled cholesterol and surgically transplanting these aortae into recipient apo-e-deficient mice that were treated with anti-vegfr3 antibody to block lymphatic regrowth or with control antibody to allow such regrowth. [2h]-cholesterol was retained in aortae of anti-vegfr3-treated mice. Thus, the lymphatic vessel route is critical for RCT from multiple tissues, including the aortic wall.

These results suggest that supporting lymphatic transport function may facilitate cholesterol clearance in therapies aimed at reversing atherosclerosis

Eur j Clin Invest 2015 Jan;45(1):100-8. doi: 10.1111/eci.12372.

Lymphatic vessels: an emerging actor in atherosclerotic plaque development.

[Kutkut I¹](#), [Meens MJ](#), [McKee TA](#), [Bochaton-Piallat ML](#), [Kwak BR](#).

Author information

Abstract

BACKGROUND:

Atherosclerosis is a chronic inflammatory disease of large- to medium-sized arteries and is the main underlying cause of death worldwide. The lymphatic vasculature is critical for processes that are intimately linked to atherogenesis such as the immune response and cholesterol metabolism. However, whether lymphatic vessels truly contribute to the pathogenesis of atherosclerosis is less clear despite increasing research efforts in this field.

RESULTS:

Current knowledge about lymphatic vessels in the arterial wall came from studies that examined the presence and location of such vessels in human atherosclerotic plaque specimens, as well as in a variety of arteries in animal models for atherosclerosis (e.g. rabbits, dogs, rats and mice). Generally, three experimental approaches have been used to investigate the functional role of plaque-associated lymphatic vessels; experimental lymphostasis was used to investigate lymphatic drainage of the arterial wall, and more recently, studies with genetic interventions and/or surgical transplantation have been performed. CONCLUSIONS:Lymphatic vessels seem to be mostly present in the adventitial layer

of the arterial walls of animals and humans. **They are involved in reverse cholesterol transport from atherosclerotic lesions, and arteries with a dense lymphatic network seem naturally protected against atherosclerosis.**

Lymphangiogenesis is a process that is an important part of the inflammatory loop in atherosclerosis. However, how augmenting or impeding the distribution of lymphatic vessels impacts disease progression remains to be investigated in future studies.



INFLAMMATION

IS

THE HEART OF THE MATTER

• **INFLAMMATION IS**
The body's protective response to toxins, pathogens, irritants, trauma, free radicals, and unrecognized molecules.

CHRONIC DEGENERATIVE DISEASE



INFLAMMATION



IMMUNE SYSTEM



LYMPHATICS



BAD GUYS ?

GOOD GUYS

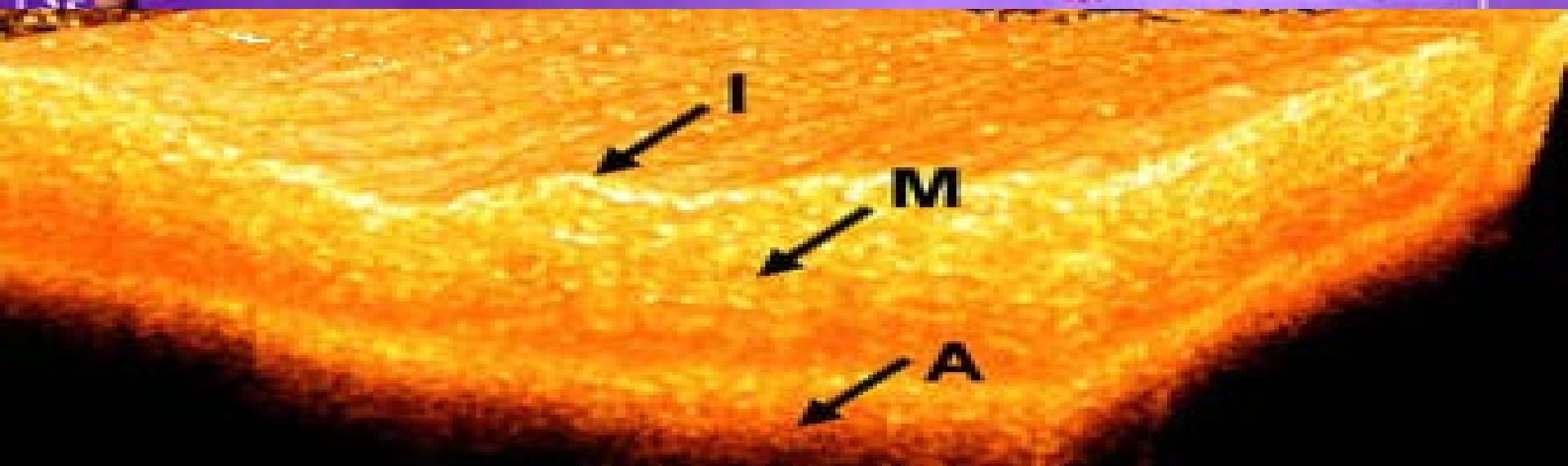
- CHOLESTEROL
- FOAM CELLS
- INFLAMMATION
- HDL?

- CHOLESTEROL
- FOAM CELLS
- INFLAMMATION
- HDL?

Lipoprotein Subclasses



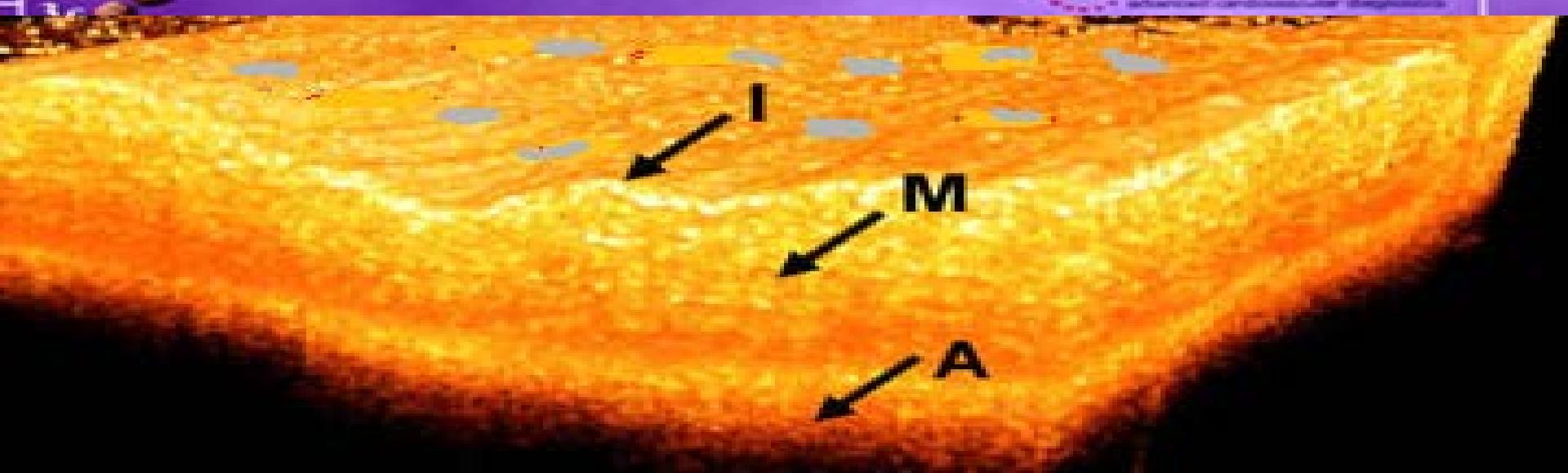
Berkeley HeartLab, Inc.
Advanced cardiovascular diagnostics



