

# 3. Gut Microbes: How They Help us Out

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Wise Traditions Workshop

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# Outline

- Gut bacteria under siege
- Infection: A novel perspective
- Influenza
- Natural resistance and antibiotics
- Summary

# **Gut Bacteria Under Siege**



# Gut Bacteria and Health\*

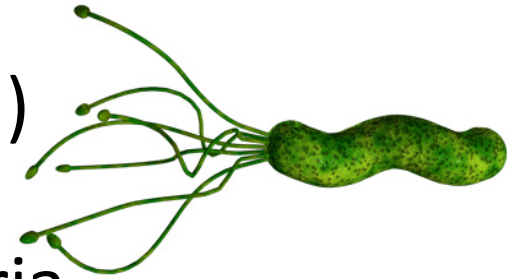
- We are an ecosystem: a community of interacting cells
  - Trillions of bacteria live in our body
  - They outnumber our own cells 10:1
  - Killing them off may make us sick or fat
- 5-8 million microbial genes in our bodies (3 million in digestive system from more than 1000 species)
- They play very essential roles in our bodies
  - Digest foods, absorb nutrients, provide enzymes, make vitamins and antiinflammatories
  - Regulate appetite and brain function
- Vaginal birth matters
- Everyone has unique set of gut bacteria



\* NPR's On Point: Your Inner Ecosystem, <http://onpoint.wbur.org/2012/06/20/bacteria-2>

# “Our microbes are under threat — and the enemy is us”\*

- “Microbiome”
  - 99% of them are benign or offer protection
  - Synthesize vitamins B12 and folate
- Birth through birth canal (v.s. C section)
  - Infant picks up mother's microbiome
- Colostrum provides food for gut bacteria
- Industrialized countries are too clean
  - Drastically altered microbiome
    - H. pylori 90% → < 10% in last hundred years in U.S.
    - Esophageal cancer and childhood asthma have risen in step



\* Liz Szabo, USA Today,

<http://www.usatoday.com/news/health/story/2012-07-13/body-bugs-microbes/56255904/1>

# H. pylori: There are Benefits!\*

- The Western world has now significantly reduced the presence of H. pylori in the gut
  - This has reduced the incidence of stomach ulcers and stomach cancer
  - But it has also increased the incidence of esophageal reflux disease and esophageal cancer
- H. pylori serve a useful role in reducing acid production by stomach: excess acid aggravates the esophagus
- We host a colony of bacteria and they work together with us for a jointly beneficial solution

\*Caroline Hadley, *EMBO reports* 7(5), 471-473, 2006

“Our biggest exposure to the environment is actually the lining of our intestines – not our lungs, not our skin. We are in fact very much dependent on the microbiota, the bacteria living in the gut, to maintain our health.”

- Dr. David Perlmutter, neurologist

Interview with Dr. Mercola\*

\*<http://articles.mercola.com/sites/articles/archive/2013/09/29/dr-perlmutter-gluten.aspx>



# Glyphosate and the Shikimate Pathway\*

- Glyphosate disrupts the shikimate pathway, leading to dysbiosis of aromatic amino acids
- Monsanto claims glyphosate is safe because human cells don't have the shikimate pathway
- However, gut bacteria are very important to human health, and they *do* have the pathway
- Dysbiosis in the gut is increasingly being recognized as a factor in modern diseases



\*A. Samsel and S. Seneff, Entropy 2013, 15, 1416-1463.

# Glyphosate and the Shikimate Pathway\*

- Glyphosate disrupts the shikimate pathway, which is responsible for the production of aromatic amino acids.
- Monsanto claims that glyphosate is safe because humans do not have the pathway.
- However, recent research indicates that humans are in fact susceptible to human health, and they *do* have the pathway.
- Dysbiosis in the gut is increasingly being recognized as a factor in modern diseases.

I will have much more to say about this in the section on glyphosate



\*A. Samsel and S. Seneff, Entropy 2013, 15, 1416-1463.

# Celiac Disease: an Epidemic\*

- Celiac disease (gluten intolerance) is found throughout the US at a rate of up to 1 in every 133 persons, several orders of magnitude higher than previously estimated
- Our food choices and environmental toxins influence which genes get expressed
- Celiac disease can be framed as a healthy response to an unhealthy food
  - Diarrhea expels the toxins quickly

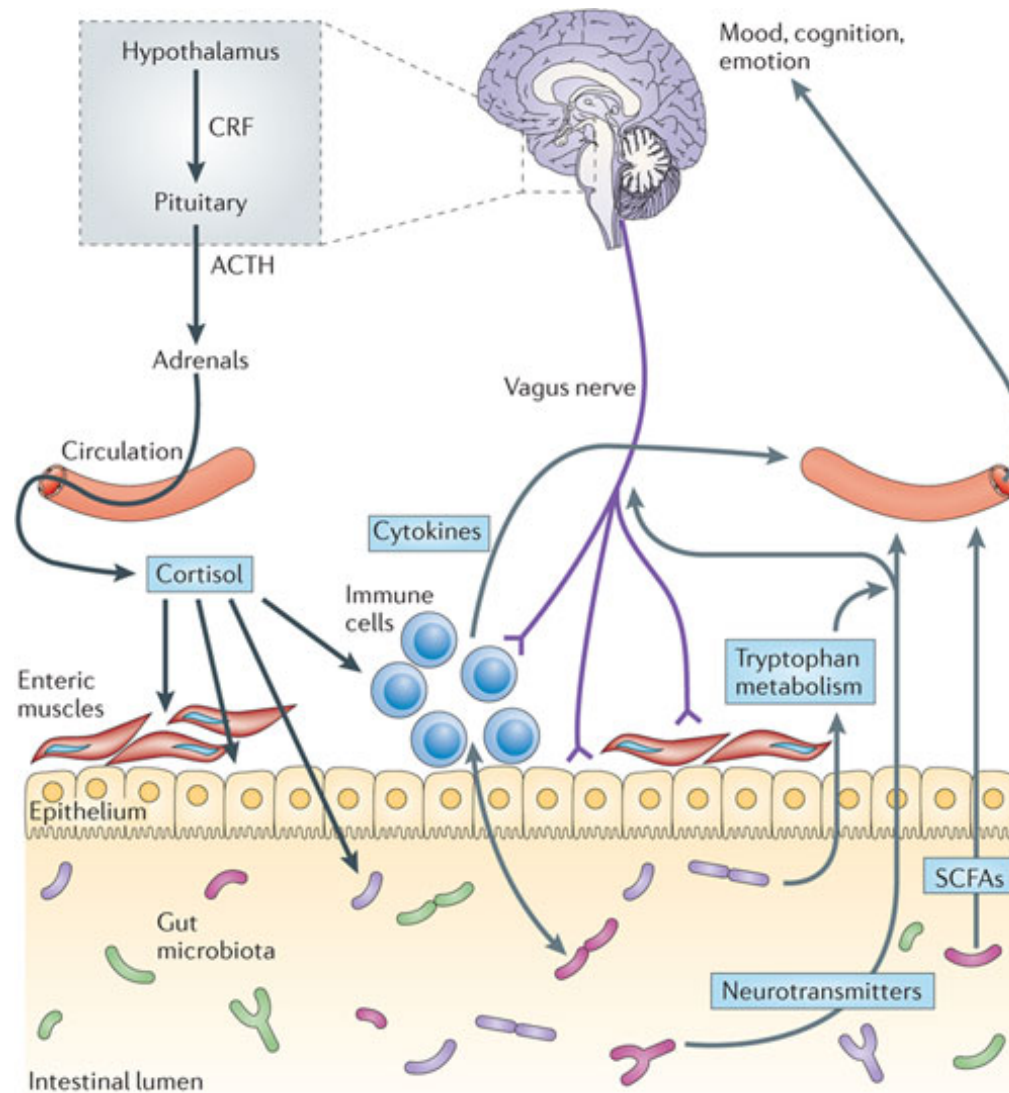
\**Sayer Ji, The Dark Side of Wheat.*

“Time and time again, we hear from patients that they never felt depressed or anxious until they started experiencing problems with their gut. Our study shows that the gut–brain connection is a two-way street.”

-- Dr. Kristin Tillisch\*

\*<http://newsroom.ucla.edu/portal/ucla/changing-gut-bacteria-through-245617.aspx>

# Connections Between the Gut and the Brain\*



\* J.F. Cryan and T.G. Dinan, Nature Reviews Neuroscience 2012, 701-712.

# Recapitulation

- Healthy gut bacteria are essential to health
- Glyphosate (Roundup) disrupts gut bacteria
- Celiac disease is a modern epidemic, likely due to glyphosate (more later)
- *H. pylori* has both pros and cons
- The gut-brain axis links gut bacterial distress to neurological diseases

