

# The Aetiology of Obesity

A New Hope

# William Banting 1796-1878

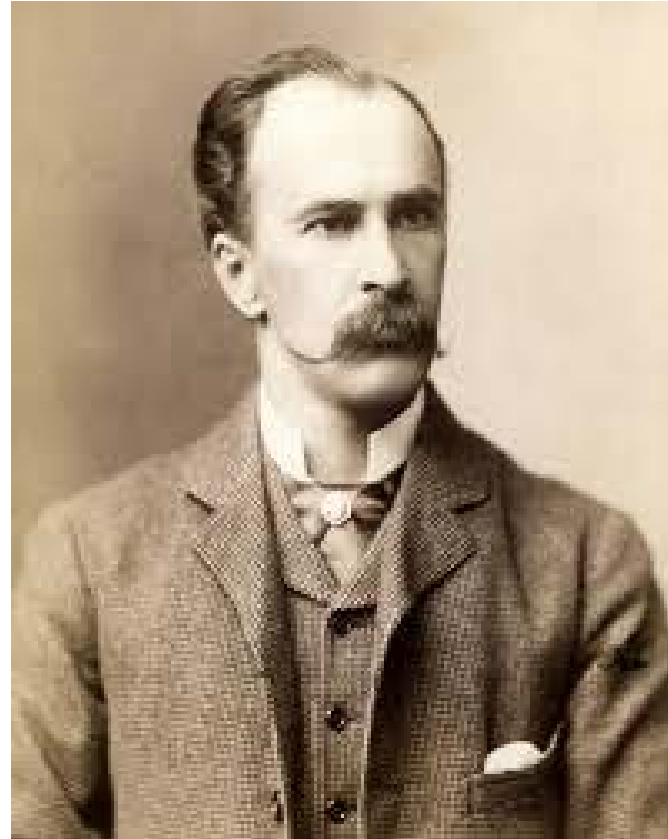
- Increased exercise and decrease caloric intake but no weight loss
- Published 16 page pamphlet “Letter on Corpulence” in 1863
- Ate 3 meals a day of meat, fish or game with an ounce or 2 of stale toast or cooked fruit on the side
- Scrupulously avoided any other food that might contain either **sugar or starch** – in particular – **bread, milk, beer, sweets, and potatoes**
- **Avoid ‘fattening’ carbohydrates**



- Age 62 weighed 202lbs and stood 5'5"

# William Osler

- Author of seminal textbook “The Principles and Practice of Medicine” 1907
  - Discussed treatment of obesity
  - These diets featured lean beef, veal, mutton and eggs
- 1882 monograph “Obesity and Its Treatment” – insisted that fatty foods were crucial because they increased satiety and so decreased fat accumulation



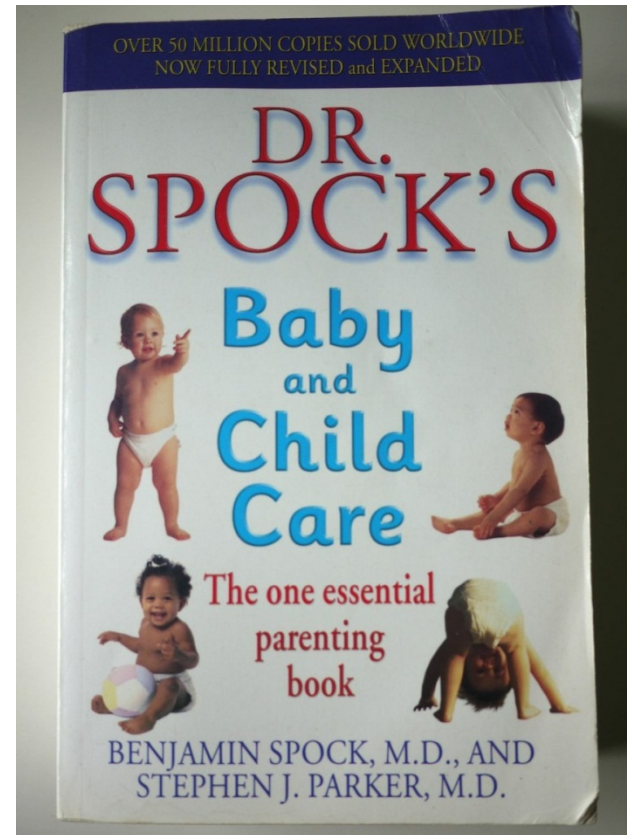
- Considered the “Father of Modern Medicine”

# University of Chicago

- 'General Rules' from Chicago
  - 1. Do not use sugar, honey, syrup, jam, jelly, or candy
  - 2. Do not use fruits canned with sugar
  - 3. Do not use cake, cookies, pie, puddings, ice cream or ices
  - 4. Do not use foods which have cornstarch or flour added such as gravy or cream sauce
  - 5. Do not use potatoes (sweet or Irish), macaroni, spaghetti, noodles, dried beans or peas
  - 6. Do not use fried foods prepared with butter, lard oil, or butter substitutes
  - 7. Do not use drinks such as Coca-Cola, ginger ale, pop or root beer
- 1943-1952 – Harvard Medical School, Stanford University, Cornell Medical School, New York Hospital – all published similar guidelines to the University of Chicago

# The Fattening Carbohydrate - Common Knowledge

- “Baby and Child Care”
  - “Rich desserts, the amount of plain, starchy foods (cereals, breads, potatoes) taken is what determines, in the case of most people, how much (weight) they gain or lose”
- 1963 –British Journal of Nutrition
  - “Every woman knows that carbohydrate is fattening: this is a piece of common knowledge, which few nutritionists would dispute”



Fattening  
Carbohydrates



Obesity

# The Great Epidemic of Coronary Disease

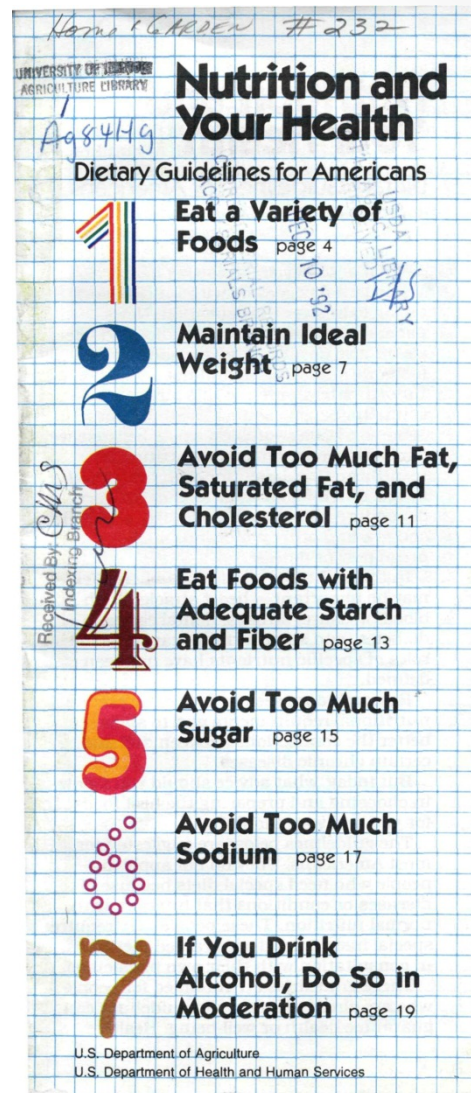
- 1950s - Dietary fat increasingly vilified for heart disease due to its effects on LDL cholesterol “Diet-Heart hypothesis”
- 1960s - the American Medical Association were insisting that low carbohydrate diets were dangerous fads (a 200 year old fad)
  - Jean Mayer claimed advocating carbohydrate-restricted diets to the public were “the equivalent of mass murder”
- Low fat, high carbohydrate diets previously unknown in human history
- BUT... the fattening carbohydrate could not be healthy (low fat) and unhealthy (causes obesity) at the same time
  - Fattening carbohydrate suddenly transformed into the healthy whole grain
  - Fat, with dense calories assumed to cause obesity
  - Calories in/ calories out model displaces traditional ‘fattening carbohydrate’ model



- Created in 1948

# Dietary Goals For the United States 1977

- First time any government institution had told Americans they could improve their health by **eating less fat**
- Dietary fat controversy was now a political issue and not a scientific one
- Dietary Goals
  - 1. Raise consumption of carbohydrates until they constituted 55-60% of calories
  - 2. Decrease fat consumption from approximately 40% to 30% of which no more than 1/3 from saturated fat



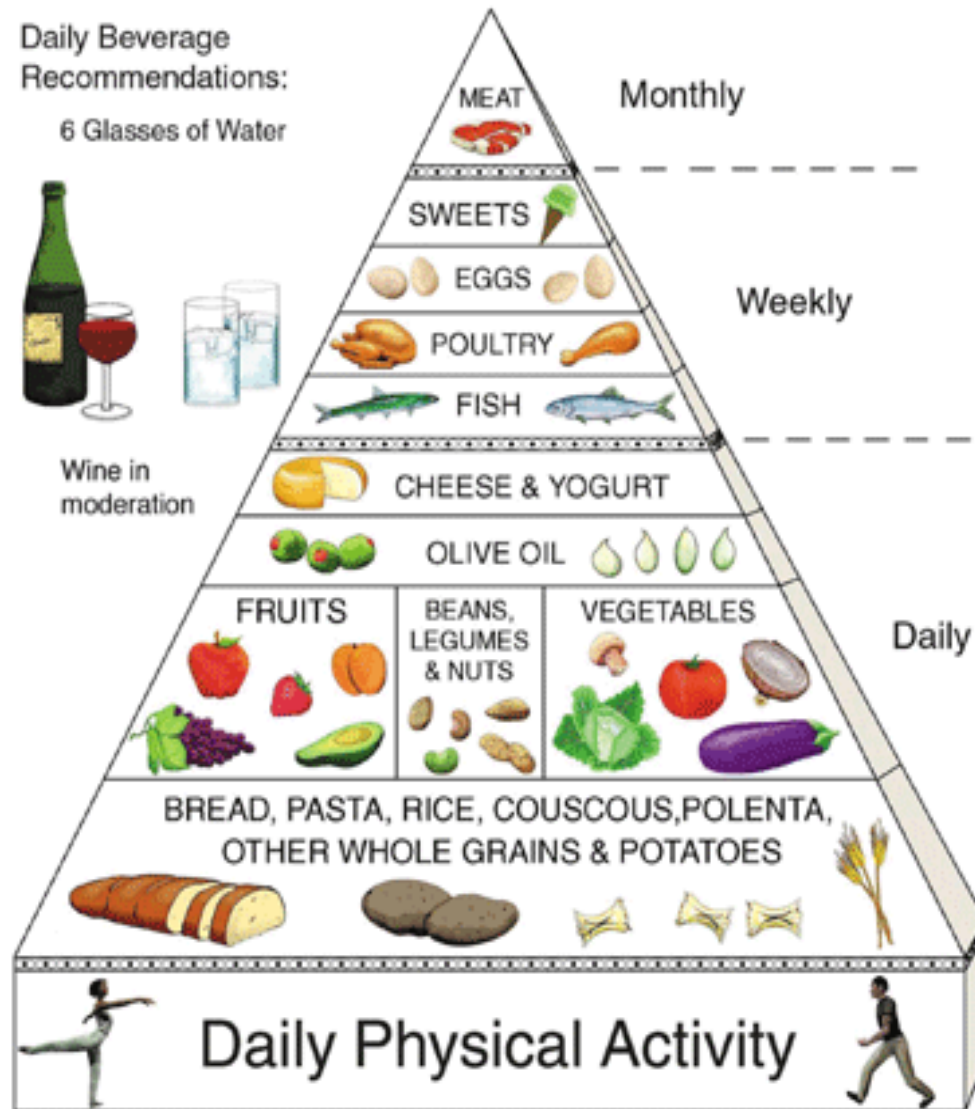
- USDA Dietary Guidelines for Americans

Daily Beverage  
Recommendations:

6 Glasses of Water



Wine in  
moderation





# An Eating Plan for Healthy Americans: The American Heart Association Diet 1995

- “To control the amount and kind of fat, saturated fatty acids and dietary cholesterol you eat, choose snacks from other food groups such as...low fat cookies, low-fat crackers...unsalted pretzels, hard candy, gum drops, **sugar\***, syrup, honey, jam, jelly, marmalade (as spreads)”

- \*WTF??



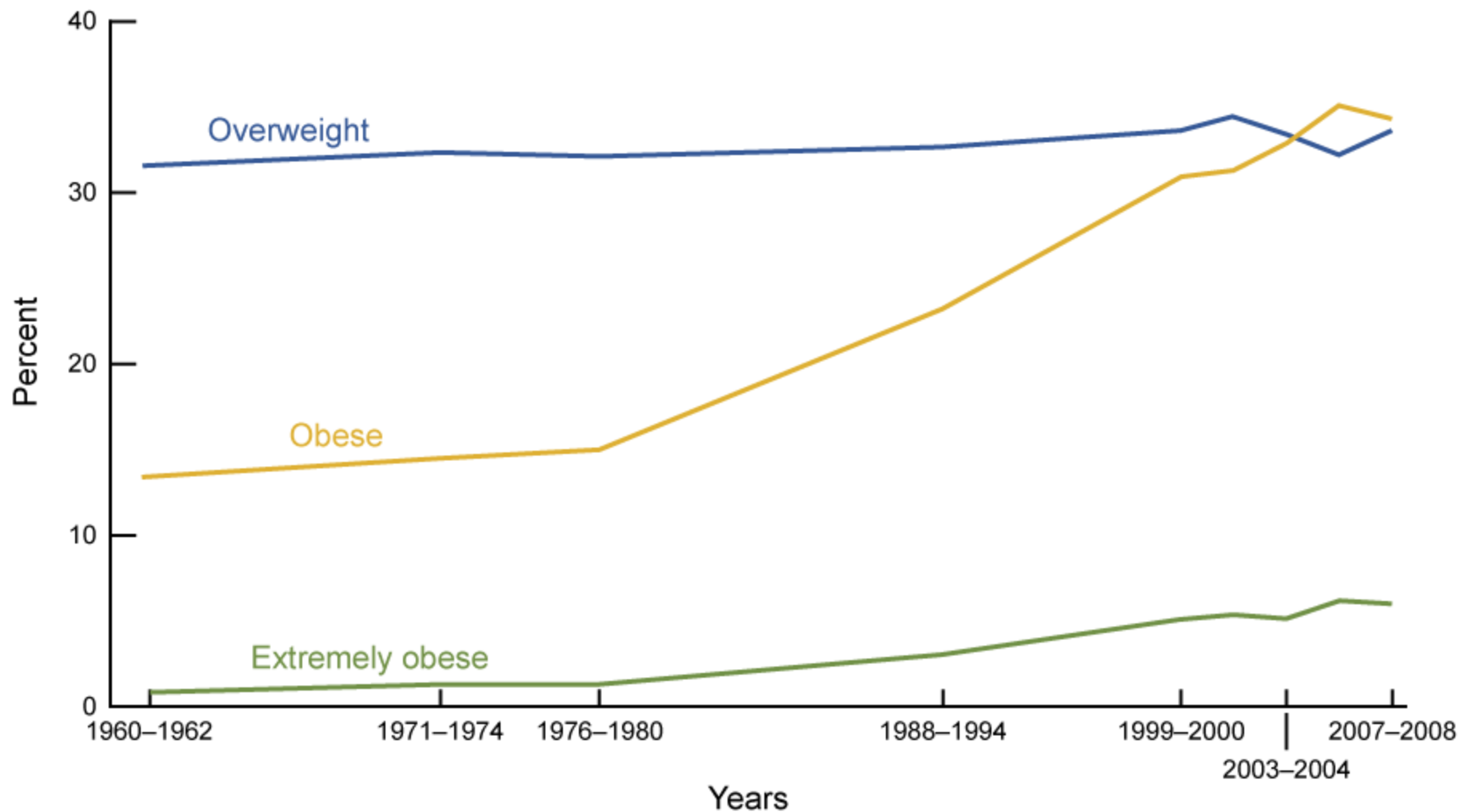
- AHA endorsed ‘healthy snacks’

# How did we do?

- Conscious effort to eat less fat, less red meat, fewer eggs
- Average fat intake of Americans (USDA) decreased **from 45% of calories to less than 35% of calories**
- Between 1976 – 1996 40% decline in hypertension
- 28% decline in hypercholesterolemia
- Percentage of smokers dropped from 33% to 25% 1979-1994
- **Clear evidence that the general public listened to the leading authorities of the day and tried to comply**
  - Rise in obesity was not simply a case of the general public not listening to conventional medical advice



