

Cardiovascular disease, studies at the cellular and molecular level

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Bioscience in the 21st Century

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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



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

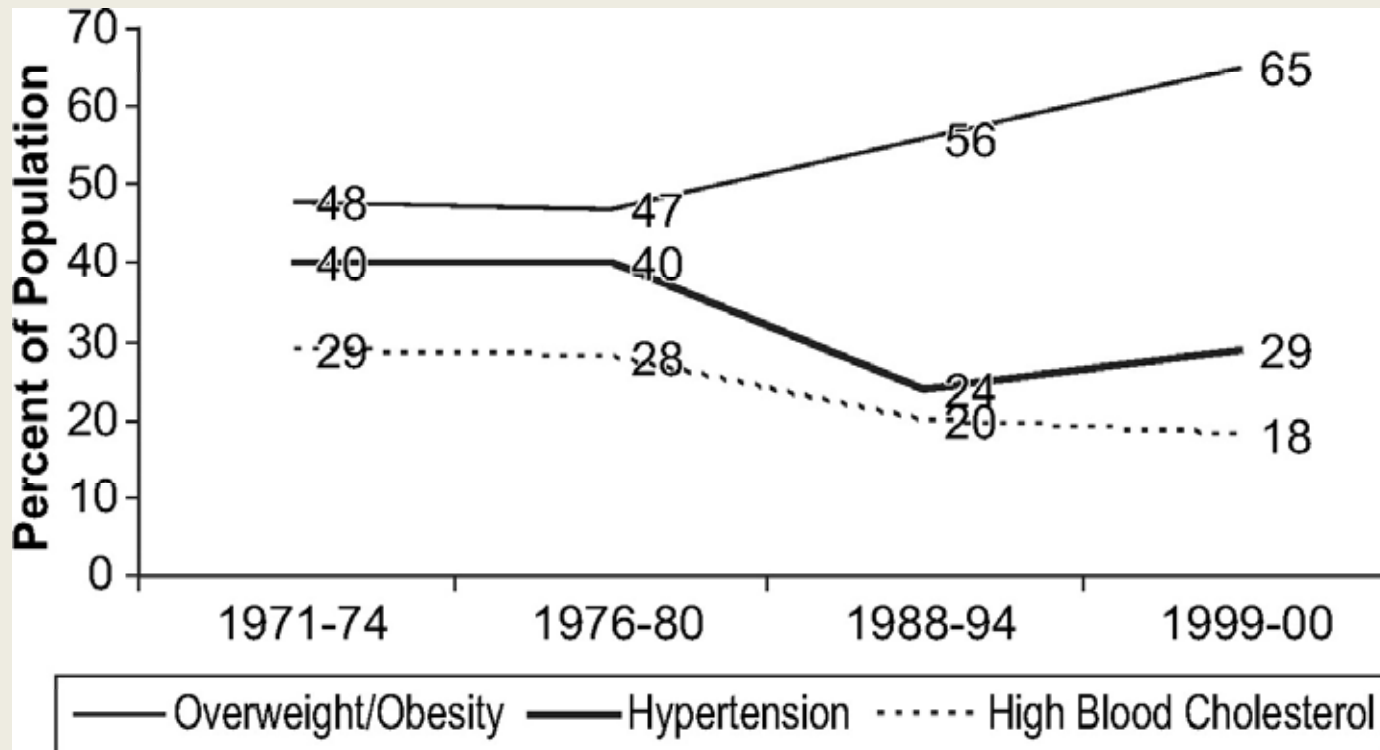
- Diet
- Portion size
- Physical Activity
- Genes



