Obesity Epidemic?

Detail of chromosome 15
From the obesity map database

Bacchus, Peter Paul Reubens, 1638
Recent Increases in Obesity

<table>
<thead>
<tr>
<th>Year</th>
<th>Obesity Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>2000</td>
<td>&gt;30%</td>
</tr>
</tbody>
</table>

Is obesity a disease?
- Not all obese people have poor health

What’s causing this unusual Increase in obesity?
- Our genes?
- Environment?
  - Fast foods
  - Sedentary lifestyle
- Dieting, especially low fat diets
- Food choices that blind our natural ability to monitor our food intake
Obesity: Environment

It’s those damn corporations

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
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Obesity: Environment

Sedentary Lifestyle
Obesity: Ridiculousness

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Obesity: Environment

- Diets too high in fat?
  - Too much meat and dairy?
- Diets too high in carbohydrates?
  - Too much sugar
  - Refined flour
  - Soft drinks
- Diet drinks make you hungry!

Let's poke carbohydrates in the eyeball
Avoiding Obesity: It’s all about self-discipline, will power, determination.
Recent Increases in Obesity

1985: <15% obese
2000: >30% obese
Sexually Dimorphic Mammalian Species

[Images of different sexually dimorphic mammalian species]
Humans are Dimorphic

- **Males**
  - Taller, heavier
  - Broader shoulder
  - *Smaller hips, buttocks*
  - Smaller breasts
  - More facial hair
  - Deeper voice
  - Larger phallus
  - Less stamina due to lower subcutaneous fat
  - More heart disease due to tendency to gain abdominal body fat
Sexual Dimorphism in Body Fat Distribution in Humans
Abdominal vs. Subcutaneous Fat Results in Apple vs. Pear Shape

Patterns of Body Fat Distribution

Abdominal (Android)  Lower Body (Gynoid)
Diabetes and Heart Risks if.

- Triglycerides ≥ 150 mg/dL
- “Good Cholesterol” = High-Density Lipoprotein Cholesterol
  - Men < 40 mg/dL
  - Women < 50 mg/dL

Plasma Triglycerides and HDL-C in Lean Men and Women and in Obese Subjects with High or Low Visceral Adipose Tissue (AT)

<table>
<thead>
<tr>
<th>Trait</th>
<th>WTH High</th>
<th>WHT Low</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puberty onset</td>
<td>late</td>
<td>early</td>
<td>1</td>
</tr>
<tr>
<td>Testosterone</td>
<td>high</td>
<td>low</td>
<td>2</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>high</td>
<td>low</td>
<td>1,3</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>high</td>
<td>low</td>
<td>1,4</td>
</tr>
<tr>
<td>Risk for Type II diabetes</td>
<td>high</td>
<td>mod-low</td>
<td>1,5</td>
</tr>
<tr>
<td>For gallbladder disease</td>
<td>high</td>
<td>mod-low</td>
<td>6</td>
</tr>
<tr>
<td>Risk for cancer (ovar., breast, uterine)</td>
<td>high</td>
<td>mod-low</td>
<td>7,8</td>
</tr>
<tr>
<td>Hypertension, stroke heart disease, mortality</td>
<td>high</td>
<td>mod-low</td>
<td>3,5,9</td>
</tr>
</tbody>
</table>
Adaptive significance of Sexual Dimorphism in Body Fat Distribution related to female lactation (fat is stored in the hips, thighs, buttocks for use in making milk during lactation)
An enzyme active in weight gain is high in thighs prior to lactation. High LPL = gaining fat Low LPL = losing fat

Rebuffe’-Scrive et al., 1974
Nonabdominal fat critical for reproduction

And it’s not unhealthy!
It might even be “protective”
against diabetes and heart disease
Regardless of female body weight

(whether the females are very fat, very lean or in between)

A large body of data supports the notion that males of North or South American or Europe strongly prefer a LOW W.T.H. ratio
Health Risks and Obesity

Abdominal (apple)

- Insulin resistance
- Hyperinsulinemia
- Hypercholesterolemia
- Low HDL cholesterol
- Diabetes mellitus
- Coronary artery disease
- Hypertension
- Stroke

Subcutaneous (pear)

- No known health risks

Science sides with Sir MixA lot
What kind of epidemic has so many healthy people?

