Cardiovascular disease, studies at the cellular and molecular level

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Bioscience in the 21st Century

October 4, 2010

Content

- Introduction – The number 1 killer in America
  - Some statistics
  - Recommendations
- The disease process
  - Damage
  - Current treatments
- Control of vascular tone
- Investigating the system
  - Metabolomics
  - Protein investigations

Risk Factors

- High blood pressure (above 120/80 mm Hg)
- High cholesterol [aim for below 100 mg/dL LDL cholesterol and above 50 mg/dL HDL, or aim for total cholesterol below 200 mg/dL]
- High Body Mass Index (BMI) [above 30]
- Smoking
- Drinking
- Diabetes

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Metabolic Syndrome

- Central obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia (blood fat disorders — mainly high triglycerides and low HDL cholesterol)
- Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
- Pro-thrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- Raised blood pressure (130/85 mmHg or higher)
- Pro-inflammatory state

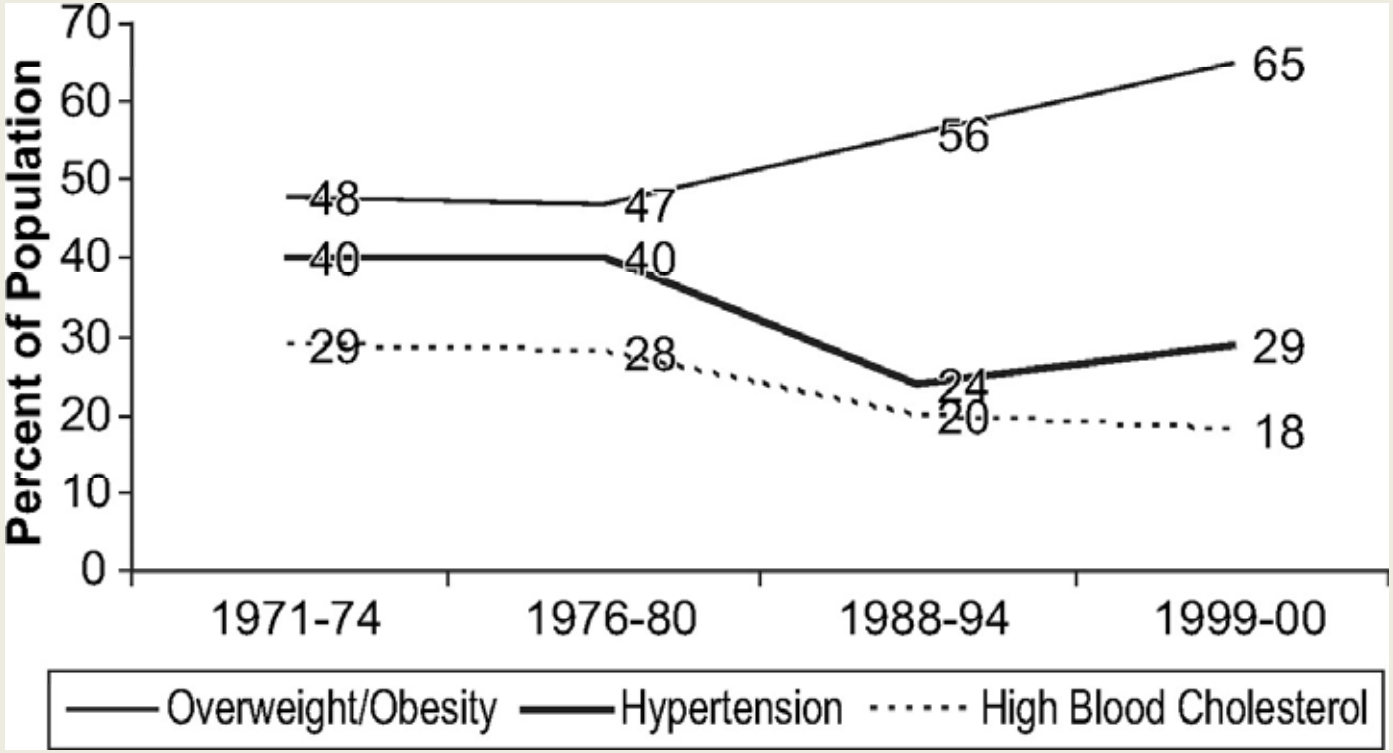
Obesity

- Diet
- Portion size
- Physical Activity
- Genes

Ob/ob mouse from “Nutritional Science”

- Fat as an endocrine tissue
  - Makes leptin – lowered desire to eat, more use of stored fat
  - Makes inflammatory signaling molecules
  - Decreases synthesis of signals that in turn cause a decrease in blood pressure – with the result being increased blood pressure

Chart 2-1 Trends in the age-adjusted prevalence of health conditions US adults ages 20 to 74



Rosamond, W. et al. Circulation 2007;115:e69-e171

Circulation

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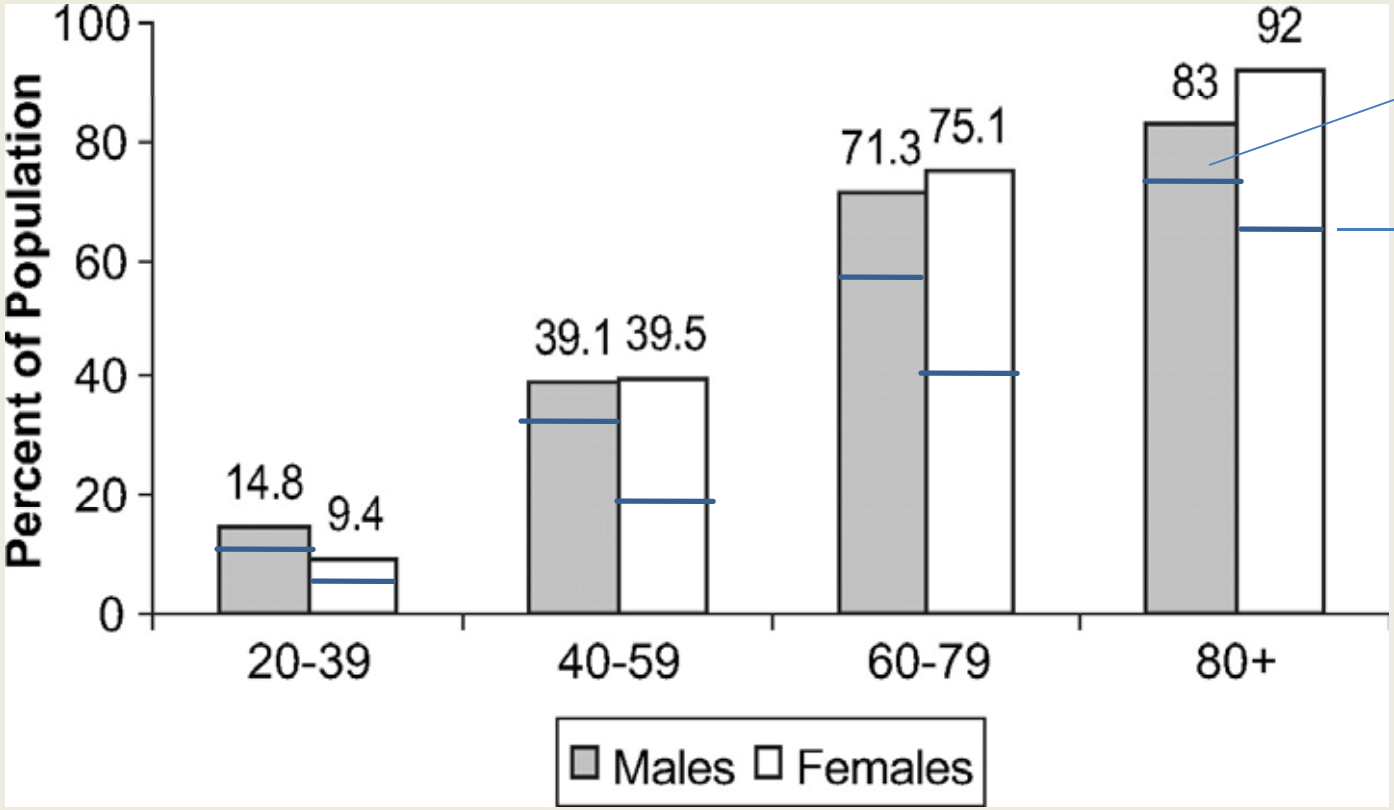
Chart 2-2. Prevalence of CVDs in adults age 20 and older by age and sex. (1999-2004)



