

A microscopic view of a blood vessel. The vessel wall is composed of several layers of cells, with the innermost layer being a smooth, endothelial lining. The lumen of the vessel is filled with numerous red blood cells, which are biconcave discs. The lighting is warm, highlighting the textures of the cells and the flow of blood.

Cardiovascular Disease (CVD) Physiology

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Doctoral Candidate

Bioscience in the 21st Century

October 5, 2012

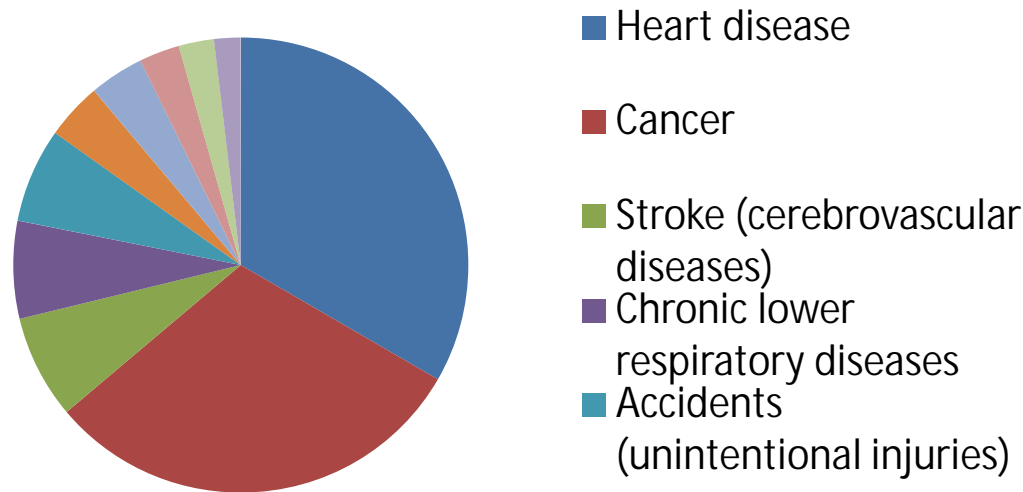
Outline

- Introduction
 - Serious nature of Cardiovascular Disease (CVD)
 - How to prevent CVD?
- The disease process
 - Damage and plaque development
 - Current treatments
- Control of vascular tone
 - Naturally and pharmacologically
- Current research here at Lehigh

Significance of CVD

- CVD is the leading cause of death in Western societies and Japan ¹
- Treatment of patients with CVD was ~\$444 billion in 2011 ²

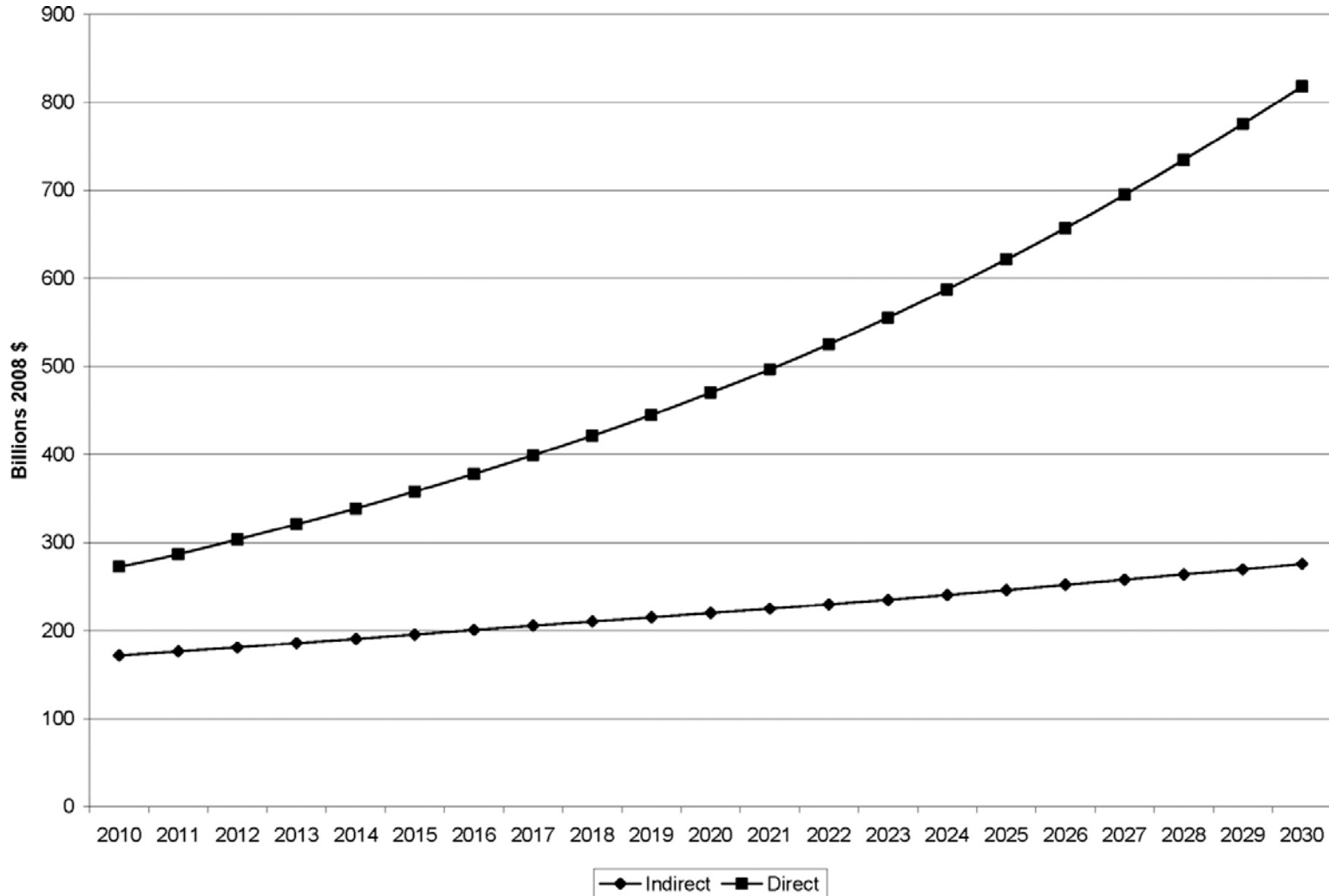
U.S. Death Rates per Year ¹



¹Centers for Disease Control; January 17, 2012

²Heidenreich P, et al. *Circulation*. 2011;123:933-944.

Projected direct and indirect costs of all CVD, 2010 to 2030 (in billions 2008\$).



Heidenreich P A et al. *Circulation* 2011;123:933-944



CVD Risk Factors

- High blood pressure (above 120/80 mmHg)
- High serum cholesterol
 - Healthy cholesterol levels:
 - < 100 mg/dL LDL cholesterol
 - > 50 mg/dL HDL cholesterol
- Body Mass Index (BMI) > 30*
- Smoking
- Excessive alcohol consumption
- Diabetes

Metabolic Syndrome

- Excessive abdominal fat
- Atherogenic dyslipidemia
 - High triglycerides and low HDL cholesterol
- Insulin resistance or glucose intolerance
 - Body cannot properly use insulin or blood sugar
- Pro-thrombotic state (pro-clotting)
- Elevated blood pressure ($\geq 130/85$ mmHg)
- Pro-inflammatory state



Obesity

- Diet
 - Portion size
 - Lack of physical activity
 - Genetics
- Fat as endocrine tissue
 - Makes leptin – lowered desire to eat, more use of stored fat
 - Makes inflammatory signaling molecules
 - Decreases synthesis of signals that cause a decrease in blood pressure
 - With the result being increased blood pressure

