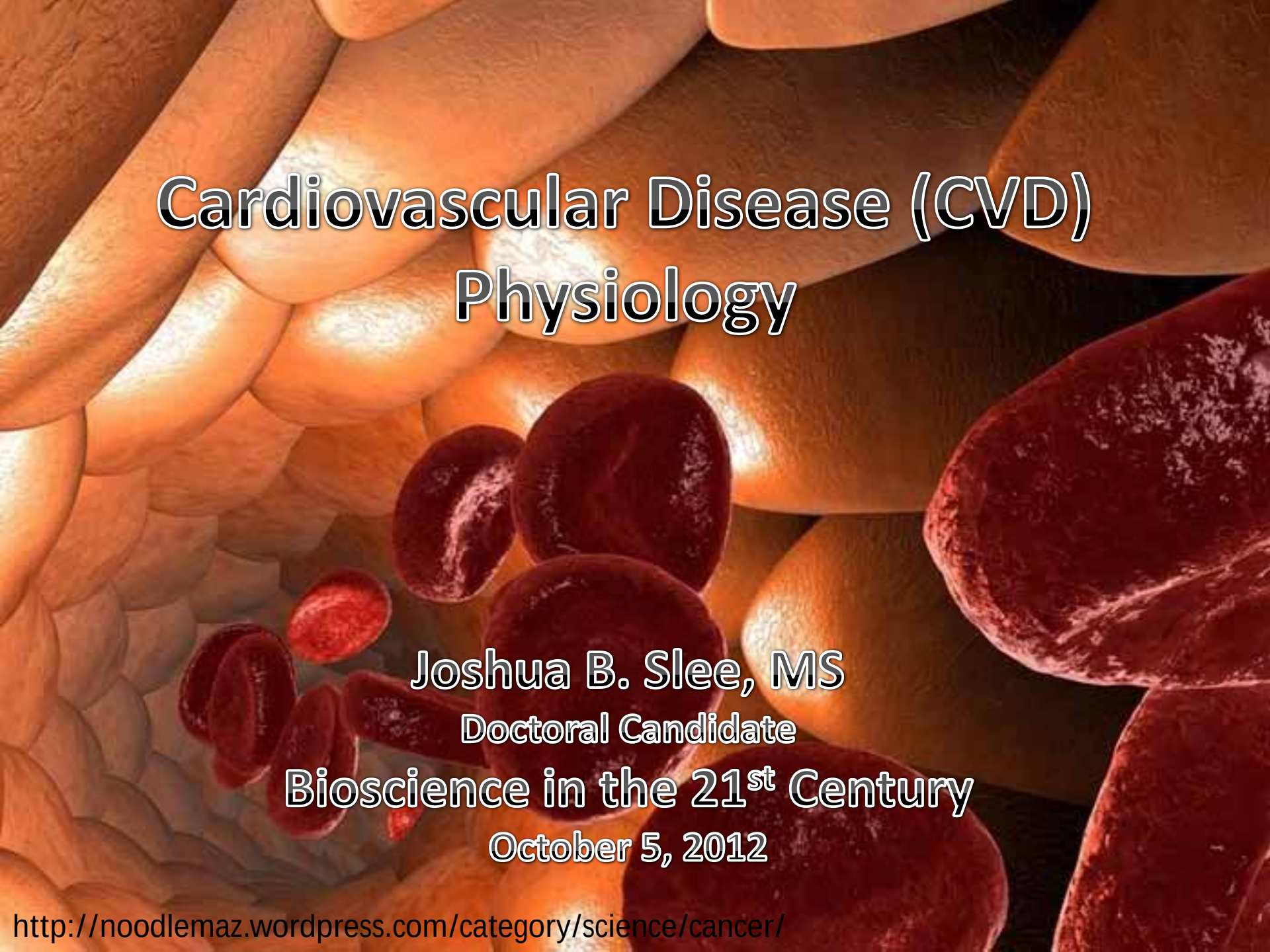


# Cardiovascular Disease (CVD) Physiology

Joshua B. Slee, MS
Doctoral Candidate

Bioscience in the 21st Century

October 5, 2012

http://noodlemaz.wordpress.com/category/science/cancer/

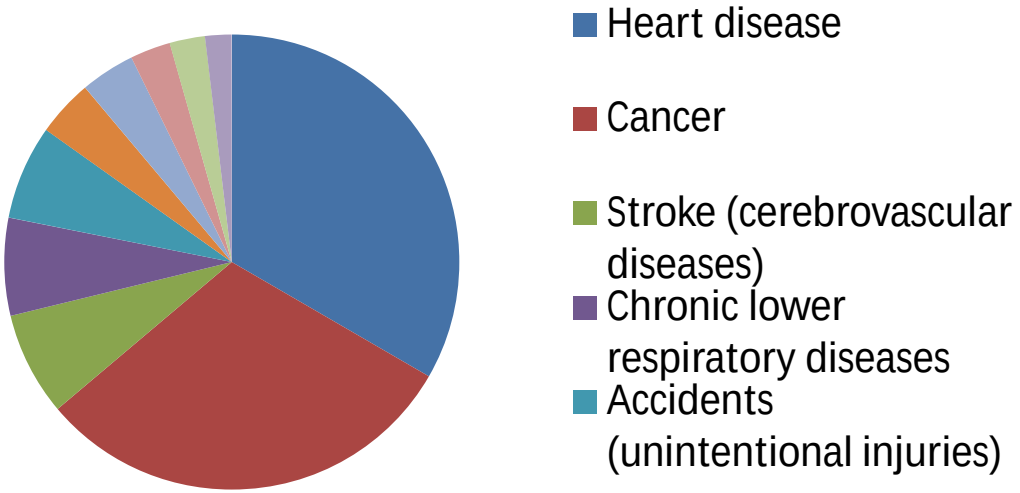
# Outline

- 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]

