The Amish - Culture, Medical Care, & Genetic Disorders
Amish

Descended from several hundred families who came to US in 1700s

- Closed community (few marry into community)
- Large families – average seven children
- Population doubles every 20 years
## Amish Population Profile, 2019

<table>
<thead>
<tr>
<th>State</th>
<th>2019 Population</th>
<th>% of the total US Amish population, 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pennsylvania</td>
<td>79,200</td>
<td>23.5%</td>
</tr>
<tr>
<td>Ohio</td>
<td>76,195</td>
<td>22.6%</td>
</tr>
<tr>
<td>Indiana</td>
<td>57,430</td>
<td>17.1%</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>22,020</td>
<td>6.5%</td>
</tr>
<tr>
<td>New York</td>
<td>20,595</td>
<td>6.1%</td>
</tr>
<tr>
<td>Michigan</td>
<td>16,410</td>
<td>4.9%</td>
</tr>
<tr>
<td>Missouri</td>
<td>13,990</td>
<td>4.2%</td>
</tr>
<tr>
<td>Kentucky</td>
<td>13,345</td>
<td>4.0%</td>
</tr>
<tr>
<td>Iowa</td>
<td>9,980</td>
<td>3.0%</td>
</tr>
<tr>
<td>Illinois</td>
<td>7,730</td>
<td>2.3%</td>
</tr>
<tr>
<td>Minnesota</td>
<td>4,680</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Total (all States)</strong></td>
<td><strong>336,235</strong></td>
<td></td>
</tr>
</tbody>
</table>

States with >1%: TN, KS, DE, MD, VA, ME, MT, OK, CO, NE, WV, MS, NC, AK, WY, FL, SD, TX, VT, ID and Canada

Amish came to North America in two waves—in the mid-1700s and again in the first half of the 1800s. Their first settlements were in southeastern Pennsylvania. Eventually they followed the frontier to other counties in Pennsylvania, then to Ohio, Indiana, and to other Midwestern states. The first Amish people in Ohio arrived in the early 1800s.
Early philosophical beliefs

- Separation of church and state
- Resistance to public education
- Nonviolence (alternative military service)
- Opposition to slavery
Amish culture today

• Church at individual family homes (every other Sunday)
• “No Sunday sales”
• Marriage at or after age 21
• Divorce prohibited
• School through 8th grade
Amish culture today

- Settlements centered around “church districts”
- Each has its own rules and dress
- “Plain” in dress; communal life
- Pridefulness, individuality discouraged
- Variability in communities is the rule*
Amish culture today

- Language – “Pennsylvania Dutch” (English second language)
- Transportation* – horse & buggy locally; hired drivers ($1 per mile) (travel for weddings, funerals common)
- No electricity* – challenges with medical equipment
- No telephones or computers* (prolific letter writers)
Taxes

- Pay all state and local taxes
- Do not pay Social Security tax
- Sign “form 4029” at age 18
- Are not eligible for Medicare, Social Security, Medicaid
Insurance

- Do not purchase insurance (homeowners, life, disability)
- No private health insurance
- No Medical assistance (form 4029)
Health care financing

- Pay cash, which limits health care
- Shop around
- Medical tourism common
- Ask discerning medical questions
  - “What do you anticipate finding with an echo; how will it affect my care?”
Preference is for natural healing & trusted remedies

- Immune boosters, liver flushes, tinctures, herbs, homeopathics
- Chiropractic heavily used (Ortman Clinic)
- Chelation, magnetic therapy, cranial treatments, alternative therapies

Western medicine often used late in an illness

- Our views of superiority viewed with some skepticism
So what is a (Western) doctor to do?