# **Infection: A Novel Perspective**

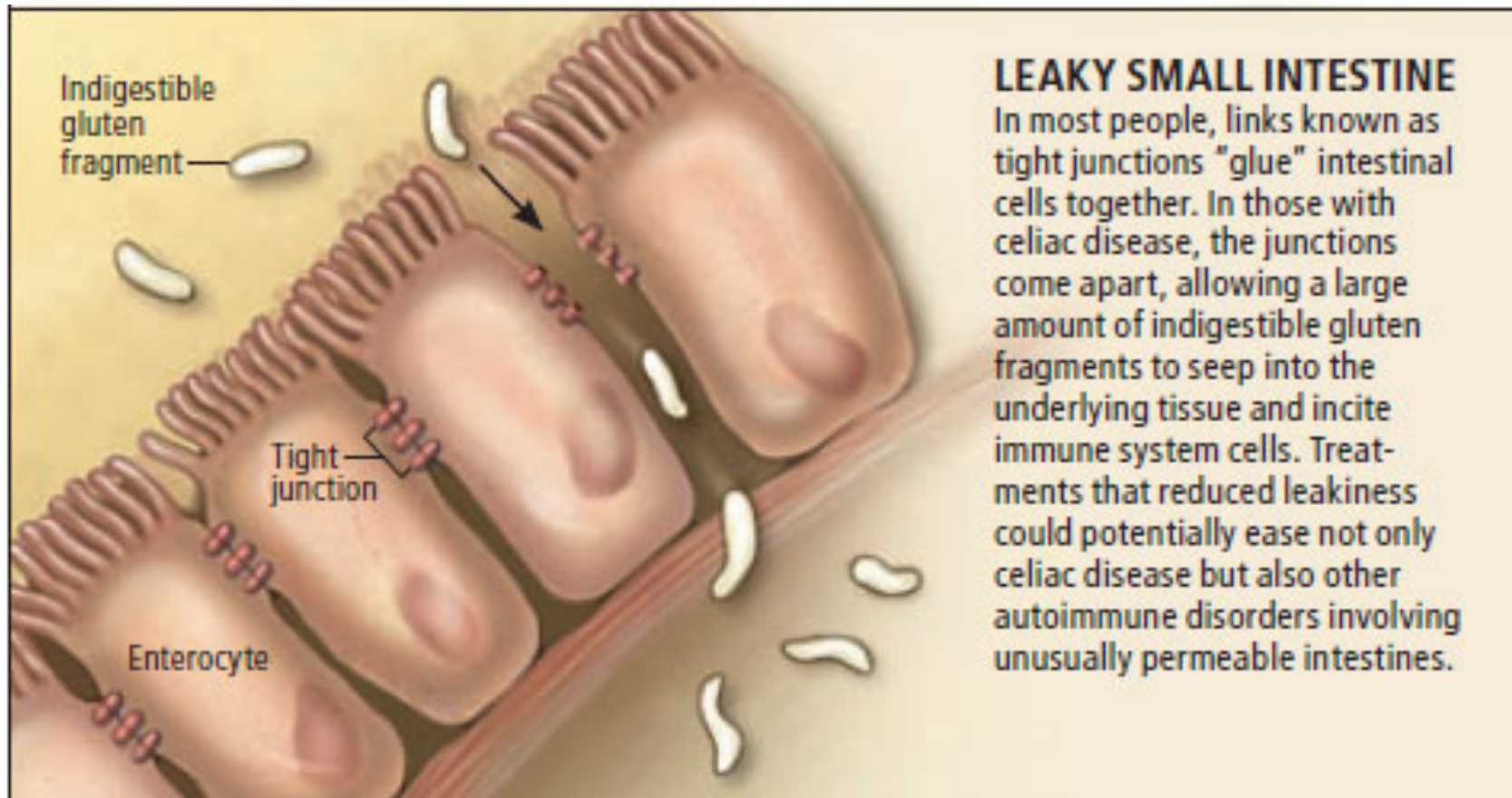
# Infection

Impaired cholesterol sulfate synthesis can lead to susceptibility to infection, which introduces widespread pathology

Infection serves a useful role in resupplying critical nutrients such as cobalamin, folate, and heparan sulfate



# Leaky Gut Syndrome\*



\* From <http://www.precisionnutrition.com/all-about-gluten>

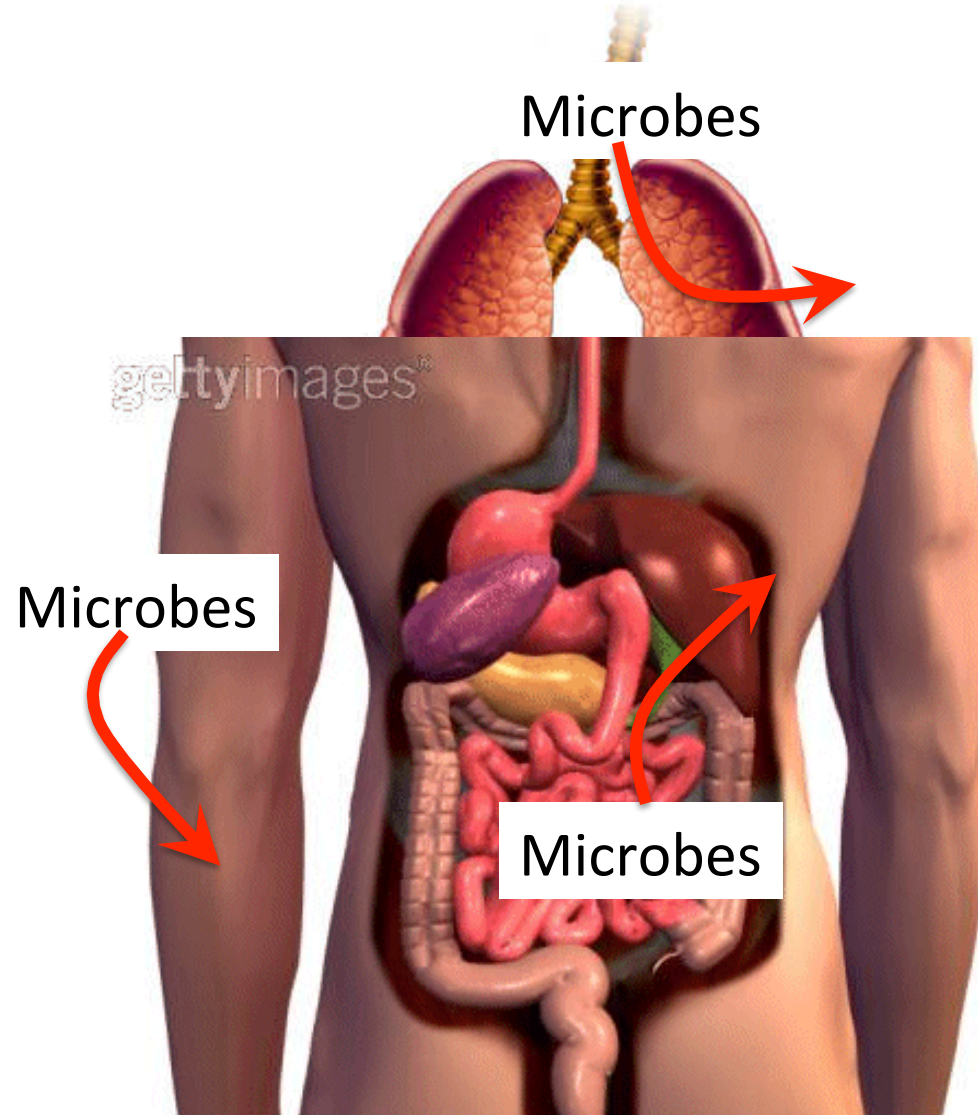
# Wild Speculation

- Leaky gut and leaky skin and leaky blood brain barrier lead to infiltration of microbes from gut or skin into brain
- Bacteria are “lured” into the body & into the brain and then killed and harvested to renew important nutrients
- Possible nutrients include:
  - Vitamin B12 (cobalamin), vitamin B9 (folate), thiamine, vitamin K and heparan sulfate



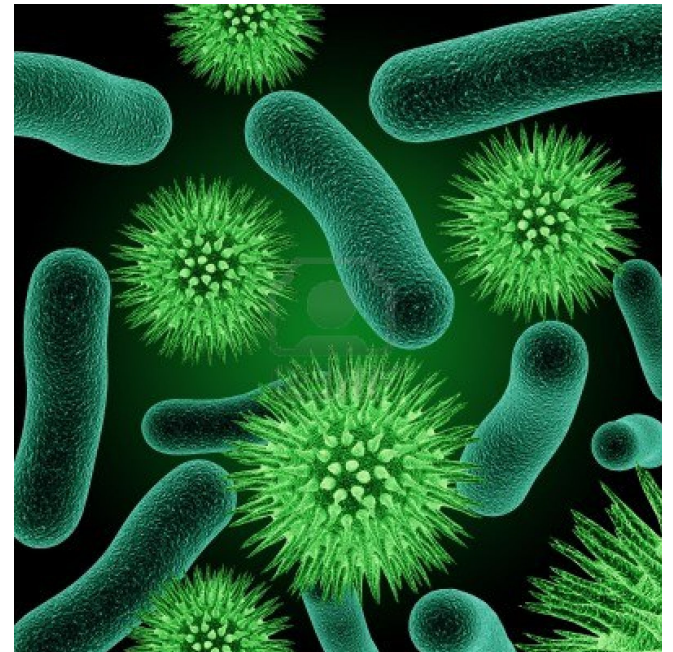
# What Causes Increased Infection?

**Impaired Cholesterol Sulfate Synthesis!**



# Adrenalin Stimulates Bacterial Growth\*

- Various species grown in culture (both gram negative and gram positive)
- Adrenalin added to medium stimulated growth
- Some species produce unknown growth-enhancing stimulus in presence of adrenalin
  - This can stimulate growth of other species as well



\*K.S. Kinney et al., Life Sciences 67 (2000) 3075–3085

# Sulfate Depletion in Colitis \*

- GAGs in intestinal mucosa greatly depleted in sulfate in association with both colitis and Crohn's disease
  - Colitis: mostly GAGs in luminal surface
  - Crohn's: mostly GAGs near blood vessels
- Serum albumin leaves vasculature and penetrates intestinal lining:
  - Insufficient negative charge results in easy access
- Serum albumin depletion has severe consequences to blood stability

\* Murch et al., The Lancet 341:711-714, Mar 20, 1993

# Sulfate Depletion in Colitis \*

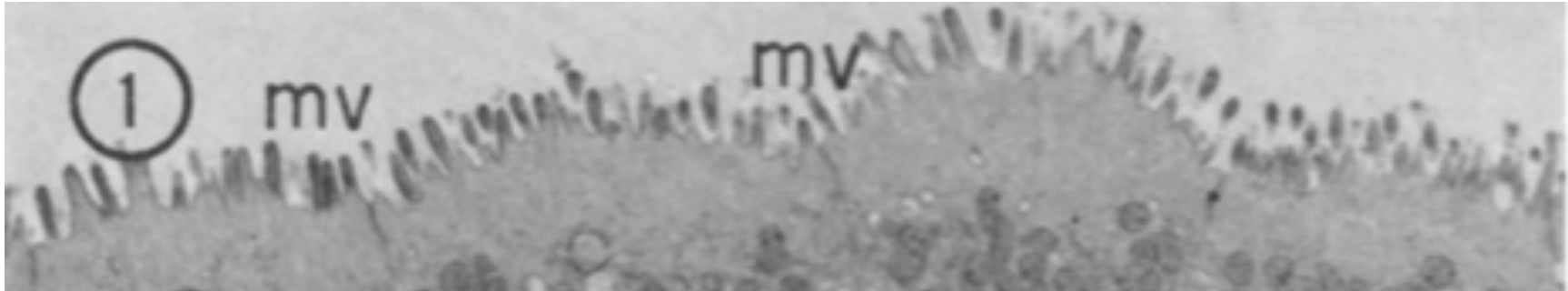
- GAGs in intestinal mucosa greatly depleted in sulfate in association with both colitis and Crohn's disease
  - 
  -
- Serum albumin depletion
  - People with colitis or Crohn's have greatly increased risk to colon cancer
  - Insufficient negative charge results in easy access
- Serum albumin depletion has severe consequences to blood stability

\* Murch et al., The Lancet 341:711-714, Mar 20, 1993

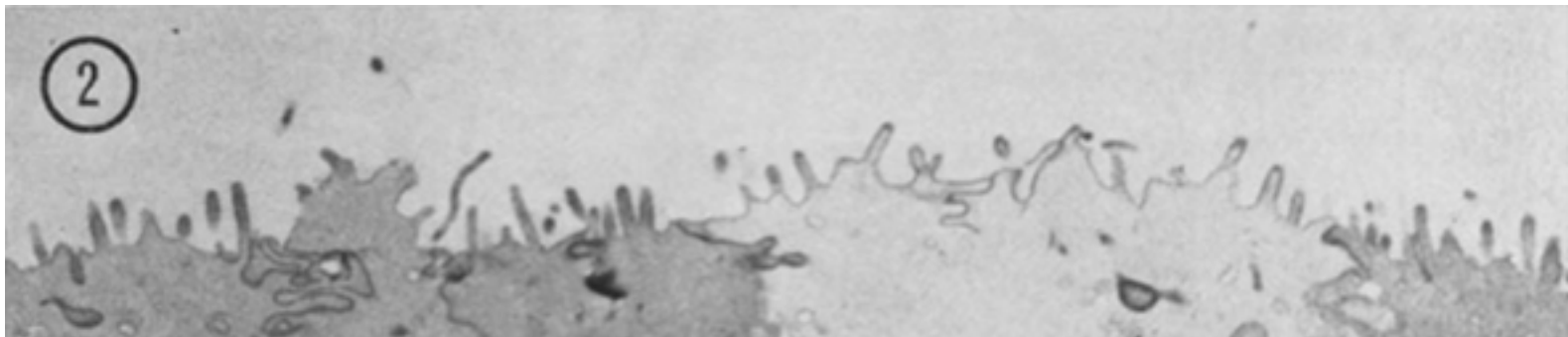
# Leaky Gut

- Reduced sulfate in the GAGs in the intestines
- Cells are defective in transporting nutrients
  - Leads to severe vitamin deficiencies (e.g., B12)
- Tight junctions between cells become loose
- Microbes can penetrate the gut wall and enter the blood stream
  - They can be harvested by macrophages!