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Circulation

http://circ.ahajournals.org/cgi/content/full/119/3/e21/FIG2191262

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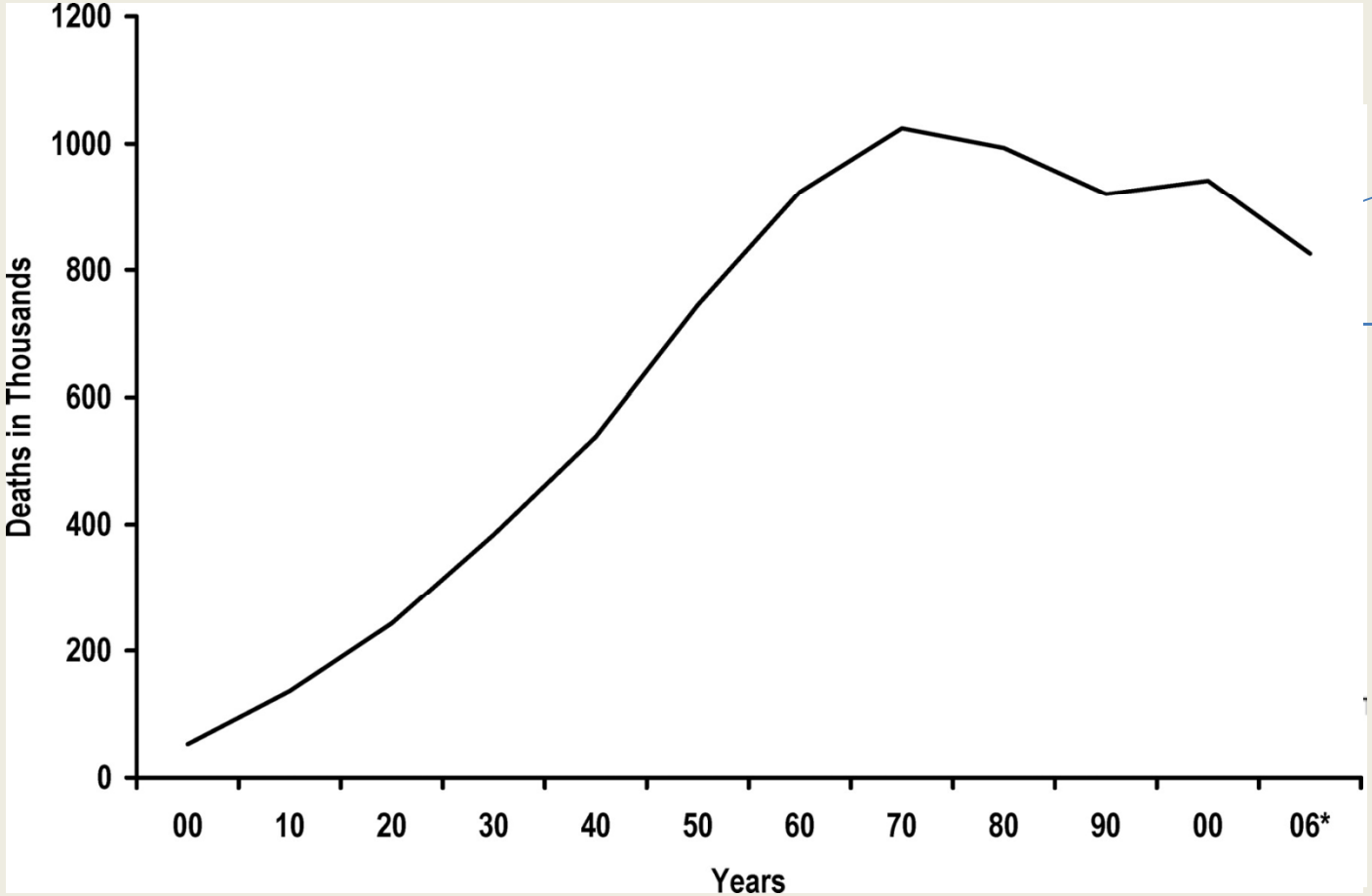