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**

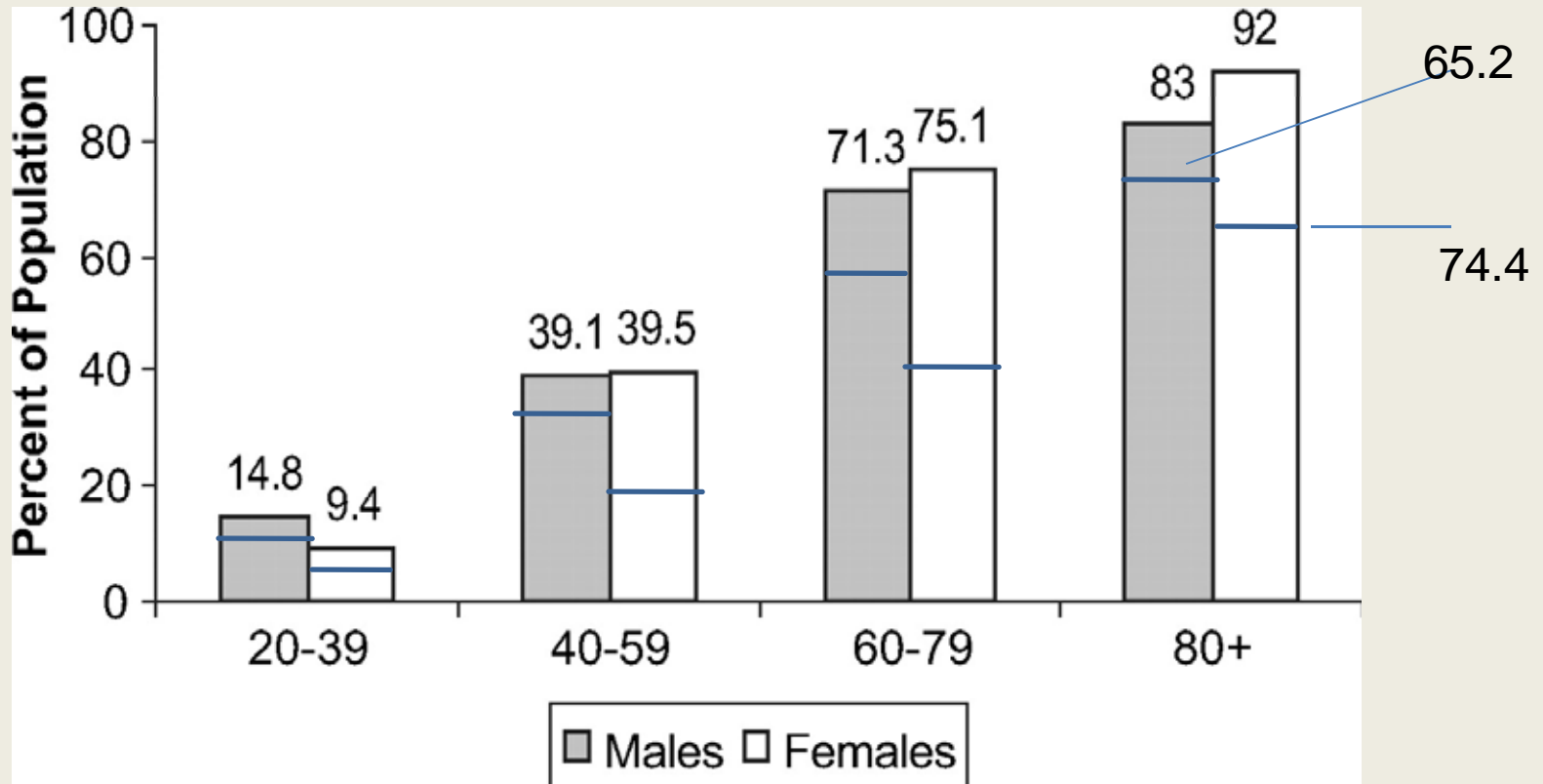


Rosamond, W. et al. *Circulation* 2007;115:e69-e171

Circulation



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



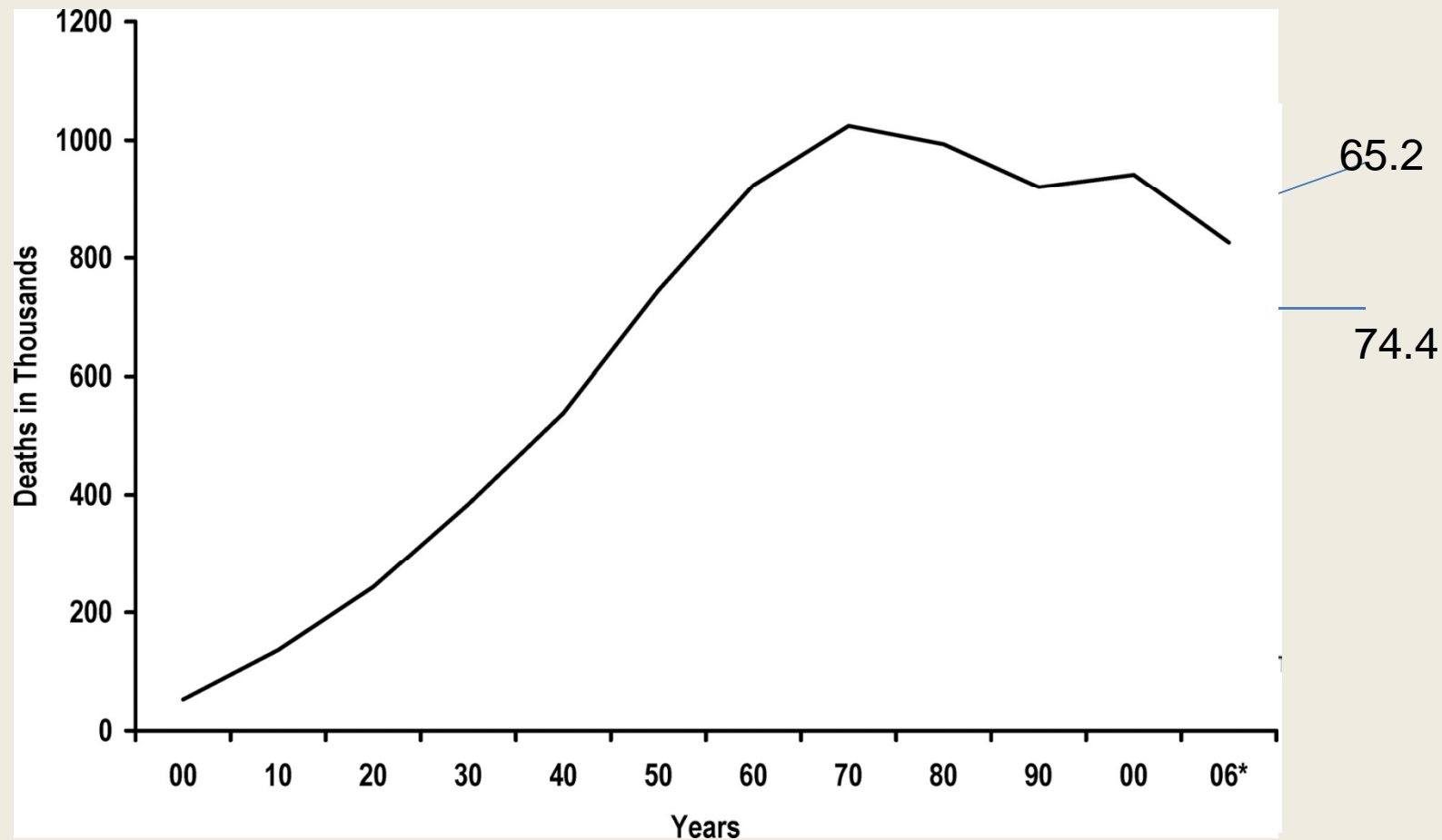
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Circulation