# Microvilli in Gall Bladder Epithelium\*



Healthy – negative charge makes them stand tall

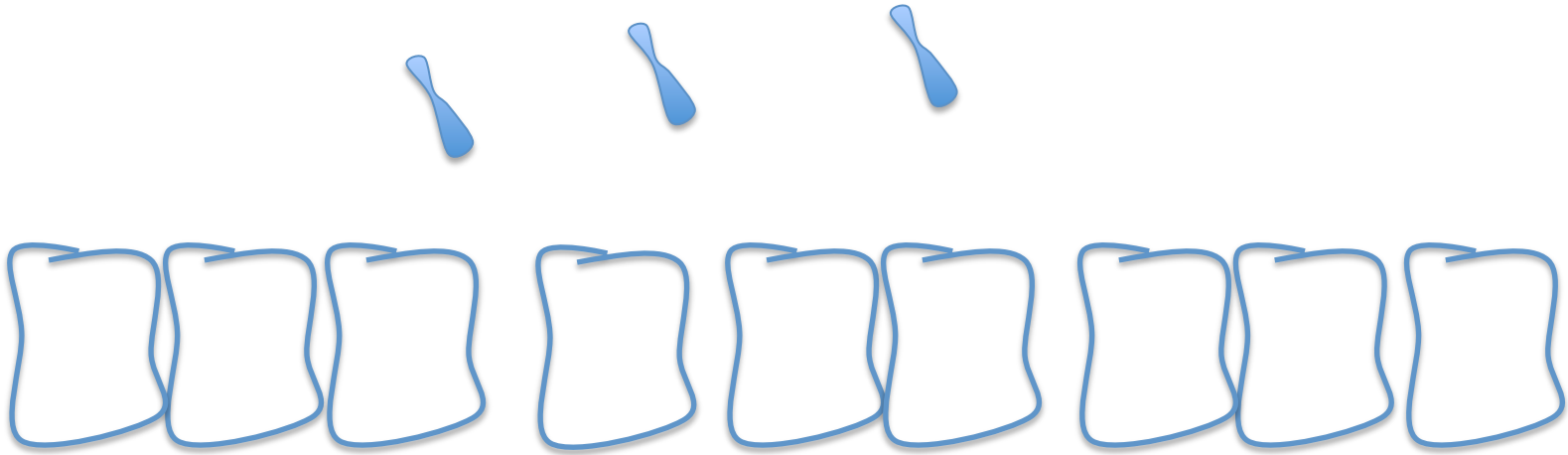


Unhealthy – addition of cationic polymer destroys them

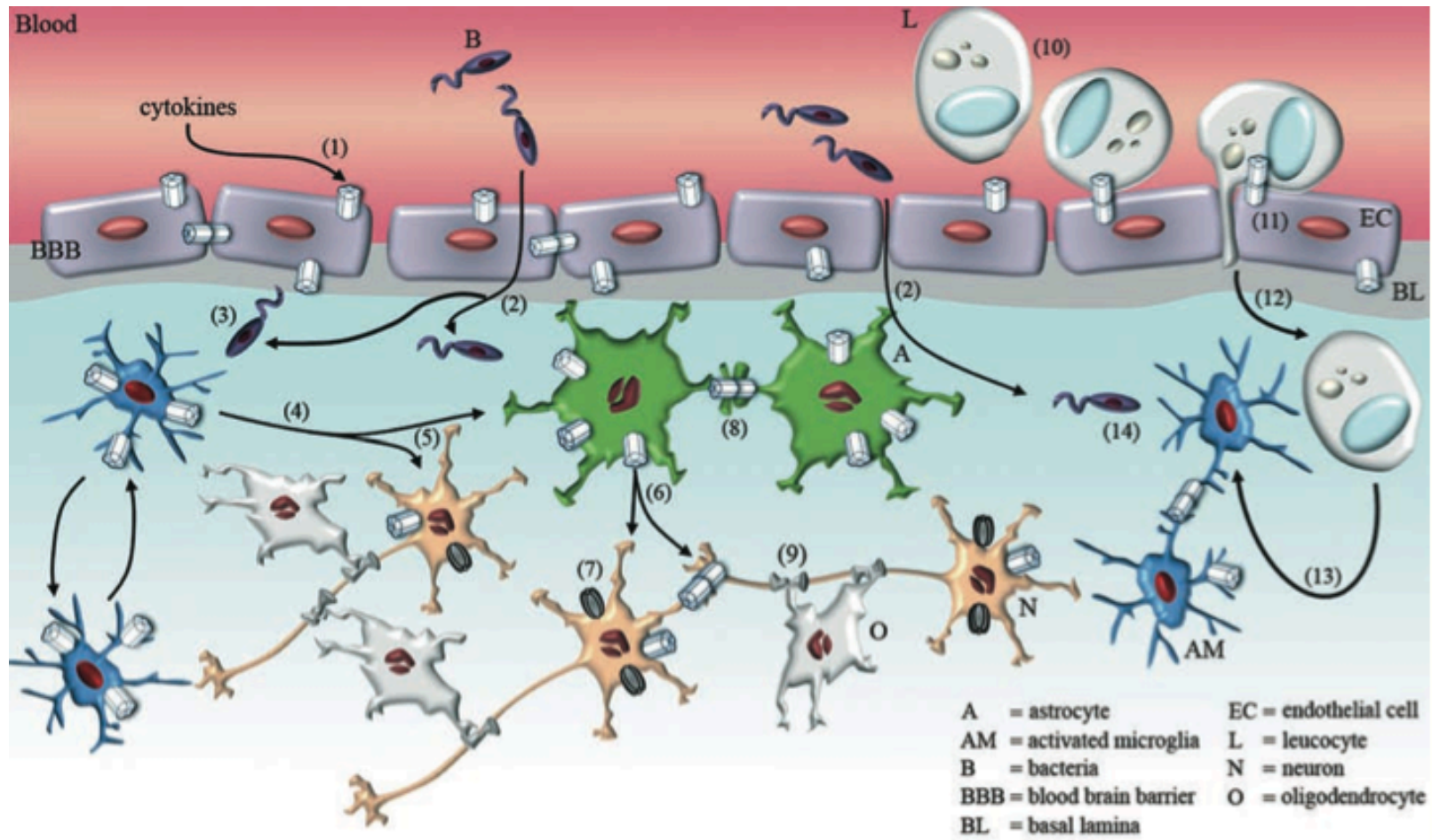
\* Figures 1 and 2 in Quinton and Philpott, J. Cell Biol. 56, 1978, 787-796.



# Bacteria can Swim Across Gut Barrier!



# Microbial Invasion through BBB\*



\* Figure 5, p. 380, J.A. Orellana et al., Antioxidants and Redox Signaling 11(2), 2009

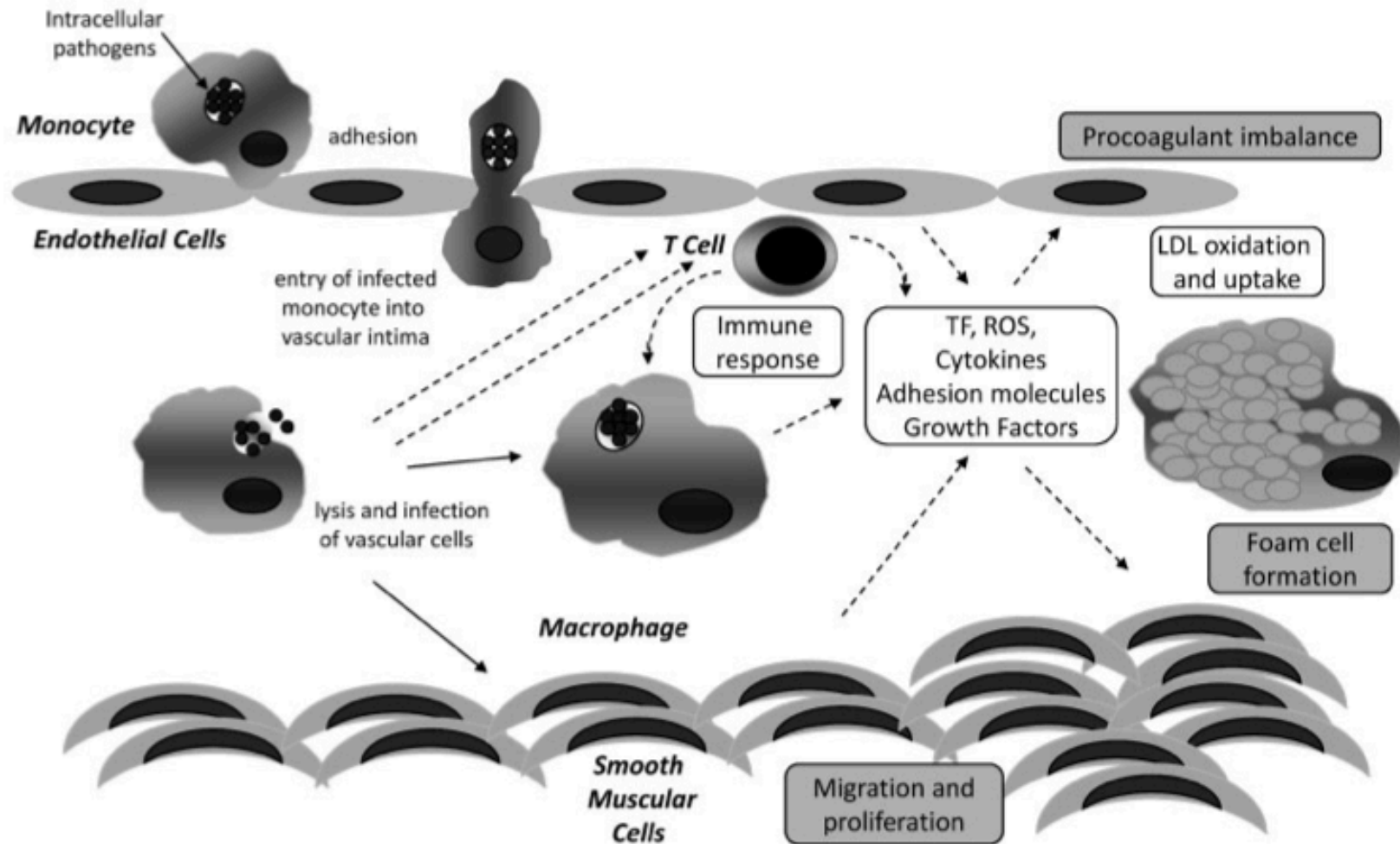
# The Good Side of Infection and Inflammation in the Brain

