The Obesogen Model as a Unifying Theory for the Global Rise in Obesity

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Director
Healthy Environment and Endocrine Disruptor Strategies

Robert Lustig, Sarah Howard, Barbara Corkey
Trends in Obesity in the U.S. 1963-2018

Source: NHANES, 1963 - 2018
Questions for Today:

What causes obesity?
When does obesity start?
Current models of obesity.
What data support the role of environmental chemicals (obesogens)?
REDOX model of obesity.
How can all these models be integrated to explain obesity?
The Causes of Obesity are Not Understood

• An Endocrine Society Scientific Statement noted, “The current lack of consensus regarding obesity pathogenesis has resulted in competing and poorly justified claims both from within and outside of the scientific community. These inconsistencies erode public trust and confidence in the scientific process as it pertains to obesity and its treatment, which only further supports nonscientific ideologies and products.” (Schwartz, Seeley et al. 2017)

• A recent perspective noted that we don’t have a clear explanation for the obesity epidemic. “This lack of adequate attention and investment in understanding of the root causes of the obesity epidemic—one of the most rapid and widespread alterations of human health in history—may at least partly owe to the belief that the foundational causes are already known.” (Mozaffarian 2022)

• There is currently a Lancet Commission on Clinical Obesity engaged in defining the disease with a report expected later this year.
Obesity - A Complex Problem

Energy intake

Energy expenditure

Environment

Genetics

Lifestyle factors

Drugs
Built Environment
Environmental chemicals
Stress
Viruses
Antibiotics
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What causes obesity?

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How can all these models be integrated to explain obesity?
Obesity in Infants

• **Even 6-month-old babies are becoming obese**
  Kim et al, Obesity 15:1107, 2006

• **Even newborns are affected**
  200 gm increase in neonatal body weight (DEXA: all fat) over the last 25 years
  (U.S., South Africa, Israel, Russia)
  Lustig et al., Biochem Pharmacol, 199:115012, 2022

Diet and exercise cannot explain obesity in infants.

Any hypothesis that attempts to explain the obesity epidemic must be able to explain why infants are also affected.
Critical Periods Must be Accounted for

• While nutrition, stress, and environmental chemicals can affect weight gain across the lifespan...

• Development (*in utero* and first years of life) is most sensitive to their effects.
Developmental Origin of Adult Disease: Barker Hypothesis

- 1989 David Barker: inverse relationship between birth weight and death from heart disease in England and Wales
- “Dutch Hunger Winter”: food supply to the Netherlands was cut off by Nazis
- Individuals born during this time had increased insulin resistance as adults

Fetal Origin of Adult Disease (FEBAD) confirmed for:
- Coronary heart disease
- Hypertension
- Type II diabetes
- Obesity

Table 1. Hazard ratios for coronary heart disease according to body size at birth

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Hazard ratio (95% CI)</th>
<th>No. of cases/No. of men</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2500</td>
<td>3.63 (2.02-6.51)</td>
<td>24/160</td>
</tr>
<tr>
<td>2500-3000</td>
<td>1.83 (1.09-3.07)</td>
<td>45/599</td>
</tr>
<tr>
<td>3000-3500</td>
<td>1.99 (1.26-3.15)</td>
<td>144/1775</td>
</tr>
<tr>
<td>3500-4000</td>
<td>2.08 (1.31-3.31)</td>
<td>123/1558</td>
</tr>
<tr>
<td>4000-4500</td>
<td>1.00</td>
<td>21/538</td>
</tr>
<tr>
<td>&gt;4500</td>
<td>1.00</td>
<td>21/538</td>
</tr>
</tbody>
</table>

P for trend: 0.006

Ponderal index (kg m⁻²)

| <25             | 1.66 (1.11-2.48)      | 104/1093                |
| 25-27           | 1.44 (0.97-2.13)      | 135/1643                |
| 27-29           | 1.18 (0.78-1.78)      | 84/1260                 |
| >29             | 1.00                  | 31/578                  |

P for trend: 0.0006

The Disease Paradigm: Developmental Origins of Health and Disease (DOHaD)

• The environment during development: stress, nutrition, infections, drugs and environmental chemicals:
  • All cells contain the same DNA. During development hormones and growth factors turn genes on and off to form specific cells and tissues: a process called epigenetic programming.
  • Environmental agents alter the epigenetic programming of cell and tissue differentiation.