Marilyn Monroe
BMI = overweight to obese

Bad Cholesterol

WHT
QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
Leptin
Significance of Leptin

- It appears that body weight is regulated
- By a “lipostat”
- Leptin commonly thought to be the lipostatic signal
- It is still hoped by many that our knowledge of leptin will lead to a cure for obesity
The Seductive Lipostatic Hypothesis

Food Intake

Mystery Signal

Body FAT
It’s OK to sleep with a hypothesis.

You should never marry one.
History

- Early evidence (1970s) for a lipostat came from mutant mice that were obese
- Ob/ob mouse
- Db/db mouse
  - Mutation in a single gene on an autosome
  - Obese (more than 30% heavier than wild type)
  - Hyperphagic (ate significantly more than wild type)
  - Diabetic (hyperglycemic)
  - Infertile (does not undergo puberty, does not mate or have estrous cycles or spermatogenesis, decreases gonadal steroids)
An obese mouse (ob/ob) is sharing its circulation with a lean wild type mouse.
How would you explain these results?

- ob/ob - +/+mouse: ob/ob lost weight
- db/db- +/+ :db/db obese, +/+ stopped eating and lost weight
- ob/ob -db/db: ob/ob stopped eating and lost weight, whereas the db/db unaffected
- An additional experiment showed that when one of a pair of +/+ parabiotic mice was overfed, its "twin" lost weight.
Conclusion?
Conclusion of Parabiosis Experiment

- The ob/ob has a mutation in the gene that codes for a circulating factor that stops the rat from eating.
- The db/db has a mutation in the gene that codes for the receptor for this factor.
Conclusions of Parabiosis Experiment

- Ob/ob lacks a factor that stops eating
- The db/db lacks the receptor for that factor
Leptin (Ob protein)

- Cloned by J. Friedman’s lab in 1994 (Zhang et al., 1995)
- Adipocyte protein secreted
  - in proportion to body fat content
  - in response to influx of fuels into adipocytes
- Plasma concentrations
  - high in fat, fed animals
  - low in lean or fasted animals
- Peripheral and central treatment decreases food intake (FI) and body weight (BW) in many different species
  - Ob/ob (leptin decreases food intake and bw)
  - Db/db (leptin treatment has no effect)
  - Wild type mouse (leptin decrease FI and BW)
  - Rats
  - Hamsters
  - Monkeys
So Is leptin the cure for obesity?

- Percentage of people who are obese because they have a mutation in the gene for leptin = miniscule (only a few people in the world have this mutation)

- Clinical trials a failure
  - gave daily leptin injections to obese patients.
  - Only a third of the patients lost weight.
  - Some patients dropped out of the study finding the injections irritating.
  - Some reported decreased appetite at first, and increased appetite after continued use (they developed leptin resistance).
  - The people gained back the weight they had lost when the leptin injections ceased.
Why is Leptin Not The Miracle Cure for Obesity?

- In addition to leptin, there are many hormones and neuropeptides that influence appetite and obesity.

- Giving leptin alone does not curtail obesity.

- Obese people have higher leptin than normal weight people.
Some Factors Involved in Energy Balance

- **Metabolic Stimuli**
  - glucose oxidation
  - ffa oxidation
  - ketone body formation, oxidation
  - influx of fuels into adipocytes, muscles, liver, etc.
  - lipolysis

- **Hormones**
  - insulin
  - glucagon
  - leptin
  - glucocorticoids (cortisol, corticosterone)
  - ghrelin
  - growth hormone
  - cholecystokinin (gut peptide)

- **Neuropeptides**
  - NPY
  - AgRP
  - Orexin
  - CART
  - a-MSH
Leptin        Insulin                     Ghrelin

NPY/AGRP                   POMC (αMSH)

Increases appetite            Decreases appetite
Leptin Re-wires the NPY and POMC Circuitry

- Wildtype mice tend to have more excitatory synapses in the leptin-to-POMC circuit, and more inhibitory synapses in the leptin-to-NPY circuit.