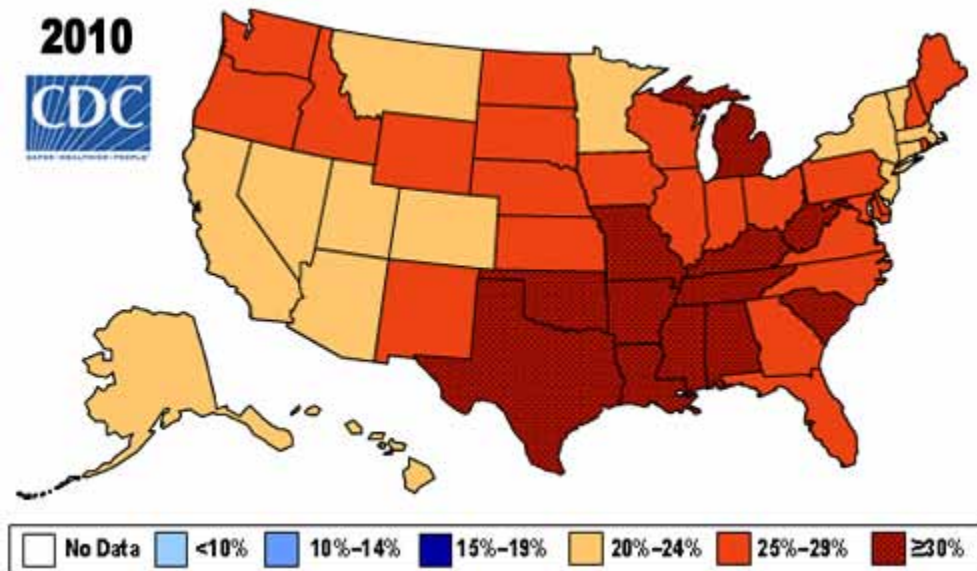
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CHILDHOOD OBESITY EPIDEMIC..

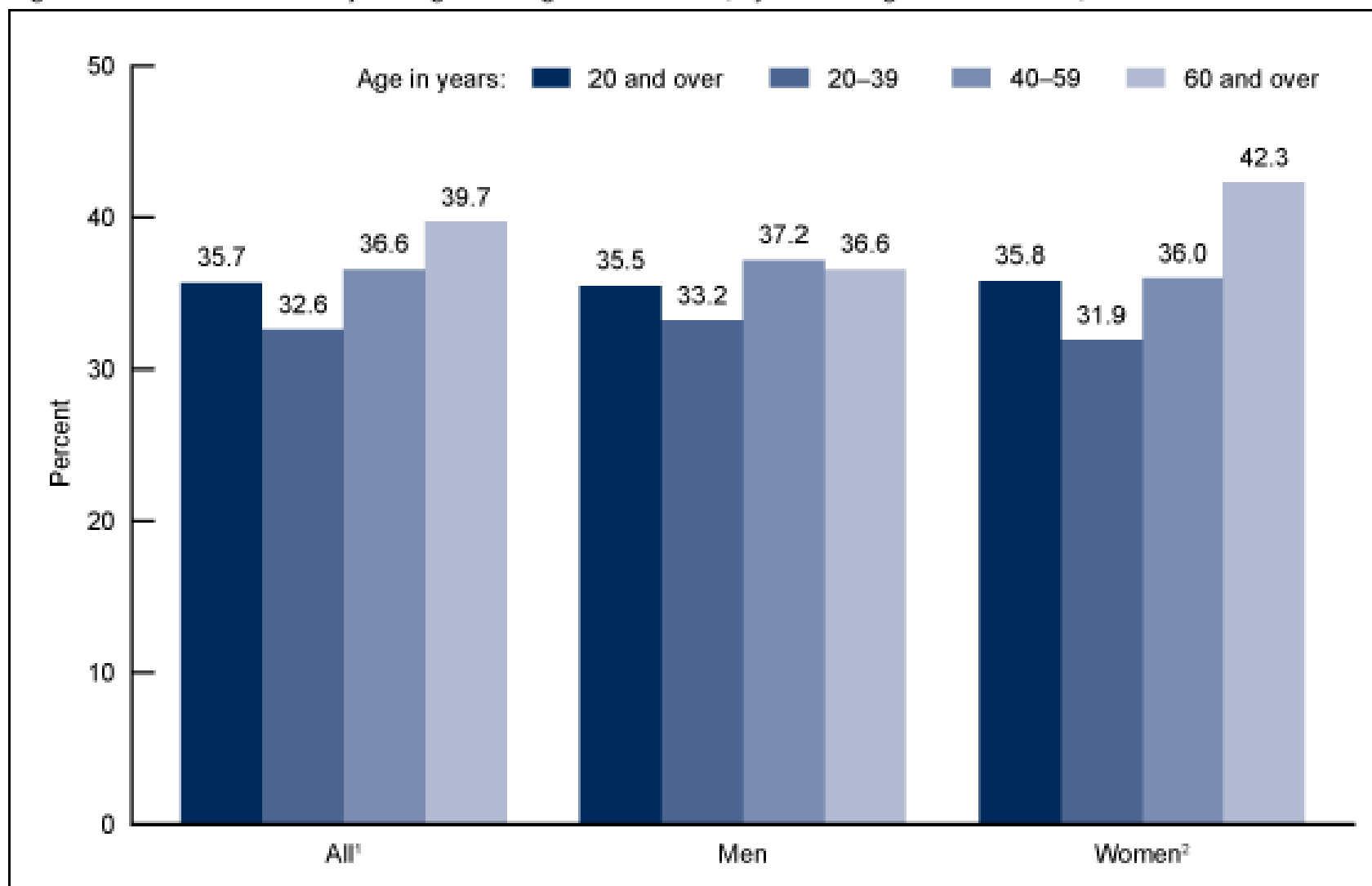
Obesity Epidemic in the US

- One-third of adults and almost 17% of children and adolescents were obese in 2009-2010.



Ogden CL et al. Prevalence of obesity in the United States, 2009–2010. NCHS data brief, no 82. Hyattsville, MD: National Center for Health Statistics. 2012.

Figure 1. Prevalence of obesity among adults aged 20 and over, by sex and age: United States, 2009–2010



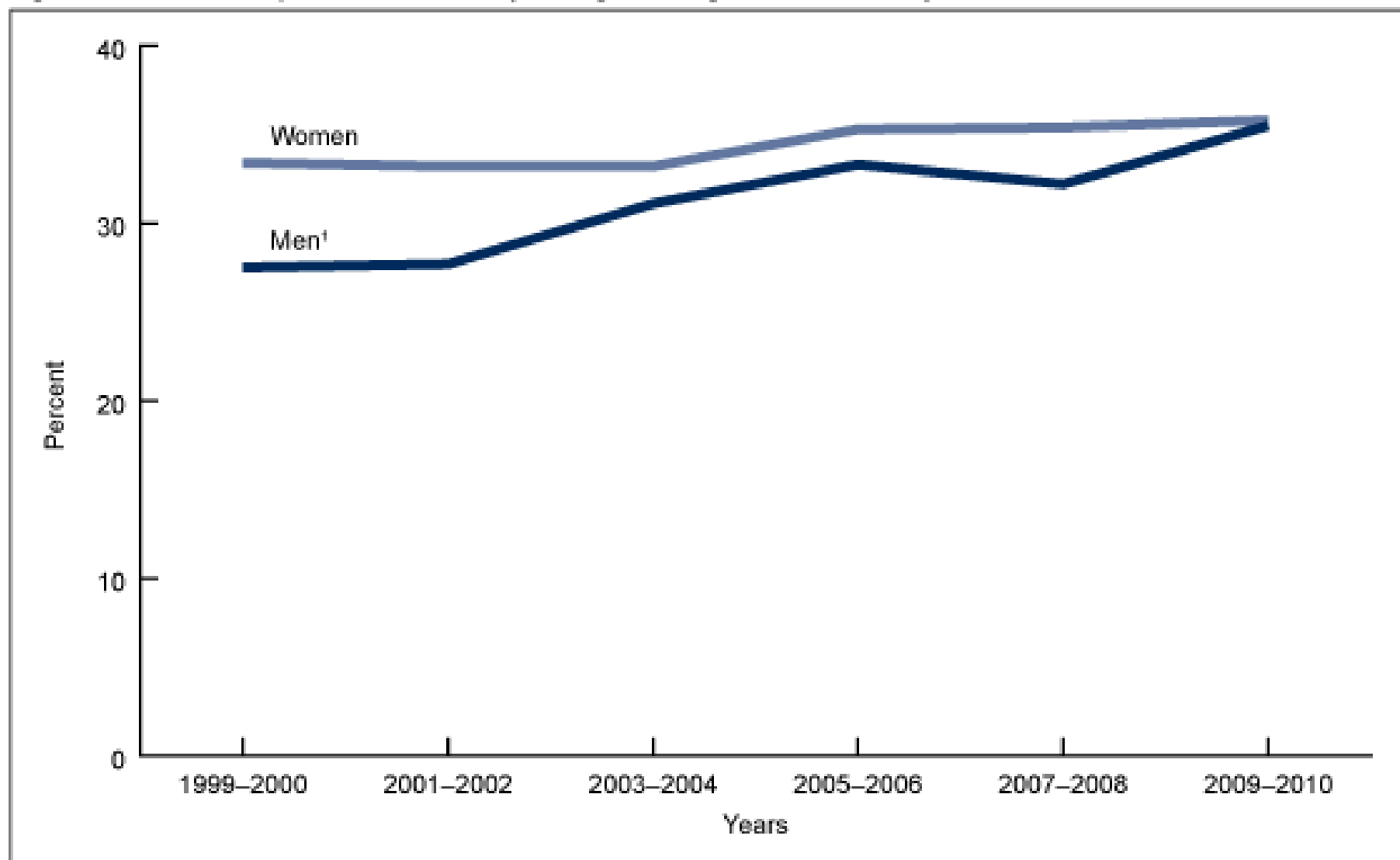
¹Significant increasing linear trend by age ($p < 0.01$).

