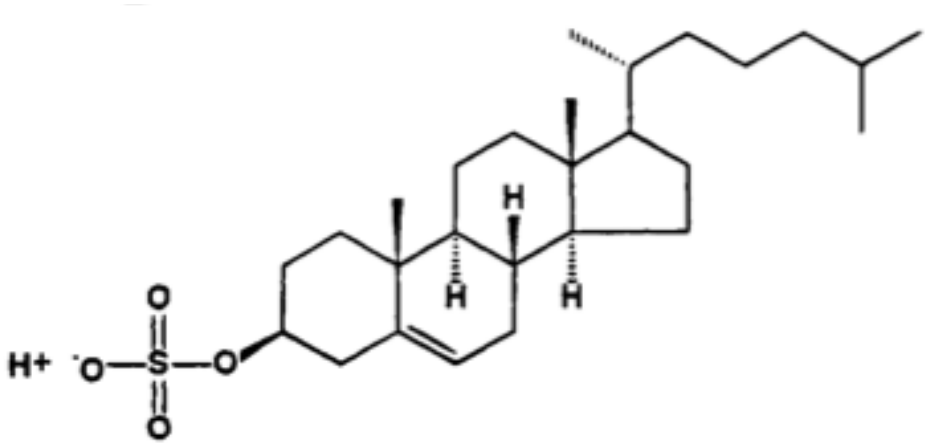
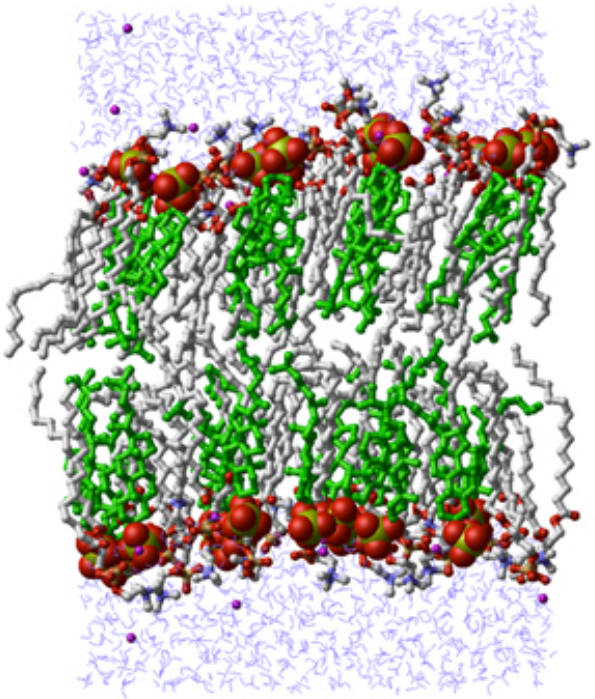
Cholesterol, Sulfate, and Heart Disease

Stephanie Seneff

Wise Traditions Workshop, London

Feb 9, 2014





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http://people.csail.mit.edu/seneff/London2014/SeneffHeartDisease2014.pptx

”If we all worked on the assumption that what is accepted as true is really true, there would be little hope of advance."

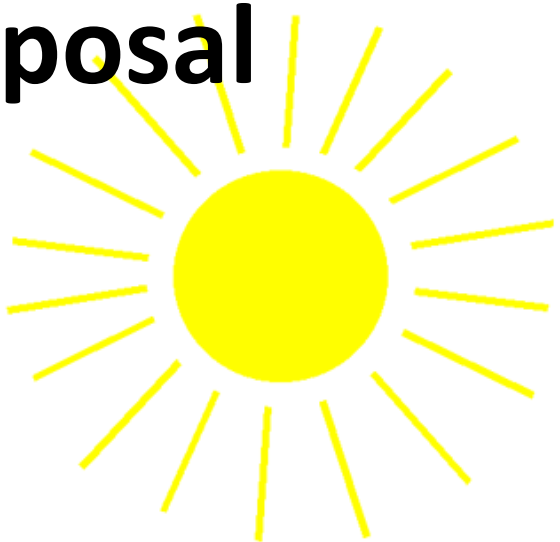
-- Orville Wright

Outline

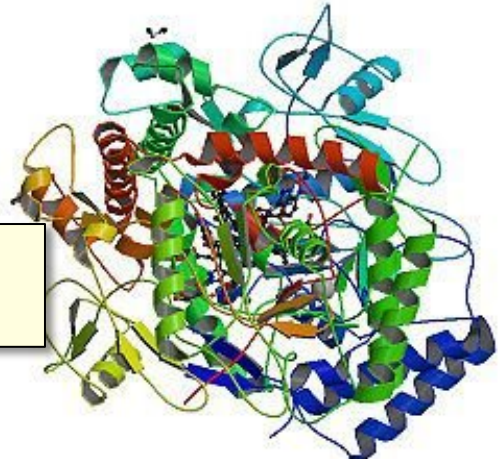
- Introduction
- Cholesterol sulfate
- Blood clots and hemorrhages
- Streaming potential
- Atherosclerosis is protective
- Summary

Introduction

A Provocative Proposal



- Cholesterol sulfate supplies oxygen, sulfur, cholesterol, energy and negative charge to all the tissues
- Sulfate is synthesized from sulfide in skin and blood stream utilizing energy in sunlight
  - Protects from UV damage and keeps microbes out
- Endothelial Nitric Oxide Synthase (eNOS) performs the magic



The skin is a solar powered battery!

High Cholesterol; Low Mortality!*

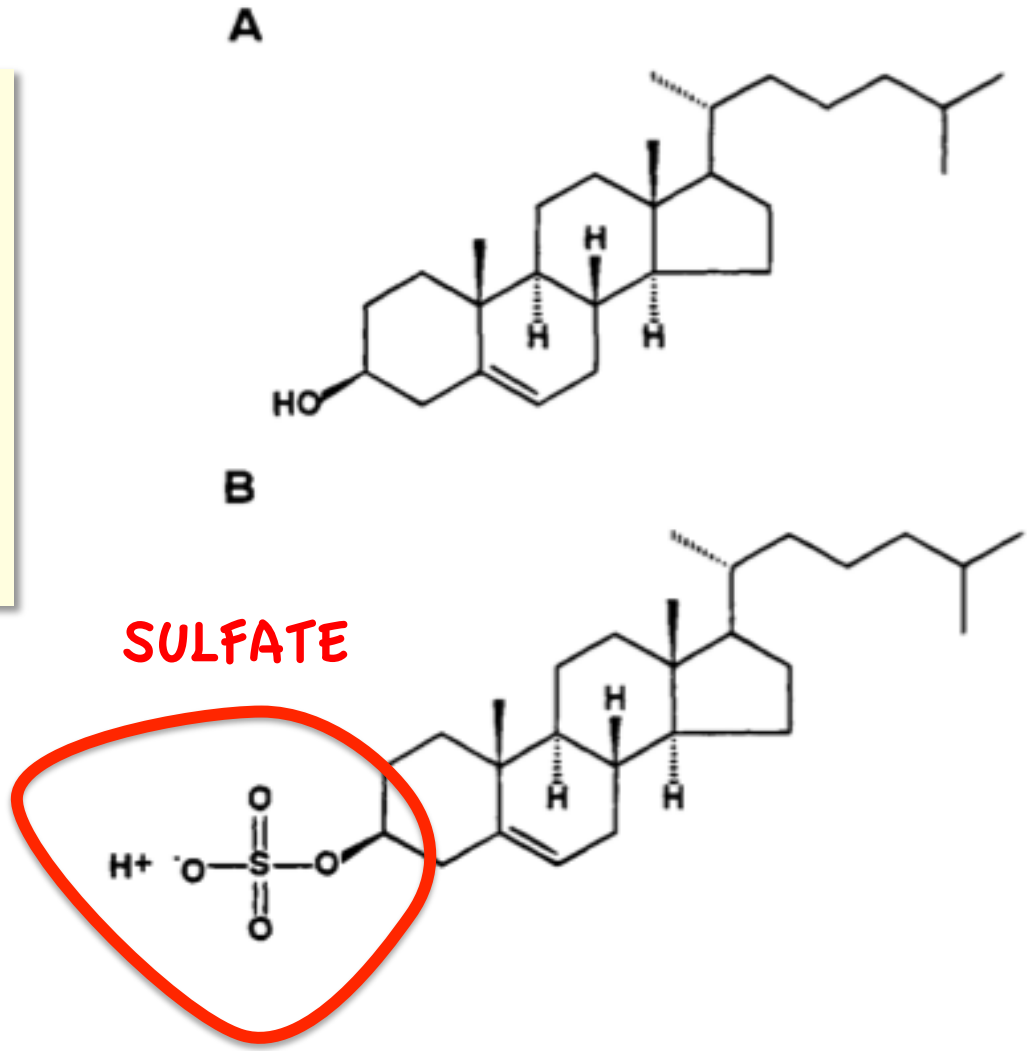
"In conclusion, our population-based study shows that high total cholesterol (TC), HDL-C, or LDL-C levels in the elderly are associated with a lower all-cause mortality compared with the group with the recommended low lipoprotein level."

"Our findings could seem controversial. However, most studies performed in older adults show an inverse association between TC and mortality [11,14]."

*L. Bathum et al., Scandinavian Journal of Primary Health Care, 2013; 31: 172–180.

Cholesterol and Cholesterol Sulfate

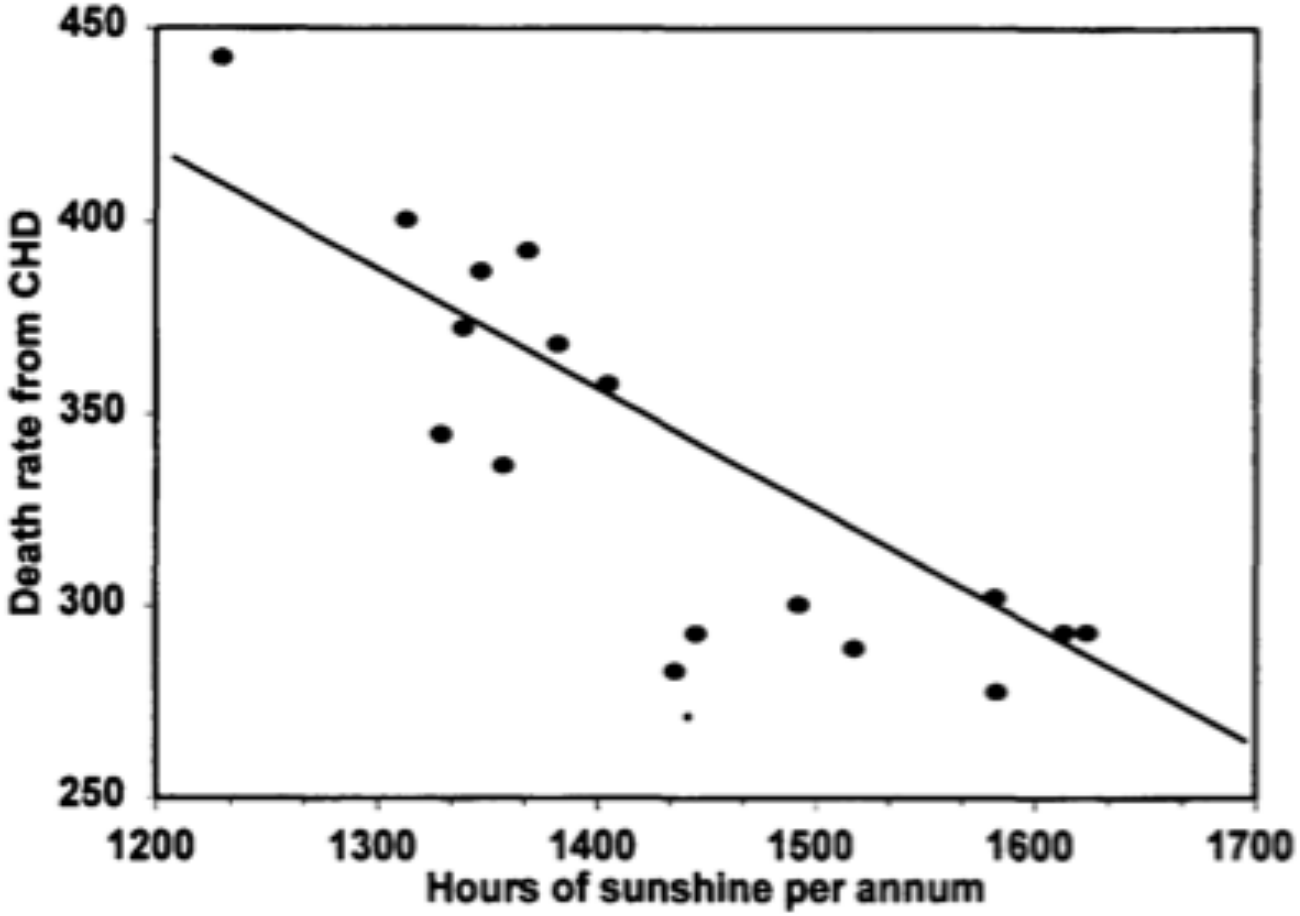
Sulfation makes cholesterol water-soluble and therefore much easier to transport



Think about Sulfate!

- Cells in the skin produce vitamin D3 *sulfate* upon exposure to the sun
  - The precursor to vitamin D3 is cholesterol
- Cells also produce an abundance of *cholesterol* sulfate
  - I believe this is the more important molecule!
- Many of the alleged benefits of vitamin D3 are actually benefits of cholesterol sulfate
  - Protection against cancer, diabetes and cardiovascular disease; improved immune function

Heart Disease Mortality and Sunlight*



*Grimes et al., Q. J. Med. 1996; 89:579-589

Cholesterol and Sepsis*

"The protective role of LDL in sepsis is well documented and the increasing incidence of ICU *sepsis* and mortality may be linked to widespread *statin* use, as is also the increasing incidence of *heart failure*, attributed by some researchers to reduced mitochondrial coenzyme Q10 through statin inhibition."

*Do healthy people with high cholesterol need statins?
imt.ie/features-opinion/2013/12/do-healthy-people-with-high-cholesterol-need-statins.html

Lack of Sunlight May Raise Stroke Risk*

- Strokes are caused by blood instability: clots and hemorrhages
  - Is this due to insufficient sulfate in blood?
- Study involved 16,500 people
- Tracked the history of where they had lived
  - Looked at weather statistics for those places
- Found 60% increased risk to stroke for lowest sun exposure (relationship with both latitude and weather patterns)

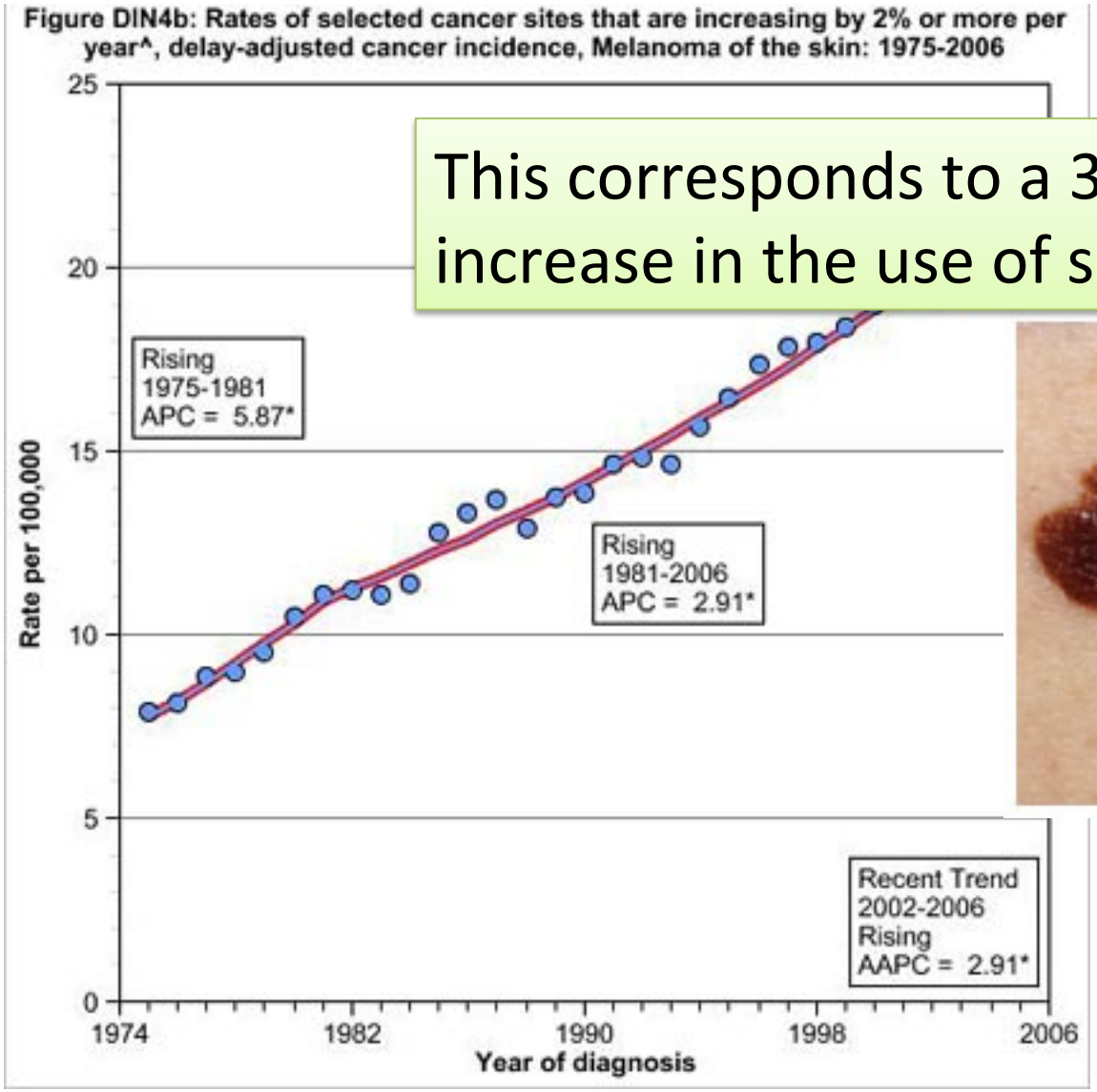
*A. Mozes, HealthDay, RSS Feed, Feb 2, 2012.

