Causes of death, 2001:

1. Heart diseases: 11.1 million
2. Cancers: 7.3 million
3. Stroke: 5.5 million
4. Respiratory diseases: 3.6 million
5. Accidents, fires, drowning, etc.: 3.5 million
6. Maternal and perinatal: 3.0 million
7. Violence (war, homicide, suicide): 1.6 million

USA

Population: 6,122,210,000
Deaths: 56,554,000

World Health Organization
World Health Report 2002
Familial Hypercholesterolemia (FH)

Heterozygotes (1:500)
- 300-500 mg/dl plasma cholesterol
- Xanthomas in third decade
- Coronary heart disease in fourth decade
- Treat w/ statins and bile acid binding resins

Homozygotes (1:10^6)
- 500-1200 mg/dl plasma cholesterol
- Xanthomas at birth
- Death by MI before age 30
- Treat w/ plasma LDL apheresis

Xanthoma
Cholesterol

1) Acetyl-CoA → HMG-CoA → Mevalonate

2) Mevalonate (C₆) + 3ATP → Isopentenyl-PP₅ (C₅ “isoprene”) + CO₂ + 3ADP + P₅

3) 6 Isoprene units (C₅) → Squalene (C₃₀)

4) Squalene (C₃₀) → Cholesterol (C₆₇)
Isopentylpyrophosphate (MEV Pathway)
Lipid Trafficking Enzymes

**Triacylglycerol** → **Fatty Acid** + **Glycerol**

**Lipoprotein Lipase, LPL**
*(located on endothelium of muscle, adipose tissue)*

**Cholesterol** + **Phosphatidylcholine** ↔ **Cholesterol Ester** + **Lysolecithin**

**Lecithin:Cholesterol Acyltransferase (LCAT)**
*(located on HDL)*

**Also CETP**
Lipoprotein Particles

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>M.W.</th>
<th>gL⁻¹</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I</td>
<td>28 kD</td>
<td>1.0-1.2</td>
<td>CMC, HDL</td>
</tr>
<tr>
<td>ApoA-II</td>
<td>17 kD</td>
<td>0.3-0.5</td>
<td>CMC, HDL</td>
</tr>
<tr>
<td>ApoA-IV</td>
<td>46 kD</td>
<td>0.15-0.16</td>
<td>CMC, HDL</td>
</tr>
<tr>
<td>ApoB-48</td>
<td>264 kD</td>
<td>0.03-0.05</td>
<td>CMC</td>
</tr>
<tr>
<td>ApoB-100</td>
<td>512 kD</td>
<td>0.7-1.0</td>
<td>VLDL, IDL, LDL; binds receptor</td>
</tr>
<tr>
<td>ApoC-I</td>
<td>7 kD</td>
<td>0.04-0.06</td>
<td>CMC, VLDL, HDL</td>
</tr>
<tr>
<td>ApoC-II</td>
<td>9 kD</td>
<td>0.03-0.05</td>
<td>CMC, VLDL, HDL; binds LPL</td>
</tr>
<tr>
<td>ApoC-III</td>
<td>9 kD</td>
<td>0.12-0.14</td>
<td>CMC, VLDL, HDL</td>
</tr>
<tr>
<td>ApoD</td>
<td>33 kD</td>
<td>0.06-0.07</td>
<td>HDL</td>
</tr>
<tr>
<td>ApoE</td>
<td>38 kD</td>
<td>0.03-0.05</td>
<td>CMC, VLDL, IDL, HDL; binds receptor</td>
</tr>
</tbody>
</table>

Diagrams of CHYLOMICRON, VLDL, LDL, and HDL with Apolipoproteins A-I, A-II, C, C-I, C-II, C-III, and E.
Sterol Regulation of Transcription by SREBP

**SREBP Transcription Factor Localization**

**SCAP/Insig proteins also (HMG CoA R)**

**ER Retention**

**Proteases**
The Statins

**Fermentation-Derived Statins**

- **Mevastatin**
- **Lovastatin**
- **Simvastatin**
- **Pravastatin**

**Synthetic Statins**

- **Atorvastatin**
- **Fluvastatin**
- **Rosuvastatin**
- **Cerivastatin**

**SHORT HISTORY**

- 1976 Mevastatin from *Penicillinum citrinum*
- 1980 Mevinolin from *Aspergillus terreus*
- 1987 FDA approves Lovastatin
- 1988 Lovastatin not effective in FH homozygotes
- 1995 Pravastatin decreases heart transplant rejection and mortality independently of lowering cholesterol levels
Isoprenoids in Humans

