Energetics - Introduction

David B. Allison, Ph.D.

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Disclosure

I have received financial and other benefits from the following entities: the Frontiers Foundation; The Federal Trade Commission; and numerous additional government, non-profit and for-profit (including publishing, food, beverage, and pharmaceutical companies) organizations with interests in obesity, nutrition, and health.

Email: Dallison@UAB.edu
Introduction

Purpose & Scope
Introductions
Dr. Dhurandhar’s Role
Grading
Expectations
Video-Taping
Outline of Today’s Lecture

• History & Definitions
• Unifying Principles
• Myths & Presumptions
• Curious Conjectures
• Roads Less Traveled
• Testing Foods
• Reporting Results
The Fire of Life

David B. Allison, Ph.D.
Prometheus Steals Fire From the Gods

Hesiod tells the story...

“For the gods kept hidden from men the means of life. Else you would easily do work enough in a day to supply you for a full year even without working.”

“So he drove out the man; and he placed at the east of the garden of Eden Cherubim, and a flaming sword which turned every way, to keep the way of the tree of life.”
Fire as Spirit

Is repaid for his freedom promoting views with fire in the ‘other Birmingham’.

http://www.answers.com/topic/joseph-priestley
"La respiration est donc une combustion."

Lavoisier: “I am a scientist.”

Tribunal: “The Revolution has no need of scientists.”

Metabolic Rate = Mass^{3/4}
This bomb calorimeter, used to measure the heat released during total combustion, is very similar to French chemist Antoine-Laurent Lavoisier's designs from the late 1700s. Lavoisier studied the heat released by the burning of fuel in this airtight chamber, and then used these findings in his studies of the similar, but more complex, process of respiration in humans and animals.

**Berthelot-type bomb calorimeter**
Made by L. Golaz, Paris, between 1885 and ca. 1910

Courtesy National Museum of American History, Smithsonian Institution

They Say the Neon Lights are Bright On Broadway


This leads to collaboration with local news on frozen desserts. “7 calorie per once Snicker-bar ice-cream!?"  
C’est impossible, le Snicker-bar Crème Glacée!, Lavoisier shouts from the grave.
Seinfeld Frozen Yogurt episode airs later that year.
Nagy Temperature Manipulation

Representative DXA Scans

Two mice at 12 wks of study

Mouse housed at 22° C

Mouse housed at 27° C
Reduction in Variability in Ambient Temperature

Effect of environmental temperature on growing-finishing pig performance

Available at: http://www.eia.doe.gov/emeu/reps/appli/us_table.html.
Available at: http://www.genome.iastate.edu/edu/PIH/prod_grow_finish.pdf.
Lambert Adolphe Jacques Quetelet.

Brings the normal distribution of errors from astronomy into epidemiology.

Published *Sur l'homme et le developpement de ses facultes, essai d'une physique sociale* (1835).

Advances idea of the ‘average man’ and deviations from it as ‘error’.

http://www.mlahanas.de/Stamps/Data/Mathematician/Q.htm
Mr. X
36 years old
5'9"; 451 lbs; BMI ~ 66
Died after bariatric surgery

- Average 36 yr old man’s life expectancy = 78 years
- Mr. X’s life expectancy = 56
- Mr. X’s life expectancy if he had lost and maintained 16% of body weight as in SOS (plus dubious assumptions) = 64
YLL at Various Ages and BMI Levels Among White Men Compared to a BMI of 24 kg/m²

Calorie Restriction and Life Span

Mean and maximum life spans in yeast, rotifers, water fleas, nematodes, fruit flies, spiders, fish, hamsters, rats, mice, and dogs have been extended significantly by decreasing normal caloric consumption by 30+ percent of *ad libitum* intake.
Caloric restriction delays disease onset and age-related deaths in rhesus monkeys

Caloric restriction delays disease onset and age-related mortality in rhesus monkeys

My candle burns at both ends
It will not last the night;
But ah, my foes, and oh, my friends -
It gives a lovely light.

Edna St. Vincent Millay, "A Few Figs from Thistles", 1920
US poet (1892 - 1950)
• Lavoisier – *The Unity of All; General Physical Principles*
• Quetelet – *There is variation, but the mean is of chief interest and the deviations are ‘errors’.*
• *Enter Galton – Impressed by Quetelet’s application of the Normal distribution to human traits, but interested in the variations, not the average.*
Francis Galton (1822-1911).

Develops method of ‘reversion’ (regression).

Develops early progenitor of twin method.

Studies heredity of ‘genius’.

Coins phrase ‘*Nature vs. Nurture*’.

Quoting one of his research subjects on the importance of perseverance for scientific achievement,

"I do all things at a white heat, but never tire of the pursuit."

Cousin of this man. http://galton.org/
FIGURE 2. Prevalence of obesity among women, by own socioeconomic status and socioeconomic status of origin.

Pearson, K. (1897) Mathematical contributions to the theory of evolution-on a form of spurious correlation which may arise when indices are used in the measurements of organs. Proc. R. Soc. Lond., 60, 489-497.
Back to the 21st Century
What if we all just ate a little bit less?

Rats on The Bottom of the Totem Pole

Perhaps It’s the Socio, Not the Economic

Perceptions matter

Nonetheless, the depressing message from *C. elegans* and *Drosophila* is clear: if you want to live longer, eat much less and don’t enjoy it.


Julian A. T. Dow
University of Glasgow
j.a.t.dow@bio.gla.ac.uk

Tying all the threads together:

An Ecological Theory About Disparity, Energetic Uncertainty, Fatness, and Aging/Longevity.
Outline of Today’s Lecture

- History & Definitions
- **Unifying Principles**
- Myths & Presumptions
- Curious Conjectures
- Roads Less Traveled
- Testing Foods
- Reporting Results
Energy Balance: You can’t do just one thing.
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Outline

1. The Concept of Energy Balance.
2. Passive Compensation
3. Active Compensation – General
4. Active Compensation in Response to Physical Activity manipulation
5. Active Compensation after Intake Manipulation
6. Active Compensation after Other Manipulations
7. Allostatic vs Homeostatic Adaptation
8. For whom and under which circumstances?
9. Conclusions
"You cannot do only one thing." ~ Garrett Hardin
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The Fallacy of Static Energetic Predictions

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Failure to Consider Energy Balance as an Adaptive System

Examples: Consider these unstated and *completely opposite* implicit assumptions:

Reduce Restaurant Dining – Implicit Assumption is undercompensation.

Eat Breakfast Everyday – Implicit assumption is overcompensation.


Kral et al. 2011
Available Models Account for Passive Compensation, Under the Assumption of No Active Compensation

- **NIDDK Body Weight Simulator:** http://bwsimulator.niddk.nih.gov/

- **Pennington Multi Subject Weight Change Predictor:** http://www.pbrc.edu/research-and-faculty/calculators/mswcp/
Pediatric Public Health Intervention Calculator Uses Model that Assumes no Active Compensation

Biological Organisms Are Adaptive Systems

A model that accounts for the fully adaptive system of energy balance will account for both passive and active compensation.

Free-living Compensation Model Project

- Free-living adults with at least one objective measure of $\geq 80\%$ compliance
- Studies $N=31$, 40 treatment arms adjusted for control effects
- Diet ($n=4$), Exercise ($n=15$), Overfeeding ($n=9$)
High agreement between “no active compensation” prediction models, $r = .98$
Observed versus “no active compensation” prediction
Observed versus no active compensation prediction
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Compensating during exercise regimen by increased EI, not decreased EE

- **Sample**: 54 middle-aged men with sedentary lifestyles (BMI: 28±3)

- **Methods**: Used synchronized accelerometry and heart rate to observe prescribed and non-prescribed PAEE during an 18-week exercise intervention, plus 2 week “detraining period”

- **Results**: No significant decrease in non-prescribed PAEE to compensate for prescribed PAEE

- **Conclusion**: Losing less weight than predicted by PAEE likely a result of increased energy intake (both groups were allowed to eat *ad libidum*)

**Figure 1.** Physical activity energy expenditure (PAEE) throughout the study, no exercise group vs. prescribed exercise

Metabolic and Behavioral CompensatoryResponses to Exercise Interventions

Potential Methods of Compensation

Increased Energy Intake

Decreased Duration of non-exercise Energy Expenditure

Energy Intake increases in compensators with intensity of exercise. No exercise (Nex), moderate (Mex), and heavy (Hex), adapted from Stubbs et al. (2004)

Duration of non-exercise physical activity during a walking weight loss trial. Before the trial (PRE), non-walking days (INT-NW), walking days (INT-W), and after the trial (POST), adapted from Colley et al. (2005)

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How about Primates?