A bad start...lasts a lifetime!

Changes"

• “Functional" changes lead to a tissue that "looks" normal but is metabolically abnormal, permanently altering how it functions.
• Changes persist throughout life.
• Effects occur across the lifespan and may require a “second hit.”
• Programming changes lead to increased susceptibility to disease across the lifespan.
### Disease Risk Increased by Developmental Exposures

#### Environmental Chemicals

<table>
<thead>
<tr>
<th>Reproductive/Endocrine</th>
<th>Brain/Nervous System</th>
<th>Pulmonary/Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breast/prostate cancer (BPA)</td>
<td>• Alzheimer’s disease (Lead)</td>
<td>• Asthma (Air Pollution)</td>
</tr>
<tr>
<td>• Endometriosis (Dioxin, PCBs)</td>
<td>• Parkinson’s disease (Pesticides)</td>
<td>• Heart disease/hypertension (BPA)</td>
</tr>
<tr>
<td>• Infertility (Phthalates, Estrogens, Pesticides)</td>
<td>• ADHD/learning disabilities, IQ (PCBs, Lead, Ethanol, Organochlorine Pesticides)</td>
<td>• Stroke (PCBs)</td>
</tr>
<tr>
<td>• Diabetes/metabolic syndrome (BPA, PCBs)</td>
<td>• Early puberty (Estrogens, BPA)</td>
<td></td>
</tr>
<tr>
<td>• Obesity (BPA, Tributyltin, Organochlorine pesticides)</td>
<td>• Obesity (Estrogens, BPA)</td>
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</tr>
<tr>
<td></td>
<td>• Autoimmune disease (Dioxin)</td>
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#### Diseases/Dysfunction

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#### Nutrition

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<th>Brain/Nervous System</th>
<th>Pulmonary/Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Maternal Obesity</td>
<td>• Alzheimer’s disease (Lead)</td>
<td>• Asthma (Air Pollution)</td>
</tr>
<tr>
<td>• Gestational Diabetes</td>
<td>• Parkinson’s disease (Pesticides)</td>
<td>• Heart disease/hypertension (BPA)</td>
</tr>
<tr>
<td>• Low birth weight/catch up growth</td>
<td>• ADHD/learning disabilities, IQ (PCBs, Lead, Ethanol, Organochlorine Pesticides)</td>
<td>• Stroke (PCBs)</td>
</tr>
<tr>
<td>• High birth weight</td>
<td>• Sensitivity to high sugar/high-fat diet</td>
<td></td>
</tr>
<tr>
<td>• Obesity</td>
<td>• Maternal Obesity</td>
<td></td>
</tr>
<tr>
<td>• Diabetes</td>
<td>• Gestational Diabetes</td>
<td></td>
</tr>
<tr>
<td>• NAFLD</td>
<td>• Low birth weight/catch up growth</td>
<td></td>
</tr>
<tr>
<td>• Cardiovascular disease</td>
<td>• High birth weight</td>
<td></td>
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Current Models of Obesity

Energy Balance Model (EBM)
- Obesity is due to overeating; a calorie is a calorie.
- The brain is responsible for controlling weight gain.

Carbohydrate-Insulin Model (CIM)
- High glycemic index carbohydrates (sugar!) stimulate insulin secretion.
- Insulin stimulates fat storage and cell growth and division.
Energy Balance Model: EBM

*Obesity, a failure to control energy balance*

**Overeating**
(energy dense tasty food) (UPF)

↑ Energy intake
(Altered brain control of eating, unconscious)

↓ Energy expenditure

↑ Circulating metabolic fuels glucose, lipids

↑ Fat storage (adipose tissue)

Obesity

We gain weight because we eat more, burn fewer calories or both.

**Hedonic**
Emotional
Addictive

**Homeostatic**
Appetite and satiety neurons

Physical inactivity (TV, computer, etc)

D.S. Ludwig, Wingspread 2022
Diets High in Ultra-processed Foods Cause Weight Gain

Diets were presented in random order and matched for provided calories, sugar, fat, fiber, and macronutrients.

