Ancestral Diet, the Microbiota and Energy Homeostasis: Should Foods Be Cellular?

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Odd one out?
A Different Way of Looking at Obesity....

• Obesity is a disorder of energy homeostasis (leptin-resistance = causal)
• Energy Homeostasis works well with pre-industrial / pre-agricultural diets

The Hypothesis Suggests:
• Obesity is a bacterial disorder
  - altered commensal signaling due to dense artificial growth media in the upper GI tract
• “Real foods” are alive / of life
  - co-evolved with bacteria, hence have defenses against bacterial degradation
• The effects of the chronically altered microbiota are manifold, including altered cytokine signaling and immune / inflammatory behaviour, and may be the enabling factor behind diseases of civilization
Overview

**Diet Induced Obesity**
- Obesity and Energy Homeostasis
- Health of non-westernized peoples
- Health from Ancestral Diets is macronutrient-independent
- Western diets perturb energy homeostasis, role of (Westernized) carbohydrates

**The GI microbiota**
- Pivotal location: small, not large intestine

**The Hypothesis**
- Hypothesis: Ileal microbiota as sensors of acellular / refined foods
- What can it explain?
- Where do we go from here?
What Do We Know?

• The obese do tend to eat more and move less

• But, the obese also **homeostatically guard their elevated weight**

  *High levels of exercise only blunt weight regain after successful short term weightloss*

  Mekary et al., 2010, Obesity

  *After weightloss, total energy expenditure drops in an effort to conserve energy and regain weight.*

  Ebbeling et al., 2012, JAMA

• Overweight: risk factor for many conditions (from cancer to cardiovascular disease)

• Abdominal adiposity is an **especially good indicator** of metabolic and CVD risk

• Metabolic syndrome: hypertension, elevated blood sugar (insulin resistance), increased waist measurement, dyslipidemia
Leptin Resistance

Hypothalamus

Intestinal Vagal Afferents

nodose

Fat tissue

Adapted from Jeffrey M Friedman
Non-westernized peoples reported as free of western diseases (by colonial MDs up until 1960s)

- Overweight / Obesity
- Heart disease
- Stroke
- Common cancers

(Others - Mental illnesses, varicose veins, acne, Crohn’s, colitis, IBS, autoimmunity, myopia, dementia)

However: *rapid adoption of western foods and lifestyles means this good health often disappeared before it could be epidemiologically verified.*
The Kitava Study

Photos: Staffan Lindeberg

100 year old man

94 year old woman
Where they are, and what they eat

~70% Energy

Kitavan Photo: Staffan Lindeberg
Lean and low leptin despite plenty to eat

Absence of overweight
Despite food abundance
(rots in streets / eaten by dogs)

Leptin several times lower
than healthy westerners

Table 4.6 Definition of weight classes and their occurrence in the 40–60-year age group in Sweden and on Kitava.

<table>
<thead>
<tr>
<th>Weight class</th>
<th>BMI (kg/m²)</th>
<th>Sweden (%)</th>
<th>Kitava (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;20</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>Normal weight</td>
<td>20–25</td>
<td>45</td>
<td>28</td>
</tr>
<tr>
<td>Overweight</td>
<td>25–30</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>Obese</td>
<td>30–35</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>≥35</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>


Fig. 1 Serum leptin versus body mass index (BMI) in males from Kitava and Sweden. Note the log scales.

Lindeberg et al., 2001, J Internal Medicine
Metabolic health markers substantially better than Westerners

Notably, HDL and Triglycerides are comparable to Westerners

CVD is virtually absent on the island

The main results of the Kitava study, that there is no ischaemic heart disease (and no stroke; see Section 4.2), are unanimously confirmed by medical experts with knowledge of the Trobriand Islands or other parts of Melanesia. Likewise, Jüptner noted no cases of angina pectoris, myocardial infarction or sudden death during his 5 years as a general practitioner on the islands at the beginning of the 1960s, when the population was roughly 12 000 (H. Jüptner, unpublished data). His experience is based partly on patients that visited him due to illness, and partly from systematic health examinations given in all the different villages at three separate times. The same observation was made by Schiefenhövel, physician and human ethologist from the Max Planck Institute in Munich (W. Schiefenhövel, unpublished data). He can speak the language of the Trobrianders, Kilivila, and


In common with Masai, Bushmen, and other hunter gatherers, and much earlier widespread reports in Africa, and the high Arctic....

