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)

Director of the Harvard School of Public Health
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. Intra-abdominal (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)

8. Life span? (mice lacking insulin receptors in adipose tissue are resistant to DIO and live longer!
Women: RR is 18.1 for BMI $\geq$ 31

Men: RR is 50.7 for BMI $\geq$ 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

1998

- Yellow: <10%
- Teal: 10-15%
- Blue: >15%
### 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>
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</thead>
<tbody>
<tr>
<td>Both Sexes</td>
<td>43.3</td>
<td>46.1</td>
<td>46.0</td>
<td>54.9</td>
<td>59.4</td>
</tr>
<tr>
<td>Men</td>
<td>48.2</td>
<td>52.9</td>
<td>51.4</td>
<td>50.7</td>
<td>61.0</td>
</tr>
<tr>
<td>Women</td>
<td>38.7</td>
<td>39.7</td>
<td>40.8</td>
<td>49.2</td>
<td>56.5</td>
</tr>
<tr>
<td>White men</td>
<td>48.8</td>
<td>53.7</td>
<td>52.3</td>
<td>61.0</td>
<td>65.8</td>
</tr>
<tr>
<td>White women</td>
<td>36.1</td>
<td>37.6</td>
<td>38.4</td>
<td>49.2</td>
<td>60.6</td>
</tr>
<tr>
<td>Black men</td>
<td>43.1</td>
<td>48.9</td>
<td>49.0</td>
<td>56.5</td>
<td>63.9</td>
</tr>
<tr>
<td>Black women</td>
<td>57.0</td>
<td>57.6</td>
<td>61.0</td>
<td>66.0</td>
<td>65.9</td>
</tr>
<tr>
<td>White, non-Hispanic men</td>
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<tr>
<td>White, non-Hispanic women</td>
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<tr>
<td>Black, non-Hispanic men</td>
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<tr>
<td>Black, non-Hispanic women</td>
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<tr>
<td>Mexican-American men</td>
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<td></td>
<td>59.7</td>
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<tr>
<td>Mexican-American women</td>
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<td></td>
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<td></td>
<td>60.1</td>
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</tbody>
</table>
Trends in Prevalence Worldwide

Percentage of population with BMI ≥ 30 kg m⁻²

- USA
- England
- Mauritius
- Australia
- Brazil

Genes
50%-90% of variation in BMI in twin studies

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
  in the 1950’s a 12 oz soda at McDonalds was king-sized; now it’s child size

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 (FatStat)

• 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 set point.

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

3. Recurrence when treatment stops.
mutant strains of mice …
Early-onset obesity, hyperphagia, decreased energy expenditure, hyperglycemia, hyperinsulinemia. Increased fat stores result from adipocyte hyperplasia (rare).
Diabetes, a New Mutation in the Mouse

Abstract. Diabetes (db), which occurred in an inbred strain of mouse, is inherited as a unit autosomal recessive and is characterized by a metabolic disturbance resembling diabetes mellitus in man. Abnormal deposition of fat at 3 to 4 weeks of age is followed shortly by hyperglycemia, polyuria, and glycosuria. Accompanying morphological changes in the islets of Langerhans suggest neogenesis to compensate for insulin depletion.
**Parabiosis Experiments**

*ob/ob* + normal: weight gain of *ob/ob* mouse suppressed.

*db/db* + 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.
3. In 1994, the leptin gene was positionally cloned from the *ob* mouse; the leptin receptor was subsequently cloned from the *db* mouse. Leptin receptors are found predominantly in the arcuate nucleus of the hypothalamus.
Leptin: Anti-obesity or Energy Sufficiency Signal?

• Leptin is secreted by fat cells.

• Circulating levels of leptin correlate with fat stores.

• Leptin receptors are abundant on neurons in the arcuate nucleus of 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

Maturity-onset obesity, yellow coat color, hyperphagia, hyperglycemia in males, hyperinsulinemia. Increased fat stores result from adipocyte hypertrophy.
Agouti in Obesity

- The agouti locus was positionally cloned in 1992.

- It encodes the secreted 131 residue agouti protein that normally antagonizes the melanocortin 1 receptor in peripheral hair follicles to control pigmentation.

- The obesity of Aγ mice results from ectopic expression of agouti in the CNS, which antagonizes the melanocortin-4 receptor in the hypothalamus.


- Mutation of the MCR4 receptor is the most commonly occurring monogenic cause of inherited morbid obesity in human beings (~4% of the patient population).
brain lesioning experiments …
Brain Lesioning Studies

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

Anorexia/weight loss from destruction of:
4. Lateral hypothalamic area (LHA)

Genetic lesioning:
5. PVN-specific restoration of Mcr4 in KO mouse corrects hyperphagia but not energy expenditure
6. Cholera toxin ablation of Agrp/NPY neurons; neonates adapt but adults starve to death.