²Significant increasing linear trend by age ($p < 0.001$).

NOTE: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2009–2010.

Figure 4. Trends in the prevalence of obesity among adults aged 20 and over, by sex: United States, 1999–2010

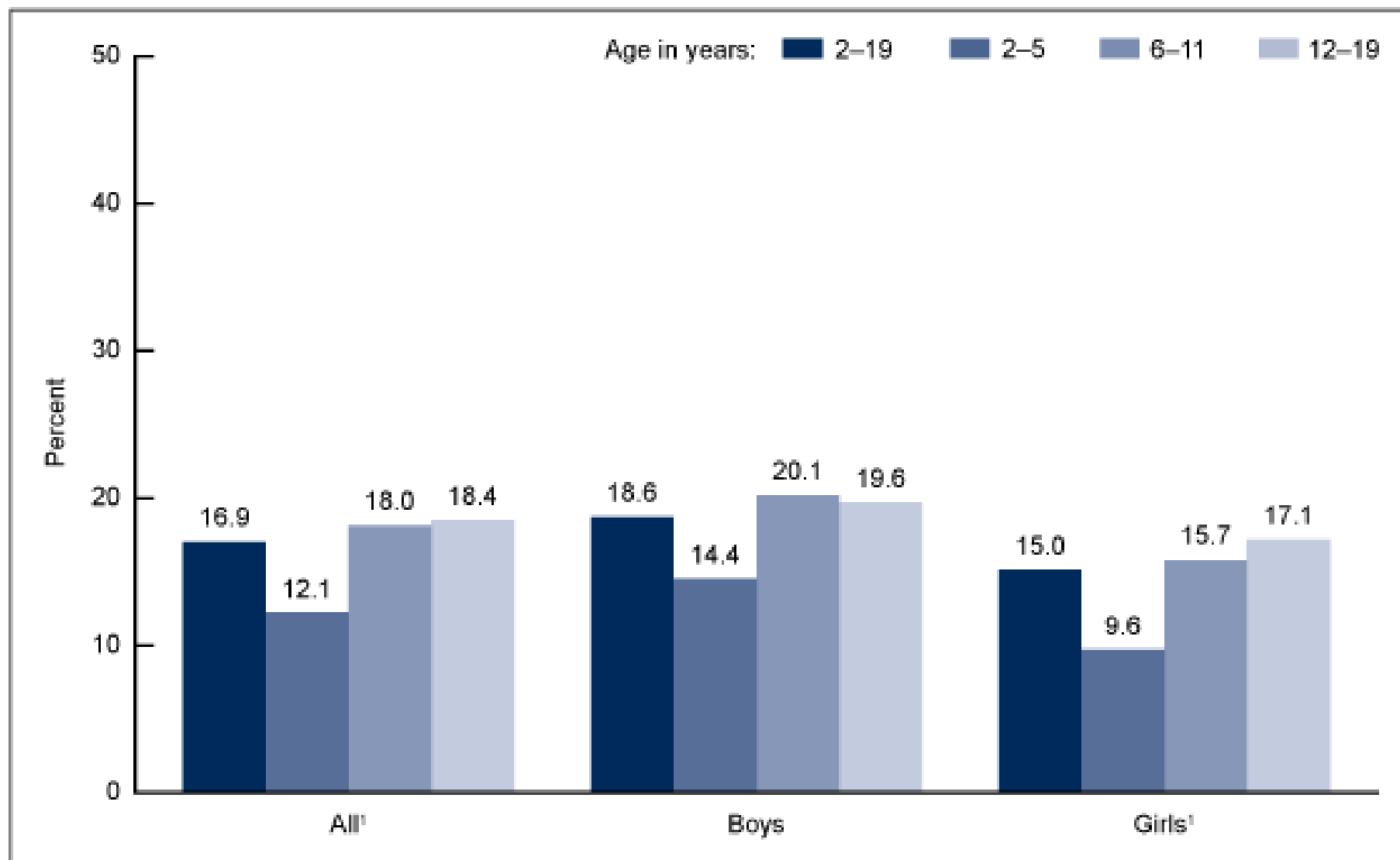


¹Significant increasing linear trend 1999–2000 to 2009–2010 ($p < 0.0001$).

NOTE: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2009–2010.

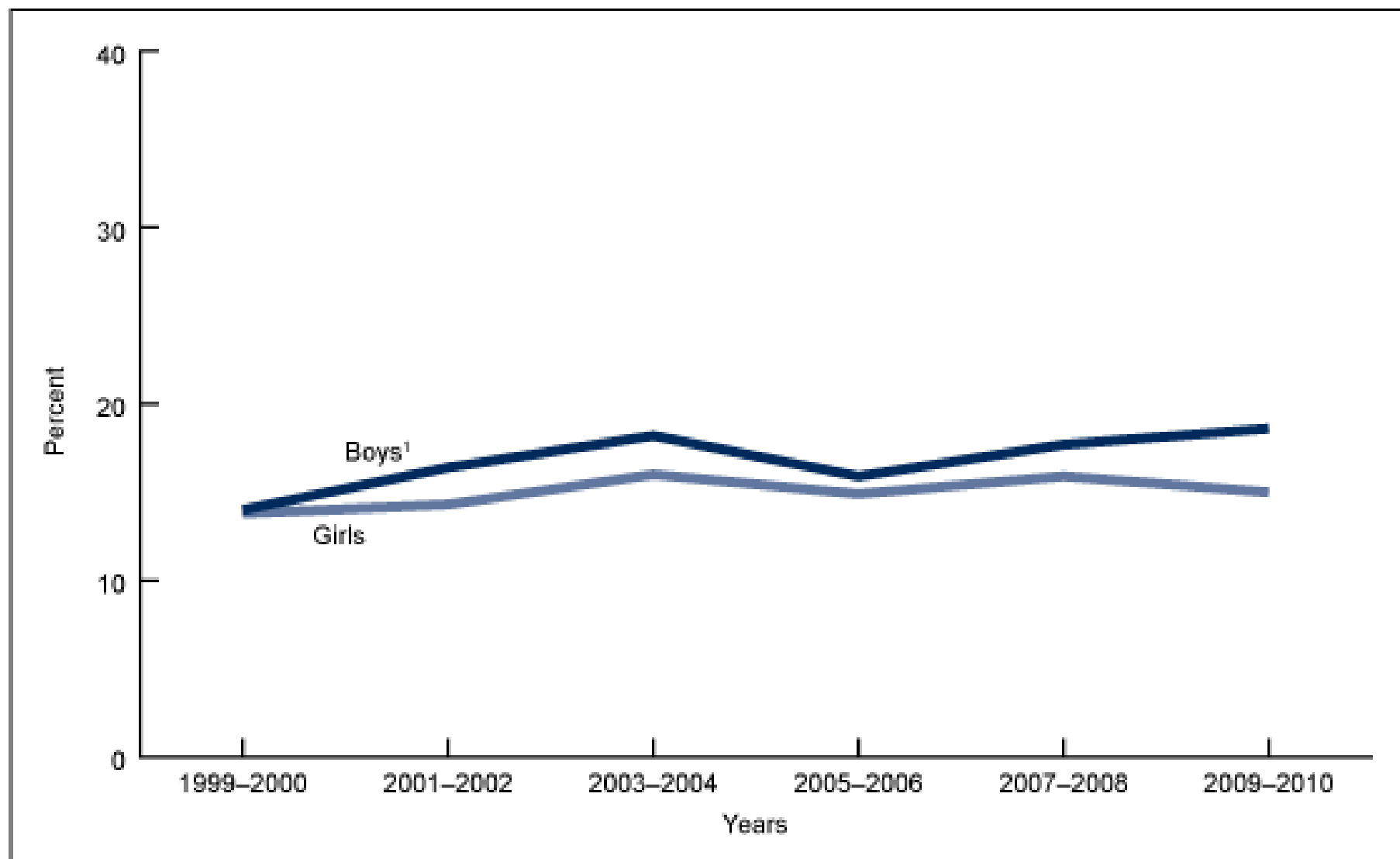
Figure 2. Prevalence of obesity among children and adolescents aged 2–19, by sex and age: United States, 2009–2010