<http://circ.ahajournals.org/cgi/content/full/115/3/e21/FIG2191262>



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

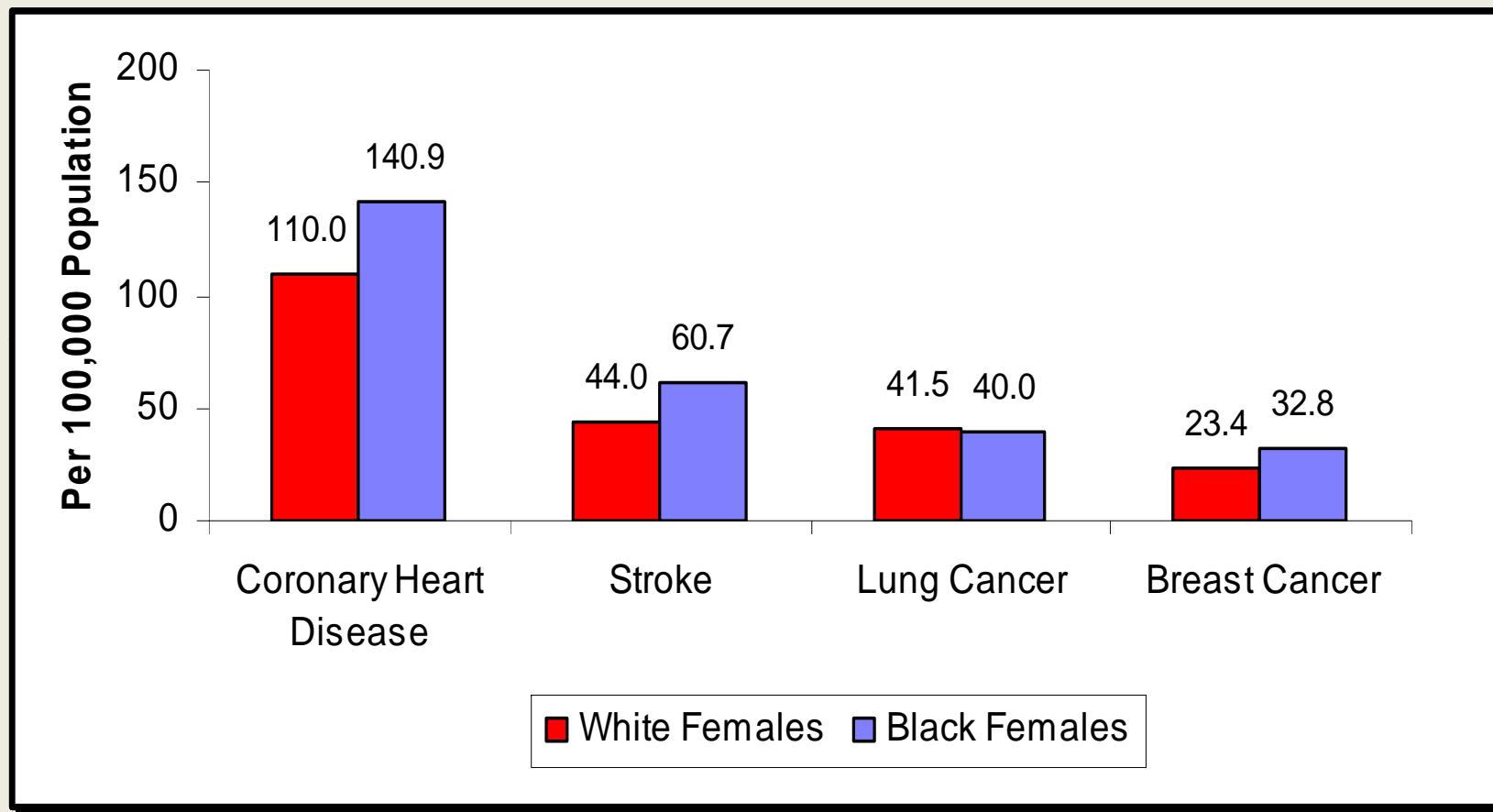


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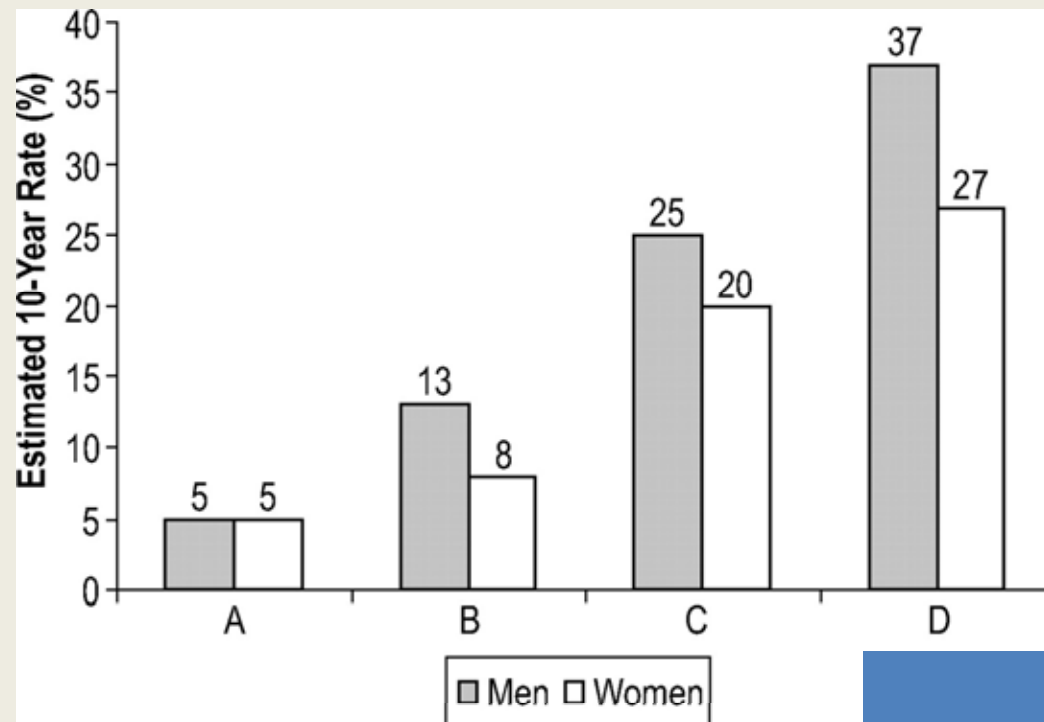




Age-adjusted death rates for CHD, stroke, lung and breast cancer for white and black females (United States: 2005).

Source: NCHS and NHLBI.