Ultraviolet Exposure and Mortality among Women in Sweden*

- 38,472 women selected in 1991-1992, aged 30-49
  - monitored for 15 years
- Questionnaire asked about frequency of sunbathing vacations and sunburn
  - *Increased* sunburn frequency associated with *reduced* all-cause mortality
  - Sunbathing vacations more than once a year *reduced* risk to cardiovascular disease and mortality

* Yang et al., Cancer Epidemiol Biomarkers Prev. 20(4):683-690, 2011

Skin Melanoma Increasing 2%/Yr since 1974*



This corresponds to a 30-fold increase in the use of sunscreen

* Andrew Schneider, Aol News, May 24, 2010
aolnews.com/2010/05/24/study-many-sunscreens-may-be-accelerating-cancer

How to Stay Healthy

- Plenty of dietary *sulfur*
- Plenty of dietary *cholesterol*
- Plenty of *sun exposure*

Cholesterol Sulfate

Cholesterol is a Miracle Worker

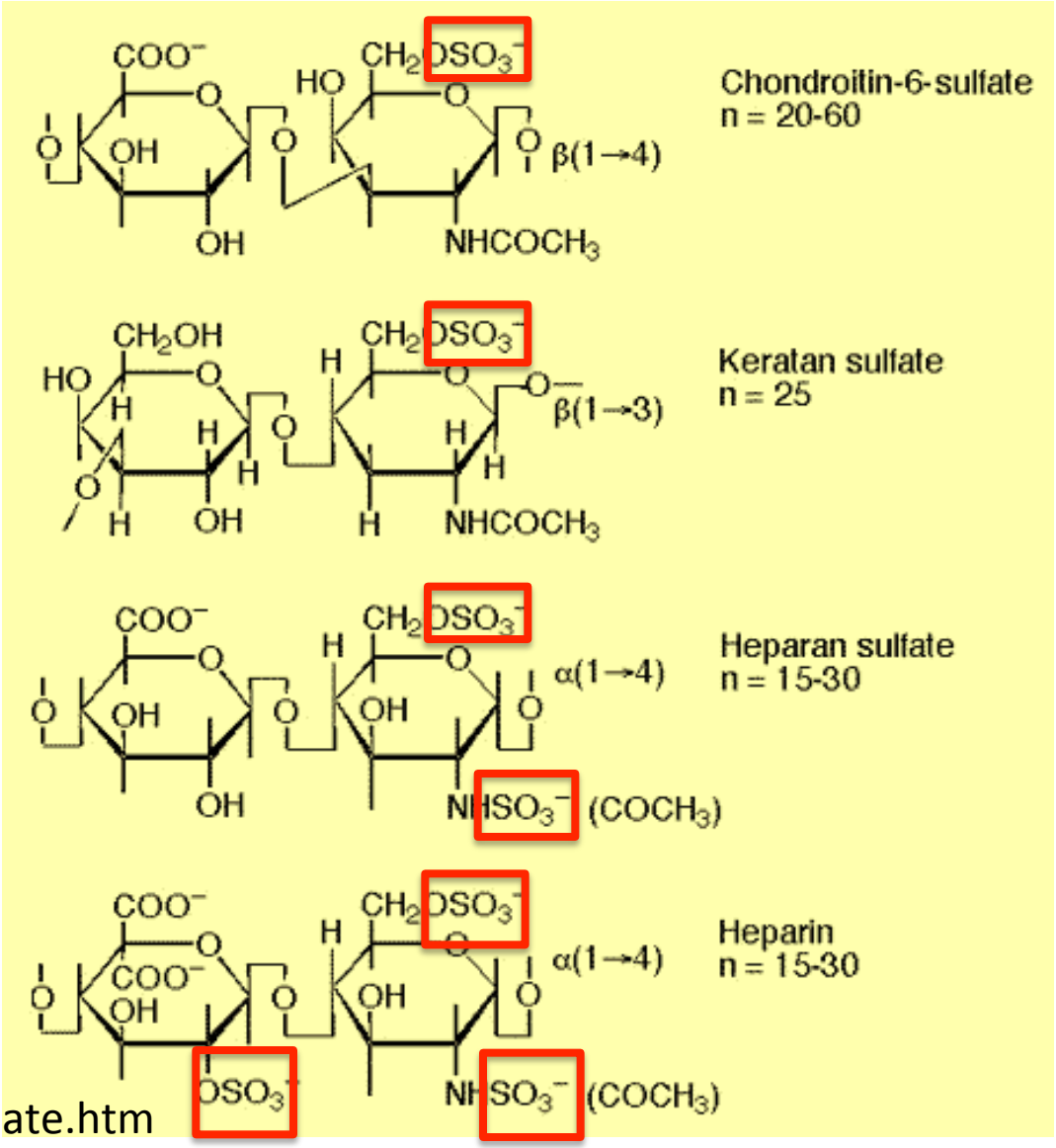
- In the brain:
  - Synapse: promotes cell-cell communication
  - Myelin sheath: insulates channel from signal loss
- In the membranes of all cells
  - Prevents ion leaks
  - Protects from pathogens (microbes)
- In the plasma lipoprotein (LDL, HDL)
  - Essential for protecting contents from oxidation and glycation damage during transport to cells
- Precursor to vital hormones
  - Vitamin D
  - All the sex hormones (testosterone, estrogen, etc.)
  - Cortisone: the stress hormone
- Aids in digestion of fats

Sulfate is Vastly Underappreciated!

- Sulfate is the 4th most abundant anion in the blood and protects it from coagulating
- Detoxifies drugs, food additives, and environmental toxins like aluminum and mercury
- Essential component of extracellular matrix proteins throughout the tissues
- Cerebroside sulfate is a major constituent of myelin sheaths surrounding axons in neurons

Sulfated Glycosaminoglycans (GAGs)

- Prominent in extracellular matrix of *all cells*
- Amount of sulfate depends on availability
- Crucial for maintaining negative charge and protecting from infection



http://www.science-autism.org/sulphate.htm

Sulfated Glycosaminoglycans (GAGs)

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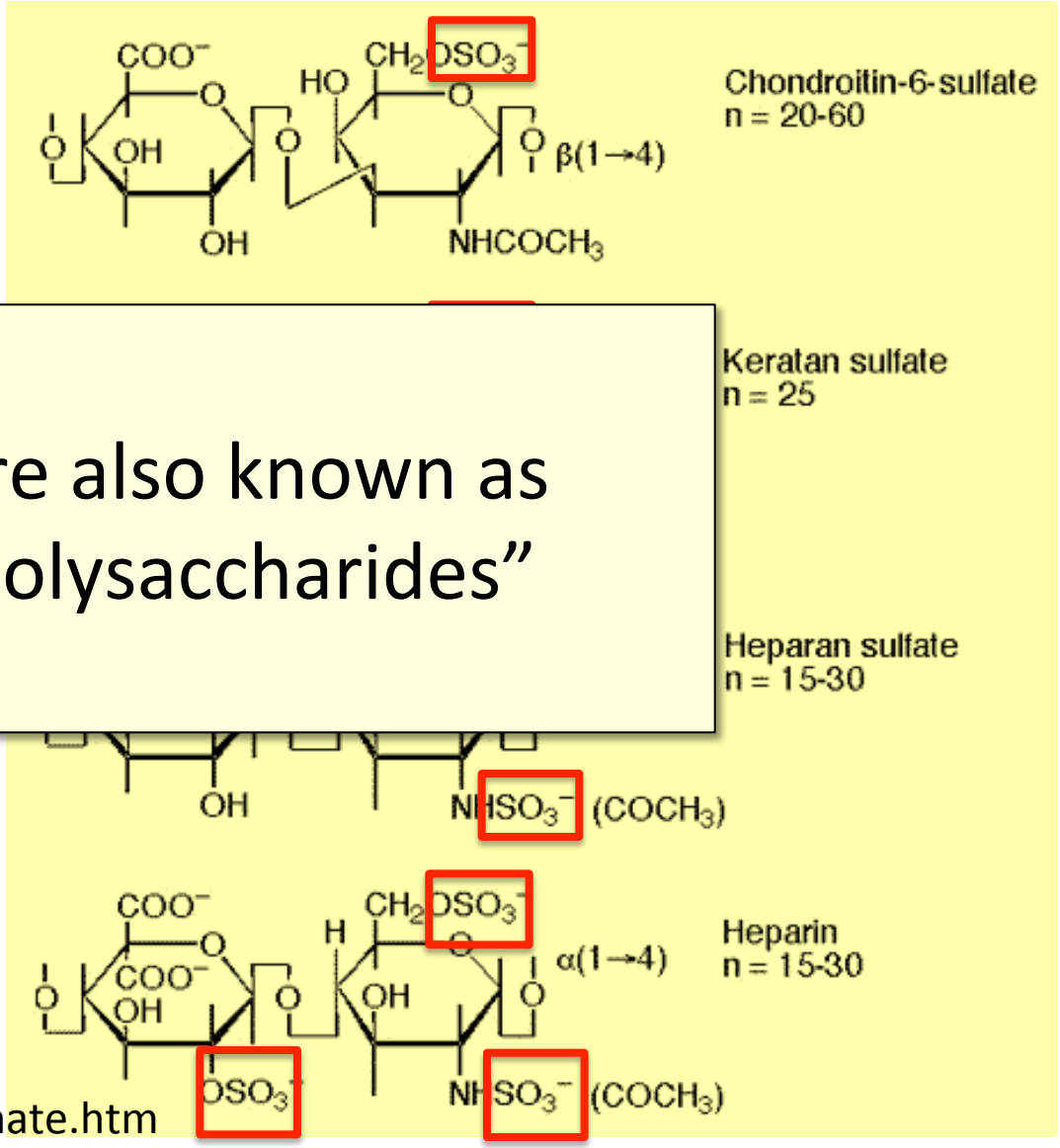

These are also known as "mucopolysaccharides"

http://www.science-autism.org/sulphate.htm

Ten Positive Effects of Mucopolysaccharides *

- A lipid-clearing effect in the blood.
- Stimulation of cellular metabolism.
- Efficient metabolism of fatty acids.
- Increase in RNA and DNA synthesis of cells.
- Increase in growth, size and quantity of normal cells.
- Anti-atherosclerosis, anti-atherogenic activities.
- Anti-inflammatory effect.
- Anti-thrombogenic and anti-coagulant activity.
- Increases the number of coronary artery branches and collateral circulation in experimental atherosclerosis.
- Accelerates healing, regeneration and repair of cardiovascular tissue

* http://www.vitaflex.com/res_csaa.php

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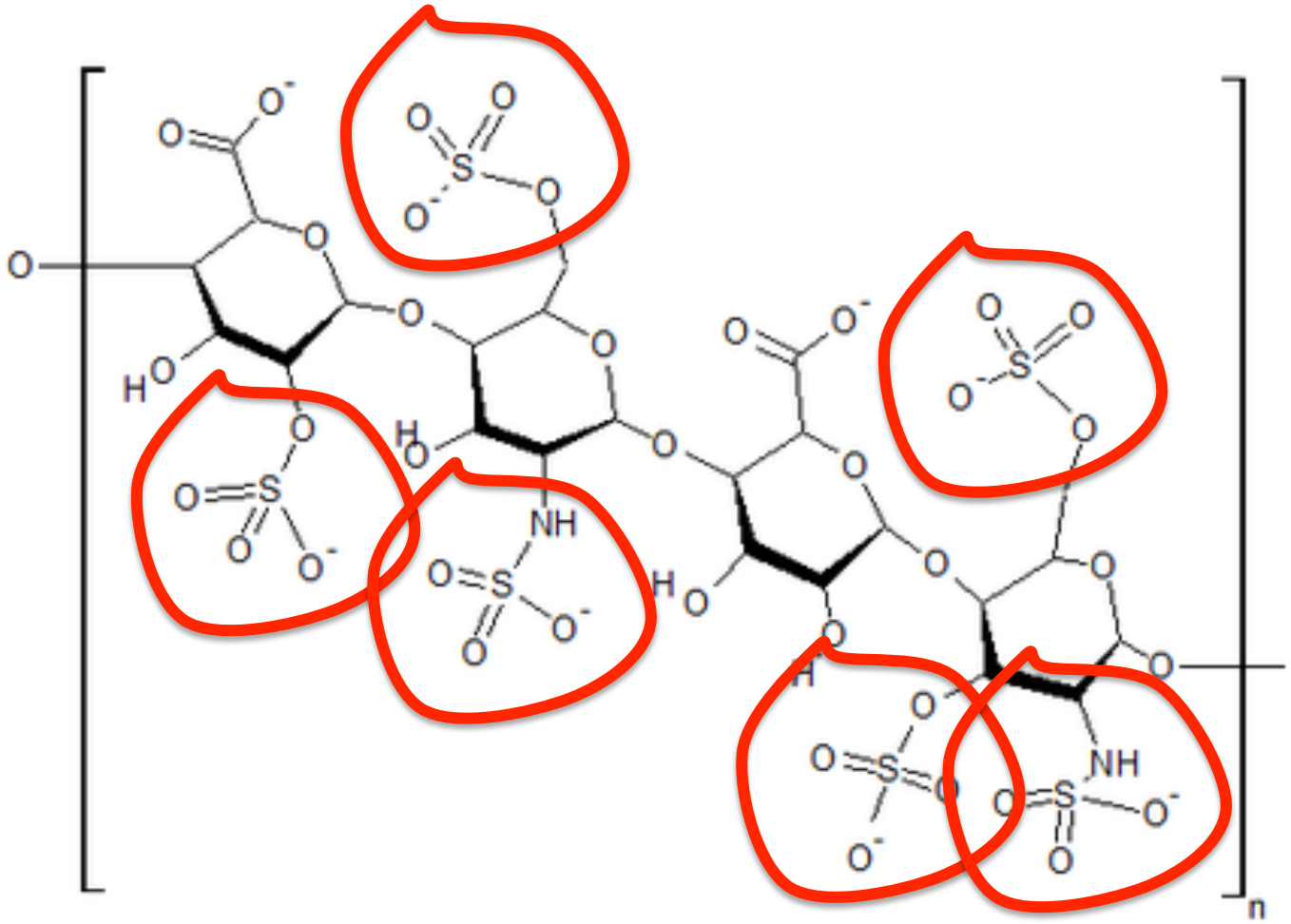
Many of these effects can be explained by the fact that they supply sulfate

* http://www.vitaflex.com/res_csaa.php

Heparan Sulfate: Wonder Worker



Polymers of sugars with attached sulfates: safe glucose storage

Disrupted Signaling when HSPGs are Depleted*

HPGs = Heparan Sulfate Proteoglycans

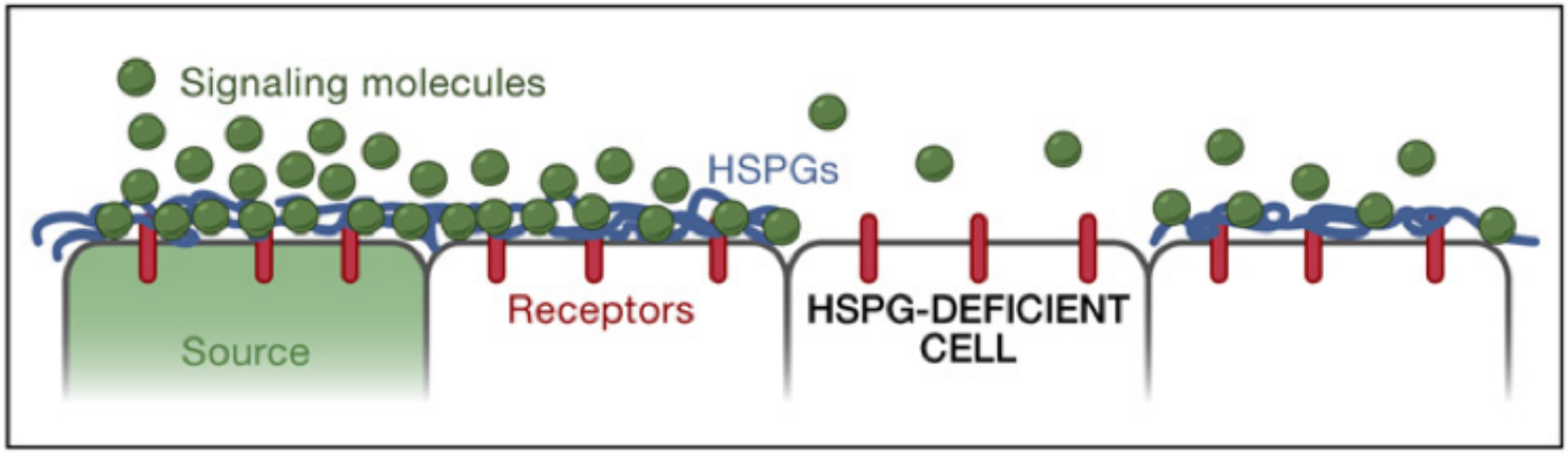


*Figure 5 in P Muller and AF Schier, Developmental Cell 21, July 19, 2011, 145-158.