- Ultra-processed Diet
- Unprocessed Diet

Ad Libitum Intake (kcal/d)

Body Weight Change (kg)

Days on Diet
# NOVA Food Groups

## Unprocessed or minimally processed foods (1)

<table>
<thead>
<tr>
<th>Breakfast sandwich</th>
<th>Other fresh fruit</th>
<th>Sweet potato</th>
<th>Other noodles</th>
<th>Other chicken dishes</th>
<th>Other real juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other eggs</td>
<td>Cantaloupe, in season</td>
<td>Other potatoes</td>
<td>Beef</td>
<td>Oysters</td>
<td>Iced tea</td>
</tr>
<tr>
<td>Cooked Cereal</td>
<td>Strawberries, Green salad in season</td>
<td>Ribs</td>
<td>Shellfish</td>
<td>Water</td>
<td></td>
</tr>
<tr>
<td>Milk on cereal</td>
<td>Watermelon, Tomatoes in season</td>
<td>Pork</td>
<td>Fried fish</td>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>Yogurt</td>
<td>Broccoli</td>
<td>Other vegetables</td>
<td>Veal, lamb</td>
<td>Other fish</td>
<td>Hot tea</td>
</tr>
<tr>
<td>Bananas</td>
<td>Carrots</td>
<td>Refried beans</td>
<td>Liver</td>
<td>Rice</td>
<td>Bean soup</td>
</tr>
<tr>
<td>Apples or pears</td>
<td>Corn</td>
<td>Other beans</td>
<td>Menudo</td>
<td>Nuts</td>
<td>Milk</td>
</tr>
<tr>
<td>Oranges or tangerines</td>
<td>Green beans</td>
<td>Vegetable stew</td>
<td>Other beef dish</td>
<td>Tomato juice</td>
<td>Total fruits</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>Spinach</td>
<td>Fried chicken</td>
<td>Spaghetti with meat sauce</td>
<td>Roast chicken</td>
<td>Real orange juice</td>
</tr>
</tbody>
</table>

## Processed culinary ingredients (2)

- Butter
- Fat/oil in cooking

## Ultra-processed foods (4)

<table>
<thead>
<tr>
<th>Breakfast sausage</th>
<th>Bacon</th>
<th>Salad dressing</th>
<th>Pancakes</th>
<th>Cold cereal</th>
<th>Mac N Cheese</th>
<th>Canned fruit</th>
<th>French Fries</th>
<th>Hamburger (cheeseburger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cole slaw</td>
<td></td>
<td></td>
<td>Pizza</td>
<td>Mac N Cheese</td>
<td>Pigs feet, variety meats</td>
<td>Biscuits</td>
<td>Burger rolls</td>
<td></td>
</tr>
<tr>
<td>Hot dogs</td>
<td></td>
<td>Lunch Meats</td>
<td>Meat loaf</td>
<td>Pigs feet, variety meats</td>
<td>Power bars</td>
<td>Breakfast bars</td>
<td>Crackers</td>
<td></td>
</tr>
<tr>
<td>Bagels, English muffins</td>
<td>White bread</td>
<td>Margarine Ketchup (catsup)</td>
<td>Donuts</td>
<td>Cake</td>
<td>Cookies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jelly</td>
<td></td>
<td>Mayonnaise Chocolate syrup</td>
<td>Pumpkin Pie</td>
<td>Other pie</td>
<td>Chocolate candy</td>
<td>Other candy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ice cream</td>
<td></td>
<td>Chocolate syrup</td>
<td>Drinks with some juice</td>
<td>Kool Aid</td>
<td>Sodas</td>
<td>Liquor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Processed foods (3)

<table>
<thead>
<tr>
<th>Cheese</th>
<th>Vegetable soup</th>
<th>Other soup</th>
<th>Tofu</th>
<th>Tacos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuna</td>
<td>Tortillas (flour)</td>
<td>Corn bread</td>
<td>Peanut butter</td>
<td>Chips</td>
</tr>
<tr>
<td>Mustard</td>
<td>Beer</td>
<td>Wine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Support and Challenges to the EBM

Support:
• It is possible to lose weight on various diets...calories count.
• Consumption of ultra-processed food causes weight gain via overeating due to altered brain control of eating.

