2010 unm evolutionary medicine – Joe Alcock MD

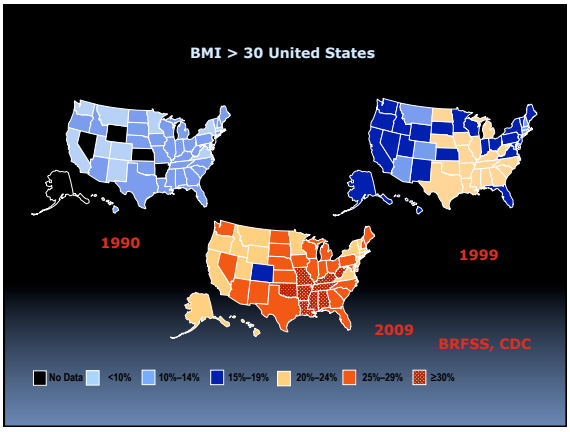
FAT & INFLAMMATION

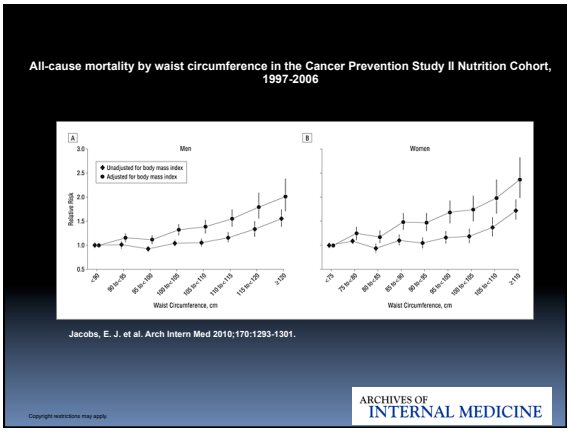
Key Questions

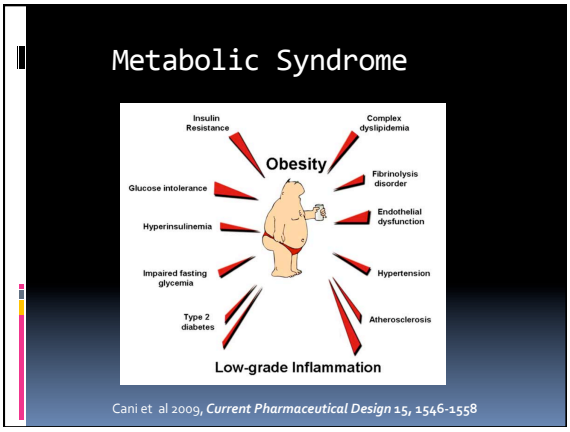
- Can we understand why overweight is epidemic?
- Is obesity harmful and why?
- What is the relationship between energy excess, energy deprivation and disease?
- What makes some foods "good for us" and others not?

Part 1

- Energy and Longevity
  - Energy Excess
  - Energy Restriction


BMI > 30 United States
1990
1999
2009
BRFSS, CDC
No Data
<10%
10%–14%
15%–19%
20%–24%
25%–29%
≥30%

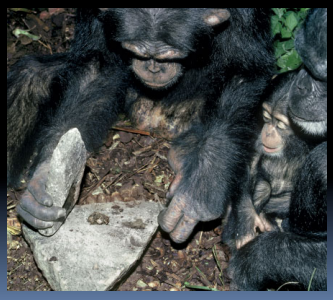

All-cause mortality by waist circumference in the Cancer Prevention Study II Nutrition Cohort, 1997-2006
Men
Women
Unadjusted for body mass index
Adjusted for body mass index
Relative Risk
Waist Circumference, cm
Jacobs, E. J. et al. Arch Intern Med 2010;170:1293-1301.
ARCHIVES OF INTERNAL MEDICINE


Metabolic Syndrome
Insulin Resistance
Complex dyslipidemia
Obesity
Glucose intolerance
Fibrinolysis disorder
Hyperinsulinemia
Endothelial dysfunction
Impaired fasting glycemia
Hypertension
Type 2 diabetes
Atherosclerosis
Low-grade Inflammation
Cani et al 2009, Current Pharmaceutical Design 15, 1546-1558

No free lunch

- Much energy spent in food gathering and preparation


Stone age food processor



Fewer calories = health?