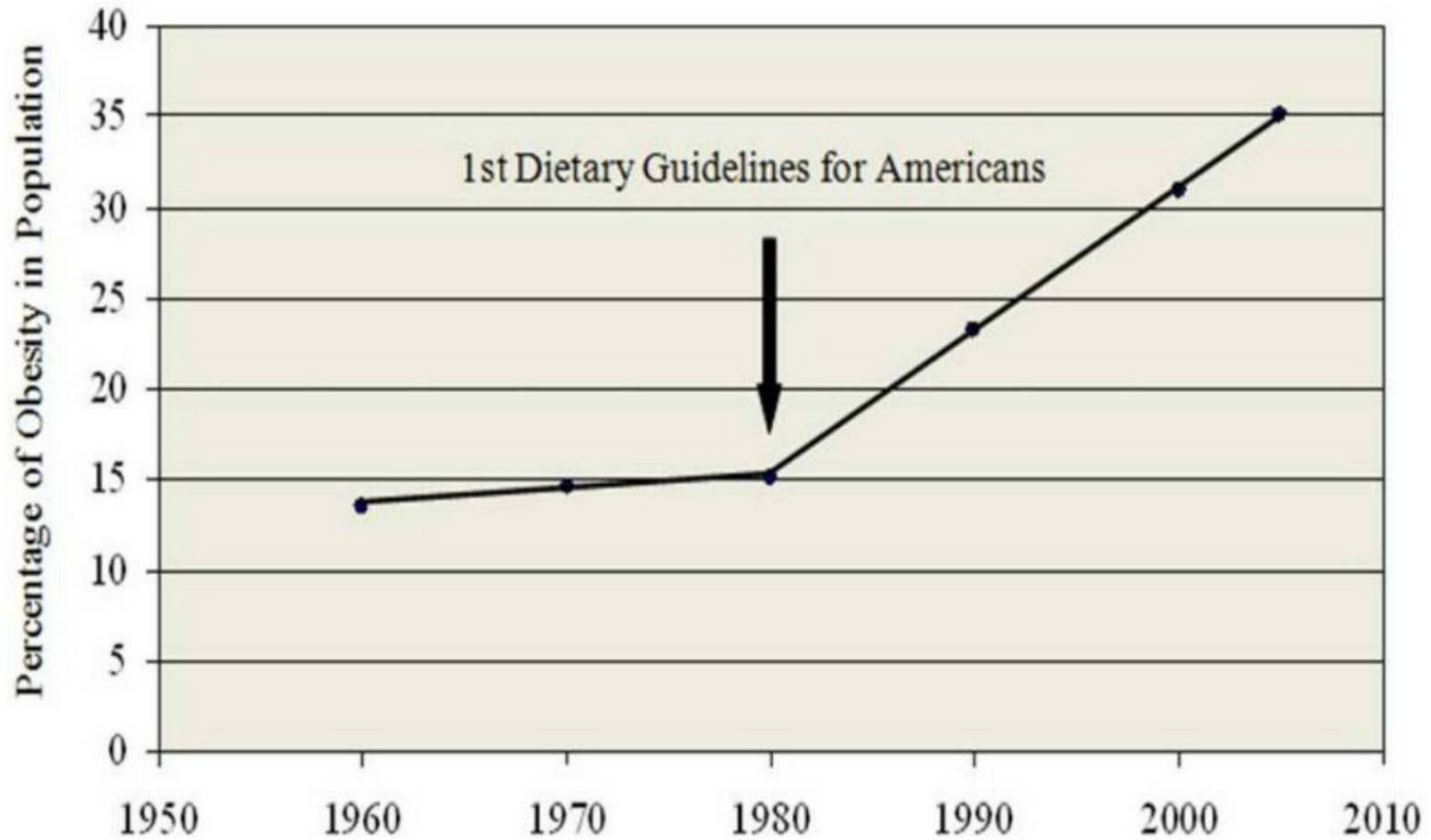
**Figure 2. Trends in overweight, obesity, and extreme obesity among adults aged 20–74 years: United States, 1960–2008**



NOTE: Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates, using the age groups 20–39, 40–59, and 60–74 years. Pregnant females were excluded. Overweight is defined as a body mass index (BMI) of 25 or greater but less than 30; obesity is a BMI greater than or equal to 30; extreme obesity is a BMI greater than or equal to 40.

SOURCE: CDC/NCHS, National Health Examination Survey cycle I (1960–1962); National Health and Nutrition Examination Survey I (1971–1974), II (1976–1980), and III (1988–1994), 1999–2000, 2001–2002, 2003–2004, 2005–2006, and 2007–2008.

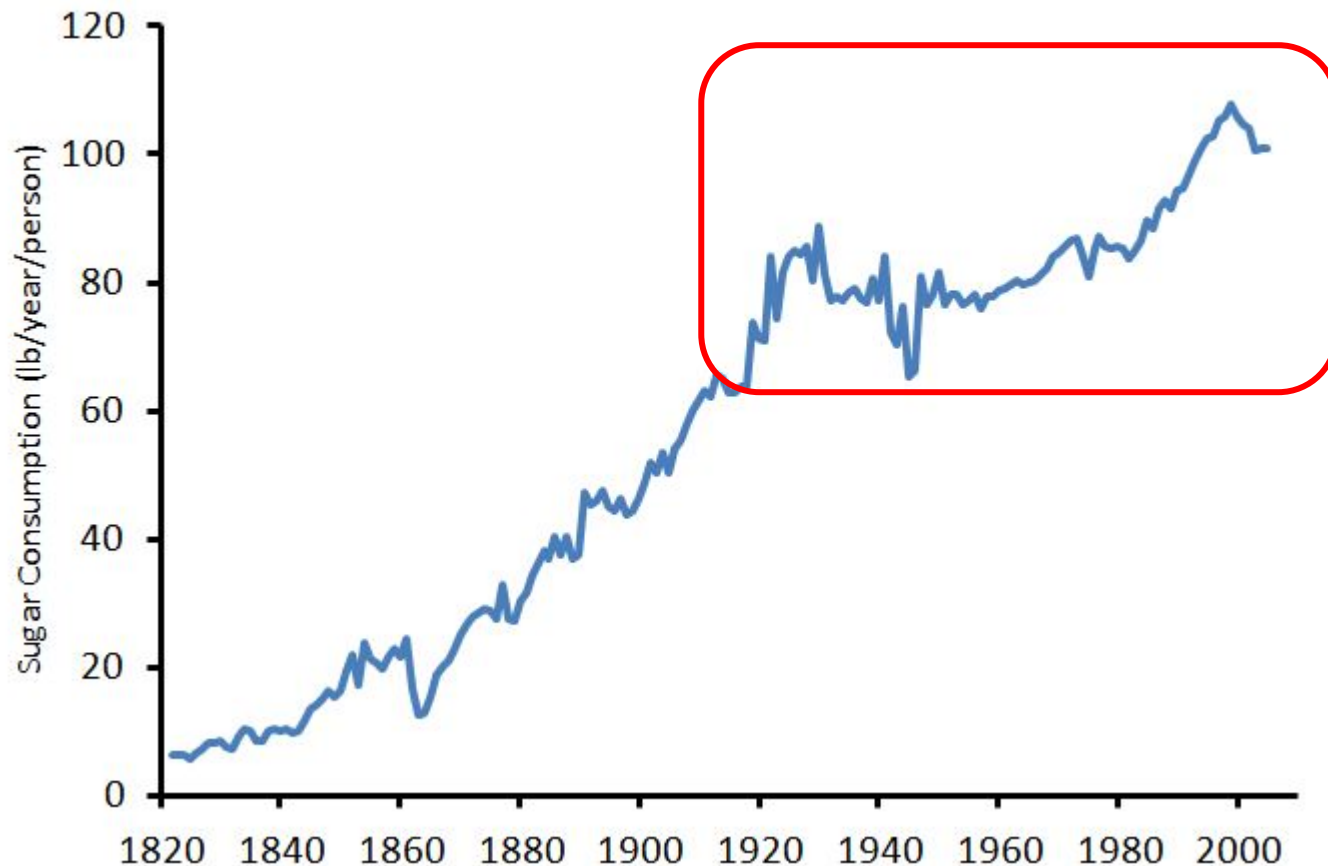
# Prevalence of Obesity among US Adults (20-74 years old)



- Nutritional advice from a politician!!

# Increasing Sugar Consumption

US Sugar Consumption, 1822-2005

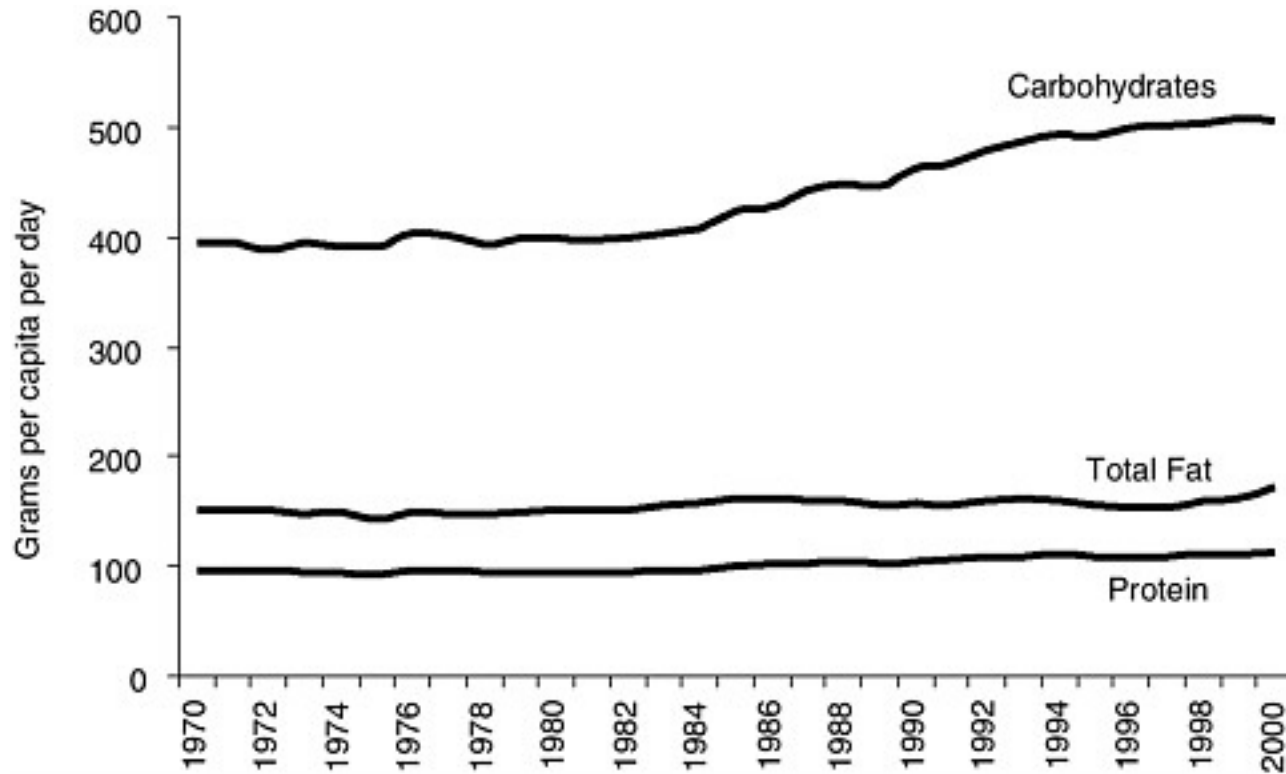


**Table 2-5****Annual average grain consumption was 45 percent higher in 2000 than in the 1970s**

Item	<i>Annual averages</i>					2000
	1950-59	1960-69	1970-79	1980-89	1990-99	
<i>Pounds per capita</i>						
Total grain products <sup>1</sup>	155.4	142.5	138.2	157.4	190.6	199.9
Wheat flour	125.7	114.4	113.6	122.8	141.8	146.3
Corn products	15.4	13.8	11.0	17.3	24.5	28.4
Rice	5.3	7.1	7.3	11.3	17.5	19.7

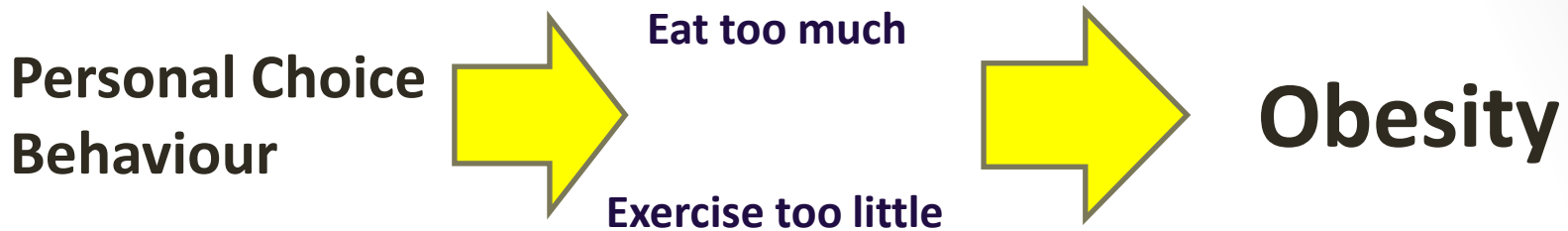
<sup>1</sup> Includes oat products, barley products, and rye flour not shown separately.

Source: USDA's Economic Research Service.



- **FIGURE 1-1** U.S. macronutrient food supply trends for carbohydrates, protein, and total fat, 1970-2000.
- SOURCES: Putnam et al., 2002; USDA, 2003

# Caloric Reduction As Primary



## Implicit Assumptions

1. "A calories is a calorie"
2. Fat stores are essentially unregulated  
Fat serves as a 'dump' for excess calories
3. Intake and Expenditure of calories are under conscious control  
Hunger and basal metabolic rates not part of equation
4. **Intake and Expenditure of calories are independent of each other**



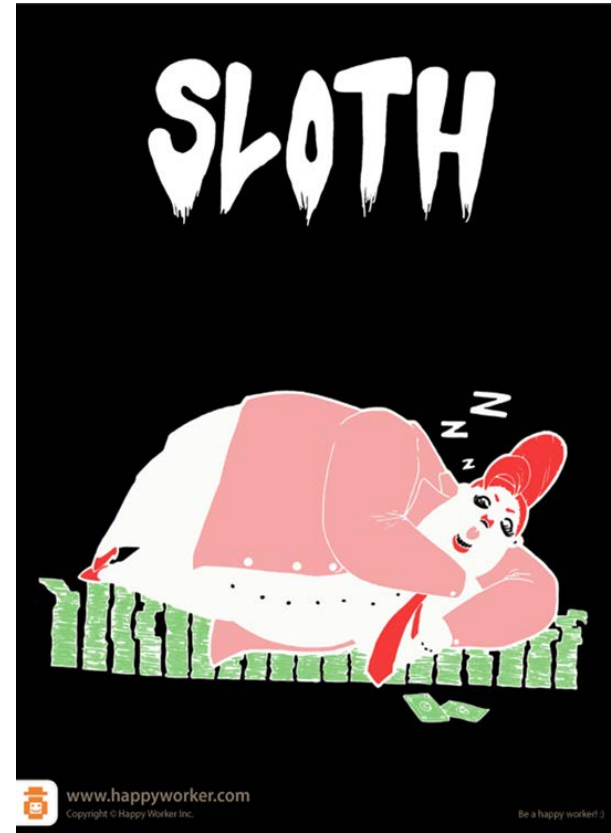
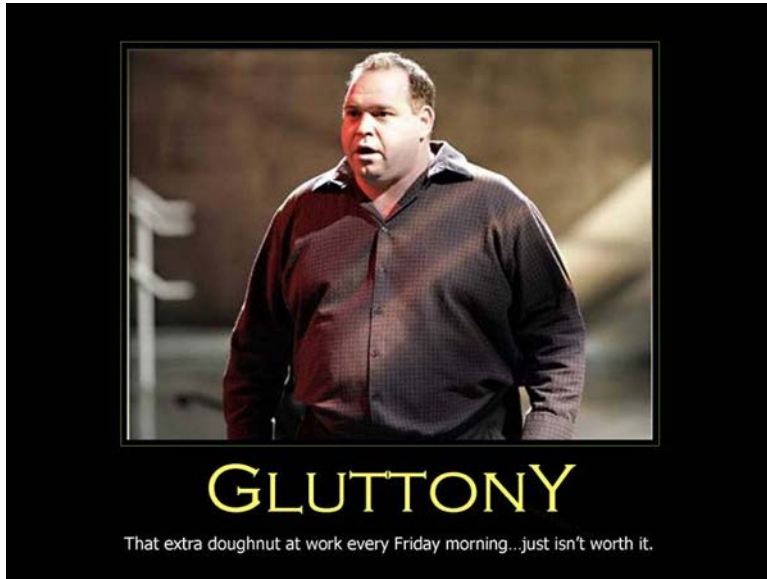
# Energy Balance Paradigm

- Accumulation of fat due to caloric imbalance
  - “First Law of Thermodynamics”
- True but completely useless
- Example – crowded airport at March Break
  - Too many people entering, too few people leaving is the cause of the crowding
  - Key question is WHY?
- American view – cause of overeating is **behavioural**



- Calories in/ Calories out model

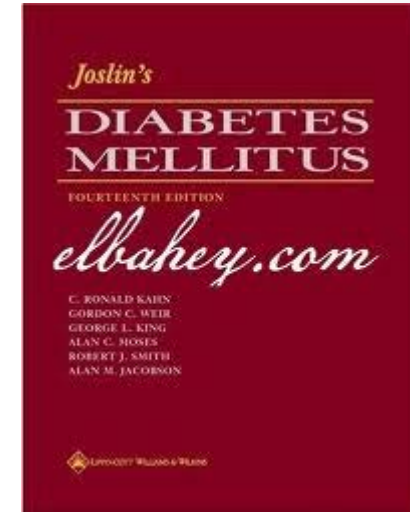
# Caloric Reduction – Popularity of Theory