HSPGs, Cholesterol and Atherosclerosis*

- Reduced sulfation is associated with inflammation and atherosclerosis and with increased age
- Vessels with half as much heparan sulfate have 4-5 fold more cholesterol retention
- ApoE & HDL promote heparan sulfate synthesis

*L. Paca et al., J. Biol. Chem. 1999, 274:4816-4823.

Are we getting enough sulfur in our diet?*

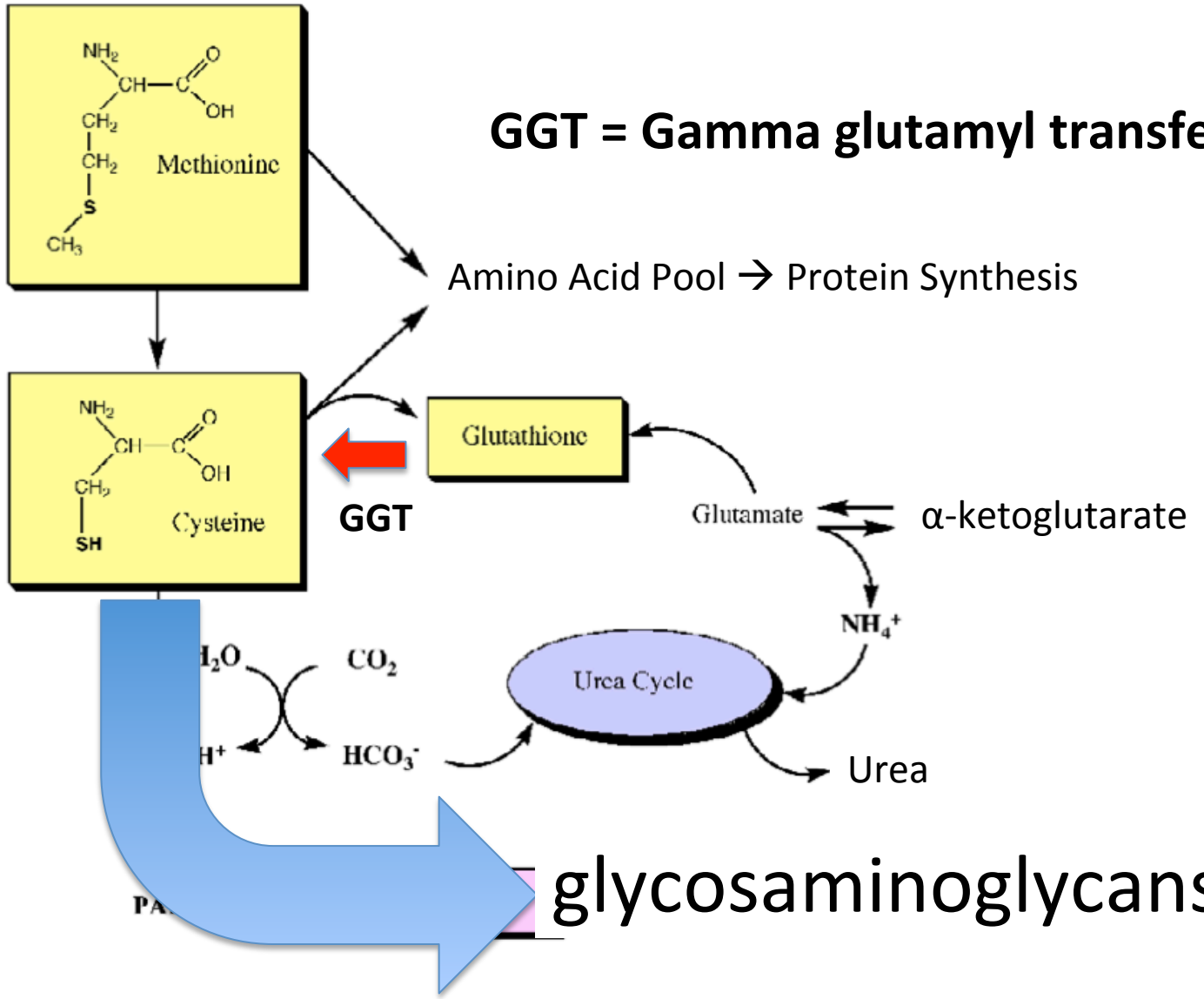


*Figure 1, ME Nimni et al., *Nutrition & Metabolism* 2007, **4**:24

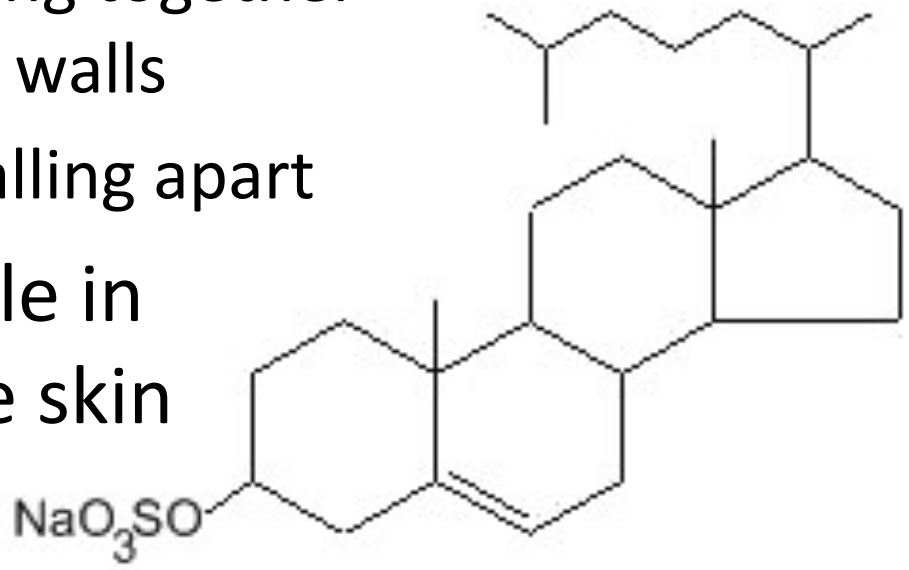
GGT is a Strong Predictor of …*

- Arterial stiffness
- Hypertension
- Coronary artery disease (CAD)
- Heart failure
- Elevated homocysteine levels
- Cardiac syndrome X: angina without CAD
- Acute pulmonary embolism

*S. Jiang et al., Role of gamma-glutamyltransferase in cardiovascular diseases. Exp Clin Cardiol 2013;18(1):53-56.

Cholesterol Sulfate: What's It All About?*

- Omnipresent in blood serum in small amounts
- Collects around exterior of red blood cells (RBCs) and gives them a negative charge field
  - Keeps cells from sticking together or sticking to capillary walls
  - Prevents RBCs from falling apart
- Plays an important role in barrier function in the skin



Cholesterol sulfate

* Strott, J. Lipid Res. 44, 2003

Cholesterol Sulfate Protects from Obesity*

- Dysregulation of glucose and lipid metabolism is a major factor in the metabolic syndrome
- SULT2B1b is a sulfotransferase that synthesizes cholesterol sulfate in the liver
  - Induced following food consumption
- Overexpression of SULT2B1b inhibits gluconeogenesis in the liver
- Gluconeogenesis is the release of glucose from stored sugars which can lead to obesity

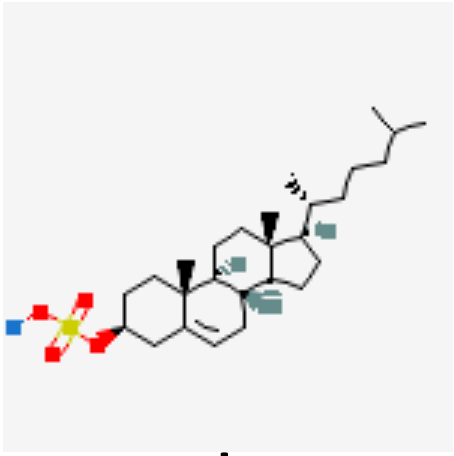
*X. Shi et al., Mol. Cell. Biol. 2014, 34(3):485.

Cholesterol Sulfate Deficiency

- Cholesterol sulfate deficiency leads to filaggrin deficiency which is associated with:
  - Atopic Dermatitis
  - Eosinophilic Esophagitis
  - Asthma
- These three conditions are on the rise and are associated with autism and celiac disease

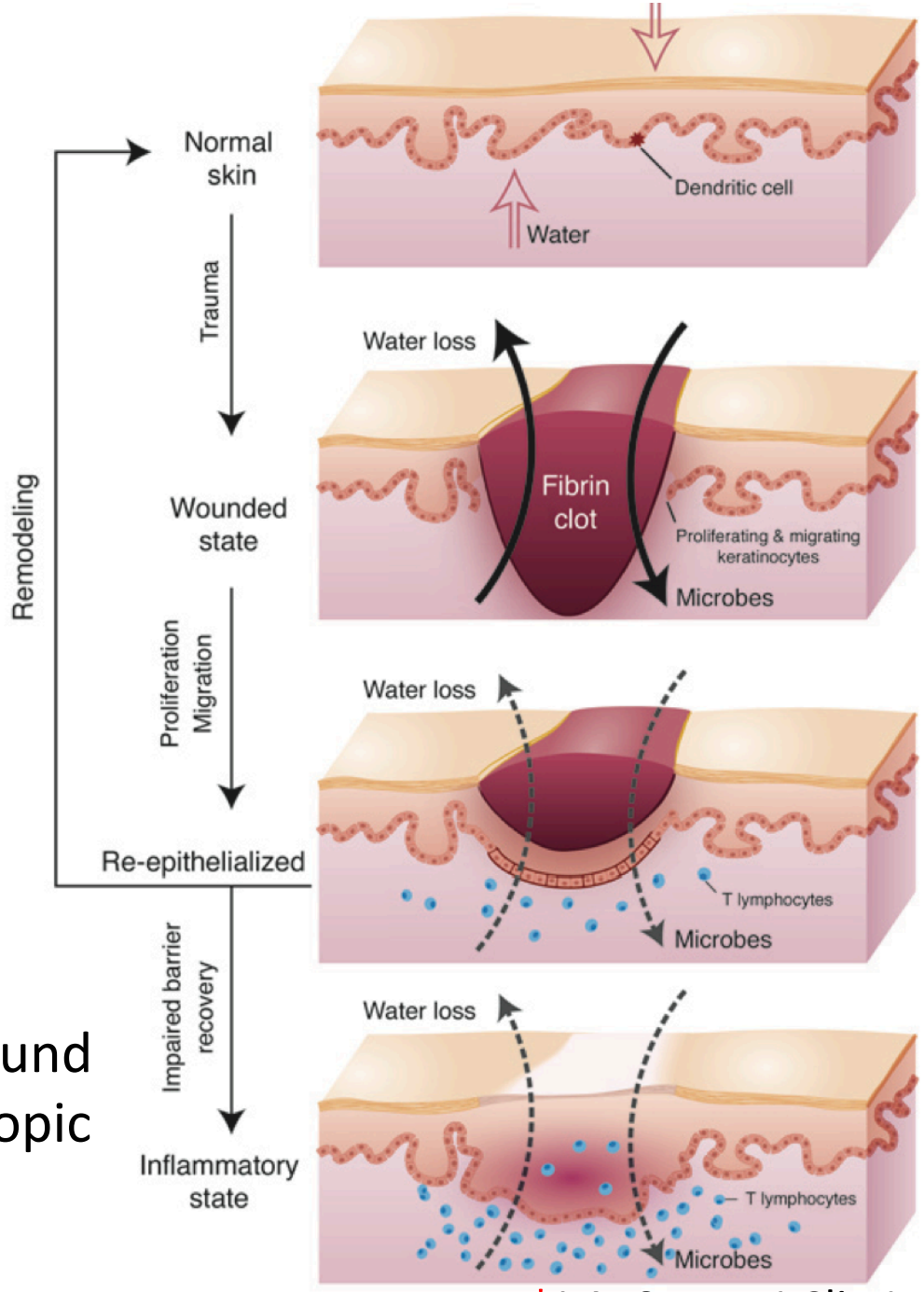
Cholesterol Sulfate Synthesis in the Skin

- Keratinocytes synthesize abundant cholesterol sulfate as they mature
  - This synthesis takes place in outer layer of the epidermis



- Cholesterol sulfate catalyzes synthesis of *profilaggrin*, one of the two key proteins forming the cross-linked mesh that protects from bacterial invasion and prevents water loss

Impaired wound healing in atopic dermatitis



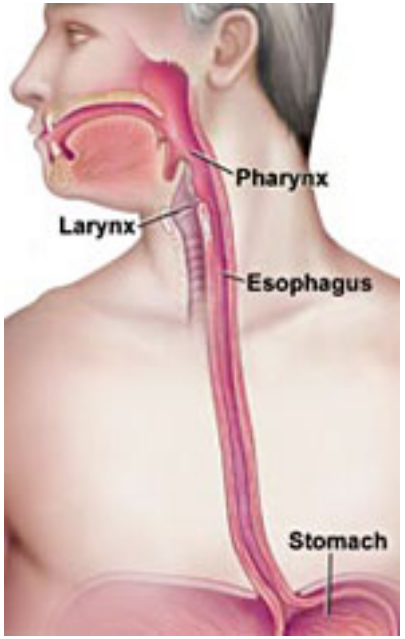
- Water loss
- Microbe penetration

*J.A. Segre, J Clin Invest.2006;116:1150-58

Filaggrin Plays a Crucial Role

- Loss of filaggrin function associated with
  - Increased skin permeability
  - Susceptibility to eczema and asthma
  - Eosinophilic Esophagitis: (EoE)*

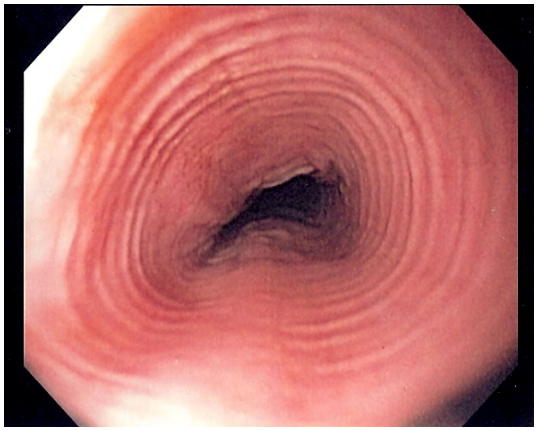
EOE is a new disease first recognized in the 1990's

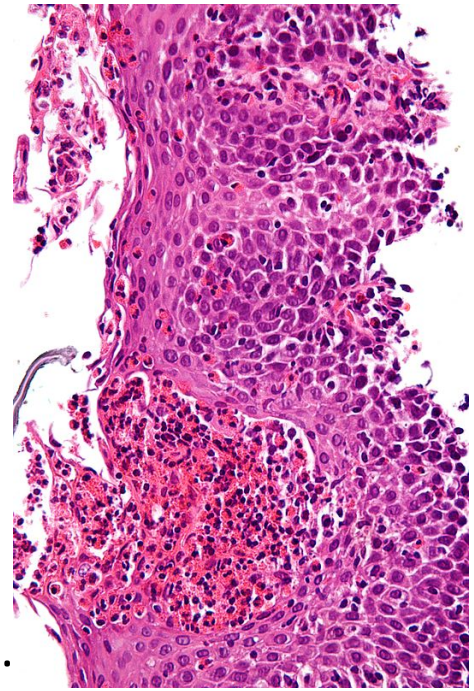


* Schroeder et al., Expert Rev clin Immunol. 6:6, 929-937, 2010.

More on EoE*

- Allergic inflammatory condition of the esophagus
- Eosinophils invade esophagus
  - Release toxins that kill viruses and induce tissue damage
- Person has *difficulty swallowing*
  - Eats very slowly
- Food gets stuck in the throat





* Schroeder et al., Expert Rev clin Immunol. 6:6, 929-937, 2010.