• Focus on service, not conversion to “our faith” (Western medicine)
• Be practical & conservative with testing
• Good *clinical* medicine – understand probability assessment in differential diagnosis
• Educate and give recommendation, but offer alternatives…
• Accept choices which would not be your first choice (have I been clear in my communication?)
Pregnancy and Childbirth in the Amish
Pregnancy in Amish

- Family and church are center of Amish life
- Birth control is almost never used
- Family size large
  (average of seven children)
Location of deliveries

• Generally home births
• Birthing center, when available
• Hospital births are almost never electively chosen
## Attendants at birth

<table>
<thead>
<tr>
<th>Attendant</th>
<th>Likelihood of Newborn Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amish midwife</td>
<td>Variable</td>
</tr>
<tr>
<td>Licensed midwife</td>
<td>High</td>
</tr>
<tr>
<td>Grandmothers</td>
<td>Low</td>
</tr>
<tr>
<td>Husband</td>
<td>Low</td>
</tr>
</tbody>
</table>
History of the Birthing Center

- Recognition of birthing complications
- Proposal for hospital-based birthing center
- Birth in clinic “by accident” 1993
- Addition of ultrasound
- Cost
  - $650 in 1993
  - $1350 in 2018 (includes all prenatal care; US; labs; delivery; PP home visit at 24-48 hours for Newborn Screen, congenital heart screen; hearing screen)
Maternal age

- Percent under 21: 3.3%
- Percent 35 and older: 24%
- Percent 40 and older: 8.4%
Maternal parity

- Nulliparous pts: 199/936 (21.0%)
- P1: 136/936 (14.5%)
- P2-P4: 259/936 (27.5%)
- ≥ P5: 332/936 (35.5%)
Prenatal visits

Average of visits/pregnancy:
- Amish: 2.5
- Mennonite: 4.4
## C-sections

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases</th>
<th>Rate of C-section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned clinic births</td>
<td>28 of 839</td>
<td>3.4%</td>
</tr>
<tr>
<td>High risk “transfer in” patients</td>
<td>7 of 88</td>
<td>8.0%</td>
</tr>
<tr>
<td>Overall C-section rate</td>
<td>35 of 927</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
# Vaginal Birth After C-section (VBAC)

<table>
<thead>
<tr>
<th></th>
<th>Success Rate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>25/28</td>
<td>89%</td>
</tr>
<tr>
<td>Subsequent</td>
<td>64/65</td>
<td>98%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>89/93</strong></td>
<td><strong>95%</strong></td>
</tr>
</tbody>
</table>
Other Clinic Birthing Statistics

Twins:
- Multiple sets delivered

Breech:
- External version, then delivery
- Vaginal Breech, incl primips

Fetal & neononatal death rate similar to in-hospital births
Interface of Birthing Program and Genetics

Mothers with disorders
- Sitosterolemia
- Hypertrophic cardiomyopathy
- Propionic Acidemia

Hx (risk) of affected babies
- Recessive disorders (Troyers, Galloway Mowat, BRAT1)
- Dominant – HCM; VWD
- X-linked – Hemophilia

Parental Screening
- Carrier Testing for individual disease (MSUD; sitosterolemia)
- Carrier Panels (future)
Genetic Disorders in the Amish and Mennonite Populations
Founder population

- Small number of individuals form a new community for reasons of ethnicity, religion, or geography
- Marriage occurs within their community
- Decrease in genetic variation occurs
- Some conditions absent; others may magnify in frequency
Founder populations

- >1000 founder populations (700 in India alone)
- Amish & Mennonites are distinct founder populations
- Lessons learned are applicable to populations across the world
  - Specific diseases
  - Approach to diagnosis
Father of study of inherited disorders in the plain population

Holmes Morton, MD
Clinic for Special Children
Deep study of disorders in a specific population

Leads to

- Pattern recognition (& institutional knowledge)
- Low cost & efficient diagnosis
- Targeted variant development (TVARs) - $50
- Lists of known diagnoses in a population become possible
## Pathogenic Alleles Table

<table>
<thead>
<tr>
<th>Pathogenic Allele</th>
<th>Patients</th>
<th>Genes</th>
<th>Disease</th>
<th>Mode of Inheritance</th>
<th>Allele</th>
<th>Interaction</th>
<th>Patient Data</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-beta-hydroxylase deficiency</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP11B1</td>
<td></td>
</tr>
<tr>
<td>21 hydroxylase deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HSD3B2</td>
<td>1</td>
</tr>
<tr>
<td>3-8-OH-steroid dehydrogenase deficiency</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP11B2</td>
<td></td>
</tr>
<tr>
<td>Aldosterone deficiency</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CYP11B2</td>
<td>5 bp deletion</td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amish albinism</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- CYP11B1: c.1343G>A
- Arg448His
- Amish
- HSD3B2: c.35G>A
- Gly11Glu
- Amish
- CYP11B2: 5 bp deletion
- Amish
Consequences of a known diagnosis