- Easy to understand
- Appeals to American sense of self-determinism – it is your ‘choice’, ‘captain of your own ship’
  - Obesity is not a medical condition, but a psychological, character defect ‘low willpower’

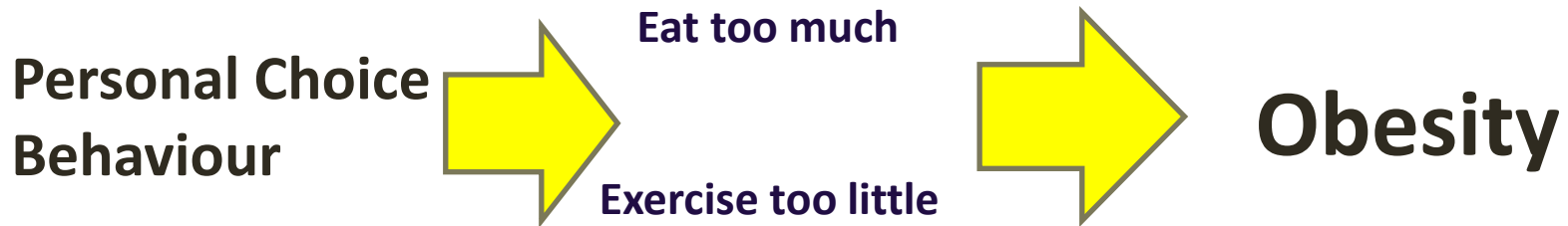
# Experts say... Eat Less and exercise more

- Joslin's Diabetes Mellitus (2005)
  - “reduction of caloric intake” is “the cornerstone of any therapy for obesity”
  - However, from low calorie to very low calorie diets “**none of these approaches has any proven merit**”
- Handbook of Obesity (1998) –
  - “Dietary therapy remains the cornerstone of treatment and the reduction of energy intake continues to be the basis of successful weight reduction programs”
  - Results of such diets are “**known to be poor and not long-lasting**”
- 2005 USDA Dietary Guidelines for Americans  
“eating fewer calories while increasing physical activity are the keys to controlling body weight”



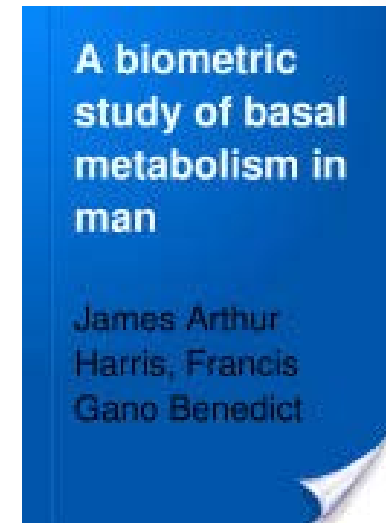
# Caloric Reduction as Primary...

## An easily tested hypothesis



# Elusive Benefits of Under-eating

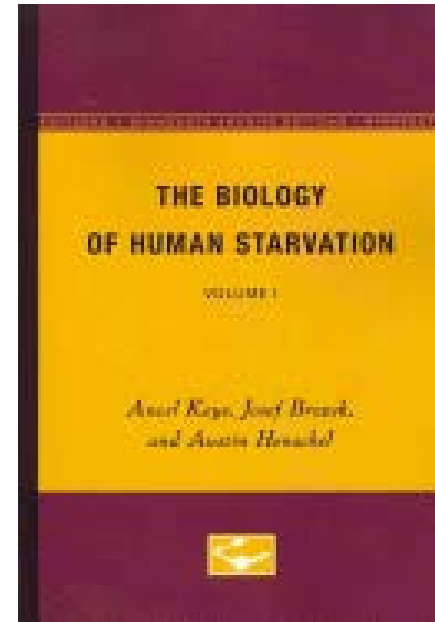
- 12 young men put on semi-starvation diets of 1400-2100 calories/day
  - Subjects lost weight, but constantly complained of hunger
  - “almost impossible to keep warm, even with an excessive amount of clothing”
- **30% decrease in metabolism**
  - reduced energy expenditure so much that if they ate more than 2100 calories/day – 30-50% less than prior to experiment, subjects would start to regain weight
- Decreases in BP, HR, inability to concentrate and marked weakness during physical activity
- Excess eating immediately after experiment



- Carnegie Institution of Washington's Nutrition Laboratory
- 1917

# The Biology of Human Starvation

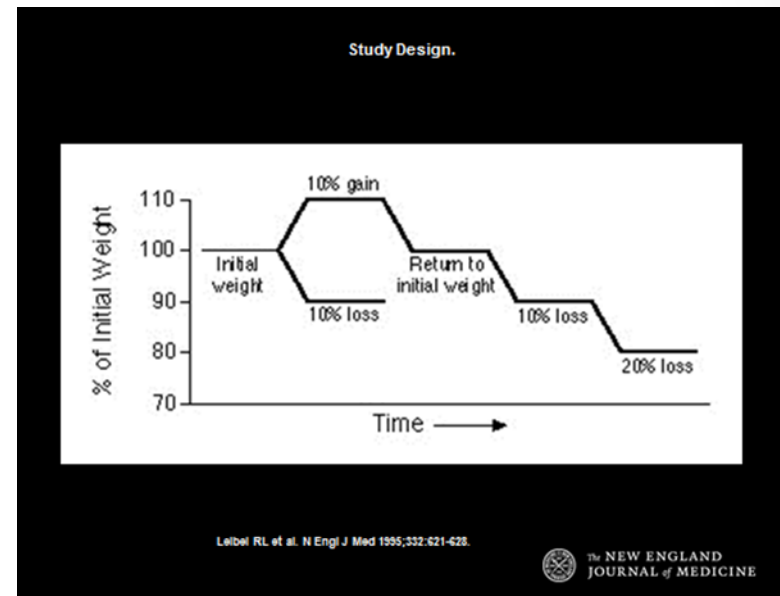
- 36 men put on a 24 weeks semi-starvation diet
- 1570 calories per day
- **The men's resting metabolic rates declined by 40 percent**
  - Heart volume shrank by 20 percent
  - Heart rate slowed
  - Body temperatures dropped
- Obsessive thoughts about food, binge eating



- 1944 Ancel Keys
- University of Minnesota

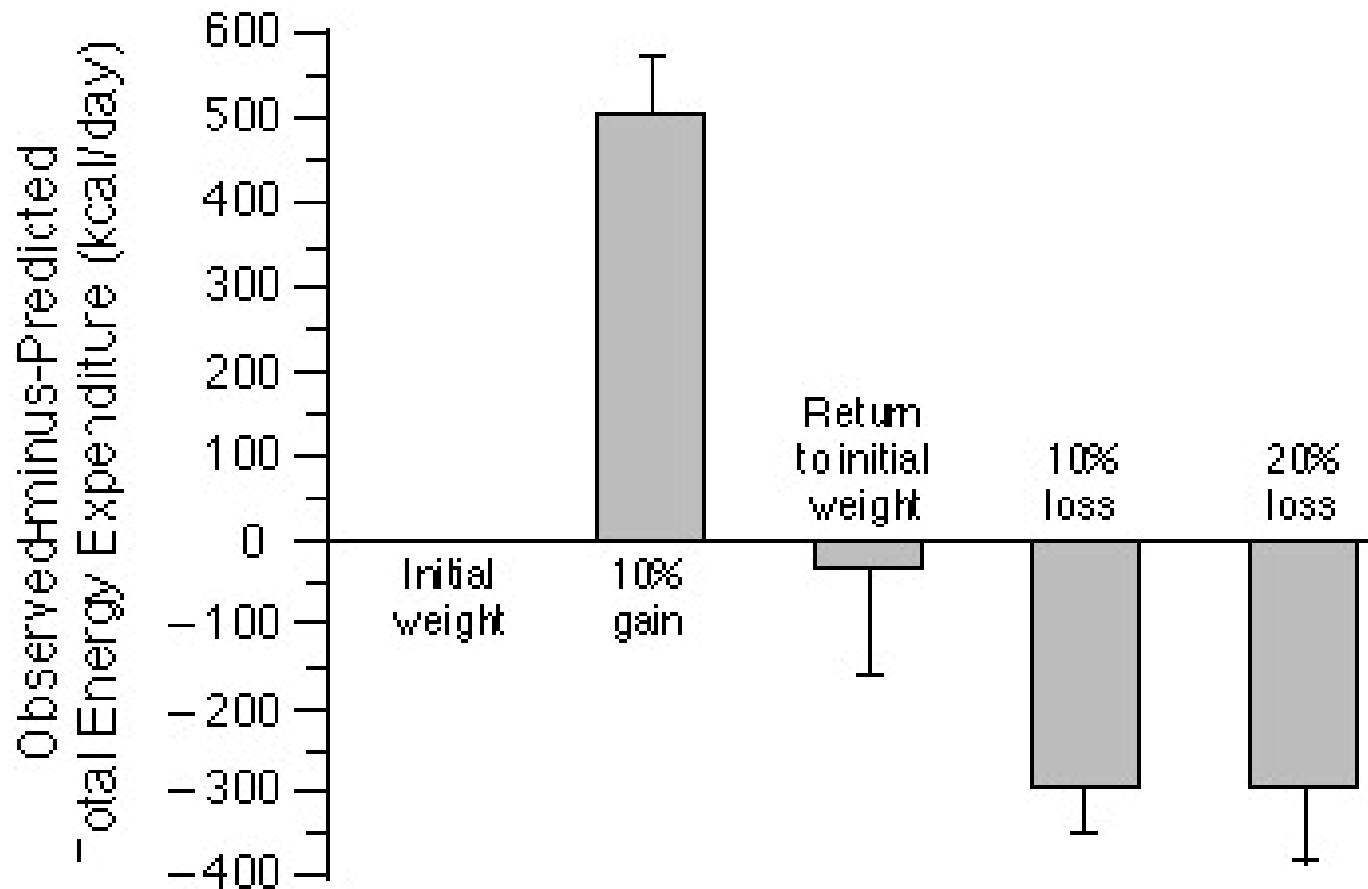
# Changes in Energy Expenditure Resulting from Altered Body Weight

- Rudolph L. Leibel NEJM 1995 march 9, 332 (10); 621-28
- 18 obese and 23 non obese subjects with a stable weight
- Fed a liquid diet of 40% fat, 45% carbohydrates and 15% protein
- Caloric intake adjusted until weight stable



- Subjects then measured for energy expenditure

Mean ( $\pm$ SD) Observed-minus-Predicted Total Energy Expenditure (Shaded Bars) Based on the Regression of Total Energy Expenditure in a Model with a Variable Combining Fat-free Mass and Fat Mass in the Same Subjects at Their Initial Weight.

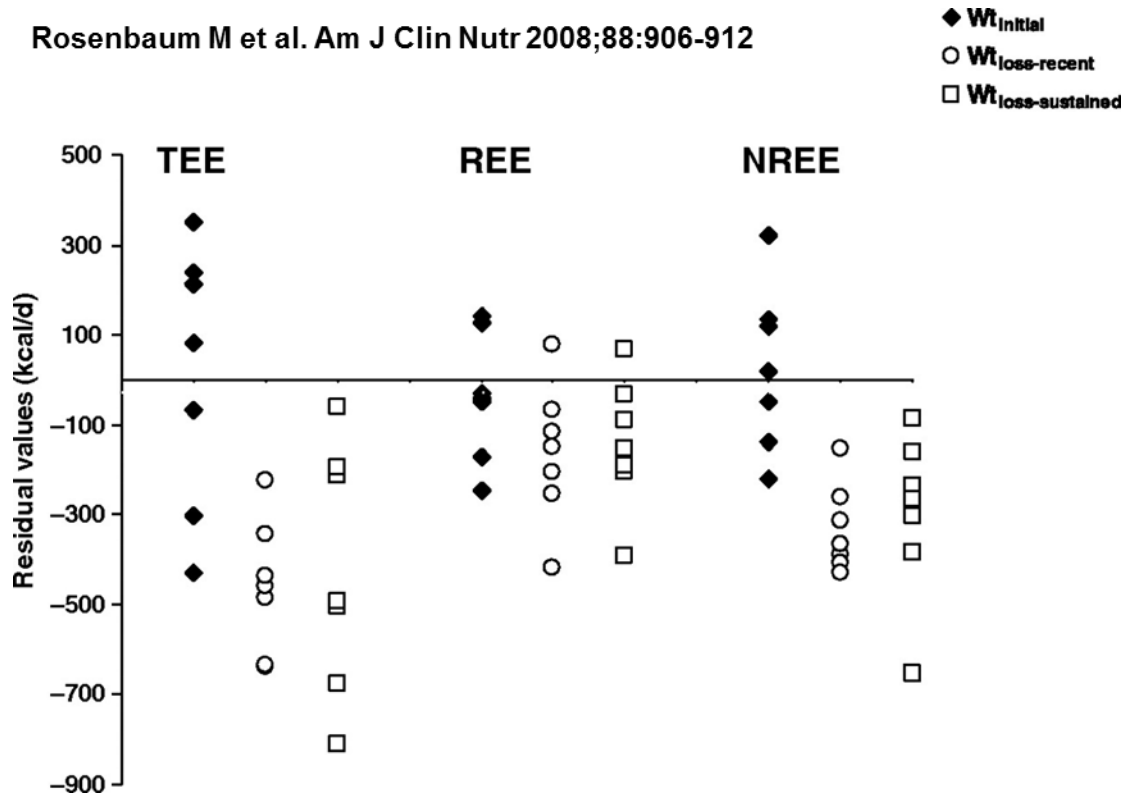


Leibel RL et al. N Engl J Med 1995;332:621-628.



# Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight

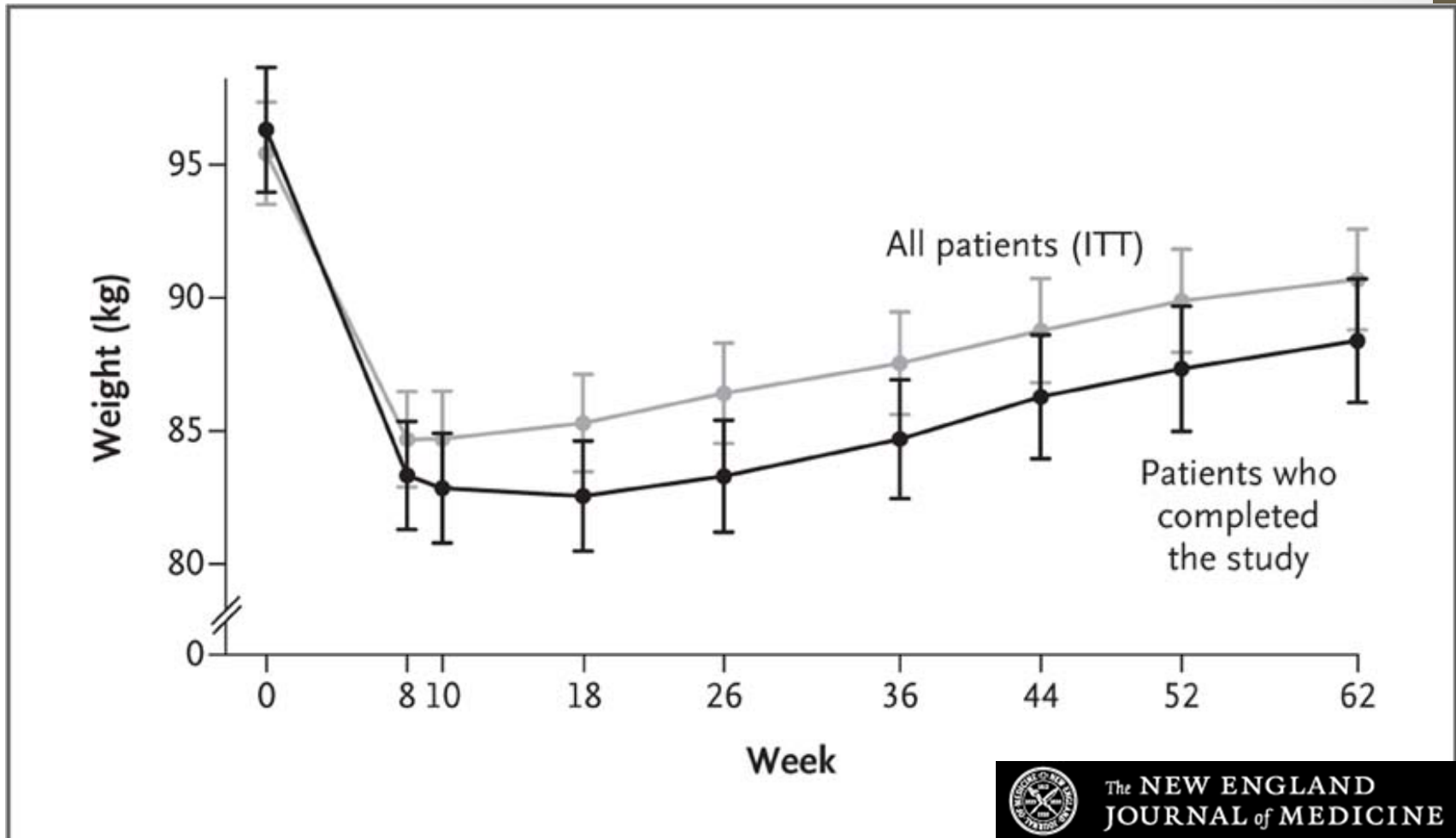
Rosenbaum M et al. Am J Clin Nutr 2008;88:906-912