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



Statins

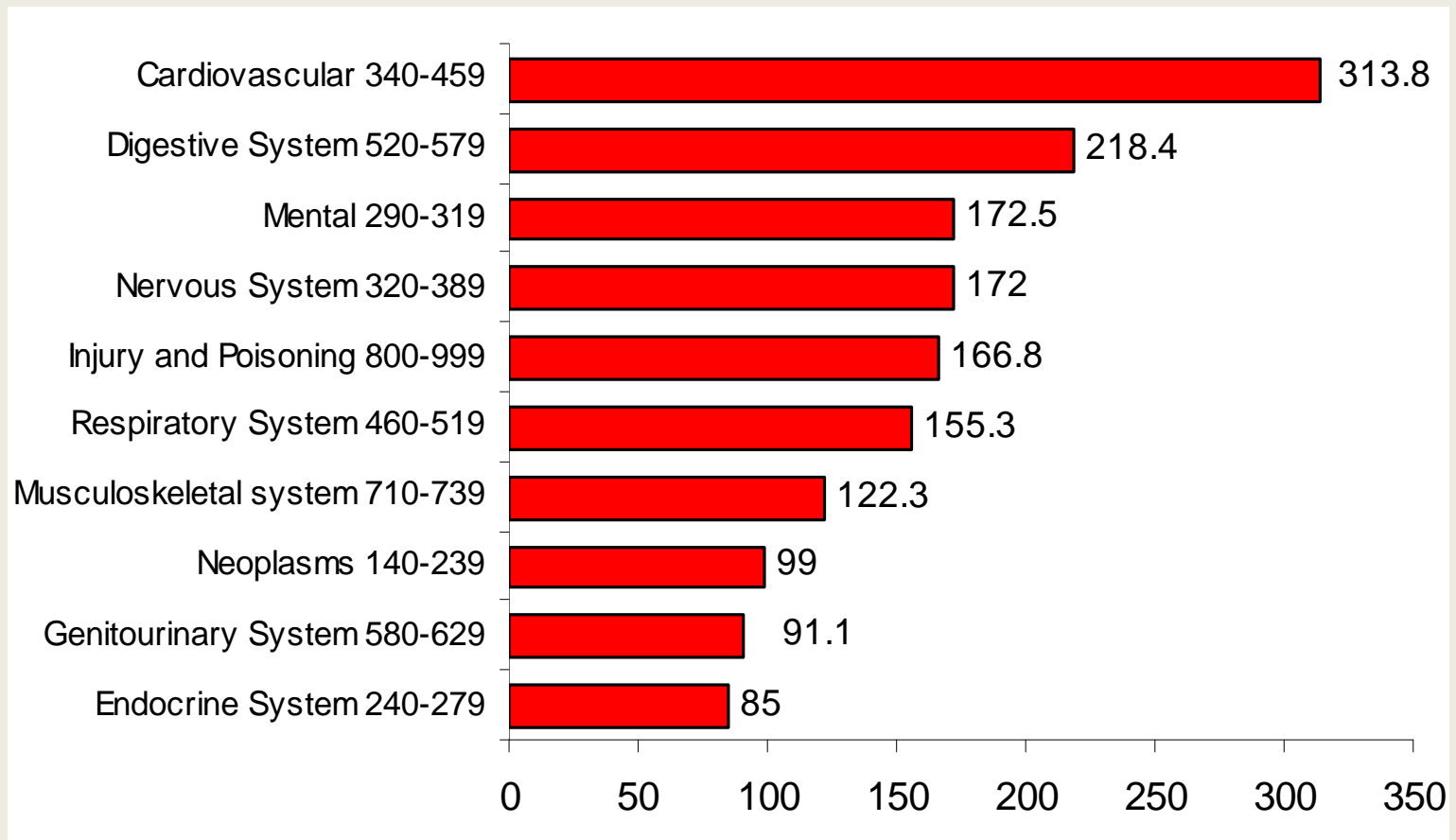
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Circulation

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	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