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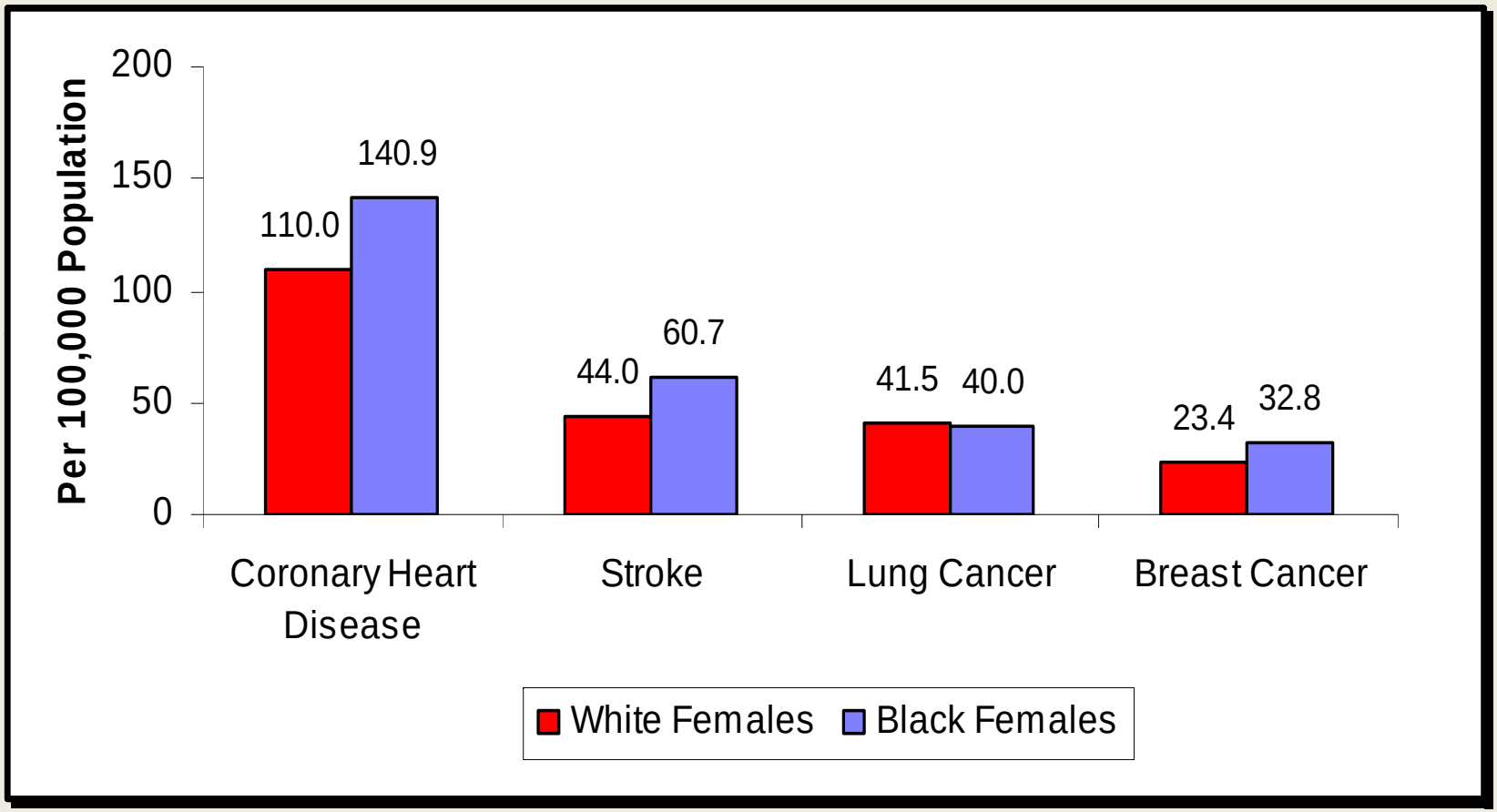
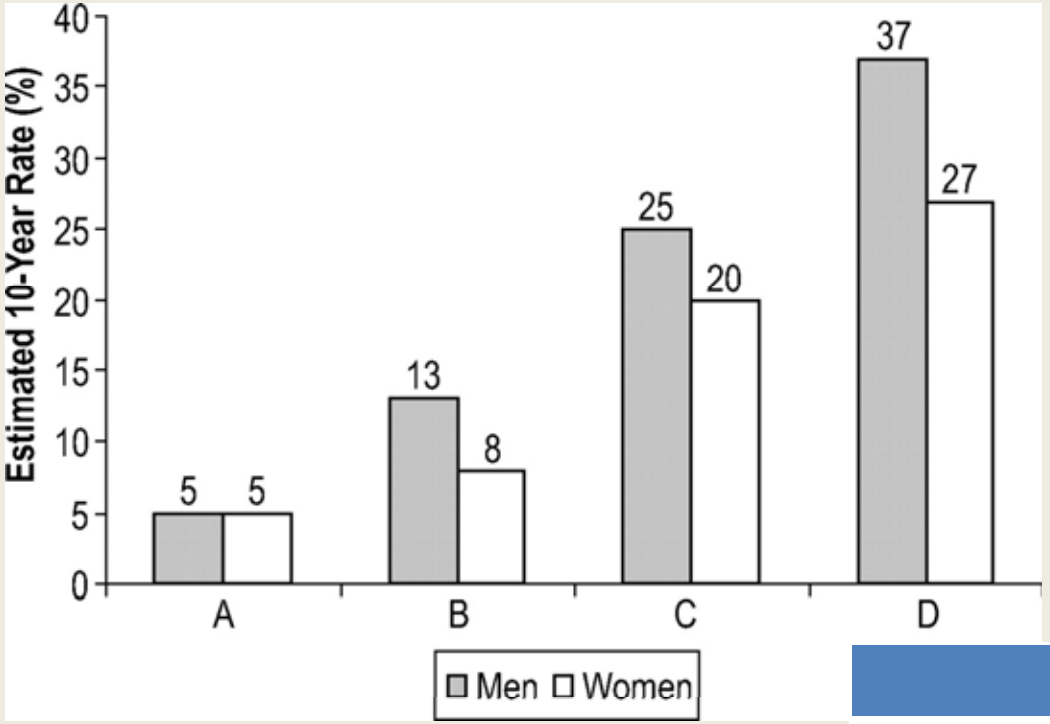


Age-adjusted death rates for CHD, stroke, lung and breast cancer for white and black females (United States: 2005).

Source: NCHS and NHLBI.

Chart 3-6. Ten year risk for CHD by risk factors



Statins

Rosamond, W. et al.
Circulation 2007;115:e69-e171

	A	B	C	D
BP, mm HG	120/ 80	140/ 90	140/ 90	140/ 90
mg/dL, Total Cholesterol	200	240	240	240
Mg/dL HDL cholesterol	50	50	40	40
Diabetes	No	No	Yes	Yes
Cigarettes	No	No	No	Yes

