Fat Chance: The Bitter Truth about Sugar
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Robert H. Lustig, MD

BIOGRAPHY:

Robert H. Lustig, M.D. is Professor of Pediatrics, in the Division of Endocrinology at University of California, San Francisco. Dr. Lustig is a neuroendocrinologist who performs research and clinical care on patients with obesity and diabetes. For the last decade, Dr. Lustig’s clinical research has focused on the regulation of energy balance by the central nervous system. He is currently investigating the contribution of biochemical, neural, hormonal, and genetic influences in the expression of the current obesity epidemic both in children and adults. He is interested in the hypothalamic signal transduction of the hormones insulin and leptin, how these two systems interact, and how they become dysfunctional in obesity. He is studying the interplay between the changes in the nutritional environment and defective hormone signaling; in particular, the role of fructose and lack of fiber in the genesis of the metabolic syndrome. He is assessing the cardiovascular morbidity associated with insulin excess, and developing methods to evaluate and prevent this phenomenon in children.

Dr. Lustig graduated from MIT in 1976, and received his M.D. from Cornell University Medical College in 1980. He completed his pediatric residency at St. Louis Children’s Hospital in 1983, and his clinical fellowship at UCSF in 1984. From there, he spent six years as a research associate in neuroendocrinology at The Rockefeller University. He is the author of many academic works, and of the popular book “Fat Chance: beating the odds against sugar, processed food, obesity, and disease”. Dr. Lustig is also President of the non-profit Institute for Responsible Nutrition, a think tank devoted to improving our food supply.
Past

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

366 million diabetics in 2011
(5% of the world’s population)
(International Diabetes Federation)

Present

8 March 2013

Diabetes Costs The US $245 Billion A Year Says New Report

Diagnosed diabetes cost the United States an estimated $245 billion in 2012, according to new research released by the American Diabetes Association (ADA) this week. The new figure represents a 41% rise in five years. In 2007, when the cost were last estimated, it came to $174 billion.

Future

Experts predict:

165 million Americans will be obese by 2030
(4 part obesity series in Lancet, 8/26/11)

42% of Americans will be obese by 2030
(Finkelstein et al. Am J Prev Med epub 5/7/12)

100 million Americans will have diabetes by 2050
(CDC Division of Diabetes Translation, 2011)
“Exclusive” view of obesity and metabolic dysfunction

Obese (30%) | Normal weight (70%)
---|---
72 million | 168 million

Obese and sick (80% of 30%)

Total: 57 million sick

“Inclusive” view of obesity and metabolic dysfunction

Obese (30%) | Normal weight (70%) | Obese, Metabolic dysfunction (40% of 70%)
---|---|---
72 million | 168 million | 57 million | 67 million

Total: 124 million sick

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

A

Trunk lax: 12.6 (i)
ASAT 0.2 (i)
ALT 4.6 (i)
IAAT/ASAT: 0.56

B

Trunk lax: 12.6 (i)
ASAT 0.9 (i)
ALT 5.5 (i)
IAAT/ASAT: 0.07

Obesity is not the problem
Obesity is not the problem

Metabolic Syndrome: where all the money goes
(75% of all healthcare dollars)

- Diabetes
- Hypertension
- Lipid abnormalities
- Cardiovascular disease
- Non-alcoholic fatty liver disease
- Polycystic ovarian disease
- Cancer
- Dementia

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The First Law of Thermodynamics

The total energy inside a closed system remains constant.

Two interpretations:

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The First Law of Thermodynamics

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The First Law of Thermodynamics

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Calories In
The First Law of Thermodynamics

Calories In

Calories Out

Weight Gain

Calories In

Calories Out

The dogma

A calorie is a calorie

The corollaries

Free will
Personal responsibility
Gluttony and sloth
Diet and exercise

Obesity is the result of two aberrant behaviors

Just a caloric bacchanalia?
Just a caloric bacchanalia?

+187 kcal/d (men), +335 kcal/d (women), +275 kcal/d (teens)
In last 25 years

The evolution of fast food

"Education consists mainly of what we have unlearned."

--Mark Twain
1. No child chooses to obese.
The quality of life of an obese child is equivalent to those on cancer chemotherapy.
(Schwimmer et al. JAMA 289:1813-1819, 2003)

2. Does diet work?

When compared with no treatment, exercise resulted in small weight losses across studies.

3. This isn’t just about America
Not just the UK, not just Australia
Childhood obesity is on the rise in:
- Canada
- Japan
- Korea
- India
- Thailand
- Philippines
- South Africa
- Every other developing country

4. The poor are disproportionately affected
They don’t have access to choices for healthy dieting and exercise
If you don’t have a choice, is it personal responsibility?
5. The prevalence of obesity in children is going up even faster than in adults

6. We even have an epidemic of obese 6-month olds

They don't exhibit any of these behaviors

(Kim et al, Obesity 15:1107, 2006)

So any hypothesis that attempts to explain the obesity epidemic, must be able to explain this as well

- Gestational diabetes has increased in prevalence
- Birthweight has increased by 200 grams throughout the world
  - South Africa
  - Israel
  - Russia
  - U.S.