Calorie consumption: The rhesus monkey on the left, Canto, eats a calorie-restricted diet and is 27 years old. The monkey on the right, Owen, consumes a normal diet and is 29.
Credit: University of Wisconsin-Madison / Jeff Miller

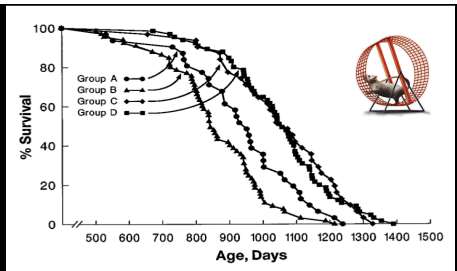


Fig. 2. Survival curves for 4 groups. Survival curve for sedentary control rats in *group B* is significantly different from that of runners in *group A* ($P < 0.02$), food-restricted runners in *group C* ($P < 0.0001$), and food-restricted sedentary rats in *group D* ($P < 0.0001$). Survival curve for runners in *group A* is significantly different from that of food-restricted runners in *group C* ($P < 0.01$) and food-restricted sedentary rats in *group D* ($P < 0.01$).

Holloszy. J Appl Physiol. 1997 Feb;82(2):399-403.

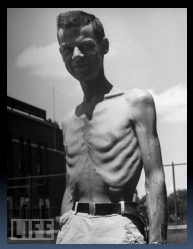
Table 3. Serial measurements of risk factors for atherosclerosis in CR individuals

	Value		
Parameter	**Pre-CR**	**=1 yr CR**	**Present**
BMI, kg/m^2	24.5 ± 2.6	20.9 ± 2.4	19.5 ± 2.1
Tchol, mg/dl	194 ± 45	161 ± 31	157 ± 38
LDL-C, mg/dl	122 ± 36	89 ± 24	86 ± 17
HDL-C, mg/dl	43 ± 8	58 ± 13	65 ± 24
Tchol/HDL-C ratio	4.1 ± 1	2.8 ± 0.5	2.5 ± 0.4
TG, mg/dl	149 ± 87	72 ± 35	54 ± 15
Systolic BP, mmHg	132 ± 15	112 ± 12	97 ± 8
Diastolic BP, mmHg	80 ± 11	69 ± 7	59 ± 5

Fontana et al Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6659-63.

Calorie Restriction: no picnic

- Low levels of circulating sex hormones
- Total testosterone
- Low thyroid hormone
- Lower bone density
- Muscle loss

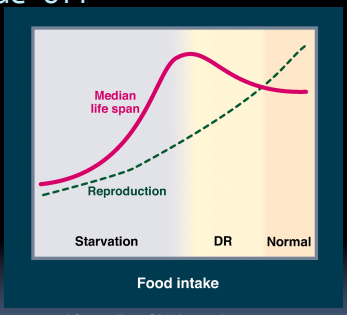


Cangemi, et al. Aging Cell. 2010 Apr;9(2):236-42. Epub 2010 Jan 20.

CR versus Starvation

- Starvation increases bacterial translocation in rodents (Nettelbladt 1997; Bark 1995)
- Human pre-natal famine exposure ⇧CVD Dutch famine winter (Roseboom 2000)
- Human post-natal famine exposure ⇧CVD siege of Leningrad (Sparen 2004).

Trade-off

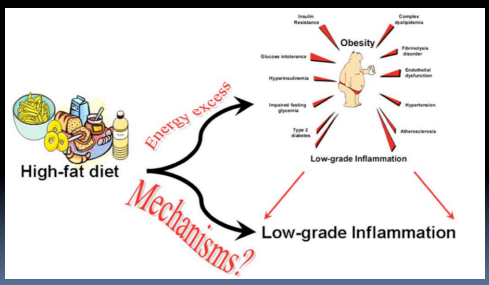


The median life span and fecundity of higher eukaryotes are negatively affected by a very low food intake

L. Fontana et al., Science 328, 321-326 (2010)

Natural Selection & Gastronomy

Energy Excess

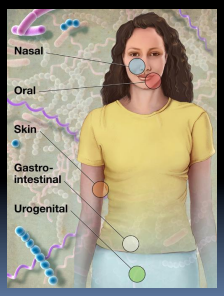


Why does energy excess = ill health?

- Why don't humans cope better with high energy food?
- Ideas?

Could it have to do with predation?

What about micro-predators



- 100 trillion cells
- 9 of 10 do not belong to you!
- Majority in your gut

Food poisoning

- "The pro-inflammatory responses to fatty foods could have evolved as protection from infectious pathogens that have been common in food, until recently"

C.E. Finch, 2007. *The Biology of Human Longevity*. Academic Press.