- Cascade testing
- Carrier testing for sibs and other relatives
- Cord blood testing at birth
Cord blood testing & early identification

Leads to

• Early effective treatment when known
• Opportunities for testing interventions early in life
• Avoidance of diagnostic odysseys
• Prompt transition to palliative care for lethal disorders
Center for Special Children

- “Clinic within a clinic”
- Manage all family members & all ages
- Birthing center
- Board includes ½ or more members from plain community (president of Board is from plain community)
Disorders

**Metabolic disorders**
- Propionic Acidemia
- Maple Syrup Urine Disease
- PKU
- Cobalamin C deficiency

**Neurodevelopment disorders (severe)**
- Galloway Mowat syndrome
- SNIP1
- Aicardi-Goutieres syndrome
- CNPNAP2 (caspr2)
- GM3 synthase deficiency
- BRAT1
- Pontocerebellar Hypoplasia

**Neurodevelopmental syndromes (less severe)**
- Troyer syndrome
- Ataxia-telangiectasia-like disorder type 2
- Amish brittle hair syndrome
- 16p11.2 duplication/deletion

**Cardiovascular**
- Sitosterolemia
- Hypertrophic cardiomyopathy
- Long QT2

**Ocular disorders**
- Oculocutaneous albinism
- Jalili syndrome
- Retinitis pigmentosa

**Congenital hearing loss**
- Connexin 26 (GJB2)
- SLITRK6

**Respiratory/Immunologic**
- Cystic Fibrosis
- Primary ciliary dyskinesia
- Cartilage hair hypoplasia
- RAG1 SCID
- DiGeorge syndrome

**Miscellaneous**
- Mucolipidosis (I cell disease)
- Corticosterone Methyloxidase 1 deficiency
- DGAT1 (protein losing enteropathy)

**Sporadic (not founder) mutations**
- Coffin Lowrey syndrome
- Williams syndrome
- Rett syndrome
- Neurofibromatosis
- Mandibulofacial dysostosis with microcephaly
- Sturge Weber syndrome
- CHD4
- GATA3
- Smith-Magenis
- ADNP/SYNGAP1

**Novel Disorders**
- CHD & ocular disease
- Developmental disability w/ SNHL
Plain Community Health Consortium
Sitostereolemia (phytostereolemia)

- Disorder of plant sterol metabolism leading to dramatic elevation in levels, esp. sitosterol and campesterol
- Accelerated atherogenesis
- Hematologic effects
- ~ 100 reported cases
- Seen in Amish, Hutterites, Chinese, Korean, Middle East
Sitosterolemia (phytosterolemia)

- Mutation in gene ABCG5 or ABCG8
- Many mutations result in same phenotype
- Amish founder mutation (ABCG8 c.1720G>A)
- Sterol levels 50 to 200X normal
Clinical features

- Accelerated atherogenesis (& aortic valve disease)
- Xanthomata (1/3 cases)
- Hematologic (hemolytic anemia; large platelets); bleeding risk?
- Orthopedic (lower extremity arthritis; Achilles’ tendonitis)
- GI distress & poor growth (in subset)
Treatment

- Ezetimibe
- Bile acid sequestrants
- Low sterol diet (limit veg. oils etc)
- Statins ineffective
- Stanols?
What have we learned about sitosterolemia?

CIMT to study state of vasculature?

A work in progress
Fasting for sterol levels

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before Meal</th>
<th>After Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>Patient 2</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Patient 3</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>Patient 4</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>Patient 5</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Patient 6</td>
<td>59</td>
<td>63</td>
</tr>
<tr>
<td>Patient 7</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>60</strong></td>
<td><strong>58</strong></td>
</tr>
</tbody>
</table>
Impact on Wound Healing

- 54 y/o man with penetrating injury to neck, involving esophagus
- Surgical intervention X5 (G-tube for months)
- Chronic open draining wound X 30 years
- After sitosterolemia Dx made, & treatment for one yr,
- Draining wound has healed and remains so
What about stanol supplementation?

Effect of consumption of plant sterol and plant stanol-enriched margarines on serum lipid and lipoprotein concentrations, and on serum plant sterol, plant stanol and lathosterol levels.