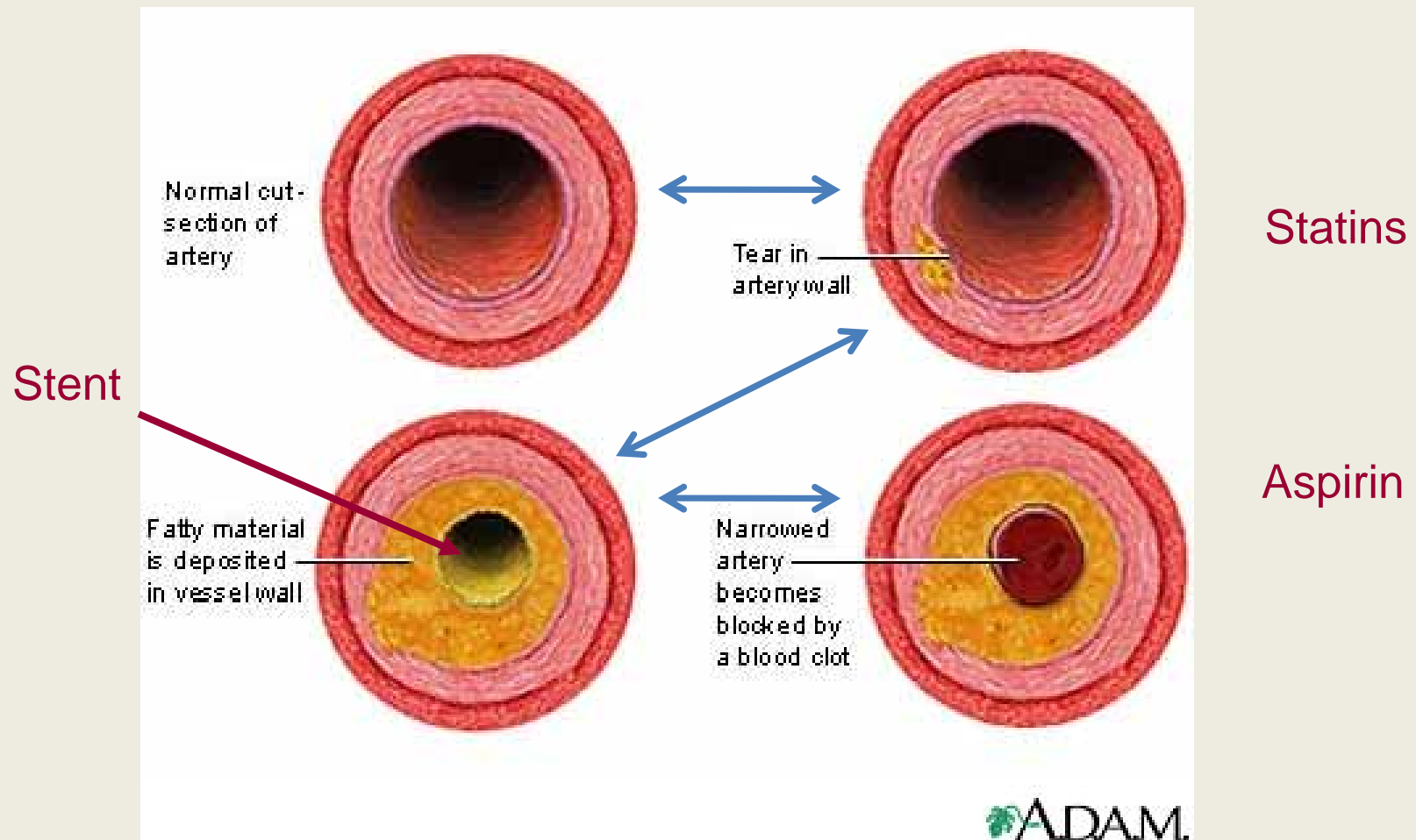


Direct Costs (Billions of dollars) of the 10 Leading Diagnostic Groups (United States: 2009). Source: NHLBI.

Recommendations

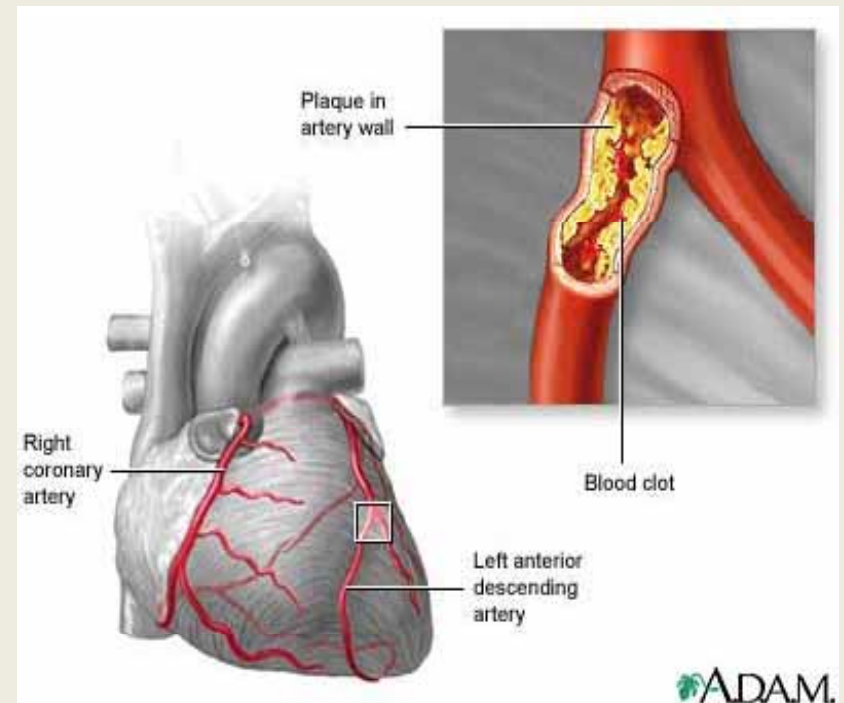
- Limit your saturated fat intake (trans fat too)
- Consume less than 200 (300) mg/day cholesterol
- Eat fish regularly
- Limit your salt intake (less than 2300 mg/day)
- Consume vegetables and whole grains
- Diet options for lowering cholesterol
 - Plant sterols and/or soluble fiber
- Eat only enough 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



Atherosclerosis

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



Bypass

Cut-section of artery



Tear in artery wall

Macrophage cell

Cholesterol deposits

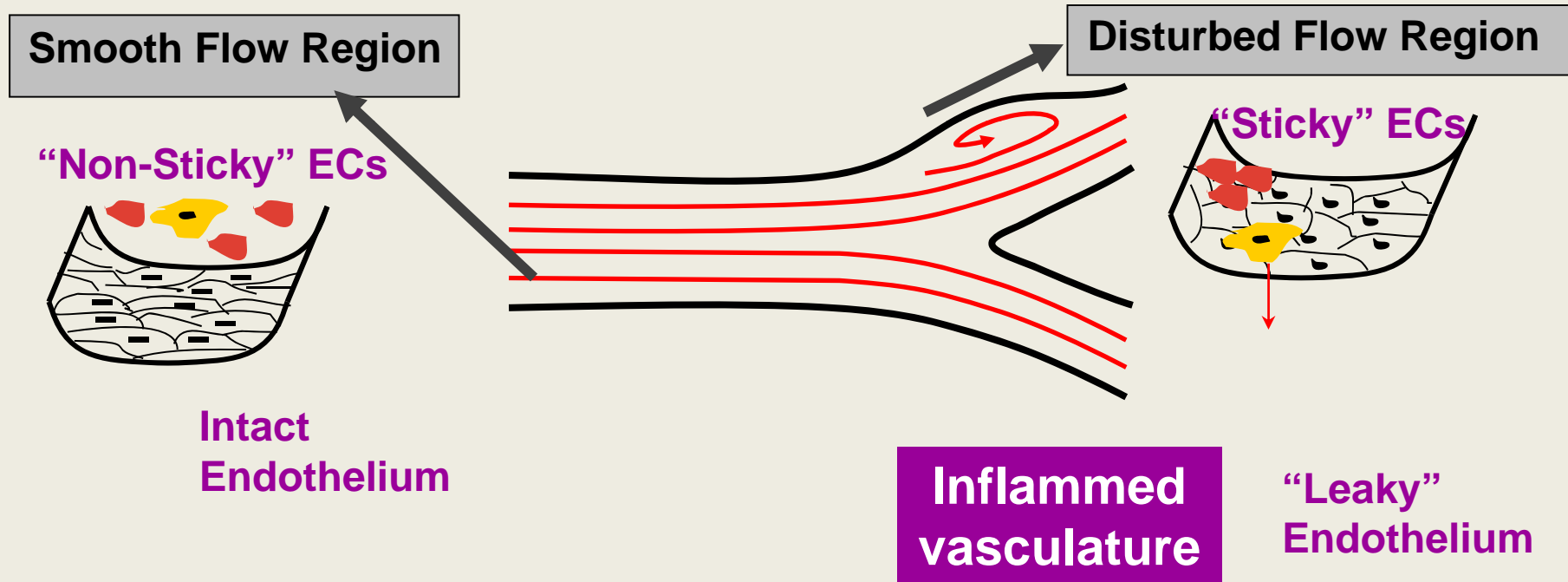
Red blood cell

Macrophage foam cell

Fat deposits

ADAM.