Lipoprotein Subclasses



Berkeley HeartLab, Inc.
Advanced cardiovascular diagnostics



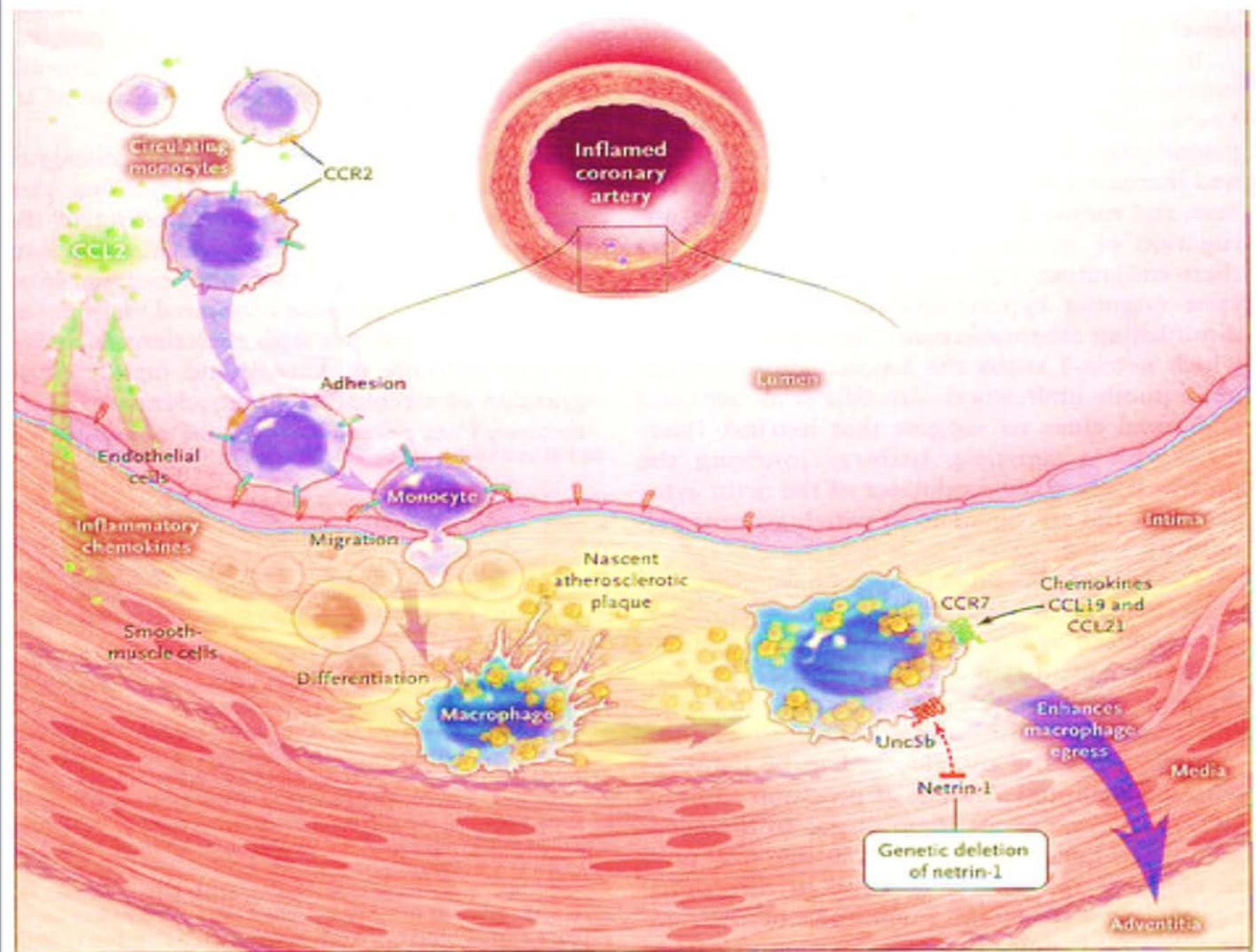
Search
Home
remedy



Consume 8-10 Glasses Of Water Daily

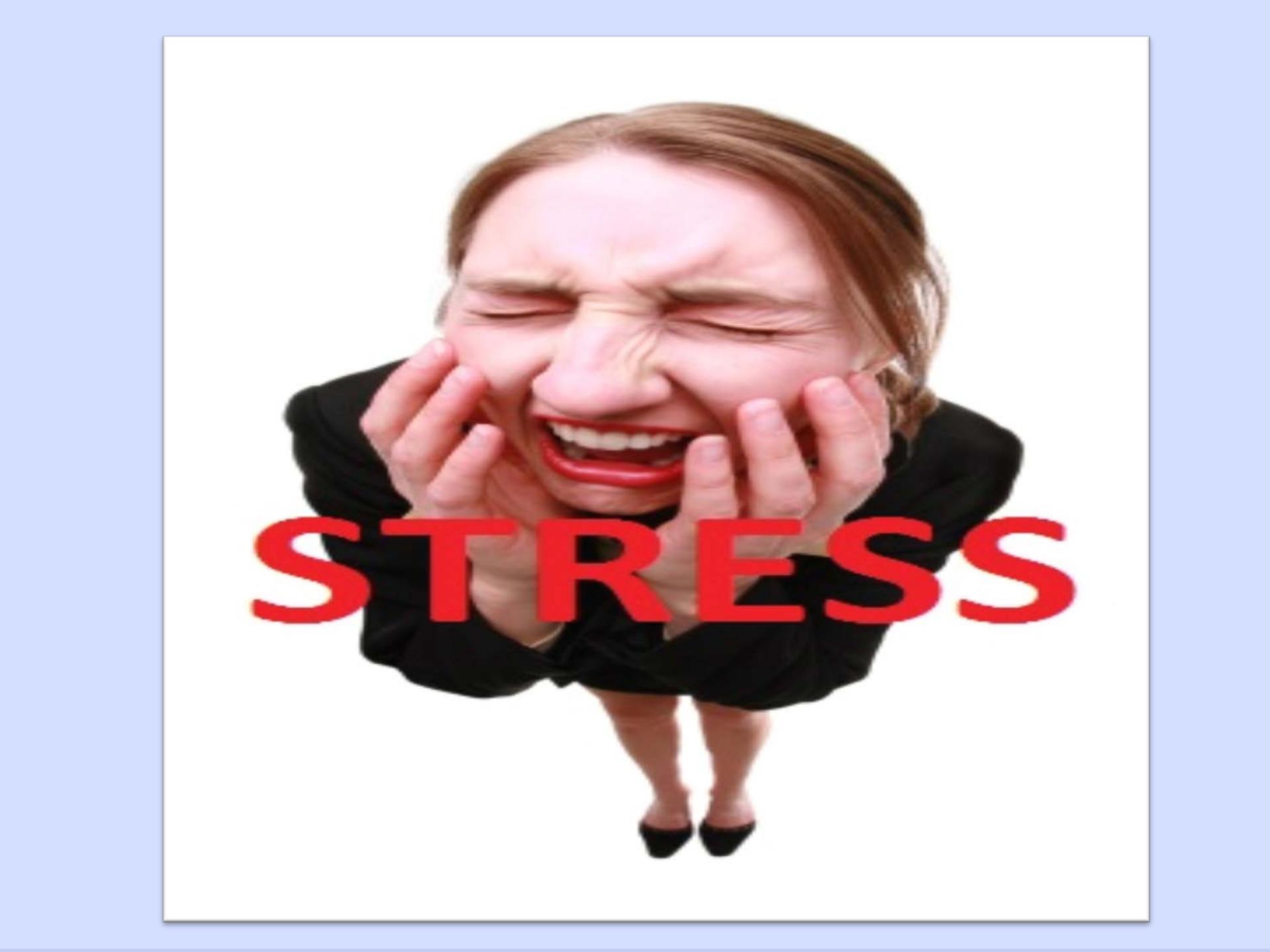






Wellness Tripod

- Stress Modification
- Exercise & Detoxification
- Diet & Supplements



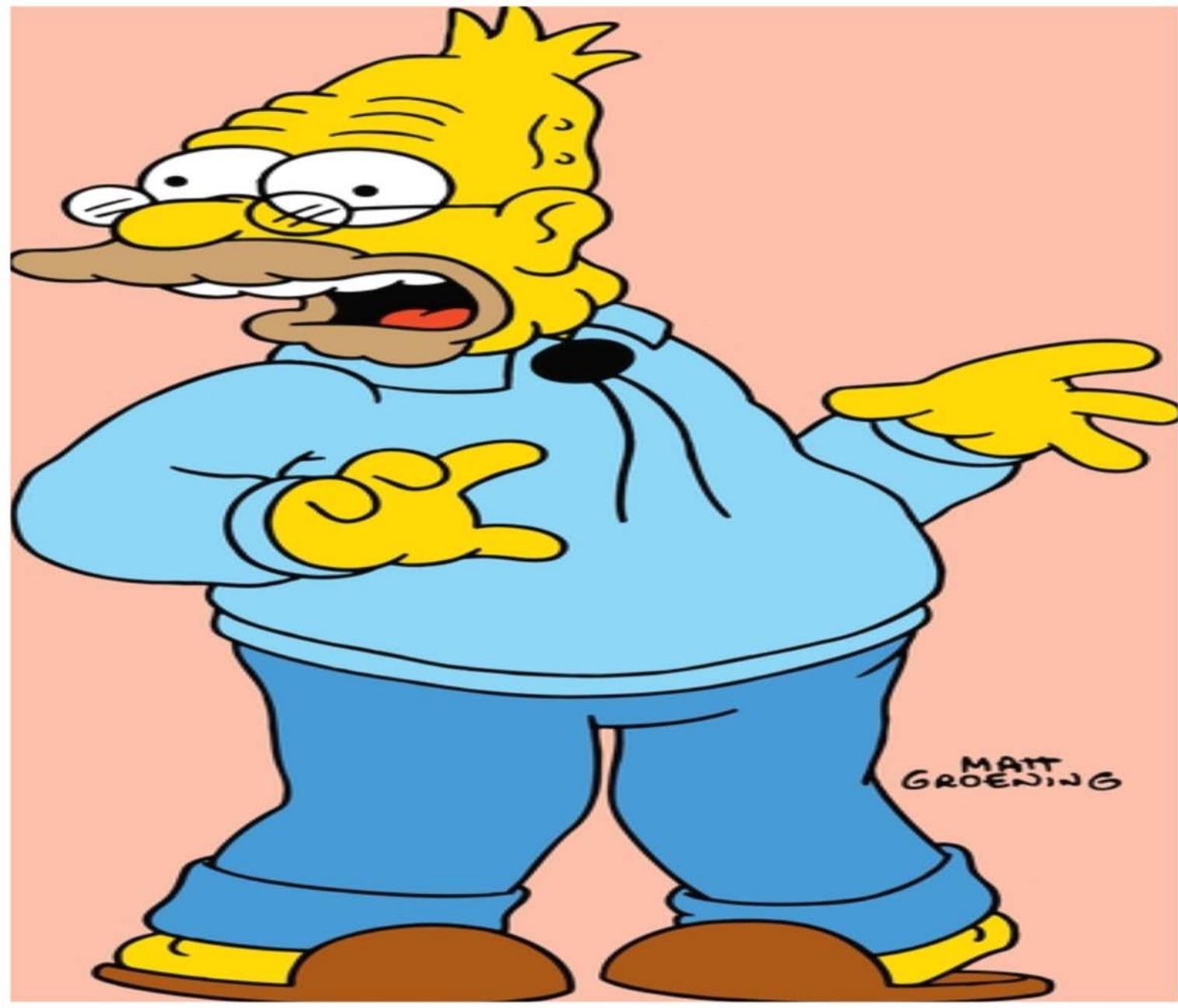
STRESS

Emotional Aspects of Heart Disease

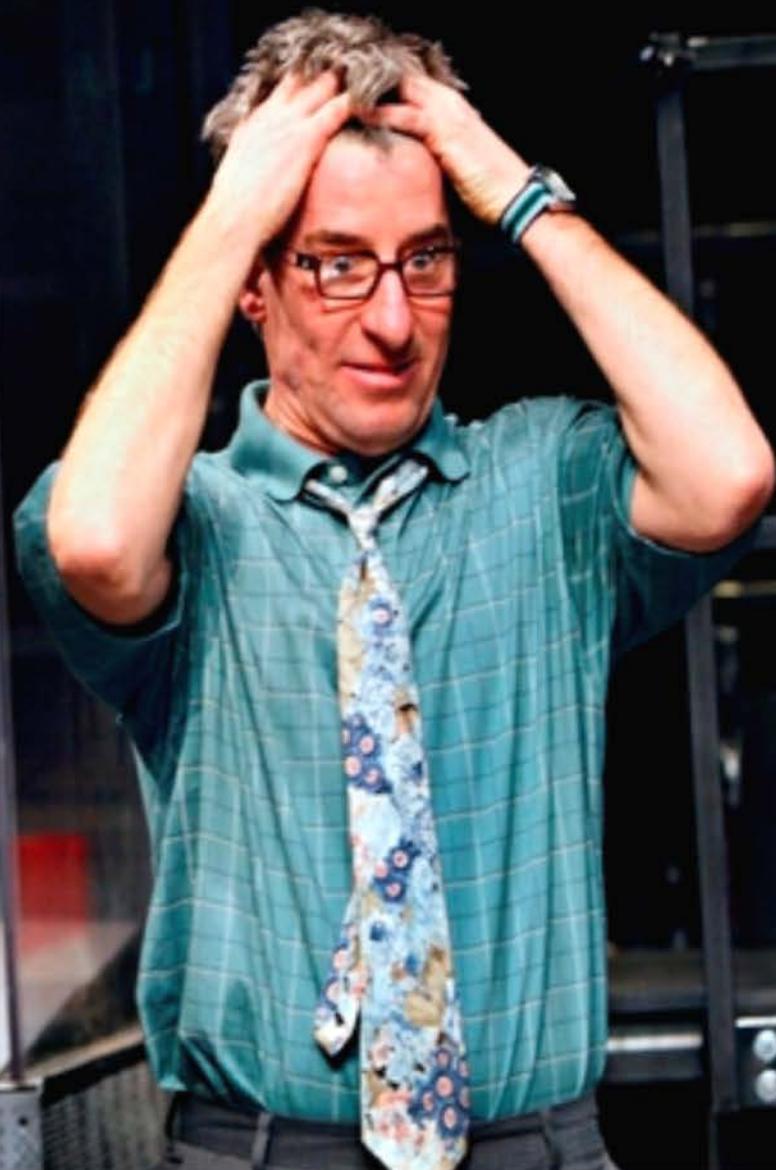
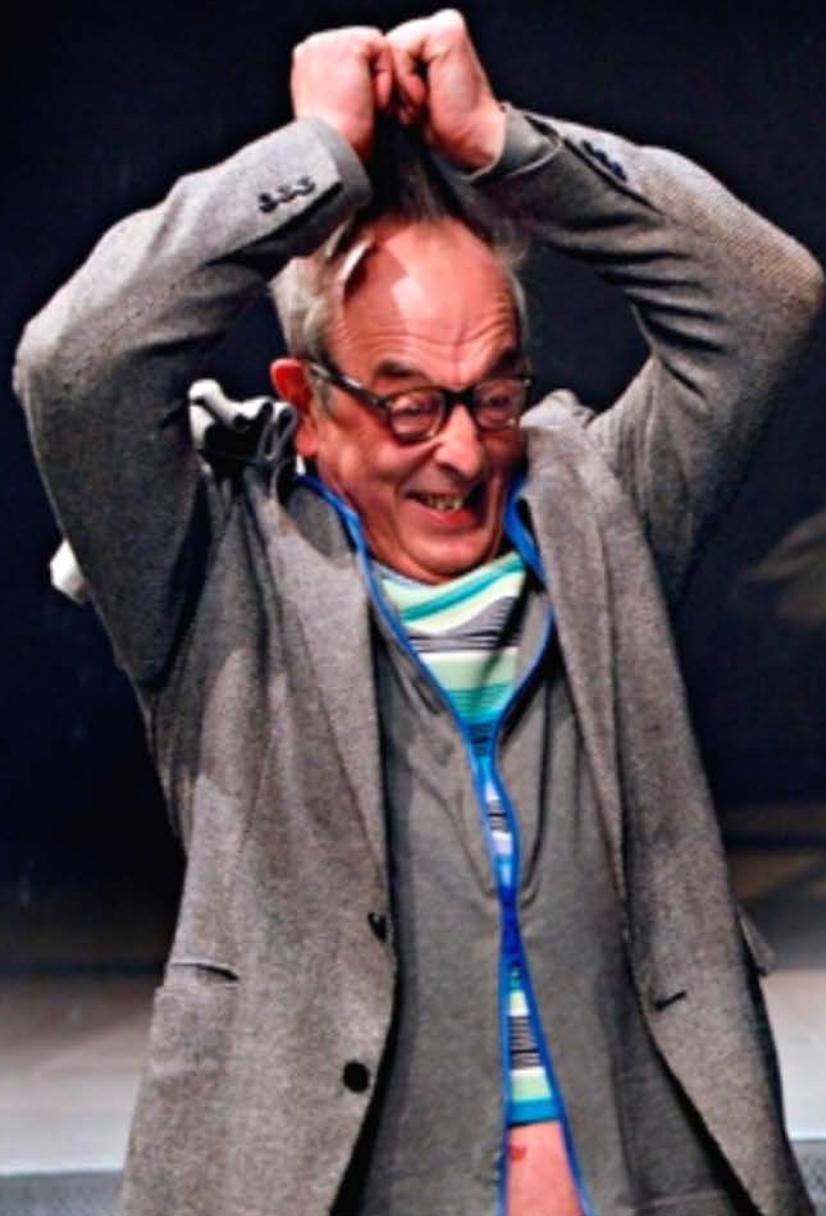
Men with highest levels of urinary cortisol produced in times of anxiety, worry or stress, correlated with men with coronary heart disease.

STRESS

- Increases Inflammation
- Suppresses Immune System
- Causes Sleep Deprivation
(Melatonin Insufficiency And B-Amyloid Clearance)









Lymphology. 2000 Mar;33(1):24-31.

Eicosanoid Production And Lymphatic Responsiveness In Human Cigarette Smokers Compared With Non-smokers.

Sinzinger H, Kaliman J, Oguogho A.

Wilhelm Auerswald Atherosclerosis Research Group Vienna, Austria. Helmut.Sinzinger@akh-wien.Ac.At

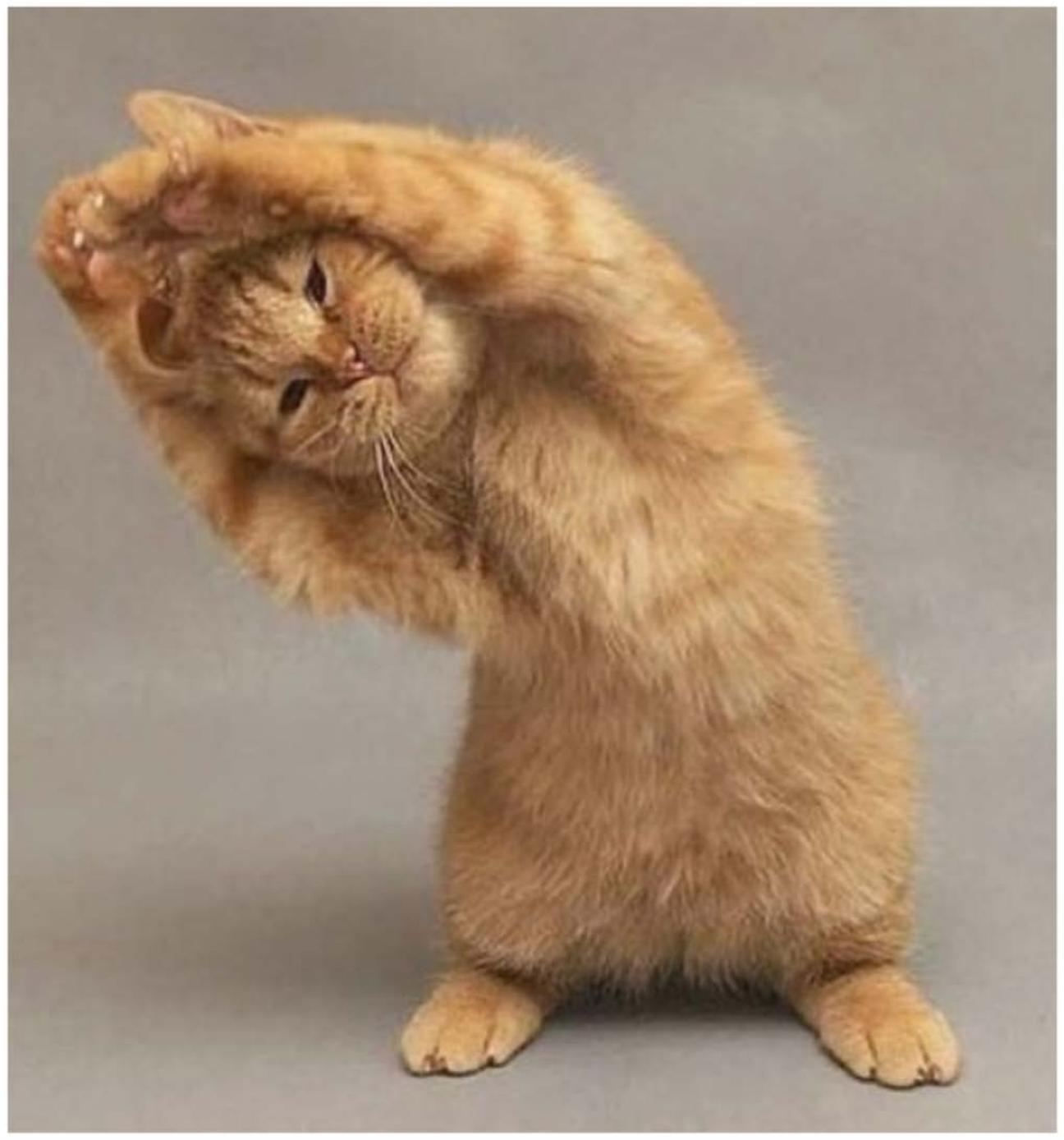
**Smoking induces oxidation injury,
promotes altered (iso-)eicosanoid
production and impacts on the function
and dysfunction of peripheral lymphatics
under normal circumstances and in a
variety of clinical disorders.**