¹Significant increasing linear trend by age ($p < 0.005$).

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2009–2010.

Figure 5. Trends in the prevalence of obesity among children and adolescents aged 2–19, by sex: United States, 1999–2010

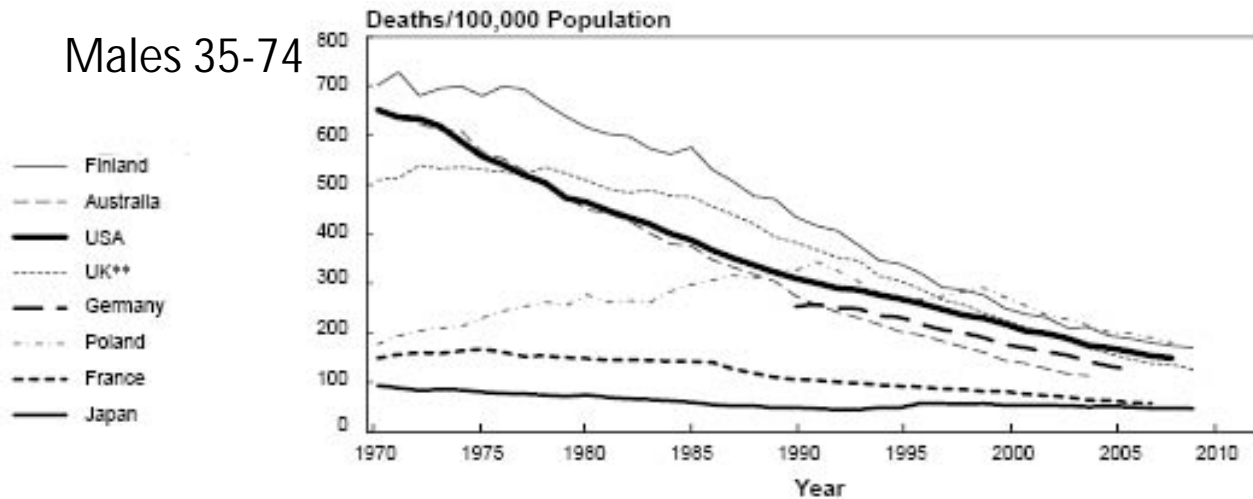


¹Significant increasing linear trend 1999–2000 to 2009–2010 ($p < 0.05$).

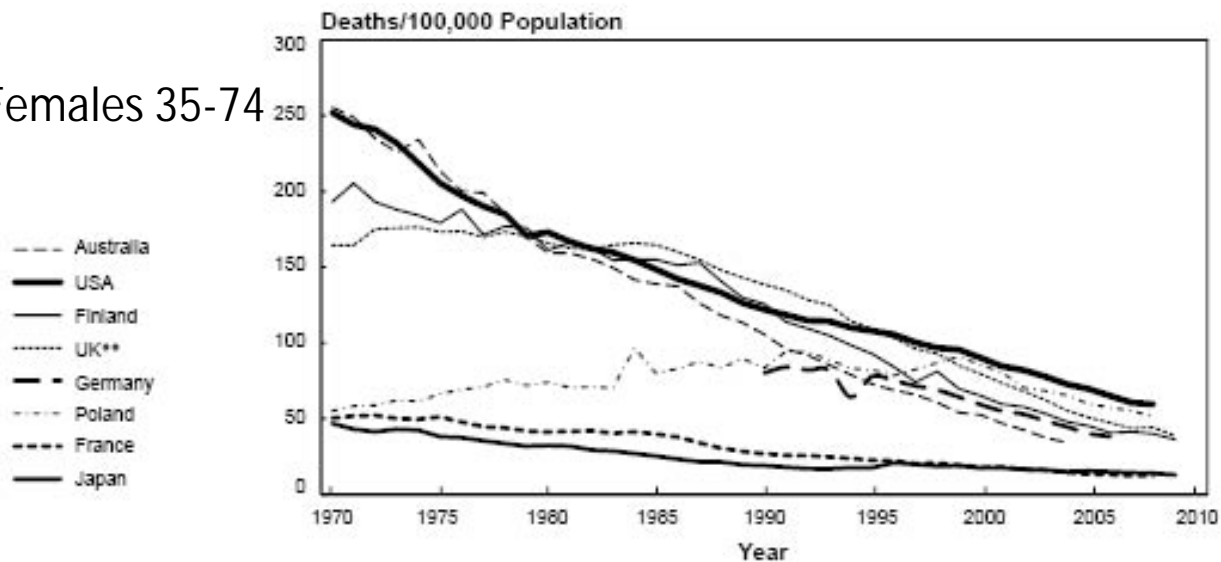
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2009–2010.