Adapted from Thomas et al, Am J Cardiology 1960
Kitavan metabolic health: Unlikely to be genetic protection

Closely related peoples in other parts of Papua New Guinea are susceptible to overweight, stroke and other diseases of civilisation.

Xavier Han, a 235 kg man living in New Ireland (Papua New Guinea). Video still: From “Saving Xavier” by SBS International / Virtual Culture Pty Ltd

Data from other non-Westernized peoples

Male Ache leptin levels lower than (leaner) male US distance runners

...Exercise cannot span this non-Westernized leptin physiology

Bribiescas & Hickey
*Nutrition and Metabolism* 2006

(AP Photo/Jorge Saenz)
Trends in Blood Pressure

Data for people between 40 – 60 years old

Adapted from “Food And Western Disease; Health And Nutrition From An Evolutionary Perspective”. Staffan Lindeberg. Oxford: Wiley-Blackwell, 2010,

data from:
Oliver et al., 1975 Circulation
Lindeberg et al., 1994 J Internal Med
Baruzzi et al., 1981
Kaminer et al., 1960 Circulation
Even early ‘westernization’ produces significant metabolic changes

Table 1. Characteristics of Women From the Traditional Shuar Villages in Relation to Women From the Yuwientsa Community

<table>
<thead>
<tr>
<th>Variable</th>
<th>Traditional Shuar Villages (n = 26)</th>
<th>Yuwientsa Community (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.0 ± 2.2</td>
<td>36.9 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.5 ± 4.1</td>
<td>161.1 ± 4.3</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52.7 ± 6.8</td>
<td>56.5 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 2.8</td>
<td>24.1 ± 2.7</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>79.7 ± 8.2</td>
<td>84.2 ± 8.3</td>
<td>NS</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>40.2 ± 6.2</td>
<td>41.0 ± 5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>11.7 ± 3.3</td>
<td>14.5 ± 4.0</td>
<td>.023</td>
</tr>
<tr>
<td>Fat mass/LBM (ratio)</td>
<td>0.30 ± 0.08</td>
<td>0.35 ± 0.09</td>
<td>.004</td>
</tr>
<tr>
<td>Fat mass (% of body weight)</td>
<td>22.1 ± 4.9</td>
<td>25.4 ± 4.9</td>
<td>.032</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>3.9 ± 0.58</td>
<td>4.1 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma insulin (pmol/L)</td>
<td>35.5 ± 12.7</td>
<td>49.8 ± 37.4</td>
<td>.013</td>
</tr>
<tr>
<td>HOMA index</td>
<td>6.1 ± 2.2</td>
<td>8.8 ± 4.8</td>
<td>.004</td>
</tr>
<tr>
<td>Plasma leptin (ng/mL)</td>
<td>4.1 ± 2.7</td>
<td>5.5 ± 3.1</td>
<td>.021</td>
</tr>
<tr>
<td>Leptin per kg body fat (ng/mL/kg)</td>
<td>0.32 ± 0.03</td>
<td>0.36 ± 0.03</td>
<td>.032</td>
</tr>
<tr>
<td>Plasma cholesterol (mmol/L)</td>
<td>4.5 ± 0.7</td>
<td>4.5 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/L)</td>
<td>1.7 ± 0.6</td>
<td>2.3 ± 1.0</td>
<td>.025</td>
</tr>
<tr>
<td>Plasma glucagon (ng/L)</td>
<td>63.3 ± 29.1</td>
<td>61.0 ± 13.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE: P indicates probability level of random difference between the groups. Abbreviations: LBM, lean body mass; HOMA, homeostasis model assessment; NS, not significant.