A rapidly occurring compensatory decrease in physical activity counteracts diet-induced weight loss in female monkeys.

“18 adult ovariectomized female monkeys were placed on a low-fat diet, and available calories were reduced by 30% compared with baseline consumption for 1 mo. Surprisingly, there was not significant weight loss.”

Projection of Effects in a Non-Adaptive System

Observed Effect in Single-Event Randomized Study (142 kcal deficit).

Erroneously predicted 1 year weight loss with 3500 kcal rule = (142*365)/3500 = 14.8 lbs.

Projected effect in of a 142 daily deficit assuming no adaptation = 4.9 lbs at 1 year.


http://www.pbrc.edu/research-and-faculty/calculators/weight-loss-predictor/
Short-Term Studies Are Insufficient: Example - *Learned* Compensation in Humans

**Learned Caloric Adjustment of Human Intake**

JEANINE LOUIS-SYLVESTRE, ALAIN TOURNIER, PHILIPPE VERGER, MICHÈLE CHABERT and BRIGITTE DELORME

*Laboratoire de Neurobiologie de la Nutrition E.P.H.E., Université Paris 6*

JOSEPH HOSSENLOPP

*Ecole Nationale des Sciences de l’Industrie Alimentaire*

*Appetite, 1989, 12, 95–103*
Metabolic and Behavioral Compensations in Response to Caloric Restriction (CR)

- **Subjects**: 48 (36.8 ± 1 y), overweight (BMI: 27.8 ± 0.7) participants randomized into 1 of 4 groups: Control, CR+Exercise (12.5%↓ EI+12.5%↑ EE), CR (25%↓ EI), and Low-Calorie Diet (LCD, 15% weight reduction and maintenance)

- **Results**: CR, LCD, and CR/LCD groups had significantly different TDEE from baseline at M3, and CR/LCD at M6; CR+EX did not have significantly different TDEE after intervention

- **Conclusion**: CR causes a “metabolic adaptation” by decreasing TDEE, but not when combined with EX as in the CR+EX group

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Lovejoy et al.

Consumption of a controlled low-fat diet containing olestra for 9 months improves health risk factors in conjunction with weight loss in obese men: the Ole' Study.

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Fig. 2. Food intake and body weight as functions of duration of exercise in normal adult rats.


See also:

**FIGURE 12-5** Body weight gain in various arctic expeditions lasting between 3 and 12 months.
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Results …indicate that simply reading about physical activity leads participants to compensate by serving themselves more snacks.

…we have consumer camp …At one of these, we said, “We’re through for the day but dinner isn’t ready yet so we’re going to take a one-mile walk around Beebe Lake.” The students who set the pace told them that it was either an exercise walk or a scenic walk.

… And it was an easy walk but the same pace and distance in both cases.

When they got back, they were given dinner, and they ended up eating more calories if they had been on the exercise walk. And most of the increase was from dessert. The exercise group estimated that they had burned more calories, and they ended up eating more calories.

[http://ht.ly/5WJCV](http://ht.ly/5WJCV)

**Design:** In a randomized, counterbalanced design, 11 active male participants completed 3 experimental trials in a fasted state: exercise in the heat (36°C), exercise in a neutral temperature (25°C), and a resting control (25°C). The exercise trials consisted of treadmill running for 40 min at 70% $\dot{V}O_2\text{peak}$. After each trial, participants were presented with a buffet-type breakfast of precisely known quantity and nutrient composition, which they could consume ad libitum.
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Because we cannot yet predict long-term changes in integrated energy balance from short-term studies of single components of energy balance, in research to determine efficacy and effectiveness (as opposed to studying potential mechanisms and promising approaches), we:

<table>
<thead>
<tr>
<th>Do Not Need</th>
<th>Need</th>
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<tr>
<td>• Surrogate or Intermediary Endpoints</td>
<td>• Ultimate Endpoints (e.g., weight, body composition)</td>
</tr>
<tr>
<td>• Weak non-randomized designs</td>
<td>• RCTs (or at minimum quasi-experiments)</td>
</tr>
<tr>
<td>• Short-term studies</td>
<td>• Long-term studies</td>
</tr>
</tbody>
</table>

“...let us take this path through the woods...”

~ Jean-Jacques Rousseau
Outline of Today’s Lecture

• History & Definitions
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• Reporting Results
Myths, Presumptions, and the Need for Probative Research in Obesity.

David B. Allison, Ph.D.D.
1. “The first [rule] was never to accept anything as true if I had not evident knowledge of its being so.” - René Descartes
2. What we think we know, but is wrong.
3. What we think we know, but do not.
4. Why do we hold erroneous beliefs?
5. How can we increase knowledge?
6. Conclusions
Obesity Prevalence: A First Exercise in Skepticism


[Image of map showing prevalence of self-reported obesity among U.S. adults BRFSS, 2011]
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**Myths:** Beliefs held true despite substantial refuting evidence.

<table>
<thead>
<tr>
<th>Myth</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large, rapid weight loss is associated with poorer long-term weight outcomes than is slow, gradual weight loss.</td>
<td></td>
</tr>
<tr>
<td>Small sustained changes in energy intake or expenditure will produce large long-term weight changes, e.g., increasing daily intake by 2 potato chips will cause 10 kg of weight gain in 10 years.</td>
<td></td>
</tr>
<tr>
<td>Setting realistic goals in weight loss therapy is important because otherwise patients will become frustrated and lose less weight.</td>
<td></td>
</tr>
<tr>
<td>Assessing “stage of change” or diet “readiness” is important in helping patients seeking weight loss treatment to lose weight.</td>
<td></td>
</tr>
<tr>
<td>Physical education classes as currently provided play an important role in preventing or reducing childhood obesity.</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding is protective against obesity.</td>
<td></td>
</tr>
<tr>
<td>A bout of sexual activity burns 100 to 300 kcal for each person involved.</td>
<td></td>
</tr>
</tbody>
</table>

Sometimes we do not stop to ask simple questions like: “How would someone know that?” and “Does this make any sense?”

**Myth: A bout of sexual activity burns 100 to 300 kcal for each person involved.**

Now, how would one figure this out?

### Table 3.—Average Vo₂ During Four Sexual Activities*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Baseline</th>
<th>Foreplay</th>
<th>Stimulation and Orgasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner stimulation</td>
<td>3.7 ± 0.8</td>
<td>4.5 ± 1.4</td>
<td>6.0 ± 1.8</td>
</tr>
<tr>
<td></td>
<td>(7 ± 2)</td>
<td>(8 ± 3)</td>
<td>(11 ± 3)</td>
</tr>
<tr>
<td>Self-stimulation</td>
<td>3.9 ± 0.7</td>
<td>4.5 ± 0.7</td>
<td>6.3 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>(7 ± 2)</td>
<td>(9 ± 2)↑</td>
<td>(12 ± 3)</td>
</tr>
<tr>
<td>Woman-on-top coitus</td>
<td>4.5 ± 0.6</td>
<td>5.1 ± 0.8</td>
<td>8.7 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>(9 ± 2)</td>
<td>(10 ± 2)</td>
<td>(16 ± 7)</td>
</tr>
<tr>
<td>Man-on-top coitus</td>
<td>4.0 ± 0.4</td>
<td>5.0 ± 1.0</td>
<td>11.7 ± 3.8</td>
</tr>
<tr>
<td></td>
<td>(8 ± 2)</td>
<td>(9 ± 2)</td>
<td>(22 ± 6)</td>
</tr>
</tbody>
</table>