Infection and Thrifty Genes

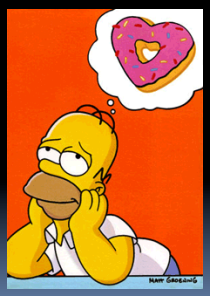
- "pro-inflammatory defenses in partnership with the metabolic syndrome infection may have provided an evolutionary advantage in the tuberculosis pandemic"

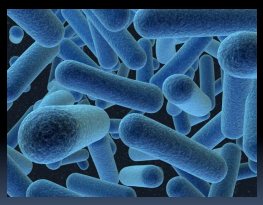
Roth 2009 *JAMA*. 301(24):2586-2588.

Part two

- The Microbiome and Obesity

You share nutrients with gut bacteria





Within minutes of your Grand Slam..

These appear in the blood:

- oxygen radicals
- inflammatory cytokines (TNF alpha, IL-6)
- lipopolysaccharide
- bacteria

(Cani et al. 2007; Cani et al. 2008; Ghanim et al. 2009).

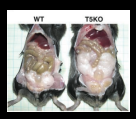
Germ free mice

- Mice raised in sterile conditions remain lean
- After exposure to a pellet of mouse fecal flora – mice rapidly become obese

Backhed et al. Proc Natl Acad Sci USA 2007; 104:979-84

Do bacteria make you fat?

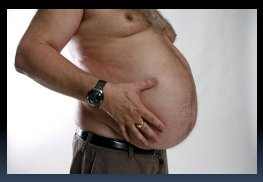
- Mice lacking TLR receptor – have different gut bacteria
- Metabolic syndrome and obesity.
- Feeding WT mice a fecal pellet from obese knockout mice induced the same phenotype



Vijay-Kumar, *et al. Science* ***328, 228 (2010)***

Overweight humans have altered microbiota

- Shifts in 2 major phyla
- Inverse relationship between Bacteroidetes & waist circumference



Tiihonen *et al. British Journal of Nutrition* (2010), 103, 1070–1078

Weight gain in pregnancy

- Mothers
  with weight gain in pregnancy have altered gut microbiota –
  Fewer Bifidobacteria
- Babies
  Fewer Bifodbacteria at 6 months

  Fewer Bacteroidetes and higher *Clostridium* spp.

Collado et al. 2010 *Am J Clin Nutr* Nov;92(5):1023-30.

Antibiotics for obesity and diabetes?

- norfloxacillin / ampicillin / neomycin
  - Reduces obesity
  - Reverses insulin resistance
  - Prevents bacterial proteins from appearing in blood

Cani et al. *Diabetes*. 2008 Jun;57(6):1470-81.

Chou et al. 2008 *Nestle Nutr Workshop Ser Pediatr Program*. 62:127-37

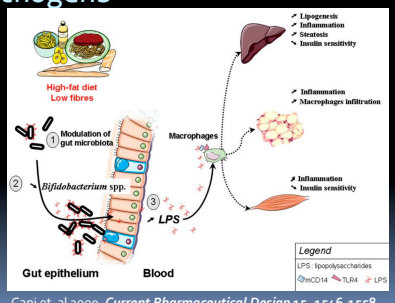
If weight gain is in response to bacteria…

- Why?
- What is the function of fat?

Part 3

Nutrients as immune modulating signals

Some foods promote potential pathogens



Cani et al 2009, *Current Pharmaceutical Design* 15, 1546-1558

Some foods act like antibiotics

VOLUME 73, NO. 1 MARCH 1998

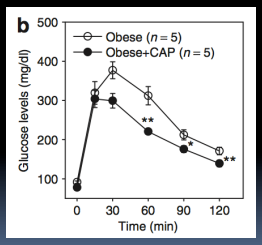
THE QUARTERLY REVIEW of BIOLOGY

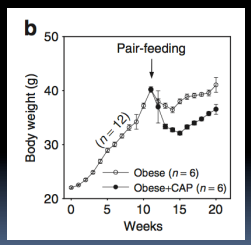
ANTIMICROBIAL FUNCTIONS OF SPICES: WHY SOME LIKE IT HOT

JENNIFER BILLING* AND PAUL W. SHERMAN

Section of Neurobiology and Behavior, Cornell University Ithaca, NY 14853 USA

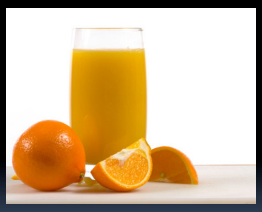
Can spices fight obesity, prevent diabetes or CVD?