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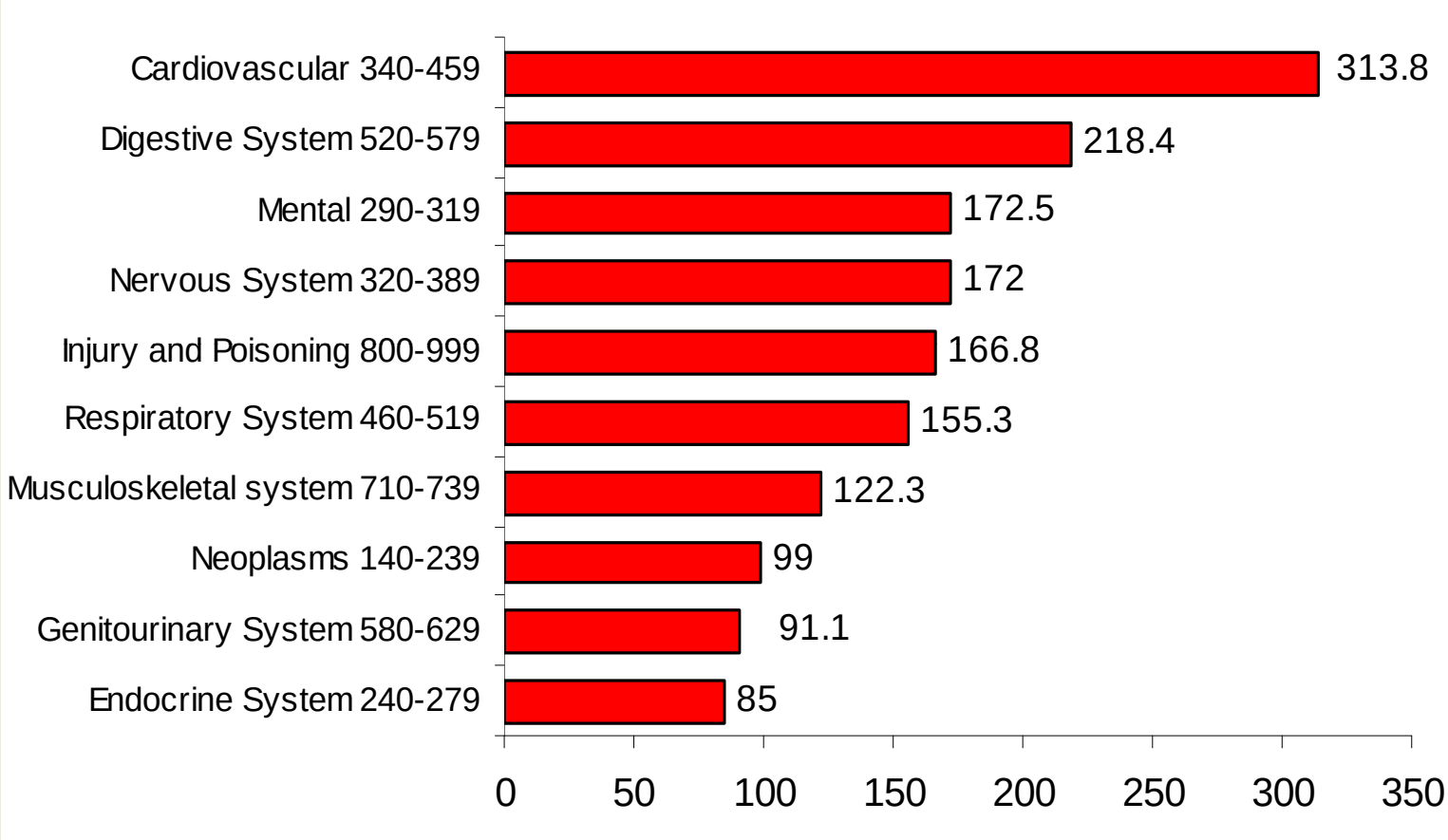
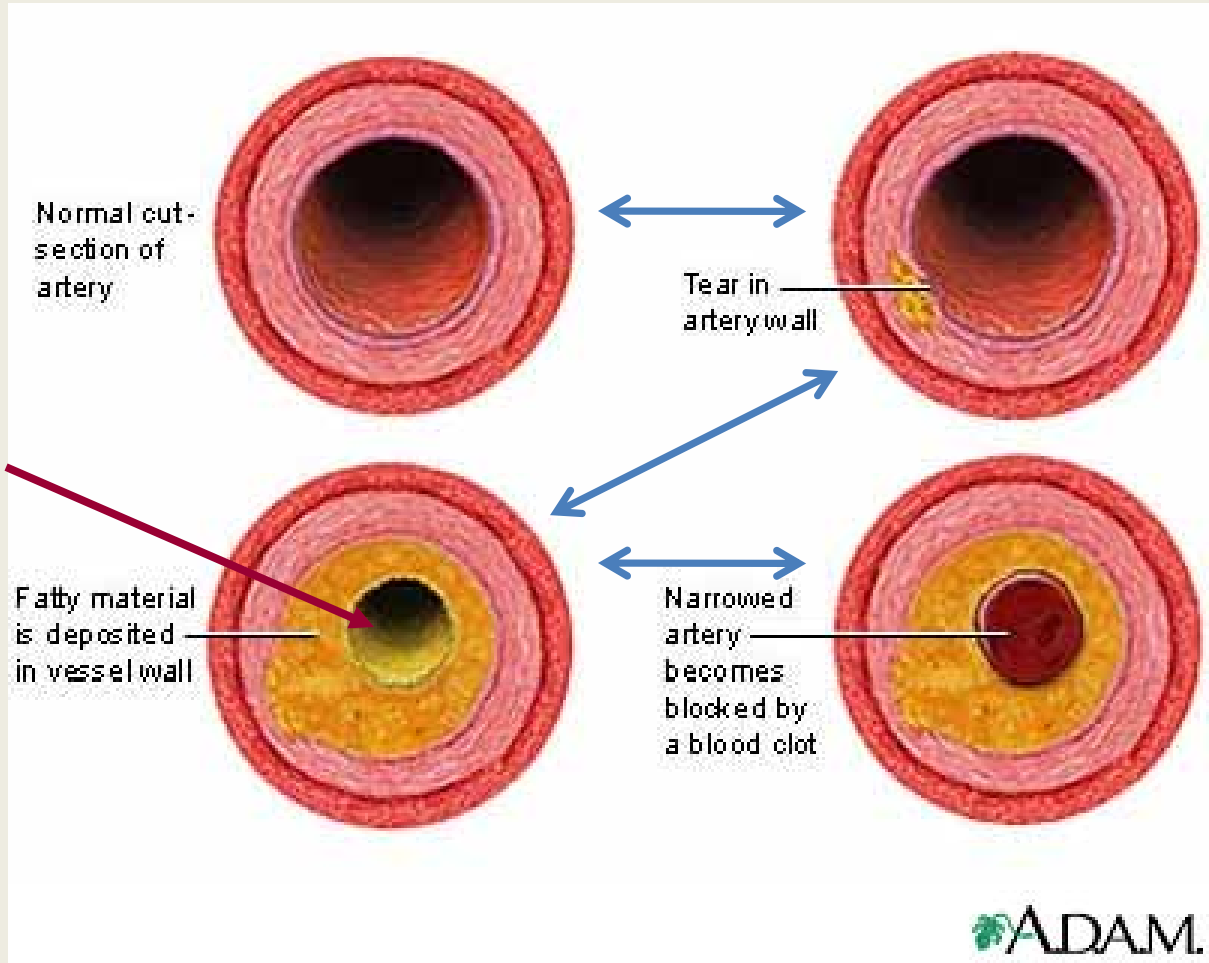


Direct Costs (Billions of dollars) of the 10 Leading Diagnostic Groups (United States: 2009). Source: NHLBI.

Recommendations

- Limit your saturated fat intake (trans fat too)
- Consume less than 200 (300) mg/day cholesterol
- Eat fish regularly
- Limit your salt intake (less than 2300 mg/day)
- Consume vegetables and whole grains
- Diet options for lowering cholesterol
    - Plant sterols and/or soluble fiber
- Eat only enough calories to maintain weight (or reach a healthy weight)
- At least 30 min of moderate physical activity/day
- http://www.americanheart.org/presenter.jhtml?identifier=851