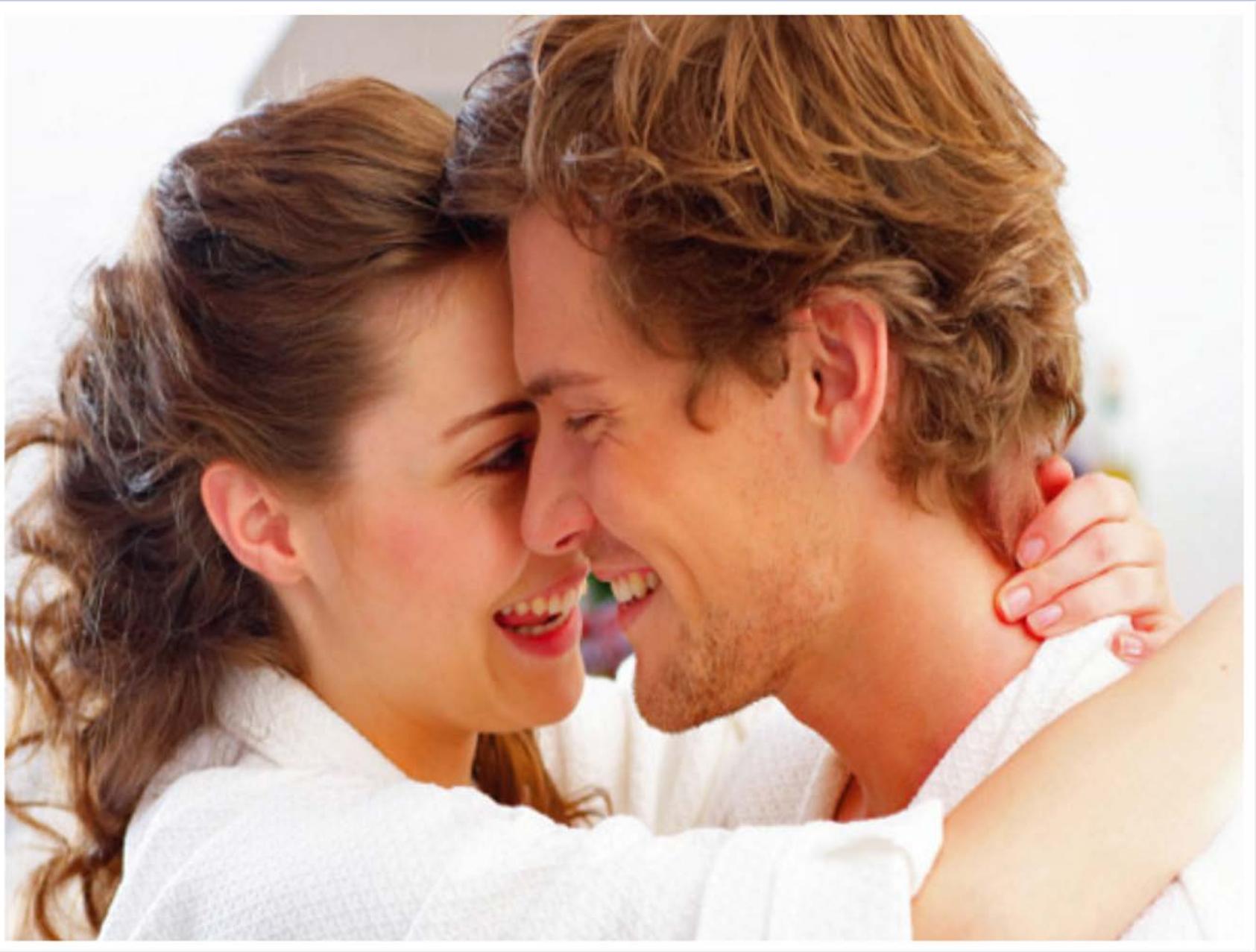
Stress Modification

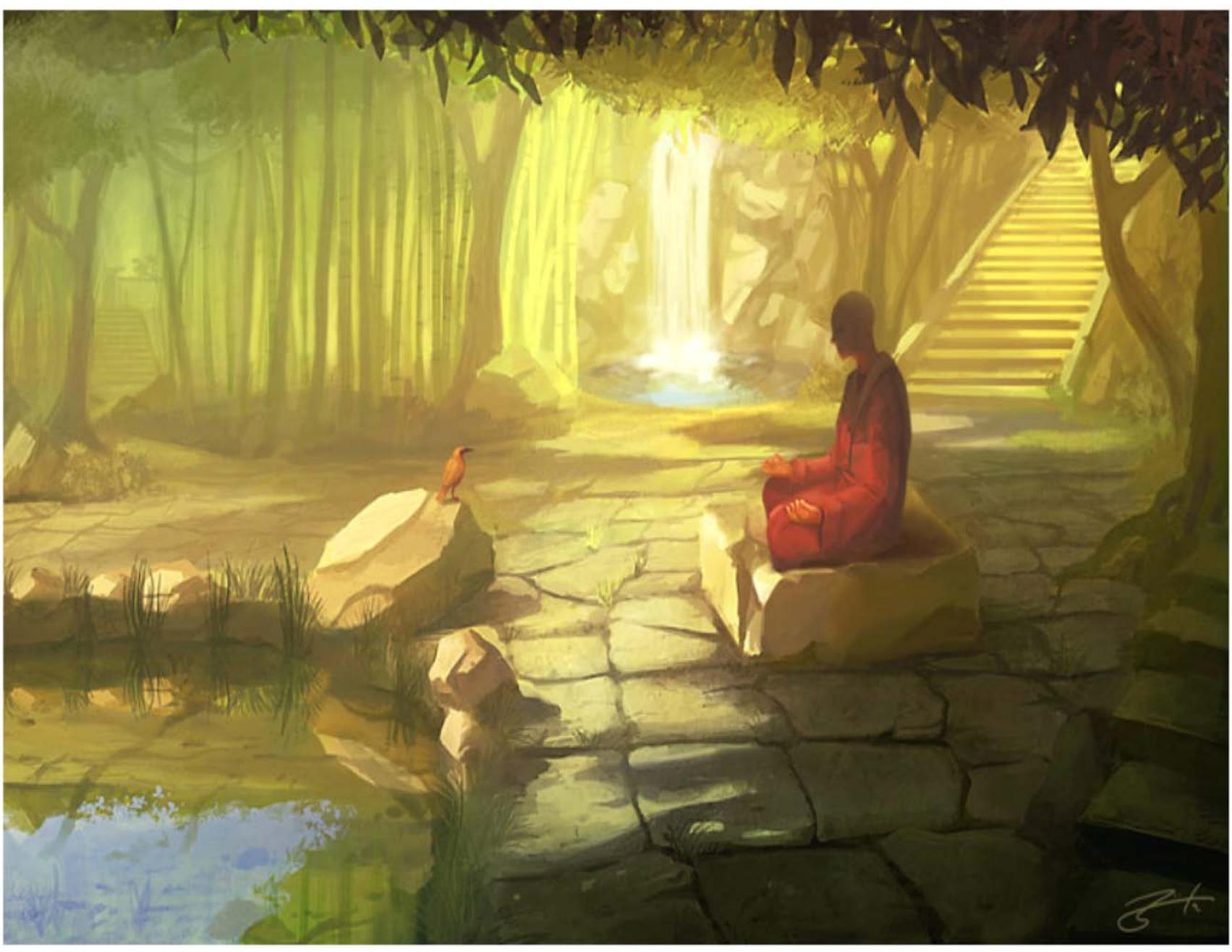
- **Lowers cortisol and epinephrine**
- **Lowers glucose level**
- **Lowers free radical formation**
- **Increases endorphins**
- **Decrease cardiovascular disease incidence**









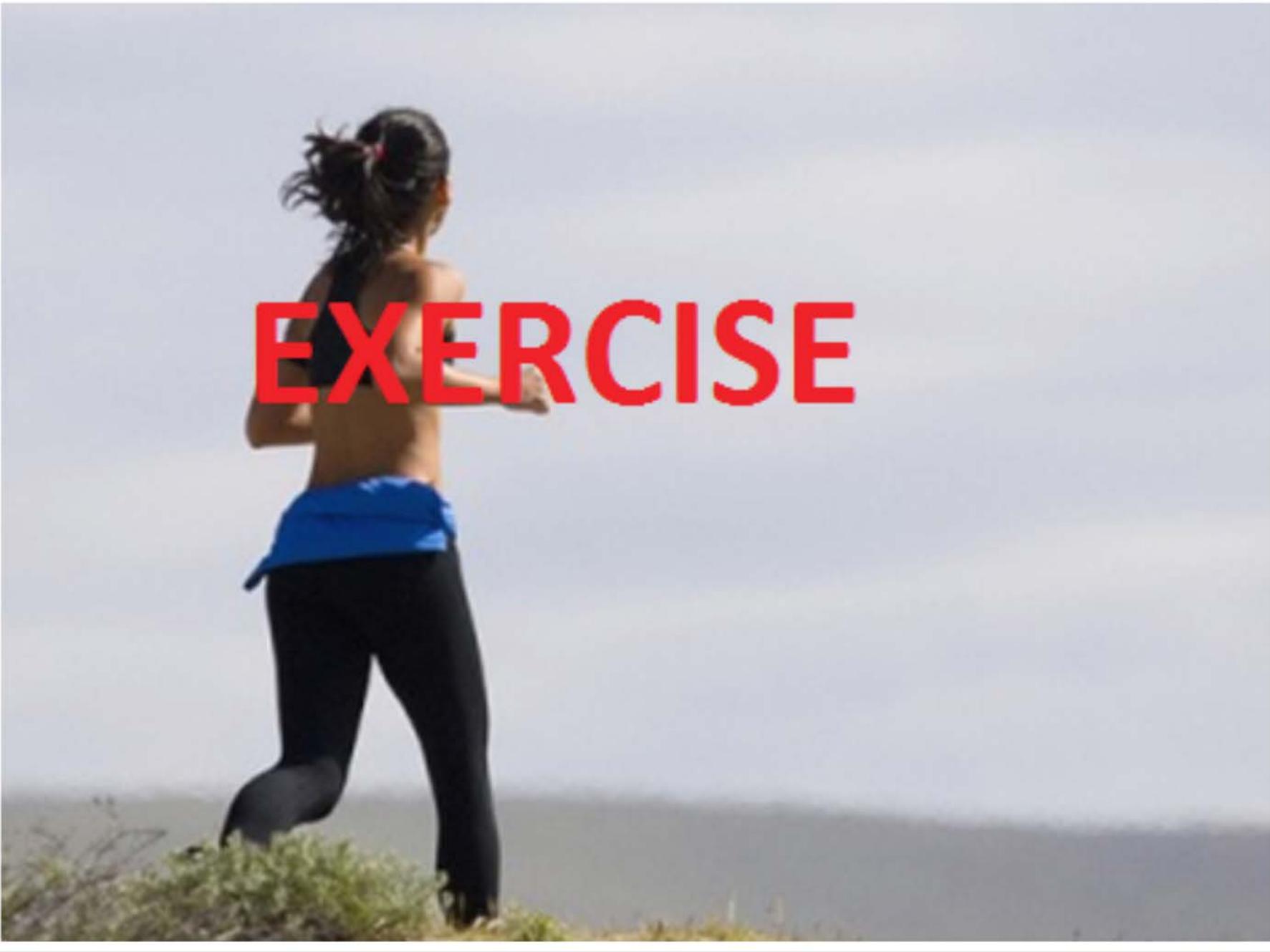


BK



Lotto

“Time Well Spent”

A photograph of a woman jogging from the side, wearing a blue headband, a blue waistband, and black leggings. She is shirtless. The background shows a hilly landscape under a clear sky. Overlaid in large, bold, red capital letters across the center of the image is the word "EXERCISE".

EXERCISE







DIET

daflon 500mg

Fraction flavonoïque purifiée micronisée

30 comprimés enrobés

DAFLON 500

Improves lymphatic drainage by increasing the frequency and intensity of lymphatic contractions, and by increasing the total number of functional lymphatic capillaries, reduces the expression of adhesion molecules (ICAM1, VCAM1) and on leukocytes (L-selectin, VLA-4, CD 11b), and inhibits the adhesion, migration, and activation of leukocytes.

This leads to a reduction in the release of inflammatory mediators, principally oxygen free radicals and prostaglandins (**PGE2, PGF2a**).







Soluble fiber can be found in foods such as oatbran, barley, nuts, seeds, beans, lentils, fruits (citrus, apples), strawberries and many vegetables



Soluble fiber sources



Insoluble fiber is found in foods such as whole wheat and whole grain products, vegetables, and wheat bran

Insoluble fiber sources





"How come they don't have mad-cauliflower disease?"

DIET

- **60% High Complex carbohydrate diet of vegetables, fruit, nuts and grain**
- **20% Good Fats – omega 3, GLA , monounsaturates**
- **20% protein**
- **Minimize meats, dairy products, fish**
- **Avoid Refined carbohydrates**
- **Incorporate a High Fiber diet**
- **Supplements**

DIET

- Plant Based
- Crucifers (Broccoli, Kale, Cauliflower , Collards)
- High Fiber (Flaxseed)
- Turmeric, Cayenne, Garlic
- Mushrooms
- Berries
- Green Tea
- Pure Water
- Fermented Soy
- Olive Oil (Sparingly)

AVOID

- Trans Fats
- Sugar
- White Flour
- Artificial Coloring
- Dairy And Processed Meats
- Excess Fat
- Omega-6 In Meats

AVOID XENOESTROGEN & ENDOCRINE DISRUPTORS

- Pesticides
- PCB, Bis-phenol A, Phthalates
- Dioxin Tainted Dairy And Meats
- Tainted Fish (From Water & Hg)
- Many Household And Cleaning Products
- Contaminated Water
- Heterocyclic Amines

MICHAEL POLLAN

“Eat real food”

MICHAEL POLLAN

“Eat real food”

“Not Much”

MICHAEL POLLAN

“Eat real food”

“Not Much”

“Mostly Vegetables”

UNIFYING CONCEPT OF ARTERIOSCLEROSIS

INITIATING AGENTS	HOMEOSTASIS (Resistance and Reparation)	CLEARANCE
<p>The diagram illustrates the components of a blood vessel wall from the lumen outward: <ul style="list-style-type: none"> BLOOD VESSEL LUMEN: Contains Oxidized Cholesterol, Oxidized Lipoproteins, Homocysteine, Bacterial Infections, sugar, Heliobacter Pylori, Chlamydia, and Cytomegalic. VESSEL WALL: Labeled MICRO-NUTRIENTS, representing the NEUROPEPTIDES column. LYMPHATICS: Contains Antioxidants (Vitamins A, C, E; Vitamins B6, B12, Folic Acid; Essential Omega-3 Fatty Acid), Minerals (Mg, Zn, etc.), Antibiotics (i.e. Tetracycline), Anti-Inflammatories, and S.O.D., Cataclase, Glutathione. </p>	<p>Antioxidants: Vitamins A, C, E Vitamins B6, B12, Folic Acid Essential Omega-3 Fatty Acid Minerals Mg, Zn, etc. Antibiotics (i.e. Tetracycline) Anti-Inflammatories S.O.D., Cataclase, Glutathione</p>	<p>Massage Exercise Deep Breathing Meditation Yoga Lymphogoges Herbal Tea Positive Attitude Prayer</p>

CHRONIC DISEASE AND LYMPH FLOW

Diseases characterized by
chronic inflammation often
present with impaired DC
migration, adaptive immunity
and a dysfunctional tolerogenic
resolution.

J Clin Invest Vol 124 #3

Emerging Roles Of Lymphatic Endothelium In Regulating Adaptive Immunity

Catherine M. Card, Shann S. Yu, And Melody A. Swartz

First Published March 3, 2014 - More Info

Emerging research on the roles of stromal cells in modulating adaptive immune responses has included a new focus on lymphatic endothelial cells (LECs).

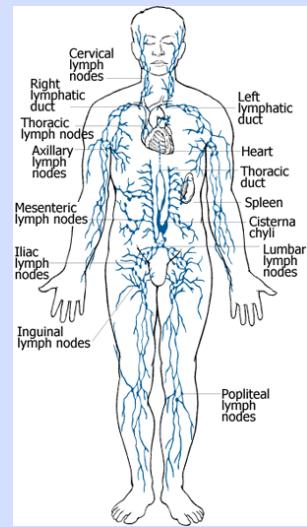
LECs are presumably the first cells that come into direct contact with peripheral antigens, cytokines, danger signals, and immune cells travelling from peripheral tissues to lymph nodes.

LECs can modulate dendritic cell function, present antigens to T cells on MHC class I and MHC class II molecules, and express immunomodulatory cytokines and receptors, which suggests that their roles in adaptive immunity are far more extensive than previously realized. This Review summarizes the emergent evidence that LECs are important in maintaining peripheral tolerance, limiting and resolving effector T cell responses, and modulating leukocyte function.

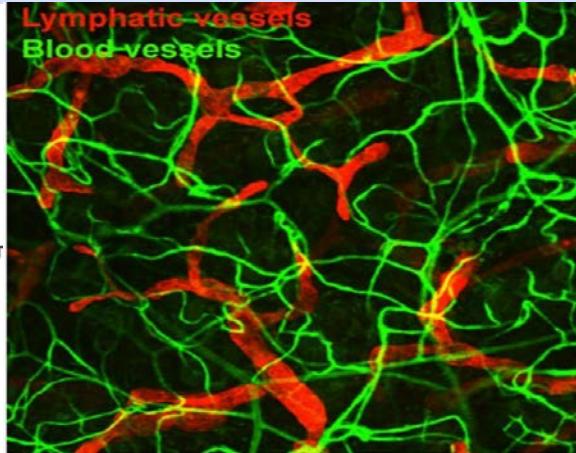
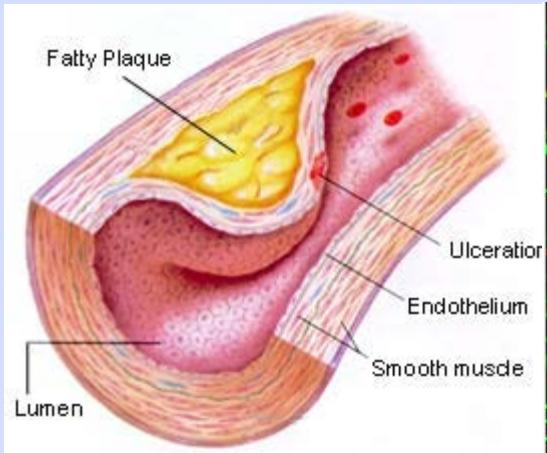


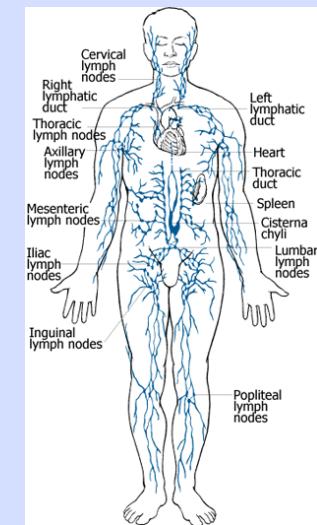
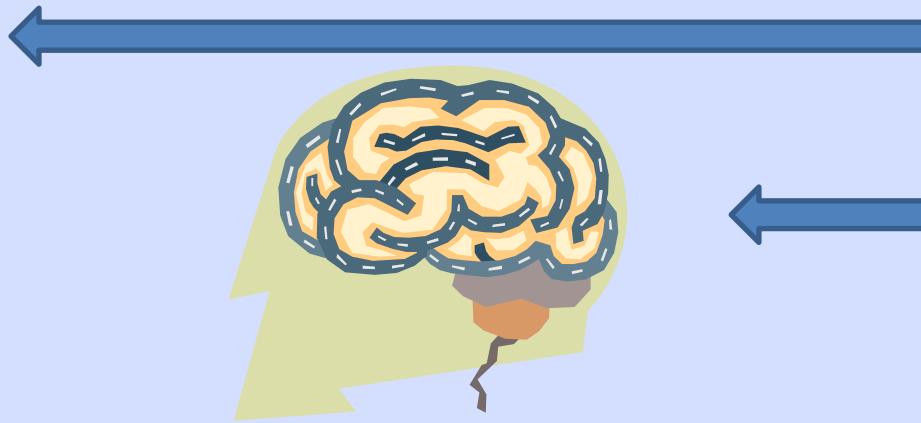
ENDOCRINE