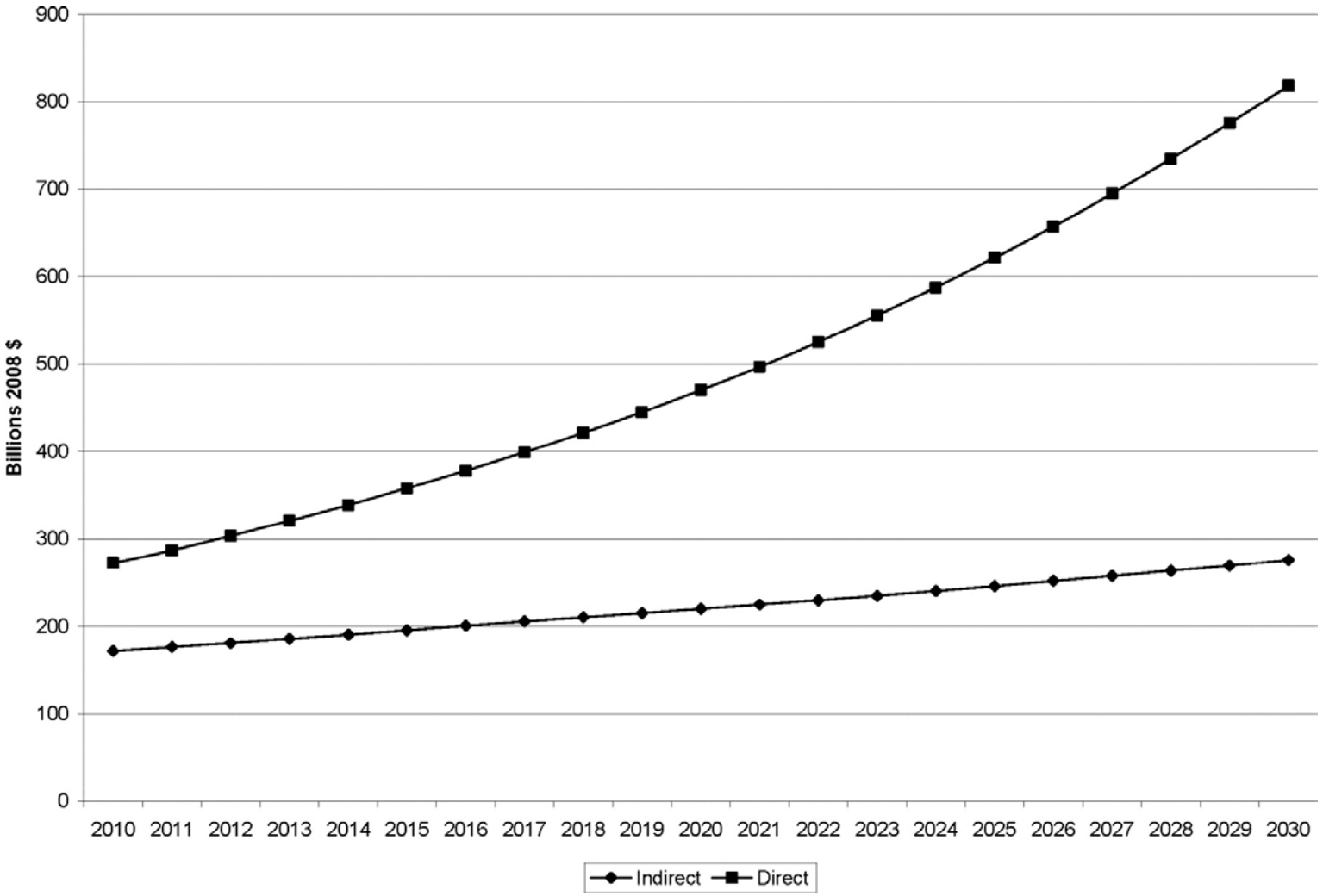
**U.S. Death Rates per Year [1]**




[1]Centers for Disease Control; January 17, 2012

[2]Heidenreich 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**

American Heart Association
*Learn and Live*

# 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

American Heart Association
*Learn and Live*

# 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-thrombic state (pro-clotting)
- Elevated blood pressure (≥130/85 mmHg)
- Pro-inflammatory state

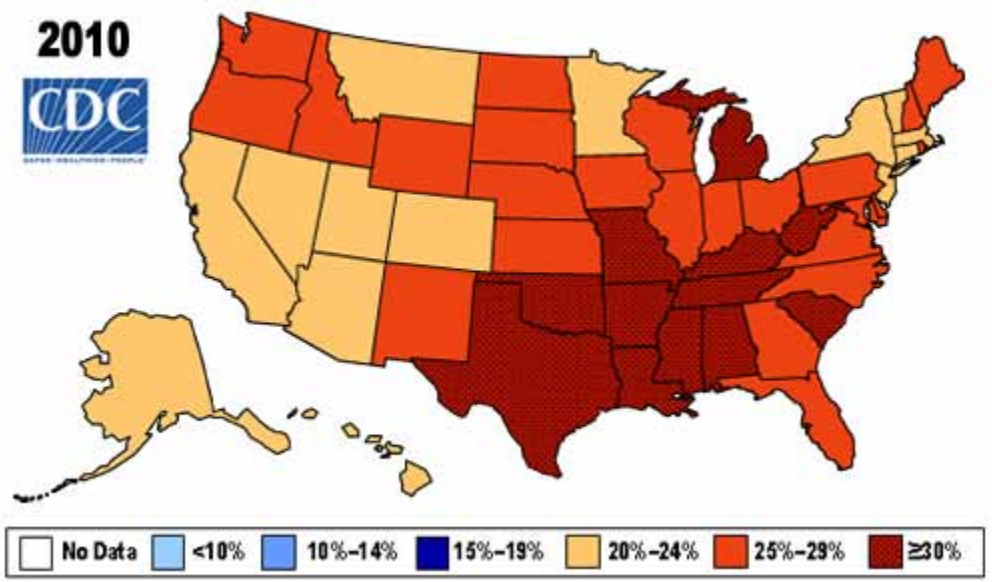
# Obesity

- Diet
- Portion size
- Lack of physical acitivty
- 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