- 21 Subjects lived in-centre and fed liquid diet of 45% carbohydrates
- Maintained weight loss of 10% over 1 year
- Measured total, resting and non resting energy expenditure

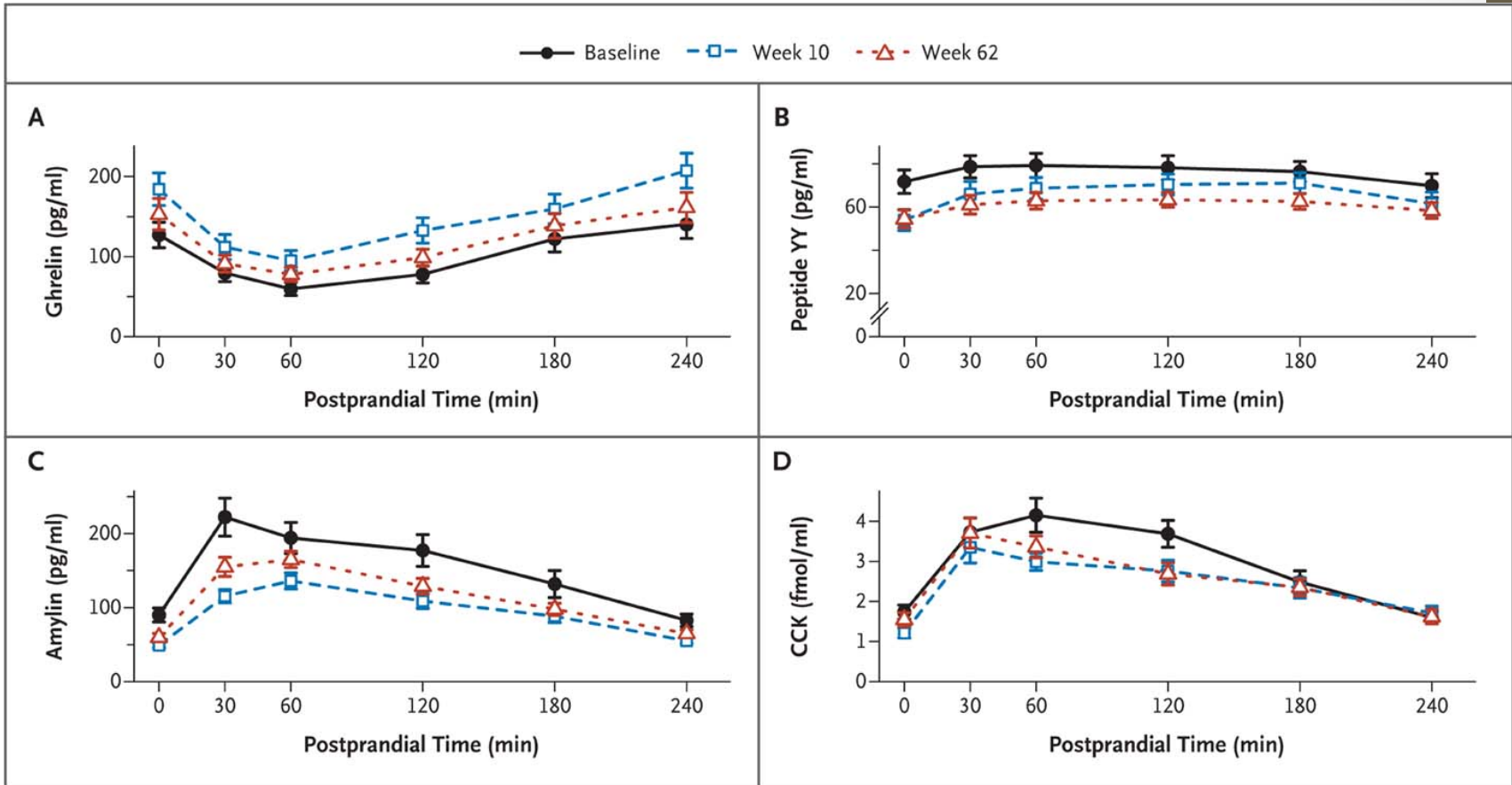
# Long-Term Persistence of Hormonal Adaptations to Weight Loss

N Engl J Med 2011; 365:1597-1604 [October 27, 2011](#)



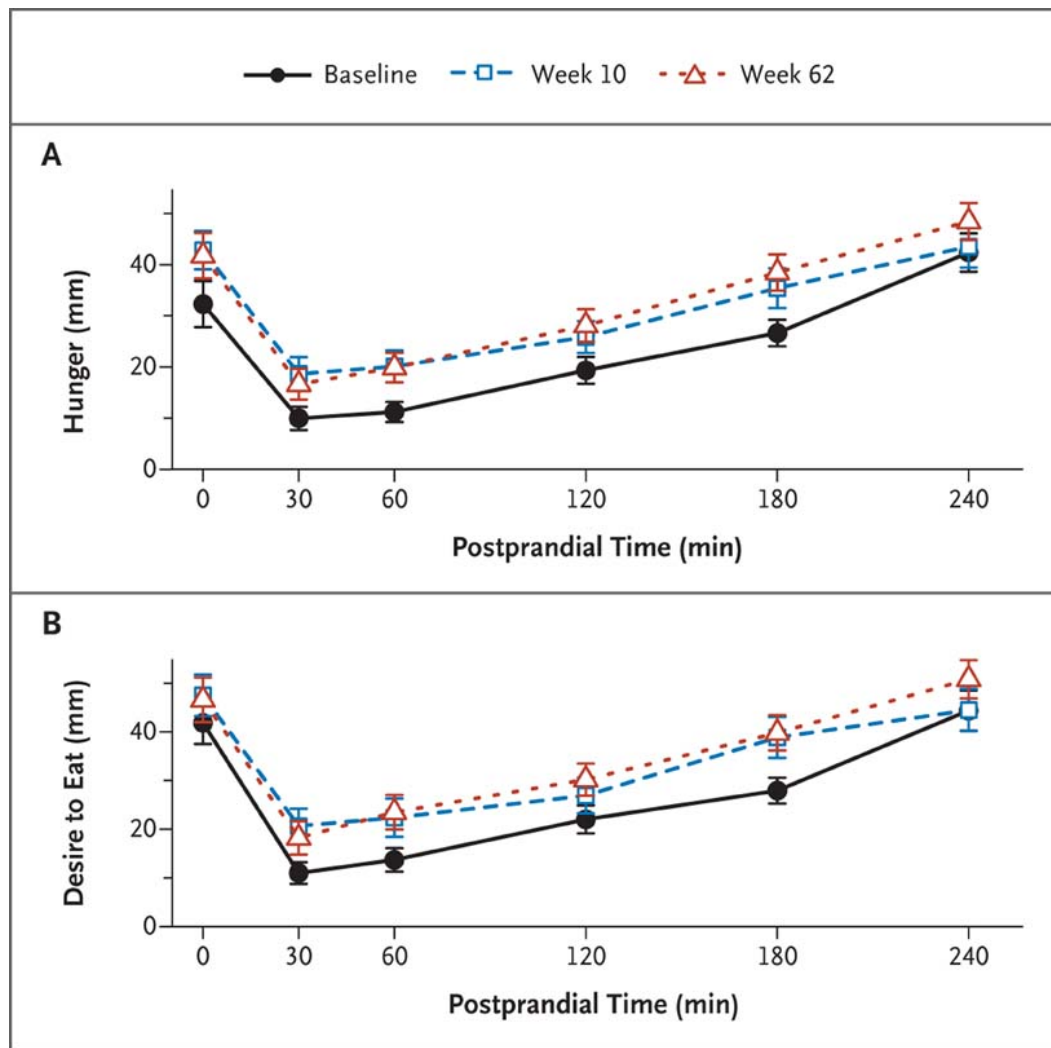
- 50 patients given 10 weeks of 500 calorie liquid shakes (51% carbohydrates)
- Hormonal analysis after 1 year of weight loss

# Long-Term Persistence of Hormonal Adaptations to Weight Loss



Bottom line – persistent increase in hunger signalling after weight loss





- One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss.
- Long-term strategies to counteract this change may be needed to prevent obesity relapse.

# Results

10% increase  
weight



16% increase  
Energy expended

10% decrease  
weight



15% decrease  
Energy expended



- **Reductions in caloric intake directly causes a reduction in energy expenditure**
  - Adapts to reduction in caloric intake by reduction in caloric expenditure
- **Reductions in caloric intake result in increased hunger**
- Body weight “thermostat”
  - Body fat is finely regulated

# Low-fat dietary pattern and weight change over 7 years: the Women's Health Initiative Dietary Modification Trial

Randomized controlled trial started in 1993

50,000 women age 50-79 enrolled

19,541 randomized to low-fat diet rich in fruits, vegetables and fibre

29,294 usual diet

Dietary counselling – goal to lower fat calories from 38% to less than 20%

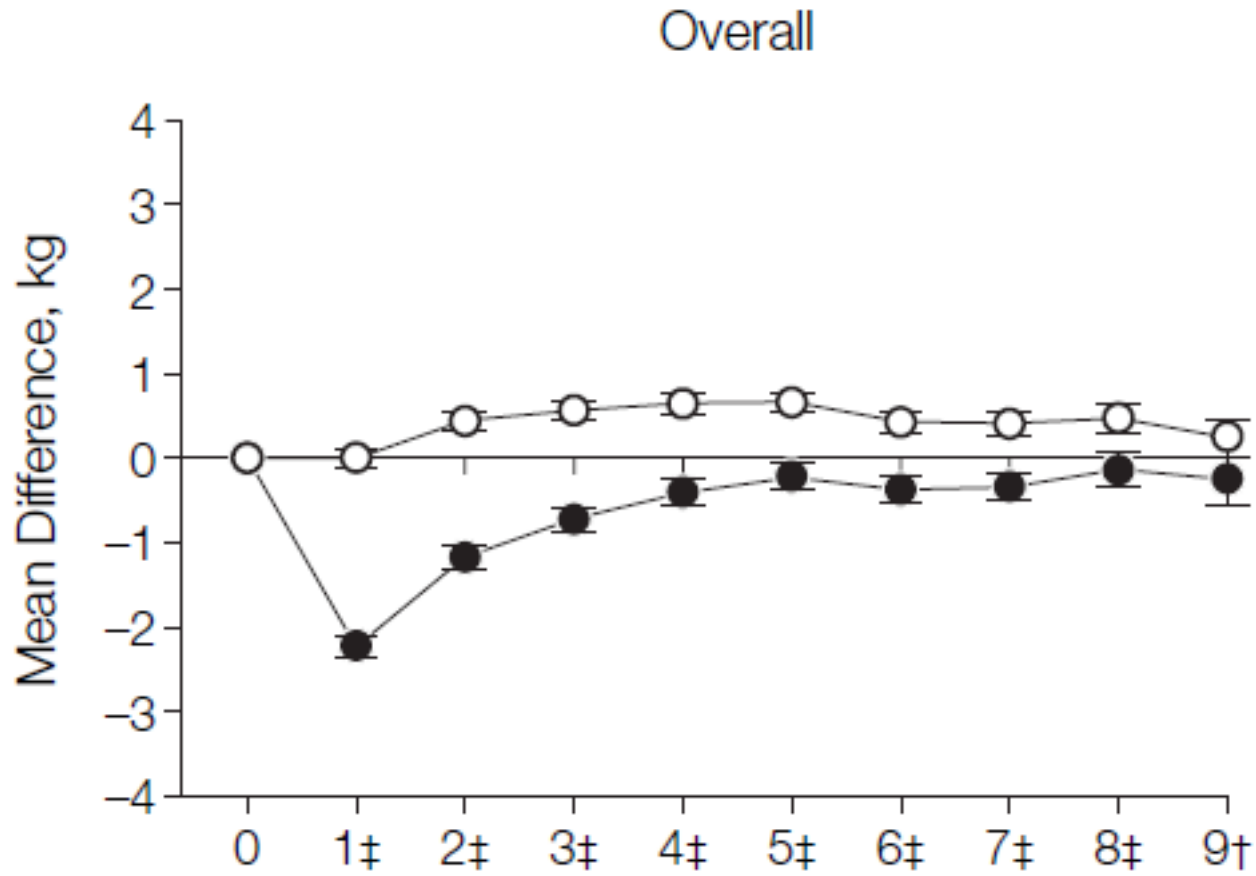
	Intervention	
	No.	Mean (SD)
Total energy, kcal		
Baseline	19 517	1788.1 (703.8)
Follow-up	14 246	1445.9 (510.1)
Change	14 246	-361.4 (653.8)
Energy from fat, %		
Baseline	19 517	38.8 (5.0)
Follow-up	14 246	29.8 (8.3)
Change	14 246	-8.8 (8.5)
Energy from saturated fat, %		
Baseline	19 517	13.6 (2.6)
Follow-up	14 246	10.1 (3.3)
Change	14 246	-3.4 (3.6)
Energy from carbohydrates, %		
Baseline	19 517	44.5 (6.2)
Follow-up	14 246	52.7 (9.8)
Change	14 246	8.2 (9.6)

- Howard BV et al. Journal of the American Medical Association 2006; 295:39-49

# Exercise more...

Fiber, g		
Baseline	19 517	14.4 (6.0)
Follow-up	14 246	16.9 (7.1)
Change	14 246	2.2 (7.0)
Fruits and vegetables, servings/d		
Baseline	19 428	3.6 (1.8)
Follow-up	14 183	5.0 (2.4)
Change	14 183	1.4 (2.3)
Grains, servings/d		
Baseline	19 428	4.7 (2.5)
Follow-up	14 183	4.1 (2.2)
Change	14 183	-0.7 (2.7)
Whole grains, servings/d		
Baseline	19 428	1.1 (0.8)
Follow-up	14 183	1.2 (0.8)
Change	14 183	0.1 (0.9)
Non-whole grains, servings/d		
Baseline	19 428	3.6 (2.1)
Follow-up	14 183	2.9 (1.7)
Change	14 183	-0.7 (2.2)
Physical activity, METs/wk		
Baseline	17 507	10.0 (11.7)
Year 1	9962	11.4 (12.8)
Change	9962	1.1 (10.4)

# What happened?





# What happened?

Women should have lost 36 pounds of fat in the first year alone

	Intervention		Control		Difference (SE)	P Value
	No.	Mean (SD)	No.	Mean (SD)		
Weight, kg						
Baseline	19 524	76.8 (16.6)	29 272	76.7 (16.5)	-0.1 (0.2)	.36
Follow-up	16 297	75.7 (17.1)	25 056	76.1 (16.9)	0.4 (0.2)	.01
Change	16 297	-0.8 (10.1)	25 056	-0.1 (10.1)	0.7 (0.1)	<.001
BMI						
Baseline	19 457	29.1 (5.9)	29 164	29.1 (5.9)	-0.03 (0.1)	.57
Follow-up	16 230	29.0 (6.1)	24 943	29.2 (5.9)	0.2 (0.1)	<.001
Change	16 230	0.03 (3.2)	24 943	0.3 (3.1)	0.3 (0.03)	<.001
Waist circumference, cm						
Baseline	19 485	89.0 (13.9)	29 216	89.0 (13.7)	0.003 (0.1)	.85
Follow-up	6 154	90.1 (14.4)	9 517	90.4 (14.2)	0.3 (0.2)	.12
Change	6 154	1.6 (8.6)	9 517	1.9 (8.8)	0.3 (0.1)	.04
WHR						
Baseline	19 475	0.82 (0.1)	29 200	0.82 (0.1)	0.0002 (0.001)	.67
Follow-up	6 123	0.83 (0.1)	9 487	0.83 (0.1)	-0.0003 (0.002)	.98
Change	6 123	0.02 (0.1)	9 487	0.02 (0.1)	0.0003 (0.001)	.85

