History

- A century ago
- Relationship between dietary fat & plasma cholesterol was discovered
- Americans had higher rate of coronary heart disease (CHD) than post war Europeans
Epidemiology

- Seven Countries Studied coronary heart disease (CHD) in different aspects:
  - Geographic
  - Social class
  - Ethnic differences

Found strong associations between average intake of saturated fats and plasma cholesterol and CHD.
Secondary Causes of Hyperlipidemia

- **Hypertriglyceridemia**
  - Obesity
  - Type II diabetes
  - Alcohol
  - Renal Failure
  - Sepsis
  - Stress
  - Cushing syndrome
  - Pregnancy
  - AIDS, Protease inhibition
  - Drugs

Secondary causes of Hyperlipidemia

- **Reduced HDL**
  - Smoking
  - Obesity
  - Type II diabetes
  - Malnutrition
  - Drugs

Pediatric Disease Associated with Hyperlipidemia

- Hypothyroidism
- Nephrotic syndrome
- Biliary atresia
- Glycogen storage disease
- Niemann-Pick disease
- Tay-Sachs
- SLE
- Hepatitis
- Anorexia nervosa

Certain Medications Associated with Hyperlipidemia

- Isotretinoin (Accutane)
- Protease inhibitors (treatment of HIV)
- Thiazide diuretics
- OCP
- Steroids
- β – Blockers
- Immunosuppressant
Primary causes of Hyperlipidemia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lipoproteins elevated</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial chylomicronemia</td>
<td>TG</td>
<td>Eruptive xanthomas, hepatosplenomegaly, pancreatitis</td>
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<tr>
<td>Familial dysbetalipoproteinemia</td>
<td>LDL, TG</td>
<td>Tubereruptive xanthomas, peripheral vascular disease</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
</tr>
<tr>
<td>Familial defective Apolipoprotein</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
</tr>
<tr>
<td>Autosomal recessive hypercholesterolomeia</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
</tr>
<tr>
<td>Sitosterolemia</td>
<td>LDL</td>
<td>Tendon xanthomas, CHD</td>
</tr>
<tr>
<td>Polygenic hypercholesterolemia</td>
<td>LDL</td>
<td>CHD</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>LDL, TG</td>
<td>CHD</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia (Frederickson type IV)</td>
<td>TG, TG+</td>
<td>Xanthomas ±CHD</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia (Frederickson type V)</td>
<td>TG, TG+</td>
<td>Xanthomas ±CHD</td>
</tr>
<tr>
<td>Familial hepatic lipase deficiency</td>
<td>VL, DL</td>
<td>CHD</td>
</tr>
</tbody>
</table>

Frederickson Classification of Lipid Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Average of overnight serum</th>
<th>Elevated particles</th>
<th>Associated clinical disorders</th>
<th>Serum TC</th>
<th>Serum TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Creamy top layer</td>
<td>Chylomicrons</td>
<td>Lipoprotein lipase deficiency, apolipoprotein C-II deficiency</td>
<td>N</td>
<td>++</td>
</tr>
<tr>
<td>IIa</td>
<td>Clear LDL</td>
<td>LDL</td>
<td>Familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia</td>
<td>++</td>
<td>N</td>
</tr>
<tr>
<td>IIb</td>
<td>Clear LDL, VLDL</td>
<td>LDL, VLDL</td>
<td>Familial combined hyperlipidemia</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>III</td>
<td>Turbid LDL</td>
<td>LDL</td>
<td>Dysbetalipoproteinemia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IV</td>
<td>Turbid VLDL</td>
<td>VLDL</td>
<td>Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes</td>
<td>N</td>
<td>++</td>
</tr>
<tr>
<td>V</td>
<td>Creamy top, turbid bottom</td>
<td>Chylomicrons, VLDL</td>
<td>Diabetes</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Lipoproteins Structure

- Phospholipid monolayer
- Triacylglycerol
- ApoB-100
- Cholesteryl esters
- Free (unesterified) cholesterol