Lindgarde et al., Metabolism, Vol 53, No 10 (October), 2004

Similar findings in a Solomon Islanders study during their Westernization

Photo: Dept of Anthropology, University of Oregon
What is our concept of ‘healthy’?

“I eat Western Foods, and I’m okay”

Figure 2.1 A schematic graph of the variation of risk for Western diseases, such as cardiovascular disease, depending on risk factor levels, such as serum cholesterol. A Westerner at average risk has been set as the reference. ‘Low’-risk Westerners have a markedly higher risk than non-Westerners.

‘Western Diseases’ are **not** a natural part of aging...

**Food and Western Disease: Health and Nutrition from an Evolutionary Perspective**

*Staffan Lindeberg*

*Wiley-Blackwell*

**Conditions that have been linked to insulin resistance**
- Type II Diabetes
- Metabolic Syndrome
- NAFLD
- Cardiovascular Disease
- Atherosclerosis
- Obstructive Sleep Apnoea
- Increased Stature
- Early Puberty
- Acne
- Prostate Hypertrophy
- Cancer
- Infertility
- Kidney Failure
- Alzheimer’s
Health from Ancestral Diets Appears Macronutrient-Independent
Looking for the mechanism: There are many ‘Ancestral Diet’s’

Table 3
Effects of latitude on carbohydrate intake (% of energy) for 229 hunter-gatherer diets

<table>
<thead>
<tr>
<th>Degrees from the equator (latitude)</th>
<th>Absolute frequency (no. of societies)</th>
<th>Relative frequency (percentage of societies)</th>
<th>Carbohydrate intake (percentage of energy/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>6</td>
<td>2.6</td>
<td>22-28</td>
</tr>
<tr>
<td>11-20</td>
<td>15</td>
<td>6.6</td>
<td>29-34</td>
</tr>
<tr>
<td>21-30</td>
<td>11</td>
<td>4.8</td>
<td>29-34</td>
</tr>
<tr>
<td>31-40</td>
<td>64</td>
<td>27.9</td>
<td>29-34</td>
</tr>
<tr>
<td>41-50</td>
<td>75</td>
<td>32.8</td>
<td>16-22</td>
</tr>
<tr>
<td>51-60</td>
<td>38</td>
<td>16.6</td>
<td>10-15</td>
</tr>
<tr>
<td>&gt;60</td>
<td>20</td>
<td>8.7</td>
<td>≤9</td>
</tr>
</tbody>
</table>

*Strohle and Hahn, 2011 Nutrition Research*
The diets of non-westernized populations have very diverse macronutrient compositions.

- Kitava (1990’s)
- Alaskan / High Arctic Eskimo / Inuit (1959-1972)
- Masai (1971)
- !Kung (1972)
- Kavirondo Kenyans (1929)

mongongo nuts!
But... flour and sugar appears to correlate with overweight and obesity – “dead simple” carbs

<table>
<thead>
<tr>
<th>People</th>
<th>Refinement or grains</th>
<th>Overweight or Obesity</th>
<th>Other health markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solomon Islanders (1974)</td>
<td>+/−</td>
<td>Lean (western-influenced islands were heavier)</td>
<td>No hypertension or cardiovascular disease. Islands with western influence show increased blood pressure</td>
</tr>
<tr>
<td>Turkana (1980-1983)</td>
<td>+</td>
<td>lean (&lt;5th percentile of western weight)</td>
<td>No increase in weight in middle age</td>
</tr>
<tr>
<td>Tarahumara (1978-1979)</td>
<td>++</td>
<td>5% BMI &gt;26</td>
<td>No hypertension, no rise in blood pressure with age</td>
</tr>
</tbody>
</table>

Adapted from Spreadbury (2012), Diabetes Metabolic Syndrome and Obesity
**Carbohydrate Clues:**

“Low-carb” produces weight loss without hunger.

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**Figure 2. Weight Change Relative to Baseline**

Low fat diets work equally well on weight loss when caloric restriction is enforced (but will cause hunger).