A Very Bad Idea

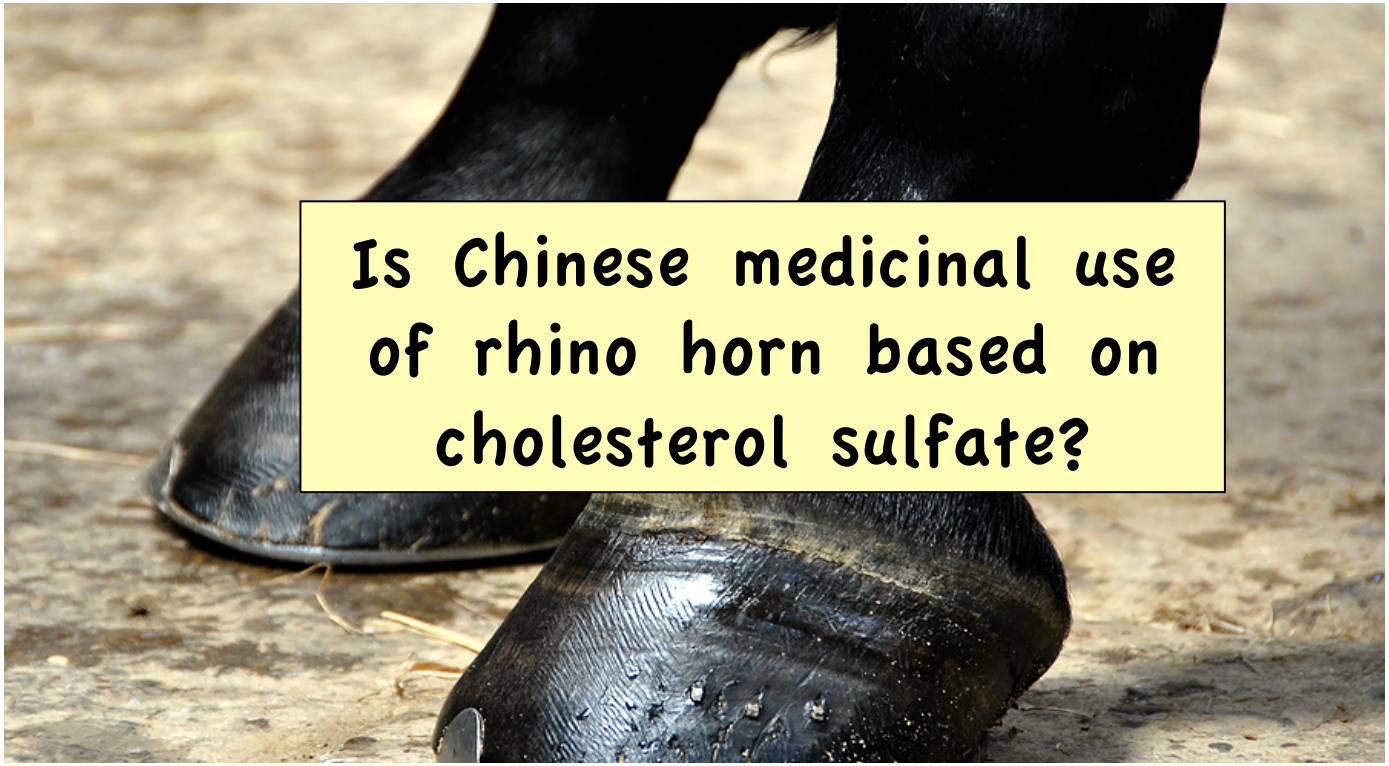
Cholesterol Sulfate in the Lungs*

Bronchial tubes produce cholesterol sulfate in the epithelial cells as they mature and form the outer layer of the bronchial epithelium

* Rearick et al., J. Cell. Physiol. 133:3, 573-578, Dec. 1987.

Cholesterol Sulfate in Horses' Hoofs! *

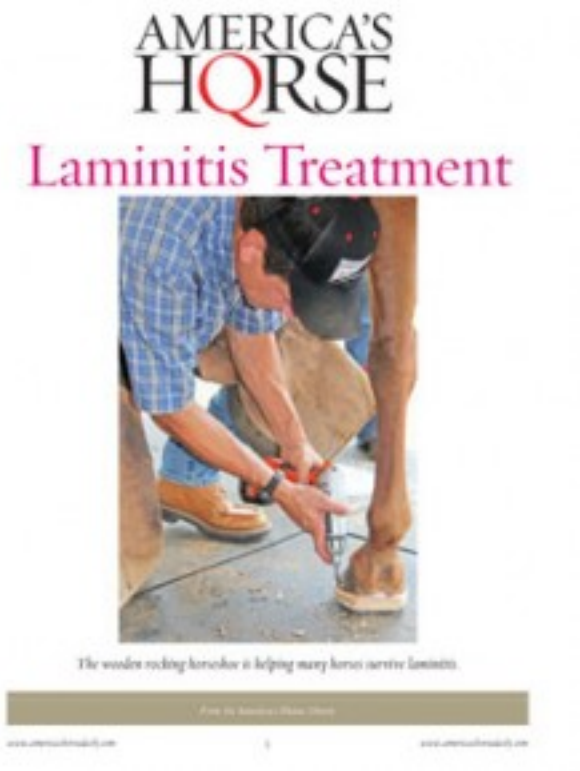
- 37-43% cholesterol
- 15-20% cholesterol sulfate



*P.W. Wertz and P.T. Downing, J Lipid Res 25, 1985, 1320-1323.

Laminitis (Founder)

- Lameness in horses due to inflammation in the hoof
- Can be caused by exposure to herbicides and nitrate fertilizers

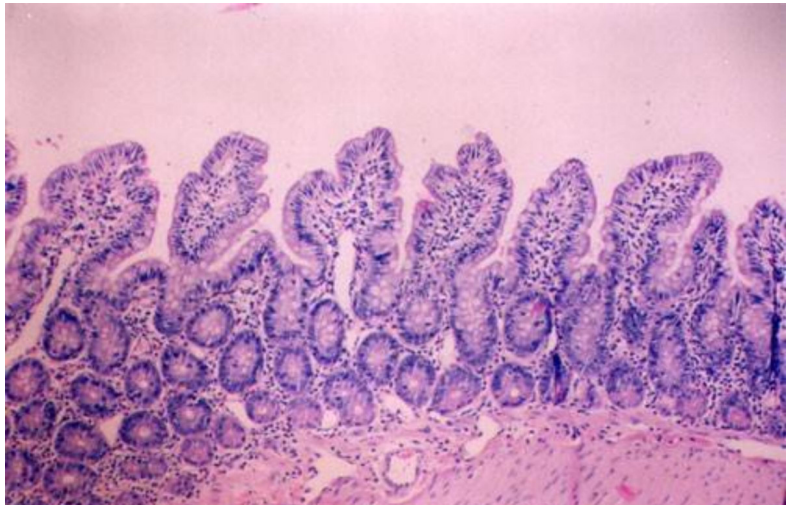


Is This due to Impaired

Cholesterol Sulfate Supply to the Hoof?

Cholesterol Sulfate and Trypsin*

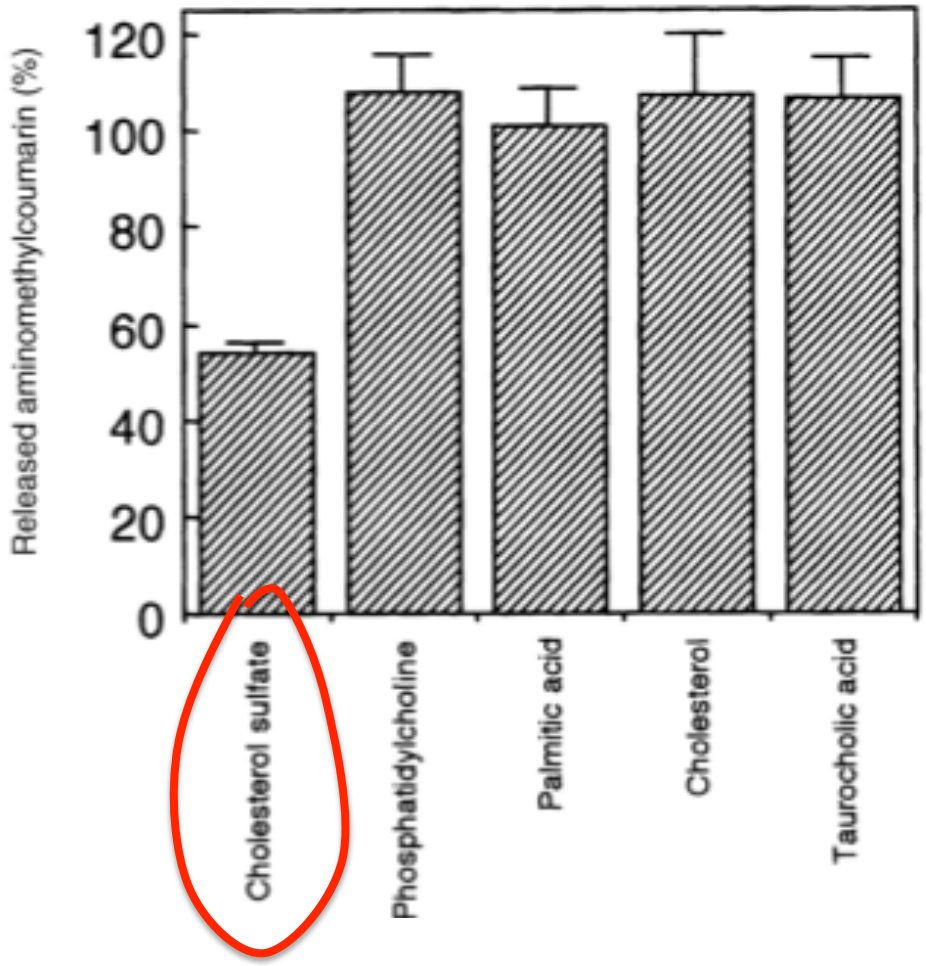
- Trypsin is an enzyme released by the pancreas, which digests proteins
- Too much trypsin leads to breakdown of collagen glue that maintains structural integrity of intestinal mucosa (GAGs)



- Cholesterol sulfate suppresses trypsin synthesis (protects mucosa from breakdown)

* Ito et al, J. Biochem. 123, 107-114, 1998.

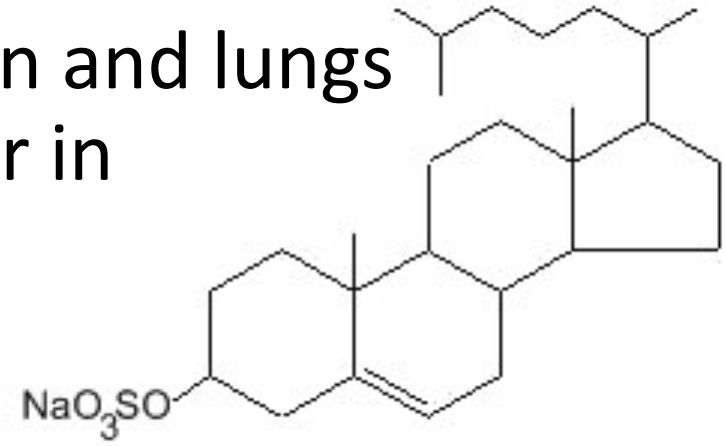
Cholesterol Sulfate Inhibits Trypsin *



* Sato et al., J. Investigative Dermatology, 11:2, 189-193, Aug 1998

Recapitulation

- Cholesterol sulfate plays many important roles in the body: skin, blood, esophagus, lungs, liver and gut
- Cholesterol sulfate in the skin and lungs keeps bacteria out and water in
- Cholesterol sulfate protects collagen from breakdown by trypsin



Cholesterol sulfate

- HSPGs play a crucial role in ion transport, nutrient uptake, and cell signaling

Blood Clots and Hemorrhages

Hemostasis

- Hemostasis keeps the blood in circulation and prevents excessive blood loss upon injury
- Maintained by coagulation system through clotting factors
- Complex coagulation cascade involving calcium, thromboplastin, phospholipids and several serum proteins
- Final product is insoluble fibrin (blood clot)

Hemostasis

- Hemostasis keeps the blood in circulation and prevent[illegible] injury
- Mainta[illegible] rough clotting
- Comple[illegible] ng calcium, thromb[illegible] everal serum proteins
- Final product is insoluble fibrin (blood clot)

Hypothesis: insufficient sulfate supply to blood leads to fragile state of constant tension between hemorrhage and blood clots

The Glycocalyx

- Negatively charged gel-like mesh lining the walls of all arteries, veins and capillaries
- Depends crucially on sulfated polysaccharides
  - Particularly heparan sulfate proteoglycans (HSPGs)
- Sulfate creates "exclusion zones"
  - Helps protect cells in wall from ion leaks and contact with enzymes suspended in blood
  - Greatly reduces amount of flowing blood (decreases resistance, lowers blood pressure)
  - Stores energy in "battery" constructed from structured water

Dr. Mercola Interviews Dr. Gerald Pollack*

- "The Fourth Phase of Water" = the Exclusion Zone (EZ)
  - Profoundly excludes things, even small molecules
  - H_3O_2 instead of H_2O -- negatively charged!
  - Fills most of your cells and the extracellular tissues
  - "polywater" - water as a polymer
- Many experiments in our laboratory confirm the existence of EZ water
  - A hydrophilic surface (sulfate!) will promote growth of EZ water upon exposure to infrared light
  - EZ water absorbs UV light (270 nm) and this builds charge!
- Water flows in small diameter tubes and the flow rate increases upon exposure to sunlight
  - Could the same thing be happening in your capillaries?
- Pressure, oxygen, light, and infrared energy all build EZ water

*http://articles.mercola.com/sites/articles/archive/2013/08/18/exclusion-zone-water.aspx

A Quote from Pollack's Book*

"And so it is with the exclusion zone. Order cannot persist without a continual supply of energy. The separated charges will slowly recombine, and order will give way to disorder. The exclusion zone's outer reaches will wear thin like an eroding beach."

– page 95, The Fourth Phase of Water

Sunlight renews the exclusion zones throughout your body!

A C ook*

"And so rder
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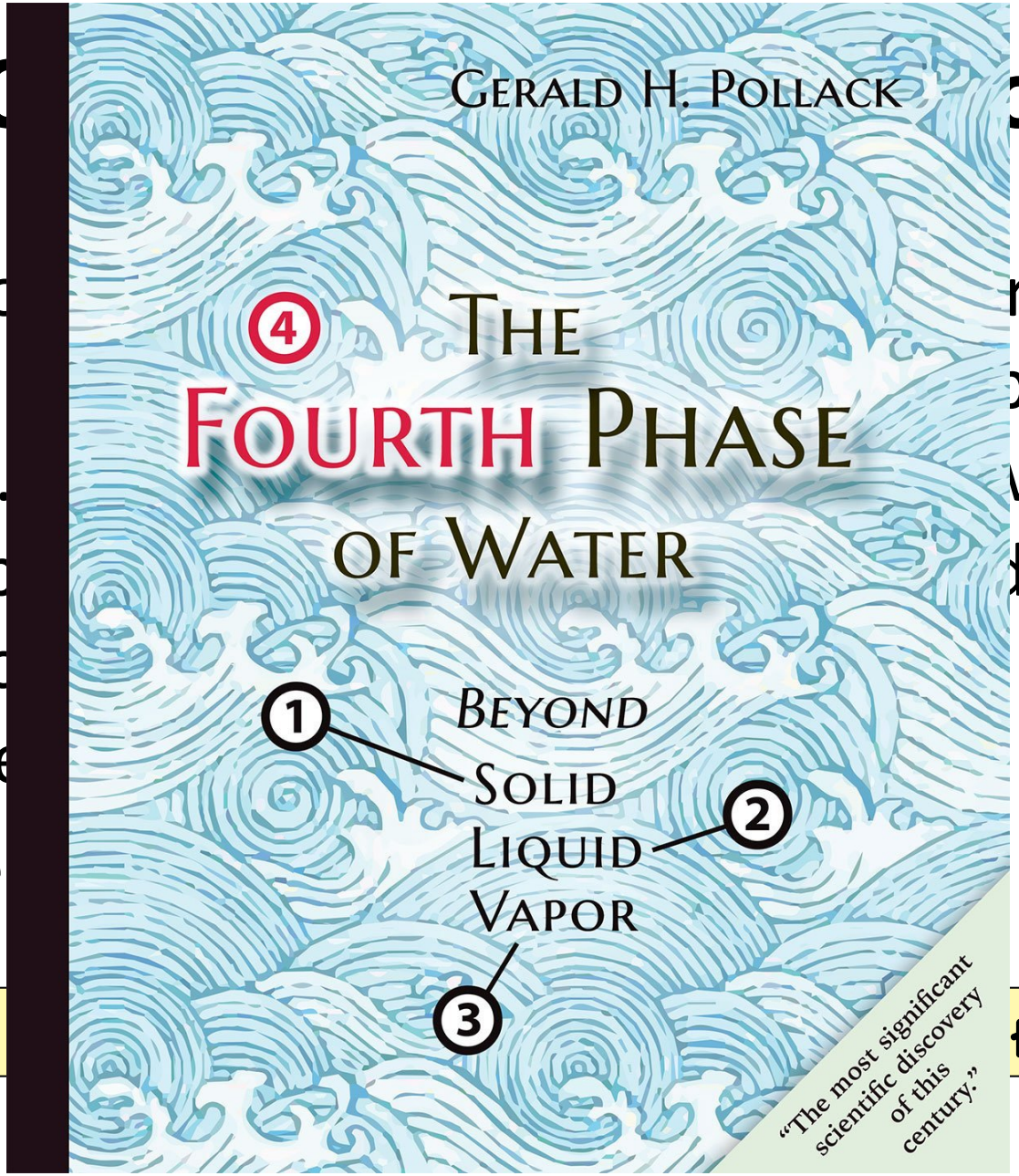


Sunlight t your body!

Therapeutic Value of Sauna Therapy (Infrared light)*

- Impaired vascular function associated with hypertension, hyperlipidemia, diabetes, obesity
- Sauna therapy ameliorates endothelial dysfunction and improves health
  - Increased eNOS synthesis in aorta in animal experiments
  - Decreased body weight and body fat in obese subjects
  - Improved cardiac function in patients with heart failure
- Infrared expands exclusion zones 4-fold**

*S. Biro et al., Exp Biol Med (Maywood). 2003 Nov;228(10):1245-9.
**B. Chai et al., J Phys Chem B. 2009 October 22; 113(42): 13953–13958.