Atherosclerosis is Geometrically Focal

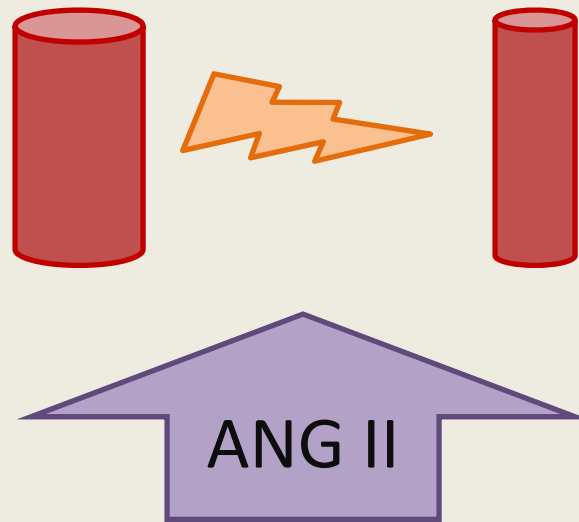


Meron Mengistu

Flow, along with other factors, contributes to risk.

Contraction of blood vessels

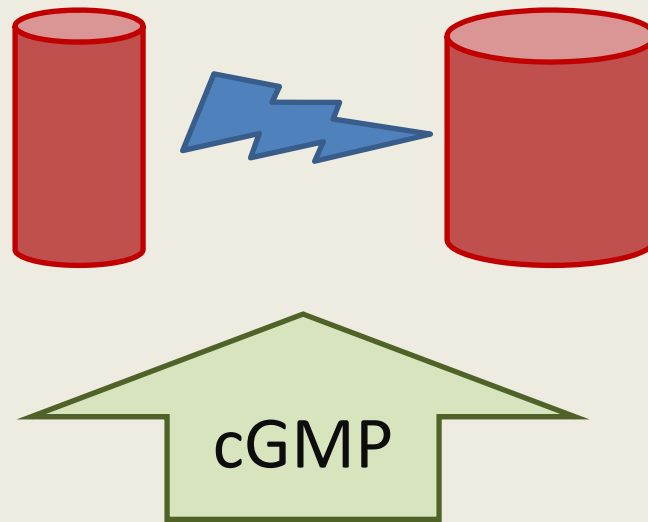
- Angiotensin is a major contraction signal that increases blood pressure transiently