*Garnder et al., 2007 JAMA*
Carbohydrate composition drives Western Diet effect on Energy Homeostasis

Ebberling et al., JAMA 2012

Energy Homeostasis Perturbation
Greatest: Low fat (high carbohydrate) >
Intermediate: Low GI >
Least: Very Low Carbohydrate
Carbohydrate Puzzler…. (we will come back to this)

- So carbohydrate levels have *something* to do with Western diet’s problems…. (Insulin? Sugar and the liver?)

- *But can be eaten as 70% of energy intake in Ancestral Diets producing world-beating metabolic health?*

Can we go back? Reversibility of Western Diet?

Return to ‘bush’ lifestyle normalized blood glucose in diabetic Australian Aborigines

Table 4.4  Effect of returning to a hunter-gatherer lifestyle for 7 weeks among ten Australian Aborigines with type 2 diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>82 ± 3</td>
<td>74 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2 ± 1.1</td>
<td>24.5 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>12 ± 1.2</td>
<td>6.6 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-hour blood glucose</td>
<td>18.5 ± 1.3</td>
<td>11.9 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>23 ± 3</td>
<td>12 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-hour insulin</td>
<td>49 ± 9</td>
<td>59 ± 11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4.0 ± 0.5</td>
<td>1.2 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.7 ± 0.2</td>
<td>5.0 ± 0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>121 ± 5</td>
<td>114 ± 4</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>80 ± 2</td>
<td>72 ± 2</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

n.s., not significant.

Originally from O’Dea et al., Diabetes 1984
Grain-free whole-food diet in Westerners – early results

Fresh whole foods: Fruit, vegetables, unprocessed meats, nuts, fish

Excluded: processed foods, cereal grains, flour, sugar, ‘vegetable’ oils, legumes, dairy products

Current trials of “paleolithic-style” diet are small (around 10-30 participants), and brief (up to 3 months)

However, effects on waist measurement, insulin, blood glucose and weight large enough: adequately powered for multiple factors
Paleolithic versus Mediterranean Diets

Better blood glucose control than Mediterranean diet

Fig. 1 Plasma glucose during OGTTs at study start (baseline, closed circles) and after 12 weeks (open circles) in the Paleolithic (a) and Consensus (b) groups. Values are means±SE. ***p<0.001


Figure 4.10 Changes in glucose response to a 75 g oral glucose load during 12 weeks of Paleolithic or Consensus diet. Values are means ± standard errors. (Adapted from Reference 1043.)

Figure 4.18 Waist loss on a Paleolithic or Consensus (Mediterranean-like) diet. Values are means ± standard errors. Waist circumference before dietary change was 105.8 ± 7.6 cm in the Paleolithic group and 106.6 ± 8.0 cm in the Consensus group. (Adapted from Reference 1043.)

**Metabolic benefits independent of reduced food intake / weight loss.**
With **Fixed** caloric intake + no weight loss:
Significant improvements in: Total cholesterol, LDL and triglyceride profiles, glucose tolerance test insulin AUC, HOMA score, diastolic blood pressure and arterial distensibility (Frassetto et al. 2009).

**All ad libitum studies: reduced food intake (15-35%)**
-Satiety increase (not from energy density, fiber or macronutrient content) (Jonsson et al 2010)

Leptin levels reduced by over 30% after 12 weeks - **best correlated with the absence of grains** (excluding rice) (Jonsson et al 2010).