Challenges:
• Why have animals also gained weight?
• What about the increased weight of babies?
• It does not address the role of developmental programming affecting weight gain.
• No mechanism to explain the altered control of food intake.
Challenges to the EBM

Secular trends challenge the primary role of “overeating”

D.S. Ludwig, Wingspread 2022  Mozaffarian. AJCN 2022 Apr 23: nqac075
Insulin & Body Weight

A dominant anabolic hormone

- Regulates storage of all metabolic fuels
  - Stimulates glucose uptake into cells.
  - Stimulates fat synthesis and deposition.
  - Inhibits fat release and oxidation.

- Excess insulin causes weight gain
  - Increased insulin makes you hungry.
  - Excessive insulin treatment in diabetes.
  - Insulin-secreting tumors.
  - Human genetic variants affecting insulin secretion.

- Decreased action causes weight loss
  - Adipocyte Insulin receptor knock-down models but not muscle receptor knock-down.

Carbohydrate-Insulin Model: CIM

A metabolic disorder of fat storage

High Glycemic Load
Dietary Carbohydrates

↑ Insulin secretion

↓ Circulating metabolic fuels (glucose, lipids)

↑ Fat storage (adipose tissue)

CNS senses decreased energy
Increased hunger/appetite

Obesity

High sugar content of diet is key!

D.S. Ludwig, Wingspread 2022
Support and Challenges to the Carb-Insulin Model

Support:
• Ketogenic and low-carbohydrate diets promote weight loss more effectively than low-fat diets.
• Inhibition of insulin secretion increased weight loss in dieting obese patients.
• The current Western diet is insulinogenic.
• May contribute to obesity in a subset of individuals.

Challenges:
• There is no focus on the role of developmental programming.
• High glycemic index processed foods contain many new ingredients that may stimulate insulin.

D.S. Ludwig, Wingspread 2022       Alemzadeh 1998
An Integrated Model of Obesity (EBM and CIM)

Push-pull model

Easily available energy-dense, palatable foods → Positive energy balance → Increased body adipose mass → Fructose consumption

Physical inactivity → High-glycaemic-load diet → High insulin-to-glucagon ratio

• Genetic risk
• Environment
• Behavioural factors
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Obesogens

- Obesogens are environmental agents that alter energy metabolism.
- They disrupt **signaling pathways** (e.g., hormone receptors and transcription factors) in various cell types and tissues that regulate energy intake and expenditure, nutrient handling, and adiposity.
- Obesogens can be:
  - natural (e.g., metals, viruses),
  - anthropogenic (prescription drugs),
  - environmental (insecticides, plastics, household chemicals, particulate matter),
  - food components (fructose, *trans*-fats, preservatives, emulsifiers).
- The majority of obesogens are endocrine disruptors.
An **endocrine disruptor** is an exogenous chemical, or a mixture of chemicals, that **interferes with any aspect of hormone action** (Zoeller et al. Endocrinology, 2012).

A chemical designed for a specific purpose but with a side effect of mimicking or antagonizing hormone action.

>300,000 chemicals in commerce

- Some % are toxic, via Alterations of DNA mutagens or general toxicity
- Some % are toxic because they interfere with some aspect of the endocrine system
- Some are toxic because they cause an increase in fat

**Obesogens**
Obesogenic Endocrine-disrupting chemicals

We are born pre-polluted!
Endocrine Control of Metabolism

All hormones and hormonal pathways are potential targets for obesogens.
Obesogens

Maternal Smoking (nicotine)
Air Pollution (PAHs, particulate matter (PM))
DDT
Perfluorinated compounds (PFAS)
Bisphenols (A, S, F, AF…)
Phthalates (DEHP, DBP, DiBP)
Tributyltin
Flame retardants (PBDEs, OPFRs)
Dioxin and polychlorinated biphenyls (PCBs)
Fructose

