**Body Weight Regulation: Why is it so hard to keep weight off?**

By STEPHANIE GASKELL

A study of 16,000 city kids found that more than one in four in obesity, and many are as young as 2 years.


Of the 10,000 children studied from the Head Start program, 27 percent were obese. Twenty-four percent of 2-year-olds, 27 percent of 3-year-olds, and 25 percent of 4-year-olds were obese. Obesity was especially prevalent in Hispanic and African-American children. Of those kids who were obese, 8 percent were Hispanic; 25 percent were African-American; 19 percent were Asian-American; and 12 percent were white.

Twenty-nine percent of boys were obese, compared to 25 percent of girls.

Children are considered obese if they have a body-mass index — which is a measure of body fat based on height and weight — in the top 95th percentile of what is considered healthy. Overweight is defined as having a body-mass index in the 85th percentile.

For example, a 2-year-old child who is 36 inches tall and weighs 35 pounds or more would be considered obese. A 4-year-old child who is 40 inches tall would be considered obese at 41 pounds or more.

Frieden urged parents to teach their children early on how to eat healthy and stay active.

“As a society, we have a responsibility to give our kids a healthier start,” he said.

“By creating healthy environments in which kids move more and eat better — free of sugar-sweetened beverages, heart disease, asthma, depression, and other serious health problems.”

Frieden said children should spend at least an hour a day being physically active.

He also urged parents to limit their kids to no more than one hour of TV or video games a day — without eating at the same time.

He also recommended parents give smaller portions to their kids and avoid sodas and junk foods.

Frieden also urged mothers to breastfeed their babies because breast-fed babies are less likely to be overweight.

Head Start is a federally funded child-development program for preschoolers and their families living below the poverty line.

A call to the regional Head Start office was not immediately returned.

Candace Young, who runs the Health Department’s Physical Activity and Nutrition Division, said it’s not only up to parents to instill healthy habits in their children.

“Caregivers and teachers can help create healthier environments for young children,” she said.

Overview

- Body weight is regulated by coordinate systems that favor weight gain and resist sustained weight loss in lean and obese individuals.
- The increasing prevalence of obesity reflects gene x environment interactions.
- The underlying biology of body weight regulation should dictate our expectations of preventative and treatment interventions, and even how we interact with our patients.
- Best research design is multidisciplinary.
What is too fat? Gender differences in perceptions of overweight.

Our Definition: The economic and health problem consuming over 100 billion dollars/year in direct health care costs and accounting for over 60% of the cases of diabetes in the U.S (probably even higher in children)

Runge, Diabetes, 56:2668, 2007
Evidence That Body Weight Is Regulated

- Genetic influences on body fatness are as potent as those on height.
- What happens to your metabolism after you’ve lost weight.
Body Fatness Runs in Families

Identical Twins

Fraternal Twins

(Borjeson, Acta Paediatrica Scand, 1976)
Heritability Estimates Based on Studies of Body Fatness Versus Other Medical Conditions*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heritability (G±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood Body Fatness (age 7)</td>
<td>0.77± 0.17</td>
</tr>
<tr>
<td>Adult Body Fatness (age 45)</td>
<td>0.64 ±0.13</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.68 ±0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.57 ±0.25</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.50 ±0.33</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>0.49 ±0.30</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.45 ±0.30</td>
</tr>
</tbody>
</table>

*Heritability refers to the proportion of the variance in a trait in the population that can be attributed to genes. Calculations are based on Stunkard et al, JAMA,256:1, 1986
### Percentage of Women Achieving Predefined Weight Loss Goals

<table>
<thead>
<tr>
<th>Weight Goal</th>
<th>% Achieving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dream Weight</td>
<td>0%</td>
</tr>
<tr>
<td>Happy Weight</td>
<td>9%</td>
</tr>
<tr>
<td>Acceptable Weight</td>
<td>14%</td>
</tr>
<tr>
<td>Disappointed Weight</td>
<td>20%</td>
</tr>
<tr>
<td>Less Than Disappointed Weight</td>
<td>47%</td>
</tr>
</tbody>
</table>

And keeping it off is even harder than losing it!

