The Physiology of Weight Regulation:
Implications for Effective Clinical Care

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Consider this …

In the past 40 years, **not a single country** in the world has experienced a reduction in the prevalence of obesity
Obesity, Weight and Body Fat

Obesity is a disorder of excess body fat

Within an individual, changes in body weight are due predominantly to changes in body fat
Competing Models of Energy Balance Regulation

Purposeful behavior **drives** the physiology of energy balance regulation

**Implications**
- Increased caloric intake drives weight gain
- All types of calories have similar effects
- Physical activity causes weight loss directly by burning calories
Implications of the Purposeful Behavior Model …

That obesity in modern society is caused primarily by increased availability and accessibility of food

… at a low financial and energy cost

**Primary assumption** of this model:

We have evolution-derived protections against starvation, but not against obesity

**Problems** with this assumption:

- Food has been abundant through most of mammalian evolution; predation is the greater risk
- The inefficiencies of carrying excess weight are more than sufficient to promote evolutionary protection (a 0.1% advantage is selected for)
- There are **at least 210 genes that when mutated lead to obesity**, indicating that for each of them, one of their roles is to help protect against obesity

*Herzog L, Kaplan LM, unpublished
Think About This …

• Why do people gain weight when started on selected medications? (hint: the medications don’t have many calories)?
  • Insulin
  • Sulfonylureas (all)
  • Corticosteroids (all)
  • Mood stabilizers (esp. clozapine, olanzapine, venlafaxine)
  • Anti-seizure medications (esp. valproate, oxcarbazepine)
  • β-blockers (all)

• Why do people gain weight when sleep deprived?

• Why do people gain weight when chronically stressed?
### Competing Models of Energy Balance Regulation

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#### Implications

**Purposeful behavior**
- Increased caloric intake drives weight gain
- All types of calories have similar effects
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**The physiological regulation of energy balance**
- Changes in the modern diet alter energy balance physiology
- The chemical nature of the calories is critical
- Re-regulation of abnormal physiology is essential for success
The Normal Physiology of Energy Balance

- Average adults require approximately 1300 kcal/day*
- Average adults consume 2000-2500 kcal/day
  - Average adults thus consume 1.5-2 times as much food as needed
  - Excess intake is available for physiological emergencies
- Maintenance of normal fat stores (and body weight) requires precise disposal of 40-50% of ingested calories daily
- Maintaining weight within 20 lbs. between ages 21 and 65 requires matching of intake and expenditure within 0.2%
  - Corresponds to accuracy of 4-5 kcal/day
  - Less than one-half potato chip

Thus, daily energy balance must be a tightly regulated physiological trait
The Body Seeks a Stable Adipose Tissue Mass

Similar to other regulated tissue mass

- Liver
- Red blood cells
Defense of a Fat Mass “Set Point”

Forced dietary manipulation

Ad libitum fed

Body Weight (g)

Days

Overfed

Control

Food Restricted

Woods SC et al., 1989
Feedback Regulation of Energy Metabolism

This process is critical to life and involves nearly 20% of the human genome.
Why is Weight Regain So Prevalent?

Sumithran et al. NEJM 2011; 365:1597-1604.
Appetitive Drives Persistently Oppose Restriction Diet-induced Weight Loss

Sumithran et al. NEJM 2011; 365:1597-1604.
Gut Hormone Changes Persistently Oppose Restriction Diet-induced Weight Loss

Sumithran et al. NEJM 2011; 365:1597-1604.
Why Defend the Fat Mass?

- The body **needs** to defend a fat mass set point
  - To recover appropriately from acute illness or injury
  - To shed the excess calories consumed daily
- The body **defends** its fat mass set point
  - Even if it is abnormally high (i.e., obesity)

Sumithran et al. NEJM 2011; 365:1597-1604.
Defense of a Body Fat Storage “Set Point”

Body Mass Index (kg/m$^2$)

Energy Intake

Energy Expenditure

(+) Energy Balance

(–) Energy Balance

Metabolic adaptation

Adapted from Weigle, 1995
Human Weight Perturbation Protocol

Dietary Restriction / Overfeeding
No Change in Fat Mass Set Point

Studies
- Energy Expenditure
- Energy Intake
- Neuroendocrine Axes
- Autonomic Physiology
- Muscle Physiology
- Brain Imaging

Leibel et al., NEJM 1995;335:521
Fat Regain Correlates with Metabolic Adaptation

“The Biggest Loser” Follow-up Study

Fothergill E, et al., Obesity 2016
Relationship to Set Point Drives Physiological Response More than Set Point Itself

- **Fat Mass Set Point**
  - **Normal**
  - **Obesity**

- Decreased appetitive drive
- Increased thermogenesis
- Increased appetitive drive
- Decreased thermogenesis
Obesity results from a failure of normal weight and energy physiological regulatory mechanisms…

…leading to an abnormally high defended fat mass
What causes the defended fat mass to be elevated in the first place (what causes obesity)?
Obesity: A Physiological Regulatory Error