DEXA scans for body composition show greater fat deposition

**Behavior**

*Stedman’s Medical Dictionary*

**Def.** A stereotyped motor response to a physiological stimulus

**Corollary:** Behavior has a biochemical basis

What are the biochemical underpinnings of gluttony and sloth?
The neuroendocrinology of energy balance

Paradox:

If you give a 5 year old kid a cookie:

Paradox:

Leptin stimulates the SNS


Paradox:

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

Paradox:

But if you give a 5 year old obese kid a cookie:
The leptin negative feedback loop

Leptin promotes weight loss in a leptin-deficient patient

Leptin Tx in Leptin Deficiency

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 due to a brain tumor

Models/Hypotheses of Hypothalamic Obesity

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

- Vagal Firing Rate
- Insulin Secretion
- Glucose Utilization
- Hyperphagia
- Obesity


Octreotide x 1 yr

Octreotide-LAR x 6 months
The cause of leptin resistance is insulin!

So where did the increased insulin come from?

Addictive and hazardous to your health
Addictive and hazardous to your health

New York Times, April 17, 2011

Hazardous to your health
“A calorie is NOT a calorie”

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

Secular trend in U.S. 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):
• 57 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% consumed at least 15% of calories from fructose

Adulteration of our food supply
Addition of fructose
• palatability (esp. with decreased fat)
• browning agent
Removal of fiber
• shelf life
• freezing
Substitution of trans-fats
• hardening agent, shelf life
• now being removed due to CVD risk
Foods that cause weight gain

Lowering sugar

Raising sugar

The first problem

Common wisdom: “Sugar is just "empty calories”

But:

• Hepatic fructose metabolism is different

• Chronic fructose exposure promotes the Metabolic Syndrome

Effects of sugar on obesity (meta-analysis)

Metabolism of Glucose

24 kcal

Hepatocyte

Glucone (40%)
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
The second problem

The browning reaction or Maillard reaction or non-enzymatic glycation

Instead of roasting 1 hour at 375 degrees we slow cook at 98.8 degrees for 75 years

The common link

Aging and costal cartilage

60 kcal (+ 12 kcal glucose)

48 kcal

Courtesy Dr. Baynes
Sucrose is necessary for NAFLD in the Methionine-Choline deficient diet


Association of fructose consumption with severity of steatosis and fibrosis


10 Most Obese States

> 30% obese

10 Laziest States

< 63% active

10 Most Unhappy States

< 63% active

10 Most Obese States

> 30% obese
10 Most Obese States 10 Laziest States

> 30% obese < 63% active

10 Most Unhappy States

Adult Death Rate

Adult Heart Disease Rate

Prevalence of diabetes, 2010

Data from Food and Agriculture Organization, World Health Organization, 2007

Global consumption of sugar/sugarcrops
Calories per day, 2007

Correlation is not causation
But we have causation too
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 = (Production + Import Quantity + Stock Variation – Export Quantity) - (Feed + Seed + Processing + Waste).
- Only industrial waste factored in.

Extracted Food Supply data for 2000 and 2007:
- Total Calories
- Roots & Tubers, Pulses, Nuts, Vegetables
- Fruits-Excluding Wine
- Meat
- Oils
- Cereals
- Sugar, Sugarcrops & Sweeteners

International Diabetes Federation (IDF)
- 2000 (1st ed) and 2007 (3rd ed)

The World Bank World Development Indicators Database
- GDP expressed in purchasing power parity in 2005 US dollars for comparability among countries

- Total 204 countries; complete data for 154 countries (50 not different)

Data monitoring and quality
- Generalized estimating equations
- Conservative fixed effects approach (Hausman test)
- Hazard model to control for selection bias (Heckman selection model)
- Longitudinal data to determine what preceded diabetes (Granger causality)
- Period effects controlled for secular trends that may have occurred as a result of changes diabetes detection capacity or importation policies.

Controlled for:
- GDP per capita
- % population living in urban areas
- Obesity
- % of population over age 85
- Physical inactivity

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

Effect of Sugar on Diabetes Prevalence

Model | # countries | Effect (95% CI)
--- | --- | ---
Sugar | | p=0.001
Sugar+controls | | p=0.001
Sugar+controls+period | | p=0.001
Overall | | p=0.001
An international longitudinal panel analysis of diet and diabetes

Context
Only changes in sugar availability correlated with changes in diabetes prevalence.
Every extra 150 calories increased diabetes prevalence by 0.1%.
But if those 150 calories were a can of soda, diabetes prevalence increased 11-fold, by 1.1%; p < 0.001.
Controlled for many confounders; obesity exacerbated, but did not confound the effect.

These data estimate that 25% of diabetes worldwide is explained by sugar.

These data meet the criteria for Causal Medical Inference:
— dose
— directionality
— duration
— precedence

Types of Proof
• Anecdotal Data
• Correlation
• Causal Inference
• Scientific Proof

What level of proof do you need to act?