Abbreviations: BMI, body

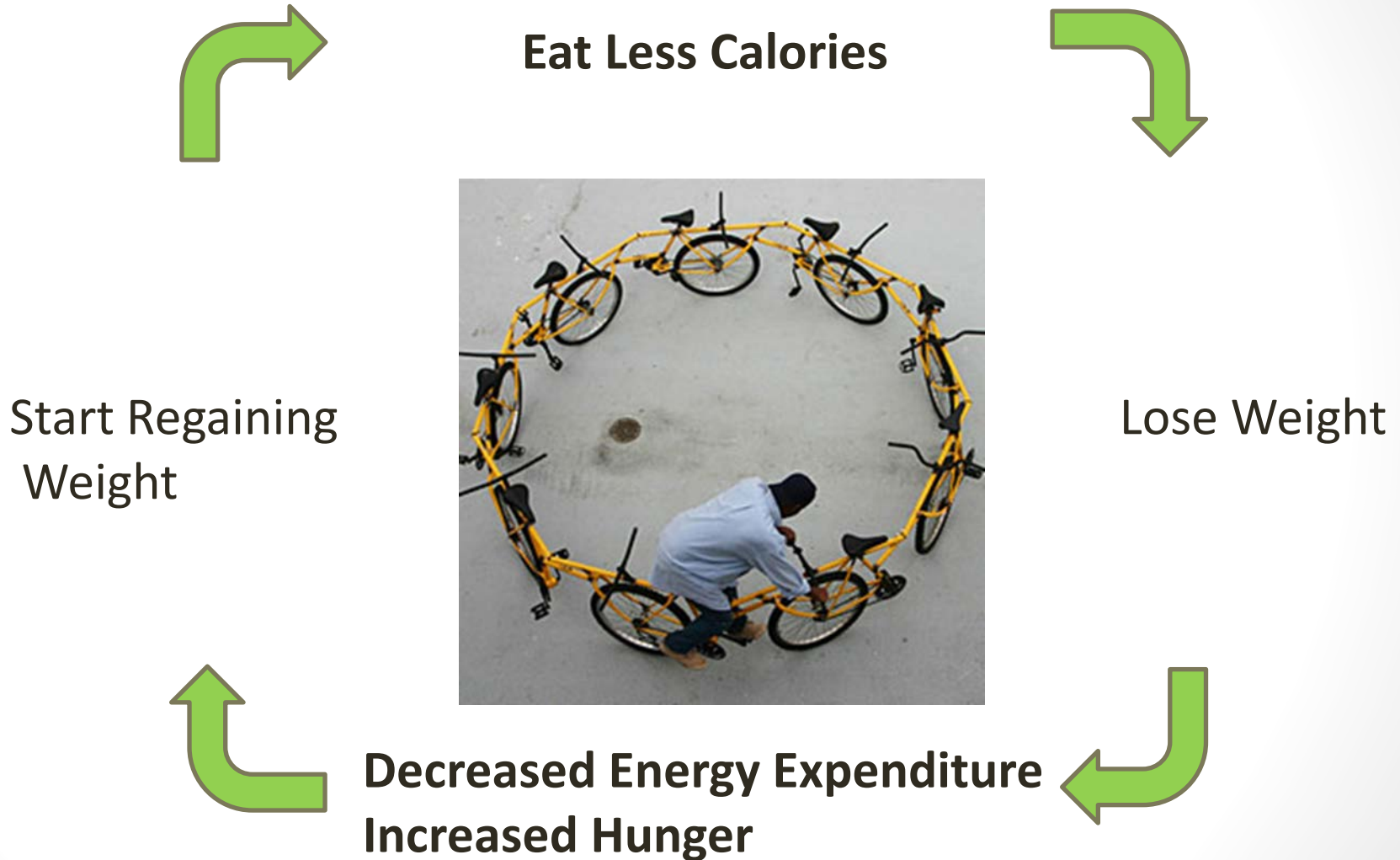
# The Cruel Hoax

- **Virtually all studies of 'semi-starvation' diets are remarkably similar and unsuccessful**
  - Consistently documented failure to lose weight
  - A perfect 35 year record **unblemished by success**
- Caloric deprivation triggers 2 adaptive mechanisms
  - 1. reduced energy output
  - 2. increased hunger



- The Cruel Hoax of the low fat, calorie-restricted diet
  - **THEY DON'T WORK!**

# Vicious Cycle of Under-eating



- Continues until it is intolerable – then we blame the victim

# The Overeating Paradox

- Studied convicts at Vermont State Prison
  - Initially raised food consumption to 4000 calories/day
    - gained some weight but then weight stabilized
  - Ate up to 10,000 calories a day, while carefully controlling exercise
- Took 4-6 months to increase weight by 20-25%
  - One man less than 10 pound weight gain
- **Metabolism increased by 50%**



- Most famous of overeating studies done in late 1960's by endocrinologist Ethan Sims
- Most returned to normal weight with surprising rapidity

# The Response to Long-Term Overfeeding in Identical Twins

- Bouchard et al. NEJM 1990 May 24; 322(21): 1477-82
- 16 healthy volunteers overfed by 1000 calories/day for 8 weeks
  - Total excess calories 84,000
  - 50% carbohydrate diet
- No increase in exercise
- Average weight gain of 8.1 kg
  - Average gain in fat mass was 5.4 kg or 52,220 kcal
  - Average gain in fat-free mass was 2.7 kg
  - Average 121 MJ (29,000 kcal) did not appear as weight gain
  - “presumably this energy was dissipated in some way”

# Caloric Reduction As Primary

- **Eating less does not result in weight loss**
  - Induces hunger and a compensatory decrease in energy expenditure
  - Physiological changes aimed at increasing the 'metabolic efficiency' and fuel supply of the tissues at a time of energy deficit
- Caloric deprivation is difficult because it is a fight against mechanisms which have evolved to precisely minimize its effects
- **Eating more does not result in weight gain**
  - In response to caloric surplus we also increase energy expenditure – may be used up in heat energy
- Body act as if it has an obesity '**set point**'

# Conclusion

- Eating a low fat calorie restricted diet virtually guarantees that you will not lose weight!
- Caloric Reduction as Primary is Wrong – calories are virtually irrelevant



# The Ultimate Proof...





# Exercise More...

- By 1966 US Public Health Service advocated increased physical activity and diet as the best ways to lose weight
- Until 1970's Americans did not believe in exercise
  - health clubs rare
  - Doctors routinely advised against exercise
- 'fitness boom' in 1980's
  - "new fitness revolution" led by running and aerobics
- 45 million health club member in USA up from 23 million in 1993
- "Experts" routinely claim that exercise is the key to weight loss

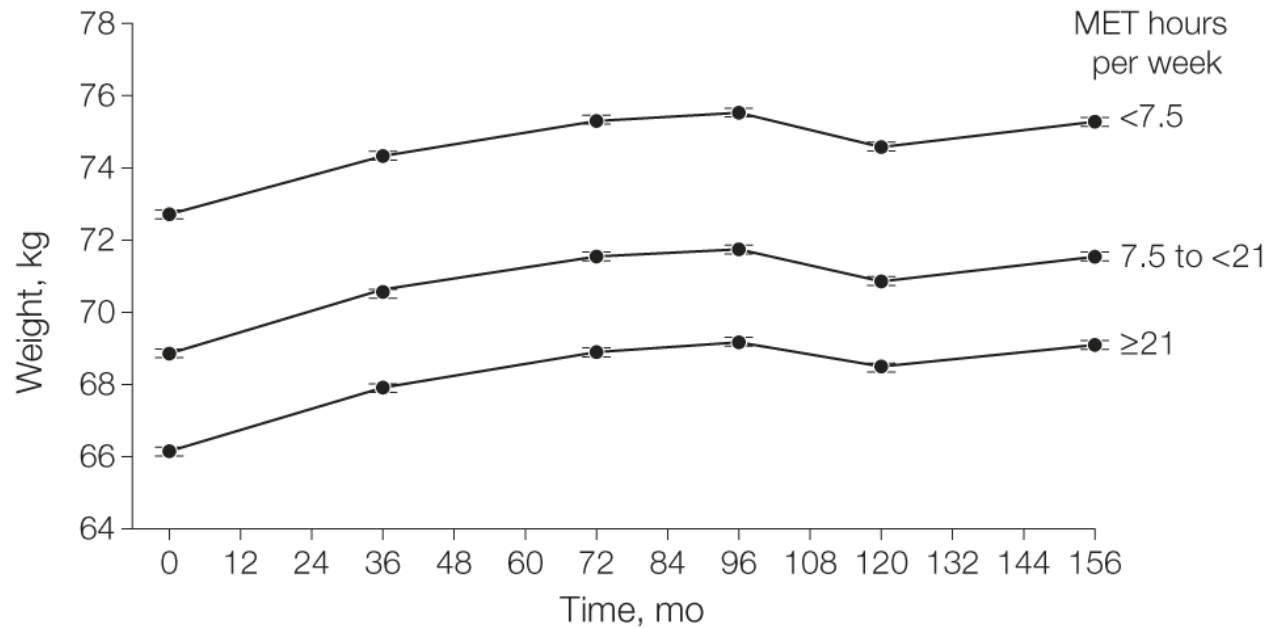


# Physical Activity and Weight Gain Prevention

- JAMA 2010;303(12): 1173-1179
- Buring et al
- Prospective cohort study (Women's Health Study) 1992-2004
- 39 876 women
- Completed health questionnaires every 6 months
- Grouped into 3 groups
  - <7.5 MET hours/ week (<150 minutes per week)
  - 7.5-21 MET
  - >21 MET (>420 minutes per week)



# Women's Health Study - Results



No. by MET hours  
per week

<7.5	16856	15634	15153	15661	13779	13353
7.5 to <21	9819	9171	9005	9260	8336	8106
≥21	7404	6924	6808	6992	6264	6107

- All women gained roughly the same weight regardless of exercise levels

# Women's Health Study - Results

**Table 2.** Mean (SD) Differences in Weight Over Any 3-Year Period by Physical Activity Level, Women's Health Study, 1992-2007<sup>a</sup>

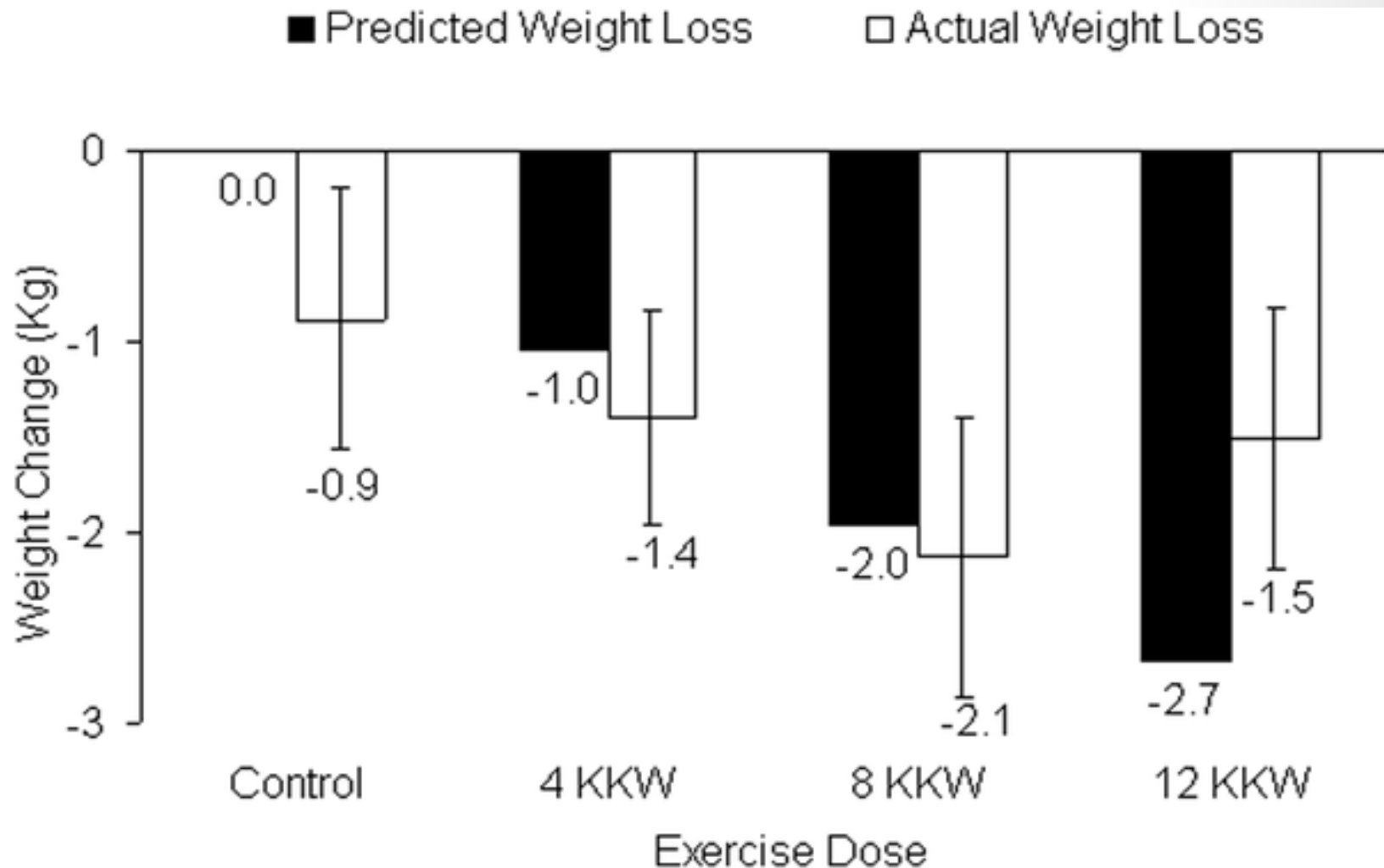
Group	No. of Women <sup>b</sup>	Physical Activity, MET Hours per Week			P Value for Trend	P Value for Interaction
		<7.5	7.5 to <21	≥21		
All women						
Analytical model <sup>c</sup>						
1		0.15 (0.04)	0.12 (0.04)	0 [Reference]	<.001	
2		0.12 (0.04)	0.11 (0.04)	0 [Reference]	<.001	
Age, y						
<55	21 363	0.12 (0.08)	0.02 (0.08)	0 [Reference]	<.001	] <.001
55-64	9699	0.24 (0.06)	0.19 (0.06)	0 [Reference]	<.001	
≥65	3017	-0.09 (0.07)	0.07 (0.07)	0 [Reference]	.13	
BMI						
<25.0	17 475	0.21 (0.04)	0.14 (0.04)	0 [Reference]	<.001	] <.001
25-29.9	10 516	-0.04 (0.06)	-0.04 (0.06)	0 [Reference]	.56	
≥30.0	6088	0.16 (0.14)	0.13 (0.16)	0 [Reference]	.50	

- Average increase in weight loss over 3 years
  - 0.12 kg
- Just over ¼ pounds weight loss in 3 years!!
- 3 years of 60 minutes per day, every day!!

# Changes in Weight, Waist Circumference and Compensatory Responses with Different Doses of Exercise among Sedentary, Overweight Postmenopausal Women

- Timothy Church et al
- PLoS One (Public Library of Science) Feb 2009 Vol 4 #2 e4515
- 464 obese women who didn't routinely exercise
- Randomly assigned to 0, 72, 136, 194 minutes per week of exercise with a trainer
- No change in dietary habits
- 24 week study duration
- Average starting weight 84.2 kg
- No difference in any of the group in weight lost!

Figure 3. Actual weight loss (white bars) and predicted weight loss (black bars) for each study group.



Church TS, Martin CK, Thompson AM, Earnest CP, et al. (2009) Changes in Weight, Waist Circumference and Compensatory Responses with Different Doses of Exercise among Sedentary, Overweight Postmenopausal Women. *PLoS ONE* 4(2): e4515. doi:10.1371/journal.pone.0004515  
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0004515>

**Table 2. Energy Intake at Baseline and Follow-up.**

	Randomization Groups				Between Groups P-Value
	Control (n = 88)	4 KKW (n = 120)	8 KKW (n = 77)	12 KKW (n = 80)	
Energy Intake, kcal/day*					
Baseline	2138 (1995, 2344)	2000 (1866, 2138)	2228 (2040, 2399)	2188 (2040, 2399)	.16
Follow-Up	1862 (1698, 1995)†	1730 (1585, 1819)†	1831 (1656, 1995)†	1870 (1698, 2040)†	.42

Abbreviations: KKW, kcal/kg/week.

\*Values are expressed as fitted mean (95% CI) of normalized data.

