Obesity and Medicine in the 21st Century

Bosch, *Gluttony*, from *The Table of the Seven Deadly Sins*, c. 1480
One of the myths of the modern world is that health is largely determined by individual choice.

— Barry R. Bloom (2000)
Body Mass Index (BMI): Medically Significant Adiposity

- BMI = weight [kg]/(height [m])²

- At a given BMI, women, on average, have more body fat.
- Morbidity and mortality increase with BMI similarly for men and women.
- Risk at a given BMI can vary between populations.
Adipocyte Hypertrophy and/or Hyperplasia

1. Subcutaneous
2. Intraabdominal (independent morbidity risk factor)
3. Muscles (particularly in older people)
Health Risks Associated with Obesity

1. Type 2 Diabetes (NIDDM)

2. Cardiovascular Disease
   a. Hypertension
   b. Dyslipidemia (high total cholesterol, low HDL, high LDL, high triglycerides)

3. Sleep-Breathing Abnormalities
   a. difficulty breathing
   b. obstructive apnea

4. Gallstones

5. Menstrual irregularity, difficulty getting pregnant

6. Osteoarthritis

7. Cancer (colon, endometrial, breast)
Women: RR is 18.1 for BMI ≥ 31

Men: RR is 50.7 for BMI ≥ 35

- WHO estimates BMI < 25 would prevent 64% of Type 2 DM in US men and 74% in US women.

- Framingham study estimates BMI < 25 would reduce coronary heart disease by 25% and strokes and congestive heart failure by 35%.
Prevalence of Obesity among U.S. Adults, BRFSS
### Combined Prevalence of Overweight and Obesity (BMI ≥ 25.0 kg/m²)

**Among Adults Age 20 to 80+ years, by Gender, Race/Ethnicity, and Age: United States, 1960-1994.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Both Sexes</td>
<td>43.3</td>
<td>46.1</td>
<td>46.0</td>
<td></td>
<td>54.9</td>
</tr>
<tr>
<td>Men</td>
<td>48.2</td>
<td>52.9</td>
<td>51.4</td>
<td></td>
<td>59.4</td>
</tr>
<tr>
<td>Women</td>
<td>38.7</td>
<td>39.7</td>
<td>40.8</td>
<td></td>
<td>50.7</td>
</tr>
<tr>
<td>White men</td>
<td>48.8</td>
<td>53.7</td>
<td>52.3</td>
<td></td>
<td>61.0</td>
</tr>
<tr>
<td>White women</td>
<td>36.1</td>
<td>37.6</td>
<td>38.4</td>
<td></td>
<td>49.2</td>
</tr>
<tr>
<td>Black men</td>
<td>43.1</td>
<td>48.9</td>
<td>49.0</td>
<td></td>
<td>56.5</td>
</tr>
<tr>
<td>Black women</td>
<td>57.0</td>
<td>57.6</td>
<td>61.0</td>
<td></td>
<td>65.8</td>
</tr>
<tr>
<td>White, non-Hispanic men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52.0</td>
</tr>
<tr>
<td>White, non-Hispanic women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60.6</td>
</tr>
<tr>
<td>Black, non-Hispanic men</td>
<td></td>
<td></td>
<td></td>
<td>48.9</td>
<td>47.4</td>
</tr>
<tr>
<td>Black, non-Hispanic women</td>
<td></td>
<td></td>
<td></td>
<td>60.6</td>
<td>56.7</td>
</tr>
<tr>
<td>Mexican-American men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59.7</td>
</tr>
<tr>
<td>Mexican-American women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63.9</td>
</tr>
<tr>
<td>Mexican-American women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60.1</td>
</tr>
</tbody>
</table>

\(\text{BMI} \geq 25.0 \text{ kg/m}^2\)
Trends in Prevalence Worldwide
Genes

50%-90% of variation in BMI

Monogenic syndromes

Susceptibility genes
(many genes, each with small effect)

Physical activity

Food intake

Environment/Lifestyle

OBESITY
“Obesogenic” Environment

A. Eat more:

Increased food availability
   calories/person/day has increased 15% since 1970
   % of food $ spent outside the home has doubled since 1970

Increased portion size
   12 oz soda at McDonalds: king-sized in 1950’s; child size now

Increased energy density (kcal/g)
   high fat foods; low fat/low cal foods

B. Do less:

Increased sedentary leisure time activities
   TV, computers. video games; cutbacks in mandatory PE

Decreased occupational physical activity

Increased use of automobiles
Energy Balance

Basal metabolism: energy expenditure of a subject relaxed and at rest, at thermoneutrality, 8–12 hours after last food ingestion.

