Darwin, diet, disease, and dollars

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- No disclosures

Past

Currently there are 30% more obese than undernourished people worldwide (World Health Organization)

371 million diabetics in 2012 (6% of the world’s population) (International Diabetes Federation)

Present

Experts predict 165 million Americans (42%) will be obese by 2030 (4 part obesity series in Lancet, August 26, 2011)

100 million Americans will have diabetes by 2050 (CDC Division of Diabetes Translation, 2011)

Medicare will be broke by 2026

Future

Venus von Willendorf, Vienna Museum of Natural History
Dated to 22,000 BCE, unearthed in 1906

Obesity has been part of the human condition since there were humans

But something’s happened—How did the world get so obese? And how so fast?
Darwin

The explanation?
- Obesity continues to worsen, both in prevalence and severity
- Obesity is increasing in all developed (and developing) countries
- Obesity is increasing in all age groups, and especially in children
- Recidivism is high

The obvious explanation:
Gluttony and sloth

The evolutionary explanation:
A mismatch between our environment and our biochemistry

What’s the selective advantage to obesity?
- Energy storage for a rainy day (month, year, decade)

How is this selective advantage achieved?
- Leptin resistance
- Insulin resistance
The neuroendocrinology of energy balance

**PARADOX:**

If you give a 5 year old kid a cookie:

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If you give a 5 year old kid a cookie:

But if you give a 5 year old obese kid a cookie:

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The leptin negative feedback loop


Leptin promotes weight loss in a leptin-deficient patient

O'Rahilly et al, JCI Oct. 2002

Obese subjects are leptin resistant

What's blocking leptin from working? If we could solve that, we could solve obesity
What does insulin do?

Anatomic leptin resistance: Hypothalamic Obesity

Models/Hypotheses of Hypothalamic Obesity

Damaged Ventromedial Nucleus
Hyperphagia
Obesity
Insulin Secretion
IGF-I Receptor
Growth


Damaged Ventromedial Nucleus
Vagal Firing Rate
Insulin Secretion
Glucose Utilization
Hyperphagia
Obesity


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Octreotide

Before Octreotide
220 lbs.
10/4/99

After 12 mos. Octreotide
172 lbs.
10/7/97

Patient #1

11/26/98
Age 10
Pre-Study
Wt 65.1 kg BMI 28.1

5/2/97
Age 10½
Octreotide x 6 mos.
Wt 57.4 kg BMI 23.9

9/1/99
Age 13
2½ yrs post octreotide
Wt 88.4 kg BMI 34.4
Octreotide x 1 yr
364 lbs.  
326 lbs.

Postulated scheme of hypothalamic obesity

YOU

YOUR FAT

OCTREOTIDE

VAGUS

CNS INSULT

GLUCOSE

INSULIN

FOOD

Leptin

The cause of leptin resistance

The cause of leptin resistance is insulin!
Insulin is an endogenous leptin antagonist (?)

Does this make Darwinian sense?

Insulin gives the human the ability to modulate weight gain acutely, by allowing hyperinsulinemia to induce leptin resistance:

1. Puberty
2. Pregnancy

Where did the hyperinsulinemia come from?

Diet
"Beating obesity will take action by all of us, based on one simple common sense fact: All calories count, no matter where they come from, including Coca-Cola and everything else with calories…"

- The Coca Cola Company, “Coming Together”, 2013

Some Calories Cause Disease More than Others

Different Calories are Metabolized Differently

A Calorie is Not A Calorie

High Fructose Corn Syrup is 42-55% Fructose; Sucrose is 50% Fructose

Secular trend in fructose consumption

Natural consumption of fruits and vegetables

• 15 gm/day

Prior to WWII (estimated):

• 16-24 gm/day

1977-1978 (USDA Nationwide Food Consumption Survey):

• 37 gm/day (8% of total caloric intake)

1994 (NHANES III):

• 54.7 gm/day (10.2% of total caloric intake)

Adolescents:

• 72.8 gm/day (12.1% of total caloric intake)

• 25% consume at least 100 gm/day, 20% of calories from fructose

Of the 600,000 items in the American food supply, 80% have added sugar (sucrose, HFCS)

Fructose is not glucose

- Fructose is 7 times more likely than glucose to form Advanced Glycation End-Products (AGE’s)
- Fructose does not suppress ghrelin
- Acute fructose does not stimulate insulin (or leptin)
- Hepatic fructose metabolism is different
- Chronic fructose exposure promotes the Metabolic Syndrome
Ethanol is a carbohydrate

\[ \text{CH}_3\text{CH}_2\text{OH} \]

But ethanol is also a toxin

Acute ethanol exposure
- CNS depression
- Vasodilatation, decreased BP
- Hypothermia
- Tachycardia
- Myocardial depression
- Variable pupillary responses
- Respiratory depression
- Diuresis
- Hypoglycemia
- Loss of fine motor control

Acute fructose exposure
What’s the difference?