### Table 4.—Duration of Four Sexual Activities*

<table>
<thead>
<tr>
<th>Activity</th>
<th>Duration, s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner stimulation</td>
<td>326 ± 179</td>
</tr>
<tr>
<td>Self-stimulation</td>
<td>196 ± 80</td>
</tr>
<tr>
<td>Woman-on-top coitus</td>
<td>352 ± 163</td>
</tr>
<tr>
<td>Man-on-top coitus</td>
<td>332 ± 257</td>
</tr>
</tbody>
</table>

(Arch Intern Med 1984;144:1745-1748)
Note, participants:
- Are 22 yrs old on average.
- Have been together for barely more than a year on average.
- Have been selected for being active and fit.
- Have been selected for describing their relationships in positive terms.
- Know they are being monitored.
Outline

1. “The first [rule] was never to accept anything as true if I had not evident knowledge of its being so.” - René Descartes

2. What we think we know, but is wrong.

3. What we think we know, but do not.

4. Why do we hold erroneous beliefs?

5. How can we increase knowledge?

6. Conclusions
Presumptions: Unproven Yet Commonly Espoused Propositions

<table>
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<tr>
<td>Regularly eating (versus skipping) breakfast is protective against obesity.</td>
</tr>
<tr>
<td>Early childhood is the period where we learn important exercise and eating</td>
</tr>
<tr>
<td>habits that influence our weight throughout life.</td>
</tr>
<tr>
<td>Eating more fruits and vegetables will produce weight loss or less weight</td>
</tr>
<tr>
<td>gain, regardless of whether one intentionally makes any other behavioral</td>
</tr>
<tr>
<td>or environmental changes.</td>
</tr>
<tr>
<td>Weight cycling (i.e. “yo-yo dieting”) increases mortality rate.</td>
</tr>
<tr>
<td>Snacking contributes to weight gain and obesity.</td>
</tr>
<tr>
<td>The built environment, in terms of sidewalk and park availability,</td>
</tr>
<tr>
<td>influences obesity.</td>
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The Benefit of Breakfast in Preventing and Reducing Obesity is Widely Espoused

“Eating a healthy breakfast is a good way to start the day and may be important in achieving and maintaining a healthy weight.”


“…there's ample evidence that the simple act of eating breakfast -- every day -- is a big part of losing weight, lots of weight.”

Jeanie Davis, WebMD

“If we always eat breakfast every day, we can impact long-term weight loss.”

Schaffner 2007 Gastroenterology Nursing

“The fact is, when you’re trying to lose body fat, you can’t skip breakfast “


“10 Weight Prevention Tips: Make sure to eat a healthy breakfast no later than 9 a.m., even if it means placing a bowl of oatmeal on your dressing table to eat while you put on your makeup.”


“Why, sometimes I've believed as many as six impossible things before breakfast.” ~ The White Queen (Through the Looking Glass, Lewis Carroll)

Fifty-two moderately obese adult women were stratified according to their baseline breakfast-eating habits and randomly assigned a weight-loss program.

The no-breakfast group ate two meals per day and the breakfast group ate three meals per day.

After 12-wk, this treatment-by-strata-by-time interaction effect (P less than 0.06) suggests that those who had to make the most substantial changes in eating habits to comply with the program achieved better results.
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In The Mass Media

**Headline:** Skipping breakfast to lose weight makes you fatter - and far more likely to raid the vending machine.

**Study:** Presentation at proceedings; MRI results and observations of how much subjects ate at lunch after skipping breakfast. No body weight, no vending machines.

**Headline:** Diet Soda Leaves Your Gut Unsatisfied, Contributes To Obesity.

**Study:** Assessment of metabolic responses to different carbohydrates loads of bacteria in vitro. Humans, diet soda, and obesity were not studied.

**Headline:** US Farm Subsidy Policies Contribute To Worsening Obesity Trends, Study Finds.

**Paper:** There is no study – paper is an author’s commentary/review on farm subsidies.

**Headline:** Drinking 5 cups of coffee everyday may lead to obesity: study.

**Headline:** Wrong amount of coffee could kill you.

**Study:** A study of mice, involving a substance found in coffee, but no coffee, showed no significant weight gain, and reported no deaths.

For references, see: [ObesityandEnergetics.org](http://ObesityandEnergetics.org).
So, Why Do We Believe So Many Unsupported Things?

1. Failure to Consider Energy Balance as an Adaptive System
2. Cognitive Biases
3. Distortions of Evidence (*White Hat Bias*)
Projection of Effects in a Non-Adaptive System

Observed Effect in Single-Event Randomized Study (142 kcal deficit).

Erroneously predicted 1 year weight loss with 3500 kcal rule = \((142\times365)/3500 = 14.8\) lbs.

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*Appetite, 1989, 12, 95–103*
Not Knowing When to Stop: The Mere Exposure Effect

‘A reliable way to make people believe in falsehoods is frequent repetition, because familiarity is not easily distinguished from truth. Authoritarian institutions and marketers have always known this fact. …you do not have to repeat the entire statement of a fact or idea to make it appear true. People who were repeatedly exposed to the phrase “the body temperature of a chicken” were more likely to accept as true the statement that “the body temperature of a chicken is 144°” (or any other arbitrary number).’

So, we often devote our journal pages, time, and resources to research that increases belief, instead of to research that increases knowledge.

Distortions in Press Releases: Example

Article (Int J Behav Phys Act):

Results: “Changes in rates of obesity for intervention school (28% baseline, 27% year 1, 30% year 2) were similar to those seen for control school (22% baseline, 22% year 1, 25% year 2) children.”

Press Release:

Kaiser Permanente Study Finds Students Eat Healthier When School-Based Nutrition Programs Involve Teachers, Staff and Parents

Tailored programs could reduce obesity, help implement federal wellness policies

In fairness, the 9th paragraph of the PR stated: “Although researchers hypothesized that these school environment and policy changes would reduce childhood obesity rates, no changes were observed.”


See also:

Cope & Allison. IJO, 2010


http://www.ijbnpa.org/content/9/1/80/abstract
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6. Conclusions
Why should we care if people exaggerate the benefits of some approaches?

Research report
Taking weight-loss supplements may elicit liberation from dietary control. A laboratory experiment

Yevvon Yi-Chi Chang a, Wen-Bin Chiou b,∗

**Grams of Candy Consumed**

<table>
<thead>
<tr>
<th></th>
<th>Purported Dietary Supplement</th>
<th>Purported Placebo</th>
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<tr>
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</tbody>
</table>
“...let us take this path through the woods...”

~ Jean-Jacques Rousseau
Outline of Today’s Lecture

• History & Definitions
• Unifying Principles
• Myths & Presumptions
• Curious Conjectures
• Roads Less Traveled
• Testing Foods
• Reporting Results
Some Time-Honored Observations.
"It is said by Confucius, 'We are not troubled with fears of poverty, but are troubled with fears of a lack of equality of wealth."

Part II - Obesity’s Final Toll

“Leave gormandizing. Know that the grave doth gape thrice wider for thee than for other men.”

-- Shakespeare

(Henry to Falstaff; Henry IV, part 2, Act 5, Scene 5)

Falstaff Reproved by King Henry (King Henry the Fifth, Part II).

Engraver: Shenner (French Artist, active late 18th century)

Designer: Bunbury, Henry William (1750-1811)
A ‘Grand Unified Theory’

- Low Social Status (Disparity)
- Perceived Energetic Uncertainty
- Energy Seeking & Storage
- Aging/Longevity
- Energy Rich Environment

+ + + ±
SES & Obesity

Nature of the relationship
FIGURE 2. Prevalence of obesity among women, by own socioeconomic status and socioeconomic status of origin.

Stunkard & Sobal’s Comprehensive Review

**Socioeconomic status and obesity: a review of the literature.**
*Sobal J, Stunkard AJ.*

“A review of 144 published studies of the relationship between socioeconomic status (SES) and obesity reveals a strong inverse relationship among women in developed societies. The relationship is inconsistent for men and children in developed societies.”
SES & Obesity

Is the relationship causal?
But is it causal?