Kang et al. Dietary Capsaicin Reduces Obesity-induced Insulin Resistance in Obese Mice Fed a High-fat Diet. Obesity (2009) doi:10.1038/oby.2009.301

Protective foods



- Citrus flavonoids
  - Anti-inflammatory
  - Associated with decreased CVD
  - Antimicrobial properties

Deopurkar et al. 2010. Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 *Diabetes care* 33(5):991-997

Hypothesis

- Anticipatory Immune Signaling
- Nutrients offer the host a signal that predicts risk from the microbiome

Fatty Acids and Inflammation

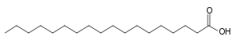
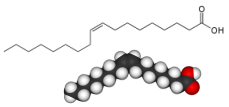
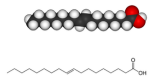



Table 1. Relative effects of lipids on inflammation

Comparison	Lipid	Inflammatory Effect	Lipid	References
1.	Unsaturated	<	Long chain saturated	[4, 8-12]
2.	Medium and short chain saturated	<	Long chain saturated	[4,7,13,14]
3.	Polyunsaturated	<	Monounsaturated	[9,10,15]
4.	Omega-3 (n-3) polyunsaturated	<	Omega-6 (n-6) polyunsaturated	[10, 16-18]
5.	Cis unsaturated	<	Trans unsaturated	[6,19-20]

Anticipatory signaling

- Prediction:
  - Nutrients that have anti-pathogen effects will serve an anti-inflammatory signaling function
  - Nutrients that promote pathogens will have a pro-inflammatory signaling function

Saturated Fat

Unsaturated fatty acids studied	Antimicrobial comparison	Saturated fatty acids studied	Pathogens studied	Are unsaturated lipids more antimicrobial?	References
even C14:1-C22:1 C18:1 elaidic C18:1 petroselinic C18:1 cis vaccenic C18:2, C18:3 C20:2, C20:3,C20:4 C20:5, C22:6	>	even C14:0 – C22:0	*Candida albicans* *Clostridium perfringens* *Clostridium botulinum* *Bacillus cereus* *Cryptosporidium parvum* *Enterococcus* *Helicobacter pylori* *Listeria monocytogenes* *Salmonella typhimurium* *Staphylococcus aureus* *Streptococcus* Group A *Streptococcus* Group B	yes (22)	(Kodicek 1945; HASSINEN et al. 1951; Willett and Morse 1966; Fuller and Moore 1967; Galbraith et al. 1971; Kabara et al. 1972; Ahlenbern 1977b; Kabara and Vrable 1977; Greenway and Dyke 1979; Carson and Daneo-Moore 1980; Dye and Kapral 1981; Knapp and Melly 1986; Ahabouch et al. 1992; Wang and Johnson 1992; Petrone et al. 1998; Sun et al. 2003; Skrivanova et al. 2005; Zheng et al. 2005; Kelsey et al. 2006; Sun et al. 2007; Schmidt and Kuhlenschmidt 2008; Bibi et al. 2009)*
even C6:1-C10:1 C16:1, C18:1 C18:2 MG C12:1 C18:1 elaidic C18:1 cis vaccenic	<	even C6:0-C10:0 C16:0, C18:0 MG C12:0	*Candida albicans* *Clostridium perfringens* *Aeromonas hydrophila* *Helicobacter pylori* *Listeria monocytogenes* *Staphylococcus aureus*	no (6)	(Canas-Rodriguez and Smith 1966; Butcher et al. 1976; Lacey and Lord 1981; van der Kooij and Hijnen 1988; Petschow et al. 1996; Mbundi et al. 2004)

Dietary fat and inflammation

Table 4.

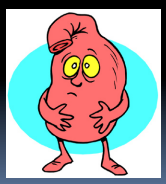
Contingency table analysis of published reports showing antimicrobial activity and inflammatory effect for lipids in different classes.