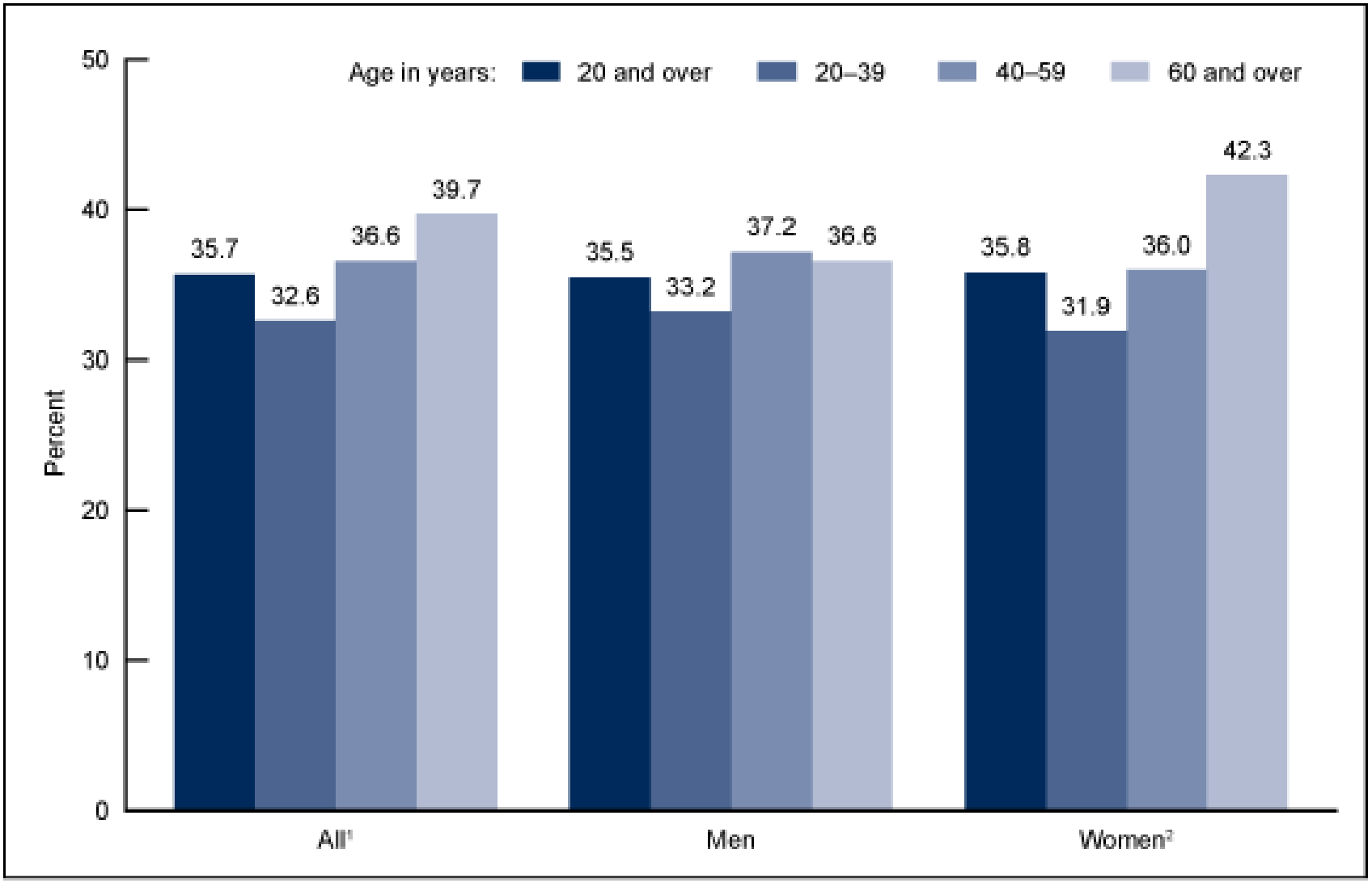
# Obesity Epidemic in the US

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



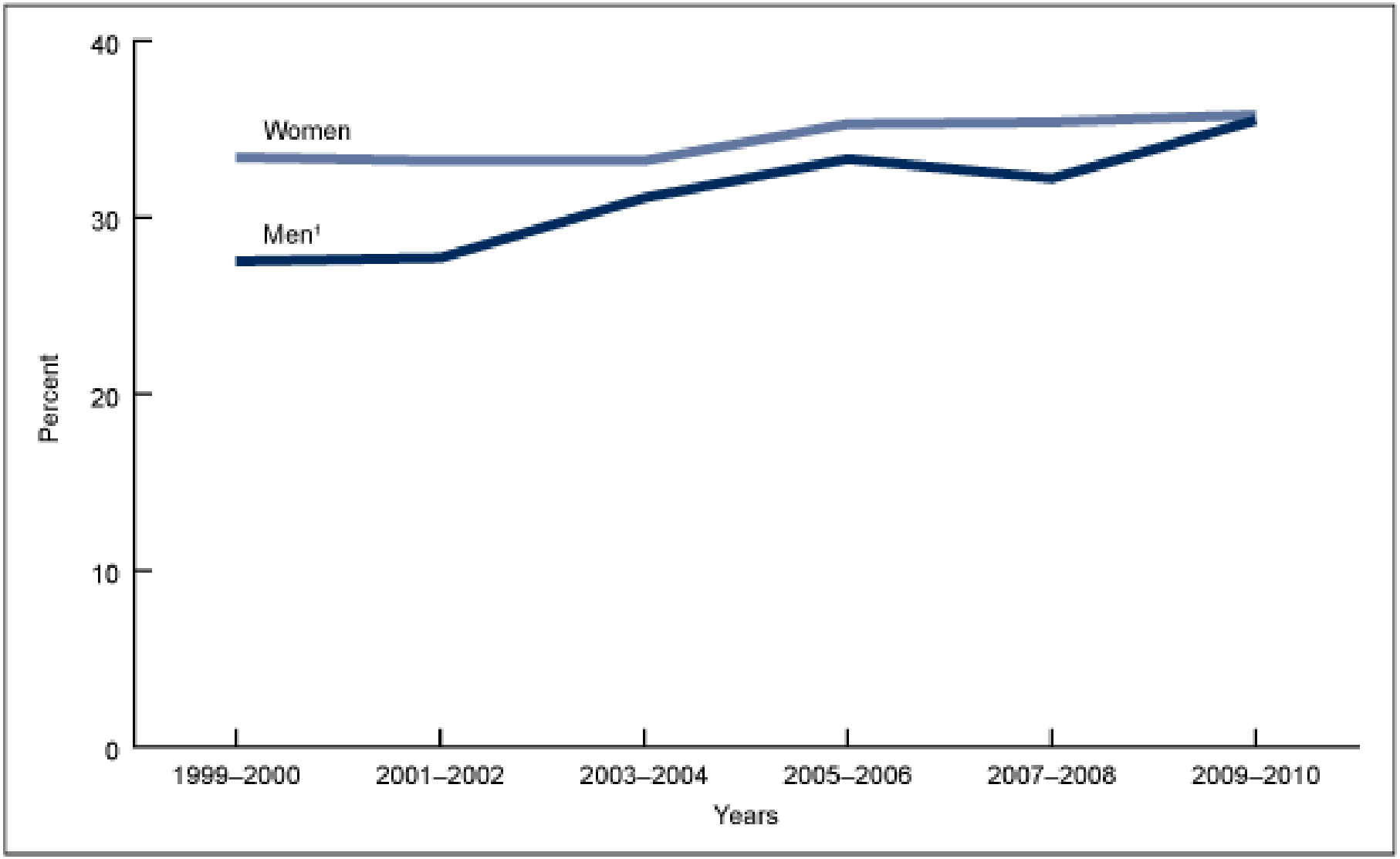

Ogden CL et al.Prevalence of obesity in the United States, 2009–2010. NCHS data brief, no 82. Hyattsville, MD: National Center for Health Statistics. 2012.

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



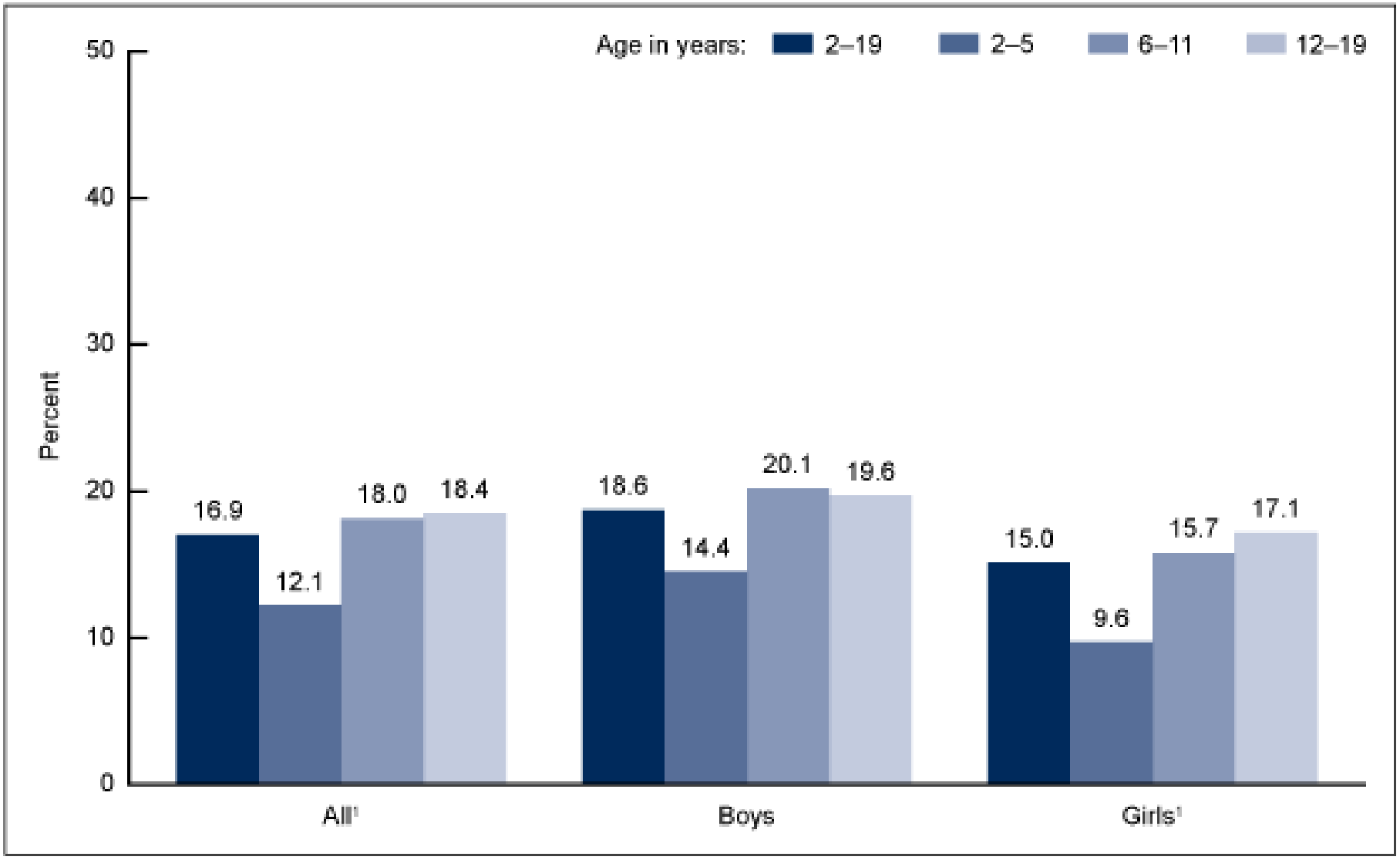

[1]Significant increasing linear trend by age ($p < 0.01$).
[2]Significant increasing linear trend by age ($p < 0.001$).
NOTE: Estimates were age adjusted by the direct method to the 2000 U.S. Census population using the age groups 20–39, 40–59, and 60 and over.
SOURCE: CDC/NCHS, National Health and 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




[1]Significant 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.