*Based on Foster et al, J Consult Clin Psychol 65:79, 1997*
1775: Antoine Lavoisier’s (chemist, tax collector) demonstration of the chemical identity of combustion and respiration shattered the predominant vitalistic views of bioenergetics.
LIFETIME CONSUMPTION

400 kg (0.5 tons) vitamins and minerals

38,350 Kg (42 Tons) Water
2840 Kg (3 Tons) Fat
2897 Kg (3 Tons) Protein
7015 Kg (8 Tons) CHO

< 1 kg carbohydrate
3.4 kg minerals
10.2 kg protein
8.8 kg fat
48 kg water

70 Kg Man

Nutrition Fundamentals: \( \Delta E = Q - W \)

10,000,000 liters of oxygen

CO\(_2\), Waste, Heat, Work
If you were in on the original design – what would you defend?

**Why defend body fatness?:**
- Increase survival.
- Increase ability of women to breastfeed.
- Decrease fertility when food is scarce.

**Why defend body thinness?:**
- Escape from predators
- Decrease likelihood of adiposity-related morbidity (but who lived long enough until recently).

Schwartz, Diabetes, 52:232, 2003
Observational Studies: Metabolic effects of reduced weight maintenance on lean and obese individuals

- Each weight plateau or loss period takes 6-8 weeks.
- Testing includes: feeding and energy expenditure; body composition; skeletal muscle physiology; neuroendocrine axis function; and ANS physiology.
Summary of Effects of Short- and Long-term Weight Loss on Energy Expenditure

Calories/day needed to maintain weight

0 1000 2000 3000 4000 5000

Thin Average Heavy Obese

50 60 70 80

Fat-Free Mass

Weight Loss

* Weight Loss

Summary of Effects of Short- and Long-term Weight Loss on Energy Expenditure
Mechanism: Changes in Activity account for 89% of the changes in TEE

Summary Of Other Weight-reduced Phenotypes in Lean and Obese Individuals

- **Skeletal Muscle:**
  - ↑ Efficiency and ↑ utilization of fat as fuel
  - ↑ Expression of more efficient isoforms of myosin heavy chain

- **Autonomic:**
  - ↑ PNS tone (100%)
  - ↓ SNS tone (48%)

- **Neuroendocrine:**
  - ↓ T3 (-6.9%), ↓ T4 (-9.1%), ↑ rT3 (5.6%)

- **Immune Function:**
  - ↓ Inflammatory cytokine release
  - ↓ T helper cells

- **Behavioral:**
  - ↓ Satiety

- **Neuronal**
  - ↑ response, ↓ restraint

**Leptin Insufficiency**

(Lep\(^{ob}\))

**Before**

(Age 3)

Wt = 42 kg

**After** (Age 7)

Wt = 31 kg

The Leptin-Threshold Model: Body Fatness, not Thinness is Defended

Feel Full
Metabolism Normal
Thyroid Normal
Fertile

Bigger Meals
Metabolism Slow
Thyroid Low
Infertile

Leptin Sufficient
Leptin Deficient

Individualized Leptin Threshold
Schematic of Protocol

- **Wtinitial**
- **Wt-10%**
- Placebo
- **100%, 90%, 80% of Wtinitial**
- **Time**
- **Randomized single blind**
- **Wt-10%**
- **Wt-10%LEP (5 weeks)**
Effects of “replacement” leptin on energy homeostasis in weight-reduced subjects

*P<0.05 compared to zero; †P<0.05 compared to Wt−10%placebo

<table>
<thead>
<tr>
<th>System</th>
<th>Weight Loss Effect</th>
<th>Leptin effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Output</td>
<td>↓ Energy Expenditure</td>
<td>Reversed</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>↑ Work Efficiency</td>
<td>Reversed</td>
</tr>
<tr>
<td>Energy Intake</td>
<td>No Change in Hunger&lt;br&gt;↓ Satiety</td>
<td>No Change&lt;br&gt;Reversed</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>↓ thyroid</td>
<td>Reversed</td>
</tr>
<tr>
<td>Autonomic</td>
<td>↑ PNS tone&lt;br&gt;↓ SNS tone</td>
<td>No Change&lt;br&gt;Reversed</td>
</tr>
<tr>
<td>Neuronal</td>
<td>↑ Response&lt;br&gt;↓ Control</td>
<td>Reversed&lt;br&gt;Reversed</td>
</tr>
</tbody>
</table>
Worst news: It doesn’t get easier over time

Residual EE values in subjects compared to values predicted from regression equations relating EE to age, fat-free mass, and fat mass in a separate group of 83 subjects studied at $W_t_{initial}$. The significant declines in energy expenditure following weight loss persist over time.