†Within Group Differences Between Baseline and Follow-Up  $P < 0.001$ .

doi:10.1371/journal.pone.0004515.t002

Church TS, Martin CK, Thompson AM, Earnest CP, et al. (2009) Changes in Weight, Waist Circumference and Compensatory Responses with Different Doses of Exercise among Sedentary, Overweight Postmenopausal Women. PLoS ONE 4(2): e4515. doi:10.1371/journal.pone.0004515  
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0004515>

# Exercise Effect on Weight and Body Fat in Men and Women

- McTiernan, Anne, et. Al
- Obesity (2007) 15, 1496-1512
- 12 month randomised, controlled trial
- 102 men and 100 women – sedentary
- 6 days per week of 1 hour moderate – vigorous exercise
- At baseline average weight
  - Women 78 kg
  - Men 96 kg
- Results – at 12 months
  - 1.4 kg! (3 pounds) – women
  - 1.8 kg! (4 pounds) - men





# Marathons must work....

- Janssen, G. M., et al. Food intake and body composition in novice athletes during a training period to run a marathon.
- International Journal of Sports Medicine, May 1989; 10(1 suppl.):S17-21
- trained sedentary subjects to run marathon over 18 months
- Men – average weight loss 5 pounds
- 9 women – no weight lost
  - “no change in body composition was observed”



# Compensation

- Multiple studies lasting more than 25 weeks that average weight loss was only 30% of predicted\*
  - Difference between actual weight loss and predicted weight loss called “compensation”
  - Relatively high doses of exercise results in compensatory mechanisms that attenuate weight loss
  - Possible mechanisms
    - Increased caloric intake
    - Decreased activity outside of prescribed exercise
- 
- \*Ross R et al Physical activity, total and regional obesity: dose-response considerations. Med Sci Sports Exerc 33: S521-527 2001

# European Congress on Obesity 2009

- Alissa Fremeaux
- Measured physical activity of 206 children aged 7-8 by accelerometer
  - Averaged 9.2 hours per week of physical education in school
- Some schools had significantly increased physical education
- No difference in total weekly activity
- **“children who got a lot of PE time at school were compensating by doing less at home, while those who got very little PE time compensated by cranking up their activity at home, so that over the week, they all accumulated the same amount”**

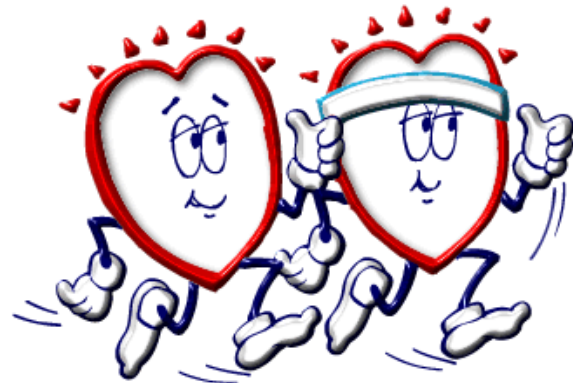


# Compensation – possible mechanisms



# Exercise More...

- Commonly assumed that majority of caloric expenditure is related to physical exercise
- Baseline Energy Expenditure estimated to 12-15 calories per pound
  - In bed bound state caloric needs is (BEE) \* 1.2
  - For 140 pound person, approximately 2200-2500 calories per day
- Caloric expenditure of 45 minute walk (150 pound person) at 2 miles per hour is 102 calories – 4% of daily caloric intake
- Majority of calories expended is NOT exercise but basal metabolic rate – mostly used in heating the body
- Why do we get so hungry after swimming?
  - water cools the body
  - We burn calories to heat our body
- Why do patients on semi-starvation diets get cold?
  - body turned down the thermostat
  - to conserve energy

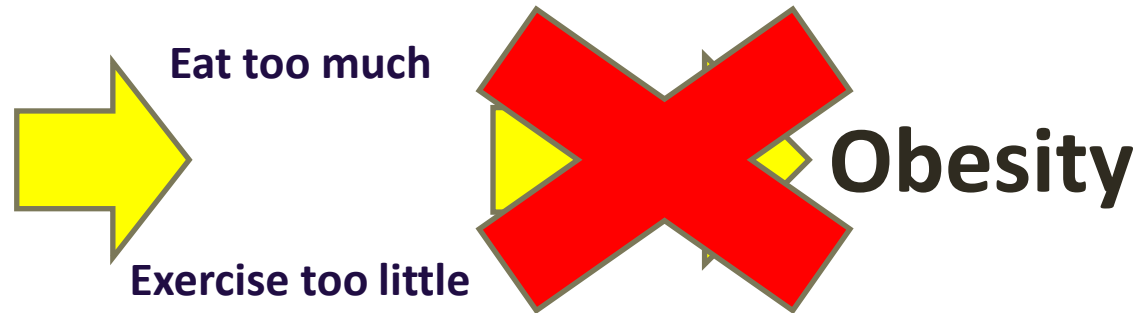


# Exercise More...

- Despite 40 years of constant and utter failure 'experts' still insist exercise is the key to weight loss
- 2 flaws in reasoning
  - 1. Burn surprising few calories with exercise
  - 2. Compensation effects
    - Increase in appetite
    - Decreased other activity
- Make no mistake – **WE SHOULD ALL GET EXERCISE** – it is simply not that effective for weight loss
  - Increase muscle tone
  - Increase insulin sensitivity of muscles
  - Decrease vascular disease
  - Increased bone density

# Eat Less... An easily tested hypothesis

Behaviour  
Gluttony/  
Sloth

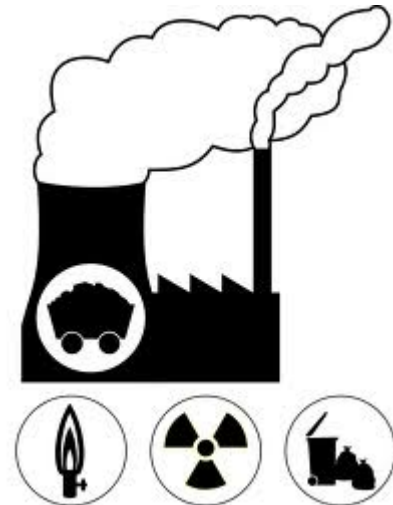
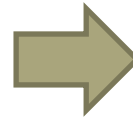
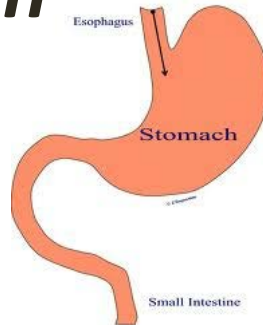


- ***Not True!***

# Hormonal Obesity Theory



***Insulin***  
***(cortisol)***





# Hormonal Obesity Theory– An Easily tested hypothesis



- **Implicit Assumptions**

- 1. **Fat, like all body systems, are regulated under hormonal control**
- 2. **Intake and Expenditure of calories are under hormonal control**
  - Hunger/ Basal metabolic Rate
- 3. **Intake and Expenditure of calories are linked to each other**

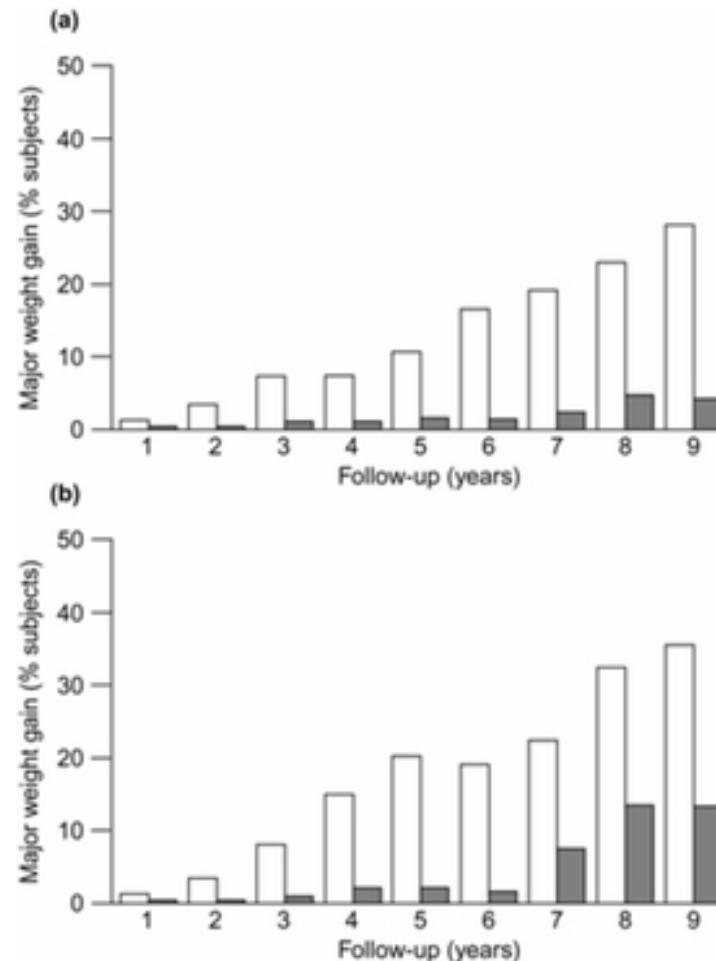
# Insulin – fattening agent

- 1923 clinicians successfully used insulin to fatten chronically underweight children
- 1930's clinicians using it regularly in Europe and USA for pathologically underweight patients
- Often gained as much as 6 pound per week using insulin and meals “rich in carbohydrates”
- 7 anorexic patients in clinic treated by Dr. Rony
  - added an average of 20 pounds in 3 months
  - All reported pronounced increase of appetite



- Insulin discovered in 1921

# I can make you fat...

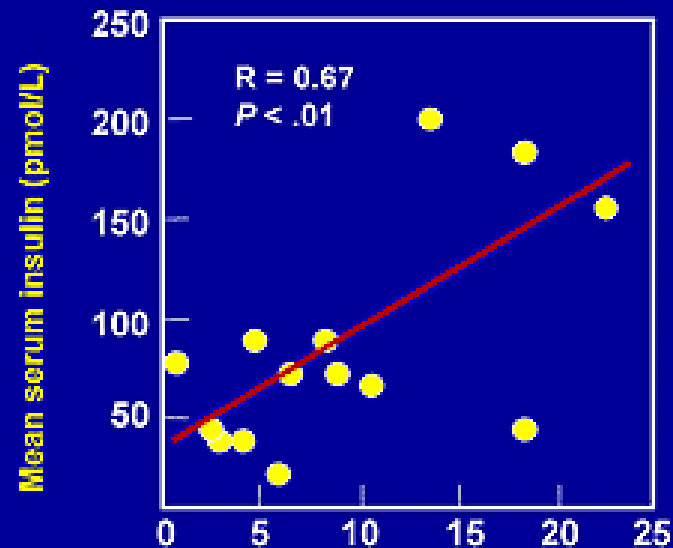
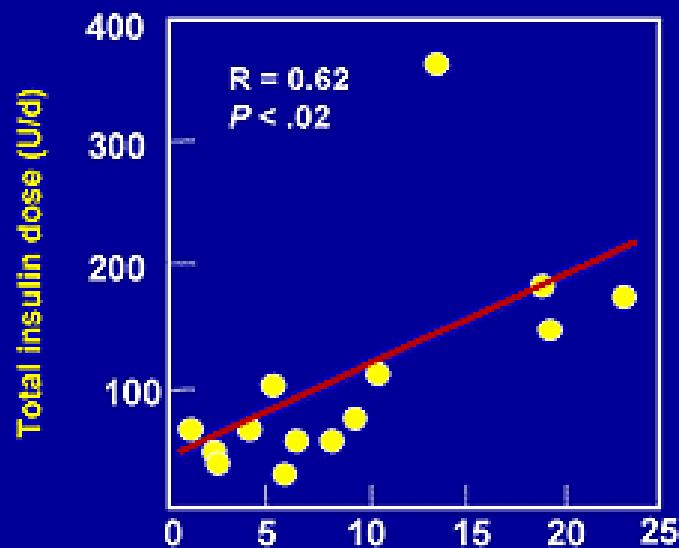


- Figure 1: The percentage of adult men (a) and women (b) with major weight gain (increase in BMI of more than 5 kg/m<sup>2</sup>) receiving intensive (white bars) or conventional (black bars) insulin therapy in the DCCT. The overall pattern of differences over time was significant ( $p < 0.01$ ) for both sexes (DCCT 2001). © 2001 *Diabetes Care* 2001, 24: 1711–172

# Correlation of insulin and weight gain

Medscape® www.medscape.com

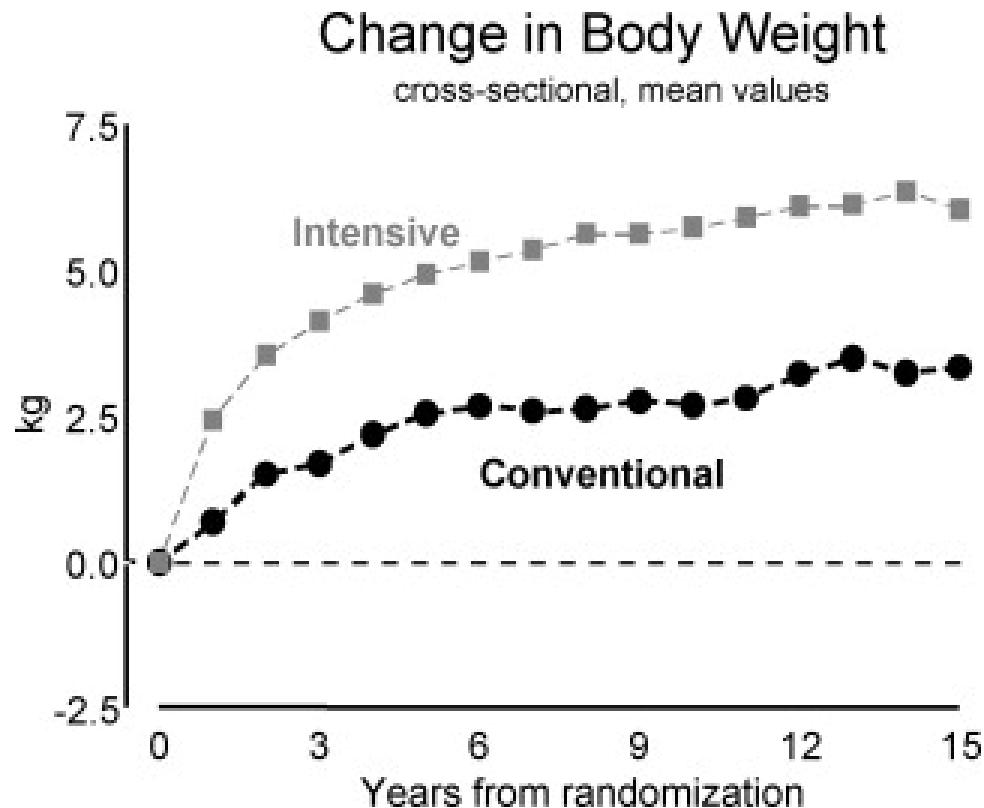
## Insulin Therapy and Weight Gain



Henry RR, et al. Diabetes Care. 1993;16:21-31.

- Intensive control of type 1 DM in DCCT trial resulted in average 4.75 kg more weight gain
- Diabetes Control and Complications (DCCT) Trial Research Group. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. Diabetes Care 2001;24:1711-21

# Weight gain during insulin therapy in patients with type 2 diabetes mellitus



- Fig. 1. Weight gain over time in type 2 diabetes patients undergoing intensive or conventional treatment with insulin or sulfonylureas. (*The Lancet*, vol. 352, 1998, pp. 837–853)

## Original Article

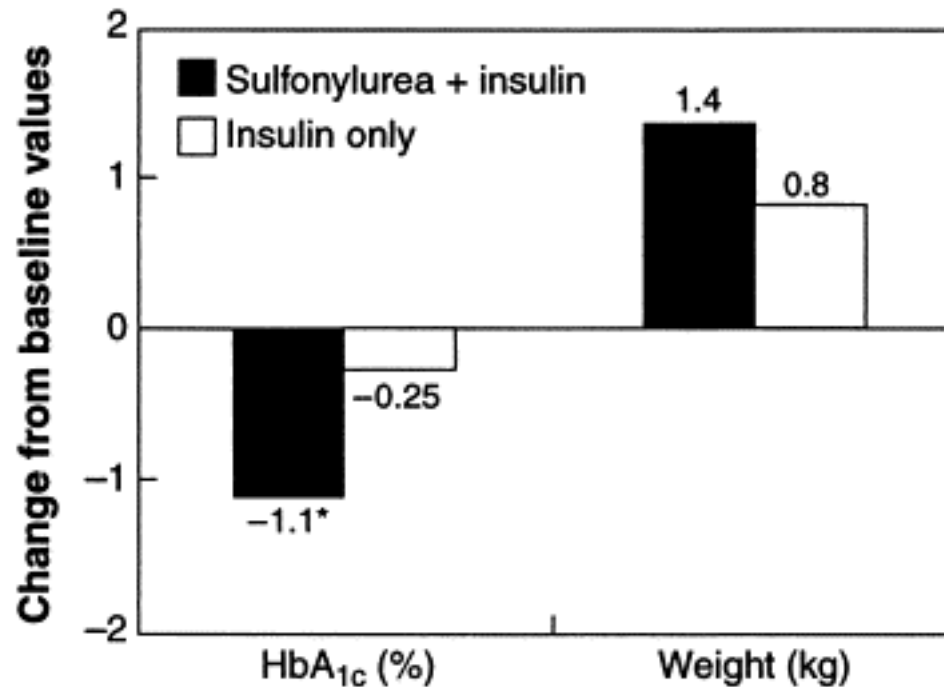
# Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators

- In this study with a 2-by-2 factorial design, patients with cardiovascular risk factors and dysglycemia or type 2 diabetes received insulin glargine or standard care.
- Insulin treatment did not affect cardiovascular events, the primary outcome.
- Participants in the insulin-glargine group gained a median of 1.6 kg, and participants in the standard-care group lost a median of 0.5 kg during a median follow-up of 6.2 years
- Difference of **2.1 kg over 6 years**