Progression of Vascular Disease



Statins

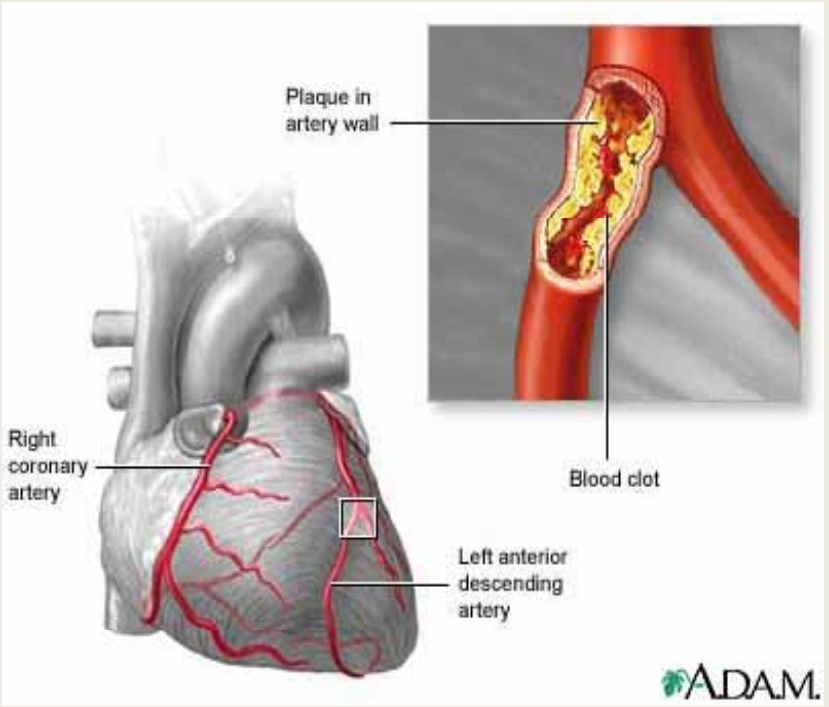
Stent

Aspirin

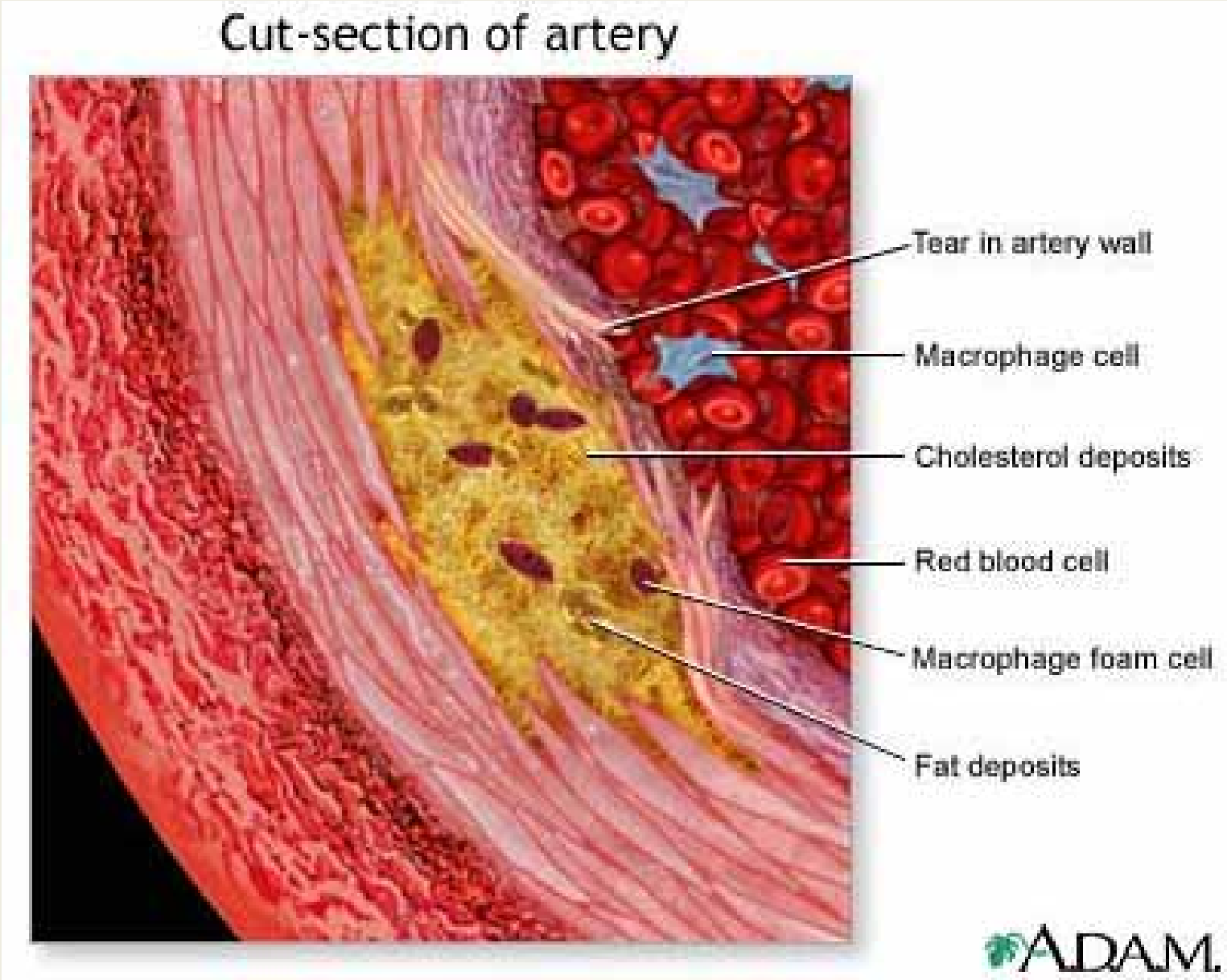
MedlinePlus Medical Encyclopedia

Atherosclerosis

- Leads to narrowing/ blocking of arteries
  - Blocked flow to the heart
    - Myocardial Infarction (heart attack)
  - Blocked flow to the brain
    - Ischemic Stroke