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

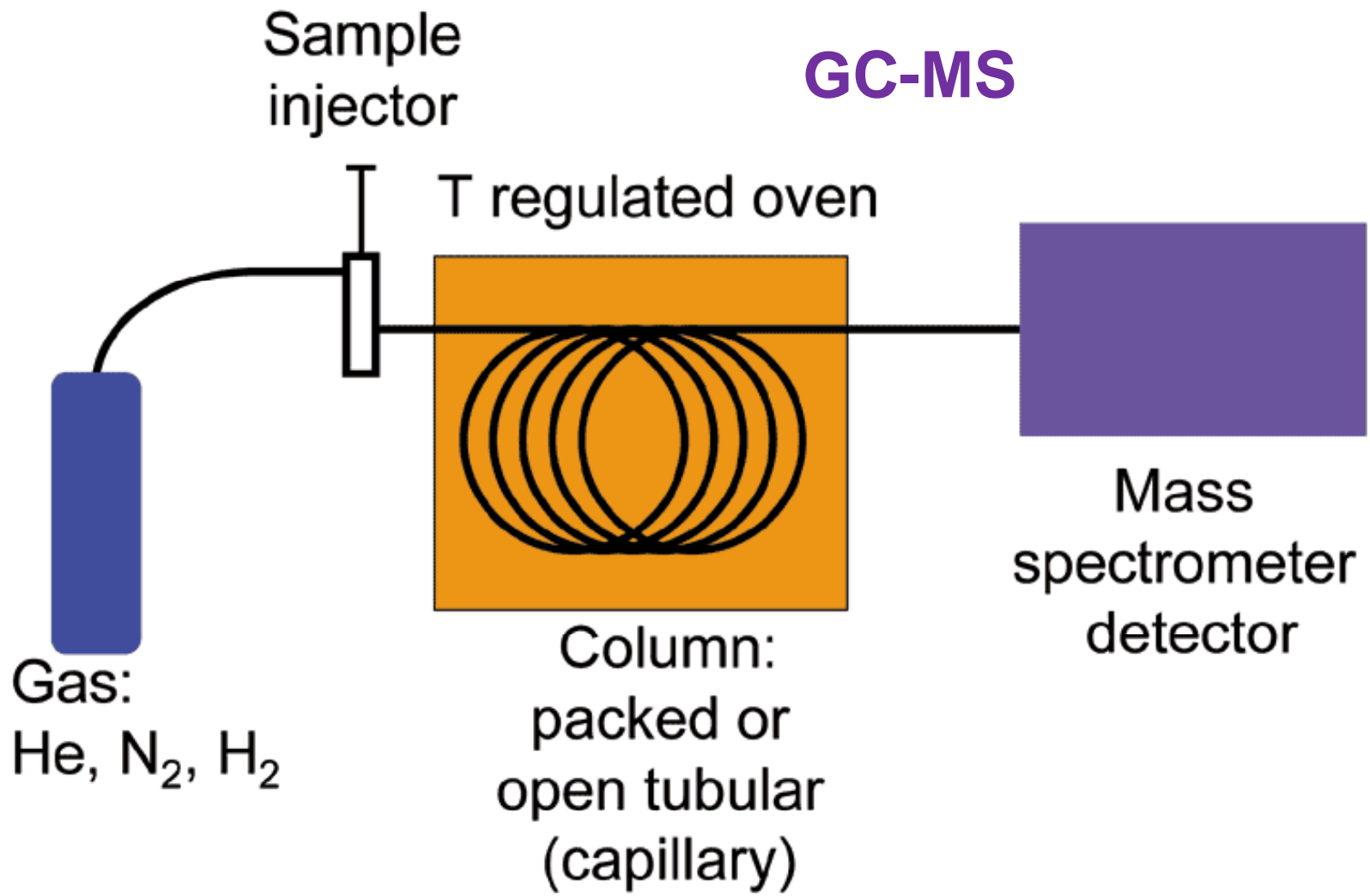
Sildenafil citrate

- 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

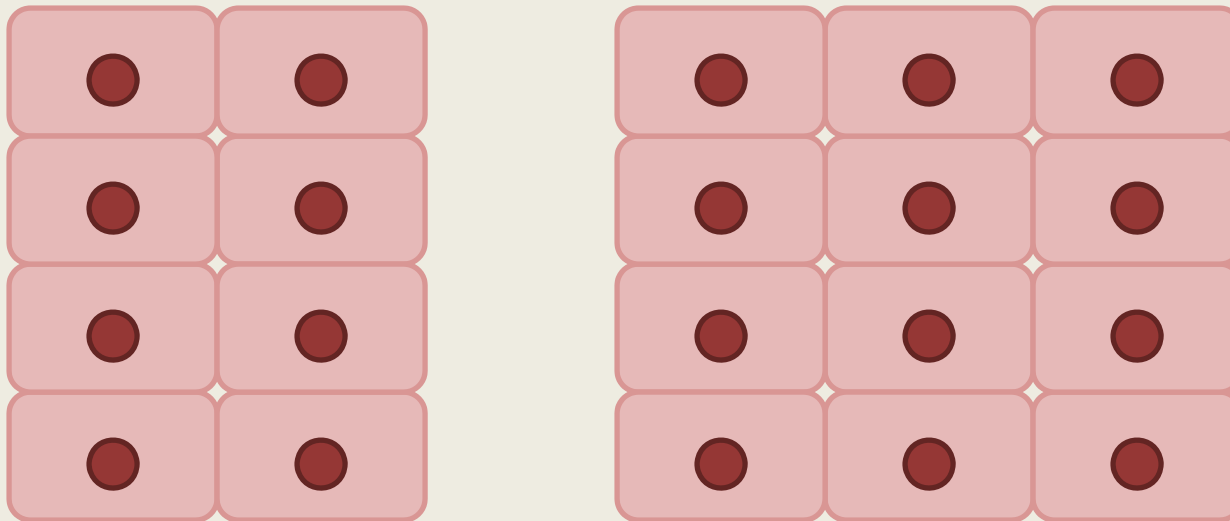
Identifying possible markers



Picture from Wikipedia

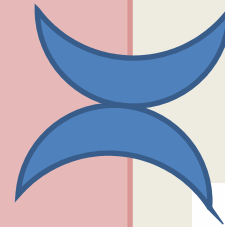
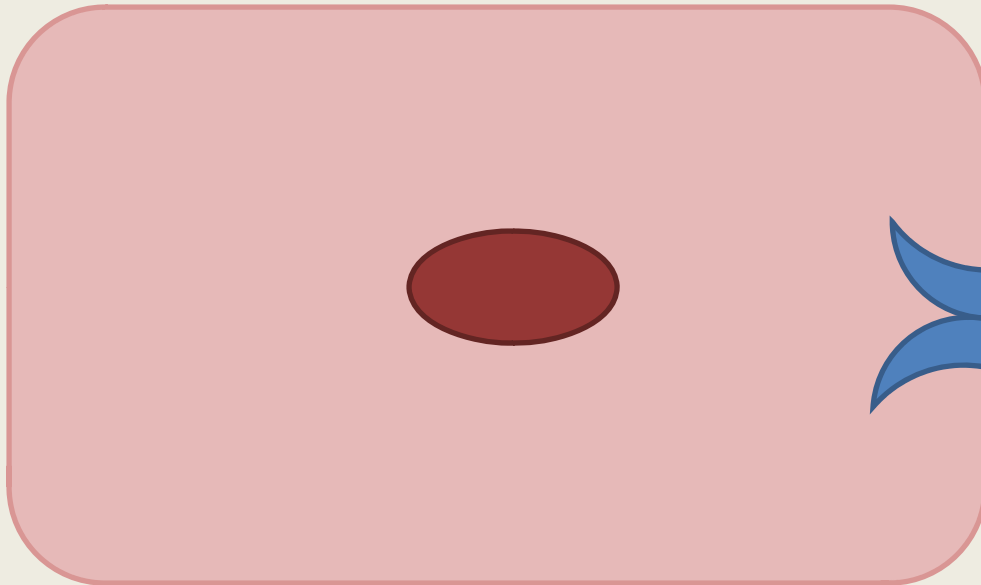
Cell proliferation and wound repair

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

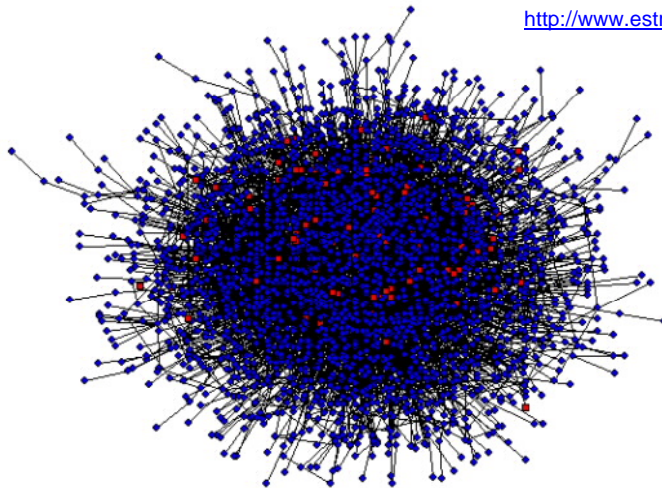


Finding a player (protein)