- Ob/ob mice tend to have more excitatory synapses in the leptin-to-NPY circuit and more inhibitory synapses in the leptin-to-POMC circuit.
Increase Food Intake

- Orexin (lateral hypothalamus)
- NPY (arcuate and PVN)
- AgRP (arcuate and PVN)
- MCH (lateral hypothalamus)
Decrease Food Intake

- POMC (αMSH) (arcuate and PVN)
- CART (arcuate nucleus)
- CRH (PVN)
Current Research

- Any particular obese individual might have mutations or variations at these obesity-related loci
- You cannot assume any one obese person is just lazy
- Many genes, peptides and neurocircuits involved
- Redundancy in the system
- A drug that influences one of these peptides can be overridden by the others
- As soon as you stop taking the “antiobesity” drug, you gain all the weight back

- **Single gene approach unlikely to solve the obesity problem.**
A Pause That Refreshes
Dieting Doesn’t Work

Dieting is a signal to the brain to become better at storing fat
Energy Balance

- **Intake**
  - Motivational (appetite)
  - Consumption

- **Storage**
  - Glycogen in muscle and liver
  - Lipid in adipose tissue and other tissues
  - Amino acids in muscle and bone (used with glycerol to make new glucose)

- **Expenditure**
  - Resting
  - Thermogenesis
  - Reproduction
  - Immune function
  - Other cellular processes (mitosis, miosis, digestion, metabolism, cell repair)
Energy Balance - No Free Rides

- **Intake**
- **Storage**
  - Glycogen in muscle and liver
  - Lipids in adipose tissue and other tissues
  - Protein (Amino acids) in muscle and bone (used with glycerol to make new glucose)
- **Expenditure**
  - Resting (Basal Metabolic Rate)
  - Thermogenesis
  - Reproduction, Immune function
Restricting Food Intake Decreases Energy Expenditure

- Ate Ad libitum
- 75% Restricted
- 50% Restricted

Eating Regimen
Rebound results from increased appetite coupled with decreased expenditure
Dieting Makes you Fat

eventually
I’m sorry, Louis

Fat doesn’t make you fat!
Diet low in simple carbs are more satisfying

You feel less hungry
You eat less
Good Fats

Linoleic Acid has two double bonds, can be hydrogenated and is a Polyunsaturated fat.

Its formula is

\[ \text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH} \]
Bad Fats

Water insoluble substances. They have a relatively large nonpolar hydrocarbon part and a small oxygen containing polar part.

Stearic acid has a 17 atom hydrocarbon chain and a carboxylic acid group.

Its chemical formula is CH₃(CH₂)₁₆COOH and it is a saturated fat.
Given two meals with the same caloric value, the low carb diet results in

- Significantly more weight loss
- Happier people
- The weight will be gained back if you go back to eating carbs
Don’t Diet

Make permanent changes

- no soft drinks
- Minimize bread and pasta
- eat carbs like vegetables and fruits and berries
Diet Drinks Make You Hungry

Growing up on diet drinks
- precludes your ability to match taste with caloric intake
- makes you significantly fatter
Diet Drinks decrease the ability to gauge the caloric value of food

- Rats were trained with a flavored premeal and then later tested for their food intake.
- Consistent Group received flavors that consistently predicted the calorie content.
- Inconsistent Group received flavors that did not have any relation to their caloric value.

Rats were given sweet flavored premeal that matched their caloric value (consistent) or did not match (inconsistent).
Good luck this weekend

- Don’t diet
- Don’t drink soft drinks, especially diet
- Eat a balance diet of real foods including polyunsaturated fat
- To Sir Mixalot with love
More References