- Inflammation activates microglia to phagocytose (eat) dying cells and Amyloid beta
- Bacterial exposure promotes phagocytosis
- *Both dying cells and bacteria can be recycled into new raw materials!*
  - *These nutrients may be essential to brain health*

# A Possible Cause-and-Effect Relationship

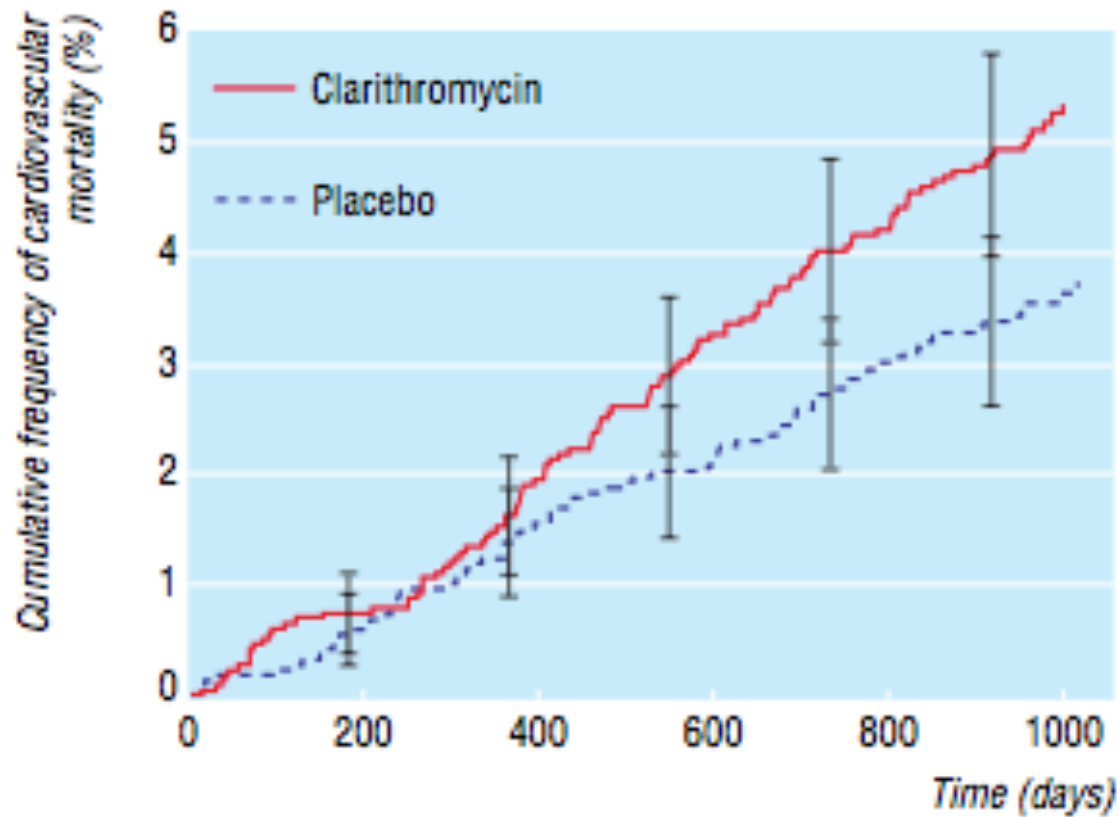
- First comes impaired barriers, impaired nutrient transport and impaired blood colloidal suspension
- Certain nutrients are desperately needed to fix the problems: e.g., cobalamin, vitamin K, heparan sulfate
  - Bacteria are invited in to provide those nutrients!
- The disease may be uncomfortable, but the alternative may be worse!

# Infection and Atherosclerosis\*



\* A. Tufano et al., Semin Thromb Hemost 2012(38), 515–523.

# What Happens if you Treat with Antibiotics?\*

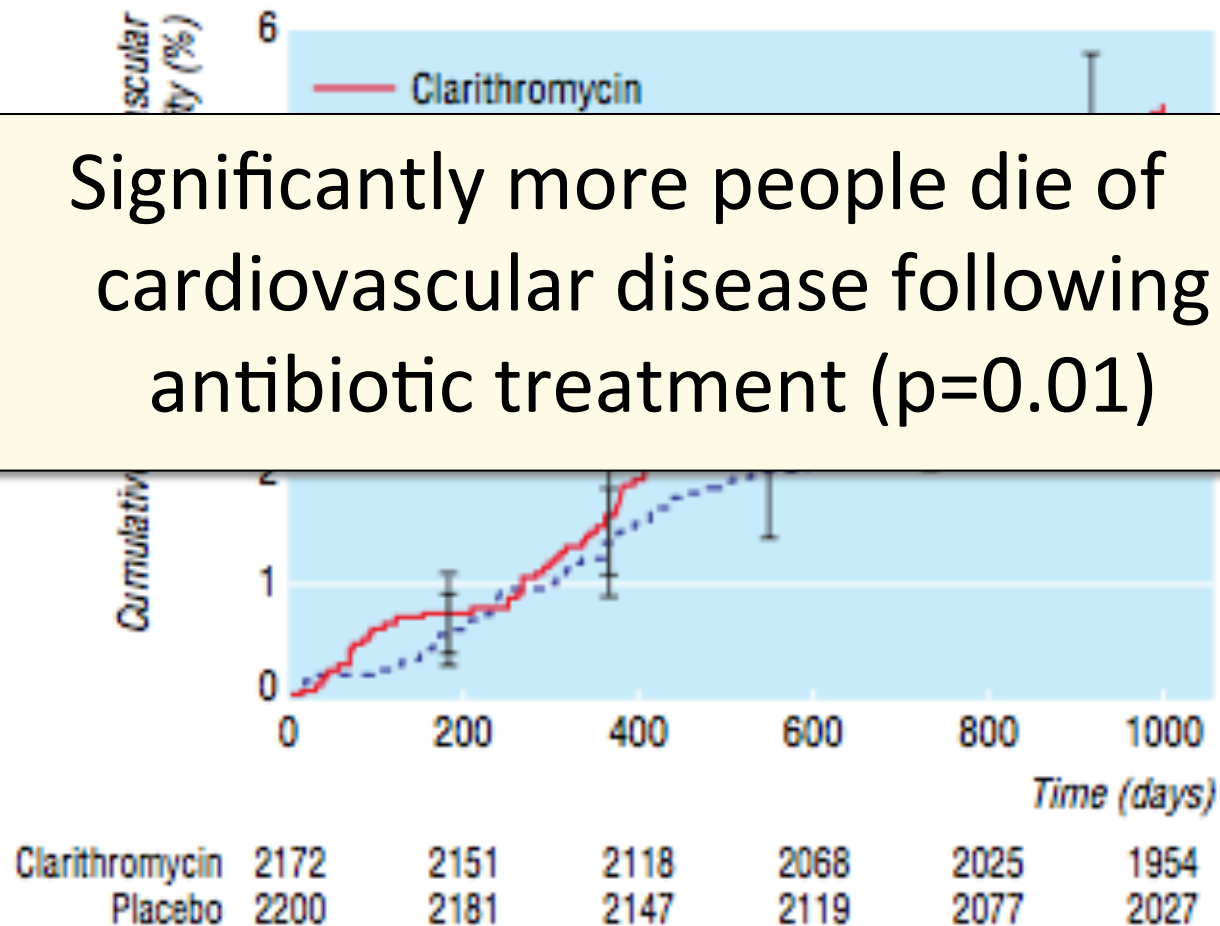


Clarithromycin	2172	2151	2118	2068	2025	1954
Placebo	2200	2181	2147	2119	2077	2027

\* A. Tufano et al., Seminars in Thrombosis & Hemostasis Vol. 38(5), 2012, 515-523.

# What Happens if you Treat with Antibiotics?\*

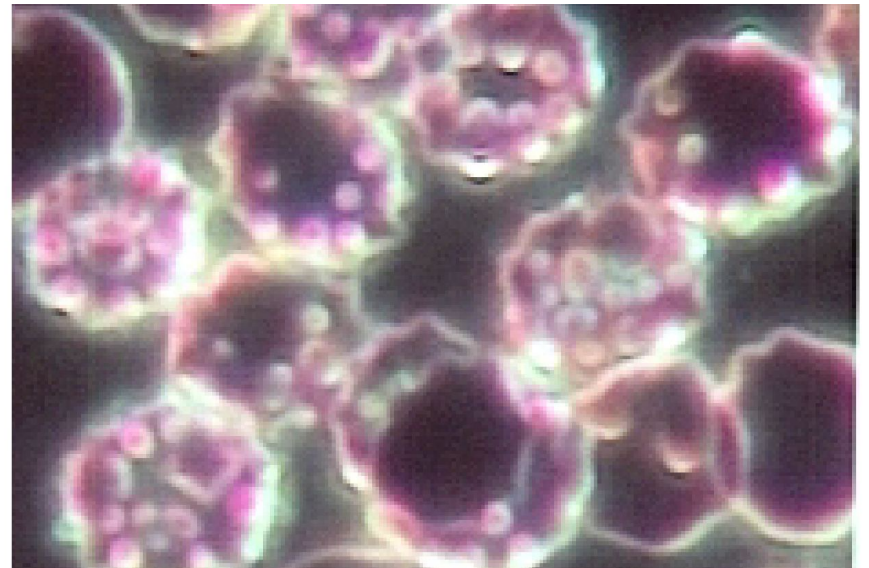
Significantly more people die of cardiovascular disease following antibiotic treatment (p=0.01)



\* A. Tufano et al., Seminars in Thrombosis & Hemostasis Vol. 38(5), 2012, 515-523.