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A Palaeolithic-type diet causes strong tissue-specific effects on ectopic fat deposition in obese postmenopausal women

M. Ryberg¹, S. Sandberg¹, C. Mellberg¹, O. Stegle²,³, B. Lindahl¹, C. Larsson⁴,⁵, J. Hauksson⁶,⁷ & T. Olsson¹

From the ¹Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; ²Max Planck Institute for Developmental Biology & Max Planck Institute for Intelligent Systems, Tübingen, Germany; ³MRC Epidemiology Unit, Cambridge, UK; ⁴Department of Food and Nutrition, Umeå University, Umeå, Sweden; ⁵Department of Food and Nutrition and Sport Science, University of Gothenburg, Gothenburg, Sweden; ⁶Department of Radiation Sciences, Umeå University, Umeå, Sweden; and ⁷Department of Radiography and Biomedical Science, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

Significant decrease (25%) in ad libitum energy intake
Non-significant trend (8%) toward increased energy output
Hepatic lipid content significantly decreased (49%)

Fig 1 Hepatic lipid content at baseline and after 5 weeks of dietary intervention (n = 10). Hepatic liver content expressed as the ratio of lipid protons to water protons. P-value refers to change from baseline to week 5 using the Wilcoxon matched-pair signed-rank test: **P < 0.01.

Ryberg et al., Journal of Internal Medicine (In Press)
Likely it’s popular because it works without sustained effort or cravings, (and seems to keep working).

Not because it’s a trendy “fad”

“Paleolithic Diet”: not just meat, and is based on living hunter gatherers and clinical evidence.

Not because of anything ‘cavemen’ did or did not do
The Role of the Microbiota

Distribution and abundance of bacteria in human gastrointestinal tract.
[Figure modified from B. Sartor Gastroenterology 2008]
GI Microbiota – Major Role in Obesity and Diabetes

• Germ free mice – resistant to most models of diet-induced obesity

• Microbiota is changed in obese animals and humans

• Overweight phenotype is transferable by stool transplant (human stool too...)

Woo hoo!
Microbiota change can alter energy homeostasis and glucose regulation

Monoclonisation of GF mice for 4 weeks with *E. coli* W3110 or the isogenic strain MLK1067 (which expresses LPS with reduced immunogenicity) resulted in impaired glucose and insulin tolerance and promoted M1 polarisation of CD11b cells in WAT. However, colonisation with *E.coli* W3110 but not MLK1067 promoted macrophage accumulation and upregulation of proinflammatory and anti-inflammatory gene expression as well as JNK phosphorylation.

Importantly indicates LPS may not be the prime driver of insulin and leptin resistance (also c.f. reduced fat diet in humans)
As well as overweight, microbiota convey propensity to liver disease and hyperglycemia.

**What are the new findings?**

- Gut microbiota markedly impacts the lipid metabolism in the liver, independently of obesity.
- The propensity to develop NAFLD features including hyperglycaemia or steatosis is transmissible by means of gut microbiota transplantation.
- Bacterial species associated with the NAFLD-resistant and NAFLD-prone phenotypes have been identified.

*Le Roy, 2012 GUT In Press*
Gastric Bypass has a bacterially transmissible element

RESEARCH ARTICLE

OBESITY

Conserved Shifts in the Gut Microbiota Due to Gastric Bypass Reduce Host Weight and Adiposity

Alice P. Liou,1 Melissa Paziuk,1 Jesus-Mario Luevano Jr.,2 Sriram Machineni,1 Peter J. Turnbaugh,2* Lee M. Kaplan1*

Liou et al., 2013 Science Translational Medicine
The power of host-bacterial interactions may be highly conserved

Drosophila Microbiome Modulates Host Developmental and Metabolic Homeostasis via Insulin Signaling


- Mutant bacteria without the enzyme to make acetic acid were transplanted into Drosophila larvae
- Insulin / insulin-like growth factor signaling was strongly modulated
- Altered: developmental rate, body size, energy metabolism, intestinal stem-cell activity
- Could be reversed with acetic acid supplement

Shin et al., Science (2011)

Leptin may also be highly conserved

Drosophila Cytokine Unpaired 2 Regulates Physiological Homeostasis by Remotely Controlling Insulin Secretion

Akhila Rajan and Norbert Perrimon

IPCs, resulting in the secretion of Dilps. Strikingly, we find that human Leptin can rescue the upd2 mutant phenotypes, suggesting that Upd2 is the functional homolog of Leptin.