NEUROLOGIC



IMMUNE

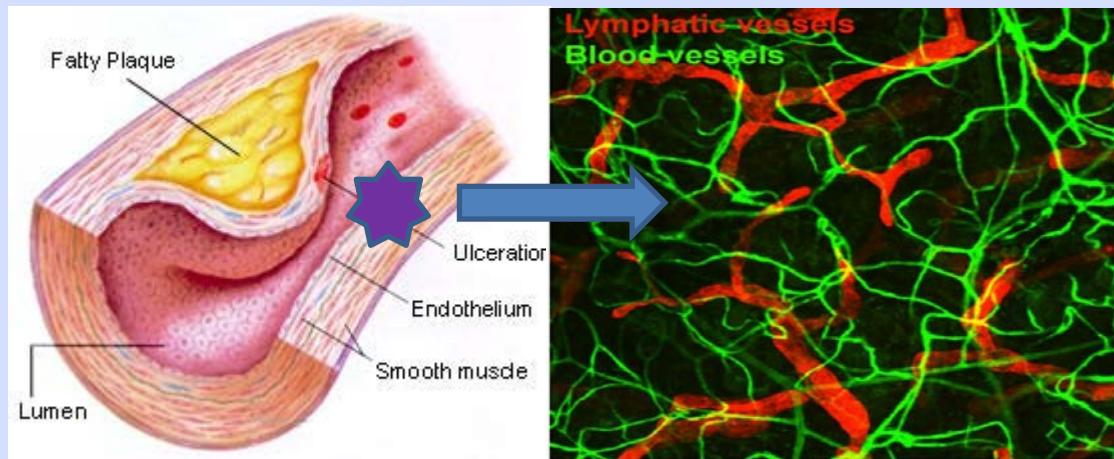


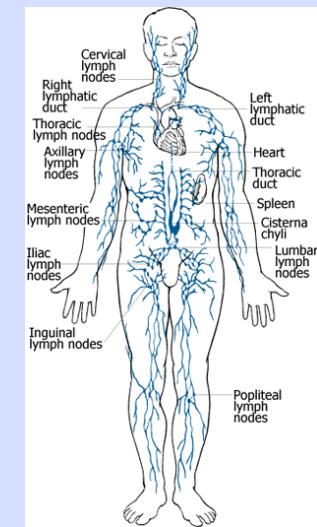
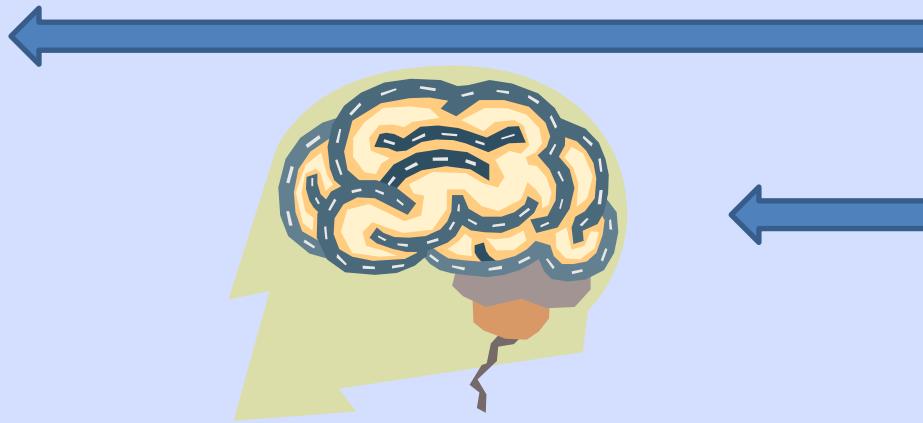


ENDOCRINE

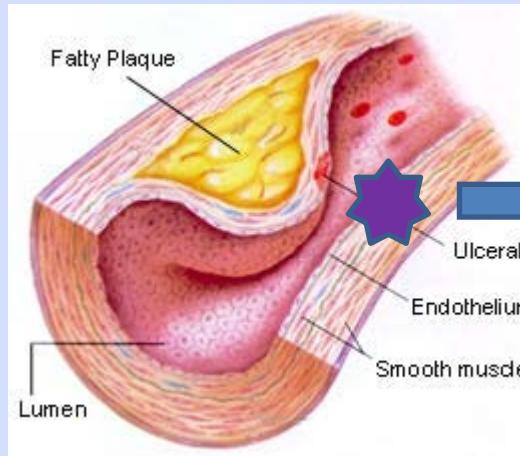
NEUROLOGIC

IMMUNE

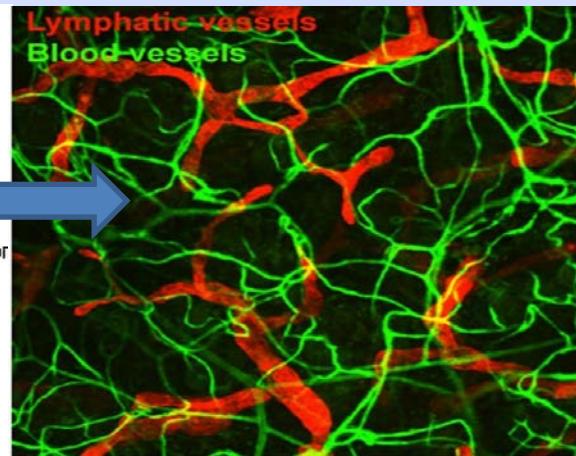




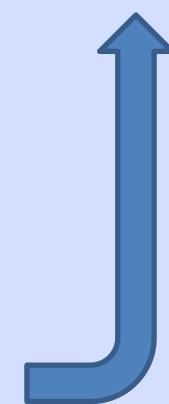
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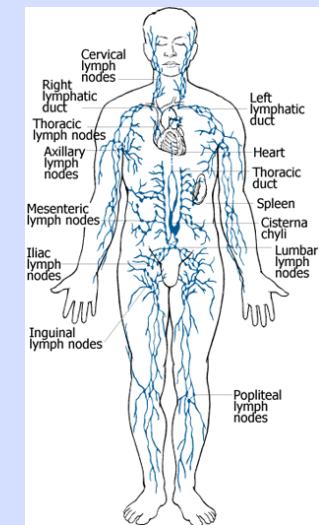
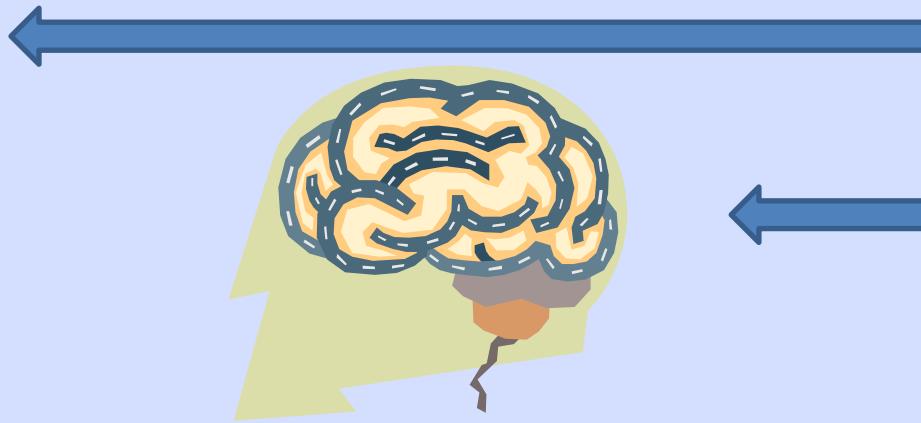


NEUROLOGIC



IMMUNE

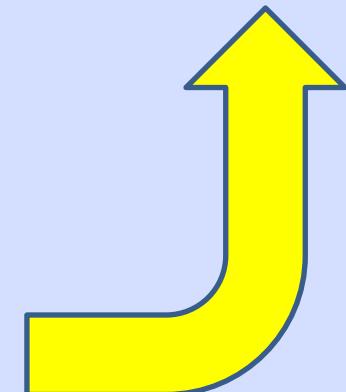
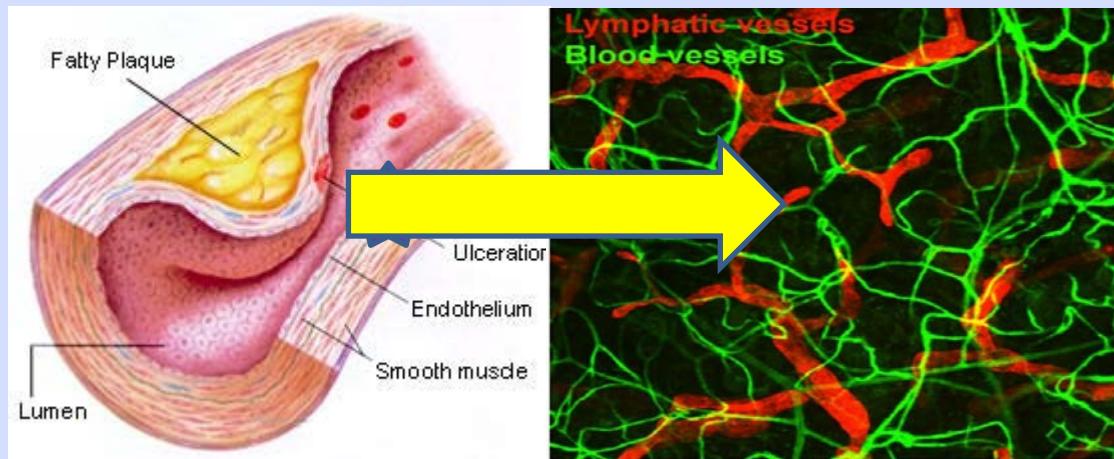


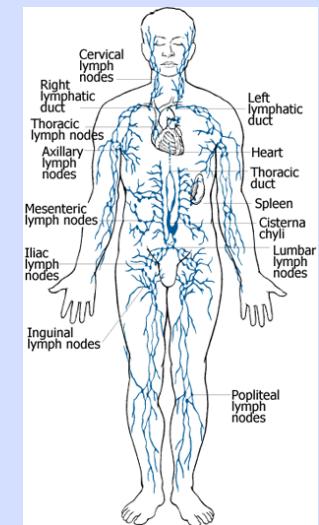
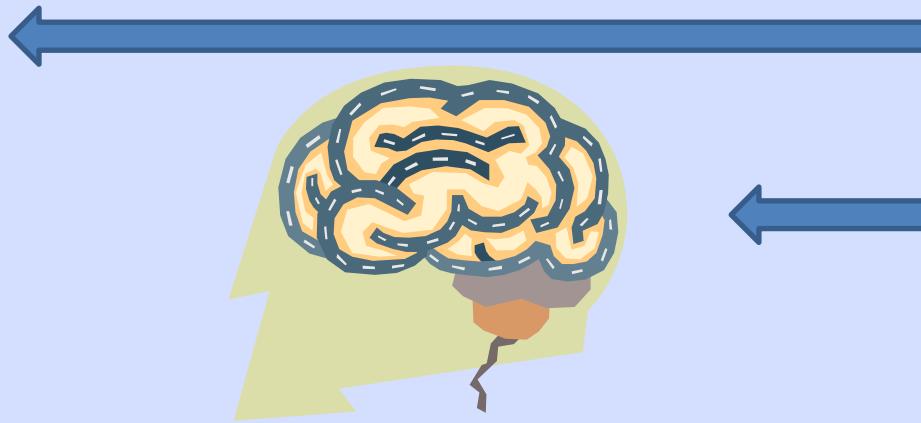


ENDOCRINE

NEUROLOGIC

IMMUNE



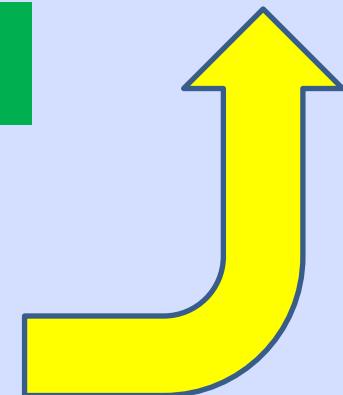
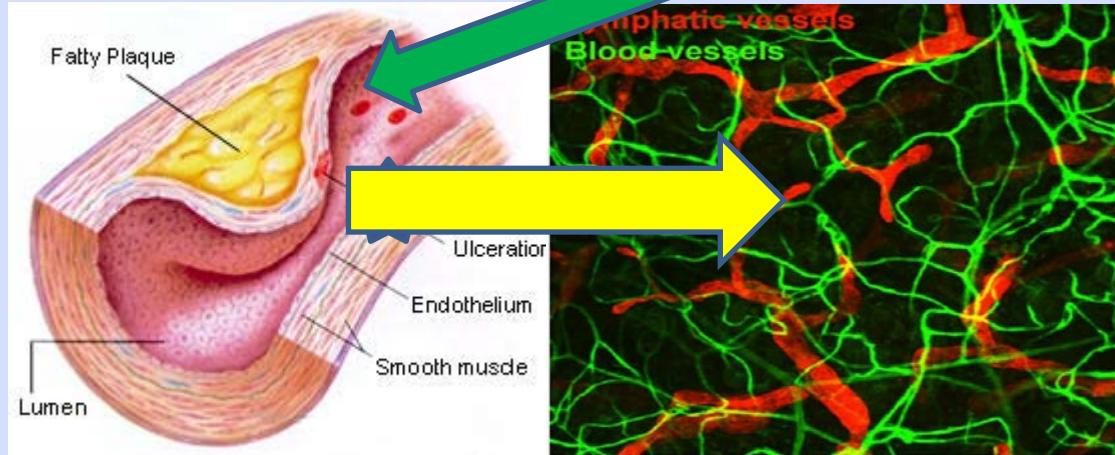


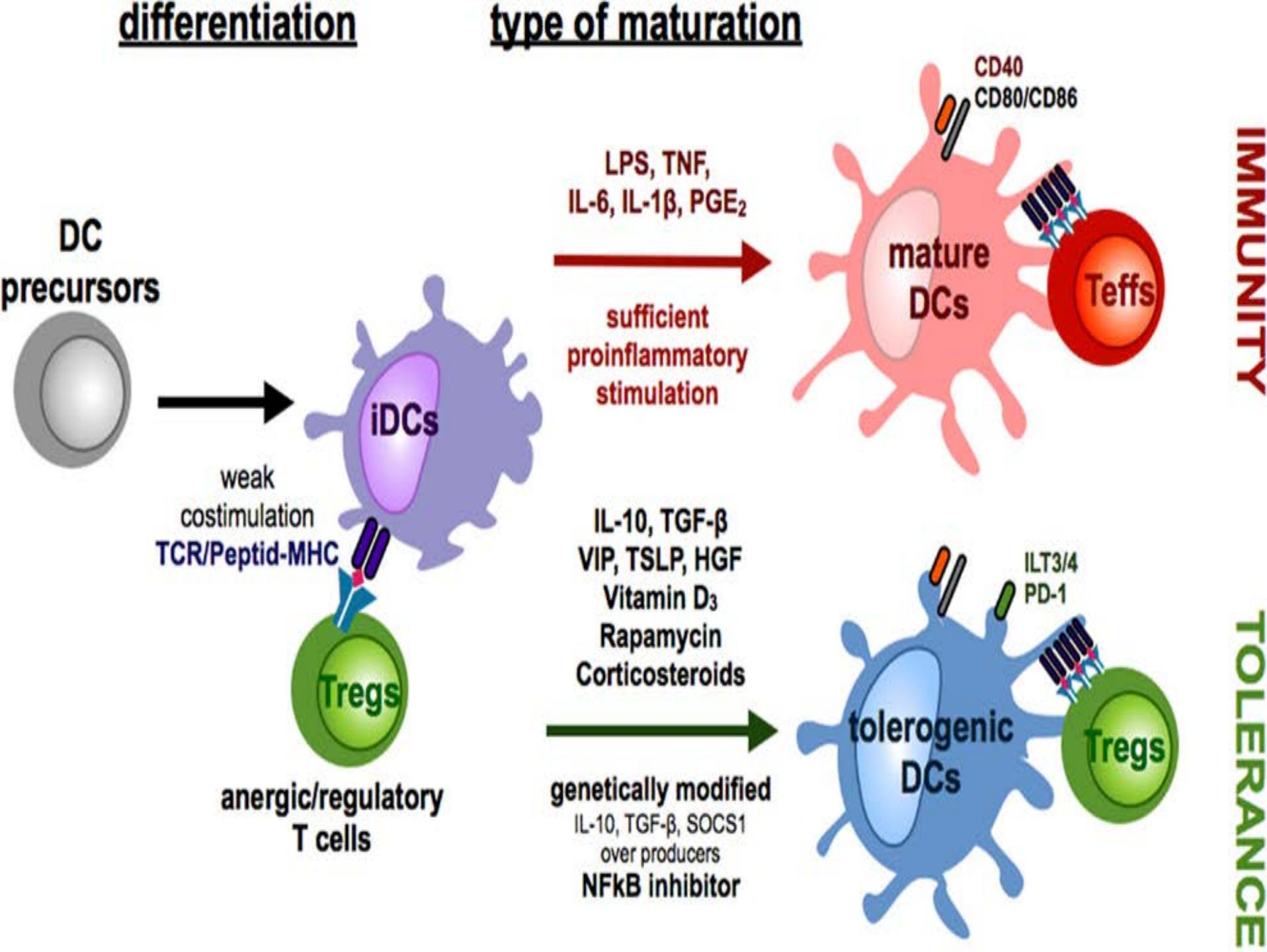
ENDOCRINE

NEUROLOGIC

IMMUNE

M2,M3





Clin Exp Immunol. 2013 May;172(2):148-57. doi: 10.1111/cei.12038.