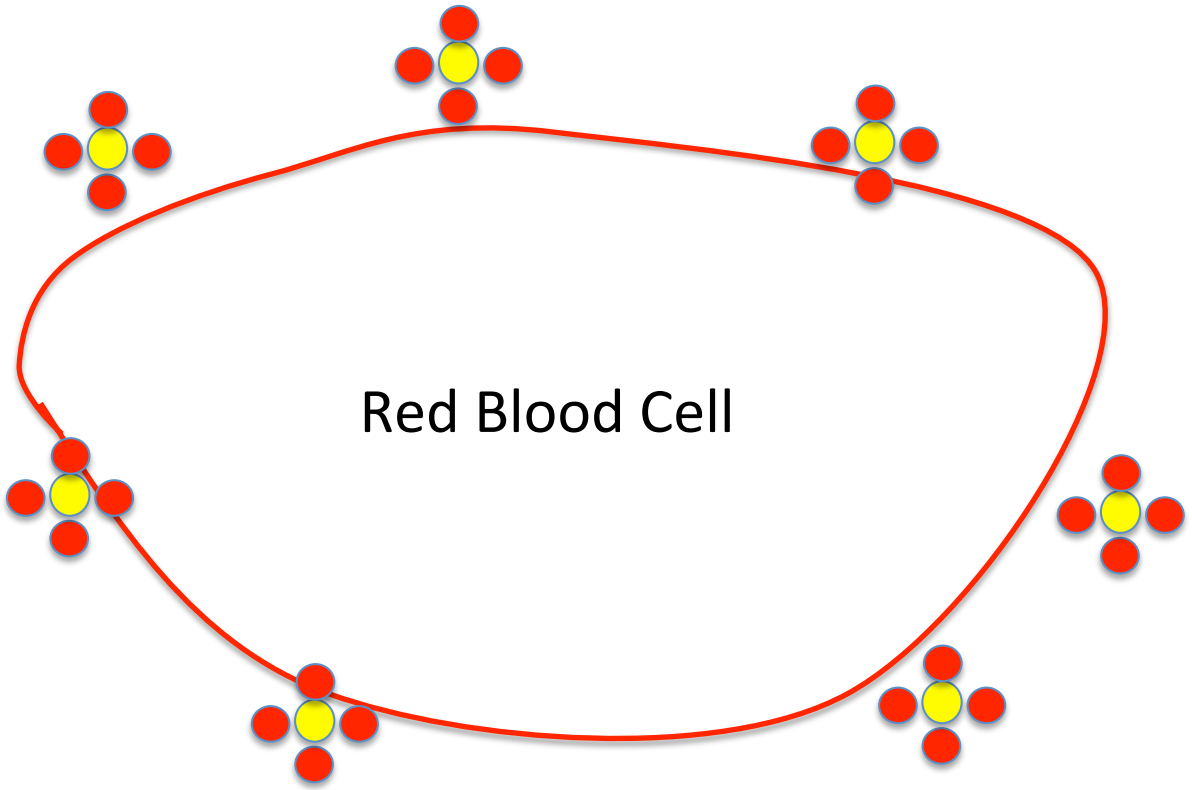
Effect of Radiant Energy on Near-Surface Water *

"The main question, however, is where the energy for building these charged, low-entropy zones might come from. It is shown that *radiant energy* profoundly expands these zones in a reversible, wavelength-dependent manner. It appears that incident radiant energy may be stored in the water as *entropy loss and charge separation*."

*B. Chai et al., J Phys Chem B. 2009 October 22; 113(42): 13953–13958.

Key Role for Sulfates

- Sulfates decorate exterior of cell, e.g., as heparan sulfate proteoglycans (HSPGs) or as cholesterol sulfate (Ch-S)
- Sulfates carry negative charge and keep cells from sticking together
- Sulfates, as kosmotropes, create exclusion zone – gel-like environment to protect cell



Zeta Potential

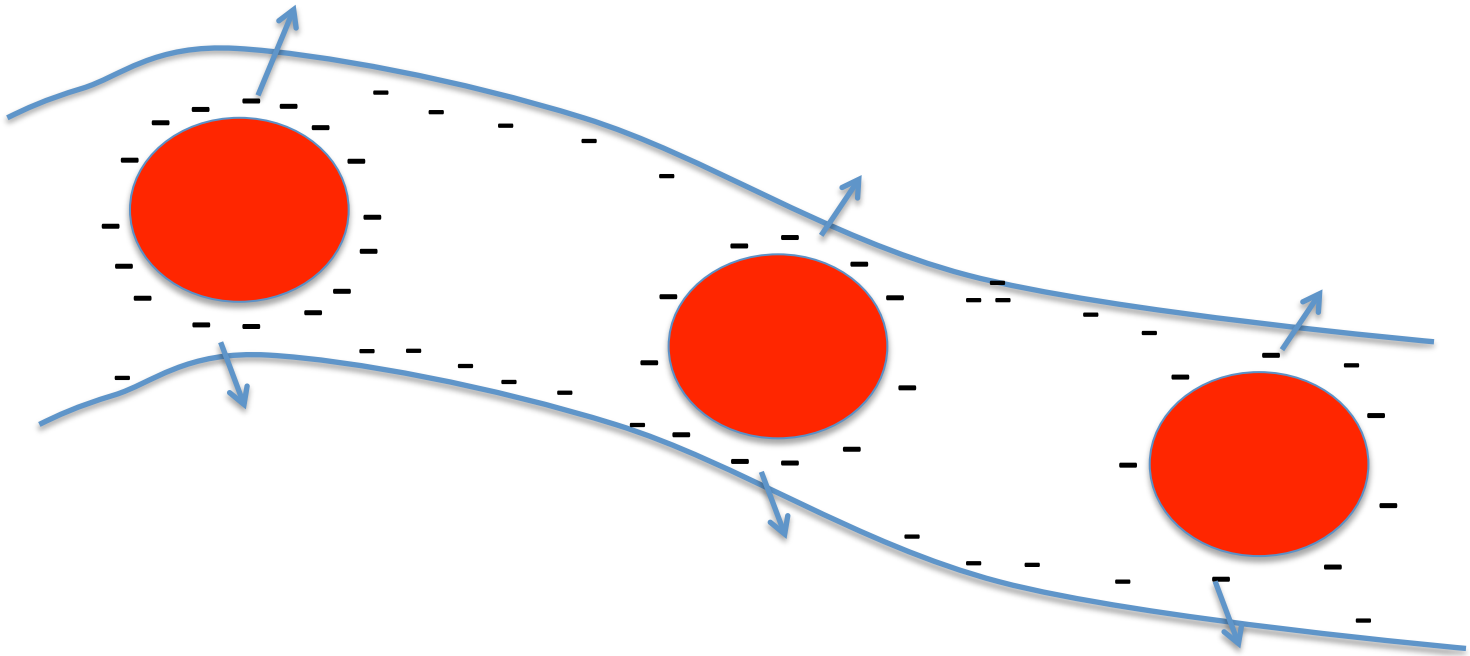
- Zeta potential indicates degree of repulsion between similarly charged particles in a dispersion (e.g., the blood)
- High zeta potential confers stability
  - RBCs and platelets resist aggregation
- Low zeta potential causes flocculation and coagulation (blood clot)
- Proposal: a steady drop in zeta potential in the blood as we age is the source of many modern diseases

Grounding the Human Body Reduces Blood Viscosity*

- Blood viscosity is strongly influenced by the surface charge on the suspended particles (like RBCs)
- A higher repulsive surface charge increases spacing between RBCs, reduces clumping, lowers viscosity, and lowers peripheral resistance to flow (blood pressure)
- Grounding transfers electrons from soil to the body
  - Increases zeta potential, lowers blood viscosity

*G. Chevalier et al., J Alternative and Complementary Medicine, 1–9, 2012

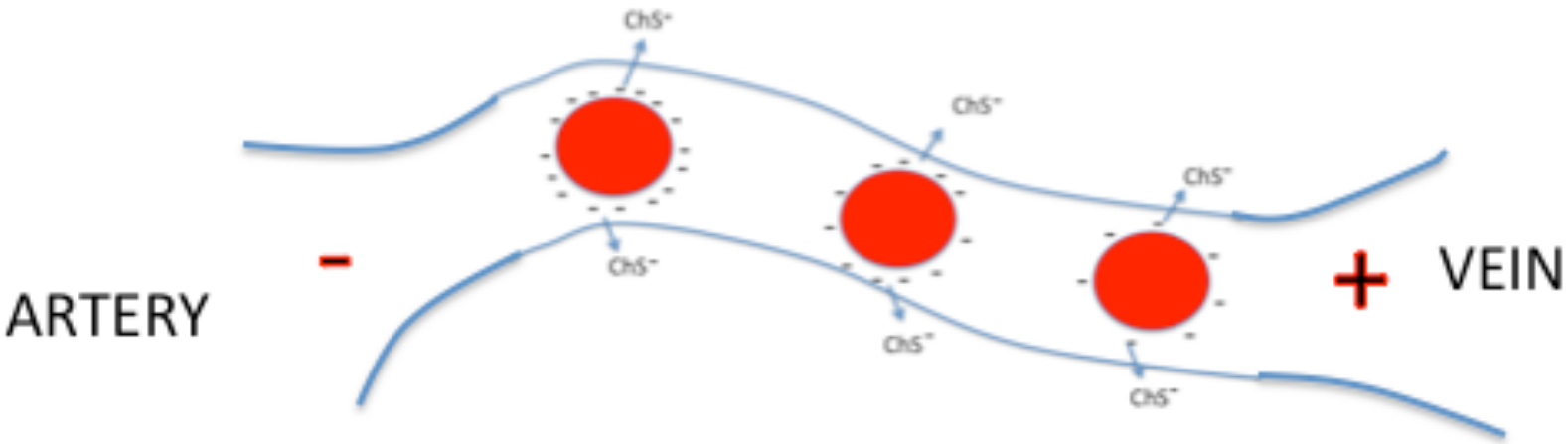
Negative Charge Builds on Artery Wall*



Red blood cells export cholesterol sulfate to the artery wall, supplying it with cholesterol, sulfate, and negative charge

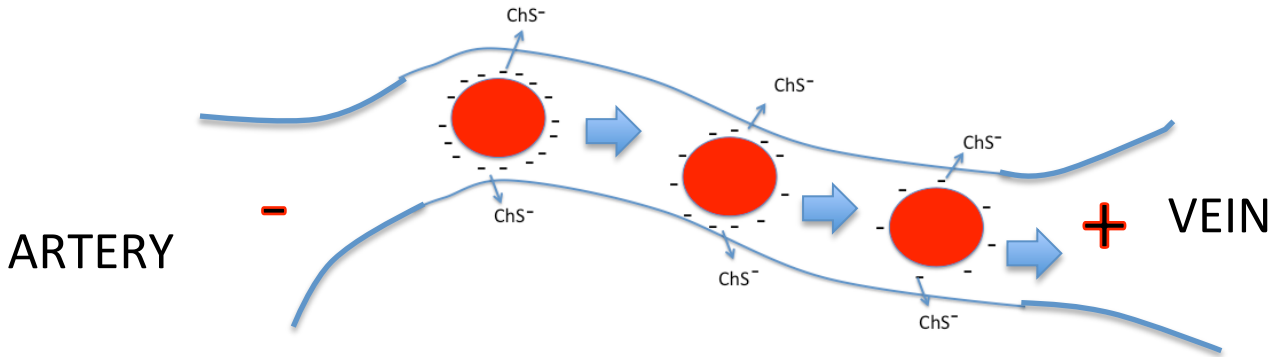
* Davidson and Seneff, Entropy 14, 1399-1442, 2012.

A Battery!



* Davidson and Seneff, Entropy 14, 1399-1442, 2012.

Battery Poles Between Artery and Vein



- RBC's lose charge as they travel through the capillary
- This sets up voltage gradient between vein and artery
- Negatively charged RBC's are propelled towards positive pole of "battery"

This creates force field that promotes blood flow

* Davidson and Seneff, Entropy 14, 1399-1442, 2012.

Zeta potential measures rate at which negatively charged particles travel in an electric force field

Hypothesis

- When blood becomes deficient in negative charge (sulfates), glycocalyx becomes unhealthy
- Endothelial cells develop gaps that allow blood to seep into tissues
- Blood clots are needed to plug the holes
- Mistakes can lead to dangerous blockage
  - Deep vein thrombosis
  - Pulmonary thrombosis

Strokes are Happening at Younger Age*

- Incidence of stroke is increasing among people under 55 years old
- 959 patients followed through 2012 (aged 18 to 50 years at time of stroke)
  - Suffered from stroke between 1980 and 2010.
  - Compared with age-matched young adults without stroke
- Stroke victims have higher risk of dying prematurely
  - 3.4-fold higher risk in the 40- to 50-year-old age group
  - 6.4 fold higher risk in the 18-29 year olds
- Underlying vascular disease remains active throughout life?

*L.C. Rutten-Jacobs et al., JAMA. 2013 Mar 20;309(11):1136-44.

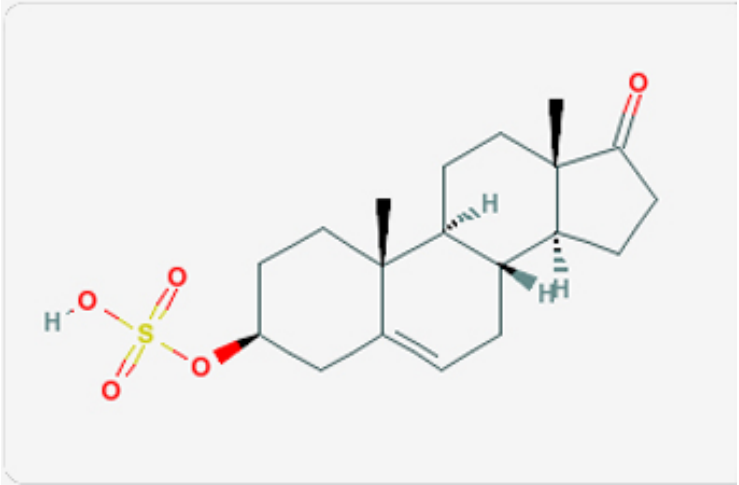
"High Cholesterol Levels Are Associated with Improved Long-term Survival after Acute Ischemic Stroke"*

- 190 stroke patients studied
- Survival rates (P= 0.0001):

3-mo	1-yr	5-yr	
100%	98%	84%	high-cholesterol group
92%	87%	57%	low-cholesterol group

*I. Markaki et al., Journal of Stroke and Cerebrovascular Diseases, 2013: 1-7.

DHEA Provides Sulfate?*



- In aging rats:
  - eNOS expression is lowered
  - Response of vascular smooth muscle to NO is decreased
  - Oxidative resistance is weakened
- DHEA supplement ameliorates these effects and delays aging process

*S. Wu et al., Gerontology 2007;53:234–237.

Recapitulation

- Hemostasis is the regulatory system that maintains blood stability
  - Tension between clotting and hemhorraging
  - Sulfates in the glycocalyx are protective
- Grounding can improve blood stability by providing negative charge through currents from the ground
- Red blood cells discharge negative charge by releasing cholesterol sulfate in capillaries
  - This helps maintain pH difference between arteries and veins to drive circulation
- Strokes are happening at a younger age, and this could be related to cholesterol sulfate deficiency

Streaming Potential

Defective Streaming Potential!

I have identified impaired blood flow as the key problem in multiple modern diseases

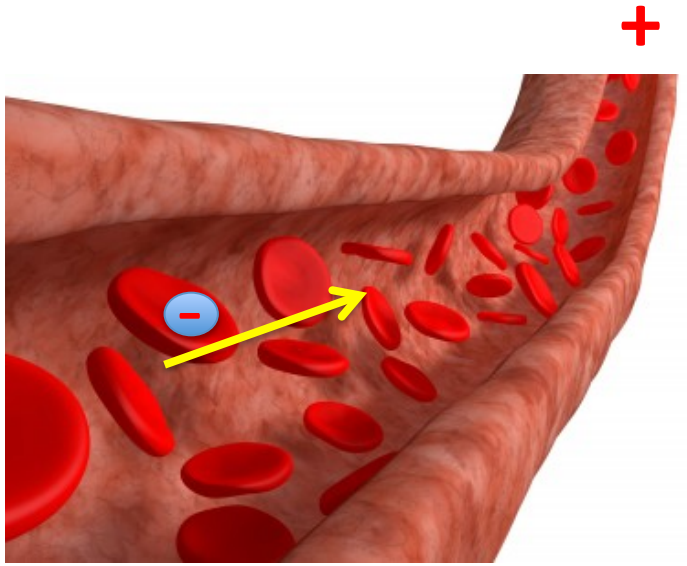
It is a direct consequence of insufficient negative charge in the blood vessels, due to insufficient supply of sulfate anions

Zeta potential is a measure of the flow rate of charged particles (e.g., red blood cells) in an electric field

The blood's zeta potential is an indicator of general health

Electrokinetic Vascular Streaming Potential (EVSP)*

- Field strength is proportional to the zeta potential → promotes blood flow
- Contains a DC component and an AC component (very low frequency, depends on pulse rate and heart rate)
- Influences endothelial cells:
  - Enhances release of nitric oxide (vasorelaxant)
  - Increases calcium-based depolarization



*D.P. Trivedi et al., Bioelectromagnetics 34:22-30, 2013.