# Chlamydia pneumoniae

- Cause pneumonia when they infect the lungs
- Show up frequently in cardiovascular plaque
- Show up frequently in Alzheimer's plaque

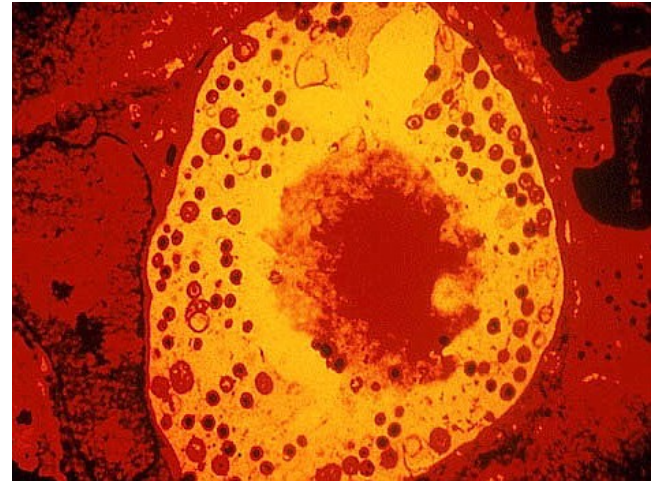


*What are they doing there???*



# Chlamydia Produce Heparan Sulfate!\*

- Chlamydia are viable only inside host cells
- They set up housekeeping in vacuoles within the cell (e.g., a macrophage in the plaque)
- They produce a glucosamine-containing sulphated polysaccharide that is nearly indistinguishable from heparan sulfate
- They have a unique set of enzymes for this



\* S.J. Rasmussen-Lathrop et al, Cell Microbiol. 2000 Apr, 2(2), 137-44.

# Special Issue Devoted to Alzheimer's and Infection: \* Key Points

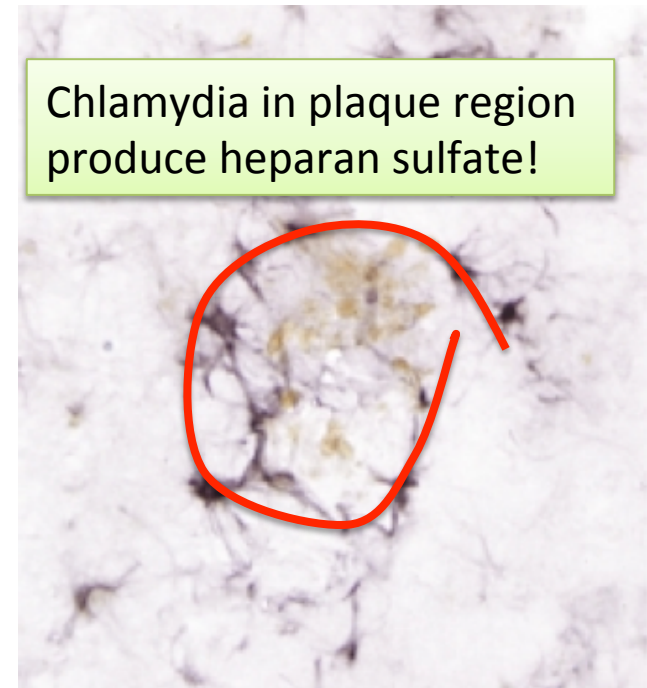
- Pathogens can produce progressive chronic diseases like Alzheimer's, asthma, and heart disease
- Alzheimer himself proposed involvement of infective agents in Alzheimer's 100 years ago
- Pathogens stimulate inflammation
- Pathogens evade host defenses and establish chronic latent infections
- Persistent superoxide, nitric oxide and peroxynitrite (ROS) cause DNA damage and apoptosis and alter gene expression

*Environmental toxins and poor nutrition weaken immune system and provide opportunity to bacteria and viruses*

\* Special Issue of the Journal of Alzheimer's Disease, 2008

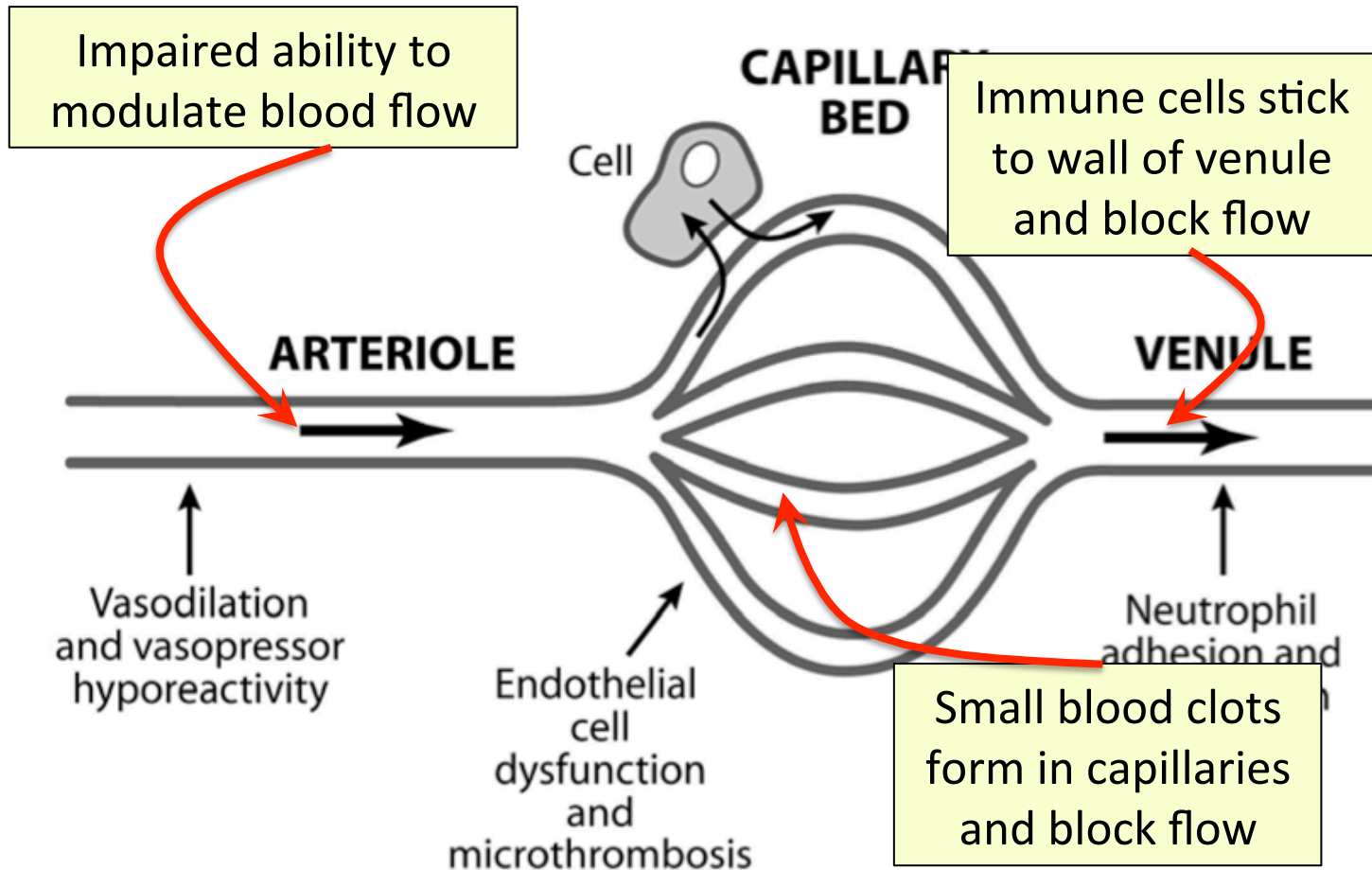
# Amyloid Plaque Structure\*

- Microglia and amyloid plaque accumulate side-by-side in a central region surrounded by astrocytes
- Microglia harbor dormant bacteria
- Should the bacteria leave, they will encounter the plaque, which will kill them
- The astrocytes guard the gates and shield the neurons from the damaging plaque



\* Microphotograph from Schwab et al., Journal of Alzheimer's Disease 13 359–369, 2008.

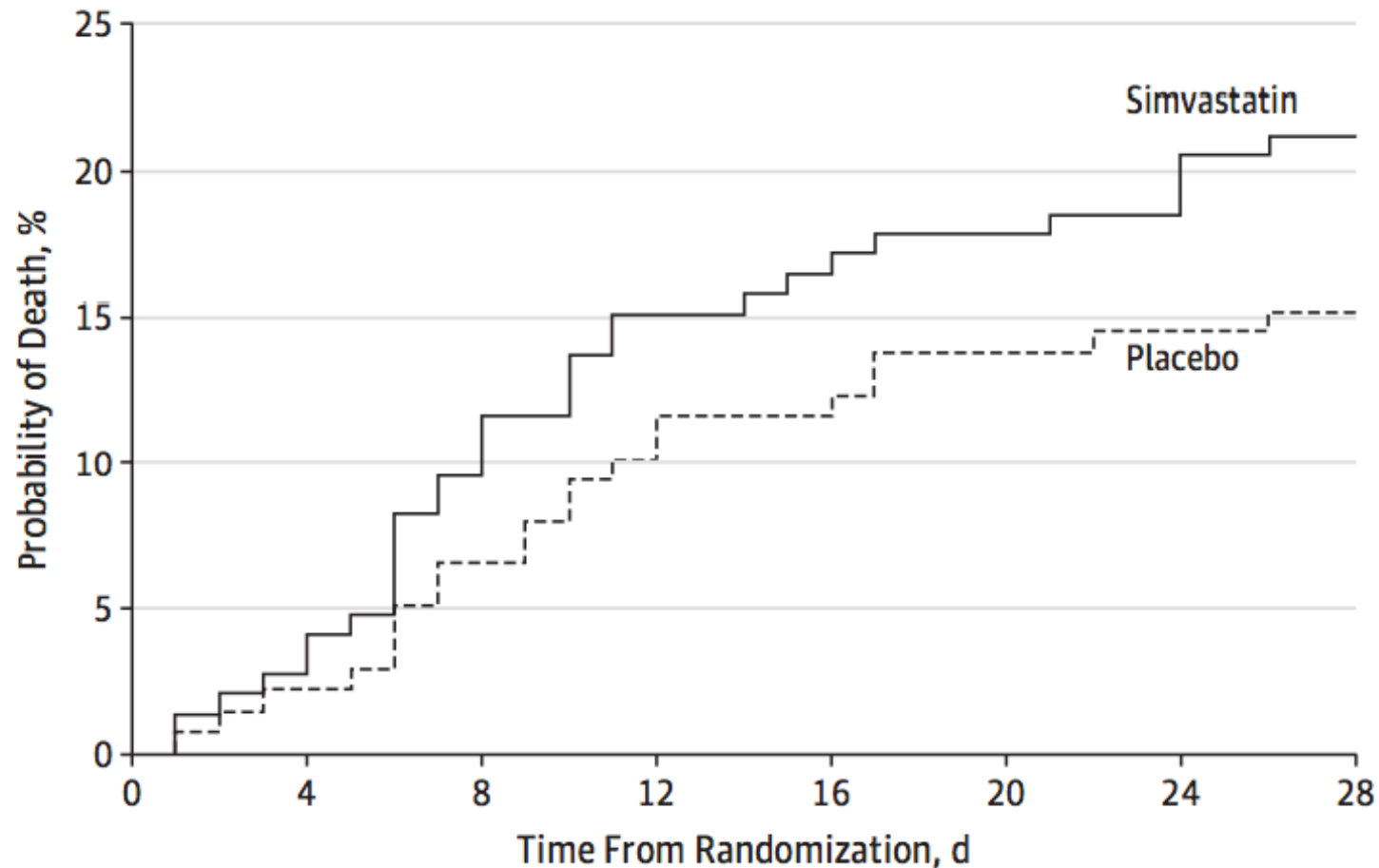
# Sepsis and the Vasculature\*



\* S. Trzeciak et al., Acad Emerg Med. 2008 May ; 15(5): 399–413

# Effect of de-novo statin treatment on patients with sepsis plus pneumonia\*

Figure 2. Proportions of Nonsurvivors in the Simvastatin and Placebo Groups



\* Laurent Papazian et al., JAMA, Oct. 9, 2013 [Epub ahead of print]

# Hypothesis

Blood flow needs to nearly shut down during sepsis; organs need to shut down; the entire body focuses on **harvesting heparan sulfate from the invasive microbes** to recover blood stability.