Tolerogenic Dendritic Cell Therapy For Rheumatoid Arthritis: Where Are We Now?

Hilkens CM¹, Isaacs JD.

¹Institute Of Cellular Medicine, Newcastle University, Newcastle Upon Tyne, UK. Catharien.Hilkens@ncl.ac.uk

Dendritic cells with tolerogenic function (tolDC) have become a promising immunotherapeutic tool for reinstating immune tolerance in rheumatoid arthritis (RA) and other autoimmune diseases.

The concept underpinning tolDC therapy is that it specifically targets the pathogenic autoimmune response while leaving protective immunity intact. Findings from human in-vitro and mouse in-vivo studies have been translated into the development of clinical grade tolDC for the treatment of autoimmune disorders.

Recently, two tolDC trials in RA and type I diabetes have been carried out and other trials are in progress are imminent.

In this review, we provide an update on tolDC therapy, in particular in relation to the treatment of RA, and discuss the challenges and the future perspectives of this new experimental immunotherapy.

A Heart-Healthy Diet May Also Prevent Cancer

Zora Djuric, PhD, research professor, University of Michigan

AICR Newsletter #122,

The Mediterranean Diet is very similar to the mostly plant-based diet that AICR recommends. It focuses on eating a wide variety of vegetables and fruits, with beans, whole grains, nuts and healthy fats like olive oil. Fish is frequently eaten, but meat, poultry and dairy foods are limited to small amounts.

Heart health was the first benefit researchers identified when results of early Mediterranean Diet studies were published in the 1990s. But recent evidence shows that eating this traditional diet may also reduce cancer risk.

Heart disease and cancer share a common risk factor: chronic inflammation.

.CANCER FINDINGS SHOW PROMISE

In her most recent study, a Mediterranean diet was shown to change the fats and micronutrients inside the colon tissue of healthy subjects. These changes had an anti-inflammatory effect, and inflammation has strong links to risk of colon cancer.

Dr. Djuric likes the Mediterranean Diet approach to cancer prevention. "**It is a way to not only reduce risk of several kinds of cancer, but to reduce risk of diabetes and heart disease as well.**"

Am J Physiol Heart Circ Physiol. 2012 Feb 1;302(3):H643-53. doi: 10.1152/Ajpheart.00606.2011. Epub 2011 Dec 9.

Impairments In The Intrinsic Contractility Of Mesenteric Collecting Lymphatics In A Rat Model Of Metabolic Syndrome.

Zawieja Sd1, Wang W, Wu X, Nepiyushchikh Zv, Zawieja Dc, Muthuchamy M.
Texas A & M

Thus, our data provide the first evidence that MetSyn induces a remodeling of collecting lymphatics, thereby effectively reducing their potential load capabilities and impairing the intrinsic contractility required for proper lymph flow.

PMID: 22159997 PMCID: PMC3353801 DOI: 10.1152/ajpheart.00606.2011

Lipopolysaccharide Modulates Neutrophil Recruitment And Macrophage Polarization On Lymphatic Vessels And Impairs Lymphatic Function In Rat Mesentery.

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¹Department Of Medical Physiology, Cardiovascular Research Institute, Division Of Lymphatic Biology, Texas A&M Health Science Center College Of Medicine, College Station, Texas; And
, Cumming School Of Medicine, University Of Calgary, Calgary, Alberta, Ca

Impairment of the lymphatic system is apparent in multiple inflammatory pathologies connected to elevated endotoxins such as LPS. However, the direct mechanisms by which LPS influences the lymphatic contractility are not well understood. We hypothesized that a dynamic modulation of innate immune cell populations in mesentery under inflammatory conditions perturbs tissue cytokine/chemokine homeostasis and subsequently influences lymphatic function. We used rats that were intraperitoneally injected with LPS (10 mg/kg) to determine the changes in the profiles of innate immune cells in the mesentery and in the stretch-mediated contractile responses of isolated lymphatic preparations. Results demonstrated a reduction in the phasic contractile activity of mesenteric lymphatic vessels from LPS-injected rats and a severe impairment of lymphatic pump function and flow. There was a significant reduction in the number of neutrophils and an increase in monocytes/macrophages present on the lymphatic vessels and in the clear pathways.

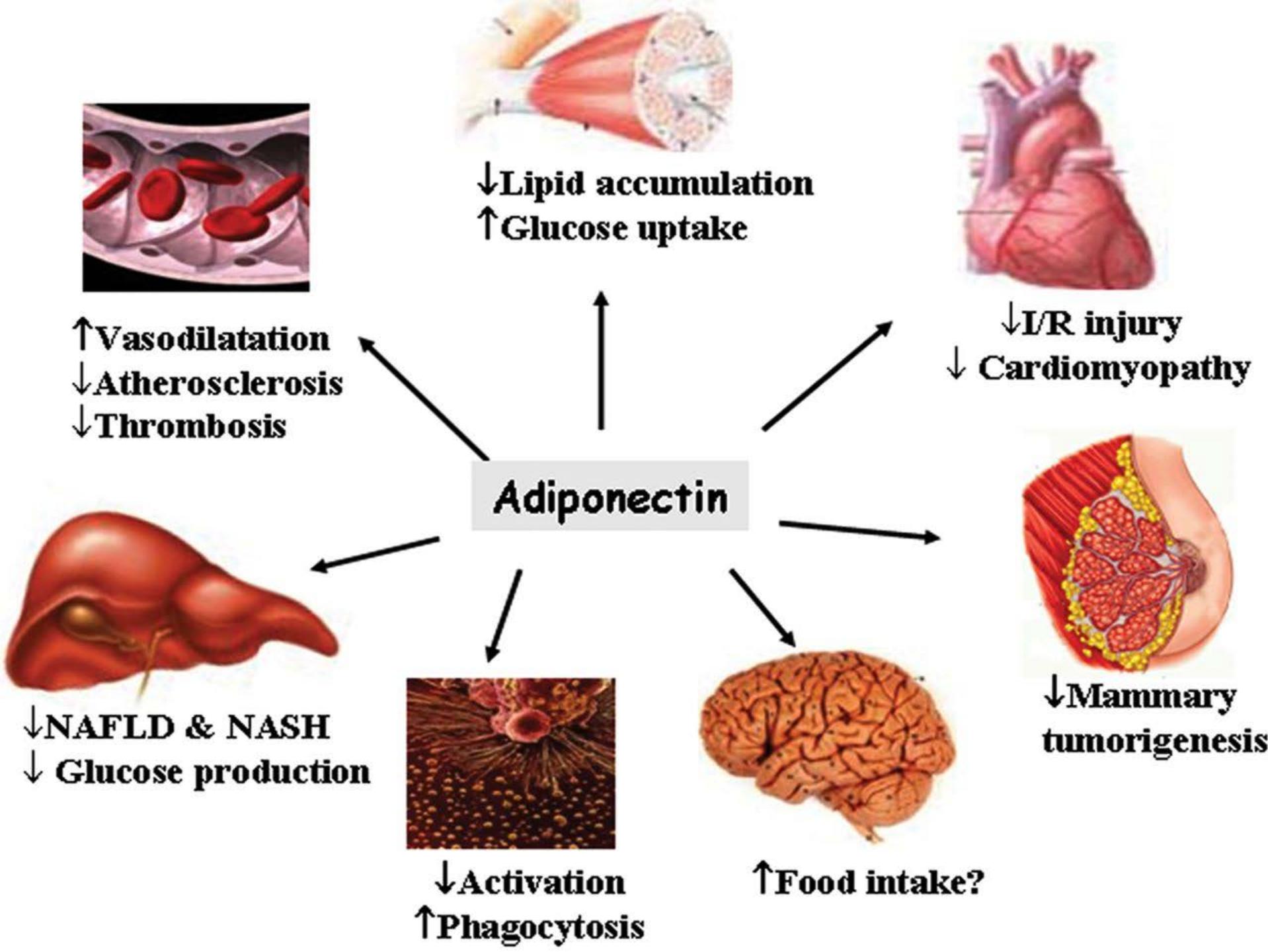
Thus, our data provide the first evidence connecting the dynamic changes in innate immune cells on or near the lymphatics and complex cytokine milieu during inflammation with lymphatic dysfunction.

The lymphatics have emerged as a central player in the process of inflammation and play active roles in both resolution and progression of inflammation (40, 76). Mesenteric lymphatics, in particular, are directly exposed to both the inflammatory activation and dyslipidemia resulting from the aberrant elevated postprandial chylomicron production in metabolic syndrome, as well as the dietary endotoxins, such as LPS associated with them (32, 37, 74).

Lymphatic vessel leakage is associated with obesity, atherosclerosis, edema and cancer. Researchers at the University of Missouri have, for the first time, linked leaky lymphatic vessels to diabetes. Using mice as a model of type 2 diabetes, researcher Joshua Scallan and colleagues determined that the lymphatic vessels of diabetic mice were **over 130 times more permeable** than the vessels of the healthy mice.

"We now know for the first time that when individuals have type 2 diabetes, the walls of their lymphatic vessels are defective and become increasingly permeable, or leaky," Scallan said

The findings have significant meaning for those with type 2 diabetes, who are already at risk for the trappings of metabolic disease. “Based on an emerging body of literature, we expect that the degree of lymphatic barrier dysfunction in diabetic mice is **sufficient to reduce lymph flow**, thereby trapping lipids and cholesterol in the tissue,” the authors state. “This effect is likely significant, because inhibiting lymphatic transport of cholesterol bound to high-density lipoprotein from the tissues to the liver exacerbates atherosclerosis. Further, these findings link lymphatic endothelial dysfunction to lymph leakage, which leads to tissue adipose deposition, obesity, fibrosis, and inflammation.”



Adiponectin protects against:

HMW Adiponectin

Endothelial Dysfunction

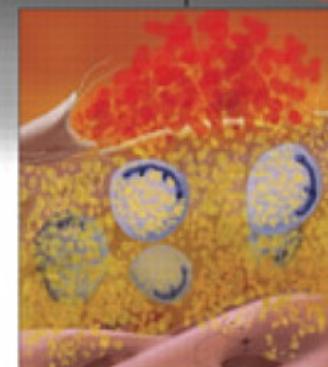
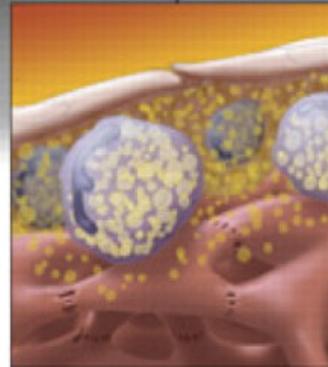
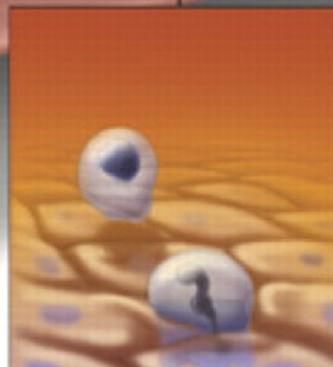
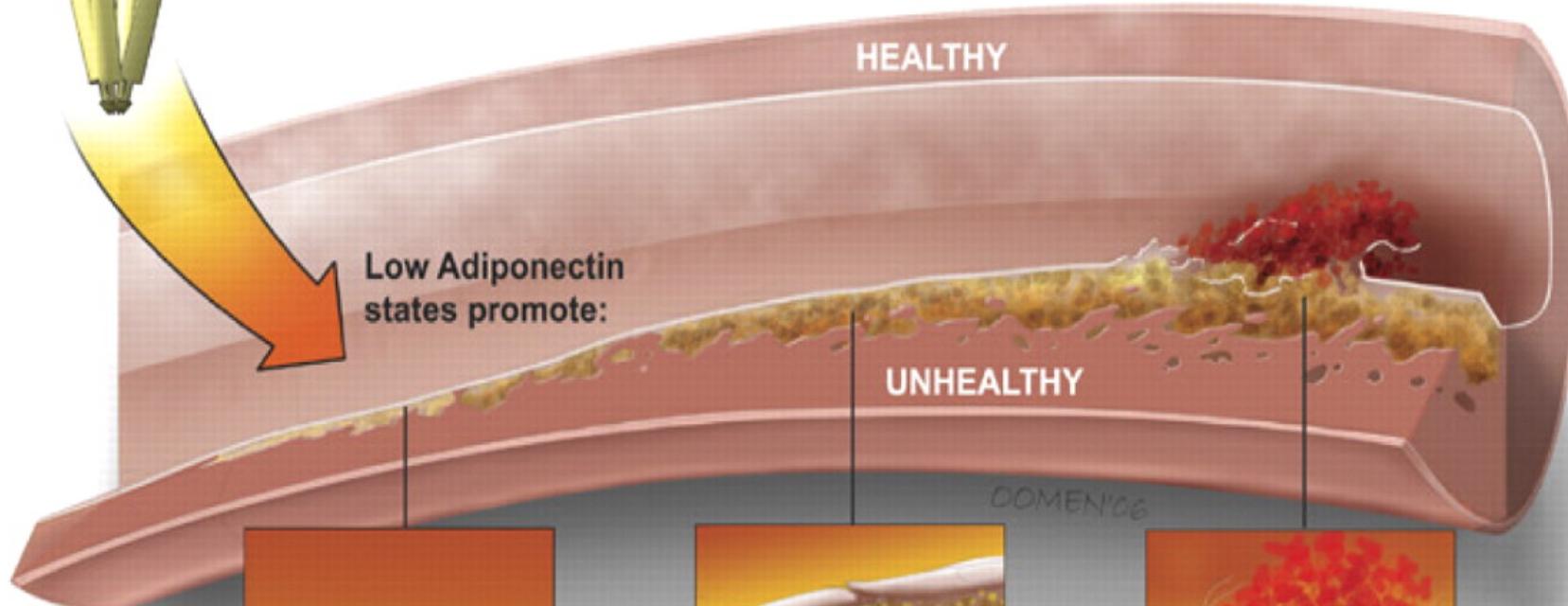
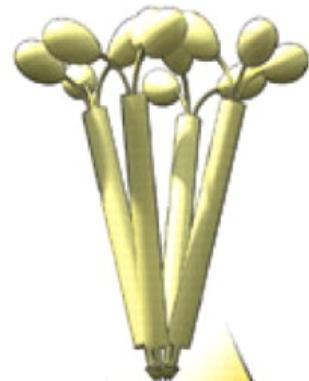
- ↑ NO
- ↑ eNOS
- ↓ EC apoptosis
- ↓ ROS formation