Streaming Potential

Streaming potential

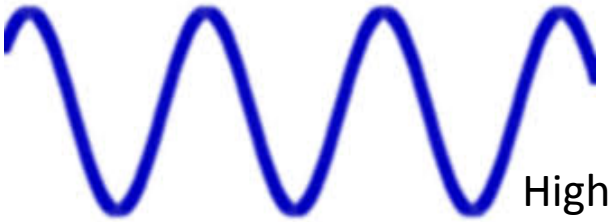
A). $E_s = [Zee_0P/nk][f(Y_a)]$

E_s = streaming potential (volts)
e = electrolyte dielectric constant
P = systolic pressure (N/m2)
k = conductivity (S/m)

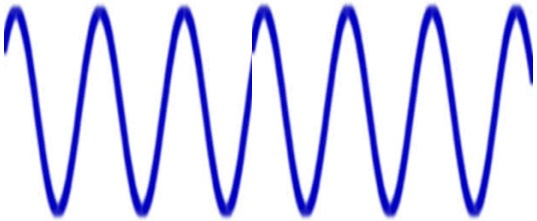
Z = zeta potential (volts)
e_0 = permittivity of free space
n = viscosity (kg/m*s)
$f(Y_a)$ = correction for pulsatile flow

Streaming Potential

Contains both DC and AC component
AC component controlled by heart rate



Higher heart rate induces stronger response



Streaming potential

↓

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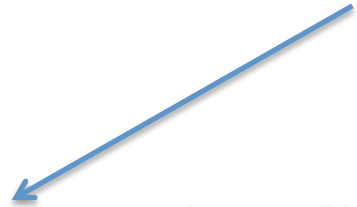
Streaming Potential

Proportional to Zeta potential



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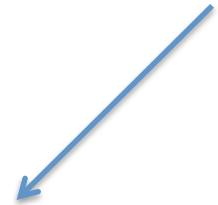
$f(Y_a)$ = correction for pulsatile flow

Streaming Potential

Proportional to blood pressure



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E_s = streaming potential (volts)
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k = conductivity (S/m)

Z = zeta potential (volts)
e_0 = permittivity of free space
n = viscosity (kg/m*s)
$f(Y_a)$ = correction for pulsatile flow

Streaming Potential

Inversely proportional to viscosity

A). $E_s = [Zee_0P/nk][f(Y_a)]$

E_s = streaming potential (volts)
e = electrolyte dielectric constant
P = systolic pressure (N/m2)
k = conductivity (S/m)

Z = zeta potential (volts)
e_0 = permittivity of free space
n = viscosity (kg/m*s)
$f(Y_a)$ = correction for pulsatile flow

Some Insights

- When zeta potential is too low (not enough bound sulfate), blood pressure must *go up* to compensate (high blood pressure)
- When viscosity is too high, blood pressure must *go up* to compensate (high blood pressure)
- Nitric oxide is produced in response to calcium entry, which is induced by the streaming potential

Nitric oxide quickly converts to nitrite which can attack the glycocalyx, releasing sulfated GAGs

These can be passed on to the capillaries to correct their deficiencies

Excessive calcium entry
leads to artery calcification

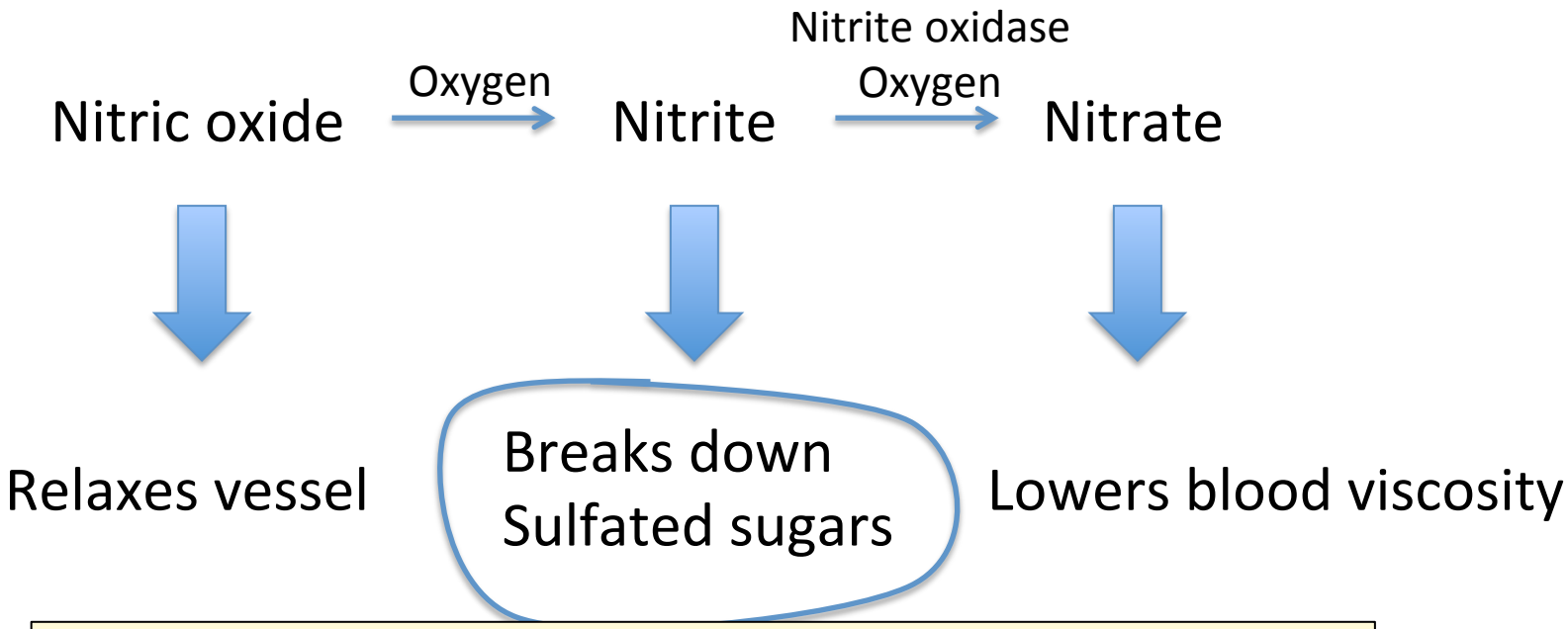
Much better solution is to maintain the capillary supply by delivering cholesterol sulfate from RBCs!!

WIKI on Biopterin*

"Biopterin is a cofactor in the production of many needed neurotransmitters in the body. A few of these include dopamine, serotonin and epinepherine. It is also key in the body's production of nitric oxide. … Though mainly in the pineal gland, it is also known to be produced in many other glands as well."

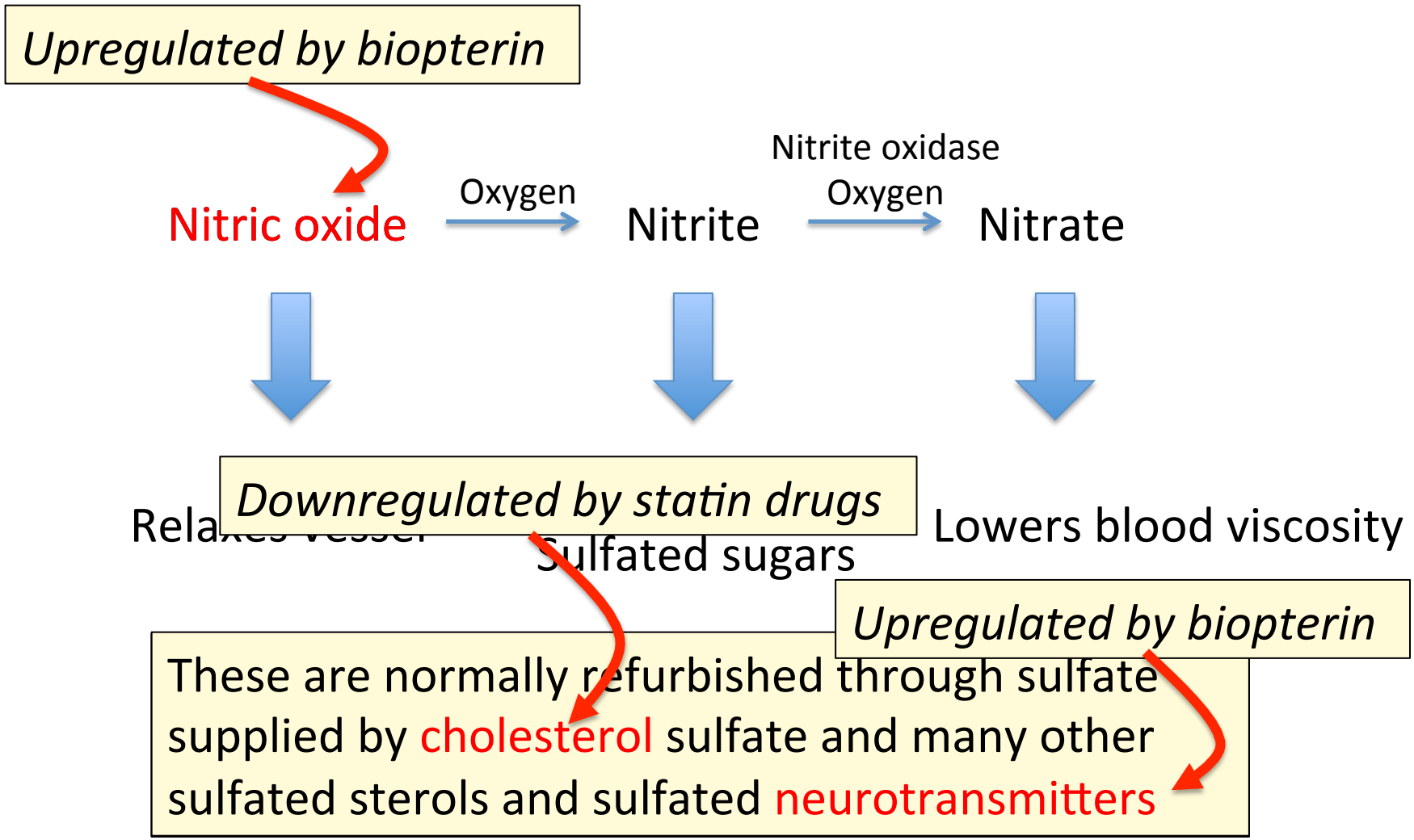
*induced by statin drugs!!

An Essential Role for Nitric Oxide

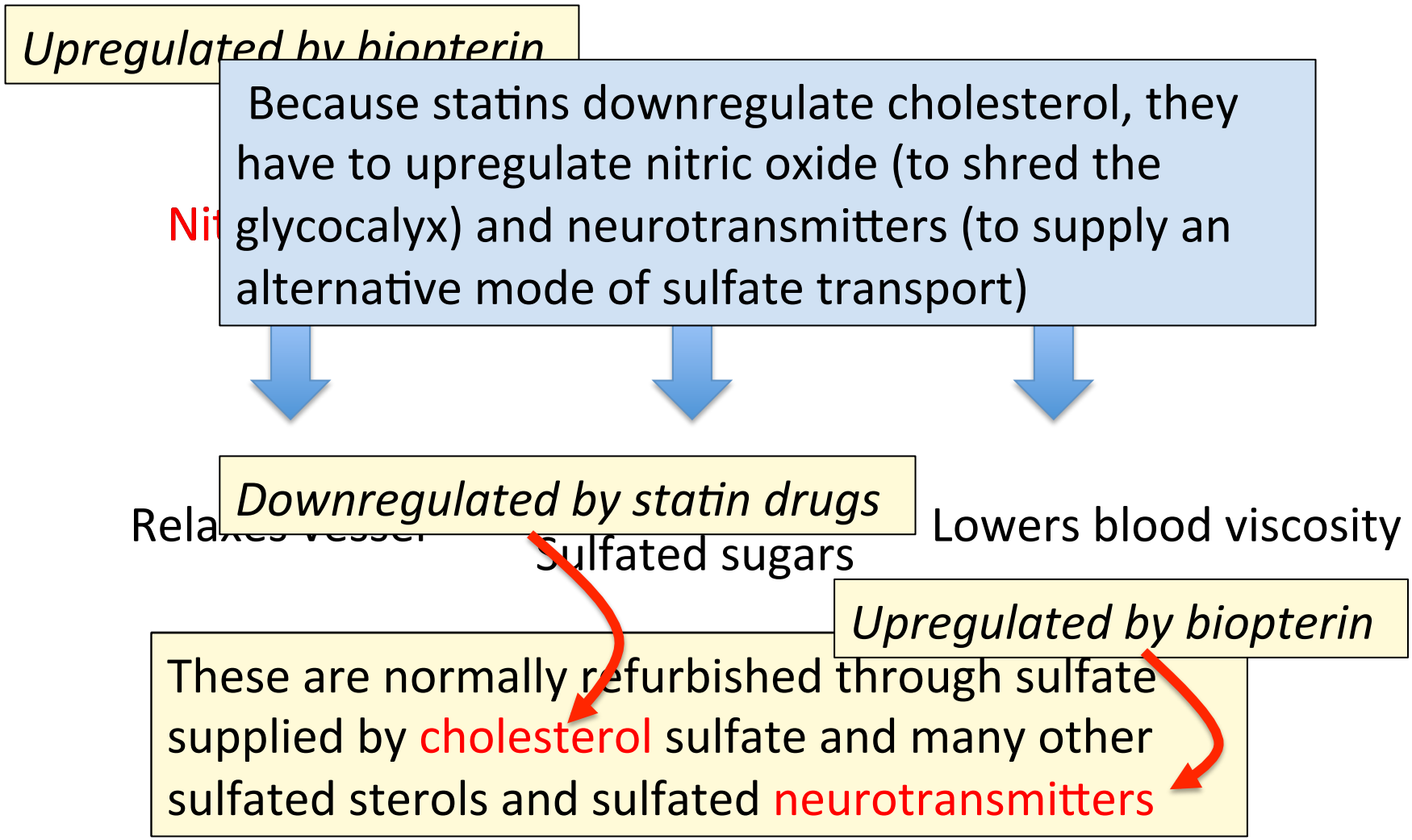


These are normally refurbished through sulfate supplied by cholesterol sulfate and many other sulfated sterols and sulfated neurotransmitters

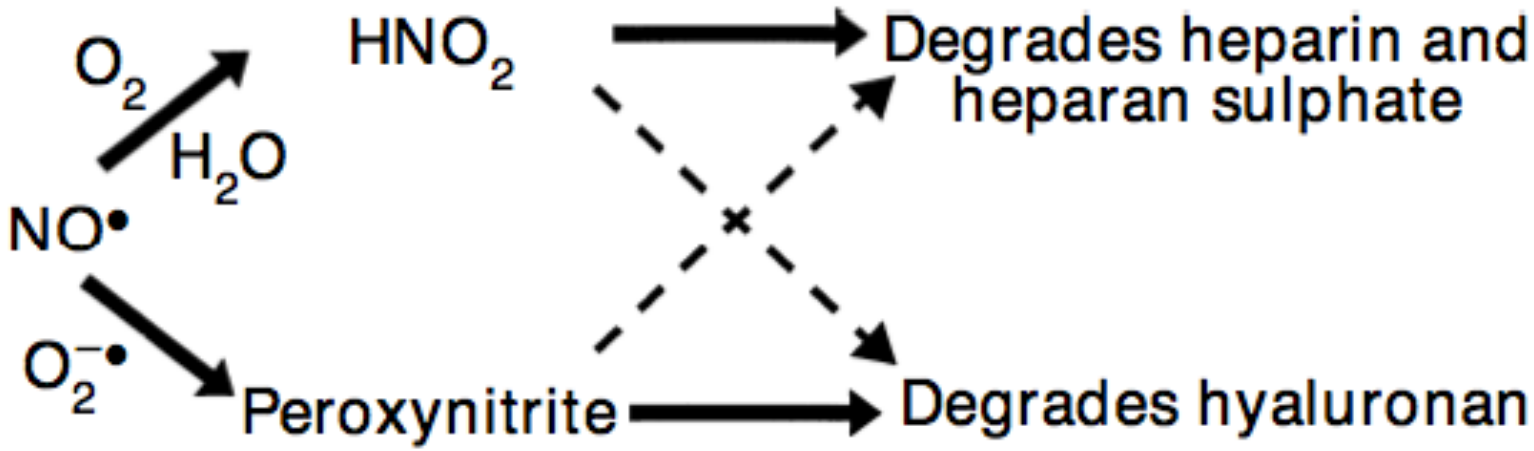
An Essential Role for Nitric Oxide



An Essential Role for Nitric Oxide



Nitric Oxide Degrades Extracellular Matrix*



Hyaluronan is a very long sugar chain that has only carbonates; no sulfates
Peroxynitrite is produced by a reaction between nitric oxide and superoxide

* Figure from RE Vilar et al., Biochem. J. (1997) 324, 473–479.

Recapitulation

- Streaming potential is an electrical field created by flowing blood –vessel walls respond to the signal it creates by releasing nitric oxide
- It depends on critical parameters: viscosity, blood pressure, zeta potential
- When zeta potential is low or viscosity is high, blood pressure must go up to compensate
- Nitric oxide can break down heparan sulfate and redistribute it – more is needed when cholesterol sulfate is in short supply (i.e., with statin therapy)

Atherosclerosis is Protective!