Cell 151, 123–137, September 28, 2012
Most GI bacteria are colonic, but the problem has to start higher up

- Fibre / resistant starches - large changes in bowel microbiota, and SCFA production (potential extra energy for host, + metabolic benefits)

- But fibre has been tested extensively (post Cleave – 1970s)
  - Has never produced metabolic effects that span the gulf between westerners and hunter-gatherers

- If not fiber - The other components of Modern or Ancestral foods have differences that exist only in the lumen of the small intestine – they’re absorbed before the bowel.

Hence, the colonic microbiota may be affected by downstream changes
Looking for the mechanism: The Vagal Afferents – central role in satiety signaling

Good evidence now exists for a role of inflammation in the upper gut

Affecting the Vagus, and its satiety signalling

From Kim et al, Nutrition (2011)
Mechanism – diet induced obesity involves microbiota changes, and ileal inflammatory markers

Not all rats get overweight on a high-fat diet

- Hyperphagia
- Increased TLR4 activation
- Ileal inflammation (MPO)
- Increased gut permeability
- Increased LPS in circulation
- Decreased lumenal alkaline phosphatase

- Decreased total bacterial density
- Decreased relative Bacteriodales and Clostridiales orders

Barbier de La Serre et al. 2010 Am J Physiol; Gastroint Liver Physiol
Neurophysiology – Hyperphagia coincides with leptin resistance in vagal afferents, only seen in DIO rats

Plasma leptin

SOCS3 (suppressor of cytokine signalling 3)

de Lartigue et al. 2011 Am J Physiol Endocrinol Metab
Obese rats’ leptin-resistant vagal afferents are also **CCK resistant**

DIO rats nodose neurons also show **enhanced** anti-satiety CB1 and MCH1R, and **impaired** pro-satiety peptide YY type 2 receptor (Y2) after feeding.

**CCK (satiety) resistance**  
![Graph showing CCK (satiety) resistance comparison between Lean and Obese groups.](image)

**Y2R (satiety) resistance**  
![Graph showing Y2R (satiety) resistance comparison between Fasted and Fed groups.](image)

**Anti-satiety signals enhanced**  
![Graph showing enhanced anti-satiety signals in Fasted and Fed conditions.](image)

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Energy intake increases over time  

![Graph showing energy intake increase over time.](image)

*de Lartigue et al. 2012 PLOS One*
Microbiota-dependent small intestinal inflammation, precedes and correlates with subsequent obesity and insulin changes

Germ free mice show no weight changes with HF diet

Ileal (and not colonic) inflammation (again, requires microbiota)

Ding et al., PLOS One 2010
Changes to hypothalamic energy homeostatic centres not seen in germ-free mice

The Gut Microbiota Reduces Leptin Sensitivity and the Expression of the Obesity-Suppressing Neuropeptides Proglucagon (Gcg) and Brain-Derived Neurotrophic Factor (Bdnf) in the Central Nervous System

Erik Schéle, Louise Grahnemo, Fredrik Anesten, Anna Hallén, Fredrik Bäckhed, and John-Olov Jansson

Endocrinology, October 2013, 154(10):3643–3651  endo.endojournals.org  3643

Microbiota somehow plugged into leptin-sensitivity
Intestinal alkaline phosphatase prevents metabolic syndrome in mice

Kaliannan et al 2013
PNAS | April 23, 2013 | vol. 110 | no. 17 | 7003–7008

Alkaline phosphatase is a gut brush border enzyme that neutralizes LPS and other bacterial pathogen-associated molecular patterns.
While leptin can help in immune defense, its STAT3 signaling is also shared with many cytokines.

Bacteria stand to gain from producing products to inhibit this pathway.

SOCS3 (suppressor of cytokine signaling 3)

From “Leptin and mucosal immunity” N M Mackey-Lawrence and W A Petri Jr, Mucosal Immunology (2012)
Diet-induced obesity in *ad libitum*-fed mice: food texture overrides the effect of macronutrient composition

- **Chow pellets**
  - High Fat Chow
  - Western-style high sugar / fat
  - Control chow

- **Powdered**
  - Not palatability driven (different flavours tested)
  - Energy-homeostasis driven (ate less HF powder *by weight*)

Desmarchelier et al., British Journal of Nutrition (2012)
Why are people with European backgrounds relatively resistant?