Addictive

(Reuters) March 28, 2010 - Bingeing on high-calorie foods may be as addictive as cocaine or nicotine, and could cause compulsive eating and obesity, according to a study published on Sunday.

The third problem

Obesity and reward

Dopamine binding correlates with glucose metabolism both in drug addiction and obesity

The mesolimbic reward system in rodents

The Ventral Tegmental Area and the Nucleus Accumbens: Sites of opiate and nicotine effects on reward

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The Ventral Tegmental Area and the Nucleus Accumbens: Sites of opiate and nicotine effects on reward

The integration of the starvation and addiction pathways
Decreased Dopamine D$_2$ Receptors in Obese Human, Monkey and Rodent

Bonnet macaques

PET [11C]raclopride

 Autoradiography [3H]spiperone

BMI = 42

BMI = 23

Weight = 650 g

BMI = 42

BMI = 23

Direct effects on the reward system:

Is fast food addictive?

Salt

- In rodents, dopamine signaling (reward) in response to salt, bingeing, cross-sensitization with amphetamines

- In humans,
  - Lower threshold physiologically fixed
  - Higher levels attributed to "preference", can retrain
  - Salt-losing congenital adrenal hyperplasia
Caffeine

• “Model drug” of dependence
• In humans, dependence shown in children, adolescents and adults
  – 30% who consume it meet DSM criteria for dependence
  – Physiologic addiction established: headache (increased cerebral blood flow), impaired task performance, fatigue

Fat

• Rodents binge but no signs of dependence
• In humans, binge foods are high fat but also high carb/sugar (e.g. pizza, ice cream)
  – Likely synergy, adding sugar increases preference for fatty foods [Drewnowski et al.]
• Atkins diet does not show dependence
• Energy density: stronger association with obesity, metabolic syndrome
Direct effects on the reward system:
Is sugar (fructose) addictive?

Sugar and opioids

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

Is there really such a thing as sugar addiction?

Need to look for similarities to drugs of dependence
- nicotine
- morphine
- amphetamine
- cocaine
- ethanol

Criteria for addiction

Anticipation → BINGEING → Tolerance

CRAVING → WITHDRAWAL ← Negative emotion

Enhanced locomotion → Cross-sensitization → Increased Consumption

Avena et al. Neurosci Biobehav Rev 32:20, 2008 (Courtesy Dr. B. Hoebel)
The birth of the “Un-Cola”

Federal Trade Commission vs. Sugar Information, 1972

Recognition at the American Heart Association

Dietary Sugars Intake and Cardiovascular Health
A Scientific Statement From the American Heart Association

- Rachel K. Johnson, PhD, MPH, RD, Cnd; Lawrence J. Appel, MD, MPH, FASA
- Michael Brands, PhD, FASA; Barbara V. Howard, PhD, FASA
- Michael Lav适用于, PhD, FASA; Robert B. Lenkinski, MD, FASA
- Lisa M. Stiffler, PhD, MPH, RD, FASA; SarahWilliams-Strother, EdD, RD

on behalf of the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Cardiovascular and Prevention

Recommends reduction in sugar intake from 22 tsp/day (males) and 6 tsp/day (females)

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
Who’s winning the war?
Stock prices of various food companies compared to the S&P500 2008-2011

The First Law of Thermodynamics

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The two aberrant behaviors are a result of our biochemistry
Our biochemistry is a result of our environment
Question 1:
Can our “toxic environment” be changed without government/societal intervention? Especially when there are potentially addictive substances involved?

Question 2:
Can we afford to wait to enact public health measures when health care will be bankrupt due to chronic metabolic disease?

Further reading

Effects of Sugar-Sweetened Beverages on Children
Andrea A. Bremer. M.D., Ph.D.†, Michele Mietus-Snyder, M.D.†, Robert H. Lustig. M.D.*
Pediatric Annals 41:23, 2012

Toward a Unifying Hypothesis of Metabolic Syndrome
Andrew A. Bremer, M.D., Ph.D.*, Michele Mietus-Snyder, M.D.†, Robert H. Lustig, M.D.**
Pediatric Annals 40:35, 2011

Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol
Robert H. Lustig, M.D.,
JAMA, 308:825, 2012

Fructose: It’s “Alcohol Without the Buzz”1-3
Robert H. Lustig*

Dietary treatment of nonalcoholic steatohepatitis
Emily R. Perti*, Luis A. Rodriguez‡, and Robert H. Lustig**
Current Opinion Gastroenterology, 29:170, 2013

The Relationship of Sugar to Population-Level Diabetes Prevalence: An Econometric Analysis of Repeated Cross-Sectional Data
Sajal Jee1*, Pauley Yaffe2, Nancy Hall3, Robert H. Lustig4

Further reading

Arterioscler Thromb Vasc Biol 25:2451, 2005
Curry Drug Abuse Rev 6:146, 2011

Is fast food addictive?
Andrew K. Garber, Robert H. Lustig

Further reading

American Dietetic Association
Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol
Robert H. Lustig, M.D.,
JAMA, 308:825, 2012

Further reading

Advances in Nutrition 4:1, 2013
Annals NY Academy of Sciences, 1, 2013