Why focus on obesity in children?

- Reduce current and future morbidity
- Great opportunities since:
  - It is preventive medicine at its finest
  - The metabolic groundwork for adult degenerative disease is laid down in childhood.
  - Pediatric obesity constitutes an independent risk factor for adult morbidity, even if the obesity does not persist.
- Unique research opportunities since:
  - Diseases that present in childhood reflect a higher degree of genetic loading
  - Less environmental input allows identification of factors that are premonitory of disease

Must et al, 1992 NEJM, 327:1350
Overall Prevalence of Overweight and Underweight in 1989, 1994, and 2000 by Sex, Age, and Race/Ethnicity*

<table>
<thead>
<tr>
<th>Category</th>
<th>1989</th>
<th>1994</th>
<th>2000</th>
<th>( \chi^2 ) Test for Trend, ( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10.70</td>
<td>11.82</td>
<td>14.32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>9.54</td>
<td>10.73</td>
<td>13.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9.39</td>
<td>10.57</td>
<td>12.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3</td>
<td>10.39</td>
<td>11.52</td>
<td>14.15</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>4</td>
<td>10.93</td>
<td>11.97</td>
<td>15.95</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7.67</td>
<td>8.33</td>
<td>11.40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African American</td>
<td>9.04</td>
<td>9.69</td>
<td>11.71</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.60</td>
<td>15.83</td>
<td>17.90</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>American Indian</td>
<td>13.78</td>
<td>15.07</td>
<td>17.09</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>10.41</td>
<td>11.75</td>
<td>13.73</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Overall, unadjusted</td>
<td>10.80</td>
<td>11.27</td>
<td>13.68</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*\( \chi^2 \) Trend tests for changes in prevalence.

And in pre-teens and teens

Trends in obesity prevalence among US children

Genes and Environment: Why we are getting fatter

Pre-industrial revolution, life is short:
• We rarely live to see morbidity.
• You want breakfast - go out and kill it.
• Lots of physical activity
• Frequent periods of undernutrition select for genes favoring body fatness.

Post industrial revolution life is longer:
• We live long enough to see morbidity.
• You want breakfast - go out and buy it.
• Increased sedentary lifestyle
• Traits that have been selected for become maladaptive.
Environmental and Population Shifts

- Calorically dense, less healthful foods not only available but more advertised and cheaper per calorie.
- Sedentary lifestyle (TV, travel)
- Better prenatal and post-natal care resulting in increased survival of SGA babies.
- Older mothers
- Less sleep
- Aromatase inhibitors
- Increased time in thermoneutral environments
- Less smoking
- Pharmaceuticals (anti-depressants, anti-psychotics, anti-diabetics, anti-histamines, and protease inhibitors)
- Shift in population demographics

Biology meets Sociology: What is regulated and who is most successful in sustaining weight loss?

- Rank order of body fatness amongst your peers is regulated.
- Your choices are your peers
- National Weight Control Study
  - Long-term lifestyle changes
  - Re-invent themselves
  - Recognize their friends may work against them
Rank order of variables

- Factors encouraging development of obesity:
  1. Environment (enabler)
  2. Genetics (susceptibility)
  3. Physiology ("set point" can be modified upward)

- Factors opposing sustained weight loss:
  1. Physiology ("set point" can’t be modified downward)
  2. Environment (success requires “reinvention” of self)
  3. Genetics (Strong traits that were once adaptive)
- Behavioral and educational intervention is more like than pharmacotherapy to work in obesity and co-morbidity prevention.
  - Identify Risk (Medical and Social Scientists)
  - Learn About Disease (Medical Scientists)
  - Intervene early (Social Scientists)

- Medical intervention is more like than behavioral therapy to work in obesity treatment.
  - “Weight maintenance” medication (Medical Scientists)
  - Surgery (Surgeons)
  - All coupled to diet and exercise (Social Scientists)
  - Track long-term effect (Medical and Social Scientists)
Prevention Example: The ROAD Project as a cooperative effort