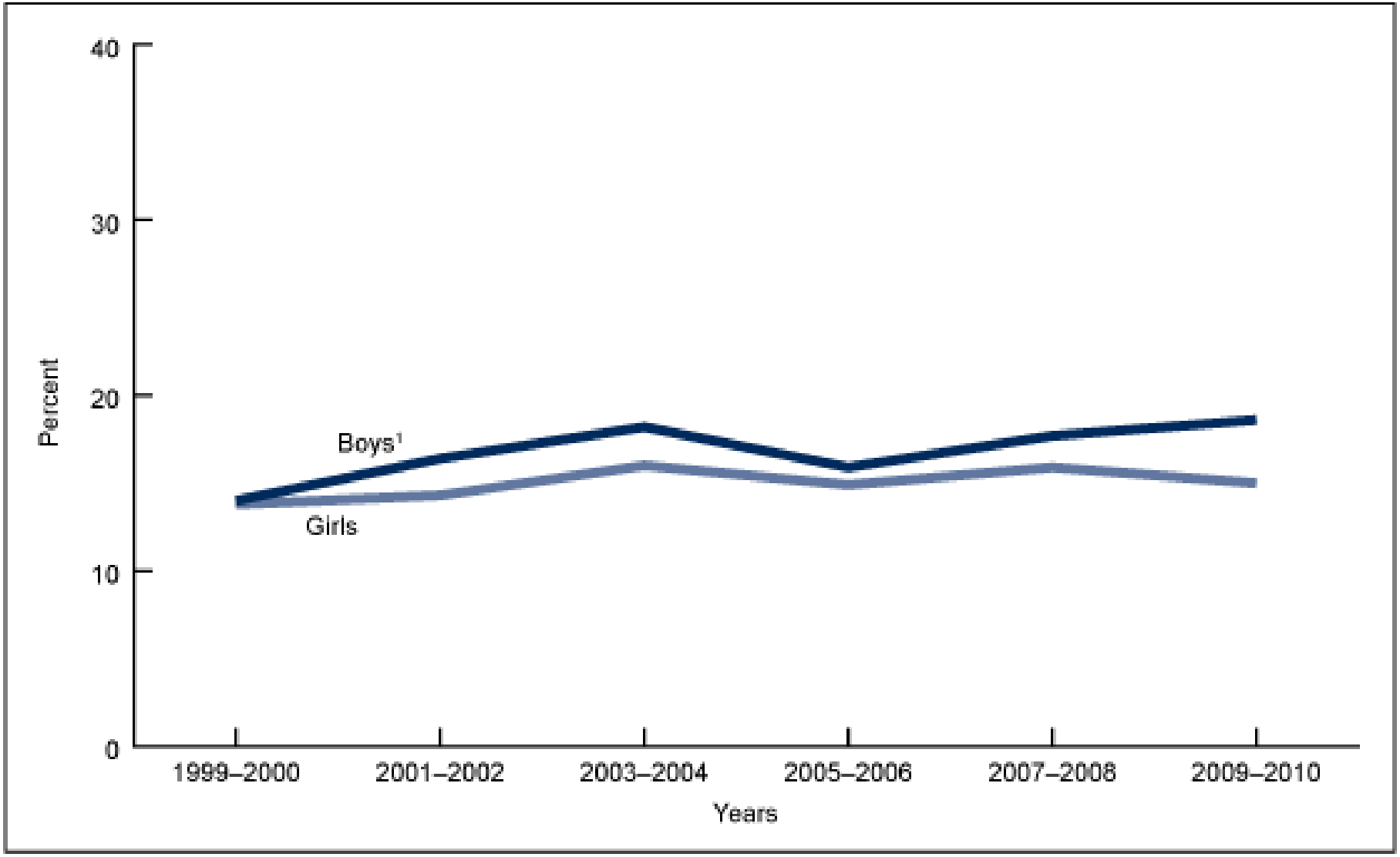
Figure 2. Prevalence of obesity among children and adolescents aged 2–19, by sex and age: United States, 2009–2010




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

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

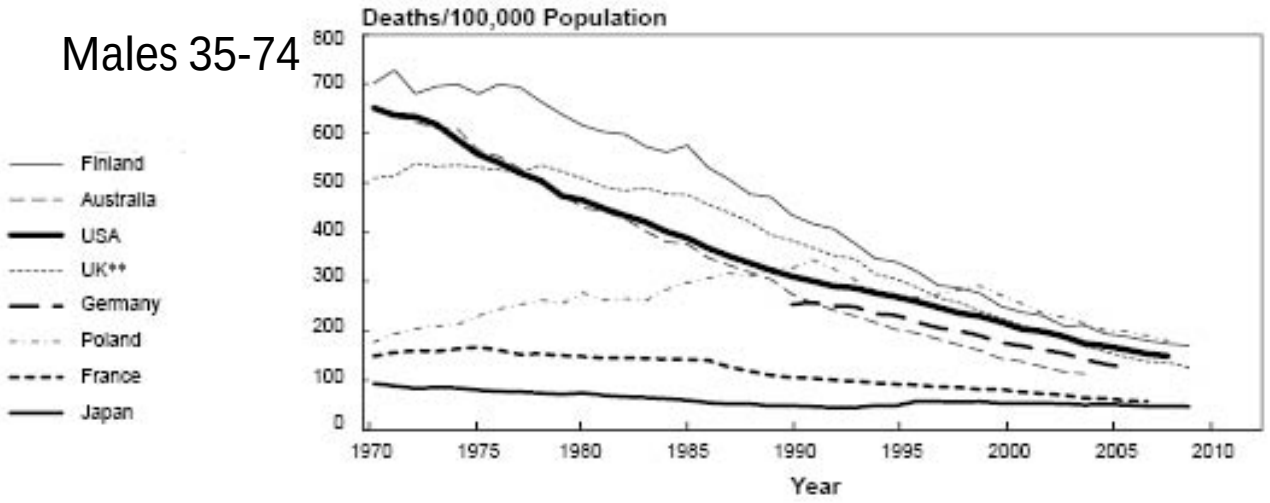
Figure 5. Trends in the prevalence of obesity among children and adolescents aged 2–19, by sex: United States, 1999–2010



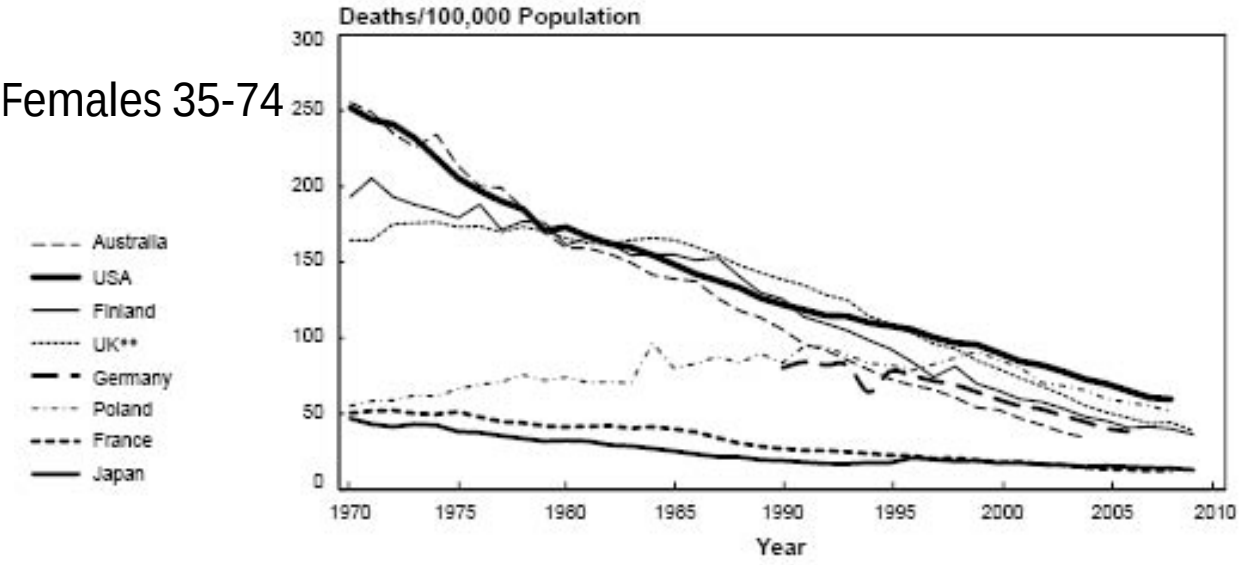

[1]Significant increasing linear trend 1999–2000 to 2009–2010 ($p < 0.05$).
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2009–2010.