Adaptive thermogenesis: energy dissipated as heat in response to environmental changes.
Energy Homeostasis

• There are very effective mechanisms to defend against body weight loss but less effective mechanisms to defend against body weight gain.

• Energy stores (adipose mass) are maintained at a set point.

• Weight loss leads to compensatory response: decreased energy expenditure, hyperphagia, and eventual restoration of body weight.

• A formerly obese person requires about 15% fewer calories to maintain a “normal” weight than someone who has not been obese because of the compensatory decrease in energy expenditure.

Therapeutic Consequences:

1. Current interventions target energy balance and fat, not the setpoint.

2. Treatment plateaus: treating obesity results in ~10% weight loss.

3. Recurrence when treatment stops.
Brain Lesioning Studies

Profound obesity from destruction of hypothalamic:
1. Ventromedial nucleus (VMN)
2. Paraventricular nucleus (PVN)
3. Dorsomedial nucleus (DMN)

Moderate feeding defects from destruction of:
4. hypothalamic arcuate nucleus (ARC)

Anorexia/weight loss from destruction of:
5. Lateral hypothalamic area (LHA)
Brain Centers in Energy Homeostasis

Obesity, hyperphagia, decreased energy expenditure, hyperglycemia, hyperinsulinemia
Parabiosis Experiments

\( ob/ob + \text{normal} \): weight gain of \( ob/ob \) mouse suppressed.

\( db/db + \text{normal} \): normal mouse slowly loses weight and dies of apparent starvation.

\( db/db + ob/ob \): \( ob/ob \) mouse rapidly loses weight and dies of apparent starvation.

Interpretation:

2. Defects in \( ob/ob \) and \( db/db \) mice may be in signal and the receptor for that signal, respectively.
Leptin: Anti-obesity or Energy Sufficiency Signal

- Leptin is secreted by fat cells.

- Circulating levels of leptin correlate with fat stores.

- Leptin receptors are present on neurons in the hypothalamus.

- Leptin levels increase within hours after a meal in rodents and after several days of overfeeding in humans.

- Administration of leptin to rodents decreases food intake increases energy expenditure, and results in weight loss due to loss of adipose tissue.

- Obese people have high leptin levels.

- Leptin levels decrease rapidly with food restriction.

- Administration of leptin during a fast prevents the starvation response (decreased thyroid and gonadal hormones, increased glucocorticoids, decreased body temperature, increased eating).
The Agouti $A^y$ Obese Mouse
Overview of the Setpoint Circuit
# Input Signals to Primary Neurons

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Made By:</th>
<th>Talks To:</th>
<th>Signal</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Pancreas β-cells</td>
<td>Arc N and Ventromedial N; PI3K</td>
<td>Gassing Up</td>
<td>Proportional to total adipose tissue; acts on same Arc N neurons as leptin; icv insulin blocks fasting ↑Agrp/Npy</td>
</tr>
<tr>
<td>Leptin</td>
<td>Adipose Tissue</td>
<td>Arc N and Ventromedial N; PI3K</td>
<td>Full!</td>
<td>Proportional to total adipose tissue; ob/ka and db mouse models; leptin admin. blocks starvation response</td>
</tr>
<tr>
<td>Cck</td>
<td>Duo. &amp; Small I.</td>
<td>Cckar and Cckbr in NTS (brainstem)</td>
<td>Over!</td>
<td>“Satiety signal” modulated by lep/ins projections from Arc→NTS; Afore-hind responds to cck but not starvation</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Stomach</td>
<td>Ghsr in Arc N and Pituitary</td>
<td>Empty!</td>
<td>↑ peaks just before a meal; ↑”s consumption at a single meal; block tonic suppression of Agrp/Npy by lep/ins?</td>
</tr>
</tbody>
</table>
## Signals Produced by Primary Neurons