Some Good News

Males 35-74



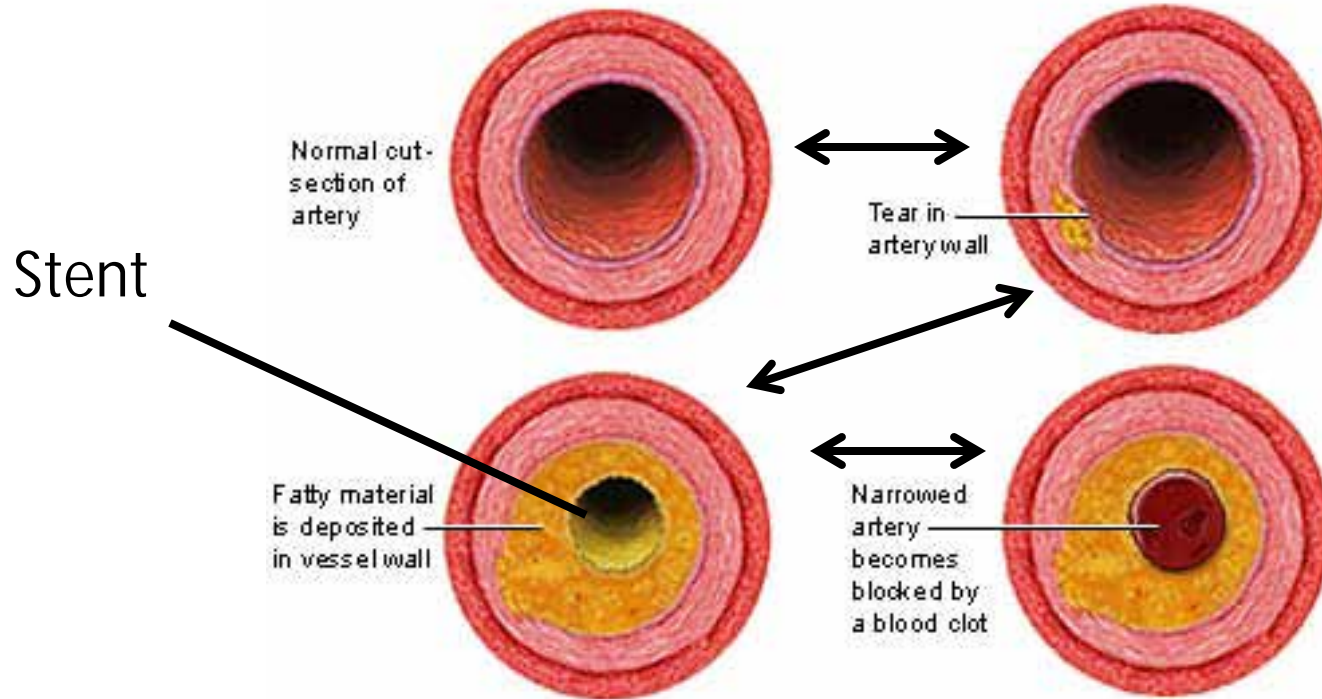
Females 35-74



So What Can You Do?

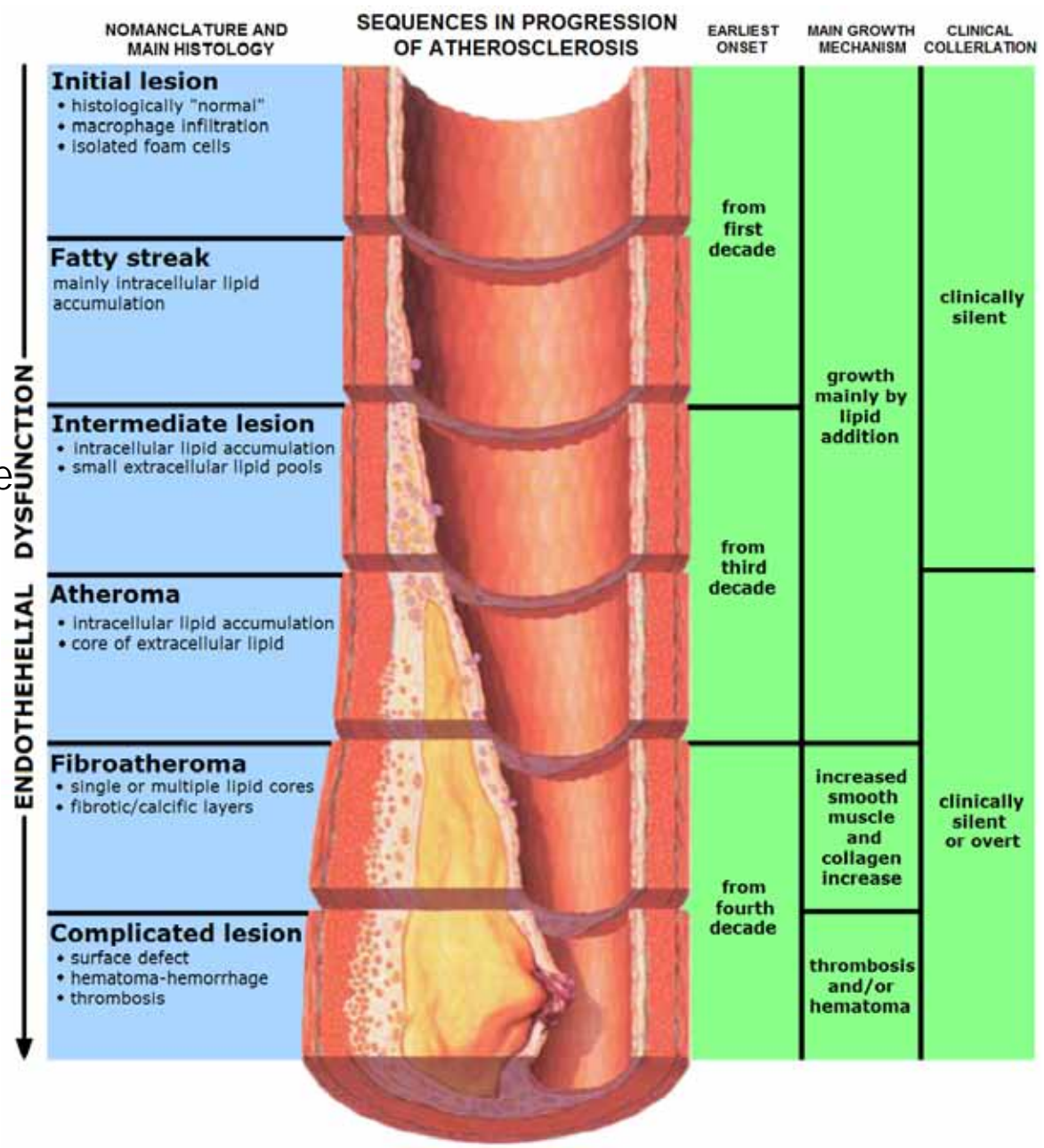
- Limit saturated fat intake (trans too)
- Consume < 200 mg/day cholesterol
- Fish may help
 - High in omega-3 fatty acids – help prevent fat build up in arteries
- Limit salt intake (<2300 mg/day)
 - Average American age 2 years and older consumes ~3,500 mg/day
- Consume vegetables and whole grains
- Diet options for lowering cholesterol
 - Plant sterols and/or soluble fiber
- Do not eat more calories than needed to maintain a healthy weight
 - Animal models indicate that caloric restriction increases longevity
- 30 mins of moderate physical activity per day
- Don't smoke
- Limit alcohol intake

Progression of Vascular Disease



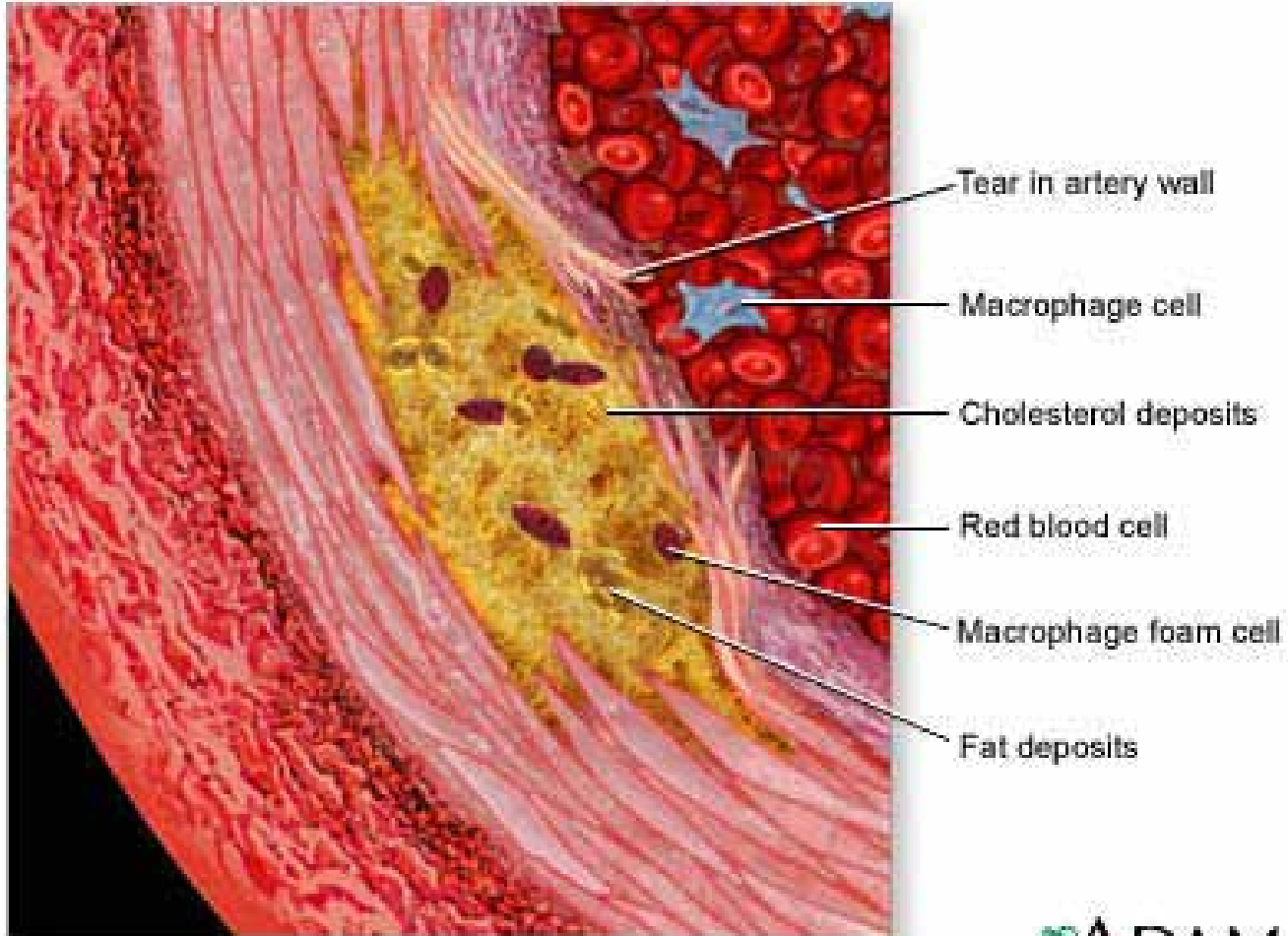
ADAM.