# Some Good News

Males 35-74




Females 35-74

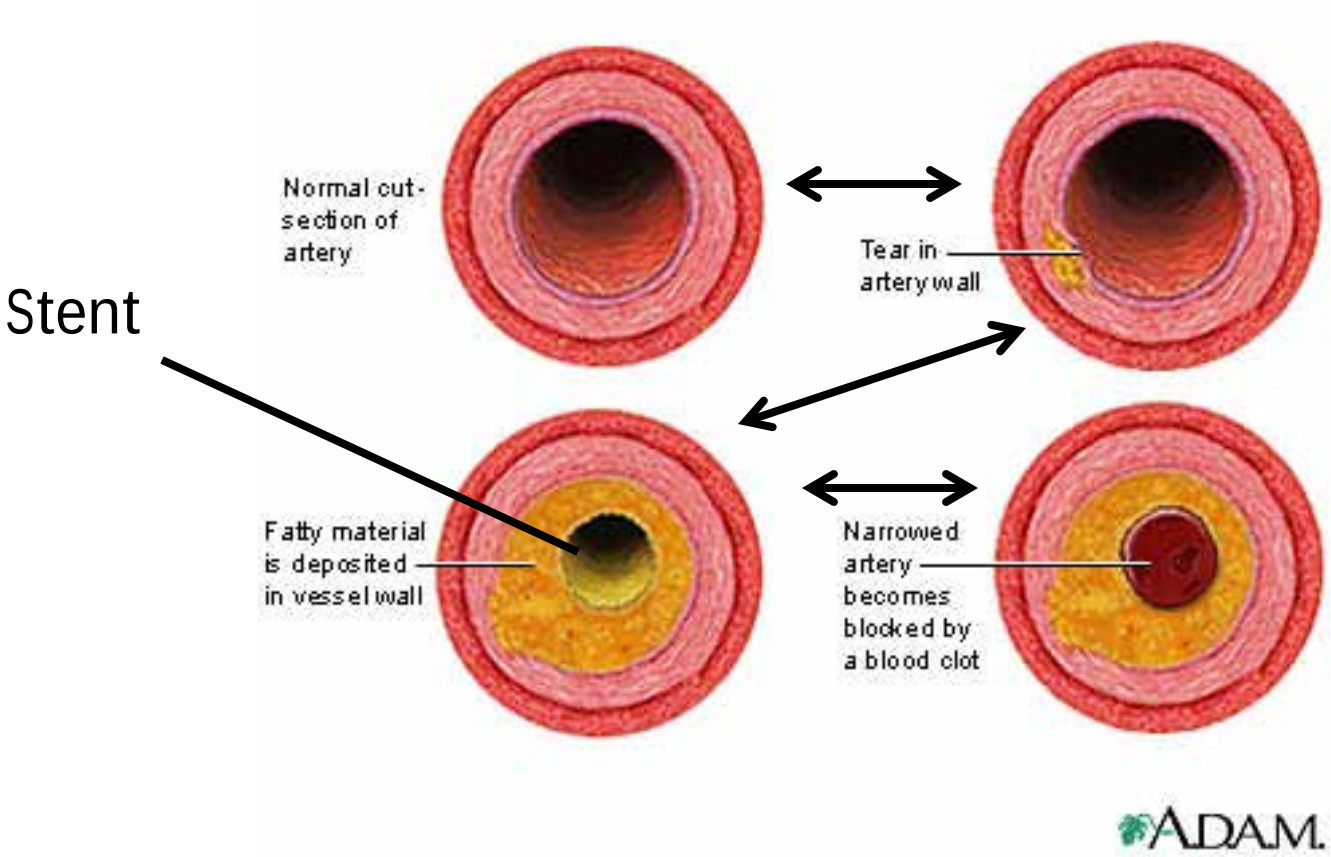



National Heart Lung and Blood Institute
People Science Health

# So What Can You Do?

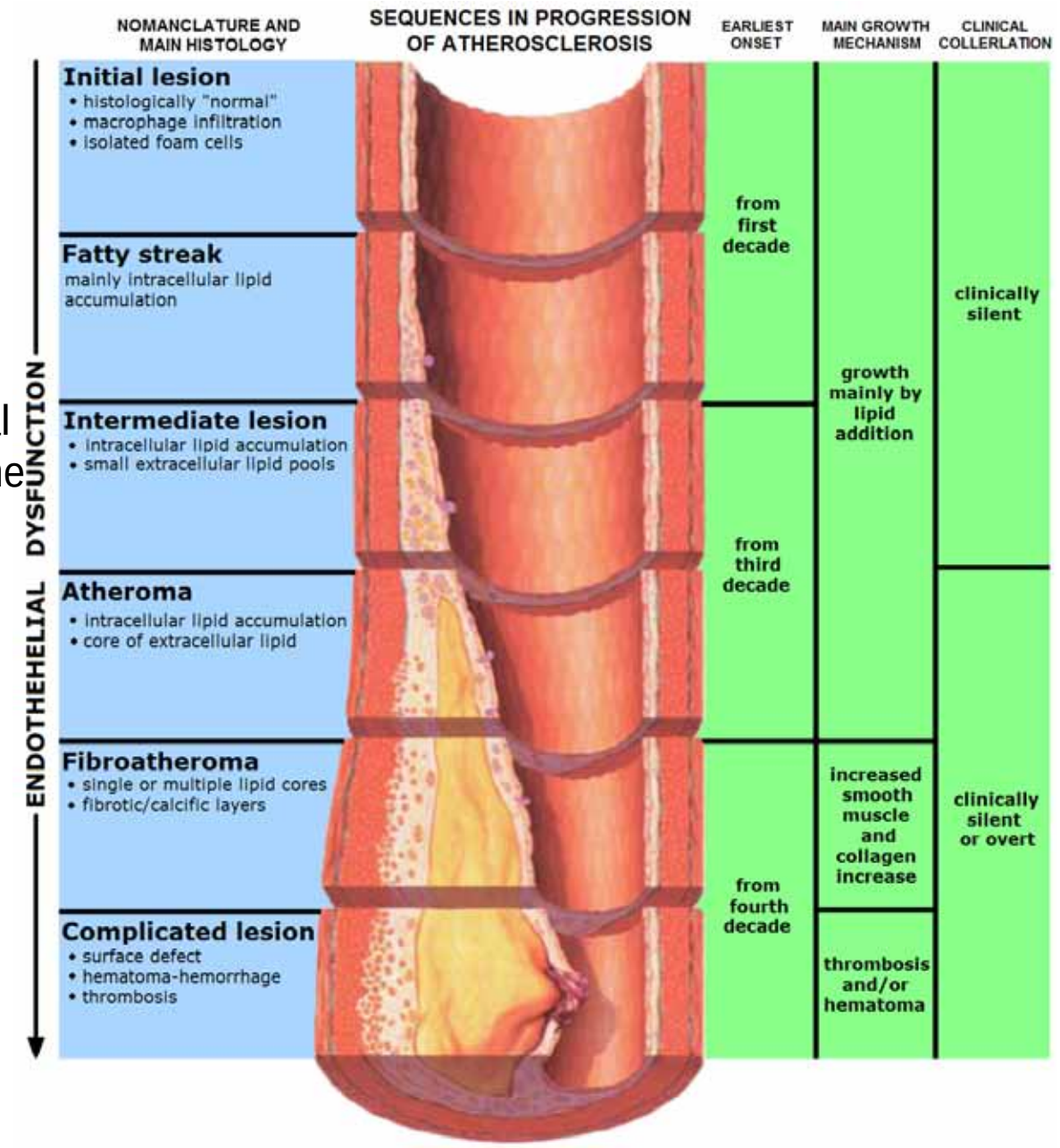
- Limit saturated fat intake (trans too)
- Consume < 200 mg/day cholesterol
- Fish may help
  - High in omega-3 fatty acids – help prevent fat build up in arteries
- Limit salt intake (<2300 mg/day)
  - Average American age 2 years and older consumes ~3,500 mg/day
- Consume vegetables and whole grains
- 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




Medline Plus Medical Encylopedia

Endothelial cells become pro-thrombic




Molecular Hallmarks of Atherosclerosis:

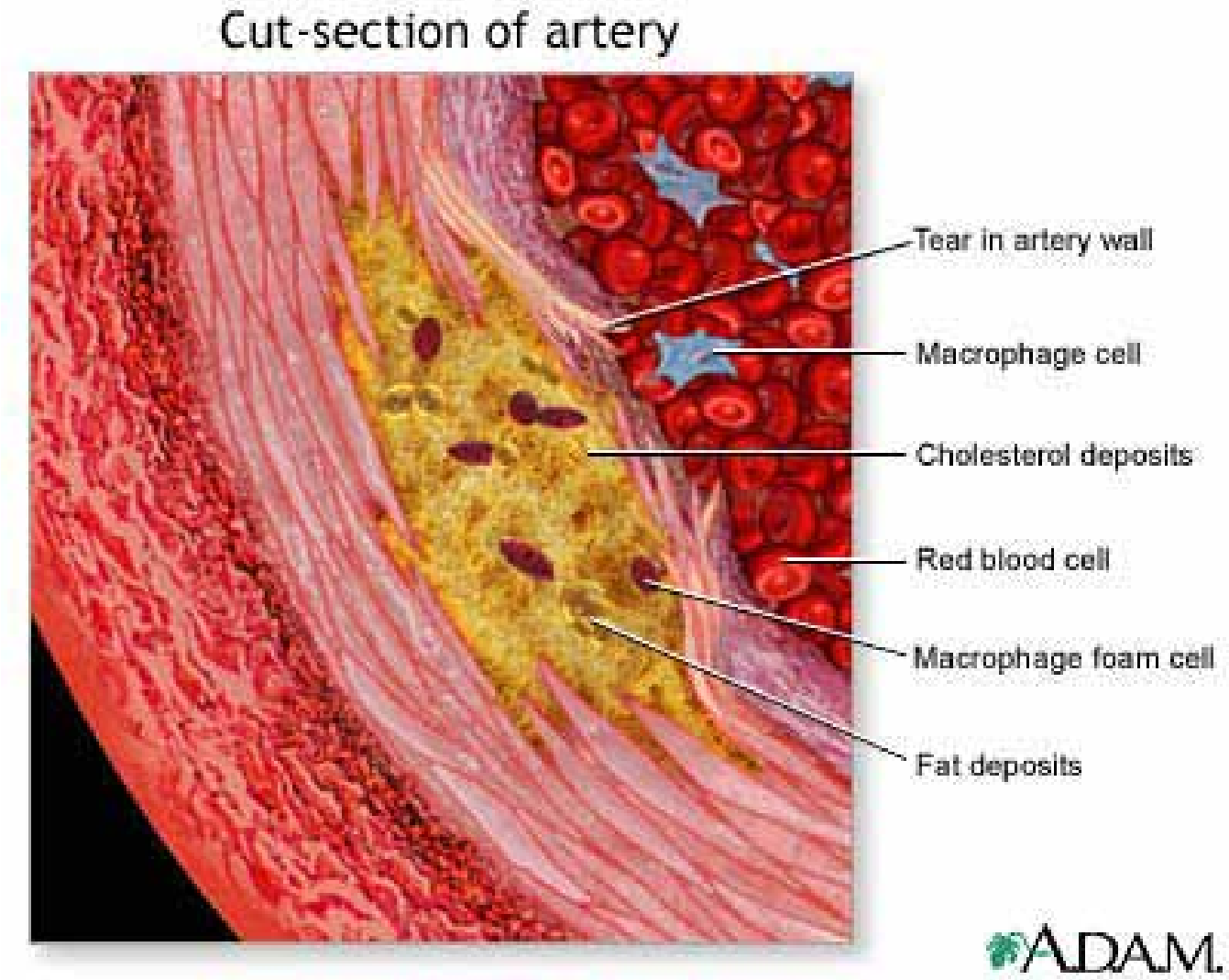
-Endothelial cell dysfunction

- Smooth muscle cell (SMC) proliferation & migration

-Inflammatory response

- Immune response

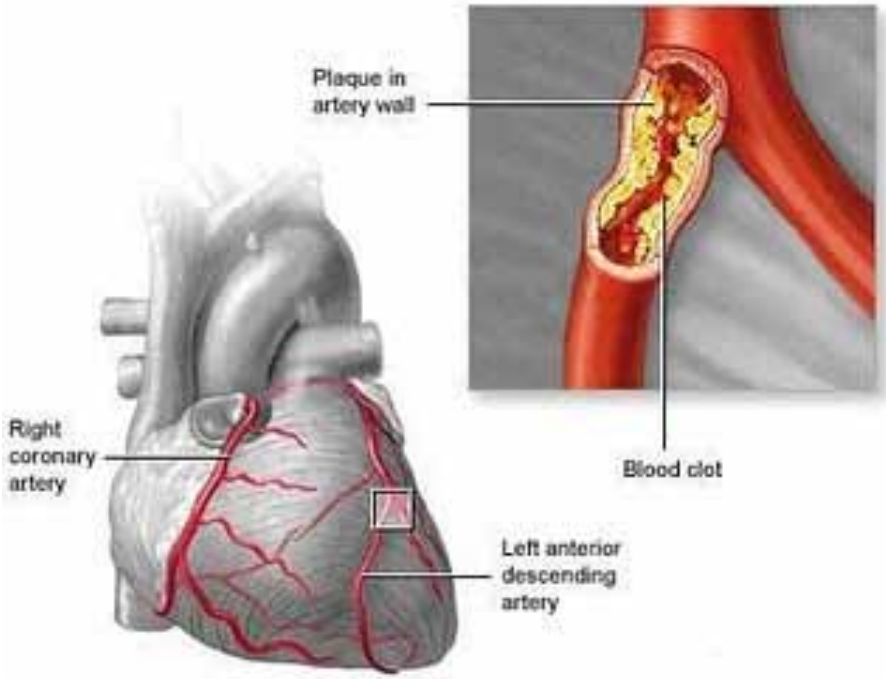
http://en.wikipedia.org/wiki/File:Endo_dysfunction_Athero.PNG




Medline Plus Medical Encylopedia

# Atherosclerosis

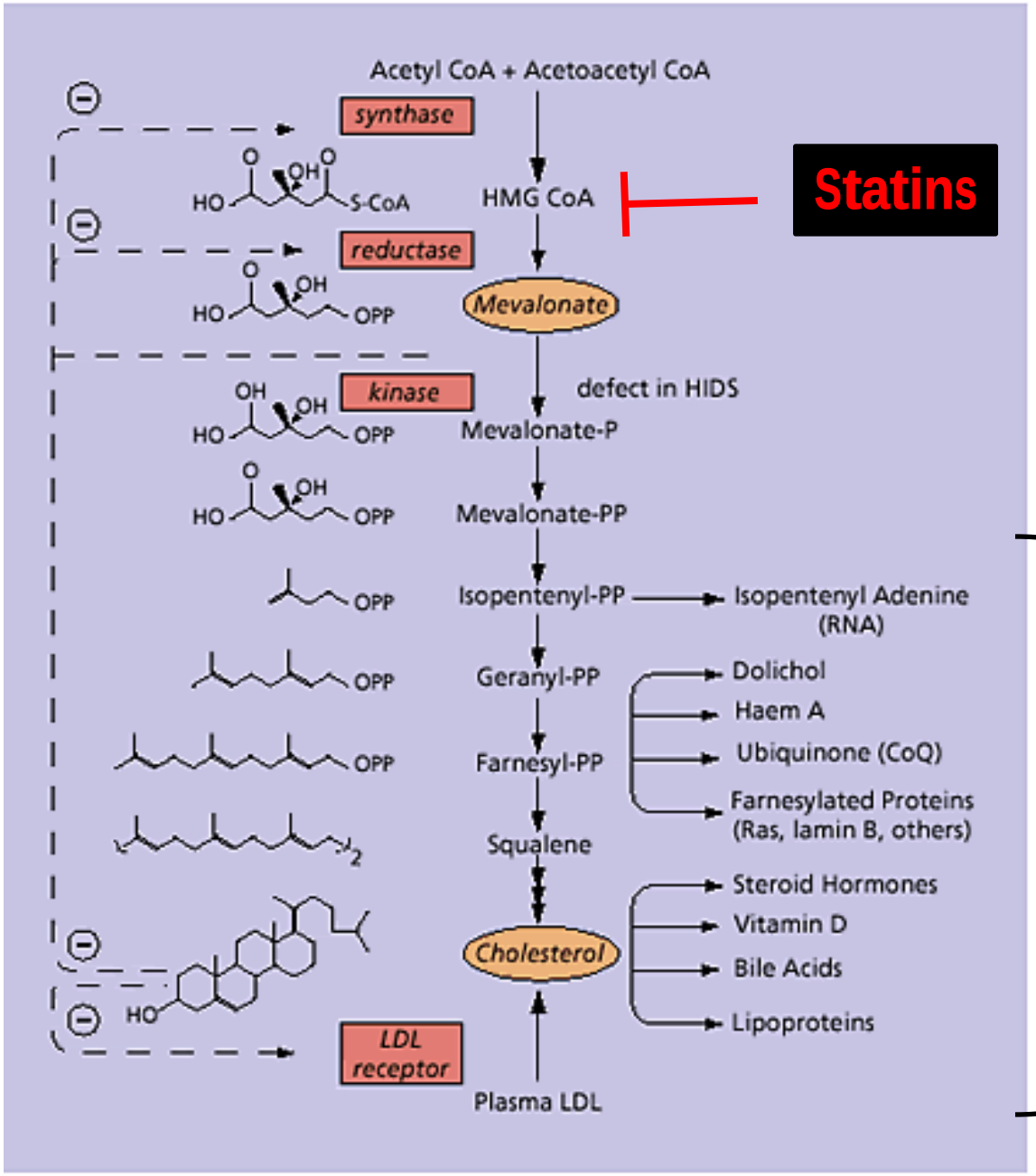
- Leads to narrowing or blockage of arteries
  - Blocked flow to the heart
    - Myocardial infarction (heart attack)
  - Blocked flow to the brain
    - Ischemic stroke
  - Blocked flow to external tissues
    - Gangrene