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Made By:</th>
<th>Talks To:</th>
<th>Signal</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrp (Agouti)</td>
<td>Arc N (Melanocytes)</td>
<td>↓ Mc3/4r @ LH and PVN (mc1r)</td>
<td>Empty!</td>
<td>ΔMc4r most common monogenic human obesity (4%); A' mouse model</td>
</tr>
<tr>
<td>Npy</td>
<td>Arc N and other areas of brain</td>
<td></td>
<td>Empty!</td>
<td></td>
</tr>
<tr>
<td>α-MSH</td>
<td>Arc N, NTS &amp; pituitary</td>
<td>↑ Mc3/4r @ LH and PVN</td>
<td>Full!</td>
<td>Product of Pomc w/ ACTH and β-endorphin; autocrine negative feedback via Mc3r</td>
</tr>
<tr>
<td>Cart</td>
<td>Arc N</td>
<td></td>
<td>Full!</td>
<td>Cocaine and amphetamine regulated transcript (misnomer)</td>
</tr>
</tbody>
</table>
Primary Neurons
# Outputs to Body and Higher Brain

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Made By:</th>
<th>Talks To:</th>
<th>Signal</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>McH</td>
<td>LH</td>
<td></td>
<td>Empty!</td>
<td>“fuel-gauge-&gt;fuel-pump”</td>
</tr>
<tr>
<td>Hypocretin/Orexin 1/2</td>
<td>LH</td>
<td></td>
<td>Empty!</td>
<td>Hormone and receptor knockouts produce narcolepsy</td>
</tr>
<tr>
<td>Trh</td>
<td>PVN</td>
<td>Pituit. (⇑Tsh) -&gt; Thyroid (⇑Thr)</td>
<td>Full!</td>
<td>“fuel-gauge-&gt;gas-pedal”; Mc4r ant. &amp; MSG block lep. ⇑Trh</td>
</tr>
<tr>
<td>Dopamine</td>
<td>SNPC/VTA</td>
<td>D1-D4 @ caudate-putamen/nucleus accumbens</td>
<td>Empty!</td>
<td>Parkinson wasting; “know hungry but don’t care”; ⇑C-P dopamine production fixes feeding but not locomotion; behaviors of motivation/reward/pleasure; no hyp. projections</td>
</tr>
<tr>
<td>AcCholine</td>
<td>Chrm3 muscarinic receptor</td>
<td>Empty!</td>
<td>ΔChrm3 respond to McH but not Agrp (potentiation)</td>
<td></td>
</tr>
</tbody>
</table>
Endocrine Efferent Outputs
Dopamine and Outputs to Striatum

SNPC: substantia nigra pars compacta, VTA: ventral tegmental area
Bias Toward Weight Gain

1. Arc destruction causes weight gain.

2. Response to weight loss bidirectional; weight gain unidirectional.

3. $\Delta \text{Mc4r} \Rightarrow$ weight gain whereas $\Delta \text{npy} \Rightarrow$ no weight loss.

4. Anabolic pathways are required for intact responses to negative energy balance (IDDM causes negative energy balance in Npy-/- mice).