Non-nutritive sweeteners
  – Aspartame
  – Sucralose
  – Saccharin

Agricultural chemicals
  – Chlorpyrifos
  – Diazinon
  – Neonicotinoids
  – Permethrin
  – Tolyfluanid

Food preservatives/additives/emulsifiers
  – Methyl and butylparaben
  – Tween 80/carboxymethylcellulose
  – 3-tert-butyl-4-hyroxyanisole (3-BHA)
  – Dioctyl sodium sulfosuccinate (DOSS)
  – Monosodium Glutamate (MSG)

Cadmium
Arsenic
Dibutyltin
Microplastics
Animal Studies: BPA is an Obesogen

Developmental exposure to BPA in mice increases body weight in female offspring.
Bisphenol A is an Obesogen

Developmental Exposure
SD Rat model
Increased weight
Increased food intake

Appetite (NPY) neurons

Satiety (POMC) neurons
Ross and Desai, 2018

BPS and BPF are obesogens
Lipid accumulation in HepG2 cell

Strong in vitro and animal data
Inconsistent human data
Animal Studies: Phthalates Are Obesogens

(A) Adult mice exposed to environmentally-relevant levels of di(2-ethylhexyl) phthalate (DEHP) for 8 weeks developed:

- higher body weight
- increased food intake
- excess visceral fat
- larger fat cells

(C/D) Developmental exposure to DEHP and assess weight at 8 weeks of age:

- higher body weight
- excess visceral fat
Human Studies: EDCs as Obesogens

• A 2020 meta-analysis identified 18 studies showing an overall positive association between exposure to Phthalates and measures of excess weight or adiposity in adults and children (Ribeiro, 2020).

• Meta-analysis showed an overall positive association between BPA exposure and obesity and abdominal obesity in children and adults (Ribeiro, 2020).

• A review of bisphenols and obesity finds “BPS median urinary concentrations ... were associated with the development of obesity.” (Alharbi et al. Int J Environ Res Public Health. 2022).

• In a pooled analysis, air pollutants, including PM2.5, PM10, and NO2 were positively associated with obesity in children (Parasin, 2021).

• A 2021 systematic review and meta-analysis identified 33 studies assessing prenatal OC exposure and obesity in early life. DDE (DDT) and HCB (hexaclorobenzene) were positively associated with BMI z-score in childhood (2-9 years) (Cano-Sancho 2017).
The Western Diet (Ultra-processed) is Obesogenic

**Western Diet**
- High fat
- High sugar
- High salt
- Low fiber
- Inadequate fresh fruit and vegetables
- Micronutrient deficient
- **High in ultra-processed food**
- Addictive

**Contains Obesogens**
- Bisphenol A
- Phthalates
- PFAS
- Fructose
- Non-nutritive sweeteners
- Methyl and butyl parabens
- Tween80/carboxy cellulose
- 3-tert-butyl-4-hydroxyanisole (3-BHA)
- Monosodium glutamate (MSG)
- Red coloring 40*
- Yellow coloring 5 and 6*
- Pesticides (PFAS)

* Potential obesogens
Consumption of ultra-processed foods associated with weight gain and obesity in adults: A multi-national cohort study

Ultra-processed Foods and Diseases

Ultra-processed food is associated with an increased risk of Crohn’s disease: a cross-sectional and prospective analysis of 187,154 participants in the UK Biobank

- Association of ultra-processed food intake with risk of inflammatory bowel disease: prospective cohort study
- Ultra-processed food and risk of type 2 diabetes: a systematic review and meta-analysis of longitudinal studies
- Ultra-processed food targets bone quality via endochondral ossification
- Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort
- Ultra-Processed Food Availability and Noncommunicable Diseases: A Systematic Review
- Association of Ultra-processed Food Consumption with risk of Dementia, a prospective cohort study
- Ultra-Processed Food Consumption and Mental Health: A Systematic Review and Meta-Analysis of Observational Studies
- Ultra-processed food consumption and excess weight among US adults
Obesogens Can Alter Many Metabolic Endpoints

- Increased food intake
- Oxidative stress
- Glucose intolerance
- Leptin resistance
- Insulin resistance
- Altered microbiome
- Inflammation
- NAFLD
- Number and size of adipocytes
- Serum lipid
- Adipocyte differentiation
- Skeletal muscle hypertrophy
- Energy expenditure
- Body weight
- Food addiction
Obesogens Affect Multiple Endpoints