Why don't supplementary fibre, vitamins and minerals work as well as fruit and vegetables?

Why does periodontal disease track with CVD?

SEEMS TO FIT :)

Energy Homeostasis

Starchy Ancestral Foods

Power of Microbiota

Western Carbohydrates - Flour and Sugar

Lack of efficacy of fibre
What factor sets these foods apart regarding leptin and insulin resistance?

“Ancestral”

“Mediterranean”

Standard American Diet
Nor must sight be lost of another point. Raw foods are resistant to bacterial decomposition, inasmuch as the cells constituting such foods are, or recently were, alive. There is no need to discuss here the biological mechanisms involved in this resistance; what matters is that such resistance is not present in inert foods, like refined sugar. Thus the sugar present in portions of sticky sweets lodged between the teeth will be fermented much more quickly than that present in pieces of raw fruit lodged in the same position.

"Cleave saw that many of the diseases of civilization could be explained as the consequences of eating refined carbohydrate, pointing out the crucial fact that refined foods are an artefact of technological civilization."

-Kenneth Heaton
Putting it all together

Microbial power over host metabolism

Western carbohydrate (flour and sugar) **BAD**

Bacteria may respond differently to
**Inert simple energy sources**
Vs.
**complex lifeforms with evolved defenses**

Old whole foods **GOOD**
Regardless of macronutrient make-up
More than just chemicals: Life meets life within life

Modern Foods

Acellular / dead chemicals
Higher carbohydrate density
Immediate release mouth onwards (amylase action on starches)
Reduced complexity – structural and molecular
Simple bacterial nutrient broth when dissolved

‘Ancestral’ Foods

Cellular / Alive
Lower carbohydrate density
Delayed release (small intestinal, not mouth)
Increased complexity – structural and molecular
Evolutionary thrust and counter thrust of animal and plant cells vs. bacteria

Different genes expressed, different pathways used
Over time – different bacterial populations
Non-fibrous carbohydrate density (per 100g) – good separation between ancestral and modern foods

Caloric density

Glycemic Index

Relevant factor?
Dilute versus rich nutrient broth

Spreadbury, Diabetes Metabolic Syndrome and Obesity 2012
We now know such changes did occur in the mouth

Professor Cooper says: "The composition of oral bacteria changed markedly with the introduction of farming, and again around 150 years ago. With the introduction of processed sugar and flour in the Industrial Revolution, we can see a dramatically decreased diversity in our oral bacteria, allowing domination by caries-causing strains. The modern mouth basically exists in a permanent disease state."

*Adler et al., Nature Genetics (2013)*

*University of Adelaide*
Impact of Cooking / Processing

“collapse of tissue organization due to cooking (20 minutes).”

Uncooked cells resemble a honeycomb with the compartments containing eggshaped starch grains (amyloplasts). The cooked version resembles a drought stricken, cracked landscape. The cell walls have disintegrated, soluble components dissolved & the starch hydrolysed to form a goo. Mag: X90 (at 10x8 size)
### Progress or progression?

#### European Diet over time

<table>
<thead>
<tr>
<th>Neolithic to 1800s</th>
<th>Post-Industrial Revolution</th>
<th>Post – 1970s</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet containing coarse flour and bread</strong>, But plenty of whole foods (Mediterranean)</td>
<td><strong>Diet containing refined sugar and refined flour</strong></td>
<td><strong>Time-poor populace eating large amounts of processed foods formulated to reduce fat and maximise profit</strong></td>
</tr>
<tr>
<td>Baseline changes in insulin and blood glucose.</td>
<td>Greater microbial change.</td>
<td>Maximised bacterial changes occur, many more will develop metabolic conditions and overweight.</td>
</tr>
<tr>
<td>Small changes in adiposity.</td>
<td>Exacerbation of metabolic and inflammatory issues in susceptible.</td>
<td>Increase in associated conditions</td>
</tr>
<tr>
<td>Increased risk of western diseases.</td>
<td>Tooth decay</td>
<td></td>
</tr>
</tbody>
</table>
Thrifty genes – how Europeans are more resistant to overweight and diabetes (longer and more severe pre-exposure to grains (winter storage granaries), and then sugar – reduced fertility in the susceptible.