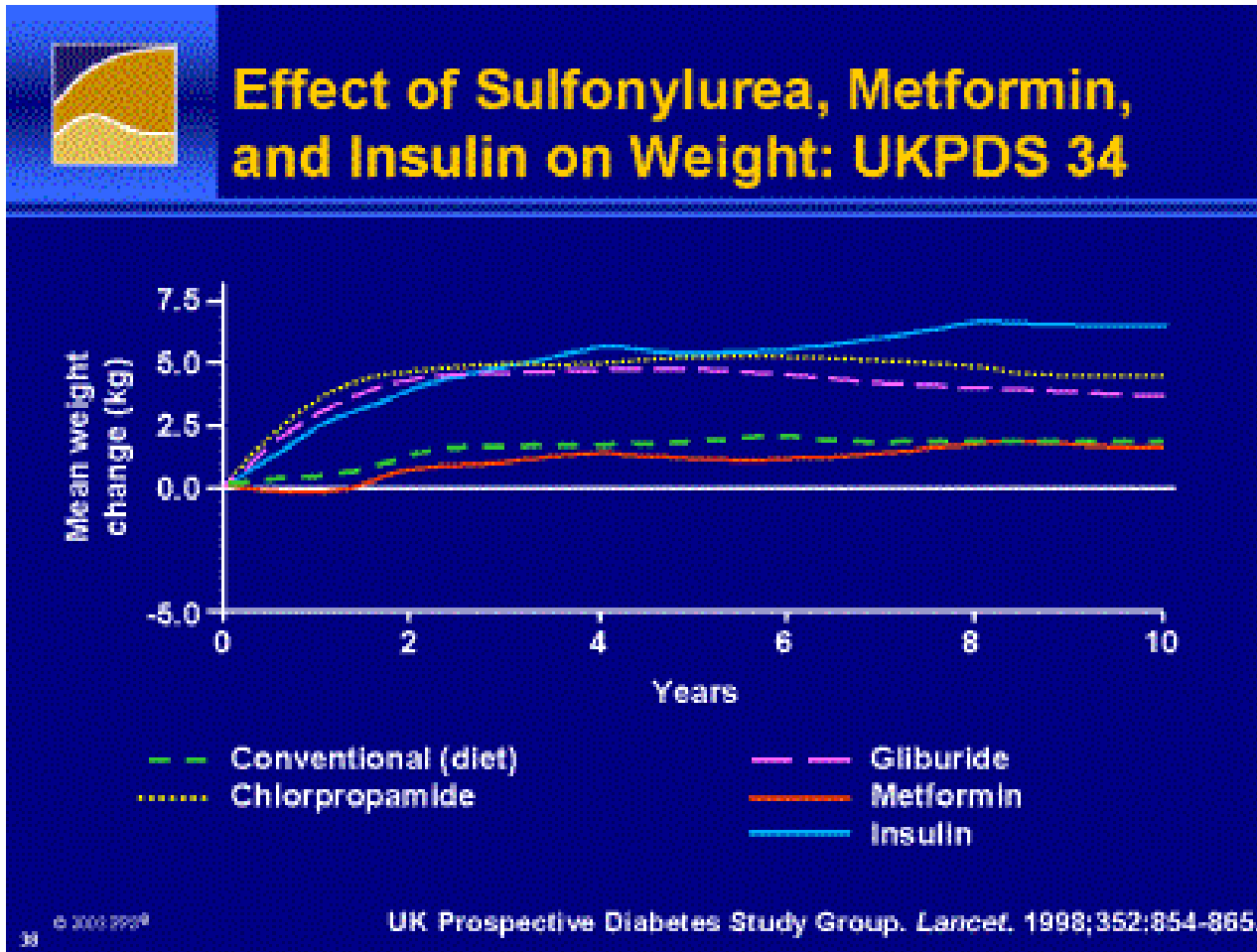


# Combining insulin and oral agents



- [The American Journal of Medicine](#)
- [Volume 108, Issue 6, Supplement 1](#), 17 April 2000, Pages 23–32
- John Buse et al

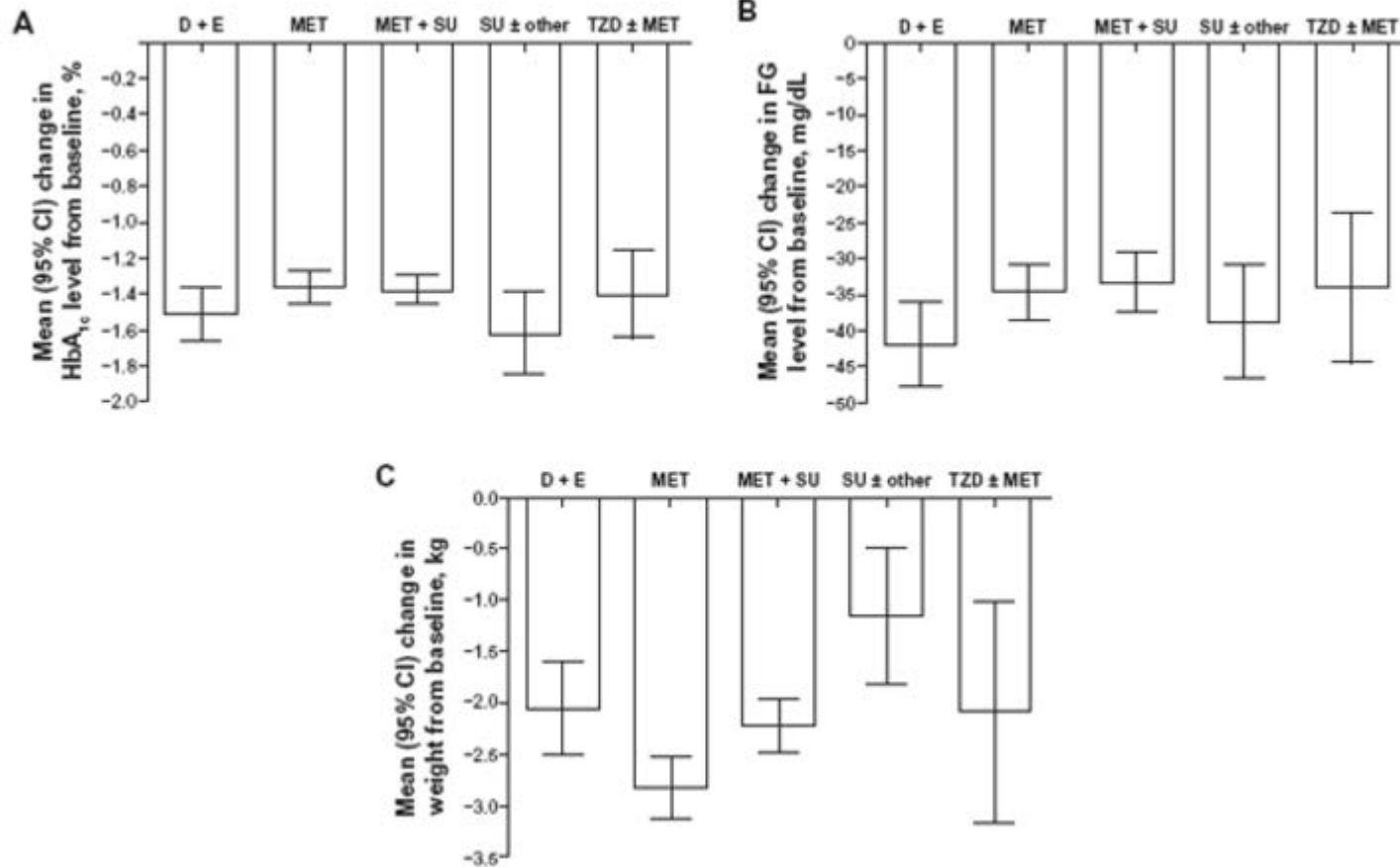
# What about Metformin?



- Is weight reduction related to its effect on blood glucose?
- Metformin does not increase insulin levels
- Increases insulin sensitivity



# Is Weight Gain related to change in blood glucose?

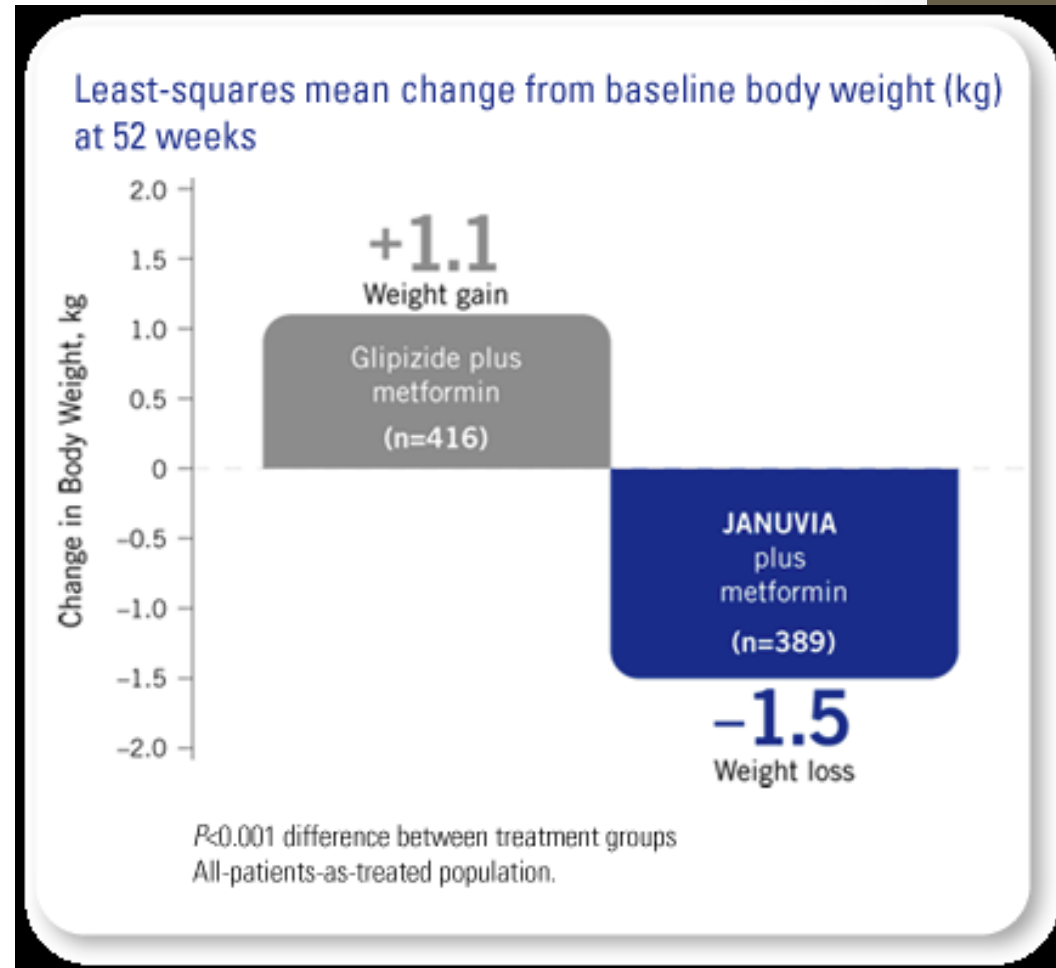


- **Postgraduate Medicine:**
- Volume 124 No. 4
- Penczek et al

- Pooled data from 7 randomized trials

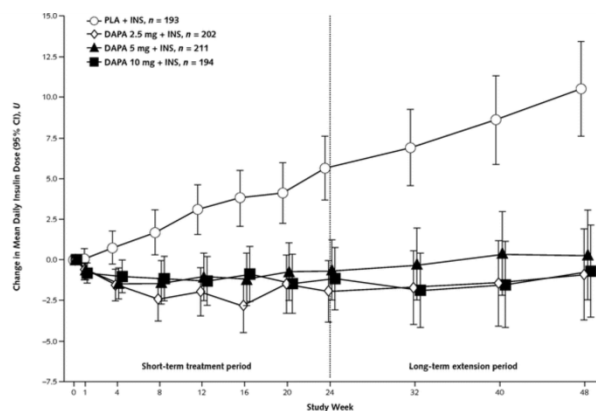
# Januvia

- DPP4 inhibitors increase glucose dependent insulin release



## From: Long-Term Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Receiving High Doses of Insulin: A Randomized Trial

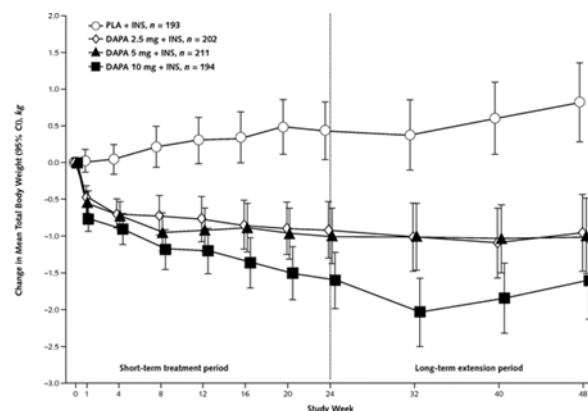
Ann Intern Med. 2012;156(6):405-415. doi:10.7326/0003-4819-156-6-201203200-00003



Sample size, n	190	185	176	171	170	165	168	164	158	157
PLA + INS	190	185	176	171	170	165	168	164	158	157
DAPA 2.5 mg + INS	200	197	189	187	186	181	180	174	176	173
DAPA 5 mg + INS	209	202	194	194	190	188	187	183	181	171
DAPA 10 mg + INS	194	189	185	183	180	178	177	175	173	166

Time and Variable	PLA + INS	DAPA 2.5 mg + INS	DAPA 5 mg + INS	DAPA 10 mg + INS
Baseline mean daily insulin dose, U	73.7	79.8	77.0	78.0
Week 24				
Adjusted mean change from baseline, U	5.65	-1.95	-0.63	-1.18
Difference vs. PLA + INS (95% CI), U	--	-7.60 (-10.32 to -4.87)	-6.28 (-8.99 to -3.58)	-6.82 (-9.56 to -4.09)
P value of difference	--	<0.001	<0.001	<0.001
Week 48				
Adjusted mean change from baseline, U	10.54	-0.92	0.30	-0.70
Difference vs. PLA + INS (95% CI), U	--	-11.46 (-15.51 to -7.41)	-10.24 (-14.27 to -6.22)	-11.25 (-15.32 to -7.18)
P value of difference	--	<0.001	<0.001	<0.001

### Change in daily Dose of insulin



Sample size, n	192	185	175	170	170	165	168	164	158	157
PLA + INS	192	185	175	170	170	165	168	164	158	157
DAPA 2.5 mg + INS	202	198	191	188	188	182	180	176	176	174
DAPA 5 mg + INS	211	201	196	193	190	188	187	184	181	174
DAPA 10 mg + INS	192	190	186	183	180	178	177	176	174	166

Time and Variable	PLA + INS	DAPA 2.5 mg + INS	DAPA 5 mg + INS	DAPA 10 mg + INS
Baseline total body weight, kg	94.5	93.0	93.4	94.5
Week 24				
Adjusted mean change from baseline, kg	0.43	-0.92	-1.00	-1.61
Difference vs. PLA + INS (95% CI), kg	--	-1.35 (-1.90 to -0.80)	-1.42 (-1.97 to -0.88)	-2.04 (-2.59 to -1.48)
P value of difference	--	<0.001	<0.001	<0.001
Week 48				
Adjusted mean change from baseline, kg	0.82	-0.96	-1.00	-1.61
Difference vs. PLA + INS (95% CI), kg	--	-1.78 (-2.53 to -1.03)	-1.82 (-2.56 to -1.07)	-2.43 (-3.18 to -1.68)
P value of difference	--	<0.001	<0.001	<0.001

### Change in Weight

Appendix

Figure 1. Adjusted mean changes in daily insulin dose over time (top) and at 48 weeks (bottom).

Samples are patients in the full analysis set with nonmissing baseline values and nonmissing values for a given time point. Sample sizes at time 0 are 191, 200, 209, and 194 for the PLA, 2.5-mg DAPA, 5-mg DAPA, and 10-mg DAPA groups, respectively. Treatment group symbols are shifted horizontally to prevent the error bars from overlapping. DAPA = dapagliflozin; INS = insulin; PLA = placebo.