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 affects of which myopathy is the most severe
- Prevents CVD:
  - Improve endothelial function
  - Modulate inflammatory responses
  - Maintain plaque stability
  - Prevent thrombus formation

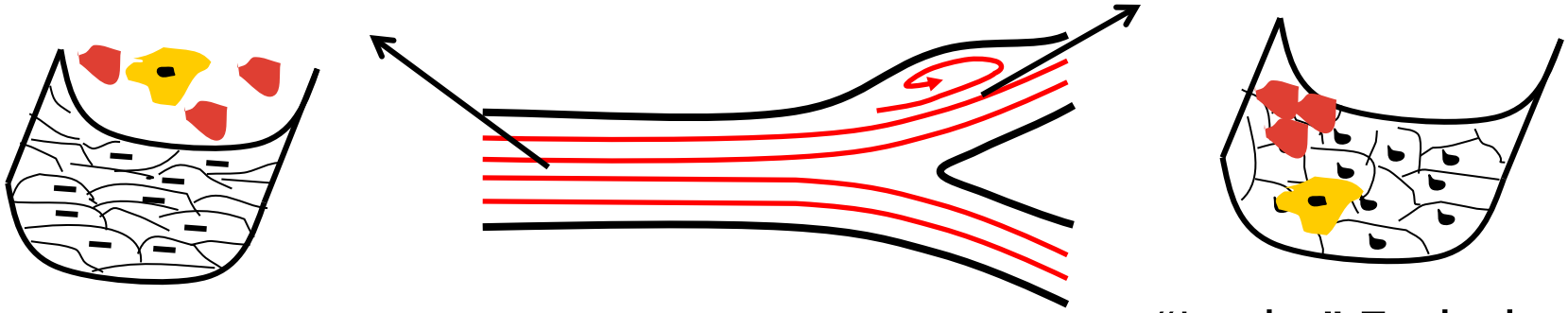



http://media.photobucket.com/image/hmg-coa%20reductase%20pathway/molbiogirl/ng0699_122.gif

# Atherosclerosis and Blood Flow

Smooth Flow Region

Turbulent Flow Region



Intact Endothelium

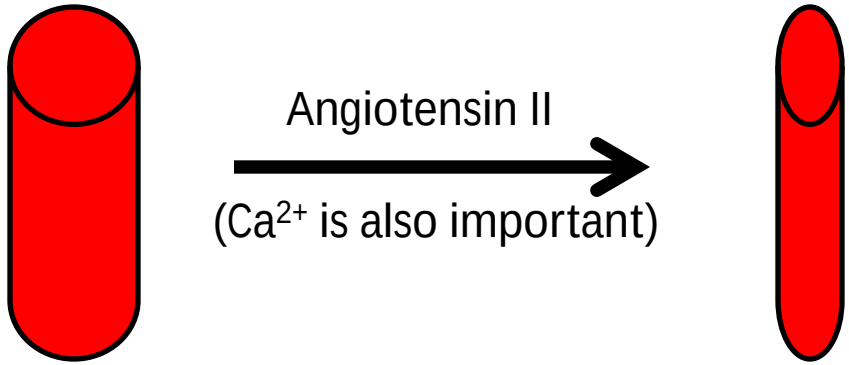
"Leaky" Endothelium

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



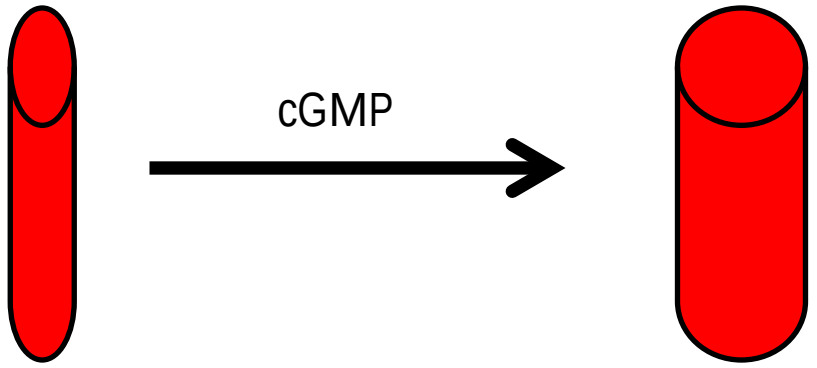

Relaxed Blood Vessel

Contracted Blood Vessel (Increased Blood Pressure)

Treatments for Hypertension:
-Diuretics
-Ace inhibitors
-β-blockers
-$Ca^{2+}$ channel blockers

# Relaxation of Blood Vessels

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

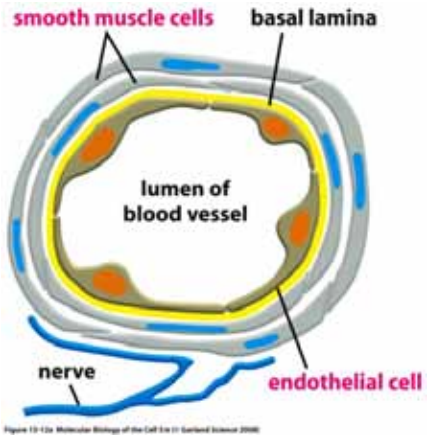



Contracted Blood Vessel (Increased Blood Pressure)