How the collapse of ancestral dental health with the arrival of Western foods is linked to the arrival of other diseases, and why oral health correlates so well with CVD

How Atkins-like diets produce weight loss without hunger (refined fats & oils – limiting factor?)

How such small changes toward Western imports or agriculture impact on health (different processing of foods, new crops, effects of long shelf life powdered imports)

Thrifty genes – how Europeans are more resistant to overweight and diabetes (longer and more severe pre-exposure to grains (winter storage granaries), and then sugar – reduced fertility in the susceptible.

How multivitamins, minerals and fibre (on top of a Western diet) don’t come close to replicating the benefits of fruit and vegetables
Can commensal microbiota affect autoimmunity and inflammatory conditions?

Commensal microbiota is fundamental for the development of inflammatory pain

F. A. Amaral*, D. Sachs*, V. V. Costa*, C. T. Fagundes*, D. Cisalpino*, T. M. Cunha¹, S. H. Ferreira¹†, F. Q. Cunha¹,
T. A. Silva², J. R. Nicoli³, L. Q. Vieira*, D. G. Souza⁴, and M. M. Teixeira⁵

PNAS | February 12, 2008 | vol. 105 | no. 6 | 2193–2197

Carageenan paw model doesn’t work in germ-free mice

LETTER
doi:10.3038/nature10554

Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination

Kerstin Berer¹, Marsilius Mues³, Michail Koutrolos¹, Zakeya Al Rasbi¹, Marina Boziki³, Caroline Johner², Hartmut Wekerle¹
& Gurumoorthy Krishnamoorthy²

Spontaneous mouse MS model doesn’t work in germ-free mice – role of Gut-associated lymphatic tissue and commensals appears crucial

(Anecdotally, ancestral-style diets commonly produce remission in autoimmune / inflammatory conditions)
Ancestral diets appear a powerful clinical tool, and should be investigated further as a matter of urgency.

Side effects problematic and generate polydrug use

Health care systems close to financial breaking point

Often not wholly effective

Side effects are all good

Patient pays, not state health care

Probably works better

Tastes better than pills
Odd one out – the answer
70% of Kitavans are smokers

Photo: Staffan Lindeberg
Acknowledgements

Many thanks to Richard McNutt and the organizing committee for their kind invitation!

Thanks also to Dr. Andrew Samis for years of debating dietary theories over lunches (that have become progressively healthier!)
The End
Dr Jean Seignalet, auteur de "l'Alimentation ou la Troisième médecine" a prôné une diététique qualitative et un retour à une nutrition de type ancestral pour se préserver de nombreuses maladies auto-immunes.

<table>
<thead>
<tr>
<th>Maladies</th>
<th>Nbre de malades</th>
<th>Rémissions complètes</th>
<th>Améliorations nettes</th>
<th>Améliorations à 50 %</th>
<th>Echecs</th>
<th>Proportions de succès</th>
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<tbody>
<tr>
<td>Polyartrhitte rhumatoïde</td>
<td>297</td>
<td>127</td>
<td>100</td>
<td>18</td>
<td>52</td>
<td>82% *</td>
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<td>Spondylarthrite ankylosante</td>
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<td>11</td>
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<td>11</td>
<td>48</td>
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<td>Lupus érythémateux disséminé</td>
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<td>6</td>
<td>3</td>
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<tr>
<td>Connectivite mixte</td>
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<td>2</td>
<td>-</td>
<td>1</td>
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</tbody>
</table>

3 cancers - Nombre attendu 30
5 infarctus - Nombre attendu 38

Association Jean Seignalet