# Recapitulation

- Infection is a consequence of impaired supply of sulfate to the barriers
- Leaky gut syndrome allows bacteria to personally deliver nutrients to the body
- Adrenalin encourages bacterial growth (to help supply nutrients under stress?)
- Atherosclerosis is associated with infective agents, but antibiotics make things worse
- Chlamydia pneumoniae can produce heparan sulfate using a unique set of enzymes
  - Do they help us out in pneumonia, heart disease and Alzheimer's?

# Influenza



# Influenza (Viral Disease)

- 1/3 of infected individuals are asymptomatic
  - These are people with plenty of sulfate?
- Flu vaccine is aggressively promoted in US and elsewhere for protection
  - Often required in healthcare workers
  - Big mistake in pregnant women (mercury)
  - Claims of effectiveness are probably exaggerated
- Treatment includes Tamiflu and dextran sulfate
- Flu can sometimes lead to pneumonia (viral or bacterial) [in vulnerable individuals]

# Flu Vaccine Increases Risk to Other Respiratory Infections\*

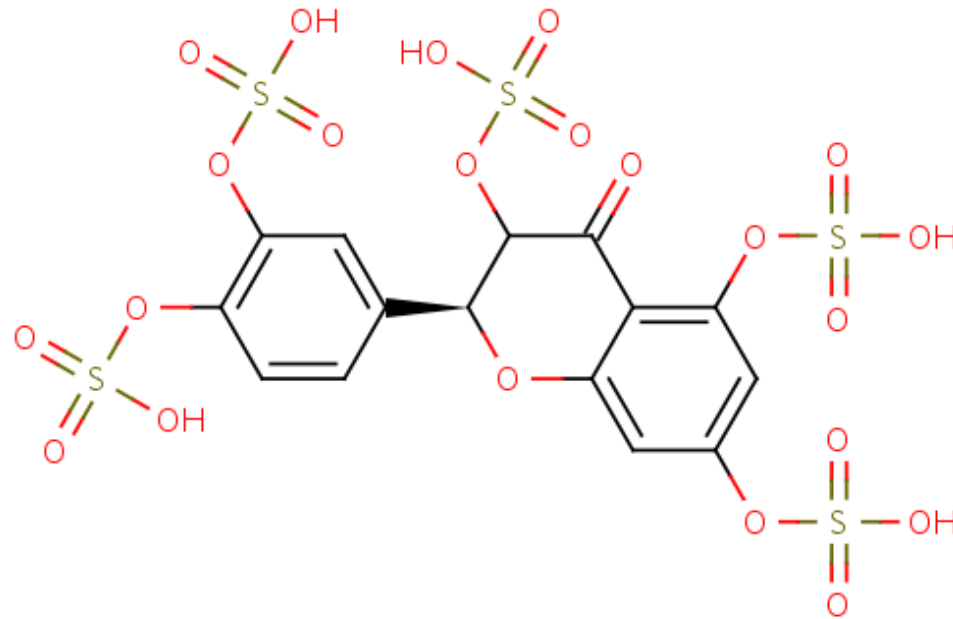
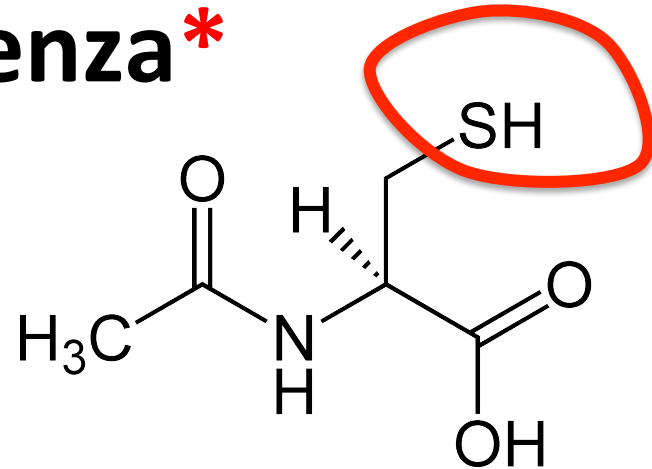
- Double-blind randomized trial conducted in Hong Kong
- 115 children aged 6–15 years
  - Received 2008–2009 seasonal trivalent influenza inactivated vaccine (TIV) or placebo
  - Monitored over following 9 months
- TIV recipients did not have a significant reduction in risk to flu
- TIV recipients had a **4.4-fold** increased risk to non-influenza infections



\*BJ Cowling et al., CID 2012:54, 1778-1783.

# Supplement and Dietary Protection from Influenza\*

- N-acetyl cysteine
- Green tea  
(catechines)



\*S. De Flora et al., Eur Respir J 10 (7): 1535–1541.

# Muscle Aches and Pains with Flu\*

“Patients with an influenza-like illness should be observed for signs and symptoms of rhabdomyolysis and myoglobinuria during the course of their illness”

*Is the virus leaching sulfate  
from the muscles?*

\*RA Minow et al., Ann Intern Med. 1974;80(3):359-361.

# Does Influenza Virus Transport Sulfate?

- Influenza virus
  - Infects muscle cells and causes muscle wasting\*
  - Incorporates sulfated mucopolysaccharides synthesized by the host cell into its own plasma membrane\*\*
  - Inhibits mucopolysaccharide incorporation into the host cell's membrane.\*\*

*Is viral infection an opportunity to steal sulfate from muscle cells and deliver it to the blood?*

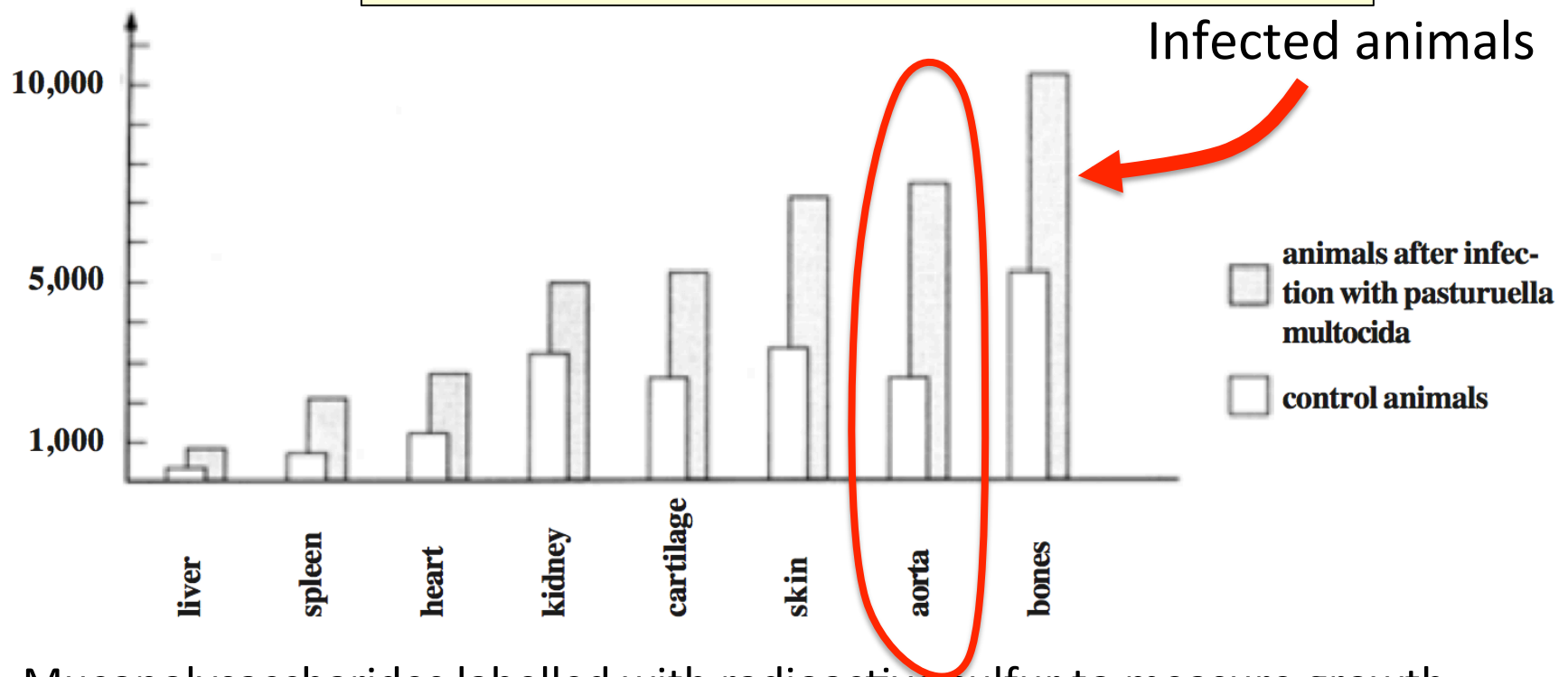
\* HA Kessler et al., JAMA 1980 243(5), 461-462.

\*\* Nakamura and Compans, Virology 79(2), 1977, 381-392.

