Which Comes First: Overeating or Obesity?

*Reinterpreting the 1st Law of Thermodynamics*

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First Law of Thermodynamics

*Energy can neither be created or destroyed*

Calorie intake - Calorie expenditure = Calories stored

(change in adiposity)
**Conventional Interpretation of the First Law**

*Obesity, a failure of voluntary control over energy balance*

- Overeating
  - (ubiquitous tasty foods)
- ↑ Energy intake
- ↓ Energy expenditure
- ↑ Circulating metabolic fuels (glucose, lipids)
- ↑ Fat storage (anabolic adipose)

*Physical inactivity (TV, computer, etc)*
Conventional Interpretation of the First Law

Obesity, a failure of voluntary control over energy balance

- Overeating (ubiquitous tasty foods)
- Physical inactivity (TV, computer, etc)
- Eat less
  - Energy intake
  - Circulating metabolic fuels (glucose, lipids)
  - Fat storage (anabolic adipose)
- Move more
  - Energy expenditure
Only 1 in 6 overweight and obese adults in the US report ever having maintained weight loss of at least 10% for 1 year.

Conventional Obesity Treatment in Children

Systematic reviews and meta-analyses

“Most pediatric obesity interventions are marked by small changes in relative weight or adiposity and substantial relapse . . .”

McGovern. JCEM 2008, 93:4600-5
Kamath. JCEM 2008, 93:4606-15
Waters. Cochrane Rev 2011, 12:CD001871
Conventional View of Obesity

Failure of voluntary control over energy balance

- Overeating (ubiquitous tasty foods)
  - **eat less** → **Energy intake**
  - **move more** → **Energy expenditure**

- Physical inactivity (TV, computer, etc)

- Circulating metabolic fuels (glucose, lipids)
  - ↑ Fat storage (anabolic adipose)

Why hasn’t this paradigm worked in practice?
Body Weight is Under Biological Control

Complex interconnected feedback mechanisms

Ahima, Gastroenterology 2007
Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Hunger

Reduced body weight

Energy Expenditure

Body Weight

Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Baseline body weight

Reduced body weight

Energy Expenditure

Body Weight

Hunger

Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Increased body weight

Hunger

Energy Expenditure

Body Weight

Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Body Weight is Under Biological Control

Physiological adaptations antagonize weight change

Body Weight is Under Biological Control

Complex interplay of biological & environmental factors

Hunger

“Body Weight Set Point”

Energy Expenditure

Body Weight
The Obesity Epidemic

Rising BMI among genetically stable populations

Key Questions:

Why has the level of defended body weight – the observed “Set Point” – increased in recent years?

What can we do about it?
Conventional View of Obesity
Failure of voluntary control over energy balance

- Overeating (ubiquitous tasty foods)
  - $\uparrow$ Energy intake
  - $\uparrow$ Circulating metabolic fuels (glucose, lipids)
  - $\uparrow$ Fat storage (anabolic adipose)

- Physical inactivity (TV, computer, etc)

- eat less
  - $\downarrow$ Energy expenditure

- move more
Conventional View of Obesity

Failure of voluntary control over energy balance

- Overeating (ubiquitous tasty foods)
  - eat less → ↑ Energy intake
  - move more → ↓ Energy expenditure

- ↑ Circulating metabolic fuels (glucose, lipids)
  - Physical inactivity (TV, computer, etc)

↑ Fat storage (anabolic adipose)
Alternative View of Obesity

Excessive anabolic drive in adipose tissue

Hunger

↑ Energy intake

↓ Energy expenditure

Fatigue, physical inactivity

↓ Circulating metabolic fuels (glucose, lipids)

↑ Fat storage (anabolic adipose)
Alternative View of Obesity

Excessive anabolic drive in adipose tissue

Hunger

↑ Energy intake

↓ Energy expenditure

↓ Circulating metabolic fuels (glucose, lipids)

↑ Fat storage (anabolic adipose)