Unfortunately, we cannot randomize children to high and low SES households…

or perhaps we have already?
How about randomizing people to higher SES neighborhoods?
Social and Physical Environmental Enrichment Differentially Affect Growth and Activity of Preadolescent and Adolescent Male Rats

Julia Zaias,1 Timothy J Queeney,2 Jonathan B Kelley,2 Elena S Zakharova,2 and Sari Izenwasser2,*

Figure 1. Body weight (g, mean ± SEM) of rats housed under different conditions beginning on postnatal (PND) 23. (A) PNDs 23 through 27. (B) PNDs 28 through 34. (C) PNDs 35 through 41. (D) PNDs 42 through 46. Data are given as a percentage of the group mean body weight on PND 23. 51 ± 1 g; (II) social deprivation (SD); (III) social enrichment (SE); (IV) no objects; (V) enriched cage with objects; and (VI) standard cage with objects.
So, if we just give people money, that will make them thin, right?
Food/Cash Programs may contribute to overweight and obesity in adults - Mexico

**FIGURE 2** Impact of the PAL on the body weight of women 18–49 y age. Values are difference-in-difference effects + SEM, estimated using individual fixed effects models. Difference-in-difference effects are the estimated change in body weight from baseline to follow-up between the treatment and control groups. Covariates included the interaction between the individual’s age group and the time of the survey, and the number of adult equivalents in the household. *Different from 0, P < 0.10; **different from 0, P < 0.05. PAL, Programa de Apoyo Alimentario.

SES & Obesity

Is perceived energetic uncertainty (in the face of a metabolizable energy surfeit) a mechanism of causation?
What An Adaptive System May Do When Its Energy Stream is Threatened


Social Status, Scarcity, and Weight Gain in Birds

Consider Fat Storage in *Parus major*

- *Parus major* (and many other birds) *increase* their fat reserves when food is scarce and variable.
- This effect is primarily among birds low in the social hierarchy.


- Subordinate status birds across many species (willow tit, great tit, greenfinch, chickadees, titmouse, nuthatch) carry greater fat reserves than dominant status birds (Gosler, 1996; Pravosudov et al., 1999).
Rats on The Bottom of the Totem Pole

Psychosocial stress induces hyperphagia and exacerbates diet-induced insulin resistance and the manifestations of the Metabolic Syndrome.


A Classic Definition of SES

A measure of an individual’s place within a social group based on various factors, including income and education.

crede.berkeley.edu/tools/glossary.html
What is the Pope’s SES?

The Vatican spokesman, Joaquín Navarro-Valls, ended speculation about the Pope’s salary, saying, "The Pope does not and has never received a salary." [07/20/2001]

From:
Perhaps It’s the Socio, Not the Economic

N.E. Adler, E.S. Epel, G. Castellazo and J.R. Ickovics, Relationship of subjective and objective social status …Health Psychology, 19, 586-592.
Team defeat and food consumption

**Study 1 (Obs):** Sat. fat and total kCal intake higher in NFL cities experiencing defeat

**Study 2 (RCT):** French sport fans consumed more sat. fat and sugar after recalling defeat in a RCT

**Study 3 (RCT):** French fans that engaged in “self-affirmation” before watching soccer game ate more healthy food regardless of victory or defeat

---


In 2005...conducted a representative survey of 435 adult residents of low-income census tracts in Massachusetts.

After adjusting for age, sex, sociodemographic characteristics and food insecurity, both participation in the Food Stamp Program (FSP) and participation in any federal nutrition programme 12 months prior to the survey were each associated with an approximate 3.0 kg/m2 higher adult BMI. ...However, prolonged participation in the FSP was associated with lower BMI.
Economic Insecurity

Why the Poor Get Fat: Weight Gain and Economic Insecurity*

Trenton G. Smith, Christiana Stoddard, and Michael G. Barnes

Abstract

Something about being poor makes people fat. Though there are many possible explanations for the income-body weight gradient, we investigate a promising but little-studied hypothesis: that changes in body weight can—at least in part—be explained as an optimal response to economic insecurity. We use data on working-age men from the 1979 National Longitudinal Survey of Youth (NLSY79) to identify the effects of various measures of economic insecurity on weight gain. We find in particular that over the 12-year period between 1988 and 2000, the average man gained about 21 pounds. A one percentage point (0.01) increase in the probability of becoming unemployed causes weight gain over this period to increase by about 0.6 pounds, and each realized 50% drop in annual income results in an increase of about 5 pounds. The mechanism also appears to work in reverse, with health insurance and intrafamily transfers protecting against weight gain.
Meal patterns of mice under systematically varying approach and unit costs for food in a closed economy.

Atalayer D, Rowland NE.

“In stratified analyses of the 23 high-income and 10 middle-income countries with less economic variation, economic level of the country explained little of the social inequality. Economic inequality as measured by Gini coefficient was more important in explaining both level of and inequality in overweight among adolescents.”


<table>
<thead>
<tr>
<th>Country prevalence of overweight</th>
<th>All 33 countries</th>
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<tr>
<td></td>
<td>Crude</td>
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<td><strong>Boys</strong></td>
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<td><strong>Girls</strong></td>
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<td>Gini</td>
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<tr>
<td>Est</td>
<td>0.0011</td>
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<td>s.e.</td>
<td>0.0013</td>
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Abbreviations: Est, estimates; s.e., standard error. <sup>a</sup>As classified according to <sup>b</sup>GNI and Gini mutually adjusted.
“…we show the reciprocal association between the incentive value of food and of money. In Study 1, hungry participants were less likely than satiated participants to donate to charity. In Study 2, participants in a room with an olfactory food cue, known to increase the desire to eat, offered less money in a give-some game compared with participants in a room free of scent. In Study 3, participants’ desire for money affected the amount of M&M’s they ate in a subsequent taste test, but only among participants who were not restricting their food intake in order to manage their weight.

Perhaps in present-day societies, the attraction to money is so powerful that people who, relatively speaking, fail in their quest for (more) money become frustrated. Accordingly, as financial and caloric resources are exchangeable, they might tend to appease their desire for money by consuming more calories than is healthy.”

“As predicted, hungry male participants preferred ideal romantic partners who were relatively heavier (>120 lbs) and satiated males preferred ideal partners who were relatively lighter (<120 lbs)...p<.01”

“As predicted, hungry male participants preferred ideal partners who were slightly older...than themselves and full males preferred ideal partners who were slightly younger...p<.001”

CR & Longevity

There is clearly a causal relationship.
Calorie Restriction and Life Span

Mean and maximum life spans in yeast, rotifers, water fleas, nematodes, fruit flies, spiders, fish, hamsters, rats, mice, and dogs have been extended significantly by decreasing normal caloric consumption by 30+ percent of *ad libitum* intake.
Caloric restriction delays disease onset and mortality in rhesus monkeys

Caloric restriction delays disease onset and age-related mortality in rhesus monkeys

OK, I admit it, it works in Madison Wisconsin, but not in Poolesville Maryland and we don’t know why (yet).

CR & Longevity

Is perceived energetic uncertainty (independent of immediate energy intake) a mechanism of causation?
Definitions: Hormeses & Allostasis

Main Entry: hor·me·sis
Pronunciation: \hόr-ˈmē-səs\ 
Function: *noun*

: a theoretical phenomenon of dose-response relationships in which something (as a heavy metal or ionizing radiation) that produces harmful biological effects at moderate to high doses may produce beneficial effects at low doses


Whereas homeostasis is the process by which bodily functions are maintained, allostasis is the process by which they change in response to environmental challenges.

A Vital Role for Hunger or Is the Perception of Restriction Necessary and Sufficient?
Perhaps not necessary:

Nonetheless, the depressing message from *C. elegans* and *Drosophila* is clear: if you want to live longer, eat much less and don’t enjoy it.