Genetic background

Developmental programming

Environmental Influences

Fat Mass Regulation

Cortex

GI Tract

Leptin

Adipose tissue

Food intake
Energy expenditure
Nutrient handling
Differences in Response to High-Fat Diets in Mice

Environment (diet) vs. Genetics

- Fat (g) over 12 weeks on HFD
  - C57 FVB
  - LF vs. HF

Fat (g)

C57

FVB
Gene-Environment Interactions

Then:

Now:

Body Mass Index

30
The current obesity epidemic results primarily from changes in the modern environment. So what are those changes?
Environmental Drivers to Obesity

- **Labor-saving devices** (decreased physical activity) (effects on muscle more than calories)
- **Chronic stress and distress** (incl. sleep, circadian) (direct impact on relevant brain areas)
- **Altered food supply** (signaling more than calories)
- **Medications** (up to 10% of obesity)

These influences act by raising the fat mass set point
The Modern Environment Causes Obesity by Driving Up the Defended Fat Mass

- Abnormal dietary constituents
- Unhealthy muscle
- Sleep deprivation
- Chronic stress
- Disrupted circadian rhythms
- Weight-inducing medications

Years of Exposure
How does the body actually gain the weight?

When the body feels a physiological (e.g., pregnancy) or pathological (e.g., obesity) need to gain weight, it drives behavior to achieve this goal.

Behaviors available to the body to regulate energy balance include BOTH food intake and energy expenditure.
The data strongly suggest ....

Overeating does not cause obesity ...

... obesity causes overeating!
As a result …

Undereating does not solve obesity …

… solving obesity (by whatever means is effective) - causes undereating
Implications for Obesity Treatment
Obesity and Its Care: A Battle of Forces that Influence the Defended Fat Mass

Bariatric Surgery

Defended body fat mass

Abnormal dietary constituents  Unhealthy muscle  Sleep deprivation  Chronic stress  Disrupted circadian rhythms  Weight gain inducing medications

Years of Exposure
Obesity Treatment Strategy

A Stepwise – and Additive – Approach
(progress through algorithm as clinically required)

- Post-surgical Combinations
- Weight Loss Surgery
- Pharmacotherapy
- Professionally-directed Lifestyle Change
- Self-directed Lifestyle Change = Patient Education
Relationship to Set Point Drives Physiological Response More than Set Point Itself

Fat Mass Set Point

Normal  Obesity

- Decreased appetitive drive
- Increased thermogenesis
- Increased appetitive drive
- Decreased thermogenesis
Physiological vs. Counter-physiological Weight Loss

- **Pre-treatment**
  - Increased appetitive drive
  - Decreased thermogenesis

- **Short-term Weight Loss**
  - Isolated calorie restriction
  - Physiological compensation

- **“Maintenance” Phase**
  - Defended Fat Mass
  - Increased appetitive drive
  - Decreased thermogenesis

**Counter-physiological Weight Loss** (e.g., dietary restriction)
Physiological vs. Counter-physiological Weight Loss

Defended Fat Mass

Physiological Weight Loss
(e.g., targeted lifestyle change, effective medications, surgery)

Fat Mass

Decreased appetitive drive
Increased thermogenesis

Pre-treatment  Initial Weight Loss  Long-term Weight Loss
(not a separate phase)
A major problem is that nearly all treatments of obesity in common usage are counter-physiological.
The Mechanism of Weight Loss Drives this Response

- Calorie restriction (very low calorie diet)
- No influence on underlying cause(s) of obesity
- No influence on physiological weight regulatory system

Sumithran et al. NEJM 2011; 365:1597-1604.
Obesity and Its Care: A Battle of Forces that Influence the Fat Mass Set Point

**Lifestyle Modification**

- Healthy diet
- Regular physical activity
- More and better sleep
- Stress reduction
- Stable eating patterns
- Weight stabilizing alternatives

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**Defended body fat mass**

- Abnormal dietary constituents
- Labor-saving Devices (unhealthy Muscle)
- Sleep deprivation
- Chronic stress
- Disrupted circadian rhythms
- Weight gain inducing medications

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**MGH 1811**
Conclusions

Regulation of obesity and energy balance is much more about the physiology (signaling and homeostasis) than the physics (calories in and out).

Drives to eating (both homeostatic and hedonic) and to autonomic thermogenesis are more a response to the body’s perceived needs than a primary driver of fat mass and weight.
Conclusions

• Although the proximal causes are diverse (lifestyle, environment, genetics, developmental), the **final common pathway** for developing obesity is a **disruption of the normal regulation** of energy balance and defended fat mass
  - Leading to an elevated defended fat mass (set point)

• **Effective long-term treatment** of obesity requires **reduction of the fat mass set point** toward normal

• The complexity of the regulatory system allows for multiple pathways of disruption, leading to **MULTIPLE obesity subtypes**
  - ... with different phenotypes
  - ... with differential responses to individual therapies

• To be effective, **treatment** – and **PREVENTION** – of obesity needs to address these biological considerations
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