NEGATIVE STAINING ELECTRON MICROGRAPHS OF HUMAN PLASMA LIPOPROTEIN

- LDL
- VLDL
- HDL

Dr. Razzaghy Azar; Dr. Nourbakhsh
Whole plasma was introduced into pre-cast gradient gels (2–27% polyacrylamide) and underwent electrophoresis at constant voltage. Gels were stained with Sudan black B, photographed and scanned for further analysis.
<table>
<thead>
<tr>
<th>Lipoprotein Class</th>
<th>Approximate NMR Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicron</td>
<td>–</td>
</tr>
<tr>
<td>VLDL</td>
<td>V6-V1</td>
</tr>
<tr>
<td>IDL</td>
<td>IDL</td>
</tr>
<tr>
<td>LDL</td>
<td>L3-L1</td>
</tr>
<tr>
<td>HDL$_2$</td>
<td>H5-H3</td>
</tr>
<tr>
<td>HDL$_3$</td>
<td>H2-H1</td>
</tr>
</tbody>
</table>

**MTP: microsomal triglyceride transfer protein**

**Production and Secretion of Chylomicrone**

**Dietary TG**

**Lymphatics**

**Small intestine**

**Blood capillary**

**Lymph vessel leading to thoracic duct**

**Extracellular fluids**

**Lipoprotein lipase**
E2, E3, and E4

- The E3/E3 genotype is the most common and found in about 60% of the human population
  - This genotype is associated with a normal level of blood cholesterol.
- Protein expressed by the E2 allele does not bind the LDL receptor and results in increased plasma VLDL-cholesterol concentration.
- E4 produces a protein with abnormally strong binding to the LDL receptor.
  - resulting in increased LDL-cholesterol concentration.
CHYLOMICRONE DISORDERS

Familial Chylomicronemia
(Type 1 hyperlipidemia)

- Autosomal Recessive 1/1000000
- Rare single gene defect
- Mutations affecting clearance of apo B containing lipoproteins
- LPL deficiency or absence
- LPL cofactor apo C-II
- Severe elevation of TG rich chylomicron

- Decreased HDL
- Turbid plasma even after prolonged fasting
- Acute pancreatitis
- Eruptive Xanthomas (arm, knee, buttocks)
- Hepatosplenomegaly

Milky plasma
Familial Chylomicronemia (Type 1 hyperlipidemia)

**Diagnosis**
Assaying lipolytic activity of TG

**Treatment**
Vigorous dietary fat restriction
Fat soluble vitamins
MCT
Fish oil

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VLDL & LDL

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**VLDL Metabolism**

MTP: assembly of lipids and proteins
Receptor mediated endocytosis

High dietary fat intake causes down-regulation of LDL receptor synthesis.

LDL assembly with apo(a)
VLDL & LDL Disorders

Familial Hypercholesterolemia

- autosomal dominant disorder
- Is caused by LDL Receptor Defect
- Two types:
  - Heterozygote
  - Homozygote

Familial hypercholesterolemia

Type IIa

- Familial Hypercholesterolemia (LDL Receptor Defect)
- Familial Ligand-Defective Apo B
- Heterozygous FH3
- Autosomal Recessive Hypercholesterolemia

Heterozygote

- presents in the heterozygous state with a 2- to 3-fold elevation in the total and LDL cholesterol
- the most common inborn errors of metabolism
- 1 in 500 worldwide
- higher incidence in certain populations, such as Afrikaners, Christian Lebanese, Finns and French-Canadians
- FH is due to one of more than 900 different mutations in the LDL receptor gene
Familial Hypercholesterolemia homozygote
- One in a million children inherit two mutant alleles for the LDL receptor,
- Presents with a 4- to 8-fold increase in LDL cholesterol levels
- FH homozygotes are classified into:
  - LDL receptor-negative (<2% of normal activity)
  - LDL receptor-defective (2-25% of normal activity)
- FH homozygotes can be found in two types:
  - Inherit two different mutant alleles (genetic compounds)
  - Two identical LDL receptor mutations (true homozygotes)

Familial Ligand-Defective Apo B (FDB)
- Heterozygotes with FDB may present with normal, moderately elevated, or markedly increased LDL cholesterol levels
- The most commonly recognized mutation in FDB is a missense mutation (R3500Q) in the LDL receptor-binding domain of apo B-100
- Frequency of FDB heterozygotes is about 1 in 1,000 in Central Europe but appears less common in other populations

Heterozygous FH3
- Clinical phenotype is indistinguishable from FH heterozygotes
- Results from a mutation in PCSK9
  - Gain of function mutation
- At present, there are two pharmaceutical products available in the United States that reduce PCSK9 activity: alirocumab and evolocumab