Relaxed Blood Vessel

Potent Vasodilator:
- Nitroglycerine

# Relaxation of Blood Vessels



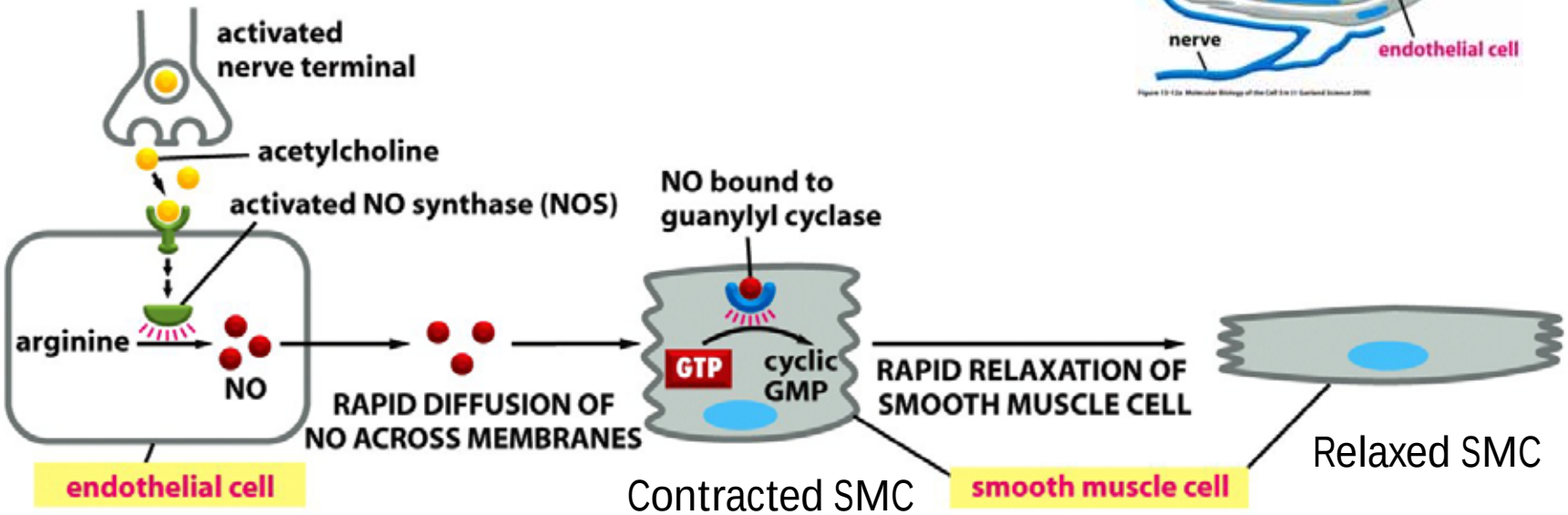
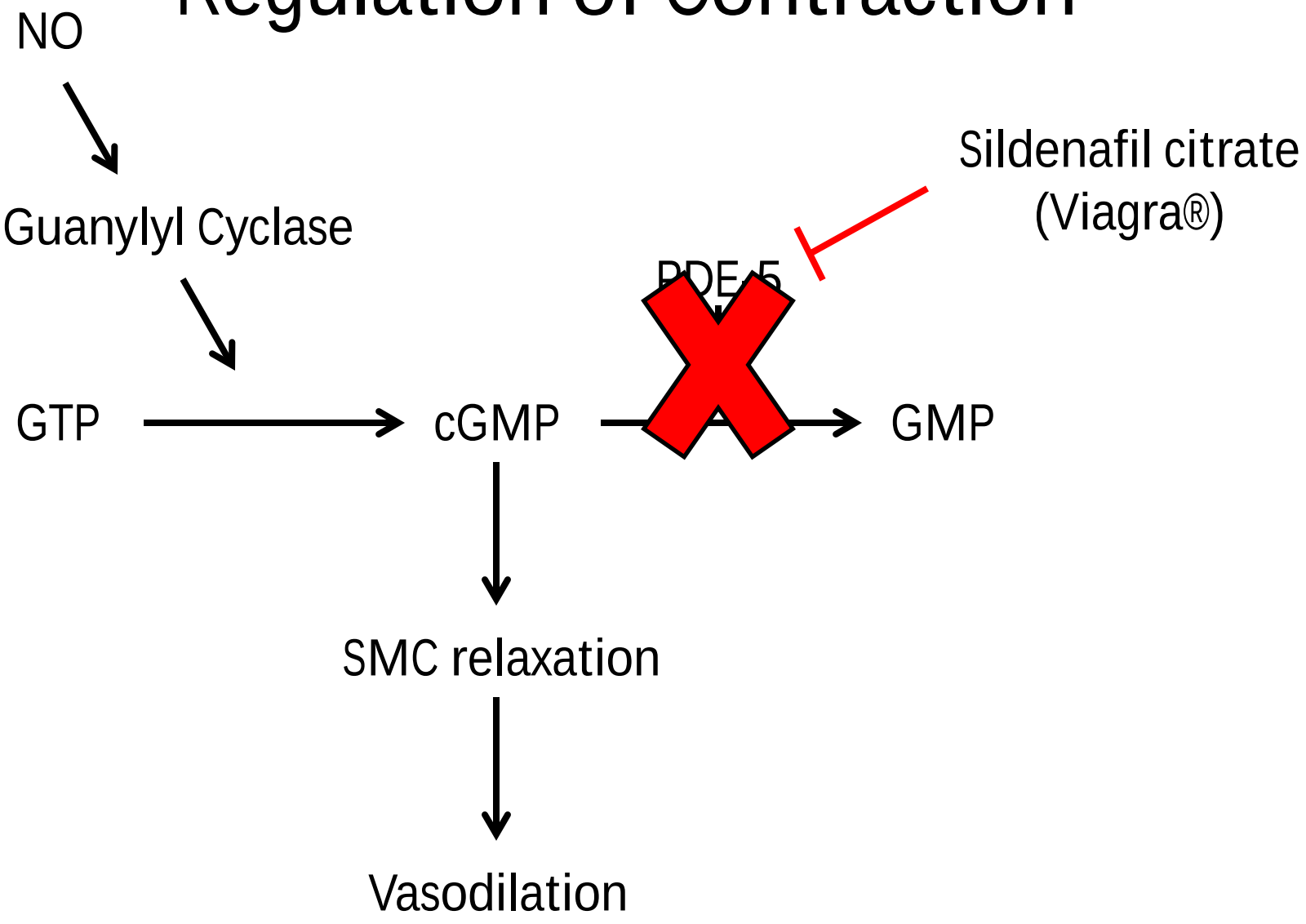




Figure 15-12b Molecular Biology of the Cell 5/e (© Garland Science 2008)

PDE-5 (Phosphodiesterases)
-Convert cGMP to GMP

# Regulation of Contraction




Modified from: Guiliano F. Eur Heart J 2002(4)H7-H12

# Current Research at Lehigh (Linda Lowe-Krentz Laboratory)

Aimed at understanding the development of atherosclerosis and reversing the damage

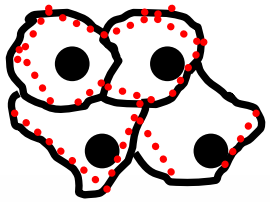
# Future Therapy for Atherosclerosis

- 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

Reviewed in: Slee and Lowe-Krentz. Nova Publishers. 2012

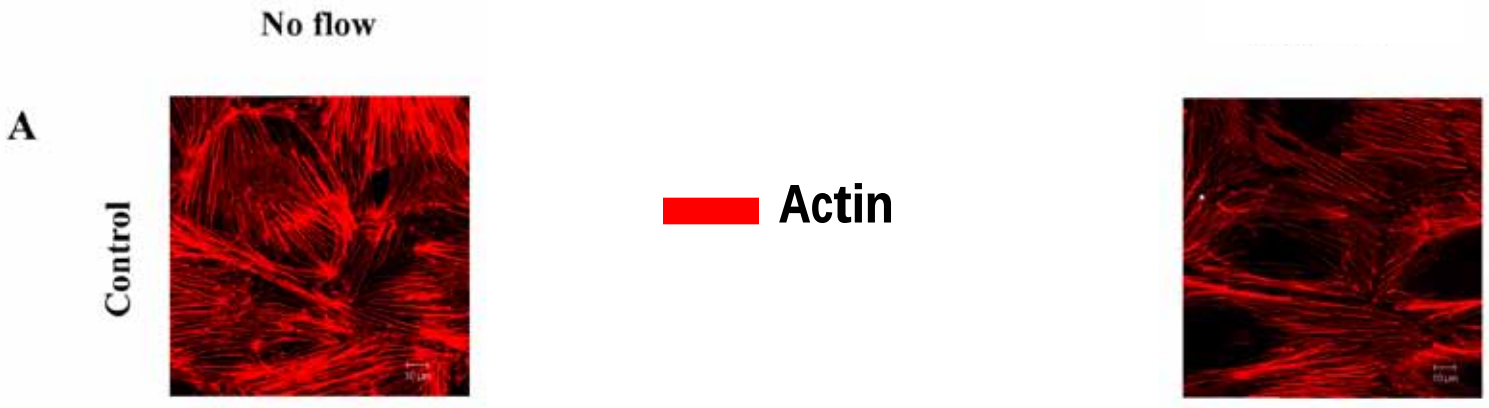
# Understanding the relationship between atherosclerosis and blood flow

**No Flow**



**Smooth Flow**

Flow




Smooth flow regions are protected against the development of atherosclerosis

Mengistu M. et al. J Cell Physiol. 2011
Mengistu, Slee, Lowe-Krentz. Nova Publishers. 2012

# 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