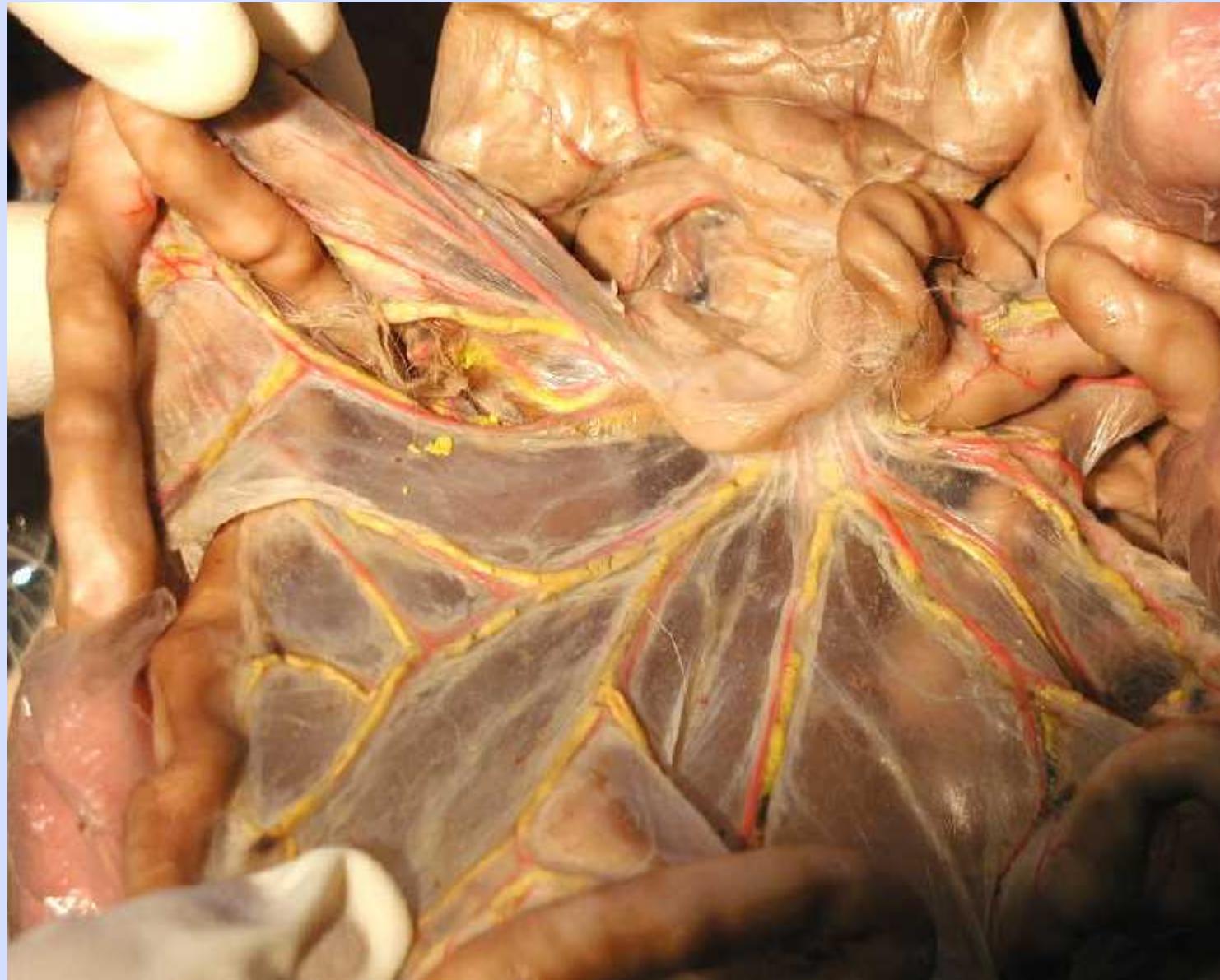
Plaque Initiation and Progression

- ↓ ICAM-1
- ↓ VCAM-1
- ↓ E-Selectin
- ↓ NF_κB
- ↓ TNF α & IL-8 activity
- ↓ Macrophage class A scavenger receptors
- ↑ IL-10

Plaque Rupture and Thrombosis

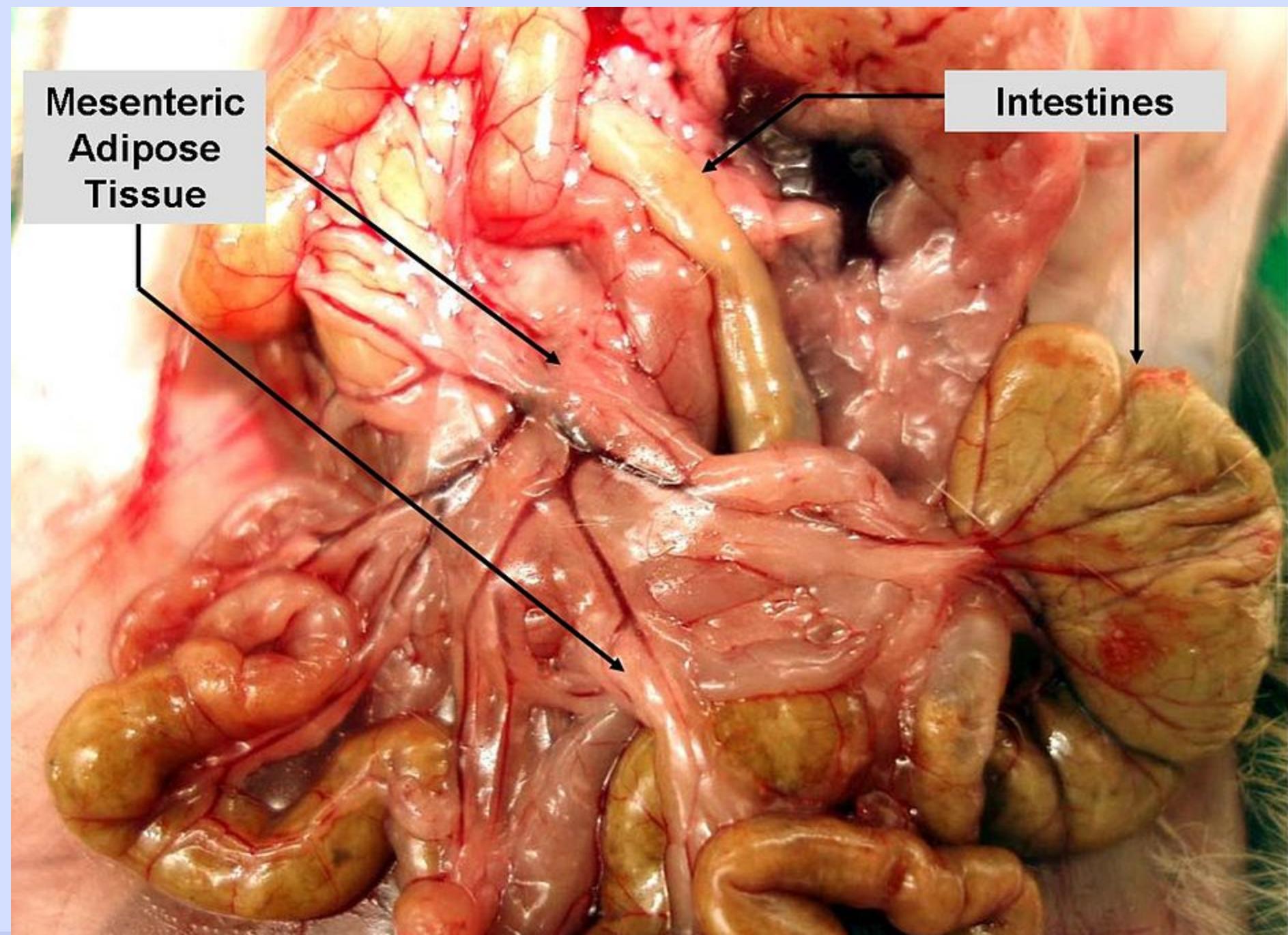
- ↑ TIMP-1
- ↓ Fibrous cap thinning
- ↓ Platelet aggregation
- ↓ Thrombus formation

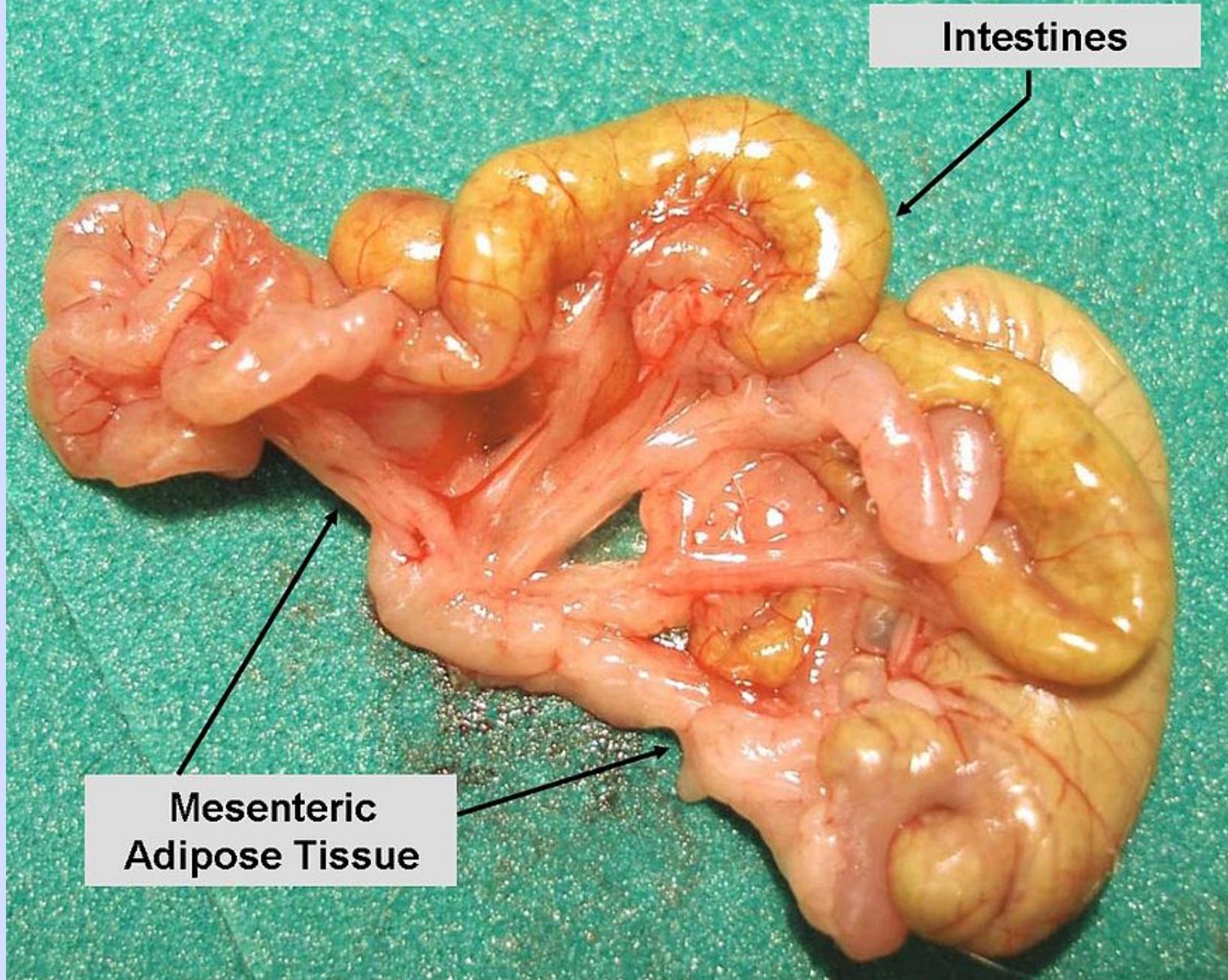




Mesenteric
Adipose
Tissue

Intestines





Clin Gastroenterol Hepatol. 2012 Oct;10(10):1096-100. doi: 10.1016/j.cgh.2012.08.012.

Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications.

Fasano Al.