Julian A. T. Dow
University of Glasgow
j.a.t.dow@bio.gla.ac.uk

Goodrick et al. Every Other Day Feeding Results

Figure 3. (A) Survival and (B) mean body weight for male C57BL/6J mice fed ad libitum (AL, dashed lines) or every other day (EOD, solid lines) from 1–2 months of age ($n = 40$ at start of experiment). Taken from Goodrick et al. (1990).

Note: These results were not obtained in all strain, sex, and age combinations.
But What About Us Humans Who Repeatedly Gain and Lose Weight?

Allison, Nagy, Smith, Vasselli, Yang - NIA funded R01 Animal Study Underway
Allison, Nagy, Smith, Vasselli, Yang (unpublished)
What Might This Imply About Calorie Restriction Mimetics?

- Rapamycin – Yes
- Acarbose – Yes (ITP; unpublished)
- Metformin – Maybe – Mixed results
- Anorexigenic compounds - ????
- Orexigenic compounds - ????
Acarbose, 17-α-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males

David E. Harrison,1* Randy Strong,2,3,4,5* David B. Allison,6 Bruce N. Ames,7 C. M. Astle,1 Hani Atamna,7 Elizabeth Fernandez,2,3,4,5 Kevin Flurkey,1 Martin A. Javors,2,8 Nancy L. Nadon,9 James F. Nelson,2,10 Scott Pletcher,11 James W. Simpkins,12 Daniel Smith,13 J. E. Wilkinson14 and Richard A. Miller15*
Metformin increases survival and improves physical performance

P = 0.02

P = < 0.001
Orexigenic LY444711, a Ghrelin analogue donated by Lilly

Return to a ‘Grand Unified Theory’

- Low Social Status (Disparity)
- Perceived Energetic Uncertainty
- Energy Seeking & Storage
- Aging/Longevity
- Energy Rich Environment

Arrows indicate positive relationships. A plus symbol (+) denotes a positive relationship between entities.
Implications
(if hypotheses are true)

1. Efforts to identify leverage points that affect *perceptions* of energetic uncertainty may be as or more important than identifying specific economic leverage points.

2. Environmental manipulations which lead to the *perception* of restricted food availability may have paradoxical effects.

3. Some CR mimetics may need to work downstream of ‘hunger’ signals to be effective.

4. Even discounting side-effects, losing weight with an anorexigen may be less beneficial than losing an equivalent amount of weight with CR.

5. It is plausible that the perception of energetic uncertainty is a signal leading to adaptive responding that both increases fat deposition when sufficient metabolizable energy is available, and leads to increased lifespan if conditions are otherwise permissive.
Transformative R01 Investigative Team

David B. Allison, PI
John R. Speakman
Neil Rowland
Alessandro Bartolomucci
Daniel Smith
Tim R. Nagy
Inga Kadish
Scott Pletcher
Daniel Hahn
Martin Young
Karen Gamble
Kathryn Kaiser
Molly Bray
2012 Transformative R01 Award Recipients

David B. Allison, Ph.D.
University of Alabama at Birmingham, AL
Project Title: *Energetics, Disparities, & Lifespan: A unified hypothesis*

The evolution and ontogeny of lifespan at the species and individual level involves multiple interacting, metabolizable energy as body fat, and socioeconomic disparities within and between these interrelations is poorly understood. Indeed, questions as fundamental as why caloric restriction leads to increased lifespan and why low-fat diets also remain unanswered. The research proposes a unified model informed by these phenomena. In this model, aging or more precisely senescence is caused by environmental insults or from metabolizing fuel. That is, mortality rate or lifespan is a phenomenon much like the control of body temperature in homeotherms. It is the energetic state of the environment. From this perspective, it is perhaps the most important factor in linking these phenomena. We test this hypothesis using metabolic regulation and other potential mechanisms.
Peavine Falls, Oak Mountain Park, Alabama
From: http://www.encyclopediaofalabama.org/face/Multimedia.jsp?id=m-2698

Thank You
Outline of Today’s Lecture

• History & Definitions
• Unifying Principles
• Myths & Presumptions
• Curious Conjectures
• Roads Less Traveled
• Testing Foods
• Reporting Results
Feral Rats in Baltimore are Getting Heavier

- Easterbrook et al. A survey of zoonotic pathogens carried by Norway rats in Baltimore, Maryland, USA. *Epidemiol Infect.* 2007 Jan 15;:1-8
The Plurality of Obesity Epidemics: Many Mammalian Populations Are Getting Heavier and Yet Have No Access to the Factors Commonly Postulated to Affect Human Obesity

“There are more things in heaven and earth, Horatio, Than are dreamt of in your philosophy.”
~ William Shakespeare

The “Beginner’s Mind”

“In the beginner’s mind there are many possibilities. In the expert’s mind there are few.”

Shunryu Suzuki
Chronic Consumption of Farmed Salmon Containing Persistent Organic Pollutants Causes Insulin Resistance and Obesity in Mice

Mohammad Madani Ibrahim⁴, Even Fjærø⁴, Erik-Jan Lock⁴, Danielle Naville⁴, Heidi Amlund⁴, Emmanuelle Meugnier⁴, Brigitte Le Magueresse Battistoni⁴, Livar Frøyland⁴, Lise Madsen⁴, Niels Jessen⁵, Sten Lund⁶, Hubert Vidal⁴, Jérôme Ruzzin⁴,⁷*
Two mice at 12 wks of study (courtesy Tim Nagy)

Mouse housed at 22° C

Mouse housed at 27° C

Ambient Temperature

Effect of environmental temperature on growing-finishing pig performance
Can genetic factors be contributing to the obesity epidemic?

“Although genes do influence individual differences in susceptibility to obesity, trends have increased; therefore, population wide obesity can be explained only by changes in environments” – Institute of Medicine (Accelerating Progress in Obesity Prevention: Solving the Weight of the Nation)


Assortative Mating

Hypothetical Data: Increasing Prevalence of Obesity as a Result of Assortative Mating

Pharmaceutical Iatrogenesis

95% CI for weight change (kg)

Numbers of visits to US doctors’ practices by patients aged ≤20 years in which antipsychotic drugs were prescribed

Cognitive Demand: Does Thinking Make You Fat?

- 45-minute cognitively demanding tasks increased *ad libitum* energy intake by 200 to 250 kcal in young normal weight women compared to resting control (Chaput JP et al. Psychosom Med. 2008, 70(7):797-80).


For review, see: J.-P. Chaput, L. Klingenberg, A. Astrup and A. M. Sjödin. Obesity Reviews (2011) 12, e12–e20. Also, see reference list at end.
It May Matter
What One Is Thinking


Results …indicate that simply reading about physical activity leads participants to compensate by serving themselves more snacks.

…we have consumer camp …At one of these, we said, “We’re through for the day but dinner isn’t ready yet so we’re going to take a one-mile walk around Beebe Lake.” The students who set the pace told them that it was either an exercise walk or a scenic walk.

…And it was an easy walk but the same pace and distance in both cases.

When they got back, they were given dinner, and they ended up eating more calories if they had been on the exercise walk. And most of the increase was from dessert. The exercise group estimated that they had burned more calories, and they ended up eating more calories.

http://ht.ly/5WJCV
Comparison of average post-exercise food intake

Figure 1 Comparison of average post-exercise food intake between the exercise group sessions with entertainment-related and exercise-related conversations (error bars with 5% error).

Daily food intake and body weight changes in OR rats during sleep deprivation

The analysis indicated that sleep-deprived OR rats’ body weight was significantly higher on the 5th (P < 0.001) day and remained significantly greater through the end of the study.