Resting energy expenditure

↑ Muscular efficiency

↑ Fatigue, physical inactivity
Alternative View of Obesity

Excessive anabolic drive in adipose tissue

- Hunger
- Energy intake: ↑
- Energy expenditure: ↓
- Resting energy expenditure
- Muscular efficiency
- Fatigue, physical inactivity

Fat storage (anabolic adipose)

Circulating metabolic fuels (glucose, lipids)

Symptomatic treatment, destined to fail in an environment with excess calories

Eat less

Move more
Alternative View of Obesity

Excessive anabolic drive in adipose tissue

Hunger

↓

↑ Energy intake

↓ Energy expenditure

↑ Resting energy expenditure

↑ Muscular efficiency

Fatigue, physical inactivity

↓ Circulating metabolic fuels (glucose, lipids)

↑ Fat storage (anabolic adipose)

Insulin secretion
**Alternative View of Obesity**

Excessive anabolic drive in adipose tissue

- **Hunger**
  - $\uparrow$ Energy intake
  - $\downarrow$ Energy expenditure
- Dietary carbohydrate
  - Insulin secretion
  - $\uparrow$ Fat storage (anabolic adipose)

- Resting energy expenditure
- Muscular efficiency
- Fatigue, physical inactivity
Carbohydrate Amount & Type

Most potent effects of all macronutrients on insulin secretion

• Amount – total carbohydrate (grams)
• Type – glycemic index
Acute Effects of Processed Carbohydrate

**Methods**

• Subjects: 12 obese adolescents
• Design: cross-over feeding study on 3 separate days
• Intervention: breakfasts with identical calories:
  - Highly processed carbohydrate (instant oatmeal)
  - Minimally processed carbohydrate (steel-cut oatmeal)
  - No processed carbohydrate (vegetable omelet with fruit)
• Blood tests and hunger followed through the morning
Acute Effects of Glycemic Load

Insulin

Acute Effects of Glycemic Load

Metabolic fuels

Acute Effects of Glycemic Load

Plasma epinephrine

Acute Effects of Glycemic Load

Cumulative food intake

Kilocalories Consumed

Time (hr)

High GI
Med GI
Low GL

Glycemic Index & Brain Function

Methods

• Subjects: 12 overweight/obese young men
• Design: Double-blind, cross-over feeding study
• Intervention: high vs. low GI liquid meals, controlled for:
  - macronutrients
  - calorie content
  - sweetness
• Neuroimaging: Arterial spin labeling 4 hr after the meal
Glycemic Index & Brain Function

Effects of test meals on plasma glucose and hunger

Plasma Glucose (mmol/L)

Hunger rating (10-pt scale)

Lennerz. AJCN 2013, 98:641-7
Glycemic Index & Brain Function

Activation of nucleus accumbens after high GI meal

p<0.001, adjusted for multiple comparisons

Lennerz. AJCN 2013, 98:641-7
Energy Expenditure & Weight Loss Maintenance

Methods

- 21 obese young adults, studied for 7 months
- 10 to 15% weight loss on a standard low calorie diet
- Then studied during weight maintenance on each of three test diets with the same calories:
  - Low fat (60% carbohydrate, 20% fat, 20% protein)
  - Low glycemic index (40% carbohydrate, 40% fat, 20% protein)
  - Atkins very low carb (10% carbohydrate, 60% fat, 30% protein)
- 1° Endpoint: Resting and total energy expenditure
Energy Expenditure & Weight Loss Maintenance

Effects on total energy expenditure (doubly labeled water)

Mean ± SE

Kcal per day

325 kcal/d

P=0.003
(LF=LGI=VLC)

Ebbeling, JAMA 2012;307:2627-34
Long-term effects of macronutrients on body weight
Behavioral Diet Studies

Characteristically little weight difference between diets

POUNDS LOST Study

Methods

• 811 overweight/obese adults, studied for 2 years
• Assigned to 4 diets designed to differ in macronutrients
  - Carbohydrate: 35 – 65%
  - Fat: 20 – 40%
  - Protein: 15 – 25%
• Intervention: individual and group behavioral counseling