1. Steroids Hormones
2. Metabolites (Vit. A, E, K; co-Q; 25,000 terpenoids)

3. Isopentyl adenosine (tRNA)
4. Dolichol (N-linked glycosylation)
5. Protein Prenylation
Isoprenoids in G Protein Signaling

Heterotrimeric (GPCR’s)
Multiple Sclerosis

- Effects up to one million worldwide
- 16,000 deaths in 2002 (0.03 %)
- Autoimmune attack of myelin in brain and spinal cord
- Progressive physical disability
- Current therapies include injected Ifn-β and copaxone (basic peptides)

Lesions on cerebellum and spinal cord of an MS patient; Jean Cruvelhier circa 1860
Immune System Overview

Inate

NK cells

Adaptive

APC

B cells

T cells

γδ

professional

CD4 helper

CD8 cytotoxic

Ifn-γ induced

IL12 from activated macrophages and dendritic cells

T_H1

IL2

Ifn-γ

TNFα

T_H2

IL4, 10

TGFβ

Ifn-β
Cell Mediated Adaptive Immune Response

The diagram illustrates the interaction between a T cell and an antigen-presenting cell. The T cell has a receptor for a costimulatory protein and a T cell receptor. The antigen-presenting cell (APC) has a foreign peptide bound to a major histocompatibility complex (MHC) protein, which is recognized by the T cell receptor. The APC also expresses cell-cell adhesion proteins and a costimulatory protein.
Tc/MHC1/CD8 \textit{versus} Th/MHC2/CD4
MHC Antigen Presentation
The MHC Molecules

Class I

Class II
Th1 Helper Cells (macrophage/inflammatory)

IN PERIPHERAL LYMPHOID ORGAN

1. Mature dendritic cell with ingested bacteria
2. B7
3. IL-12 receptor
4. IL-12
5. CD28
6. T cell receptor
7. MHC protein
8. Class II
9. Naïve helper T cell

AT SITE OF INFECTION

1. Effector TH1 cell
2. CD40 ligand
3. Interferon-γ receptor
4. Interferon-γ
5. INFECTED DENDRITIC CELL STIMULATES NAÏVE HELPER T CELL TO DIFFERENTIATE INTO EFFECITOR TH1 CELL
6. Effector TH1 cell activates infected macrophage to kill the intracellular bacteria

INFECTED MACROPHAGE

INFECTED MACROPHAGE

INFECTED MACROPHAGE

INFECTED MACROPHAGE
Th2 Helper Cells (B cell response)

also mast cell degranulation and eosinophil activation
high [antigen], nonprofessional
Th1 vs. Th2 Maturation

Extracellular pathogens e.g. helminths also oral antigens

Microbe (pathogen A) skin

LFA-1!

Lympoid Organ

IL-12

Mature dendritic cell

costimulatory molecules (B7)

Cytokine X

T helper cell

Effector Th1 cell

Th1 Cell Activation

Th2 Cell Activation

Killed microbe
Th1 vs. Th2 Antagonism
MHC II Transcription by CIITA
Immune System Overview

Inate

NK cells

Adaptive

APC

B cells

T cells

γδ

professional

CD4 helper

CD8 cytotoxic

Ifn-γ induced

IL12 from activated macrophages and dendritic cells

T_H1

T_H2

IL2

Ifn-γ

TNFα

IL4, 10

TGFβ

Ifn-β
How Do Statins Work?

Reported to:

- Decrease occurrence of AD by 70% in retrospective study
- Suppress MS (clinical trials)
- Block SMC proliferation/migration in vitro
- Modulate NF-κB Function in vitro
- Block IFN-γ induced MHCII expression in vitro
- Suppress expression/secretion of immunoinflammatory molecules in vitro
- Direct inhibition of LFA-1

Most in vitro effects reversed by mevalonate, transF, transGG, but not cisF, cisGG, squalene, isopentyl adenosine or ubiquinone