<table>
<thead>
<tr>
<th></th>
<th>Control condition</th>
<th>Plant sterol condition</th>
<th>Plant stanol condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.56 ± 1.07</td>
<td>5.26 ± 1.08$^1$</td>
<td>5.27 ± 1.11$^1$</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.36 ± 1.06</td>
<td>3.08 ± 1.01$^1$</td>
<td>3.10 ± 1.05$^1$</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.69 ± 0.39</td>
<td>1.65 ± 0.39</td>
<td>1.68 ± 0.39</td>
</tr>
<tr>
<td>Total cholesterol/HDL</td>
<td>3.46 ± 1.00</td>
<td>3.32 ± 0.93$^2$</td>
<td>3.28 ± 0.96$^3$</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>1.14 ± 0.40</td>
<td>1.18 ± 0.44</td>
<td>1.08 ± 0.41</td>
</tr>
<tr>
<td>ApoB100 (g/L)</td>
<td>0.97 ± 0.25</td>
<td>0.93 ± 0.24$^3$</td>
<td>0.92 ± 0.26$^3$</td>
</tr>
<tr>
<td>ApoA1 (g/L)</td>
<td>1.57 ± 0.31</td>
<td>1.55 ± 0.31</td>
<td>1.55 ± 0.27</td>
</tr>
<tr>
<td>Sitosterol$^*$</td>
<td>140 ± 69</td>
<td>226 ± 255$^3$</td>
<td>88 ± 35$^4$</td>
</tr>
<tr>
<td>Campesterol</td>
<td>214 ± 83</td>
<td>346 ± 172$^1$</td>
<td>131 ± 59$^1$,$^4$</td>
</tr>
<tr>
<td>Sitostanol</td>
<td>4.3 ± 3.3</td>
<td>5.5 ± 5.7</td>
<td>22.4 ± 11.7$^{1,4}$</td>
</tr>
<tr>
<td>Campestanol</td>
<td>2.8 ± 1.6</td>
<td>3.5 ± 2.0</td>
<td>13.1 ± 7.1$^{1,4}$</td>
</tr>
<tr>
<td>Lathosterol</td>
<td>115 ± 57</td>
<td>134 ± 56$^3$</td>
<td>130 ± 55$^2$</td>
</tr>
<tr>
<td>Cholestanol</td>
<td>165 ± 0.33</td>
<td>153 ± 32$^2$</td>
<td>155 ± 32$^2$</td>
</tr>
</tbody>
</table>

*Department of Human Metabolism, MRC/Wellcome Trust Centre for Human Nutrition Research, Cambridge, UK.

$^1$Institute of Clinical Chemistry and Clinical Pharmacology, University of Bern, Bern, Switzerland.

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Effects of plant sterol- or stanol-enriched margarine on fasting plasma oxysterol concentrations in healthy subjects

Sabine Baumgartner$^a$, Ronald P. Mensink$^a$, Constanze Husche$^b$, Dieter Lüsijohann$^b$, Jogchum Plat$^a$$^b$.

$^a$Department of Human Metabolism, MRC/Wellcome Trust Centre for Human Nutrition Research, Cambridge, UK.

$^b$Institute of Clinical Chemistry and Clinical Pharmacology, University of Bern, Bern, Switzerland.
Xanthomata, before and after treatment
Management of sterols during pregnancy

![Graph showing changes in sitosterol levels during pregnancy with medications]

- Normal Sitosterol
- Ezetimibe
- Sitosterol Level
- Cholestryramine Level
Bleeding risk

- Platelet function studies normal
- Reassuring family history from two adult women (18 pregnancies – no transfusions, transfer to hospital, etc)
- Personal experience in two deliveries
• Fetal doppler flow studies (2nd trimester)– normal

• Platelet function studies - normal

• Placental pathology - a window to the microvasculature?

• 2 deliveries (one patient) - normal
The Future in Genetic Assessment
Panels: For diagnosis  
For couple screening

Clinic for Special Children
- >1000 mutations
- $490 (goal pricing: $100-$200)

DDC Clinic
- 125 disorders
- $400 (goal pricing: $100-$200)

UW-Madison (from filter paper)
- 100+ mutations
- Goal: $100
Questions?