Results

• No difference in body weight according to diet group

Sacks. NEJM 2009, 360:859-73
Behavioral Diet Studies
Characteristically little weight difference between diets

POUNDS LOST Study

Major Limitation: Did not achieve targeted dietary goals

- Reported maximum differences in intakes less than half intended:
  - Fat intake range: 9% absolute difference
  - Protein intake range: 5% absolute difference

- Even these relatively small differences may be overestimated, due to social-desirability bias inherent to self reporting

- Biomarkers demonstrated poor compliance at 2 years:
  - No difference in triglycerides (marker of carbohydrate intake)
  - Nonsignificant difference in N2 excretion (protein intake)
  - RQ differed only slightly throughout study among diets (.81-.84)

Sacks. NEJM 2009, 360:859-73
Feeding Studies
Characteristically substantial effect of dietary composition

DIRECT Study

Methods

- 322 obese adults, studied for 2 years
- Assigned to 3 diets designed to differ in macronutrients
  - Low fat, calorie-restricted
  - Mediterranean, calorie-restricted
  - Low carbohydrate, not calorie-restricted
- Intervention based at a work site, with partial food provision
- Completion rates approaching 90%

Shai. NEJM 2008, 359:229-41
Feeding Studies

Characteristically substantial effect of dietary composition

Shai. NEJM 2008, 359:229-41
Alternative View of Obesity

Excessive anabolic drive in adipose tissue

Hunger

↓ Energy intake

↑ Energy expenditure

↓ Energy expenditure

↑ Resting energy expenditure

Muscular efficiency

Resting energy expenditure

Fatigue, physical inactivity

Dietary carbohydrate

Insulin secretion

↑ Fat storage (anabolic adipose)

↓ Circulating metabolic fuels (glucose, lipids)
**Alternative View of Obesity**

*Excessive anabolic drive in adipose tissue*

- **Hunger**
  - ↓ Energy intake
  - ↑ Energy expenditure
- **Fatigue, physical inactivity**
- **Fat storage** (anabolic adipose)
- **Dietary carbohydrate**
  - ↓ Insulin secretion
  - ↑ Fat storage
- **Circulating metabolic fuels** (glucose, lipids)
  - ↓ Resting energy expenditure
  - ↑ Muscular efficiency
- **Pro- prebiotics** (gut microbiome)
- **Protein** (type/amount)
- **Fatty acid profile**
- **Micronutrients phytochemicals**
Alternative View of Obesity

Excessive anabolic drive in adipose tissue

Hunger

↓ Energy intake

↑ Energy expenditure

↓ Energy expenditure

Resting energy expenditure

Muscular efficiency

Fatigue, physical inactivity

Sleep, stress, physical activity

↓ Circulating metabolic fuels (glucose, lipids)

Insulin secretion

↑ Fat storage (anabolic adipose)

Dietary carbohydrate

Fatty acid profile

Pro-prebiotics (gut microbiome)

Protein (type/amount)

Micronutrients phytochemicals
Low Glycemic Load Pyramid

Copyright: Ebbeling & Ludwig 2007
1. The conventional approach to weight loss, the calorie-restricted diet, has poor efficacy in an environment with unlimited calorie availability.

2. An alternative approach aims to reduce anabolic drive, leading to reduced adiposity with *ad libitum conditions*.

3. Reduced anabolic drive may be achieved by lowering carbohydrate amount and/or glycemic index, and other qualitative changes in diet.

4. Findings from behavioral RCTs must be interpreted cautiously, as they often fail to achieve significant changes in dietary intakes.

5. Future research is needed to compare strategies to improve dietary composition vs. reduce calorie intake in the treatment of obesity.
The editors of a leading medical journal wrote:

“When we read that ‘the fat woman has the remedy in her own hands – or rather between her own teeth’ . . . there is an implication that obesity is usually merely the result of unsatisfactory dietary bookkeeping. . . [Although logic suggests that body fat] may be decreased by altering the balance sheet through diminished intake, or increased output, or both . . . [t]he problem is not really so simple and uncomplicated as it is pictured.”

JAMA 1924, 83(13):1003


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