Other:
7. Severing the fore-brain to hind-brain connection blocks the effects of ghrelin but not of CCK
Brain Centers in Energy Homeostasis

biochemistry …
DVC: Dorsal Vagal Complex
# Gutkines

## On Obesity

<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; acts on GH secretagog receptor</td>
<td>Peaks prior to meal; potently stimulates appetite in humans and rats when given peripherally; decreased in obese individuals, unless they are dieting; Δghrelin or Δreceptor has no impact on body weight.</td>
</tr>
<tr>
<td>CCK</td>
<td>Upper small intestine</td>
<td>Nucleus of solitary tract and DVC via vagal nerve</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; peri in humans =&gt; ~30% reduction in food intake; central increases appetite; decreased levels in ob individuals</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); antagonized by Δextendin; inactivated by DPP-IV; in humans reduces free food intake ~19%; suppresses ghrelin</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Gut/brain from prepro-glucagon, L cells</td>
<td>Dorsal vagal complex pancreas brainstem, Arc, PVN</td>
<td>Incretin; ICV to PVN in rats potently inhibits food intake; antagonist Δextendin increases food intake; peri in humans =&gt; small but reproducible reduction in food intake; decreases gastric emptying; works in advanced diabetics</td>
</tr>
<tr>
<td>GIP</td>
<td>dudodenal K cells</td>
<td></td>
<td>Incretin; receptor k.o. protects against obesity in diet-induced and ob/ob mice</td>
</tr>
</tbody>
</table>
# Adipokines and Pancreakines

## Adipokines

<table>
<thead>
<tr>
<th>Adipokine</th>
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<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>Visceral Adipose Tissue</td>
<td>Insulin receptor</td>
<td>agonist of insulin receptor but acts at novel site; stimulates glucose uptake by adipocytes and muscle cells</td>
</tr>
</tbody>
</table>

## Pancreatic Hormone

<table>
<thead>
<tr>
<th>Pancreatic Hormone</th>
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<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>Y4/5R in brainstem and Arc</td>
<td>90 minute peri PP infusion at 10 pmol/kg/min reduces food intake ~25% in healthy volunteers; central increases app.</td>
</tr>
<tr>
<td>Amylin</td>
<td>B Cells</td>
<td>Area postrema</td>
<td>cosecreted with insulin; decreases food intake and delays gastric emptying in animal models; pramlintide induces weight loss in diabetics</td>
</tr>
</tbody>
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Overview of the FatStat

Diagram showing the interaction between the hypothalamus and hindbrain with various neurotransmitters and hormones involved in feeding, gastric emptying, and metabolic rate.
# Dominant Inputs 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/фа and db mouse models; leptin admin. blocks starvation response</td>
</tr>
<tr>
<td>Cck</td>
<td>Duo. &amp; Small I. Endocrine Cells</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 Endocrine Cells</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>
Inputs
## Signals Produced by Primary Neurons

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Agrp (Agouti)</td>
<td>Arc N (Melanocytes)</td>
<td>(\downarrow) Mc3/4r @ LH and PVN (mcI1r)</td>
<td>Empty!</td>
<td>(\Delta Mc4r) 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>(\alpha)-MSH</td>
<td>Arc N, NTS &amp; pituitary</td>
<td>(\uparrow) Mc3/4r @ LH and PVN</td>
<td>Full!</td>
<td>Product of (Pomc) w/ ACTH and (\beta)-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>
<tr>
<td>AcCholine</td>
<td>(Chrm3) muscarinic receptor</td>
<td></td>
<td>Empty!</td>
<td>(\Delta Chrm3) respond to Mch but not Agrp (potentiation)</td>
</tr>
</tbody>
</table>
## Outputs to Body and Higher Brain

<table>
<thead>
<tr>
<th>Hormone</th>
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<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-guage-&gt;fuel-pump”</td>
</tr>
<tr>
<td>Hypocretin</td>
<td>LH</td>
<td></td>
<td>Empty!</td>
<td>Hormone and receptor knockouts produce narcolepsy</td>
</tr>
<tr>
<td>Orexin 1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trh</td>
<td>PVN</td>
<td>Pituit.(↑Tsh)-&gt;Thyroid(↑Thr)</td>
<td>Full!</td>
<td>“fuel-guage-&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>
</tbody>
</table>
Endocrine Efferent Outputs
Dopamine and Outputs to Striatum

Amphetamines remove a GABAergic block on dopamine production (DRI's). They increase activity and suppress appetite, and were initially used to treat obesity. In humans, BMI is anti-correlated with #D2 receptors in the striatum.

SNPC: substantia nigra pars compacta
VTA: ventral tegmental area
Dopamine in the NA leads to feeling of happiness.
Bias Toward Weight Gain

1. Arc destruction causes moderate 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. \text{AgRP/Npy} neurons are more sensitive to adiposity signals than \text{Pomc/Cart} neurons.

HOWEVER:

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

6. Anabolic pathways are required for response to decreased leptin (Npy-/- over ob/ob mice show reduced hyperphagia).
Currently Approved Therapies

1. Orlistat (interferes with fatty acid hydrolysis); => moderate clinical effects; side effects include gas/diarrhea.

2. Sibutramine (central norepinephrine-serotonin RI); => moderate clinical effects; side effects include tachycardia and hypertension.

3. Rimonabant (Acomplia; CR1 endocannabinoid antagonist). => moderate clinical effects, 10% ceiling on loss. Side effects of anxiety and depression.

Next Line Therapies

5. SNAP-7941 (potent MCH receptor antagonist)

SNAP-7941
Synaptic Pharmaceutical Corporation.

Borowsky et al., Nat. Med. 8:825-30 (2002)

Filled Squares: Control
Open Diamonds: Fenfen
Filled Circles: SNAP-7941
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; independent of Mcr4)

9. Ghrelin (treatment of anorexia)

10. SOCS-3 KO (combat insulin/leptin resistance)

SOCS3: Suppressor of Cytokine Signaling

- Socs3 binds leptin/insulin receptor through SH2 domain; blocks JAK TK through N-terminal pseudo-substrate domain.
- Negatively regulates leptin and insulin signaling.
The Search for Obesity Genes