End Stage Kidney Disease and Cardiovascular Disease*

- High serum cholesterol
- High blood pressure
- High serum homocysteine
- Obesity
- Inflammation

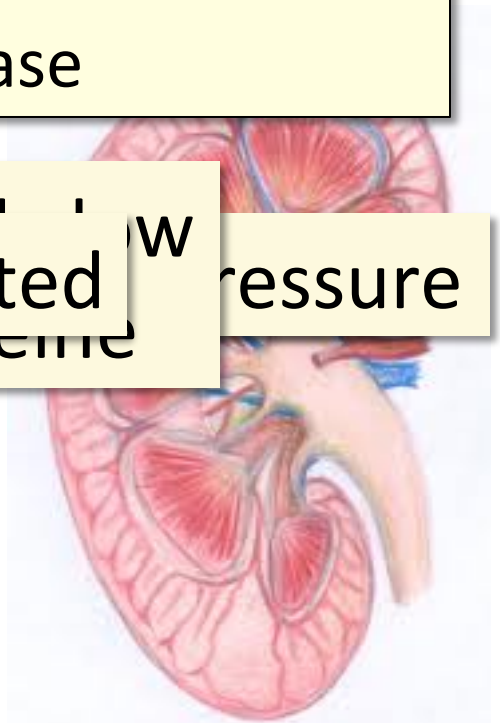
Dialysis patients have extreme risk to cardiovascular disease

Abnorm

Ab

Emaciated

ressure



* Kalantar-Zadeh et al., American Journal of Kidney Diseases 42:5 864-881, 2003

My Conclusion from This

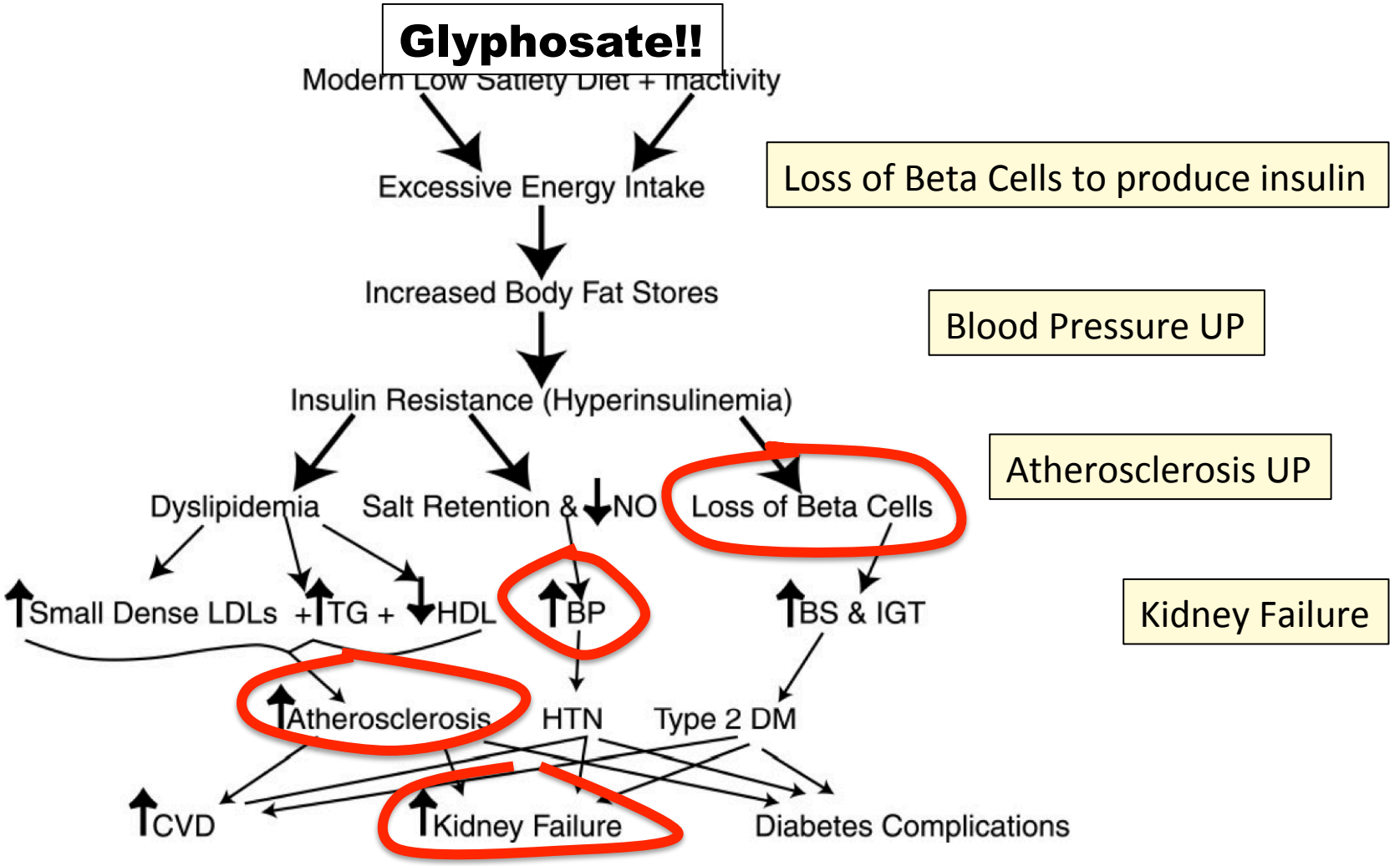
Inflammation is the *ONLY*
"Risk Factor" that counts:
All the other "Risk Factors" are
protective measures!

Frustration in Treating Cardiovascular Disease for Dialysis Patients*

"Reducing mortality from cardiovascular disease among patients undergoing dialysis is a global public health challenge. The past 10 years have seen trials of many interventions designed to improve survival and cardiovascular outcomes in these patients. Unfortunately, none of these interventions have been shown to be effective, despite *beneficial effects in surrogate markers*. It appears that *statins* have now joined this group of 'promising but ineffective' interventions."

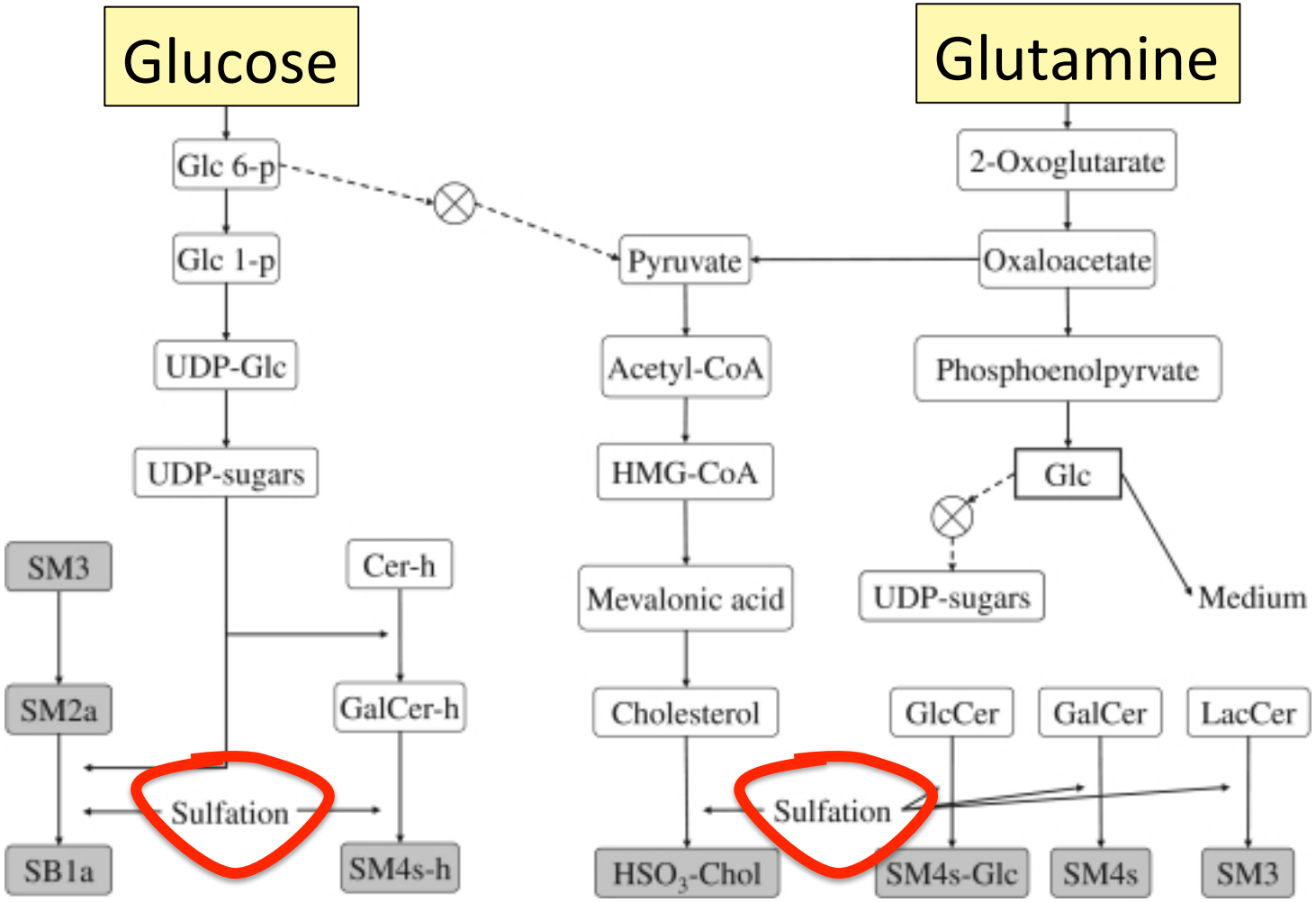
*Strippoli and Craig, N Engl J Med 2009; 360:1455-1457.

Diabetes Progression*



*JJ Kenney, **Diet to Prevent and Reverse Insulin Resistance and Type 2 Diabetes**
http://foodandhealth.com/cpecourses/insulin.php

Sulfates in the Kidneys*



*K.-I. Nagai et al., Proc Jpn Acad Ser B Phys Biol Sci. 2008 January; 84(1): 24–29

Statins and Kidney Failure*

- Kidney failure is alarmingly on the rise in the US and elsewhere
  - associated with a 23-fold increase in risk to heart disease!
- Statins are being overprescribed for patients with kidney failure
  - Severe muscle pain & rhabdomyolysis
  - Increased risk to dementia and diabetes
  - No improvement in kidney function

* M.A. Lanaspa et al., Nature Communications, 2013; Aug 24. [Epub ahead of print]

Heart Disease: A Theory!

Cardiovascular plaque develops as an alternative mechanism to produce cholesterol sulfate from damaged LDL and homocysteine

A Recent Paper

S. Seneff, A. Lauritzen, R. Davidson, and L. Lentz-Marino.

"Is Endothelial Nitric Oxide Synthase a Moonlighting Protein Whose Day Job is Cholesterol Sulfate Synthesis? Implications for Cholesterol Transport, Diabetes and Cardiovascular Disease."

Entropy 2012, 14, 2492-2530.

What Happens when Cholesterol Sulfate Synthesis is Impaired??

Cardiovascular disease!!!

Activities in Plaque Produce
Cholesterol Sulfate to Supply the Heart

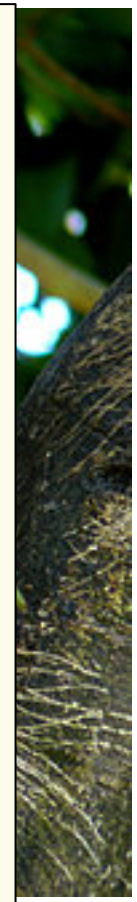
They Knew a Long Time Ago*

- Article published in 1960
- Fed cholesterol to monkeys
  - induced atherosclerosis
- If sulfur-containing nutrients are added, atherosclerosis is prevented
- These nutrients provide source of sulfate to enable cholesterol transport

* G.V. Mann et al., Am. J. Clin. Nutr. 8, 491-497, *1960*.

They Knew a Long Time Ago*

"A form of vascular disease resembling human atherosclerosis has been produced in the New World primate Cebus fatuella. ... In order to produce these phenomena, the diets had to be rich in cholesterol, choline and neutral fat but relatively *low in organic sulfur compounds.* Without this deprivation of organic sulfur the response of the serum lipids to cholesterol feeding was small."



* G.V. Mann et al., Am. J. Clin. Nutr. 8, 491-497, 1960.

Steps in Atherosclerosis*

1. Inflamed endothelium provides adhesion molecules to trap and hold macrophages
2. Macrophages take up oxidized LDL and become foam cells
3. Smooth muscle cells proliferate (artery thickening)
4. Extracellular matrix proteins are degraded
5. Vulnerable plaque eruption: thrombosis

* Libby et al., Circulation 105:1135-1143, 2002

Many Good Reasons for ROS

- ROS (reactive oxygen species) are a key component of inflammation in the artery
- ROS are needed to produce sulfate *
- Oxidation of glycated LDL makes it accessible to macrophages for breakdown**
- Peroxynitrite (product of reaction between superoxide and nitric oxide) is toxic to pathogens***

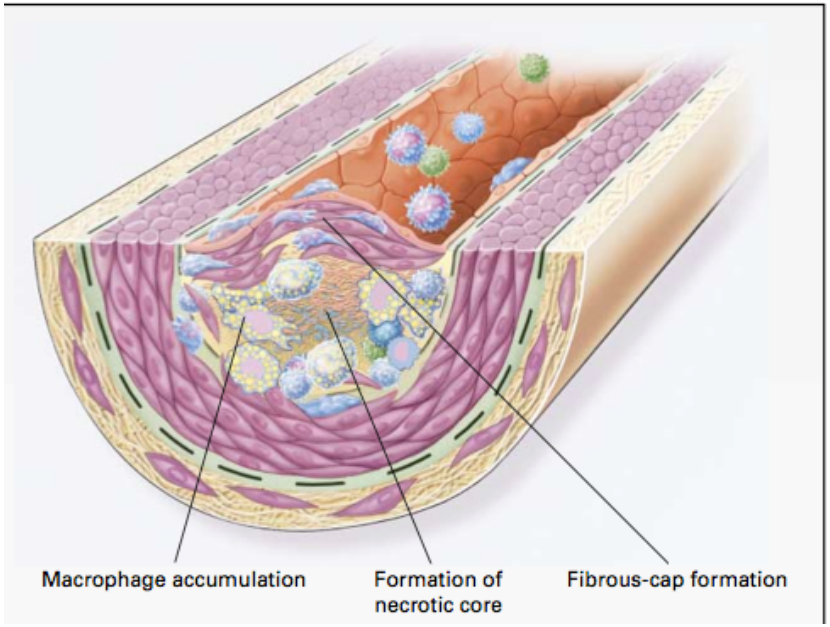
* Mitsuhashi et al. Shock 24(6) 529-34, 2005.

** Kaplan and Aviram, Arterioscler Thromb Vasc Biol 21(3) 386-93 2001.

*** Alvarez et al., J. Biol. Chem. 286, 6627-6640, 2011.

Macrophages and Cholesterol*

- Macrophages in artery wall take up oxidized LDL and export extracted cholesterol to HDL-A1
- *Unsaturated* fatty acids interfere with export process
- Macrophages eventually become damaged by exposure to oxidizing and glycating agents → necrotic core



* Wang and Oram, J. Biol. Chem. 277 (7) , 5692–5697, 2002

Quote from the Abstract*

"These findings raise the possibility that an increased supply of *unsaturated* fatty acids in the artery wall *promotes* atherogenesis by impairing the ABCA1 cholesterol secretory pathway in macrophages."