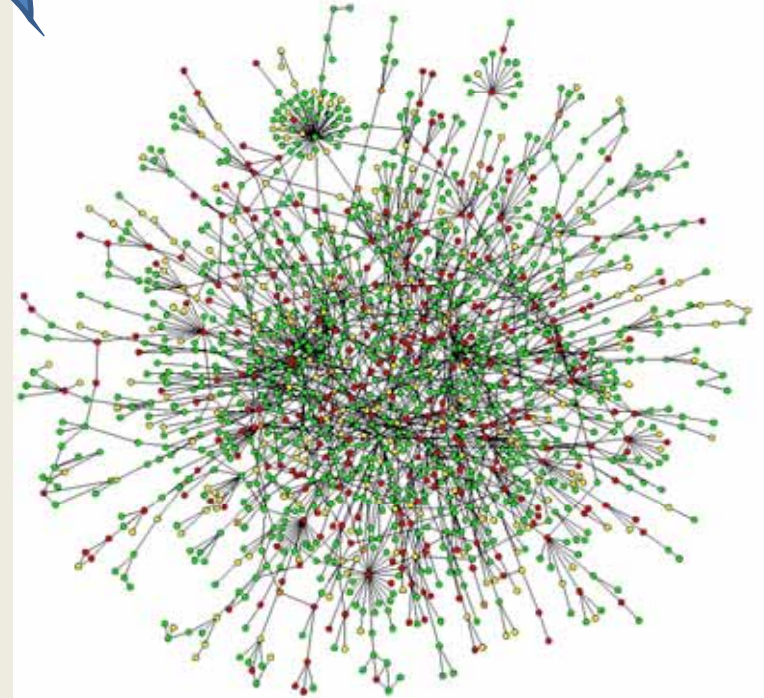
The human genome has only about 23,000 protein-encoding genes; it seems like the search should be possible, if not easy.



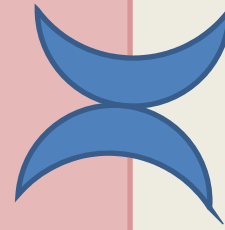
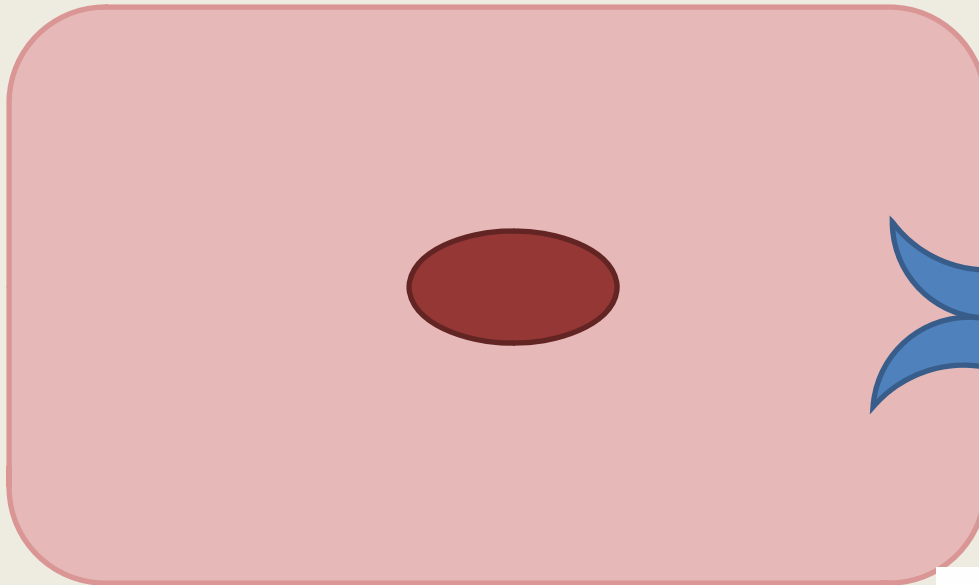
<http://www.bordalierinstitute.com/target1.html>



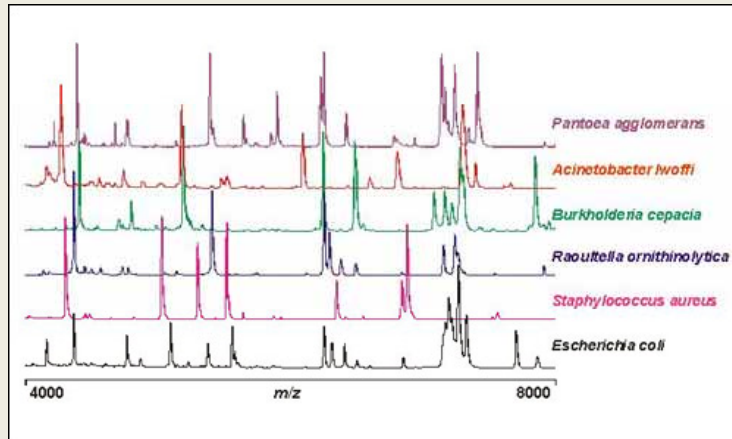
<http://www.estradalab.org/research/index.html>



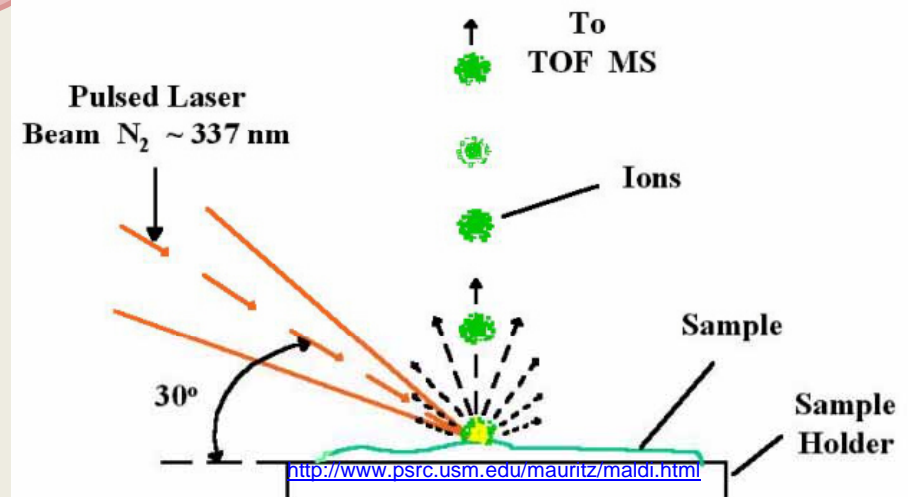
Finding a player (protein)



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>



What can you know about the protein you identify?

AGACYSSTRKGQN.....

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