Endothelial cells become pro-thrombic



- Molecular Hallmarks of Atherosclerosis:
- Endothelial cell dysfunction
 - Smooth muscle cell (SMC) proliferation & migration
 - Inflammatory response
 - Immune response

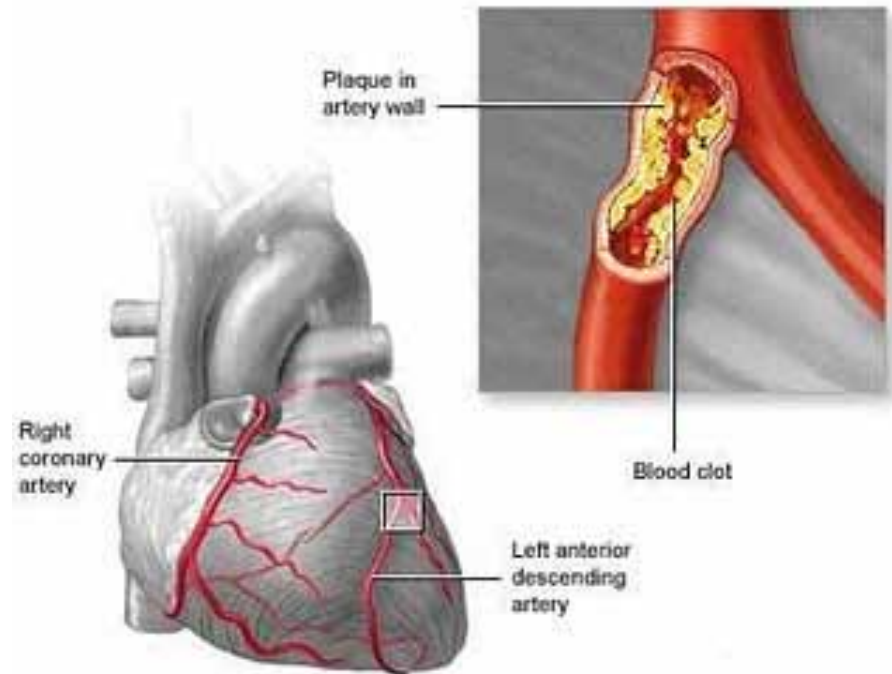
Cut-section of artery



ADAM.

Atherosclerosis

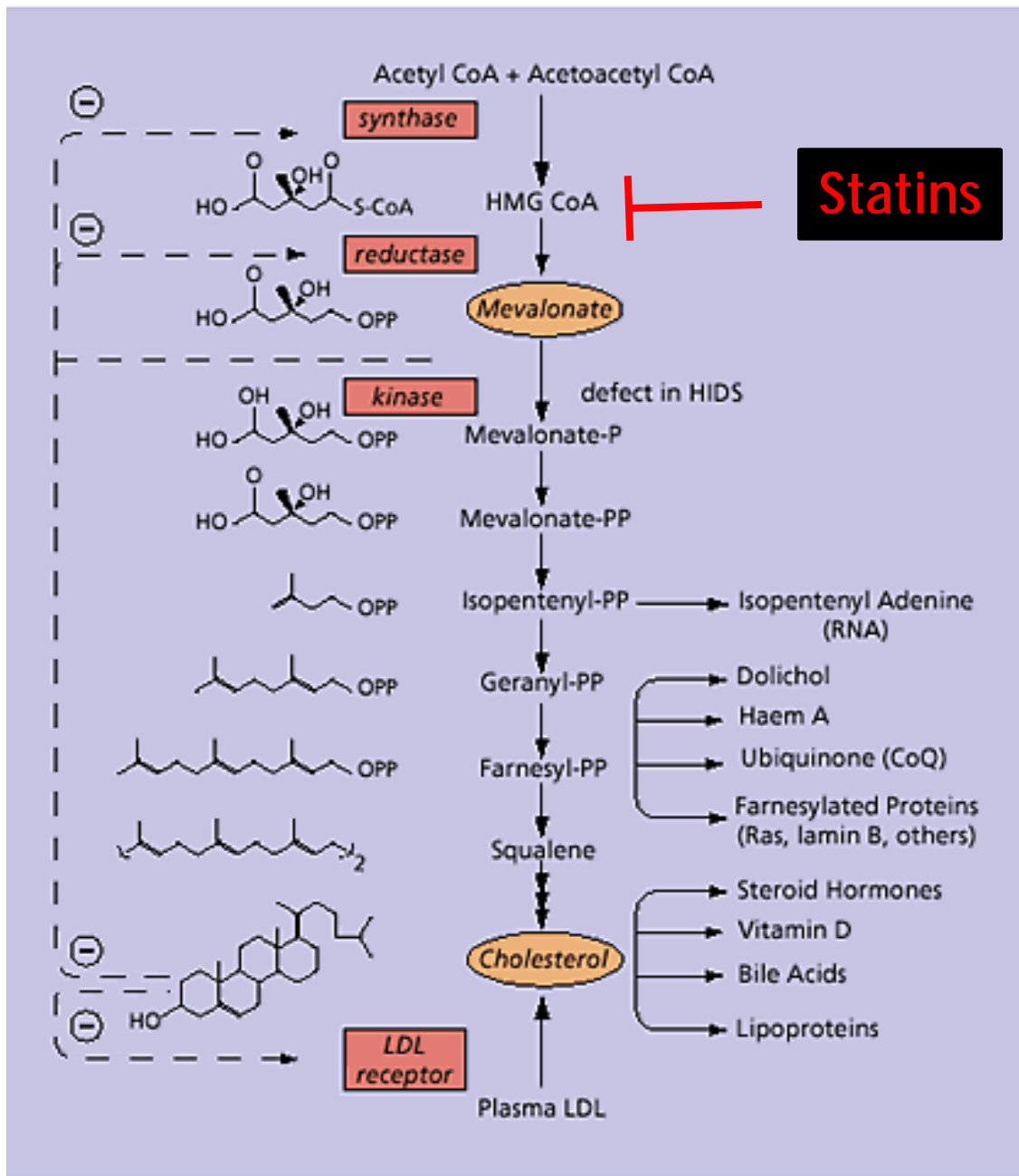
- Leads to narrowing or blockage of arteries
 - Blocked flow to the heart
 - Myocardial infarction (heart attack)
 - Blocked flow to the brain
 - Ischemic stroke
 - Blocked flow to external tissues
 - Gangrene