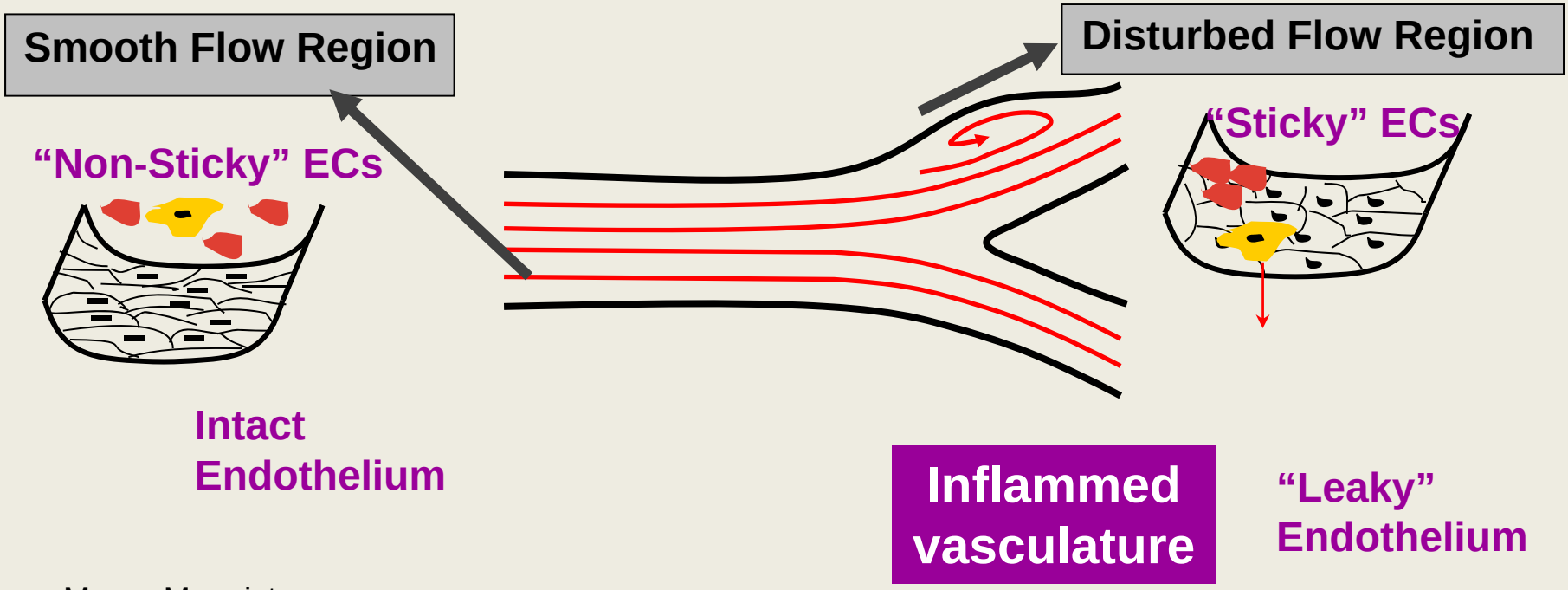


Bypass



MedlinePlus Medical Encyclopedia

Atherosclerosis is Geometrically Focal

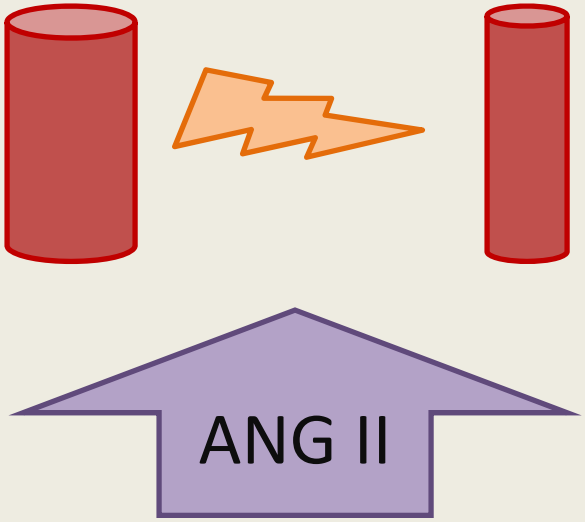


Meron Mengistu

Flow, along with other factors, contributes to risk.

Contraction of blood vessels

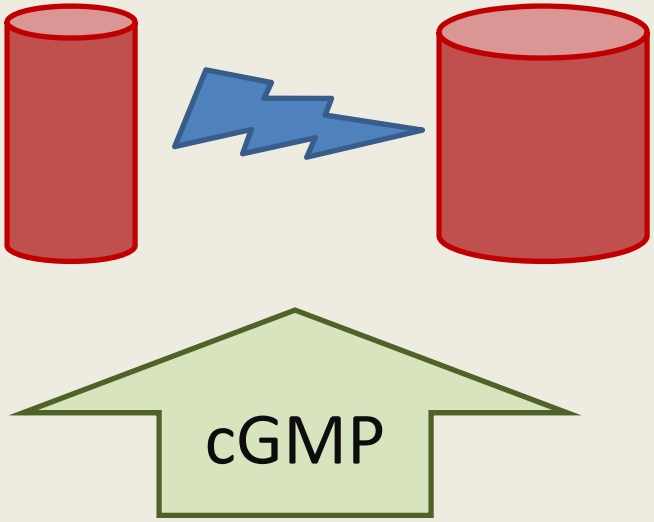
- Angiotensin is a major contraction signal that increases blood pressure transiently



Diuretics,
Ace inhibitors,
β-blockers,
Calcium channel blockers

Relaxation of blood vessels

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



Nitroglycerin

- But cGMP is typically rapidly degraded by proteins called PDEs

- PDE3 is primarily in cardiac muscle
- PDE6 is primarily in the retinas
- PDE5 is primarily in vascular smooth muscle

Sildenafil citrate

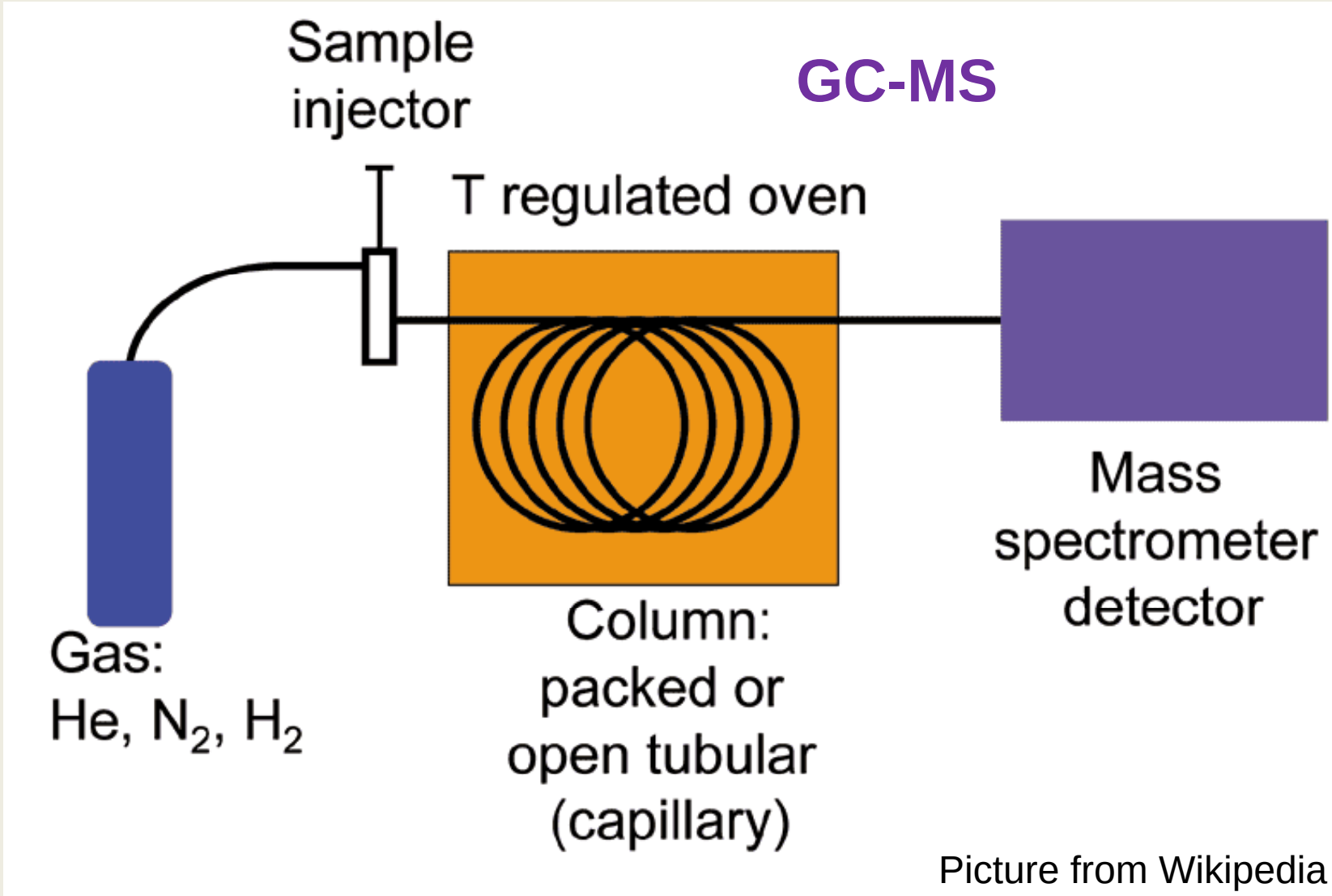
- Blocks PDE5 80 to 4000 times more effectively than it blocks other PDE isoforms (except PDE6)
- Therefore in vascular smooth muscle cells cGMP remains elevated longer.