Mavanji V; Teske JA; Billington CJ; Kotz CM. (2012). Partial sleep deprivation by environmental noise increases food intake and body weight in obesity resistant rats. Obesity; http://dx.doi.org/10.1002/oby.20182
Insufficient sleep undermines dietary efforts to reduce adiposity

Arlet V. Nedeltcheva, MD, Jennifer M. Kilkus, MS, Jacqueline Imperial, RN, Dale A. Schoeller, PhD, and Plamen D. Penev, MD, PhD
Four Interlinked Modern-Day Lifestyle Factors:

1. Light Exposure at Night
2. Less Sleep
3. Disrupted Circadian Rhythms
4. High Cognitive Demand Activities

(Fonken et al., PNAS, 2010)
Association of light at night with BMI with humans

P = 0.047

Light and placebo interventions – dynamics of body mass

**Fig. 1.** Dynamics of body mass and subjective scores following light and placebo interventions in 34 women wishing to lose excess weight. The week 0 value is assigned to 100%. Difference between corresponding values at light and placebo sessions: * p < 0.05, ** p < 0.01, *** p < 0.001, by either paired Student t-test (for body mass) or paired sign test (for subjective scores), based on absolute values (see column ‘ΔΔ’ in table 3).

## Microorganism-Induced Obesity

### Characteristics of Twins Sample (n=28)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antibody Positive</th>
<th>Antibody Negative</th>
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<tr>
<td>Age (years)</td>
<td>33.0 ± 15.7</td>
<td>33.0 ± 15.7</td>
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<tr>
<td>Sex (female/male) (%)</td>
<td>79/21</td>
<td>79/21</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 9.8</td>
<td>24.5 ± 9.5*</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>29.6 ± 9.5</td>
<td>27.5 ± 9.9*</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.73 ± 1.37</td>
<td>4.75 ± 1.26</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)†</td>
<td>1.48 ± 0.59</td>
<td>1.48 ± 0.42</td>
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</table>

±Standard deviation; *P<.04 vs antibody positive; †triglycerides measured on only 16 of the twin pairs because the others were not fasting.

Putative Contributors to the Secular Increase in Obesity: Exploring the Roads Less Traveled

“‘They left out global warming. I'm saying that in jest,’ said a skeptical Dr. Thomas Robinson, director of the Center for Healthy Weight at Lucile Packard Children's Hospital at Stanford University.”


Marmots fatten up on climate change

Rodent population boom linked to bigger bellies and longer summers.

Lucas Laursen

In the Upper East River Valley of Colorado’s Rocky Mountains, yellow-bellied marmots (Marmota flaviventris) are thriving thanks to climate change. The rodents’ startling population boom — their numbers have tripled in ten years — has now been linked to the increasing size of their bellies, which is probably caused by climate-driven changes in hibernation patterns.


The Dynamics of Phenotypic Change and the Shrinking Sheep of St. Kilda

Arpat Ozgul,1 Shripad Tuljapurkar,2 Tim G. Benton,3 Josephine M. Pemberton,4 Tim H. Clutton-Brock,5 Tim Coulson6*

Environmental change, including climate change, can cause rapid phenotypic change via both ecological and evolutionary processes. Because ecological and evolutionary dynamics are intimately linked, a major challenge is to identify their relative roles. We exactly decomposed the change in mean body weight in a free-living population of Soay sheep into all the processes that contribute to change. Ecological processes contribute most with selection— the underlying mechanisms that determine the observed phenotypic trend. Nevertheless, a systematic change in the underlying population has so little effect even though it is the cause of the change. Evolutionary change has


Science 24 July 2009
325: 464-467
Social and Physical Environmental Enrichment Differentially Affect Growth and Activity of Preadolescent and Adolescent Male Rats

Julia Zaias, Timothy J Queeney, Jonathan B Kelley, Elena S Zakhrova, and Sari Izenwasser

Figure 1. Body weight (g, mean ± SEM) of rats housed under different conditions beginning on postnatal day 23. (A) PND 23 through 27. (B) PND 24 through 28. (C) PND 25 through 29. (D) PND 26 through 30. Data are given as a percentage of the group mean body weight on PND 23. Symbols represent the group as follows: I, isolated; E1, enriched with an object; E2, enriched with a wire cage; E3, enriched with a box; E4, enriched with a large cage and a box. Error bars represent SEM.
Another Perspective on Socioeconomic Status


A Final Conjecture: Could Beneficence, Security, Equality and Education be the Answer?


“...let us take this path through the woods...”

~ Jean-Jacques Rousseau
Outline of Today’s Lecture

• History & Definitions
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• Testing Foods
• Reporting Results
Are Some Foods More Fattening than Others?

What Does this Mean and How do we Test It?

David B. Allison, Ph.D.D.
Disclosure

I have received financial and other benefits from the following entities: the Frontiers Foundation; The Federal Trade Commission; and numerous additional government, non-profit and for-profit (including publishing, food, beverage, and pharmaceutical companies) organizations with interests in obesity, nutrition, and health.

Email: Dallison@UAB.edu

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Emily Dhurandhar
Andrew Brown
Dwight Lewis
Greg Pavela
Suzanne Judd
1. Gedankenexperiments
2. The Laws of Thermodynamics
3. A General Model of Conceivable Effects
4. Questions Which Can Be Asked & Parallel Play
5. The Inadequacy of Non-Randomized Studies for This Context
6. Specific Design Issues
7. Conclusions
Imagine a hypothetical world similar to our own in which the same laws of thermodynamics hold, but in which there is no measurement error and distributions of variables among humans may be different than they are in our world. In this hypothetical world, there is also an obesity epidemic and investigators wish to know why. Some investigators are predisposed to see energy intake (EI) as the key problem, whereas others are predisposed to see energy expenditure (EE) as the key problem.
Gedankenexperiment - II

To investigate this, Investigator A carefully plans an epidemiologic study. Based on prior research, he develops a method to select people who are currently in energy balance but are predicted to gain weight over some interval of time. His algorithm works beautifully and he successfully recruits 1 million people of optimal weight, of exactly the same height, all born on the same day 20 years prior to the study, who are all in energy balance at baseline. He then follows them until time $t$. At $t$, he amazingly finds that every single person in the sample has increased their body energy stores by $d$ units. Examination of the EI and EE data reveal that every single person increased their EI zero units and decreased their EE $c$ units. Investigator A concludes “Well, among people who gain excess weight there is no increase in EI and a decrease in EE, so all the weight gain is due to decreased EE.”
In contrast, Investigator B plans an alternative study. He takes a *random sample* of 1 million people of optimal weight, of exactly the same height, all born on the same day 20 years prior to the study, who are all in energy balance at baseline. He also follows them until time $t$. At $t$, he amazingly finds that half the people in his sample increased their body energy stores by $d$ units. Examination of the EI and EE data reveal that every single one of the people who increased their energy stores by $d$ units also increased their EI zero units and decreased their EE $c$ units. This is the same result that Investigator A obtained. In the other half of the sample, Investigator B finds that everyone stayed in perfect energy balance such that change in body energy stores was zero for everyone. Interestingly, even in this second half of the sample, examination of the EE data reveal that every single one of the people who maintained stable energy stores also decreased their EE $c$ units, just like the weight gainers. However, they all also decreased their EI $c$ units resulting in energy balance. Investigator B looks at his data and says “Gee, weight gainers and weight maintainers do not differ at all in the changes in EE. In contrast, I can perfectly predict who will gain weight by examining changes in EI, so all the weight gain is due to energy intake.”
Who, if either, is correct?
Example of Real Epidemiologic Study

• “…strategies to help people consume fewer calories may be most effective when particular foods and beverages are targeted for decreased (or increased) consumption.”
  
A Hypothetical Perfect Epidemiological Study

• Objective: To test whether some foods increase energy stores ($S$) more than other foods.