<http://www.tappmedical.com/atherosclerosis.htm>

Statin Therapy

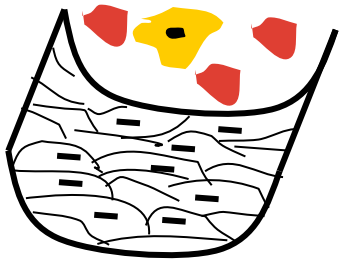
- Lowers serum cholesterol
 - Blocks cholesterol biosynthesis in the liver
 - Unfortunately statins target an enzyme well upstream of cholesterol, so there are many side effects of which myopathy is the most severe
- Prevents CVD:
 - Improve endothelial function
 - Modulate inflammatory responses
 - Maintain plaque stability
 - Prevent thrombus formation



All decreased as a result of statin therapy

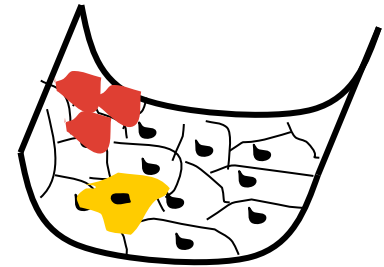
Atherosclerosis and Blood Flow

Smooth Flow Region



Intact Endothelium

Turbulent Flow Region

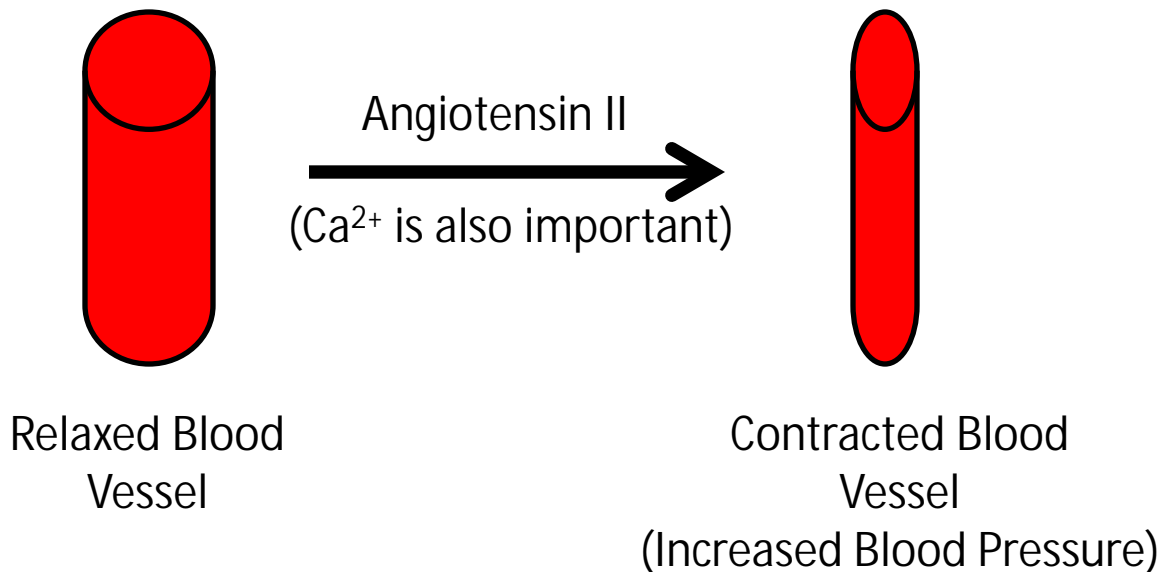


"Leaky" Endothelium
Plaque formation!

Blood flow and other factors contributes to risk of atherosclerosis

Contraction of Blood Vessels

- Angiotensin is a major contraction signal that transiently increases blood pressure

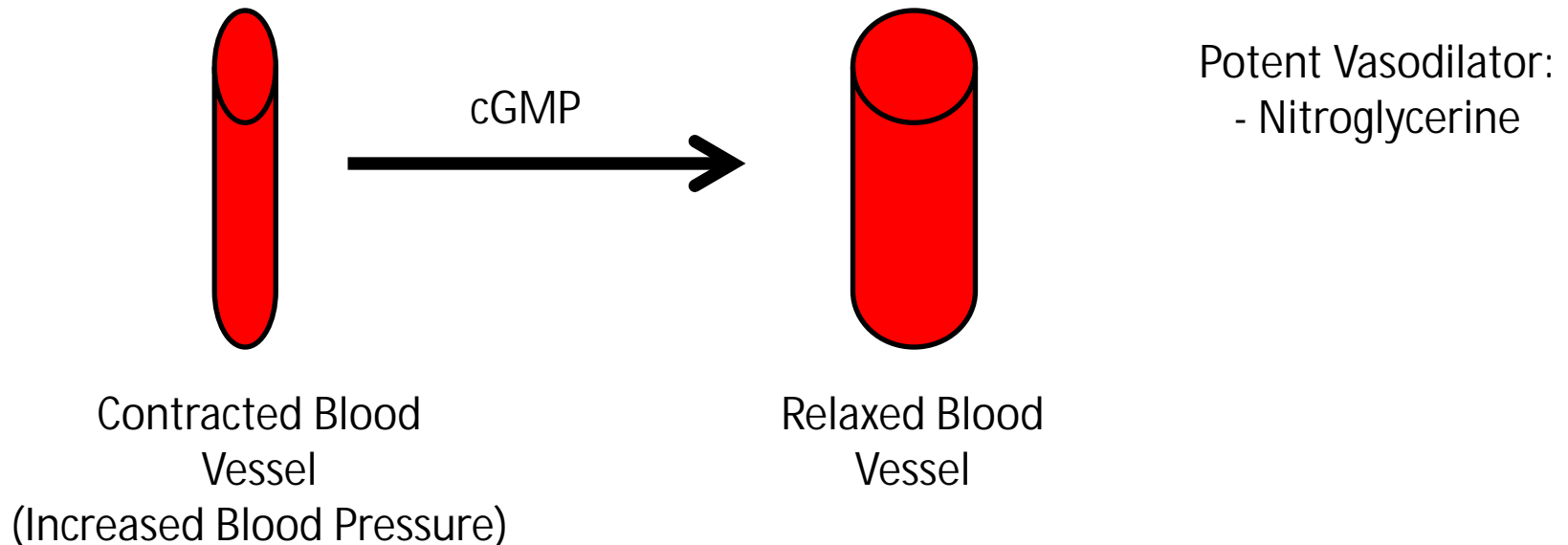


Treatments for Hypertension:

- Diuretics
- Ace inhibitors
- β -blockers
- Ca²⁺ channel blockers

Relaxation of Blood Vessels

- NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP



Relaxation of Blood Vessels

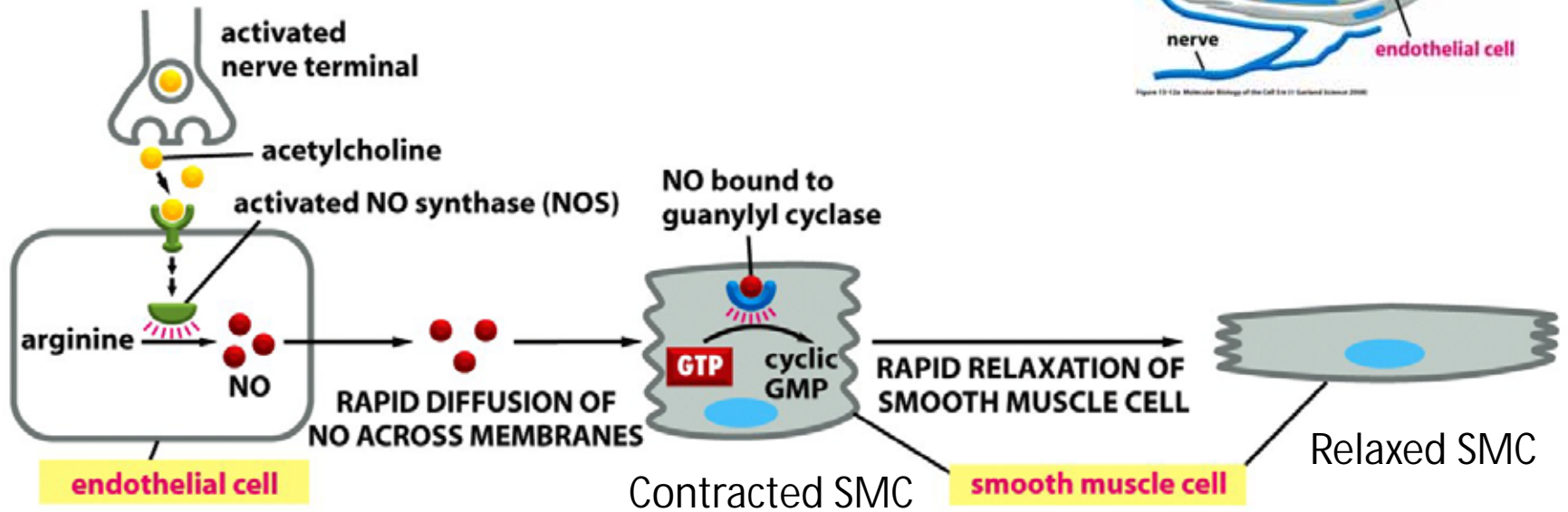
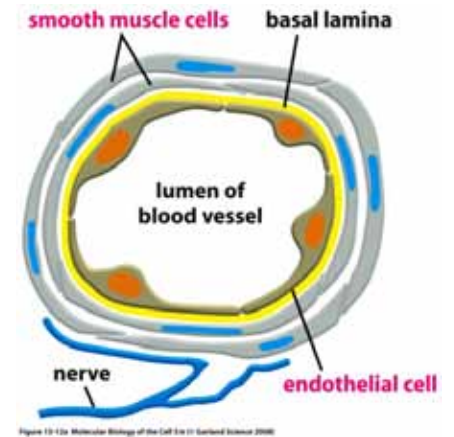
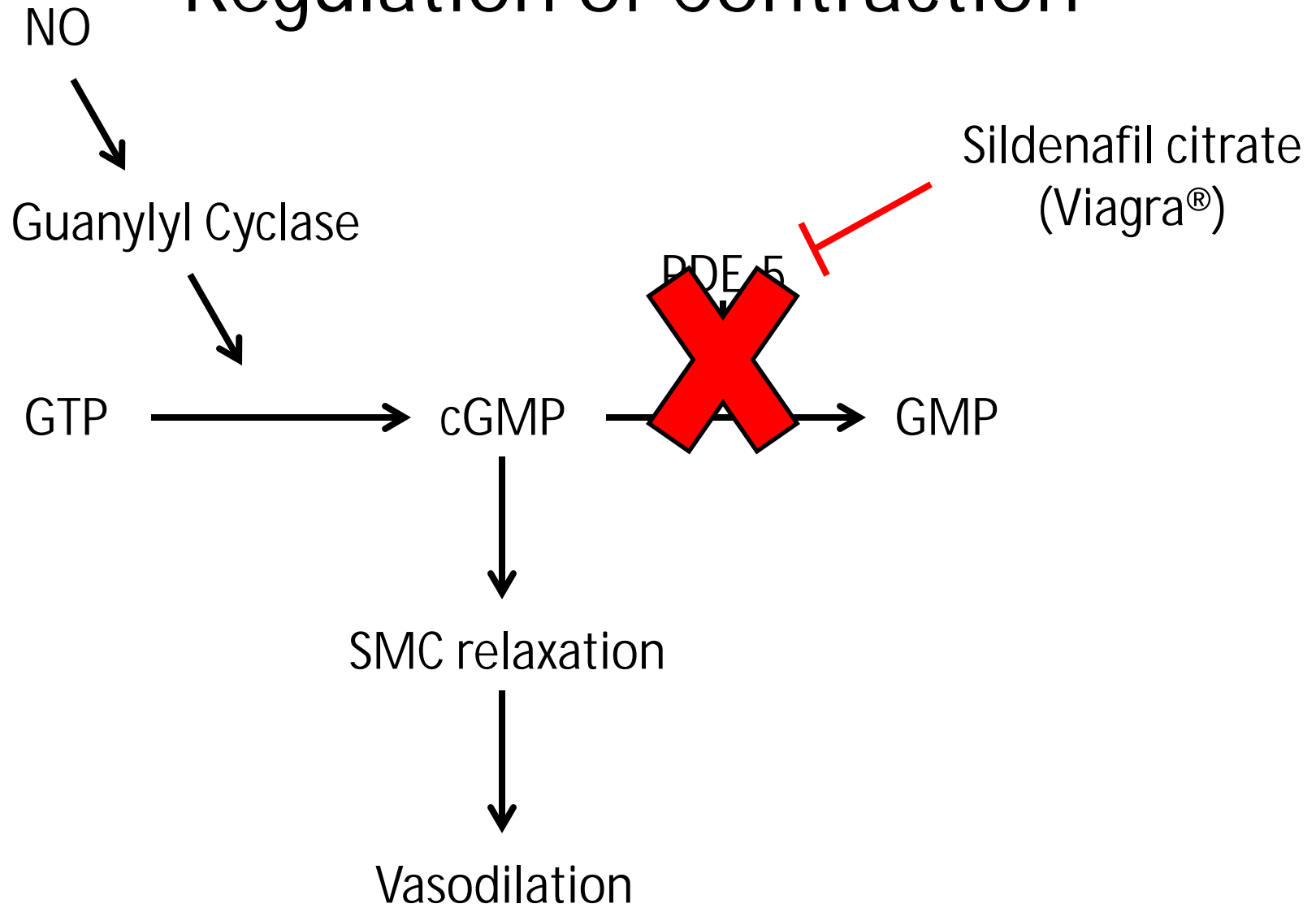


Figure 15-12b Molecular Biology of the Cell 5/e (© Garland Science 2008)

PDE-5 (Phosphodiesterases)
-Convert cGMP to GMP

Regulation of Contraction



Current Research at Lehigh (Linda Lowe-Krentz Laboratory)

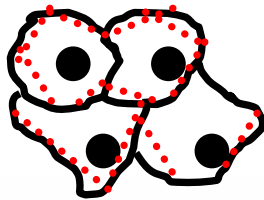
Aimed at understanding the
development of atherosclerosis and
reversing the damage

Future Therapy for Atherosclerosis

- Heparin is a soluble molecule released by mast cells at sites of infection/inflammation
- Currently used in medicine as an anti-coagulant
- Data from our lab and the literature indicates that heparin blocks SMC proliferation at the G1 phase of the cell cycle
 - Helpful in the case of atherosclerosis in which one of the problems is SMC proliferation

Understanding the relationship between atherosclerosis and blood flow

No Flow



No flow

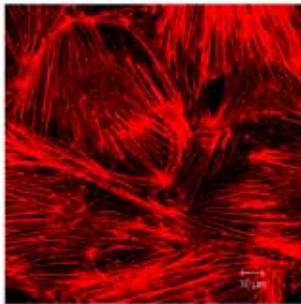
Smooth Flow



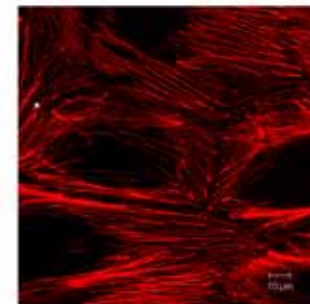
← Flow

A

Control



Actin



Smooth flow regions are protected against the development of atherosclerosis

Homework!

- Please watch the following video on youtube.
- <http://www.youtube.com/watch?v=fLonh7ZesKs>
- It summarizes the development of CVD extremely well.

Linda Lowe-Krentz Laboratory



THE LOWE-KRENTZ LAB (FALL 2012)

front row (l-r): Sara Lynn Farwell, Tamara Huson, Aislinn Rowan, Linda Lowe-Krentz, Ph.D.,
Yaqiu Li, Kathryn Swanson

back row (l-r): Erin Kennedy, Joshua Slee, Tenzen Deyang, Kathryn Schnall, Trista Barthol,
Wutigri Nimlamool, Tina Penska

If you have further questions or are interested in learning more, please contact me at: jbs208@lehigh.edu