# Is This True More Generally?\*

More sulfur showed up in multiple tissues following infection

$^{35}\text{S}$ -cpm/100 $\mu\text{g}$  SMPS



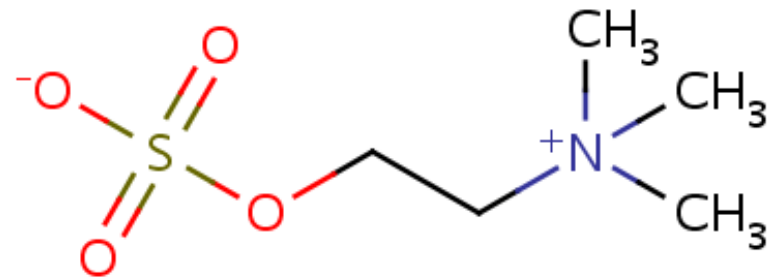
Mucopolysaccharides labelled with radioactive sulfur to measure growth

\*Bernhard Muschlien, Inflammations and Their Therapy by Means of Isopathy

# Choline sulfate!!\*

- Produced by plants, lichens, algae, fungi, and several bacterial species
- Experiment demonstrated that it had superior capabilities to inhibit amyloid formation in pancreatic beta cells

– Amyloid in beta cells is akin to amyloid beta in Alzheimer's disease and plays a major role in type-II diabetes



\*M. Hagihara et al., FEBS Open Bio 2 (2012) 20–25.

Tamiflu and dextran sulfate are drugs to suppress flu virus replication that are imitations of products produced by gut bacteria



# “Flu is a threat and Tamiflu is the answer?”\*

Side effects include:

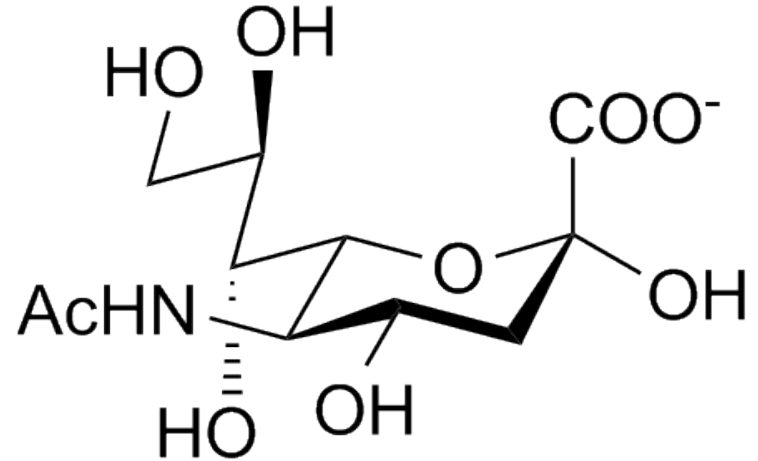
- Convulsions, delirium and delusions
- Allergic reactions including anaphylaxis
- Hepatitis and elevated liver enzymes
- Nausea, diarrhea
- Nightmares
- Headache
- Skin rash



\*<http://articles.mercola.com/sites/articles/archive/2012/02/07/recommended-tamiflu-has-flawed-results.aspx>

# Neuraminic Acid and Tamiflu

- Neuraminic Acid: Basic unit in sialic acids in human GAGs
- Broken down by *neuraminidase* produced by flu virus
- *Tamiflu* inactivates neuraminidase
  - This prevents viral entry into cell
  - Shikimate is a precursor to active ingredient in Tamiflu
  - Shikimate is produced by gut bacteria



# Inhibition of Neuraminidase by Dextran Sulfate\*

- Negatively charged, sulfated polysaccharide
  - Synthesized from sucrose by lactic-acid bacteria
  - Suppresses replication of influenza A virus strain
  - Induces viral aggregation at cell surface
  - Inhibits neuraminidase activity (likely due to its negative charge)
  - Used as drug to treat flu

\*H Yamada et al., Antiviral Res. 2012 Dec;96(3):344-52.

# Inhibition of Neuraminidase by Dextran Sulfate\*

- Negatively charged, sulfated polysaccharide

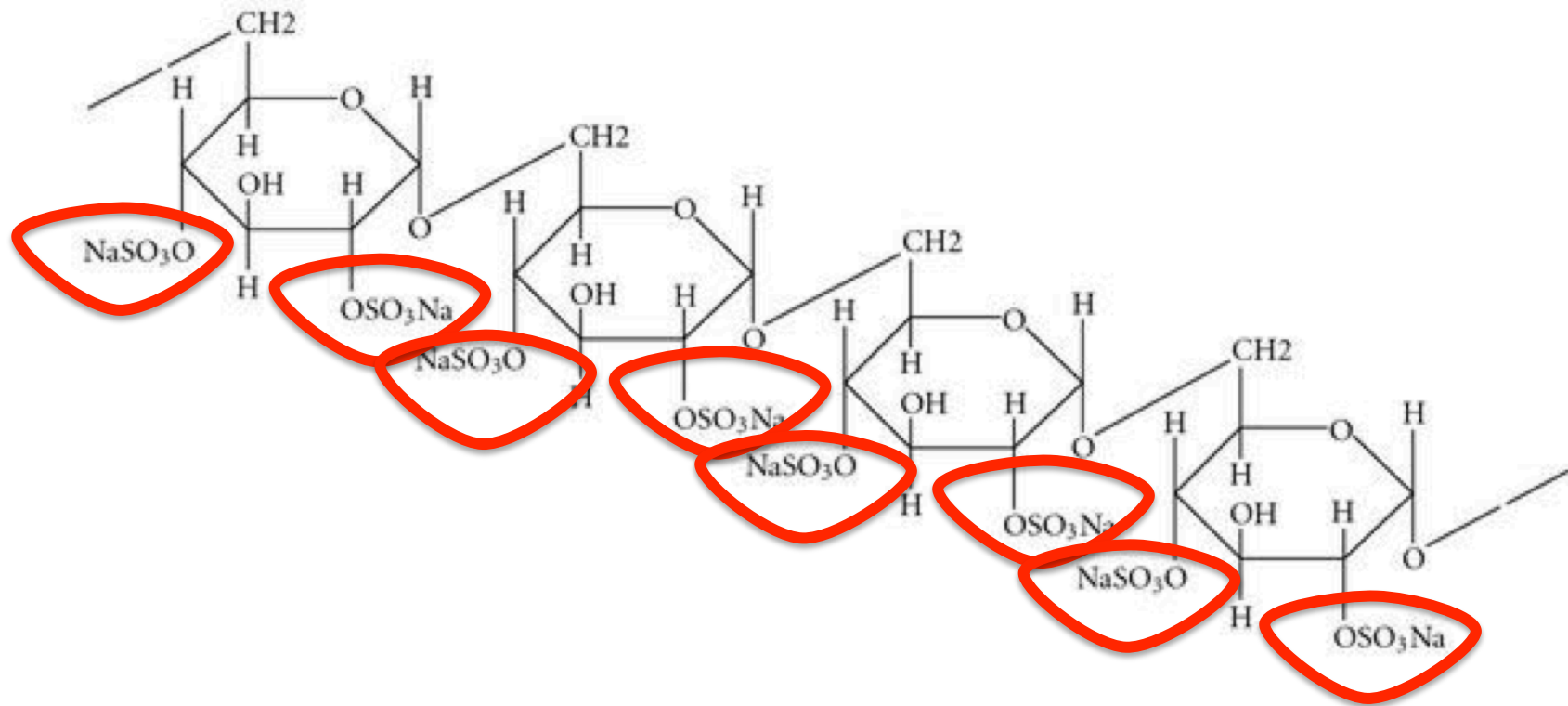
A bacterium that interferes with flu virus can transport the dextran sulfate to distant places. Dextran sulfate as a drug is a “trick”.

negative charge)

- Used as drug to treat flu

\*H Yamada et al., Antiviral Res. 2012 Dec;96(3):344-52.

# Dextran Sulfate



# WIKI on Dextran

The antithrombotic effect of dextran is mediated through its binding of red blood cells, platelets, and the endothelial cells in the vascular wall, increasing their *electronegativity* and thus reducing red blood cell *aggregation* and platelet *adhesiveness*.

# Side Effects from Dextran Sulfate Treatment

- Anaphylaxis (itchy rash, throat swelling, and low blood pressure)
- Excess fluid in blood
- Pulmonary edema
- Cerebral edema
- Platelet dysfunction

The molecule by itself can't multiply whereas bacteria that produce it can!!

# Phase II Trial: Hepatitis C Drug\*

- Trial halted early due to 9 hospitalizations and 1 death
  - Drug works by thwarting viral replication machinery
  - Drug is toxic to heart and kidney
- Side effects of hepatitis C treatments, more generally, include anemia, cardiac arrhythmias, severe depression, and flu-like symptoms
- Cholesterol sulfate is a natural inhibitor of Hepatitis C\*\*

\*<http://www.the-scientist.com/?articles.view/articleNo/32552/title/Clinical-Trial-Misfortune/>

\*\*A Furuta et al., J Enzyme Inhib Med Chem. 2013 Feb 25. [Epub ahead of print]



# Recapitulation

- Better to prevent flu than to treat it
- Better to prevent flu through nutrition than through vaccines
- Flu is associated with aching muscles: is the virus forcing muscles to give up their sulfate?
- Treating flu can lead to severe “side effects”
  - Are these the consequence of the virus being aborted early before it can follow through on its promise to deliver sulfate to the blood stream?
- I suspect many other viruses (e.g., hepatitis C) provide much-needed sulfate to the body

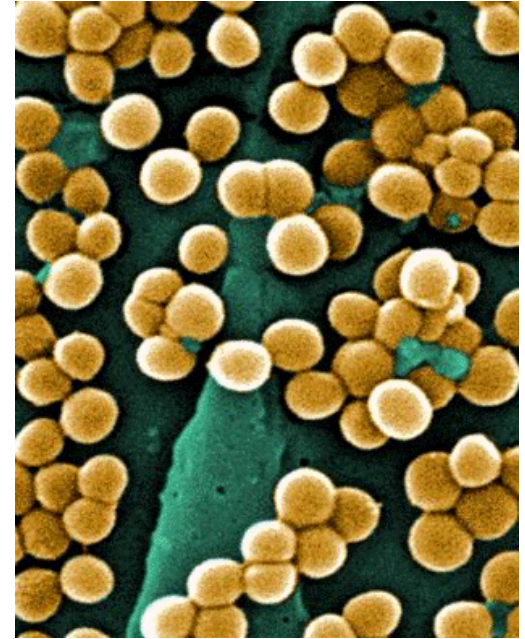
# **Natural Resistance and Antibiotics**

# Multiple Antibiotic Resistance

- Antibiotic resistance is a serious and growing threat in modern times
- Organisms become resistant to "first-line" antibiotics, necessitating second-line agents that are more potent and more toxic to humans
- Sequentially, microbes become resistant to second- and even third-line defenses.
- Result is MRSA: Multiple resistant Staph aureus.

