

**Science of Fat**  
**2004 Holiday Lectures on Science**  
**Chapter List**

Lecture One

Deconstructing Obesity

Jeffrey M. Friedman, M.D., Ph.D.

1. Start of Lecture One
2. Introduction by HHMI President Dr. Thomas Cech
3. Introductory interview with Dr. Jeffrey Friedman
4. Understanding human diversity through science
5. People have opinions about what causes obesity
6. Obesity is associated with many diseases
7. Definition of obesity and the body mass index (BMI)
8. Animation: BMI and body shape
9. Limitations of BMI
10. What causes obesity?
11. Is the lack of willpower the main cause of obesity?
12. Obesity as a result of energy input/output imbalance
13. Eating is a basic biological drive and can overwhelm willpower
14. The role of environment as a cause of obesity may be exaggerated
15. Q&A: Why the difference in obesity between U.S. and Europe?
16. Q&A: Is obesity linked to depression or other emotional states?
17. Q&A: Are there racial differences in the tendency to be obese?
18. Adoption and twin studies show that obesity is highly heritable
19. A genetic example of obesity: Leptin deficiency
20. Genetically engineered leptin-deficient mouse
21. Leptin, a hormone secreted by fat, influences appetite
22. Animation: Leptin feedback-control system
23. Leptin deficiency causes obesity; leptin replacement cures it
24. In most obese people, leptin sensitivity is reduced.
25. Only a subset of obese people responds to leptin therapy
26. Biology is the main cause of obesity
27. Q&A: Are there other hormones that control weight?
28. Q&A: Is there a connection between leptin and age?
29. Q&A: Have you thought about marketing leptin injections?
30. Closing remarks by HHMI President Dr. Thomas Cech

## Lecture Two

### Understanding Fat: Syndrome X and Beyond

Ronald M. Evans, Ph.D.

1. Start of Lecture Two
2. Introduction by HHMI Vice President Dr. Peter Bruns
3. Introductory interview with Dr. Ronald Evans
4. What changed in the last 30 years to cause an obesity epidemic?
5. Food, particularly fat, is irresistible
6. Contributing factors to obesity
7. How many calories are in one ounce of fat?
8. Portion sizes have gone up
9. Sedentary lifestyle and marketing are also factors
10. Obesity trends worldwide and in the U.S.
11. BMI and its shortcomings
12. Environment can affect obesity: The Pima Indian example
13. Animation: How dietary fat ends up in fat tissue
14. Q&A: Can differences in Pima tribes be attributed to genetics?
15. Q&A: Have adoption studies looked for Pima genetic changes?
16. Q&A: What do the four heaviest states have in common?
17. Q&A: Are fast-food restaurants responsible for obesity?
18. Is obesity related to laziness?
19. Video: Behavior of obese and normal mice
20. Health consequences of being overweight
21. Animation: Timeline of obesity-related health problems
22. Animation: How a heart attack occurs
23. The role of fat tissue
24. The link between fat and sugar
25. Diet and exercise are key
26. Q&A: How long have you been a researcher in fat?
27. Q&A: What disease is caused by glucose gridlock?
28. Q&A: What is the difference between good fat and bad fat?
29. Q&A: How are LDL and HDL levels controlled?
30. Q&A: Why is adipose tissue in the muscle?
31. Q&A: How does the body decide where to store fat?
32. Q&A: What are the effects of gaining fat centrally and elsewhere?
33. Q&A: What research is there relating depression and obesity?
34. Closing remarks by HHMI Vice President Dr. Peter Bruns

Lecture Three  
Balancing the Fat Equation  
Ronald M. Evans, Ph.D.

1. Start of Lecture Three
2. Introduction by HHMI President Dr. Thomas Cech
3. Introductory interview with Dr. Ronald Evans
4. Review of Lecture Two and a look at models of fat and muscle
5. Fat molecule can act as a hormone
6. Two types of hormone action: At the membrane and at the nucleus
7. Examples of nuclear hormone receptors
8. PPAR receptors act as nuclear fat sensors
9. Functions of PPAR-gamma
10. Animation: PPAR-gamma activation in the fat cell
11. Fat tissue in an obese person has an imbalance of hormones
12. PPAR-gamma can reverse insulin resistance
13. Q&A: Is there any advantage to storing fat in one area?
14. Q&A: Can you use PPAR-gamma to cure diabetes?
15. Q&A: Can you develop a tolerance to the PPAR-gamma drug?
16. Q&A: Does saturated fat not bind to PPARs?
17. The U.S. is three billion pounds overweight
18. Science may be able to change appetite and energy expenditure
19. Can we use PPAR-delta to increase metabolism?
20. Two types of muscle fibers: Fast twitch and slow twitch
21. Animation: PPAR-delta activation in the muscle cell
22. Increasing PPAR-delta activity increases slow-twitch fiber numbers
23. Can revving up PPAR-delta cause a mouse to run better?
24. Video PPAR-delta mouse on a treadmill
25. PPAR-delta mouse: a remarkable example of an engineered runner
26. PPAR-delta protects against obesity even without special exercise
27. Are you ready for the future?
28. Q&A: Are people more sensitive to insulin after exercise?
29. Q&A: Are there side effects from the PPAR-delta drug?
30. Q&A: How quickly does the PPAR-delta drug take effect?
31. Q&A: Can you affect the repressor proteins of the PPAR system?
32. Closing remarks by HHMI President Dr. Thomas Cech

## Lecture Four

### Exploring Obesity: From the Depths of the Brain to the Far Pacific

Jeffrey M. Friedman, M.D., Ph.D.

1. Start of Lecture Four
2. Introduction by HHMI Program Director Dr. Dennis Liu
3. Introductory interview with Dr. Jeffrey Friedman
4. Outline of Lecture Four
5. Obesity is usually caused by leptin resistance, not leptin deficiency
6. How does leptin act on a neuron?
7. Animation: Neuroanatomy of the mouse hypothalamus
8. Functions of the hypothalamus
9. The leptin circuit in the hypothalamus
10. How to label two neuronal types differently
11. How does leptin affect the activity of hypothalamic neurons.
12. Animation: Leptin rewiring neuronal connectivity
13. Leptin rapidly rewires feeding circuits
14. We need to understand the overall wiring diagram
15. Feeding is a complex motivational behavior
16. Method for tracing connected neurons using the Cre recombinase
17. Where are the neuronal inputs to the leptin circuit?
18. Q&A: How did you initially isolate NPY and MSH neurons?
19. Q&A: Connections between skin pigmentation and eating?
20. How does variation in genes lead to obesity?
21. Hunter-gatherer and Fertile Crescent genes
22. Pacific island of Kosrae: A site to study genetic variation
23. Tracing inheritance of single nucleotide polymorphisms (SNPs)
24. Using DNA chips to analyze many SNPs at once
25. Studies of isolated populations can find rare single-gene disorders
26. Mapping rare genetic markers by analyzing homozygous individuals
27. Developing a genetic framework to understand how leptin works
28. It's important not to blame and stigmatize the obese
29. Q&A: Disadvantages of studying an isolated population?
30. Q&A: Does the research provide any benefit to the Kosraeans?
31. Q&A: How often do you need to inject leptin?
32. Q&A: Can anorexia be caused by leptin oversensitivity?
33. Q&A: Is there a connection between depression and leptin?
34. Closing remarks by HHMI President Dr. Thomas Cech