# Drugs that act by increasing basal insulin

## Increase

- Insulin
- Sulfonylureas
  - Glyburide
  - Glicizide

## No Increase

- Metformin
- DPP IV inhibitors
  - Januvia
  - Onglyza
  - Trajenta
- SGLT – 2

# Drugs that cause weight gain

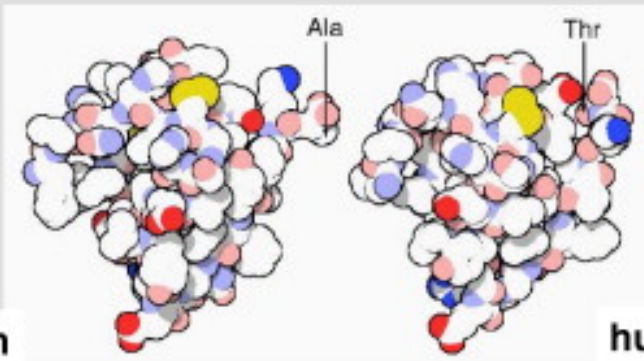
## Increase

- Insulin
- Sulfonylureas
  - Glyburide
  - Glicizide

## No Increase

- Metformin
- DPP IV inhibitors
  - Januvia
  - Onglyza
  - Trajenta
- SGLT – 2

# Insulin Analogues

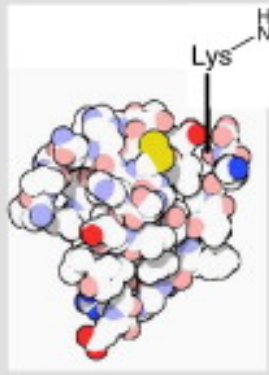


porcine insulin

human insulin

Ala


Thr



Lys

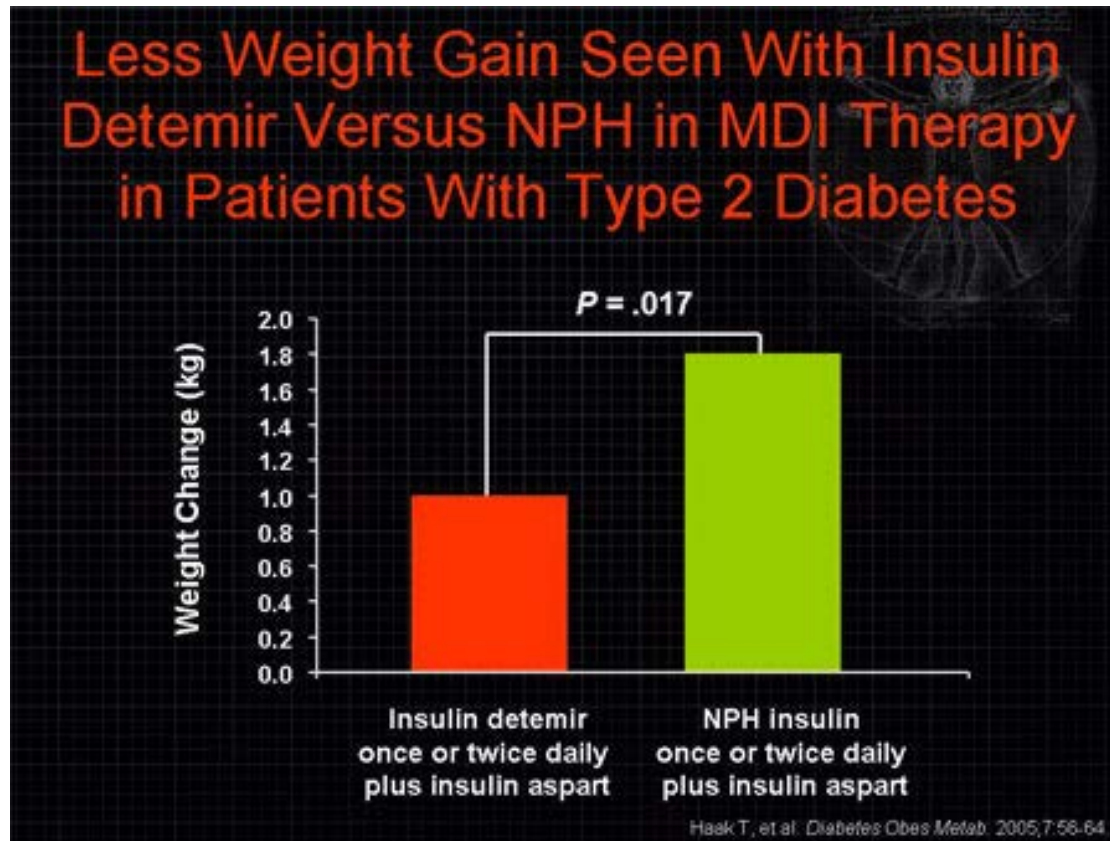
CCCCCCCCCCCCCCCC(=O)N

**Levemir® - insulin detemir**  
Engineered by omitting an amino acid, threonine, in position B29 and attaching the fatty acid myristic acid to the introduced amino acid lysine



Levemir® FlexPen®  
insulin detemir (CMAA analog) injection

# Levemir and weight gain



- Insulin analogue has same effect on sugars but lesser effect on obesity

# Insulin Lipohypertrophy

- Insulin acts through LPL (lipoprotein Lipase) – and HSL (hormone sensitive lipase)
- ‘lipogenic’ effect of insulin – self injections of insulin can lead to masses of fat at site of injection (needs a picture)





# I can make you thin...

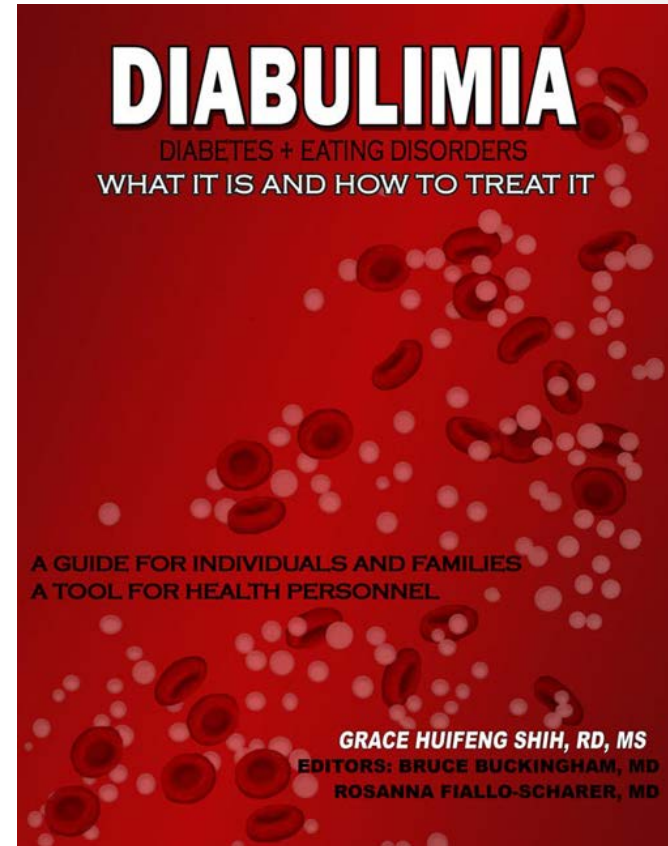
- Type 1 diabetes
  - Lack of insulin
- Aretaeus' classic description "Diabetes is ...a **melting down of the flesh and limbs into urine...**
- Lack of insulin leads to rapid loss of weight and fat
  - – internal starvation
- Lose all fat! No matter how many calories are ingested



- Untreated and treated Type 1 Diabetes Mellitus

# Diabulimia

- **Diabulimia** (*diabetes* and *bulimia*) refers to an eating disorder in which people with Type 1 diabetes deliberately give themselves less insulin than they need, for the purpose of weight loss
- Well known in Type 1 DM community that a lack of insulin causes immediate and substantial weight loss
  - Irrespective of exercise, caloric intake, 'toxic environment' etc



# I can make you fat...

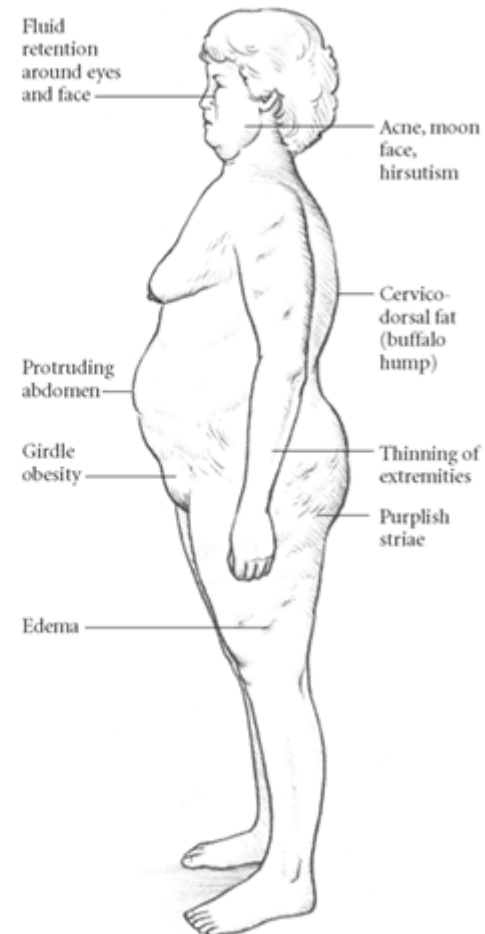
- Excess cortisol result in weight gain
  - Exogenous – steroids, prednisone
  - Endogenous – Cushing's syndrome
- Has nothing to do with gluttony/ sloth
- Excess fat deposition due to hormonal dys-regulation – not character defect (lack of willpower)
- "the hallmark sign of **Cushing's syndrome** is accelerated **weight gain**"

## SYMPTOMS OF CUSHINGOID SYNDROME

Chronic depression, alcoholism, and long-term treatment with corticosteroids may produce an adverse effect called *cushingoid syndrome*—a condition marked by obvious fat deposits between the shoulders and around the waist, and widespread systemic abnormalities.

Differentiating between cushingoid syndrome and Cushing's syndrome can be difficult, so in addition to the symptoms shown in the illustration at right, observe for signs of hypertension, renal disorders, hyperglycemia, tissue wasting, muscle weakness, and labile emotional state. The patient may also have amenorrhea and glycosuria.

Resolution of the underlying disorder results in disappearance of cushingoid symptoms.



# I can make you thin....

- Lack of cortisol results called Addison's disease
- “Most patients with **Addison's disease** experience fatigue, generalized weakness, loss of appetite and **weight loss**”



# Hormones are the Key!

↑ Insulin = ↑ Weight  
↓ Insulin = ↓ Weight

↑ Cortisol = ↑ Weight  
↓ Cortisol = ↓ Weight

- **What makes us fat?**
- Eat too much
- Exercise too little
- **Hormones! Obesity is a hormonal dysregulation of fat!**
- Insulin (cortisol)

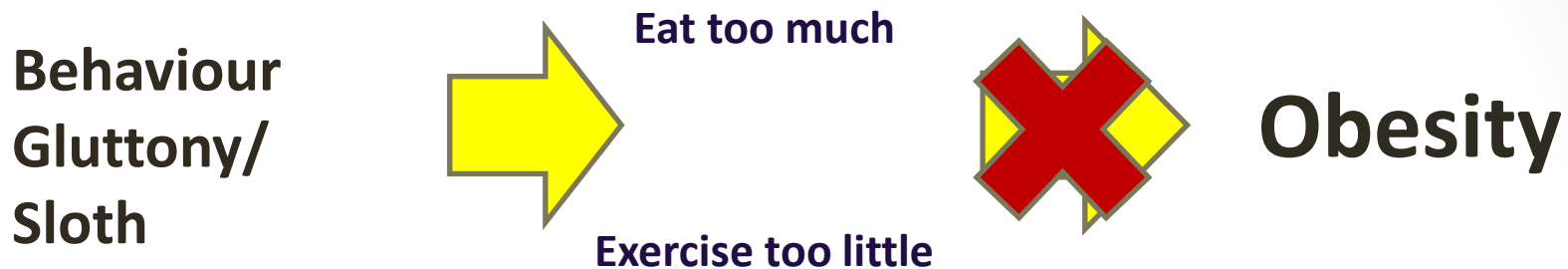


# Hormonal Obesity Theory

- This HOT hypothesis contains 3 propositions
  - Obesity caused by regulatory defect in fat metabolism – defect in the distribution of energy rather than an imbalance of intake/ expenditure
  - Insulin plays the primary role in this fattening process
  - **Fattening carbohydrates** are the prime suspects in the chronic elevation of insulin



# Caloric Reduction As Primary



- Belief in CRAP theory led to singular research focus on behavioural/ psychological issue (lack of willpower, overeating, lack of exercise)
- Entire generation including doctors/ dietician endorsing low fat caloric restriction as treatment
- Uninterrupted 35 year string of failure in treatment of obesity  
“a perfect record - unblemished by success”

# Hormonal Theory of Obesity



- Overeating and under-activity are the **result** not the **cause** of obesity
- Calories are primarily pushed into storage leaving inadequate amounts for energy expenditure – thus either increase caloric intake or decrease energy expenditure
- **We do not get fat because we overeat**
- **We overeat because we get fat!**



# The Aetiology of Obesity

- The absolutely crucial question in obesity is not how many calories am I eating
  - **Calories are largely irrelevant** – increased caloric intake will be matched by increase caloric expenditure
    - More calories in, more calories out
- **What is driving my insulin levels up?**
- **Answer – The fattening carbohydrates**



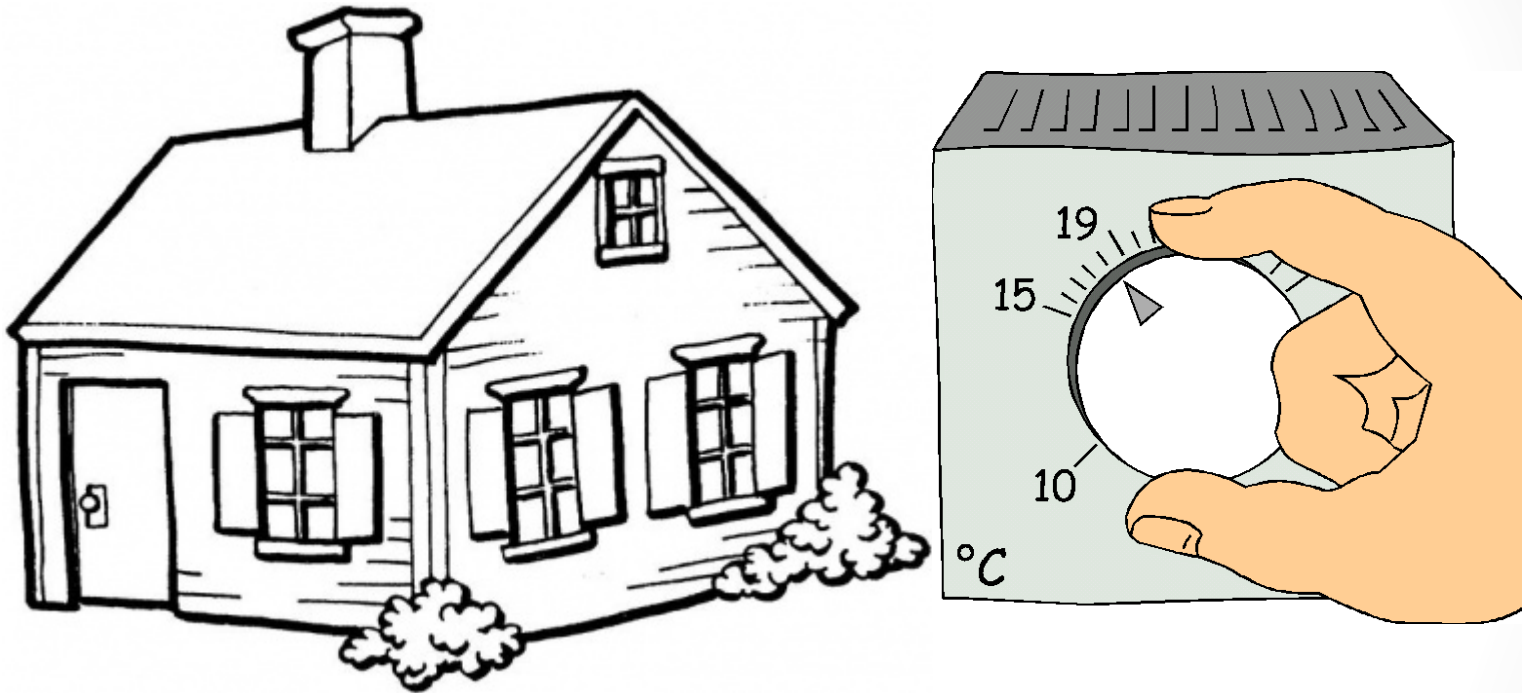
# Banting's understanding



- Current scientific understanding



# Obesity Set Point



- Insulin adjusts the “body weight setpoint”

# The Practice of Endocrinology

## 1951

- Food to be avoided:
  - 1. Bread, and everything else made with flour
  - 2. Cereals, including breakfast cereals and milk puddings
  - 3. Potatoes and all other white root vegetables
  - 4. Foods containing much sugar
  - 5. All sweets
- You can **eat as much as you like** of the following foods:
  - 1. Meat, fish, birds
  - 2. All green vegetables
  - 3. Eggs, dried or fresh
  - 4. Cheese
  - 5. Fruit, if unsweetened, except bananas, and grapes



# CARBS/INSULIN 4 DUMMIES

NORMAL PERSON



EATS BAD CARBS



INSULIN LEVELS GO CUCKOO



BLACK BOX GETS EFFED-UP



OBESE PERSON



CUTS CARBS



INSULIN LEVELS NORMALIZE



BLACK BOX IS FIXED



# Weight Loss and Nutrition Clinics

Referrals:

Dr. Jason Fung

78 Corporate Dr. Unit #10

Scarborough ON

M1H 3G4

Fax: 416-279-0857