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<tr>
<th>Calories from</th>
<th>Fructose</th>
<th>Other Carbs</th>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>75 kcal</td>
<td>75 kcal</td>
<td>90 kcal</td>
</tr>
<tr>
<td>%</td>
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Fructose induces insulin resistance, which induces leptin resistance.
Does this make Darwinian sense?

Seasonal insulin resistance:
- Fructose was available at harvest, 1-2 months per year
- Followed by 4-5 months of winter, with no food available
- If leptin worked all the time, you couldn't store energy
- Selective advantage by inducing seasonal insulin resistance by gorging on fruit, while it was available

But fructose is now available globally 24/7/365, and consumed in unlimited amounts
And unopposed by fiber (read: orange juice)

Fructose induces insulin resistance, which induces leptin resistance

Is sugar addictive?
The lay public seems to know....

Seasonal fruit binges in orangutans

Taste buds
Sugar hides:
- salty (Chex mix, honey roasted peanuts)
- sour (German wines, lemonade)
- umami (sweet-and-sour pork)
- bitter (milk chocolate)

Does this make Darwinian sense?
There are no foodstuffs in nature that are both sweet and acutely poisonous
Our sugar craving is also Darwinian.

Sweet-Ease increases endogenous opioids to reduce pain, even in neonates.

"Exclusive" view of obesity and metabolic dysfunction:

- 240 million adults in U.S.
- 72 million Normal weight (30%)
- 168 million Obese and sick (80% of 30%)
- Total: 57 million sick

"Inclusive" view of obesity and metabolic dysfunction:

- 240 million adults in U.S.
- 72 million Normal weight (30%)
- 168 million Obese and sick (80% of 30%)
- Normal weight (70%)
- Total: 124 million sick
The key to the kingdom:

It’s not about obesity —
It’s about metabolic dysfunction (anyone can get it!) of which obesity is a result, not a cause.

Relation between visceral and subcutaneous obesity
TOFI (thin on the outside, fat on the inside)

Correlation is not causation
But we have causation too

What about the world’s food supply
predicts diabetes prevalence over the decade?

Prevalence of diabetes, 2010

- 30% obese
- < 63% active

An international longitudinal panel analysis of diet and diabetes
Food and Agriculture Organization (FAO); FAOSTAT
Food Supply data in kcal/capita/day calculation:
Food Supply = \left( \text{Production} + \text{Import Quantity} + \text{Stock Variation} - \text{Export Quantity} \right) - \left( \text{Feed} + \text{Seed} + \text{Processing} + \text{Waste} \right).
Only industrial waste factored in.

Extracted Food Supply data for 2000 through 2010:
- Total Calories
- Roots & Tubers, Pulses, Nuts, Vegetables
- Fruits, Excluding Wine
- Meats
- Oils
- Cereals
- Sugar, Sugarcrops & Sweeteners

International Diabetes Federation (IDF)
2000 through 2010
The World Bank World Development Indicators Database
GDP expressed in purchasing power parity in 2005 US dollars for comparability among countries
Toward a unifying hypothesis of metabolic syndrome

Diabetes prevalence rose from 5.5% to 7.0% for 204 countries 2000-2007

No drug target

Mitochondrial overload promotes lipogenesis, leading to hepatic insulin resistance, and metabolic syndrome

Only options are:
- reduce substrate availability (diet)
- reduce hepatic flux (fiber)
- increase clearance (exercise)

Dollars

Who’s winning the war?
• Despite the economic downturn of 2008, McDonald’s revenues and stock price continues to rise; and Coke and Pepsi still fared better than the S&P 500

Societal intervention requires “externalities”
If you smoke, drink, or take drugs, it’s bad for me
• second hand smoke
• car accidents
• declining housing prices
• altered work productivity and absenteeism
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How does your obesity affect me?
- $274 million extra for jet fuel (?)
- discomfort on the subway (?)
- sinking of boats due to the weight (?)

We believe higher taxation on “sugary” food and drinks would be the best option to reduce sugar intake and help fund the fast-growing healthcare costs associated with diabetes type II and obesity.

Summary: The Darwinian explanation for the obesity epidemic
- Obesity means leptin resistance, or “brain starvation”
- The starvation response causes recidivism
- Energy expenditure and quality of life are the same thing
- Defects in insulin signaling promote leptin resistance
- Insulin appears to be an “endogenous leptin antagonist”
- Fructose, through de novo lipogenesis, induces hepatic insulin resistance, driving metabolic syndrome, and wasting health care dollars
- Fructose is addictive, and drives excess food consumption
- Our food environment is fructosified; we have to “get the insulin down”
- The food industry has no impetus to change its practices

DISEASE VECTOR

Old medicine: infections microbes
New medicine: chronic disease multinational corporations

Lancet 361:576, 2013