• Data: $Y$ years of perfectly recorded energy expenditures ($E$) and energy intake from each food source ($I_1 \ldots n$), all expressed in energy units.

$$\Delta S = -\beta E + \beta I_1 + \beta I_2 + \ldots \beta I_n$$

Doesn’t the 1st Law of Thermodynamics Require that $\beta$ is a constant?
Outline

1. Gedankenexperiments
2. The Laws of Thermodynamics
3. A General Model of Conceivable Effects
4. Questions Which Can Be Asked & Parallel Play
5. The Inadequacy of Non-Randomized Studies for This Context
6. Specific Design Issues
7. Conclusions
(a) The First Law of Thermodynamics
Energy transformation

Energy before → Energy after

(b) The Second Law of Thermodynamics
Energy transformation

Energy before → Usable energy after

Closed system
Energy is transformed → Unusable energy
Free energy

From: https://smartsite.ucdavis.edu/access/content/user/00002950/bis10v/week2/2webimages/figure-06-03b.jpg

Outline

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4. Questions Which Can Be Asked & Parallel Play
5. The Inadequacy of Non-Randomized Studies for This Context
6. Specific Design Issues
7. Conclusions
How Foods May Be Fattening

**T₀: Consumption of Food A**

1. Compared to other foods, intake of food A leads to more subsequent intake of food A (yumminess or ‘addiction’).
2. Compared to intake of other foods, intake of food A suppresses intake of subsequent foods less.
3. Intake of food A decreases physical activity energy expenditure.
4. Intake of food A decreases metabolic rate.
5. Intake of food A affects nutrient partitioning.

**T₁: Body Fat Stores**
Outline

1. Gedankenexperiments
2. The Laws of Thermodynamics
3. A General Model of Conceivable Effects
4. Questions Which Can Be Asked & Parallel Play
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7. Conclusions
Parallel Play

From: http://adambowker.wordpress.com/tag/play/
Is Dietary Fat “Fattening”? A Comprehensive Research Synthesis

JAMES M. SHIKANY,1,6 LAURA K. VAUGHAN,2,6 MONICA L. BASKIN,3,6 MARK B. COPE,4,6 JAMES O. HILL,5 and DAVID B. ALLISON2,6

<table>
<thead>
<tr>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) “What are the effects on body weight and body fat if the prescribed proportion of ingested energy from fat under isoenergetic conditions is altered?”</td>
</tr>
<tr>
<td>2) “What are the effects on body weight and body fat if the prescribed proportion of ingested energy from fat under <em>ad libitum</em> but confined conditions is altered?”</td>
</tr>
<tr>
<td>3) “What are the effects on body weight and body fat if the prescribed proportion of ingested energy from fat under <em>ad libitum</em>, non-confined conditions is altered?”</td>
</tr>
<tr>
<td>4) “What are the effects on body weight and body fat if the prescribed proportion of ingested energy from fat in a defined subset of the diet – a daily snack – under <em>ad libitum</em>, non-confined conditions is altered?”</td>
</tr>
</tbody>
</table>

• “...apparent disagreements [concerning dietary fat on body weight and adiposity] occur in large part because authors implicitly have been addressing distinct and separate questions that have not been articulated crisply.”
<table>
<thead>
<tr>
<th>Condition</th>
<th>Oversimplified Results - Effect of high fat vs. low fat on weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoenergetic</td>
<td>High-Fat dieters had greater weight loss</td>
</tr>
<tr>
<td>ad libitum, but confined</td>
<td>No effect</td>
</tr>
<tr>
<td>ad libitum, non-confined</td>
<td>Reduced-fat dieters had greater weight loss</td>
</tr>
<tr>
<td>snacking ad libitum, non-confined</td>
<td>No effect</td>
</tr>
</tbody>
</table>
Outline

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Observational Study Results Are Often Discordant with RCT Results in Nutrition

The Measurement Problem

Self-report–based estimates of energy intake offer an inadequate basis for scientific conclusions

Dale A Schoeller
Diana Thomas
Edward Archer
Steven B Heymsfield
Steven N Blair
Michael I Goran
James O Hall
Richard L Atkinson
Barbara E Corkey
John Foreyt
Nikhil V Dhandhukar
John G Kral
Kevin D Hall
Barbara C Hansen
Berit Lilienthal Heitmann
Eric Ravussin
David R Allison


Just because the measurement method one has is the best available, does not make it adequate.
Why? Non-Random Assignment & Confounding

The Lanarkshire Milk Experiment: In the spring of 1930, a large scale nutritional was carried out in the schools of Lanarkshire. For four months, 5000 children received raw milk, 5000 received pasteurized milk, and 10,000 were controls.

DV: Height & Weight
Assignment: Teachers broke from randomization.
Results: No significant differences.
WHAT WENT WRONG?

Suppose we could effectively eliminate measurement error, genetic variation, smoking, socioeconomic status, and other ‘usual’ suspects as confounders?

Would An Observational Study Then Recapitulate a Randomized Effect Estimate?

But, within *ad lib* group, the correlation between self-selected average lifetime daily intake and lifespan is positive \((r=0.45, p=0.0056)\).

Allison, Yang, Smith, & Nagy (ongoing study)
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“Let the experiment be made.”
~ Benjamin Franklin

Commission included Antoine Lavoisier, Benjamin Franklin, Jean Sylvain Bailly, and Joseph-Ignace Guillotin
Food Energy Estimation

- Gross Energy
- Digestible Energy
- Metabolizable Energy
- Net Energy

Feces
Urine and Heat
Discrepancy between the Atwater factor predicted and empirically measured energy values of almonds in human diets \(^1,^2,^3,^4\)

Janet A Novotny, Sarah K Gebauer, and David J Baer

**Empirical**

32% overestimation

kcal per 28 g serving: 129 \hspace{1em} 169

So, *let us not sweep fecal losses under the rug.*
Controlling for Non-specific Effects: Consider 2 Different Studies

**Treatment**
- Biweekly home delivery of water and diet drinks for 1st year
- Monthly motivational phone calls and written messages for 1st year

**Control**
- Mailed $50 supermarket gift cards at 4- and 8-month mark of year-1

**Treatment**
- Custom 1 can/day non-caloric artificially sweetened drink

**Control**
- Custom 1 can/day caloric sugar-containing drink that was packaged and tasted very similar to treatment’s

A Randomized Trial of Sugar-Sweetened Beverages and Adolescent Body Weight
Cara B. Ebbeling, Ph.D., Henry A. Feldman, Ph.D., Virginia R. Chomitz, Ph.D., Tracy A. Antonelli, M.P.H., Steven L. Gortmaker, Ph.D., Stavroula K. Osganian, M.D., Sc.D., and David S. Ludwig, M.D., Ph.D.

A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children
Janne C. de Ruyter, M.Sc., Margreet R. Olthof, Ph.D., Jacob C. Seidell, Ph.D., and Martijn B. Katan, Ph.D.

N Engl J Med. 2012 October; 367(15)
Short-Term Studies Are Insufficient: Example - *Learned* Compensation in Humans

![Graphs showing learned caloric adjustment of human intake.](image)

*Appetite, 1989, 12, 95–103*

**Learned Caloric Adjustment of Human Intake**

JEANINE LOUIS-SYLVESTRE, ALAIN TOURNIER, PHILIPPE VERGER, MICHELE CHABERT and BRIGITTE DELORME

*Laboratoire de Neurobiologie de la Nutrition E.P.H.E., Université Paris 6*

JOSEPH Hosstenlopp

*Ecole Nationale des Sciences de l'Industrie Alimentaire*
Consider this Hypothetical 2-Arm RCT of an Isocaloric Feeding Study

Interpretation: “Low Carb Diets Produce More Weight Loss.”

New Interpretation: “Macronutrient Deficient Diets Produce More Weight Loss.”

Interpretation: “Low Carb Diets Produce More Weight Loss”
An Extreme Example of Confounding Conceptual IV with Operationalization

“The eight-week pilot study compared adoption of five different dietary approaches: vegan, vegetarian, pesco-vegetarian, semi-vegetarian, or omnivorous, on weight loss in 63 adults affected …."

A ‘fair’ control group would have been a group permitted to eat only red meat.
Complexities in Testing Foods: What Are we Really Testing?

- High Carbohydrate Diet
  - Low Chewing Diet
  - Low Macho Diet
    - Perceptions?
    - Beliefs?
    - Experimenter Expectancies?
    - Palatability?
    - etc

- Low Carbohydrate Diet
  - High Chewing Diet
  - High Macho Diet

If one believes one is testing the physiochemical effects of the food, does one need to do this blinded?
A double-blind, placebo-controlled test of 2 d of calorie deprivation: effects on cognition, activity, sleep, and interstitial glucose concentrations\textsuperscript{1-4}

Harris R Lieberman, Christina M Caruso, Philip J Niro, Gina E Adam, Mark D Kellogg, Bradley C Nindl, and F Matthew Kramer
But, What If Cephalic Phase Response Is Key to Effect?