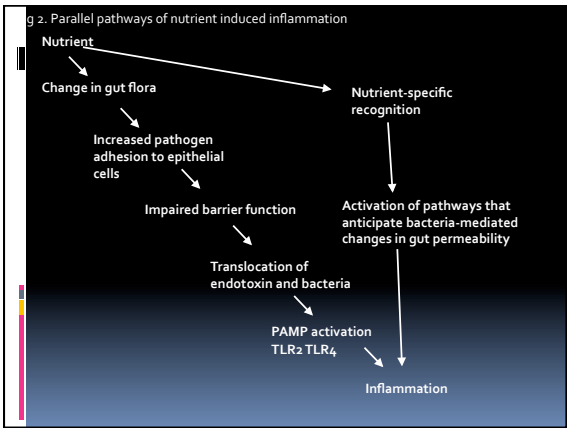
Fatty acid	More Antimicrobial Lipid*	More Inflammatory Lipid**	p value (Fisher's exact test)
Saturated	6	8	p < 0.001
Unsaturated	22	0	
Long Chain Saturated	3	3	p = 0.007
Short/Medium Chain Saturated	35	1	
Monounsaturated	5	4	p = 0.004
Polyunsaturated	23	0	
Omega 6	8	7	p = 0.035
Omega 3	14	1	
trans fatty acid	1	4	p = 0.01
cis fatty acid	7	0	

©Alcock Franklin and Kuzawa, unpublished data

Gut Barrier

- Saturated fats worsen barrier function



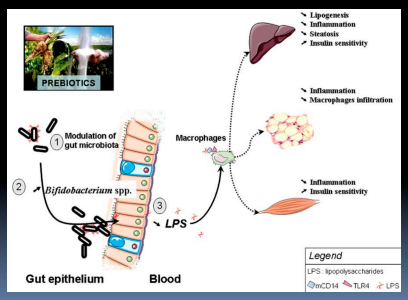


How about Carbohydrates?

- Fructose increases permeability to endotoxin in mice, an effect that is reduced when antibiotics are co-administered (Bergheim 2008).

Apple a day…

Oligosaccharides



Effects of diet on the brain

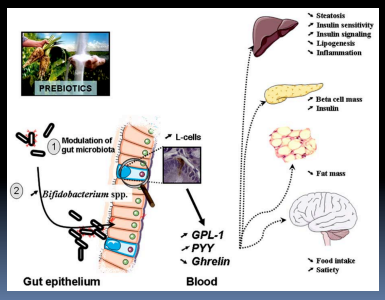


Fig 3a. Host immune compensation depends on nutrient contribution or impairment of host barrier function.

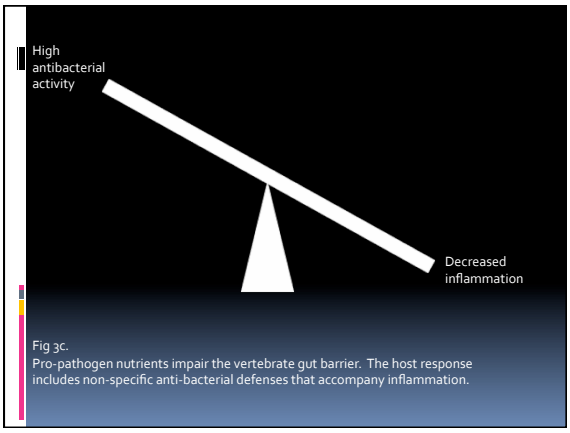
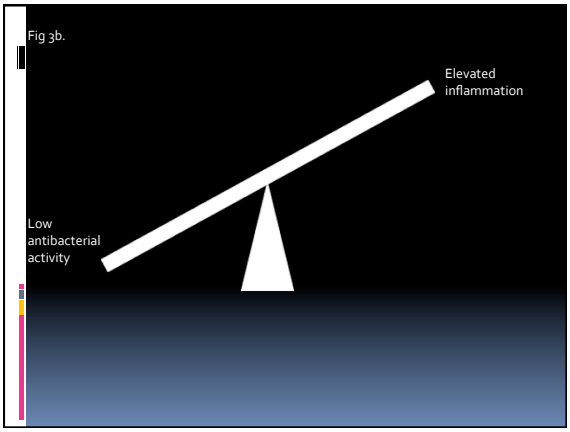


Fig 3c.
Pro-pathogen nutrients impair the vertebrate gut barrier. The host response includes non-specific anti-bacterial defenses that accompany inflammation.



Summary Points

- Both under and over-nutrition are harmful- because both states give advantages to pathogens
- "Good" foods feed benign intestinal bacteria
- "Bad" foods feed pathogens
- Pathogens force host to invest in costly defenses
- Defenses can turn on the host…