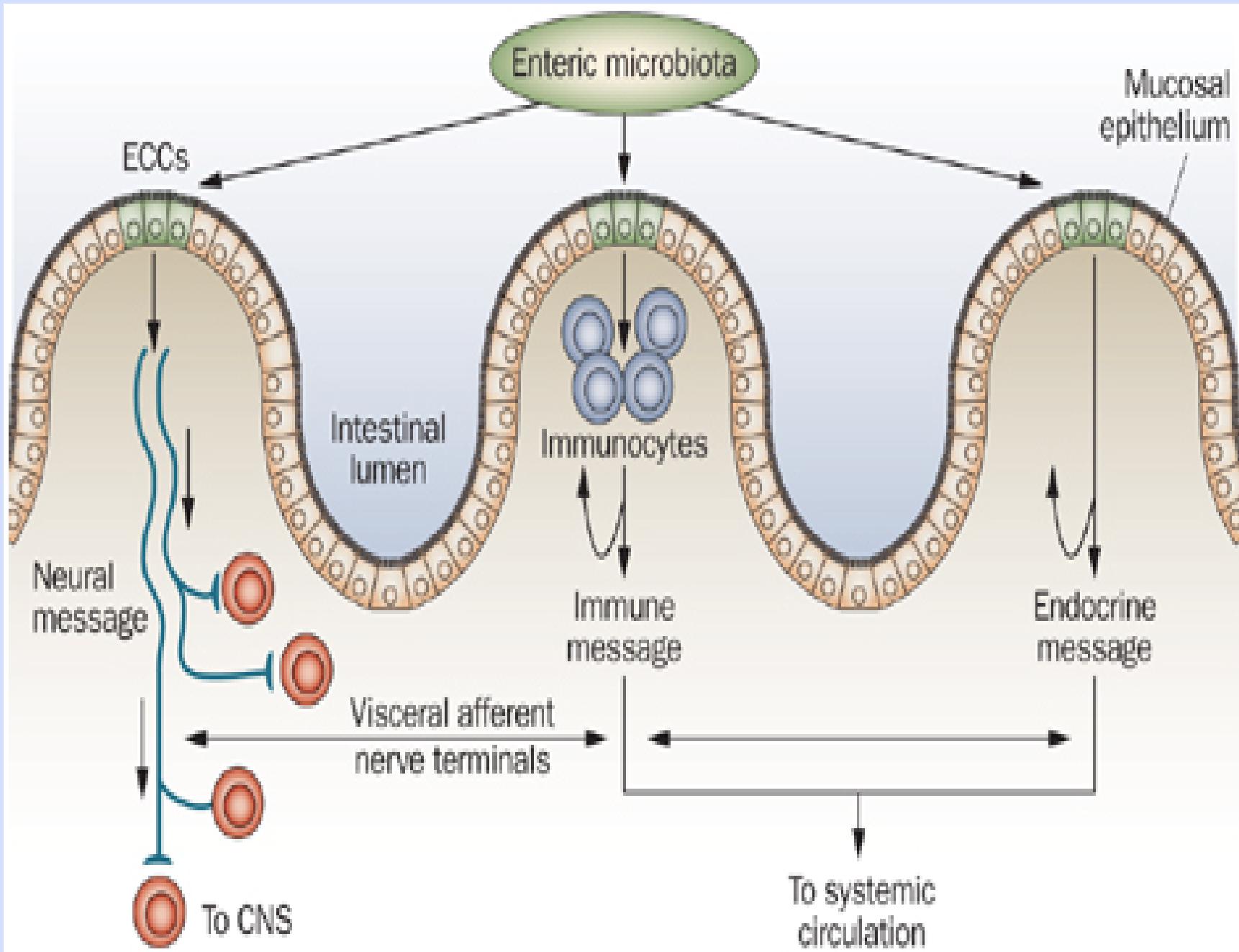
Abstract

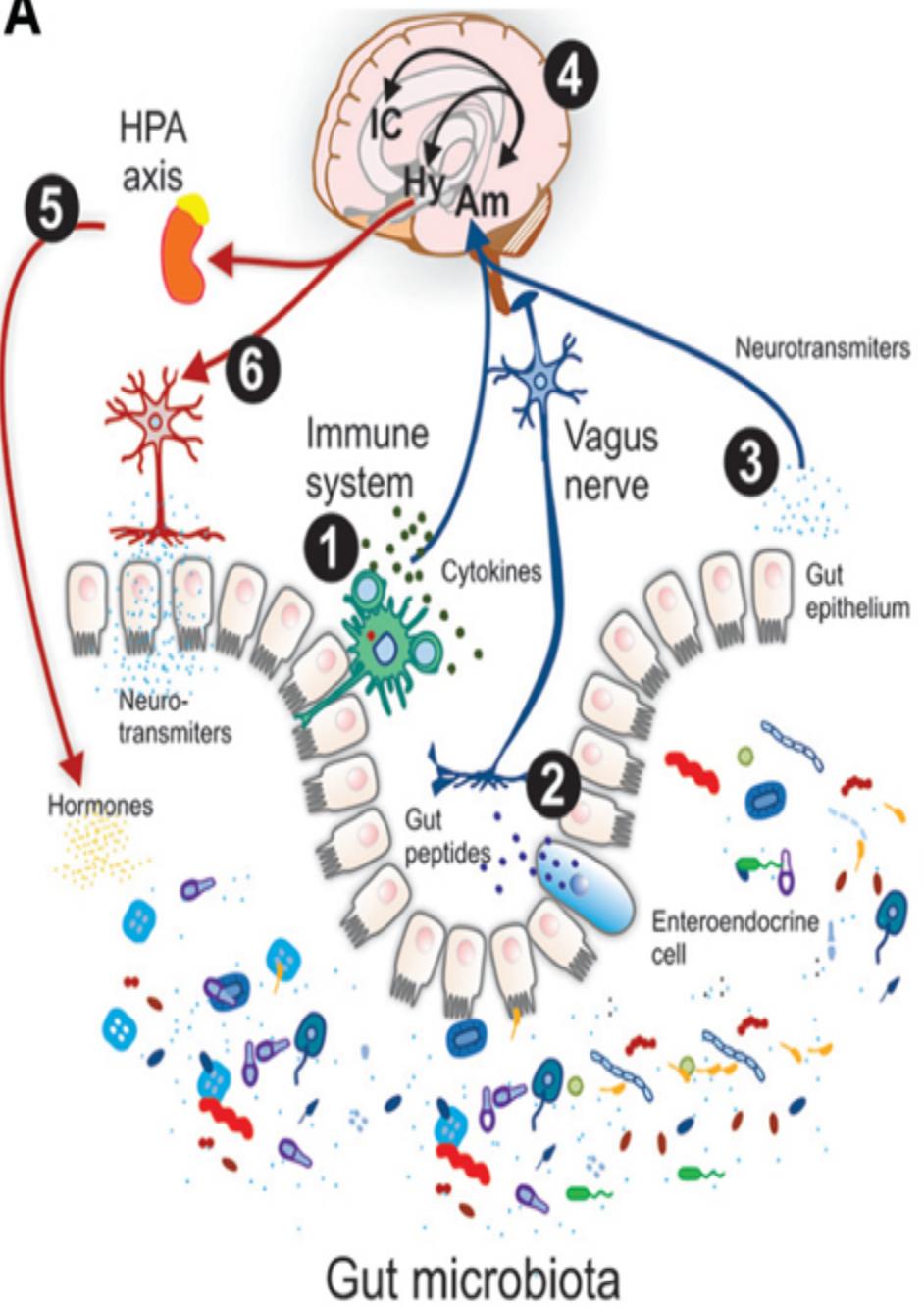
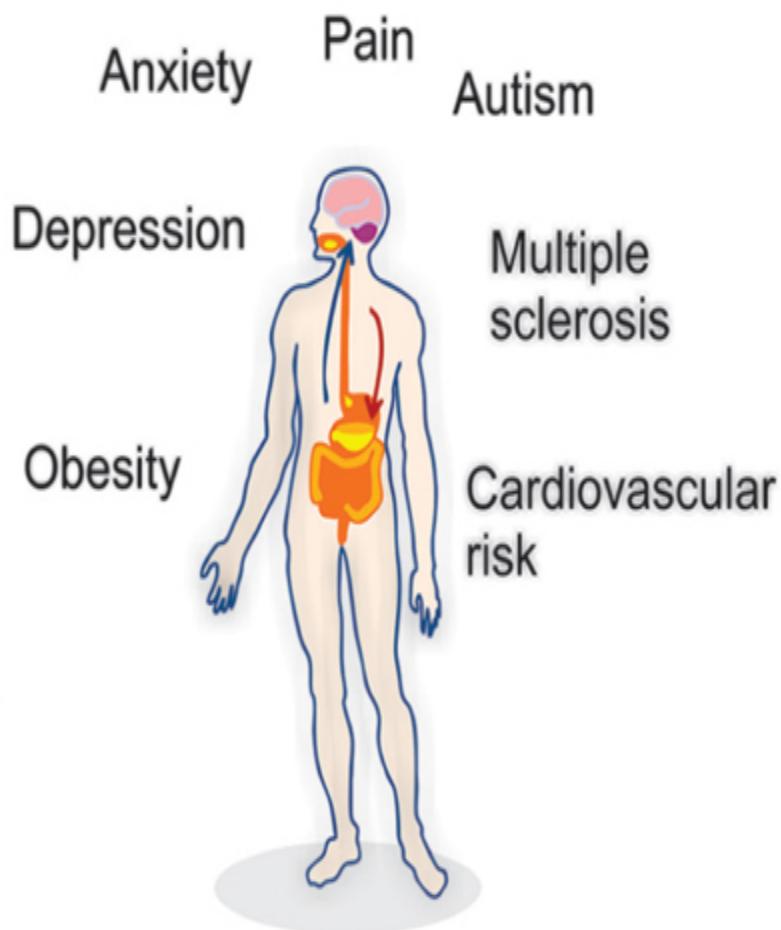
One of the most important and overlooked functions of the gastrointestinal tract is to provide a dynamic barrier to tightly controlled antigen trafficking through both the transcellular and paracellular pathways. Intercellular tight junctions (TJ) are the key structures regulating paracellular trafficking of macromolecules. Although steady progress has been made in understanding TJ ultrastructure, relatively little is known about their pathophysiological regulation. Our discovery of **zonulin, the only known physiological modulator of intercellular TJ described so far**, increased understanding of the intricate mechanisms that regulate gut permeability and led us to appreciate that its up-regulation in genetically susceptible individuals may lead to immune-mediated diseases. This information has translational implications, because the zonulin pathway is currently exploited to develop both diagnostic and therapeutic applications pertinent to a variety of immune-mediated diseases.

Leaky gut and autoimmune diseases.

Fasano AL

Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on the role of impaired intestinal barrier function on autoimmune pathogenesis. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens. Zonulin is the only physiologic modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the zonulin pathway is deregulated in genetically susceptible individuals, autoimmune disorders can occur. This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing the zonulin-dependent intestinal barrier function. Both animal models and recent clinical evidence support this new paradigm and provide the rationale for innovative approaches to prevent and treat autoimmune diseases.



A**B****Gut microbiota**

INFLAMMATORY BOWEL DISEASE



FOCAL PLANE

24

CERVICAL LYMAPHATICS AND BRAIN WASTES CLEARANCE

Phosphodiesterase III Inhibitor Promotes Drainage Of Cerebrovascular B-amyloid

Ann Clin Transl Neurol. 2014 Aug; 1(8): 519–533

Takakuni Maki,^{1,2} Yoko Okamoto,^{1,3} Roxana O Carare,⁴ Yoshiki Hase,¹ Yorito Hattori,^{1,5} Cheryl A Hawkes

¹department Of Neurology, Graduate School Of Medicine, Kyoto University, Kyoto, Japan

- The CNS is devoid of conventional lymphatic vessels, unlike other organs that contain networks of lymphatic vessels.....However, the perivascular drainage system in the brain performs the main function assigned to systemic

lymphatic vessels. Animal studies using various tracers have demonstrated that interstitial fluid and solutes drain rapidly via perivascular “lymphatic” pathways from brain parenchyma along basement membranes in the walls of capillaries and arteries in the opposite direction of the arterial blood flow **to cervical lymph nodes**

- This drainage route corresponds very closely with the distribution of A_{Beta} in the basement membranes of capillary and artery walls in CAA.⁴⁵ The failure of this drainage in the ageing brain and in the presence of CAA results in the accumulation of insoluble and soluble A_{Beta} and probably other metabolites that would lead to loss of homeostasis of the neuronal environment.^{15,42}

This notion is also supported by the experimental data that the vascular A_{Beta} deposition is increased following bilateral common carotid artery stenosis of CAA model mice or middle cerebral artery occlusion model mice. Such “lymphatic” congestion of the brain may be improved by vasoactive cilostazol.

A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules.

[Aspelund A¹](#), [Antila S¹](#), [Proulx ST²](#), [Karlsen TV³](#), [Karaman S²](#), [Detmar M²](#), [Wiig H³](#), [Alitalo K⁴](#).

Author information

Abstract

The central nervous system (CNS) is considered an organ devoid of lymphatic vasculature. Yet, part of the cerebrospinal fluid (CSF) drains into the cervical lymph nodes (LN_s). The mechanism of CSF entry into the LN_s has been unclear. Here we report the surprising finding of a lymphatic vessel network in the dura mater of the mouse brain. We show that dural lymphatic vessels absorb CSF from the adjacent subarachnoid space and brain interstitial fluid (ISF) via the glymphatic system. Dural lymphatic vessels transport fluid into deep cervical LN_s (dcLN_s) via foramina at the base of the skull. In a transgenic mouse model expressing a VEGF-C/D trap and displaying complete aplasia of the dural lymphatic vessels, macromolecule clearance from the brain was attenuated and transport from the subarachnoid space into dcLN_s was abrogated. Surprisingly, brain ISF pressure and water content were unaffected. **Overall, these findings indicate that the mechanism of CSF flow into the dcLN_s is directly via an adjacent dural lymphatic network, which may be important for the clearance of macromolecules from the brain.** Importantly, these results call for a reexamination of the role of the lymphatic system in CNS physiology and disease.

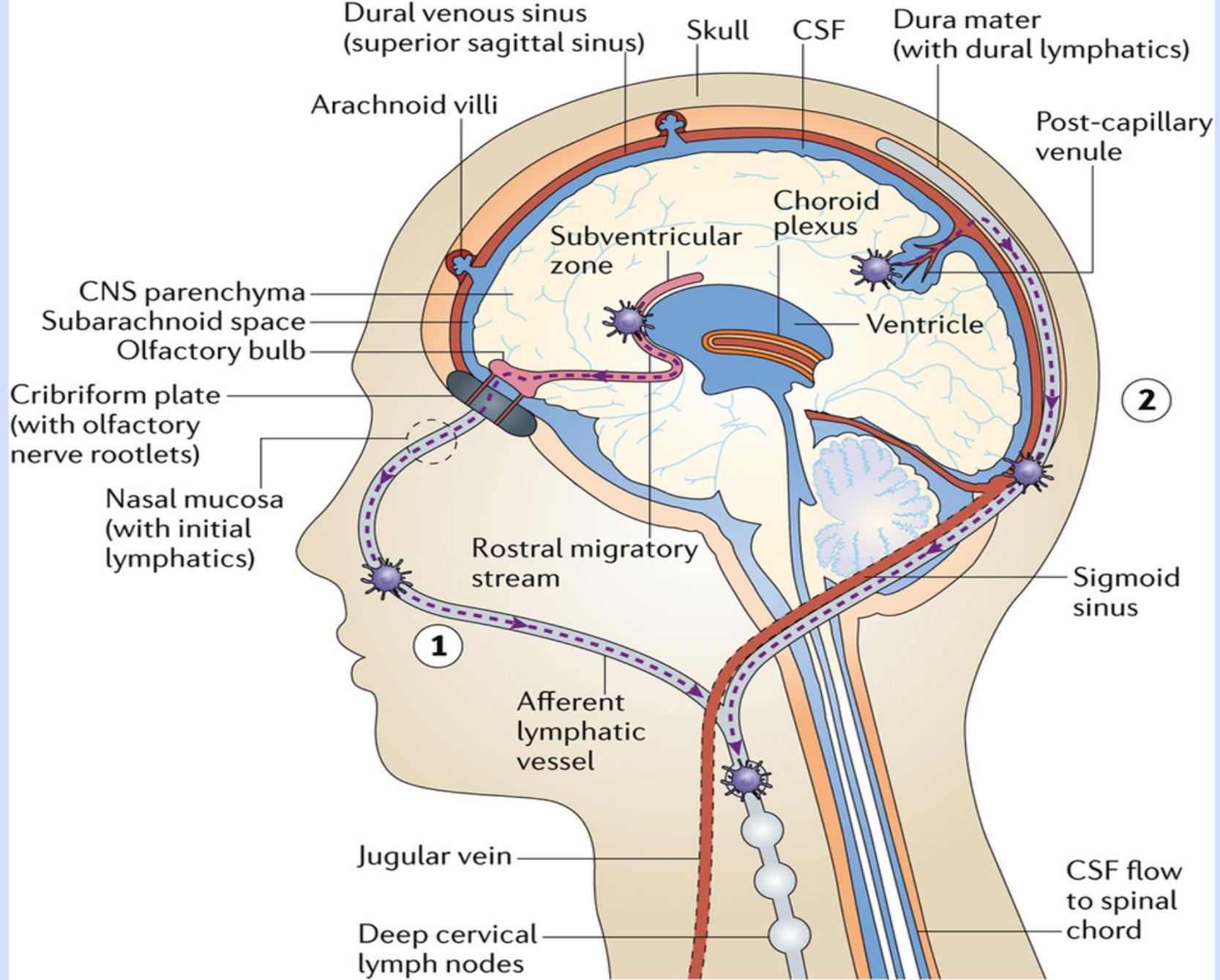
Understanding The Functions And Relationships Of The Glymphatic System And Meningeal Lymphatics 2017

Antoine Louveau,¹ Benjamin A. Plog,² Salli Antila,³ Kari Alitalo,³ Maiken Nedergaard,^{2,4} And Jonathan Kipnis¹

Recent discoveries of the glymphatic system and of meningeal lymphatic vessels have generated a lot of excitement, along with some degree of skepticism. Here, we summarize the state of the field and point out the gaps of knowledge that should be filled through further research. We discuss the glymphatic system as a system that allows CNS perfusion by the cerebrospinal fluid (CSF) and interstitial fluid (ISF).

We also describe the recently characterized meningeal lymphatic vessels and their role in drainage of the brain ISF, CSF, CNS-derived molecules, and immune cells from the CNS and meninges to the peripheral (CNS-draining) lymph nodes. **We speculate on the relationship between the two systems and their malfunction that may underlie some neurological diseases.**

Although much remains to be investigated, these new discoveries have changed our understanding of mechanisms underlying CNS immune privilege and CNS drainage. Future studies should explore the communications between the glymphatic system and meningeal lymphatics in CNS disorders and develop new therapeutic modalities targeting these systems.



Commensal Microbiota And Myelin Autoantigen Cooperate To Trigger Autoimmune Demyelination

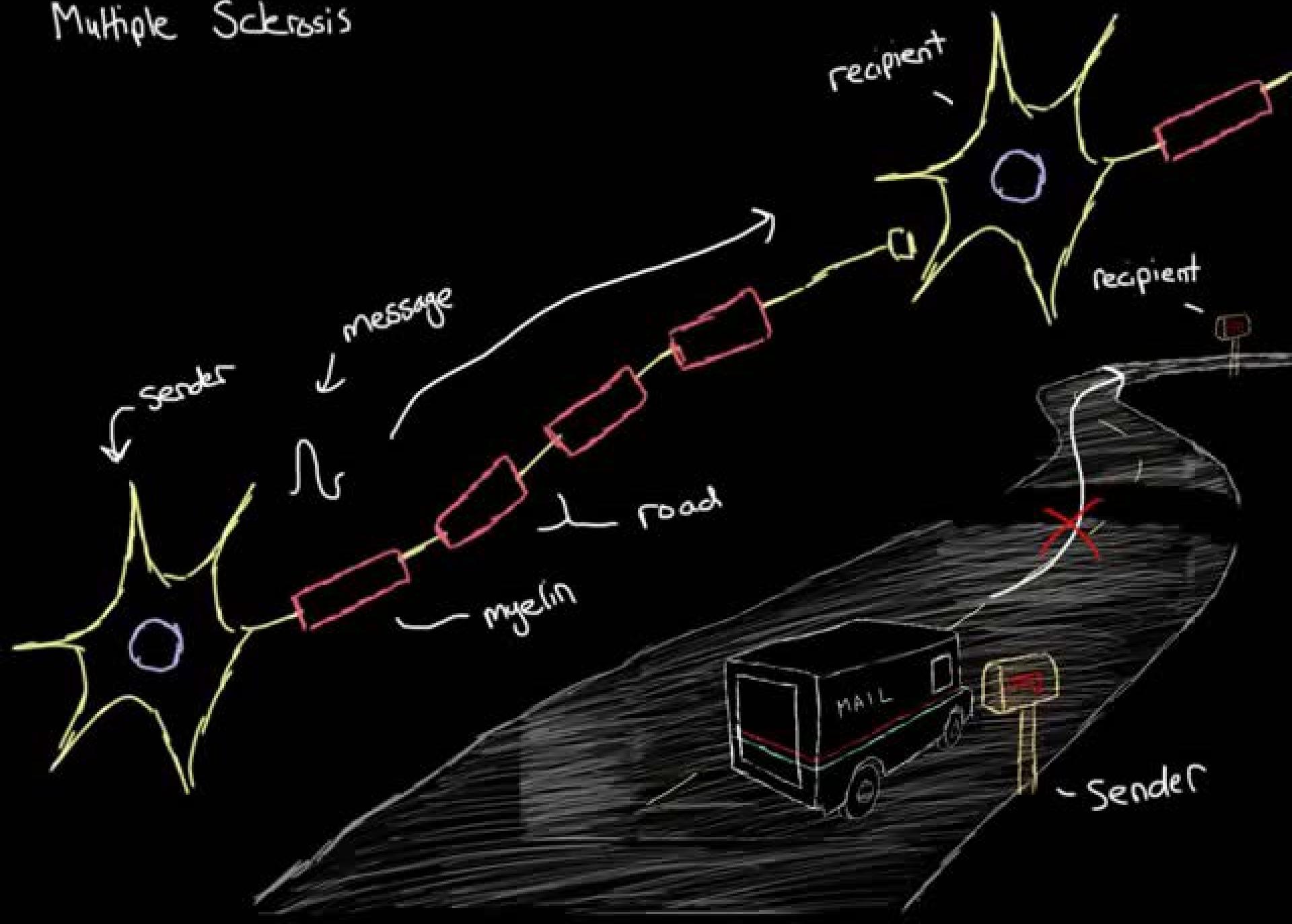
Kerstin Berer¹, Marsilius Mues¹, Michail Koutrolos¹, Zakeya Al Rasbi¹, Marina Boziki¹, Caroline Johner², Hartmut Wekerle¹ & Gurumoorthy Krishnamoorthy¹

Active multiple sclerosis lesions show inflammatory changes suggestive of a combined attack by autoreactive T and B lymphocytes against brain white matter¹. These pathogenic immune cells derive from progenitors that are normal, innocuous components of the healthy immune **But become autoaggressive upon pathological activation.** The stimuli triggering this autoimmune conversion have been commonly attributed to environmental factors, in particular microbial infection.

We show that the commensal gut flora—in the absence of pathogenic agents—is essential in triggering immune processes, leading to a relapsing–remitting autoimmune disease driven by myelin-specific CD41 T cells.