Begin by assessing obesity/cormorbidities in a large population of 6th – 8th graders:

1. Historical: Family history of Type 2 DM
2. Clinical: Height, weight, % body fat, waist circ.
3. Biochemical: Fasting lipids, glucose, insulin, IL-6, TNF-α, CRP, and ACRP30
   - I.v. glucose (25 gm) 3 min push; insulin drawn at 3 and 5 minutes (rapid IVGTT)
   - Acute insulin response (AIR)
   - Insulin sensitivity = QUICKI
   - Glucose Disposal Index (GDI) to “adjust” AIR for QUICKI = \( \log_{10} (AIR \times \frac{[\text{glucose}]}{[\text{insulin}]}) \)
Body Fatness: Additive intervention effects

Everyone benefits regardless of risk factors!

* p<0.05 compared to control

Rosenbaum et al, JCEM, 92:504, 2007
% Change from first testing session

QUICKI    AIR    GDI

Everyone benefits regardless of risk factors!

Insulin sensitivity: Additive intervention effects
*p<0.05 compared to control

Rosenbaum et al, JCEM, 92:504, 2007
Examples of a new biology: How does leptin differ from weight loss drugs?

• **Current therapies:**
  Increase energy expenditure or decrease appetite to abnormal levels which cannot be sustained over long periods of time.

• **Leptin signaling pathway stimulation:**
  May promote reduced weight maintenance, but not weight loss by getting your body to work with you.
What else can we do?

**Prevention: Benefits Everyone**
Lactation
Ambulation
Education

**Intervention: Politics and Community**
- School: Remove vending machines selling soda and candy (if economically feasible), improve lunch, mandate PE and health education.
- Community: Safe parks, family education
- Politics: Raise awareness of policy makers to allot more funds for school health education and PE.
- Calorie tax is okay – how about healthful food tax breaks.
Separate medical interventions are made for obesity and its co-morbidities. Behavioral Intervention should not be geared solely towards adiposity reduction.

- Obesity is a disease that conveys significant risk for other co-morbid diseases but not everyone who is overweight is diabetic, hypertensive, etc.,.
- It is possible to improve health without reducing weight:
  - Make elevators less accessible so people use the stairs.
  - Improve macronutrient content of school diet with or without associated calorie reduction.
  - Improve how portions of food are presented, time allotted for school lunch and PE, etc.,.
- This type of intervention benefits EVERYONE – not just those who are overweight or at high risk for co-moribidity.
Summary: Regulation of Energy Storage

F (Ideal - Actual energy store)

CNS: Definition of ‘ideal’ energy store

Energy Intake

Partitioning of Energy Stores

Protein and Carbohydrate

‘Signal’ of Energy Stored

Adipose Tissue

Energy Output
Reach across the aisle

- **Social Scientists:**
  - Add clinical and/or laboratory outcome variables to assess mechanism and effectiveness.
  - Prevention of disease is more behavioral but assessing the efficacy of the prevention is more medical.
  - Most preventive behavioral interventions are beneficial to everyone regardless of weight status.
  - There are many interventions that will improve health without necessarily reducing weight.

- **Medical Scientists:**
  - Get help designing behavioral interventions.
  - Basic science of treatment is more medical but implementing diet and exercise interventions and assessing practicality are more behavioral.

- **Others:**
  - Lobbyists, economists, industry, educators, parents…
COLLABORATORS

All our volunteers, Rudy Leibel, Jules Hirsch, Steve Heymsfield, Dympna Gallagher, Rich Smiley, Judy Korner, Lou Aronne, Rochelle Goldsmith, Denis Joanisse, Rachel Kolb, David Markel, Ellen Murphy, Kate Pavlovich, Elisabeth Shamoon, Ken Baldwin, Joy Hirsch, Harry Kissileff, Cathy Nonas, Ilene Fennoy, Rich Weill, The Nutrition/GCRC staff at Columbia and Rockefeller University The NIH, AMDeC, Cornell University Institute for the Social Sciences

Real Message: Sustained Weight Loss is Hard

THANKS!