Autosomal Recessive Hypercholesterolemia
- Cholesterol levels intermediate between FH heterozygotes and FH homozygotes
- Results from a defect in ARH which prevents internalization of the LDL receptor
Clinical features of hypercholesterolemia

Homozygous Familial Hypercholesterolemia

Severe atherosclerosis
- Aortic root
- Coronary arteries
- Xanthomas
- Thickening of Achilles or extensor tendons of the hands

Cutaneous lesions
- Hands
- Elbows
- Knees
- Buttocks
- Corneal arcus

[Images of medical conditions]
**Familial Hypercholesterolemia**

**Diagnosis**
- Family history of premature heart disease
- Phenotypic expression

**Confirmed by**
- LDL receptor activity
  - In cultured skin fibroblasts
  - On surface of lymphocytes

**Familial Hypercholesterolemia prognosis**
- Rarely survive to adulthood
- Coronary insufficiency
- Sudden death
Familial Hypercholesterolemia
treatment
- LDL apheresis
- Liver transplantation
- HMGA CoA reductase inhibitors
  - Depending on the specific class of LDL receptor defect
- Ezetimibe
  - Selectively blocking cholesterol adsorption in the gut replaced bile acid sequestrants
- Microsomal triglyceride transfer protein (MTP) inhibitor (Lomitapide)

Heterozygous Familial Hypercholesterolemia
- 50% of 1st degree relatives have the disease
- 25% of 2nd degree relatives
- 10 million people worldwide

Symptoms of CHD presents at:
- 45 – 48 yr in males
- 55 – 58 yr in females

Heterozygous Familial Hypercholesterolemia
- Children should have blood testing if:
  - Family history of premature CHD
  - Parental hypercholesterolemia
- U.S.MED-PED
  - Make early diagnosis – prevent early death
- 4% of general population with total Ch. 310 mg/dL have familial hypercholesterolemia
- 95% of 1st degree relatives of known cases, have hypercholesterolemia

Heterozygous Familial Hypercholesterolemia
- Reverse screening of the parents and relatives
- 88% chance of having FH in a child < 18 yr if:
  - Cholesterol: 270 mg/dL
  - And/or LDL-C: 200 mg/dL
- Criteria for diagnosis in a child with 1st degree known case
  - Total cholesterol 220 mg/dL
  - LDL-C 155 mg/dL
Heterozygous Familial Hypercholesterolemia

Treatment

• Vigorous low-fat diet
• Drugs in children at least 10 yr of age + history of premature heart disease with:
  – LDL-C > 160 mg/dL
  With absence of positive family history:
  – LDL-C > 190 mg/dL
Ezetimibe lower total Ch. 20 – 30 mg/dL
HMGA-CoA reductase (risk of complications as adults)

Familial Combined Hyperlipidemia (FCHL)

Type IIb
• Autosomal Dominant
• Moderate elevation in LDL, Cholesterol, TG & reduced HDL
• Prevalence: 1/200
• No single metabolic aberration
• 20 % CHD by 60 yr
• Family history of premature heart disease

Diagnosis:
• At least two 1st degree relatives have evidence of one of 3 types of dyslipidemia

1. > 90th percentile LDL
2. > 90th percentile TG
3. > 90th percentile LDL & TG

• Individuals switch from one phenotype to another
• Xanthomas are not feature

Elevated apo B
• Increased small dense LDL
• Coexisting adiposity, hypertension, hyperinsulinemia (Metabolic Synd.)
• National Cholesterol Education Program (NCEP), adult treatment panel III (ATP III) identifies 6 major components:
  1. Abdominal obesity
  2. Atherogenic dyslipidemia
  3. Hypertension
  4. Insulin resistance + IGT
  5. Evidence of vascular inflammation
  6. Prothrombotic state
FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL)

- 30% of overweight adults fulfill criteria of metabolic syndrome
- 6.5% of those have FCHL
- Visceral adiposity increase with age
- Importance in children is limited
- BMI remains surrogate for adiposity

Cornerstone of Management

Lifestyle modification
- Diet low in saturated fat, trans fat and cholesterol
- Reduced consumption of simple sugars
- Increase dietary intake of fruits and vegetables
- One hr physical activity daily
- Small incremental steps

