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)
• Serum cholesterol [aim for below 100 mg/dL LDL cholesterol and above 50 mg/dL HDL, or aim for total cholesterol below 200 mg/dL]
• 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)
- **Prothrombotic state** (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
- **Raised blood pressure** (130/85 mmHg or higher)
- **Proinflammatory state**
Obesity

- Diet
- Portion size
- Physical Activity
- Genes

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

Ob/ob mouse from “Nutritional Science”

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

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mm HG</td>
<td>120/80</td>
<td>140/90</td>
<td>140/90</td>
<td>140/90</td>
</tr>
<tr>
<td>mg/dL, Total Cholesterol</td>
<td>200</td>
<td>240</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Mg/dL HDL cholesterol</td>
<td>50</td>
<td>50</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Statins

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

In many western developed countries, deaths from coronary heart disease have decreased steadily as treatment options have improved, and as people have made lifestyle changes.
### Direct and Indirect Economic Costs of Illness by Major Diagnosis, U.S., 2010

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Direct Costs (Dollars in Billions)</th>
<th>Morbidity (Dollars in Billions)</th>
<th>Mortality (Dollars in Billions)</th>
<th>Total (Dollars in Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>$324.1</td>
<td>$41.7</td>
<td>$137.4</td>
<td>$503.2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>453.0</td>
<td>74.4</td>
<td>177.4</td>
<td>704.8</td>
</tr>
<tr>
<td>Diseases of the Digestive System</td>
<td>227.4</td>
<td>12.6</td>
<td>30.6</td>
<td>270.6</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>102.8</td>
<td>20.9</td>
<td>140.1</td>
<td>263.8</td>
</tr>
<tr>
<td>Mental Disorders</td>
<td>180.8</td>
<td>32.4</td>
<td>12.5</td>
<td>225.7</td>
</tr>
<tr>
<td>Diseases of the Nervous System</td>
<td>157.7</td>
<td>9.6</td>
<td>16.4</td>
<td>183.7</td>
</tr>
<tr>
<td>Total</td>
<td>2,176.6</td>
<td>244.9</td>
<td>679.3</td>
<td>3,100.8</td>
</tr>
</tbody>
</table>

**NHLBI numbers:** Categories above $100 billion are listed

**Source:** Estimates by NHLBI; data from the NCHS, the CMS, the Bureau of the Census, and the Institute for Health and Aging, University of California.
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
Progression of Vascular Disease

- Stent
- Aspirin
- Statins

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
Atherosclerosis is geometrically focal.

Smooth Flow Region

Intact Endothelium

“Non-Sticky” ECs

Disturbed Flow Region

Inflamed vasculature

“Sticky” ECs

“Leaky” Endothelium

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
• But cGMP is typically rapidly degraded by proteins called PDEs

\[
\text{cGMP} \rightarrow \text{GMP}
\]

• 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

GC-MS

Sample injector

T regulated oven

Column: packed or open tubular (capillary)

Mass spectrometer detector

Gas: He, N₂, H₂

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.estradalab.org/research/index.html

Human protein interaction network

Yeast protein interaction network

http://www.bordalierinstitute.com/target1.html
Finding a player (protein)

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

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

http://www.pharmaceutical-technology.com/contractors/imaging-analysis/anagnostec/anagnostec2.html
What can you know about the protein you identify?

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

AGACYSSTRKGQN...