Etiology of Chronic Diseases

- Complex Diseases
- Genes and Environment Initiative
## Top 10 Causes of Mortality in 2003

<table>
<thead>
<tr>
<th>Cause</th>
<th>Death Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>232</td>
</tr>
<tr>
<td>Cancer</td>
<td>190</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>54</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>43</td>
</tr>
<tr>
<td>Injuries</td>
<td>37</td>
</tr>
<tr>
<td>Diabetes</td>
<td>25</td>
</tr>
<tr>
<td>Influenza and pneumonia</td>
<td>22</td>
</tr>
<tr>
<td>Suicide</td>
<td>11</td>
</tr>
<tr>
<td>Chronic liver disease/cirrhosis</td>
<td>9</td>
</tr>
<tr>
<td>Homicide</td>
<td>6</td>
</tr>
</tbody>
</table>

CDC: NCHS. DHHS Pub No. 2005-1232
Etiology of Chronic Human Diseases

- 70-90% of the major diseases in the USA are caused by reversible behaviors and exposures
- Single gene mutations are the major cause of cancers and CVD in < 5% of the cases

Willett. *Science* 2002;296:695
Scientific Challenges and Opportunities

Complex Human Diseases

- Acute and chronic lung diseases
- Neurodegenerative conditions
- Reproductive disorders
- Several types of cancer
- Metabolic disorders - obesity
- Immune mediated diseases
Use Environmental Sciences to Understand Human Biology and Human Diseases

Complex Human Disease

Unique Exposures

Gene - Environment - Disease Phenotype
Exposures Can Simplify Complex Diseases

- Asthma
- House Dust Mite
- Biological Phenotype

- Asthma
- Ozone
- Biological Phenotype

- Asthma
- Endotoxin
- Biological Phenotype
Polymorphisms in *TLR4* blunt the response to inhaled LPS in humans

Brian Schutte et al.

Polymorphisms in *TLR4* protect humans from atherosclerosis

Steven Kiechl et al.
Genes and Environment Initiative

EXPOSURE BIOLOGY PROGRAM

$88M

- Develop technology and biomarkers
  - Diet
  - Physical Activity
  - Environmental Exposures
  - Psychosocial Stress and Addictive Substances

GENETICS PROGRAM

$104M

- Identify genetic variants
  - GWA Studies
  - Data Analysis
  - Replication
  - Sequencing
  - Database
  - Function
  - Translation
Genome-Wide Association to Clinical Translation

- Initial Genome-Wide Association (GWA) Studies
- Replication/Fine Mapping
- Sequencing/Genotyping
- Functional Studies
- Translational Studies
International HapMap Project

www.hapmap.org
Are the SNPs correlated with their neighbors?
These three SNPs could theoretically occur in 8 different haplotypes

...C...A...A...
...C...A...G...
...C...C...A...
...C...C...G...
...T...A...A...
...T...A...G...
...T...C...A...
...T...C...G...
But in practice, only two are observed

...C...A...A...
...C...A...G...
...C...C...A...
...C...C...G...
...T...A...A...
...T...A...G...
...T...C...A...
...T...C...G...
Pre-HapMap
- 10 million SNPs
- 1000 cases/1000 controls
- 20 billion genotypes
- 50 cents/genotype
- $10 billion/disease

Post-HapMap
- 300,000 tag SNPs
- 1000 cases/1000 controls
- 600 million genotypes
- 0.3 cents/genotype
- $2 million/disease

5000 fold decrease in cost
Genes and Environment Initiative: Exposure Biology Program

EXPOSURE BIOLOGY PROGRAM

- Develop technology and biomarkers
  - Diet
  - Physical Activity
  - Environmental Exposures
  - Psychosocial Stress and Addictive Substances

GENETICS PROGRAM

- Identify genetic variants
Current Exposure Assessment: Needs Improved Specificity and Accuracy
Exposure Assessment: Need More Precise Markers of Exposure

Environment Activity Diet → External contact → Internal dose → Biological response → Early markers of Disease → Clinical disease

Body burden measures of exposure

Adapted from National Research Council, 1987
CDC: National Report on Human Exposure to Environmental Chemicals
[148 Chemicals Measured]

- Metals
- Tobacco (cotinine)
- PAHs
- Dioxins, Dibenzofurans
- PCBs
- Phthalates
- Phytoestrogens
- Organochlorine and Organophosphate pesticides
- Herbicides
- Other pesticides and insecticides

http://www.cdc.gov/exposurereport/
Exposure Biology Program

Environment Activity Diet → External contact → Internal dose → Biological response → Early markers of Disease → Clinical disease

Links personal exposures to biology to disease

Adapted from National Research Council, 1987