- Viagra is a trade name for sildenafil citrate

Statins and complications?

- Some individuals do not tolerate statins well, and they sometimes develop myopathy.
- How can we detect this early?
- Searching for a marker.
- "omics"
  - Genomics (transcriptomics)
  - Proteomics
  - Metabolomics
    - Examining metabolic products and/or intermediates

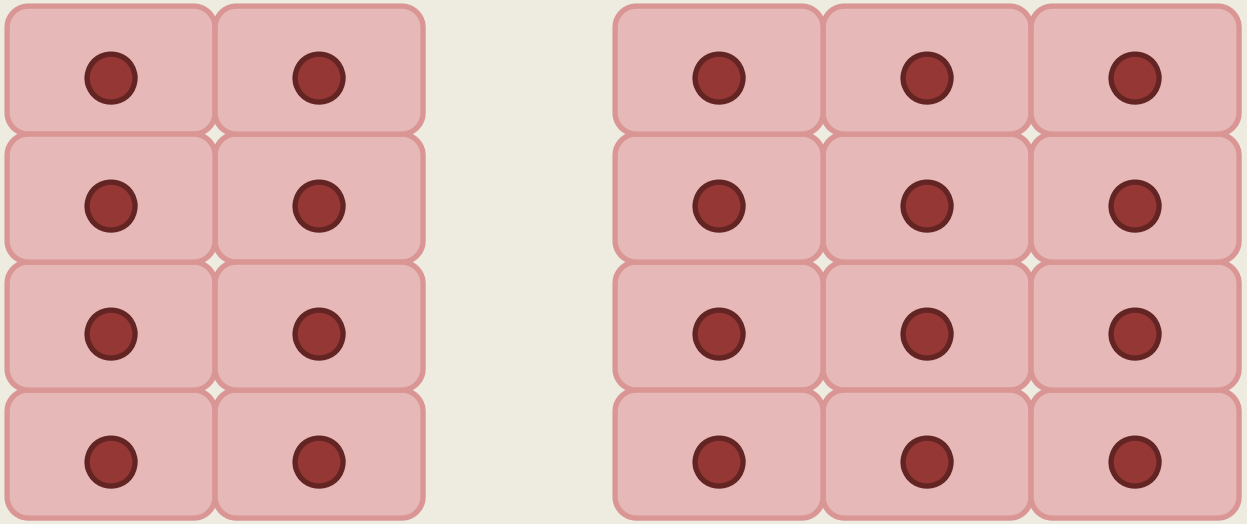
Identifying possible markers



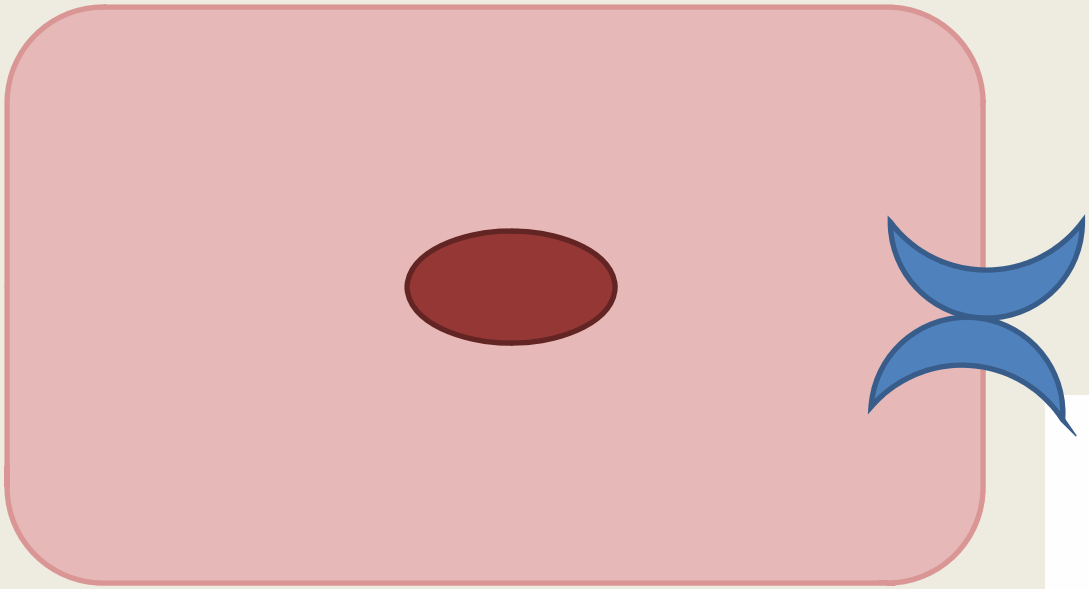
Picture from Wikipedia

Cell proliferation and wound repair

- Lack of contact, damaging chemicals, etc.
- Growth factors, Angiotensin
- Immune system

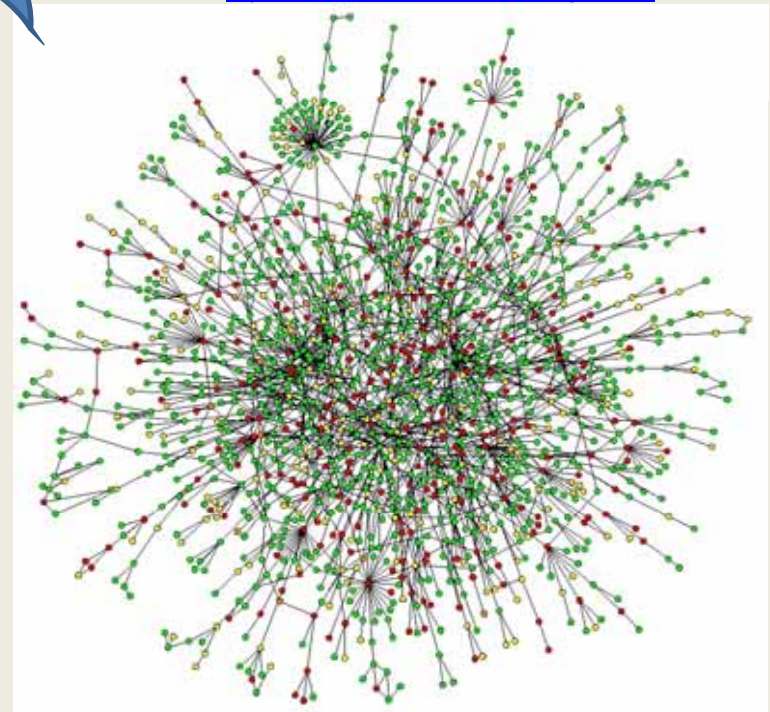


Finding a player (protein)