We show further that recruitment and activation of autoantibody-producing B cells from the endogenous immune repertoire depends on availability of the target autoantigen, myelin oligodendrocyte glycoprotein (MOG), and commensal microbiota. Our observations identify a sequence of events triggering organ-specific autoimmune disease and these processes may offer novel therapeutic targets. The relapsing–remitting (RR) mouse model uses transgenic SJL/J mice expressing, in a large proportion of their CD41 T cells, a transgenic T-cell antigen receptor (TCR) recognizing MOG peptide 92–106 in the context of MHC class II, I-As. These mice spontaneously develop experimental autoimmune encephalomyelitis (EAE) with successive disease bouts that often affect different central nervous system (CNS) tissues. The disease is initiated by the transgenic CD41 T cells, which first infiltrate the CNS, and by MOG-autoantibody-producing B cells recruited from the natural immune repertoire³. Whereas in our facility close to 80% of RR mice developed spontaneous EAE within 3–8 months of age, the rate was variable in other institutions, with spontaneous EAE incidences ranging from 35–90% (unpublished data). This recalled previous investigations that also observed that the frequency of spontaneous EAE in myelin-specific TCR transgenic mice varied in different breeding centres⁴. Because our mice were reared under specific pathogen-free (SPF) conditions, we tested the possible contributions of the non-pathogenic commensal flora to the triggering of a spontaneous CNS-specific autoimmune disease. We first compared the incidence of spontaneous EAE between RR mice housed under SPF and completely germ-free conditions. The differences were marked. Whereas, as reported before, most SPF-bred RR mice came down with EAE within 3–8 months³, germ-free RR mice remained fully protected throughout their life (Fig. 1a). As the commensal microbiota have a central function in driving the correct development of the immune system⁵, the absence of spontaneous EAE in germ-free RR mice may have reflected a general immune deficiency due to missing microbial stimuli. However, two observations argue against a profound and irreversible non-reactivity. First, RR mice, which had been germ free (and disease free) for 6–12 weeks, promptly developed EAE when re-colonized with conventional commensal microbiota (Fig. 1b.). This suggests that the immune system of germ-free mice had grown efficient enough to mount a full autoimmune attack within a relatively brief period of time) Recent studies established that components of the commensal microbiota profoundly shape the gut-associated lymphatic tissue (GALT),

Multiple Sclerosis



Brain Behav Immun. 2014 Feb;36:9-14. doi: 10.1016/j.bbi.2013.10.012. Epub 2013 Oct 18.

Afferent And Efferent Immunological Pathways Of The Brain. Anatomy, Function And Failure.

Carare Ro¹, Hawkes Ca², Weller Ro².

Here we review: (1) the structure and function of afferent lymphatic drainage of ISF and CSF, (2) mechanisms involved in the efferent pathways by which lymphocytes enter the brain and (3) the failure of lymphatic drainage of the brain parenchyma with age and the role of such failure in the pathogenesis of Alzheimer's disease.

Clearance Of Beta-amyloid In The Brain.

Ueno M, Chiba Y, Matsumoto K, Nakagawa T, Miyanaka H¹.

Kagawa University

Intravascular substances invade extracellular spaces in the brain via endothelial cells in the sites without bloodbrain barrier (BBB) and move not only in the cerebrospinal fluid (CSF) but also in the interstitial fluid (ISF) of brain parenchyma adjacent to non-BBB sites. It is likely that CSF drains directly into the blood via arachnoid villi and granulations and also to lymph nodes via subarachnoid spaces in the brain and nasal lymphatics, whereas ISF drains to cervical lymph nodes through pathways along vascular wall of capillaries and arteries.

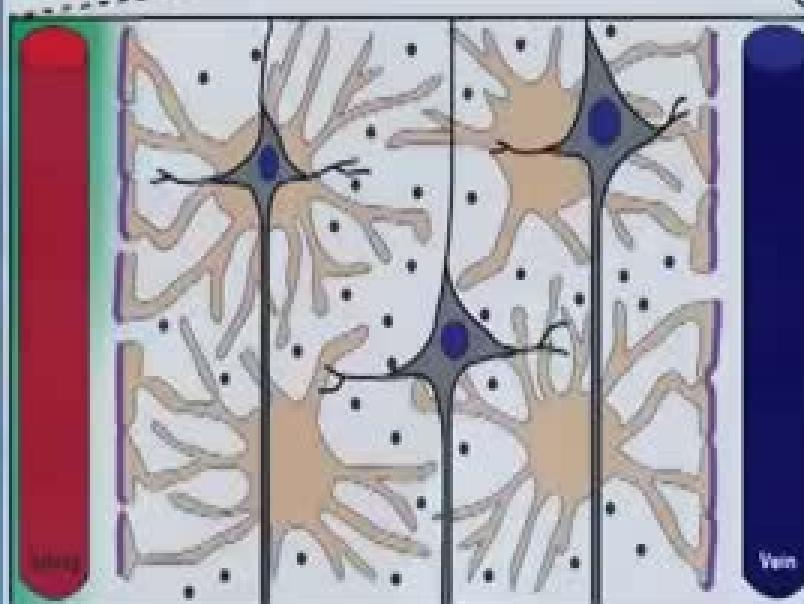
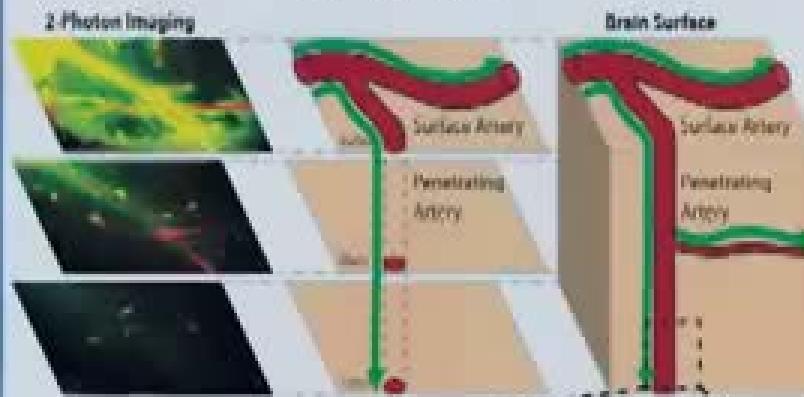
As the supposed pathways of fluids seem to be critical for the maintenance of normal brain function, it is reasonable to suspect that an obstacle to the passage of fluids through these pathways likely induces some kinds of brain dysfunction such as Alzheimer's disease.

According to assumed pathways for the elimination of amyloid- β (A β) from the brain, A β peptides produced mainly in neurons are degraded by peptidases, flow out of the brain parenchyma into the blood through efflux transporters located in cerebral vessels, drain through perivascular pathways into the cervical lymph nodes, or are taken up by some kinds of cells in the brain. As for the perivascular pathways, ISF including A β peptides diffuses in the extracellular spaces of the brain parenchyma, enters basement membranes of capillaries, passes into the tunica media of arteries, and drains out of the brain. In this review, these pathways for the clearance of fluids including A β from the brain into the blood are briefly reviewed and the relationship between dysfunction of these pathways and brain diseases is discussed

ALZHEIMERS DISEASE

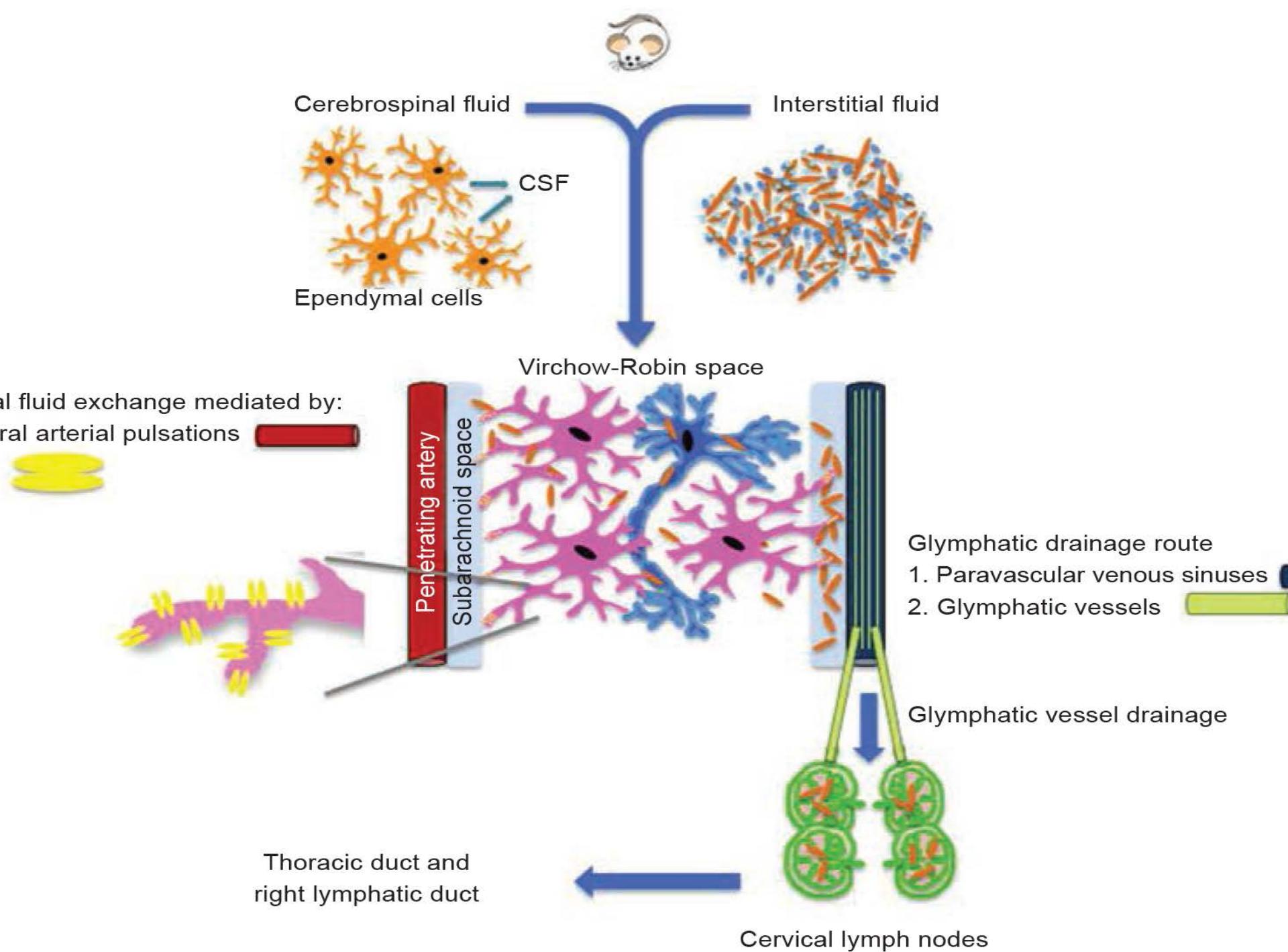
The Glymphatic Pathway

Para-Arterial CSF Influx

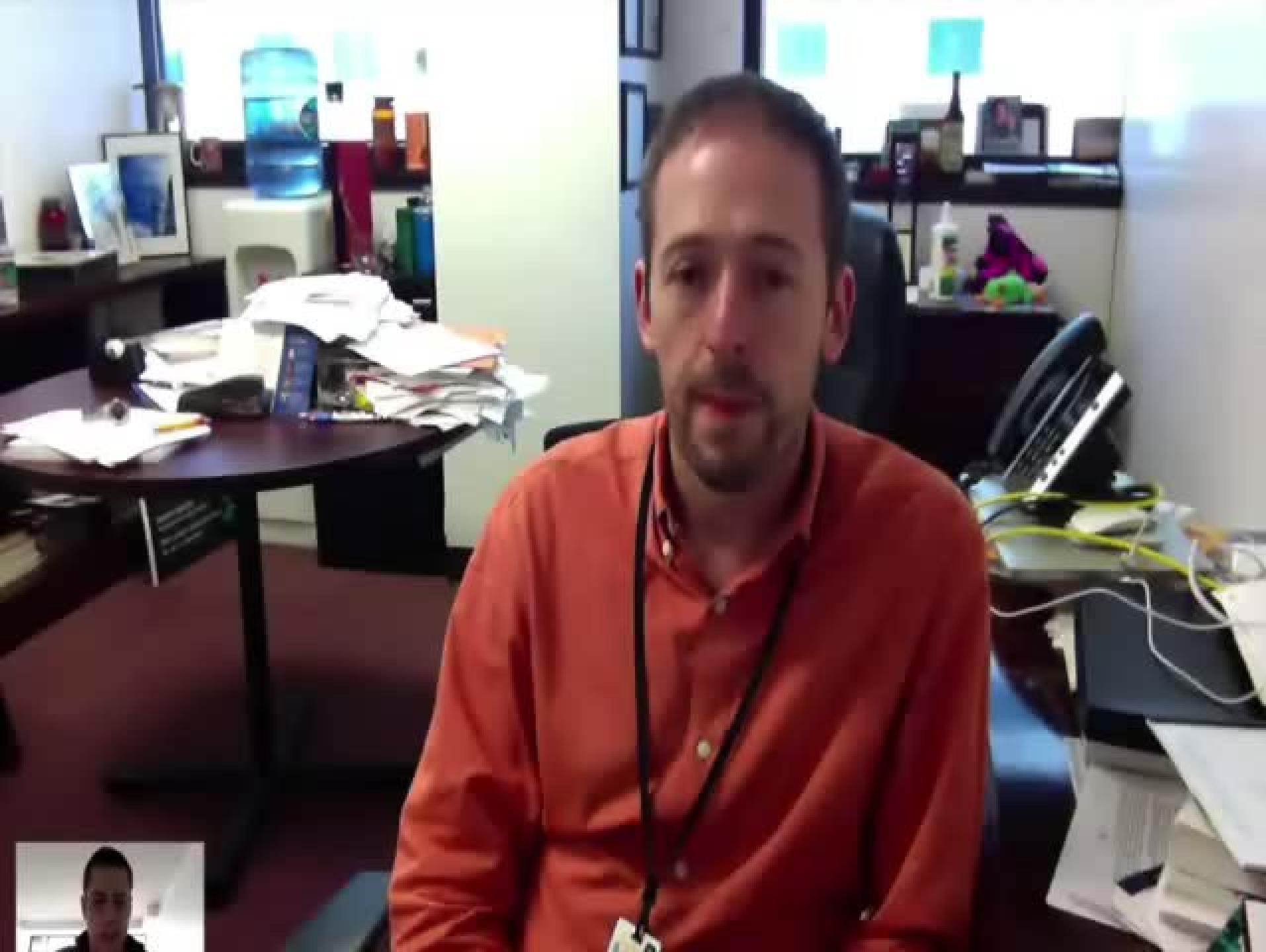


Metabolic Waste Clearance









POSITIONED

- **Cardiovascular disease is a chronic degenerative immune system disorder (CDD) caused by inflammation.**
- **The lymphatics play a major role in the clearance of pro- inflammatory substances.**
- **Exit of high density lipoprotein, as well as macrophage and dendritic cell migration is dependent on the lymphatic system.**
- **Other CDD may have immune and lymphatic dysfunction**

Cerebrospinal Fluid Stasis And Its Clinical Significance

James M. Whedon, DCA Instructor At The Dartmouth Institute For Health Policy And Clinical Practice In Lebanon, New Hampshire,
Donald Glassey, MSW, DC, LMTA

We hypothesize that stasis of the cerebrospinal fluid (CSF) occurs commonly and is detrimental to health. Physiologic factors affecting the normal circulation of CSF include cardiovascular, respiratory, and vasomotor influences. The CSF maintains the electrolytic environment of the central nervous system (CNS), influences systemic acid-base balance, serves as a medium for the supply of nutrients to neuronal and glial cells, functions as a lymphatic system for the CNS by removing the waste products of cellular metabolism, and transports hormones, neurotransmitters, releasing factors, and other neuropeptides throughout the CNS. Physiologic impedance or cessation of CSF flow may occur commonly in the absence of degenerative changes or pathology and may compromise the normal physiologic functions of the CSF. CSF appears to be particularly prone to stasis within the spinal canal. CSF stasis may be associated with adverse mechanical cord tension, vertebral subluxation syndrome, reduced cranial rhythmic impulse, and restricted respiratory function. Increased sympathetic tone, facilitated spinal segments, dural tension, and decreased CSF flow have been described as closely related aspects of an overall pattern of structural and energetic dysfunction in the axial skeleton and CNS.

Therapies directed at affecting CSF flow include osteopathic care (especially cranial manipulation), craniosacral therapy, chiropractic adjustment of the spine and cranium, Network Care (formerly Network Chiropractic), massage therapy (including lymphatic drainage techniques), yoga, therapeutic breathwork,

and cerebrospinal fluid technique. Further investigation into the nature and causation of CSF stasis, its potential effects upon human health, and effective therapies for its correction is warranted.