- BPA, BPS
- Phthalates
- PFAS
- PBDE
- TCDD
- PCBs
- PAH (Air pollution)
- Methyl paraben
- Triclosan

- BPA
- DEHP
- TBT
- OPFR (flame retardant)

Larger effect with HFD
- BPA
- Butyl benzyl phthalate
- DEHP
- TBT
- Nicotine
- Chlorpyrifos
- Imidacloprid
- DDT
- Permethrin
- Atrazine

- BPA
- TBT
- DEHP
- PBDEs
- Triclosan
- CMC
- PM$_{2.5}$
- Western diet

- BPA
- DEHP
- TBT
- DDT
- PCBs
- BaP
- Triclosan

- BPA
- DEHP
- TBT
- TCP

Increase ROS
- BPA
- TBT
- BBP
- DEHP
- PFAS
- Atrazine
- Cadmium
- Chlorpyrifos
- {CBs
- PBDE
- Air pollution
Transgenerational Epigenetic Inheritance of Obesity

- **Positive results**
  - Tributyl tin (M and F)
  - DDT (M and F)
  - Hydrocarbon mixture (jet fuel) (M and F)
  - BPA, DEHP, DBP (M and F)
  - BPA
  - Nutrition

- **Negative results**
  - Permethrin/DEET mixture
  - Vinclozolin
  - Dioxin

Exposure (F0)
Assess Weight Gain (F4)
Prenatal Exposure to Tributyl Tin: Higher Fat Diet Causes Obesity in F4 Males

Chamorro-Garcia et al., Nature Comm 2017

Resistant to fat loss!

Gain weight more easily and harder to lose weight!
Obesogen Model: OBS

* A multiorgan disruption of metabolism

Obesogens → Interfere with hormone and signaling pathways

↑ Food Intake
↑ ROS
↑ Number and size of adipocytes
↑ Inflammation
↑ NAFLD
↑ Insulin
↑ Insulin & leptin resistance
Alter microbiome
Dysfunctional adipocytes

→ Fat storage (anabolic adipose)
→ Weight Gain
Can Obesogens Explain Why Diets Fail?

• POUNDS Lost study: two-year randomized clinical trial compared four diets on body weight.
  • Healthy diet
  • High protein/low glycemic index
  • High protein/high glycemic index
  • Low protein/low glycemic index
  • Low protein/high glycemic index

• Most weight loss occurred in the first six months, followed by weight regain through 24 months, with no differences between diet regimens.

• Perfluorinated chemicals (PFAS) were associated with:
  – Greater weight regain
  – Greater decline in basal metabolic rate during weight loss
  – Less increase in basal metabolic rate during the weight regain

Liu et al Plos Medicine 2018
Grandjean et al Obesity 2023
Support and Challenges to the OBS Model

Support:
• In vitro, animal and human studies.
• Developmental and adult exposures cause weight gain.
• Affects endpoints considered part of EBM and CIM.
• Human exposure to a variety of obesogens across the lifespan.

Challenges:
• Lack of developmental biomarkers that indicate susceptibility to weight gain later in life.
• Lack of data showing the effects of obesogens in clinical-type studies.
• Lack of data showing a decrease in exposure results in lower weight gain.
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Current models of obesity.
What data support the role of environmental chemicals (obesogens)?
Redox model of obesity.
How can all these models be integrated to explain obesity?
Redox Model of Obesity

- REDOX is an energy-responsive communication system that changes with fuel needs.
- Normal response to fuel is to increase reactive oxygen species (ROS) transiently.
- ROS signals to store fuel by increasing insulin, altering brain control of food intake, and stimulating triglyceride synthesis in adipose tissue.
- A ROS signal is inappropriate when fuel is normal... but stimulated by an outside force.
Energy Reduction-Oxidation Model: REDOX

Food Consumption

↑ Mito NADH

↑ ROS (Transient)

↑ Insulin secretion

↓ Food Intake (Brain)

↓ Liver Gluconeogenesis

↑ Nutrient storage (adipose tissue and liver)
Redox Sharing Among Metabolic Organs via the Bloodstream

B. Corkey and O. Shirhai, Trends Endocrinol Metab 2012
Is Obesity a Metabolic Disorder of the Control of Redox?

What has changed in the last ~50 years that is responsible for inappropriate increases ROS?