Familial Dysbetalipoproteinemia

- FDBL (type III hyperlipoproteinemia)
- 1/10 000
- Mutation in apo E
- Apo E (in chylomicron & VLDL remnants) binds to hepatic receptors
Familial Dysbetalipoproteinemia

Presentation
- Tuberoeruptive xanthomas (small grapelike clusters) on the knee, buttocks & elbows
- Prominent orange-yellow discoloration of the creases on the hands
- Palmar Xanthomas is typically present

Diagnosis
- Lipoprotein electrophoresis broad beta band
- Direct measurement of VLDL by ultracentrifugation in special lipid laboratories
- VLDL/Total TG > 0.3
- Genotyping for apoE2 homozygosity
  Negative results does not rule out (different mutation)
**Familial Dysbetalipoproteinemia**

**Treatment**
- HMG CoA reductase inhibitors
- Nicotinic acid
- Fibrates
- Responsive to recommended dietary restriction

**Familial Hypertriglyceridemia**

**Diagnosis**
- Lower LDL
- Normal apo B
- More severe Hypertriglyceridemia
- Increased level of chylomicrons + VLDL (Type V Fredrickson)
- TG > 1000
- Rarely seen in children
- LPL or apo C-II deficiency is not present
- Eruptive Xanthomas
- Acute Pancreatitis

**Familial Hypertriglyceridemia, FHTG Type IV Hyperlipidemia**

- Autosomal Dominant
- Unknown etiology
- 1/500
- TG > 90th % (250 – 1000 mg/dL)
- Slight elevation of chol.
- Low HDL
- Expressed in 20% of affected children
- Not highly atherogenic
- Overproduction or defective breakdown of VLDL

**Familial Hypertriglyceridemia**

**Diagnosis**
- Exacerbated by Alcohol and Estrogen therapy
- Secondary causes should be ruled out before making a diagnosis of FHTG
  - Diet high in simple sugars
  - Excessive alcohol consumption
  - Estrogen therapy may exacerbate HTG
  - Excessive consumption of soda
  - Other sweetened drinks
- Reduction of weight decreases TG & HDL rises
**HEPATIC LIPASE DEFICIENCY**

- Autosomal Recessive
- Increased Cholesterol & TG
- HDL increase (Diagnostic)
- Laboratory confirmation
  - Measuring hepatic lipase activity in heparinized plasma

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**Lecithin cholesterol acyl transferase (LCAT)**

- **Phosphatidyl choline (lecithin)**
  - **Phosphate**
  - **Choline**

**Lysolecithin**

- **Phosphate**
- **Choline**

**Cholesteryl Ester**

- **Fatty acid**
- **Cholesterol**

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**HDL**

- Activates LCAT

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**Intestine**

- **HDL**

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**Liver**

- **HDL**

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**Phospholipid (PL)**

- **Cholesterol**
- **Fatty acid**
- **Phosphate**
- **Choline**

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**Lecithin cholesterol acyl transferase (LCAT)**

- **Phosphatidyl choline (lecithin)**
  - **Phosphate**
  - **Choline**

**Lyssolecithin**

- **Phosphate**
- **Choline**
HDL Disorders

- Unusual condition
- Decrease risk of CHD
- HDL-C > 80 mg/dl
**PRIMARY HYPO ALPHA LIPOPROTEINEMIA**
- Isolated low HDL-C
- Familial
- Autosomal Dominant
- Independent of family history
- The most common of HDL disorders
- HDL <10% for gender and age
- Normal TG & LDL
- Rapid atherosclerosis

**FAMILIAL APO-A1 DEFICIENCY**
- Mutation in apo A-1 gene
- Complete absence of plasma HDL
- Reduction of apo A-1 synthesis or increased catabolism of HDL
- If HDL-C 15-30 mg/dL is not associated with atherogenesis

**TANGIER DISEASE**
- Autosomal-dominant disease
- HDL-C < 5 mg/dL
- Mutations in ABCA-1 protein
- Accumulation of free chol. in reticuloendothelial system
- Intermittent peripheral neuropathy may occur from chol. accumulation in schwann cells
**Familial Lecithin-Cholesterol Acyltransferase (LCAT) Deficiency**

- Mutation in LCAT
- Free chol. in plasma increases
- HDL-C < 10 mg/dl

**Progressive Renal Insufficiency Early in Adulthood**

- Does not cause atherosclerosis
- Lab. Confirmation
  - Decrease cholesterol esterification in the plasma