* Wang and Oram, J. Biol. Chem. 277 (7) , 5692–5697, 2002

Macrophage Proliferation in Plaque*

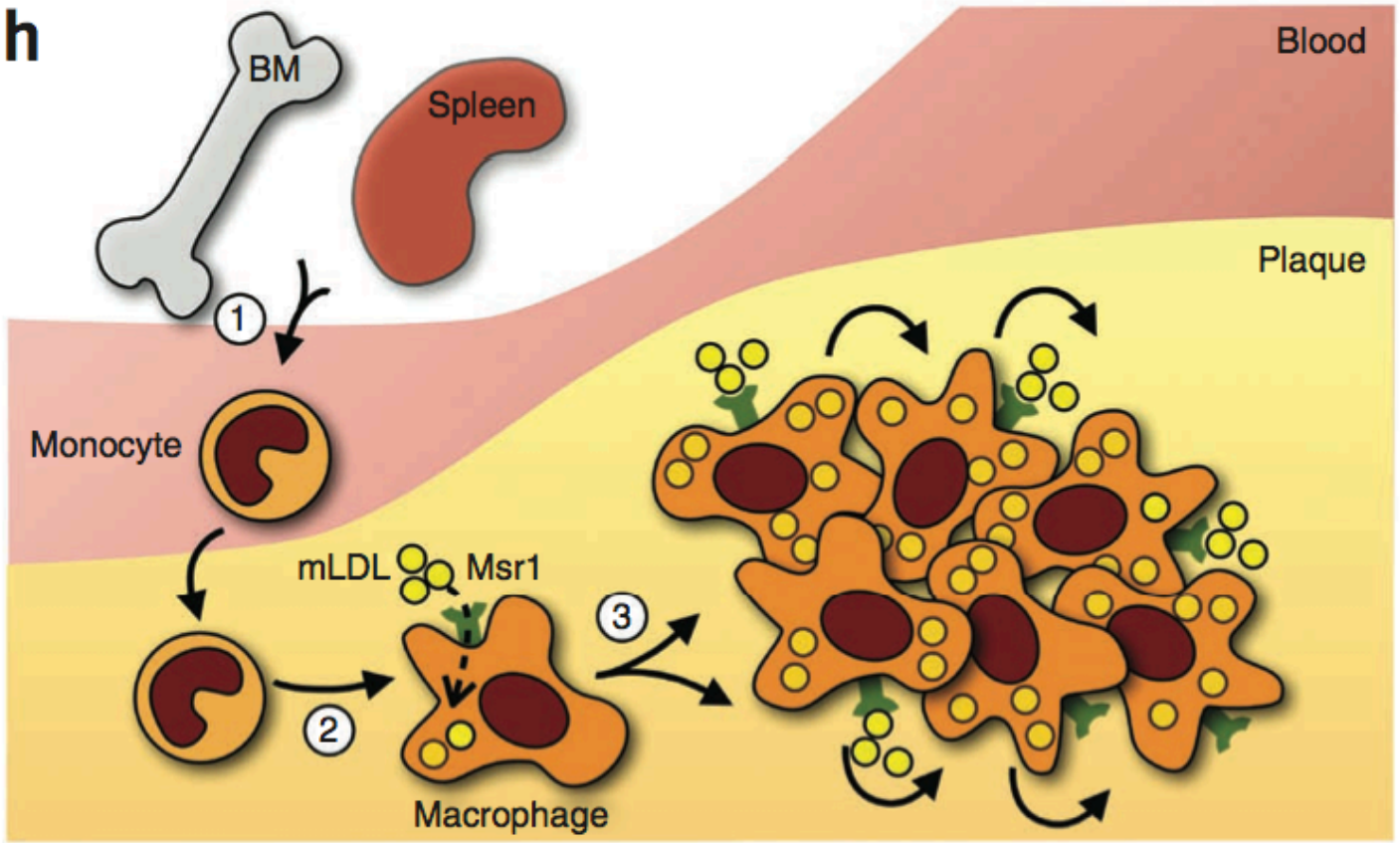


*Figure 4, C.S. Robbins et al., Nature Medicine, Aug. 2013 [ePub ahead of print]

Declaring War on Macrophages*

- Macrophages replicate inside plaque
  - Suppressing their entry into plaque is not enough!
- Proposal: develop new therapy that suppresses proliferation of macrophages in plaque

"It's a bit like killing off the army to be sure there's no collateral damage when invaders attack your country"

--David Diamond, Member of THINCS

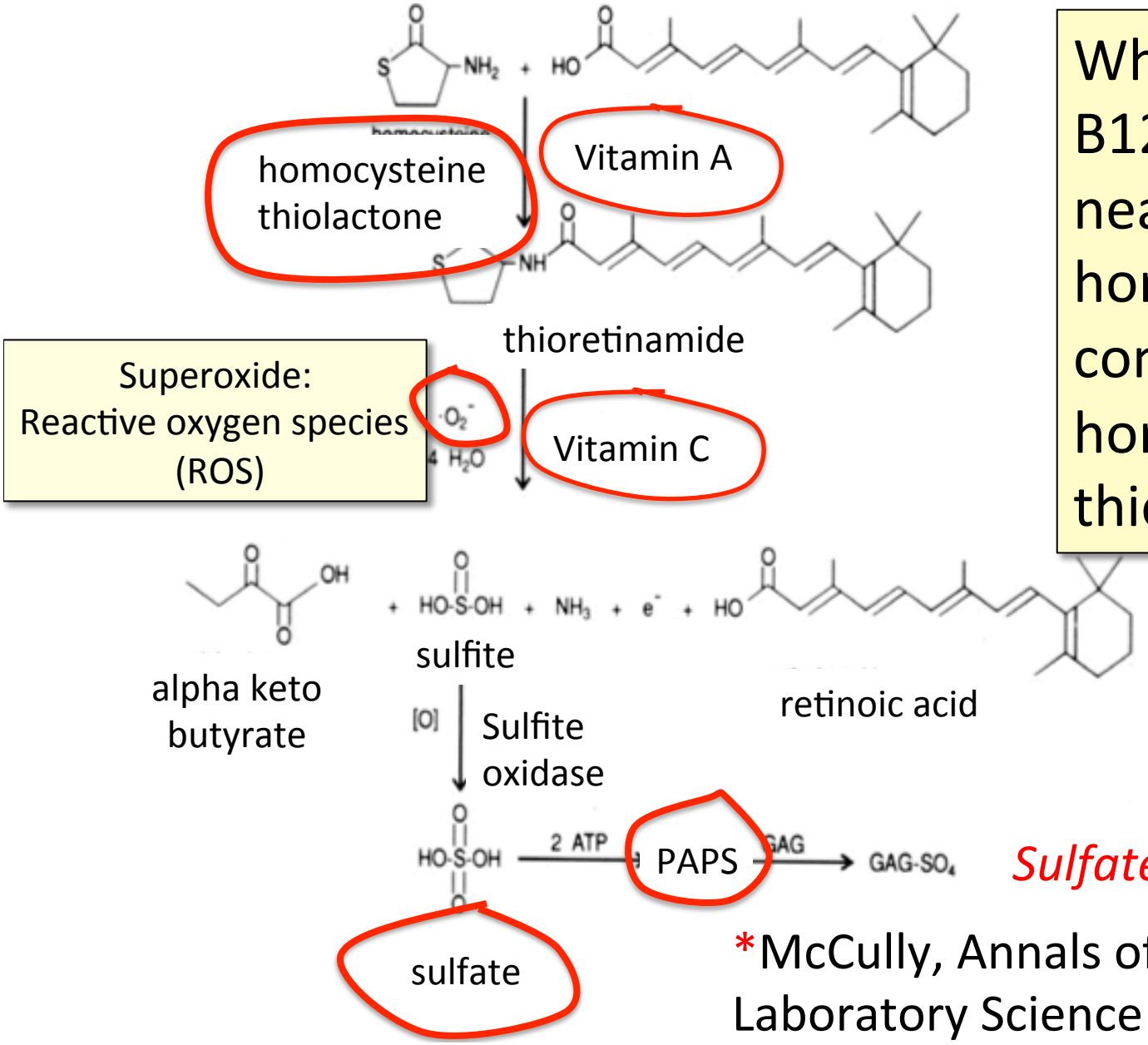
*C.S. Robbins et al., Nature Medicine, Aug. 2013 [ePub ahead of print]

Elevated Homocysteine and Heart Disease*

- 587 patients with coronary artery disease followed over median period of 4.6 years
- Homocysteine > 15 micromol/Liter
  → *6.5-fold increase* in death rate
  compared to homocysteine < 10 micromol/L

*P.O. Lim et al., Journal of Human Hypertension (2002) 16, 411–415.

Pathway from Homocysteine to Sulfate*

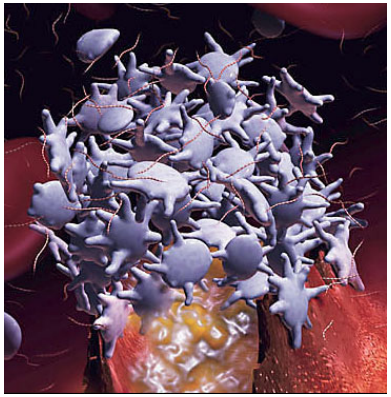


When folate and B12 are deficient, nearly all homocysteine is converted to homocysteine thiolactone

Sulfated GAG

*McCully, Annals of Clinical and Laboratory Science 41:4, 300-313, 2011

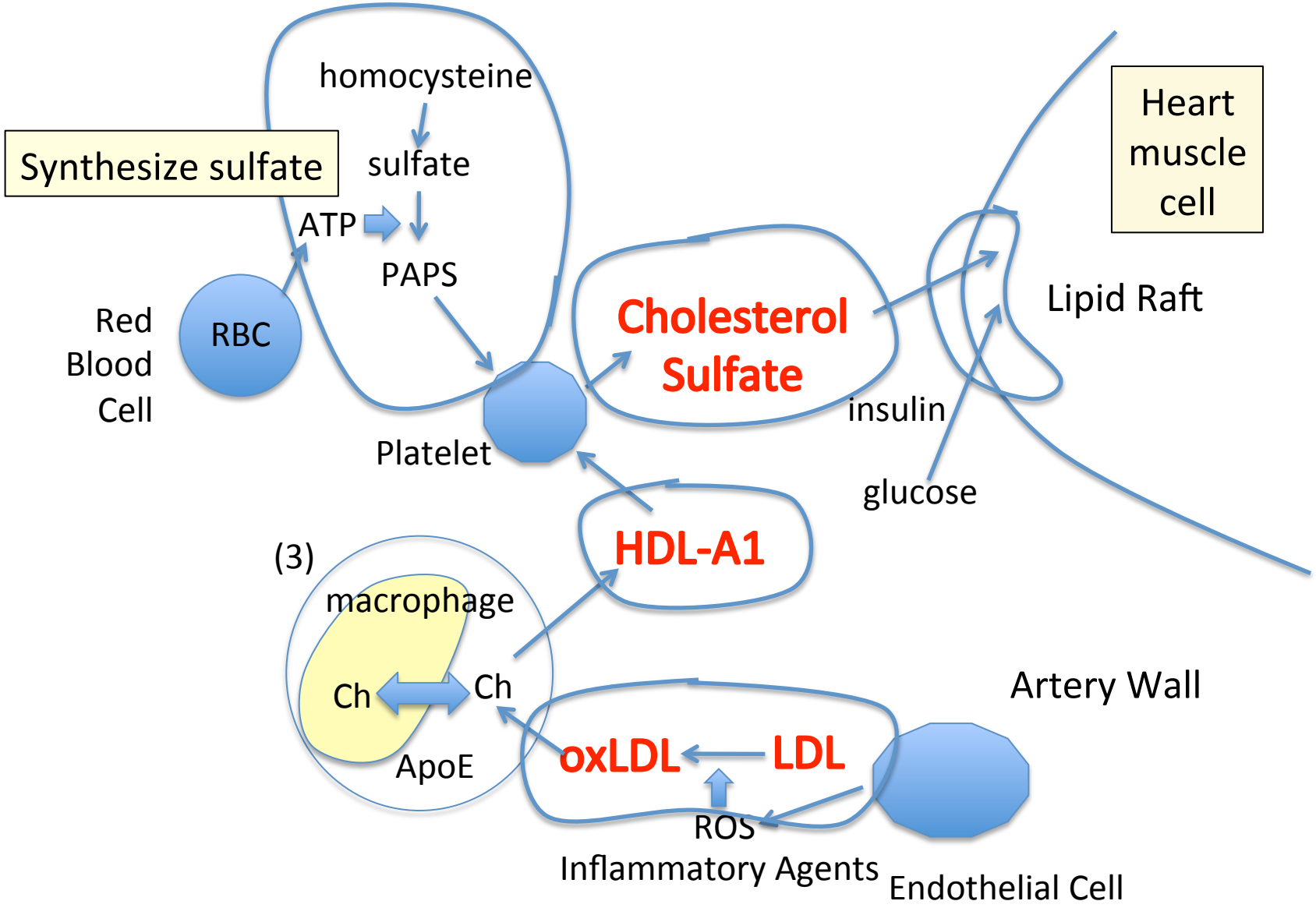
Platelets and Cholesterol Sulfate*



- Platelets and RBCs both synthesize cholesterol sulfate (Ch-S)
  - Ch-S is present in the atherosclerotic lesions in the aorta
  - Platelets will accept cholesterol *only from HDL-A1*
  - Platelet synthesis rate increases 300-fold when PAPS is available.
  - PAPS is formed from ATP and sulfate
- Platelet aggregation leads to thrombosis
  - HDL suppresses aggregation; LDL promotes it

* Yanai et al, Circulation 109, 92-96, 2004

Putting it All Together



Brits Love Statins*

- Eight million Britons now take statins compared to five million a decade ago.
- Top prescriber of anti-cholesterol drugs in Europe
- One in five who take statins suffer side effects including muscle pain, memory disturbance, cataracts and diabetes.

*Daniel Martin, MailOnLine
dailymail.co.uk/health/article-2529283/
UK-statins-capital-Europe-With-1-8-taking-
cholesterol-busting-drugs-used-replacement-healthier-living.html

Statins Increase Plaque Calcification*

- 6673 people studied (2413 on statins 4260 not on statins)
- Mean age 59, 55% male
- Evaluated using coronary CT angiography - noninvasive method to visualize atherosclerotic features
- Statin use was associated with *increased* prevalence of calcified plaque and *increasing* numbers of coronary segments possessing calcified plaque

*R. Nakazato et al. Atherosclerosis 225(1), 148-153, November 2012.

"Heart Stents Still Overused, Experts Say"*

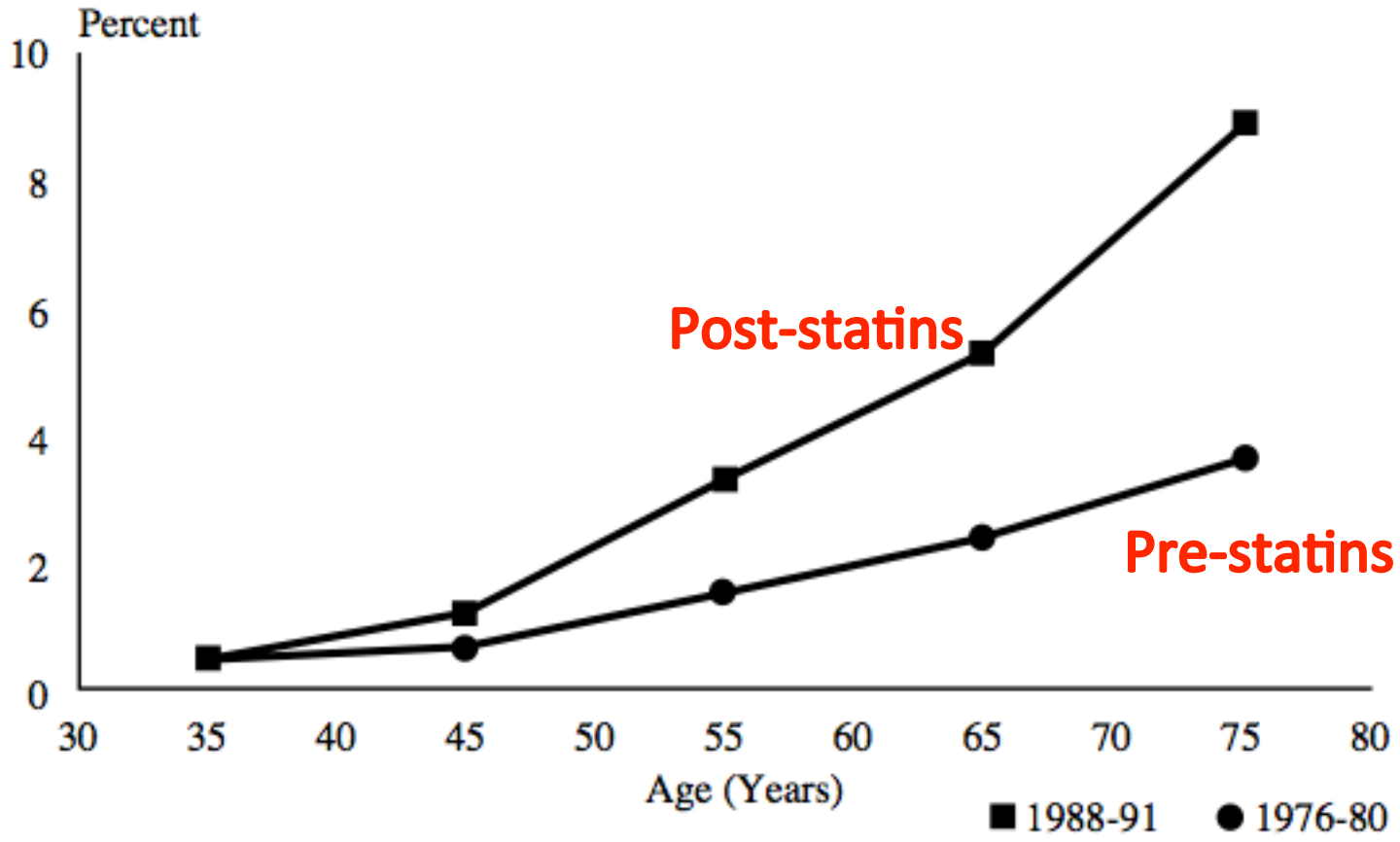
- Two misconceptions
  - Heart attack caused by blocked artery
  - Eating fatty foods induces fat build-up
- Heart attack is actually caused by thrombus formation (blood clot) that often occurs in a region of the artery where plaque is not obstructive
- Stent insertion is expensive and is not living up to the promise of protection

*Anahad O'Connor, NY Times, Aug. 16, 2013

I hypothesize that treatments aimed at reducing the supply of cholesterol to the plaque will eventually lead to severe deficiencies in cholesterol and sulfate supply to the heart, resulting in heart failure.

Figure 5

Prevalence of CHF, by Age, 1976-80 and 1988-91



Source: National Health and Nutrition Examination Survey (1976-80 and 1988-91), National Center for Health Statistics.

National Heart, Lung, and Blood Institute National Institutes of Health Data Fact Sheet

Recapitulation

- Kidney disease is associated with inversion of factors for heart disease risk
  - Kidneys depend critically on sulfates for function
  - Inflammation is required to synthesize sulfate
- Cardiovascular disease can be best characterized as a factory to supply *cholesterol* and *sulfate* to the heart (and kidney)
- Statin drugs, through their ability to deplete the supply of cholesterol to the plaque, can lead to *heart failure and kidney failure* down the road

Summary

- Sunlight-catalyzed cholesterol sulfate synthesis in the skin is essential for long-term health
  - Heart disease is a compensatory mechanism to synthesize cholesterol sulfate
- Hemostasis depends on adequate sulfate in the blood
  - High blood pressure and high heart rate compensate for low zeta potential
- Heparan sulfate proteoglycans (HSPGs) are pervasive in the body, and sulfate depletion leads to diabetes, heart disease, and kidney disease
- I predict that statin drugs, by depleting cholesterol sulfate supplies, can lead to heart failure