- Environmental Chemicals (Obesogens) that generate inflammation (ROS)
- Ultra-processed foods that contain Obesogens
- Ultra-processed carbohydrates
- Inadequate ROS scavenging capacity to meet the excess demand
Energy Reduction-Oxidation Model: REDOX
A metabolic disorder due to obesogen-mediated ROS

Excess Food Consumption (Ultra-processed food) → ↑↑ ROS (Inappropriate) → ↑ Food Intake → Hyperinsulinemia → ↑ Increased Fat

Obesogens (Inappropriate signal) → Hyperlipidemia

↑ Nutrient storage (adipose tissue)
↑ Adipose Inflammation
Summary and Implications (OBS-REDOX)

1. Ultra-processed food (especially carbohydrates) and obesogens change redox and generate ROS shared among all organs.
2. Such ROS constitutes a misleading signal.
3. Redox couples are transported among cells via circulation, thus interconnecting all organs.
4. ROS and redox changes impact function in an organ-specific manner.
5. The increase in inappropriate ROS causes hyperinsulinemia, hyperlipidemia, increased appetite and fat disposition.
Support and Challenges to REDOX Model

Support:
• The circulating redox state becomes more oxidized with age and disease.
• The changes in redox response to fuel consumption and obesogens are well documented.
• ROS impacts cell function in an organ-specific manner.

Challenges:
• The redox model is largely hypothetical.
• Strong evidence requires identifying the specific chemicals in human circulation and testing their ability to generate ROS.
• Documentation that removal of relevant chemicals can alter the redox state.
Integrating REDOX and OBS Models

Abnormal Increase ROS: TBT, BBP, DEHP, PFAS, Atrazine, BPA, Cadmium, Chlorpyrifos, PCBs, PBDE, Air Pollution, Ultra-processed Food

Circulating Master Metabolic REDOX Regulators (ROS)

Liver
- Glucose Release

Fat cell
- Lipolysis
- Lipid Synthesis

Brain
- Hunger Satiety

Pancreas
- Insulin Secretion
The OBS/REDOX Model Contributes to a Unifying Theory for the Global Rise in Obesity
The OBS/REDOX Model Contributes to a Unifying Theory
A Focus on Obesogens

Diet → Stimulate ROS → Energy Balance Model
• Increased food intake
• Altered brain control of food intake
• Altered metabolic rate
• Disrupted microbiome

Interfere with hormone signaling → Carbohydrate-Insulin Model
• Increase insulin
• Insulin resistance
• Increase number and size of fat cell

Obesogen
(In utero and across the lifespan and generations)

Weight gain
Key Points

• The cause of obesity is unknown…but it is multifactorial.
• There are four major models.
• Each model makes essential contributions to understanding the pathogenesis of obesity.
• We propose an integrated model that can explain all the major changes that are responsible for weight gain.
  • Developmental programming
  • Increased food intake
  • Weight gain without increased food intake
  • Increased insulin secretion
  • Altered microbiome
  • NAFLD
  • Increased number and size of adipocytes
  • Inflammation
  • Increased ROS
• Our model puts a focus on obesogens.
• Acceptance of this integrated model will focus on preventing obesity by reducing exposure to obesogens.
Good News: A Focus on Obesogens Changes the Narrative to Prevention

There are personal changes that can help.

• Reduce exposure to environmental chemicals before and during pregnancy
  • Filtered drinking water
  • Organic household products, cleaners, pesticides
  • Eliminate plastics/canned food (ultra-processed food)
  • Careful with cosmetics/sunscreens

• Watch nutrition, increase exercise, and decrease chemical exposures throughout life...to reduce the impact of second hits.

Obesity is a public health problem!

• Provide affordable, sustainable, healthy food
• Reduce exposures to obesogens via policy and regulatory changes
Not the end but just the end of the beginning of solving the obesity pandemic!