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Conclusions

• There are many different meanings to the questions of whether one food is more fattening than another and each demands a different design and may have a different answer.

• Observational studies are not reliable substitutes for randomized experiments.

• Operationalize one’s independent variable is vital to interpretation of any observed effect and use of unblinded foods creates challenges.

• Expectancy, placebo, and other non-specific effects need to be considered and controlled as appropriate.
“...let us take this path through the woods...”

~ Jean-Jacques Rousseau

Peavine Falls, Oak Mountain, Al

Outline of Today’s Lecture

• History & Definitions
• Unifying Principles
• Myths & Presumptions
• Curious Conjectures
• Roads Less Traveled
• Testing Foods
• Reporting Results
Simple steps that could improve the use, reporting, and interpretation of epidemiologic research
Outline

1. Historical context

2. Psychological Context

3. Some Challenges and Potential Solutions
   A. Causal Language
   B. Distorted Press Releases
   C. Analytic Fiddling/Bungling
   D. Undisclosed multiple testing
   E. Not knowing when to stop
   F. Publication Bias
   G. Reporting Bias
   H. Measurement error
   I. Selective or mis-citation
Historical Context
Historical Context: The Problem is Not New

- Brother Gregor Mendel
- Louis Pasteur
- Sir Cyril Burt
- Dominique Cassini’s suppression of Ole Roemer’s 1676 demonstration of the finite speed of the light.
- Leopold Kronecker’s attempted suppression of Cantor's work on infinities.
- And even the great Sir Isaac in corresponding with Leibniz about the calculus: “…because I cannot proceed with the explanation of it now, I have preferred to conceal it thus: 6accdae13eff7i3l9n4o4qrr4s8t12ux.”
Psychological Context
Which would you choose to stand closer to, chocolate or dog feces?

Causal Language
Use of Causal Language in Observational Studies of Obesity and Nutrition

Stacey S. Cofield\textsuperscript{a}  Rachel V. Corona\textsuperscript{b}  David B. Allison\textsuperscript{a,c}

Percent of articles using unjustified causal language.
Statement on matching language to the type of evidence used in describing observational studies vs. randomized trials

Editors of the Heart Group Journals*

<table>
<thead>
<tr>
<th>Type of language</th>
<th>Randomized trial</th>
<th>Observational study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive statements</td>
<td>'reduced the risk by'</td>
<td>'a lower risk was observed'</td>
</tr>
<tr>
<td>Descriptive nouns</td>
<td>'relative risk reduction'</td>
<td>'there is a relationship'</td>
</tr>
<tr>
<td>Verbs</td>
<td>'affected'</td>
<td>'is associated with'</td>
</tr>
<tr>
<td>Incorrect terms/avoid using</td>
<td>'caused'</td>
<td>'correlates with'</td>
</tr>
<tr>
<td></td>
<td>'modulated risk'</td>
<td>'risk ratio'</td>
</tr>
<tr>
<td></td>
<td>'treatment resulted in'</td>
<td>'difference in risk'</td>
</tr>
<tr>
<td></td>
<td>'reduced hazard'</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>'reduced risk' (active verb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'lowered risk' (active verb)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>'benefit'</td>
</tr>
</tbody>
</table>
Distorted Press Releases
Distortions in Press Releases and Media Interviews: Example

Article (Int J Behav Phys Act):

Results: “Changes in rates of obesity for intervention school (28% baseline, 27% year 1, 30% year 2) were similar to those seen for control school (22% baseline, 22% year 1, 25% year 2) children.”

Press Release:

Kaiser Permanente Study Finds Students Eat Healthier When School-Based Nutrition Programs Involve Teachers, Staff and Parents

Tailored programs could reduce obesity, help implement federal wellness policies

In fairness, the 9th paragraph of the PR stated: “Although researchers hypothesized that these school environment and policy changes would reduce childhood obesity rates, no changes were observed.”

See also:
-Cope & Allison. IJO, 2010
Suggestion: Peer-Reviewed Press Releases Issued by Journal
Analytic Fiddling/Bungling
Distortions via Statistical Fiddling & Bungling

Simulated Distribution of p-values all nulls true.

Simulated Distribution of p-values some nulls false.

Simulated p-values all nulls true + ‘Fiddling’.

Real data (N=347 obesity RCTs; p for dip = .052)

Suggested mitigators:

1. Public disclosure of data analysis plan before publication.
2. Public availability of raw data.
3. Build in expectations and resources for high-level analysis checking.
Undisclosed multiple testing

- See Stan’s Presentation
- Again, public documentation of pre-analysis plan
Not Knowing When to Stop
‘A reliable way to make people believe in falsehoods is frequent repetition, because familiarity is not easily distinguished from truth. Authoritarian institutions and marketers have always known this fact. …you do not have to repeat the entire statement of a fact or idea to make it appear true. People who were repeatedly exposed to the phrase “the body temperature of a chicken” were more likely to accept as true the statement that “the body temperature of a chicken is $144^\circ$” (or any other arbitrary number).’

So, we often devote our journal pages, time, and resources to research that increases belief, instead of to research that increases knowledge. **Solution:** Without creating publication bias, more effectively limit rewards for minimally informative research.
Publication Bias
Distortions Via Publication Bias

Simulated Data

WHO Report on Breast-Feeding and Obesity

Norma Terrin, Christopher H. Schmid, Joseph Lau
Journal of Clinical Epidemiology, Volume 58, Issue 9, September 2005, Pages 894–901
http://dx.doi.org/10.1016/j.jclinepi.2005.01.006

Proposed Solution to Publication Bias

• Mandatory Publication for all studies done:
  – At non-profit institutions
  – With human subjects
  – With government or philanthropic funds

• Can be simple self-publication of technical report on government or institution website.
Reporting Bias
Reporting Inconsistent with Trial Registration

From ClinicalTrials.Gov.
http://clinicaltrials.gov/ct2/show/NCT00777647?term=NCT00777647&rank=1

• Title of trial is “Effect of Carbonated Soft Drinks on the Body Weight”

• “Primary Outcome Measures: •Body Weight; MR spectroscopy; MRI; DEXA scan.”

From: Paper (AJCN):
http://www.ajcn.org/content/early/2011/12/26/ajcn.111.022533.full.pdf

• Title of paper is: “Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study”

• From methods: “Our main aim was to test the hypothesis that sucrose-sweetened cola increases ectopic fat including VAT4, total body fat accumulation, and metabolic risk factors…”.

• From results: “No significant differences in the changes in body weight or total fat mass (determined by DXA) were found…”
Proposed Solution to Reporting Bias

• Better build standard of conduct into research training.
• Promote use of study registration, including analytic plan, before data availability.
• Provide journals with resources to do appropriate checking and give approval seals.
Measurement error

3-Step Solution

1. Admit you have a problem.

2. Get help.

3. Just say ‘no’.

Just because the measurement method one has is the best available, does not make it acceptable.

http://riskfactor.cancer.gov/measurementerror/
Selective or mis-citation
Papers citing Ebbeling et al. 2006. None exaggerated the results in a negative direction by neglecting to mention the significant subgroup finding, but nearly 50% of the papers misleadingly exaggerated the observed effects, for example not mentioning that the result was only significant in a secondary analysis and a subgroup.
Proposed Solutions to Citation Bias

• Better build standard of conduct into research training.

• Provide journals (or others) with resources to do appropriate checking and give approval seals.
Conclusion: What We Can Do That Will Plausibly Help and Accords with Our Discipline of Science

• In training, emphasize science as a discipline and vocation, not a ‘job’.
• Develop a set of ‘meta-methods’ which will collectively buttress/ensure the implementation of the fundamental scientific methods that already exist.
• Bite the financial bullet and put resources in place to implement those meta-methods.
“...let us take this path through the woods...”

~ Jean-Jacques Rousseau