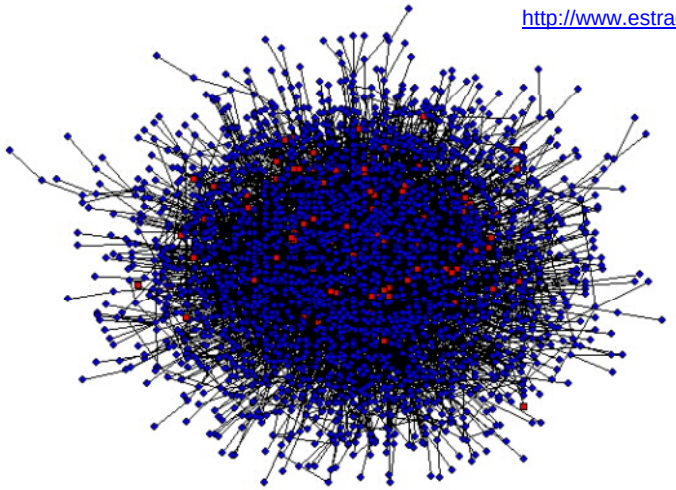


The human genome has only about 23,000 protein-encoding genes; it seems like the search should be possible, if not easy.

http://www.bordalierinstitute.com/target1.html



http://www.estradalab.org/research/index.html



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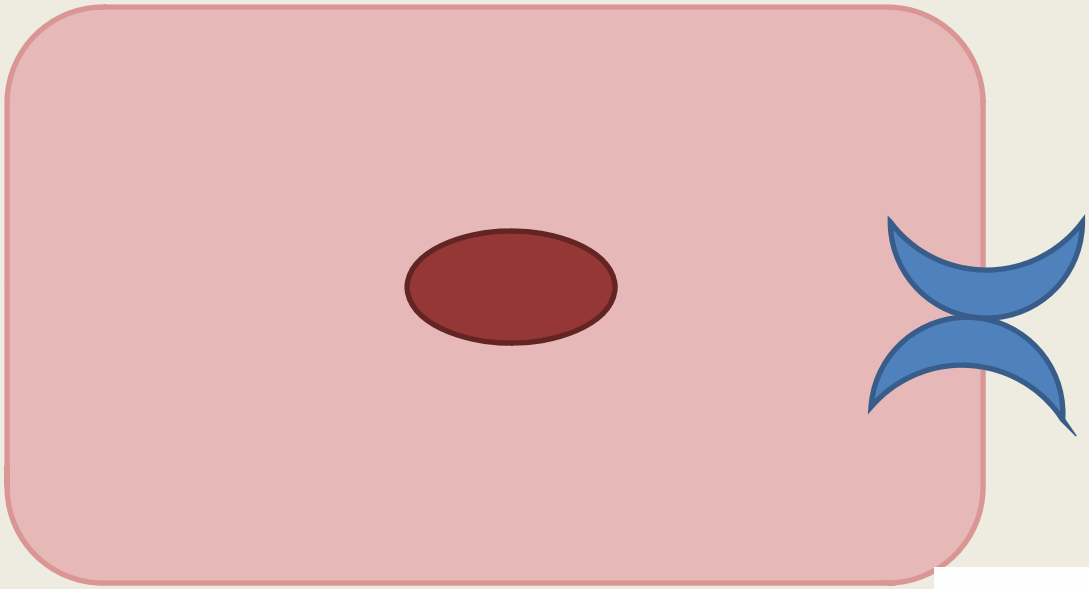
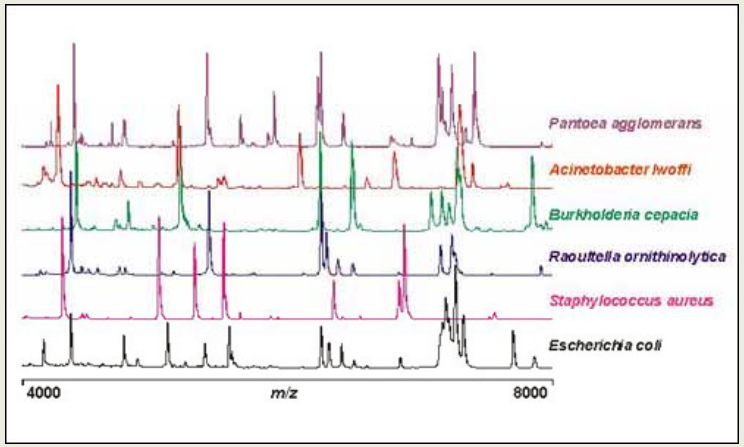
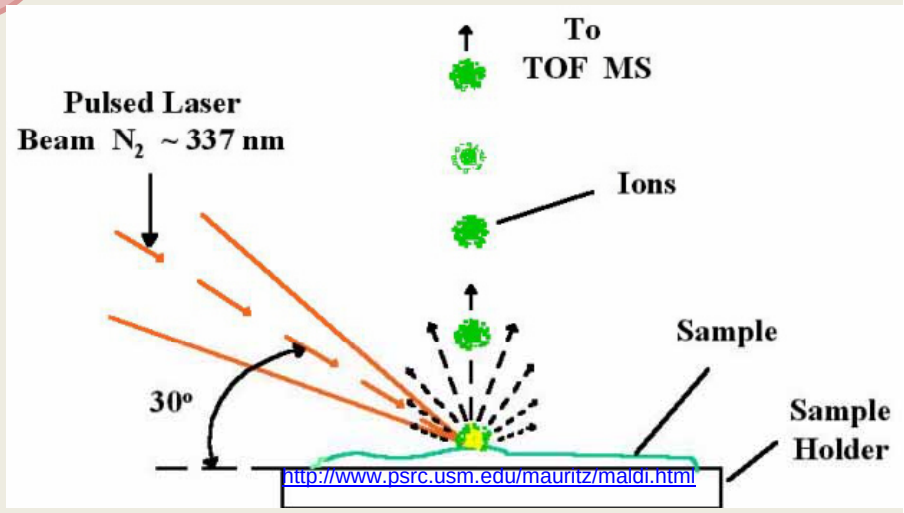


Matrix-assisted laser desorption/ionization Mass Spectrometry, a technique sometimes used to characterize and/or identify proteins



http://www.pharmaceutical-technology.com/contractors/imaging-analysis/anagnostec/anagnostec2.html



http://www.psrc.usm.edu/mauritz/maldi.html

What can you know about the protein you identify?

AGACYSSTRKGQN…..

- Sequence of the protein – gene source
- Location
- Structure
- Function
- Amounts present