5. Anabolic pathways required for response to decreased leptin. (Npy-/- over ob/ob mice show reduced hyperphagia).

6. AgRP/Npy neurons are more sensitive to adiposity signals than MSH/Cart neurons.
Profusion of Peripheral Signals
# Gutkines

<table>
<thead>
<tr>
<th>Gut Hormone</th>
<th>Made at:</th>
<th>Acts at:</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghrelin</td>
<td>Stomach</td>
<td>Arc via vagal nerve</td>
<td>Peaks prior to meal; potently stimulates appetite in humans and rats when given peripherally. normal in obese individuals, unless they are dieting</td>
</tr>
<tr>
<td>CCK</td>
<td>Upper small intestine</td>
<td>Nucleus of solitary tract</td>
<td>Satiety signal; rats lacking receptor are diabetic, hyperphagic and obese; receptor deficient mice are normal; peripheral administration at nonphysiological concentrations in humans suppresses appetite.</td>
</tr>
<tr>
<td>pYY</td>
<td>Gut L cells</td>
<td>Arc Y2R/ hypothalamus</td>
<td>NPY class; peripheral administration in humans suppresses appetite; ~30% reduction in food intake; decreased levels in obese individuals</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Gut/brain from prepro-glucagon</td>
<td>GLP-1 receptors pancreas (insulin release) brainstem, Arc, PVN, dorsal vagal complex</td>
<td>ICV to PVN in rats potently inhibits food intake; antagonist (extendin truncation) increases food intake; peripheral in humans produces small but reproducible reduction in food intake; decreases gastric emptying; works in advanced diabetics</td>
</tr>
<tr>
<td>Oxyntomod</td>
<td>Gut/brain from prepro-glucagon</td>
<td>Arc</td>
<td>ICV and IP in rats inhibits food intake (stronger than GLP-1); blocked by extendin; IV in humans reduces free food intake ~19%; suppresses ghrelin</td>
</tr>
<tr>
<td>GIP</td>
<td>dudodenal K cells</td>
<td>receptor k.o. protects diet induced obesity in normal and ob/ob mice</td>
<td></td>
</tr>
</tbody>
</table>
## Adipokines and Pancreakines

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Made at:</th>
<th>Acts at:</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Adipose Tissue</td>
<td>Arc</td>
<td>Correlates with adipose tissue mass; incr. concentration and resistance in obese individuals; ineffective peripherally in humans.</td>
</tr>
<tr>
<td>Resistin</td>
<td>Adipose Tissue</td>
<td></td>
<td>induced in obesity; leads to insulin resistance</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Adipose Tissue</td>
<td></td>
<td>Insulin sensitizing and anti-inflammatory; suppressed in obesity paralleling insulin resistance</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Adipose Tissue</td>
<td></td>
<td>newly discovered; agonist of insulin receptor but acts at novel site; stimulates glucose uptake by adipocytes and muscle cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pancreatic Hormone</th>
<th>Made at:</th>
<th>Acts at:</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>B Cells</td>
<td>Arc</td>
<td></td>
</tr>
<tr>
<td>Pancreatic Polypeptide</td>
<td>PP cells of islets</td>
<td>Y4R in brainstem and Arc</td>
<td>90 minute PP infusion at 10 pmol/kg/min reduces food intake ~25% in healthy volunteers</td>
</tr>
<tr>
<td>Amylin</td>
<td>B Cells</td>
<td></td>
<td>coawc Greted with insulin; decreases food intake and delays gastric emptying in animal models; pramlintide induces weight loss in diabetics</td>
</tr>
</tbody>
</table>
Synthesis at Primary Neurons
Currently Approved Therapies

1. Orlistat (interfers with fatty acid hydrolysis)
2. Sibutramine (central norepinephrine/serotonin RI)
3. Roux-en-Y gastric bypass (absorption and hormonal)
Next Line Therapies

4. Rimonabant (Acomplia; CR1 antagonists)

5. SNAP-7941 (potent MCH receptor antagonist)

SNAP-7941
Synaptic Pharmaceutical Corporation.

Filled Squares: Control
Open Diamonds: Fenfen
Filled Diamonds: SNAP-7941

Graph showing body weight over days with drug treatment.
Further Out

6. Exendin-4 (Gila Monster DPP-IV resistant GLP-1)

7. Pramlintide (amylin analog, anti-obesity for diabetics)

8. PYY analogs (small molecule mimics lacking)

9. Ghrelin (treatment of anorexia)

10. SOCS-3 KO (combat insulin/leptin resistance)
The Next Blockbuster Drug?