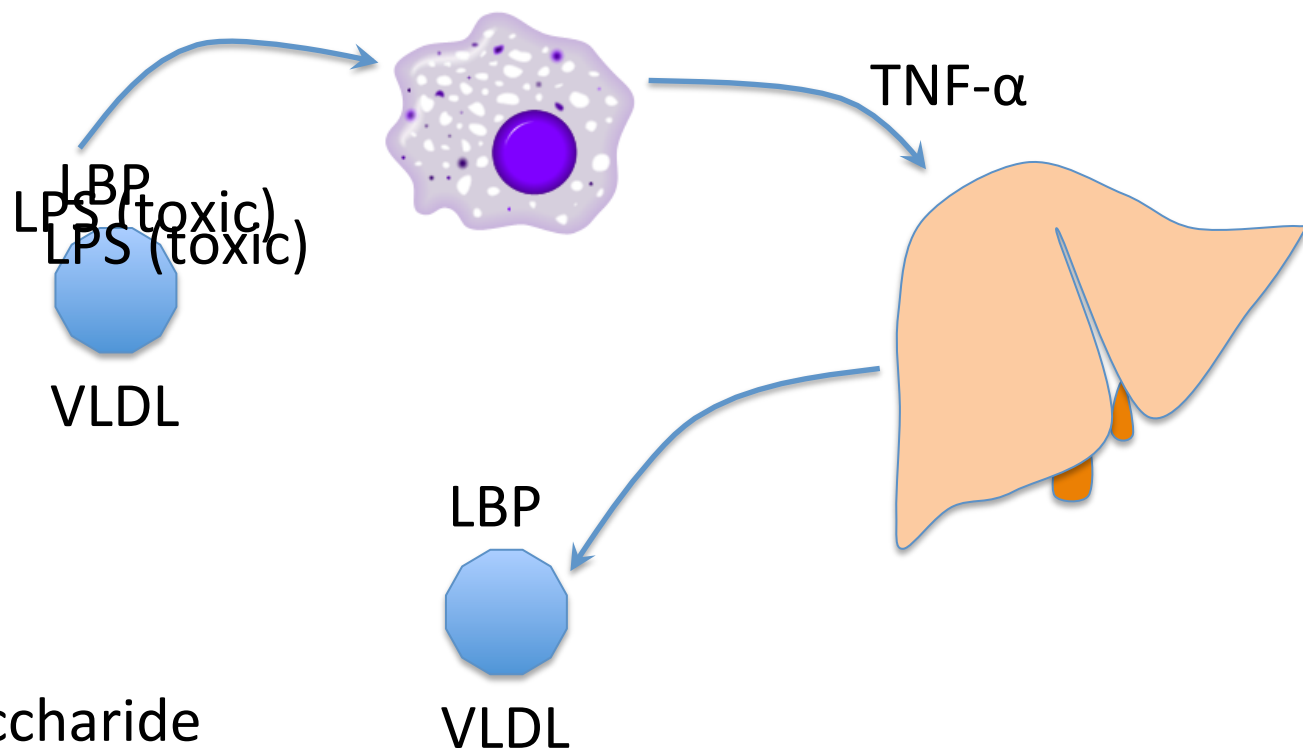
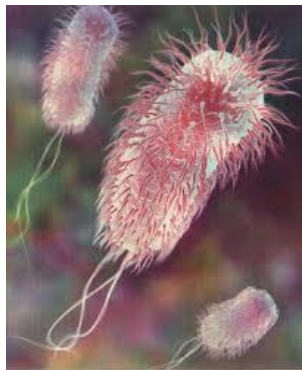
# LDL Protects from MRSA\*

- Methicillin-resistant Staphylococcus aureus (MRSA) has become a major problem in hospitals worldwide
- ApoB in LDL limits invasion by binding to and neutralizing a key enzyme responsible for promoting invasion through the skin
- Skin penetration and bacterial density were significantly greater in ApoB-deficient mice.



\* Peterson et al., Cell Host Microbe 4(6): 555–566, 2008

# The Cholesterol Connection: VLDL Fights Infections\*

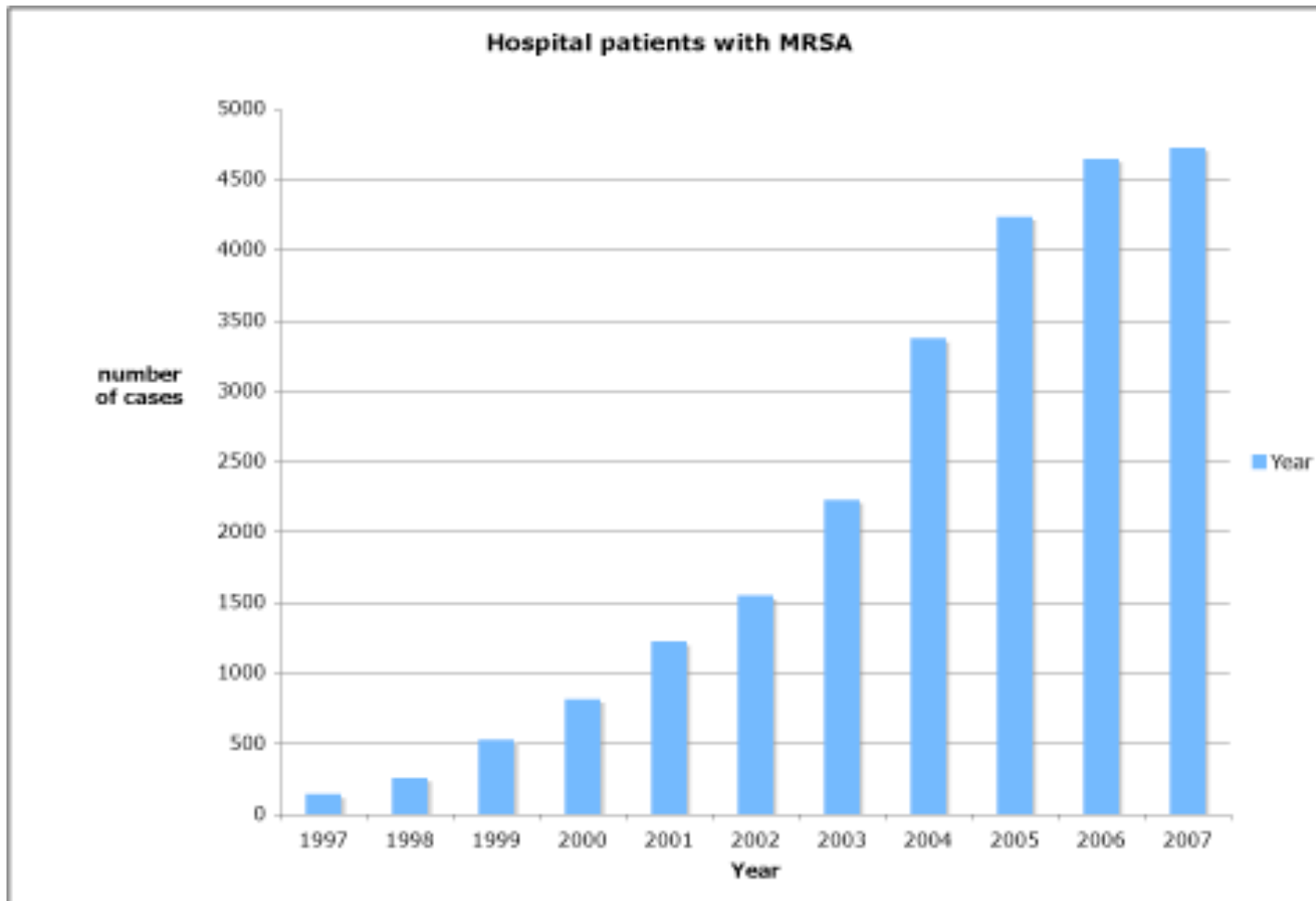


LPS: Lipopolysaccharide

LBP: Lipopolysaccharide binding protein

\* Barcia and Harris, "Triglyceride Rich Lipoproteins as Agents of Innate Immunity CID, 2005

# The MRSA Epidemic\*



Data were obtained and graphed from the Seattle Times, 11-16-2008.

\*M. Berens and K. Armstrong  
How our hospitals unleashed a MRSA epidemic  
Seattle Times 11-16, 2008

# MRSA in Children On The Rise\*

- The infections overwhelmingly resulted in hospitalization (91%); 6% were fatal.
- Most of the affected kids (68%) had another underlying medical condition, most commonly prematurity (19%) or a skin condition such as eczema or abscesses (18%).
- Black children also had a disproportionate share, accounting for 59% of the cases, with an incidence of 6.7 versus 1.6 per 100,000 among other children.

\*Crystal Phend , Medpage Today Sept. 23, 2013

# Clostridium Difficile and Klebsiella Pneumoniae Are Coming\*

- Two super bugs resistant to nearly all antibiotics
- Breakouts in hospitals are dire threats
- Susceptibility
  - Weakened immune system
  - Disrupted gut bacteria
- Clostridium difficile (C. diff)
  - Spores are nearly indestructible
- New kid on the block: Klebsiella pneumonia super strain
  - Resistant to every single antibiotic in the medical arsenal.
  - Enclosed by a *polysaccharide* capsule that protects from antibiotics
  - Initially flu-like symptoms
    - high fever, chills, cough
    - copious amounts of viscous and bloody mucous in the lungs.
  - Half the cases lead to permanent scarring of lungs



\*[www.jonbarron.org/topic/clostridium-difficile-and-klebsiella-pneumoniae-are-coming](http://www.jonbarron.org/topic/clostridium-difficile-and-klebsiella-pneumoniae-are-coming)



# Fluoroquinones: Toxic Antibiotics!\*

- Among the most commonly prescribed antibiotics in the US
  - Inhibit bacterial DNA synthesis
  - Fluoride increases penetration into BBB
- Symptoms include:
  - Nervous system symptoms (tingling, numbness, anxiety, memory loss, psychosis ..)
  - Musculoskeletal symptoms (tendonitis, weakness, joint swelling ...)
  - Sensory symptoms (tinnitus, altered vision, ...)
  - Cardiovascular symptoms (tachycardia, chest pain, palpitations ...)
  - Skin reactions (rashes, hair loss, sweating ...)
  - Gastrointestinal symptoms (nausea, vomiting, diarrhea...)

\*[articles.mercola.com/sites/articles/archive/2013/09/25/fluoroquinolone-antibiotics.aspx](http://articles.mercola.com/sites/articles/archive/2013/09/25/fluoroquinolone-antibiotics.aspx)

# Recapitulation

- Multiple antibiotic resistance is a growing problem
  - Could it be due to insufficient cholesterol and insufficient sulfate?
- Fighting disease with antibiotics is a losing proposition
  - Drug resistant microbes lead to ever more toxic antibiotics
  - Side effects of the antibiotics can kill you

# Summary

- Our gut bacteria are under siege!
- Leaky gut syndrome allows bacteria to personally deliver nutrients to the body
  - Adrenalin encourages bacterial growth (to help supply nutrients under stress?)
- Atherosclerosis is associated with infective agents, but antibiotics make things worse
- Chlamydia pneumoniae can produce heparan sulfate using a unique set of enzymes
  - Do they help us out in pneumonia, heart disease and Alzheimer's?
- Influenza infection has a silver lining
- MRSA is on the rise, and antibiotics to treat it have dangerous side effects