Learning from Patients: The Science of Medicine
2003 Holiday Lectures on Science
Chapter List

Lecture One
Research Mechanics: Putting the Brakes on Cancer
Bert Vogelstein, M.D.

1. Start of Lecture 1
2. Introduction by HHMI President Dr. Thomas Cech
3. Introductory interview with Dr. Bert Vogelstein
4. Outline of the lectures
5. Nature of cancer: Benign tumors
6. Nature of cancer: Malignancy and metastasis
7. Animation: Tumor growth and metastasis
8. Examples of metastatic cancer
9. Many types of cancer
10. Tumors and ratio of cell birth to death
11. Compound-interest analogy
12. Cell birth and death in normal and tumorous cells
13. Review of tumor definitions
14. Q&A: How can you tell if a benign tumor will become malignant?
15. Q&A: Do cancer cells selectively metastasize to specific tissues?
16. Q&A: Are malignant tumors harder to control than metastatic tumors?
17. Q&A: Can we paralyze cells so they stop multiplying?
18. Theories on what causes cancer
19. Cancer compared with other genetic diseases
20. Clonal expansion as a model of cancer
21. Cancer is usually not hereditary
22. Types of genes that are mutated in cancer
23. Why has evolution not made DNA replication perfect?
24. Two main kinds of familial colon cancer: FAP and HNPCC
25. Animation: DNA mismatch repair
26. HNPCC can progress much faster than FAP
27. Colorectal cancer pathway
28. p53 gene is mutated in most cancers
29. Animation: p53 regulates transcription
30. Examples of proteins regulated by p53
31. An example of an oncogene mutation in cancer
32. Q&A: How do mutagens cause such specific mutations?
33. Q&A: Is there a reason why mutagens change bases to thymine?
34. Q&A: Can you fix a mutated gene in hereditary cancer?
35. Q&A: How would I distinguish my tumors as benign or malignant?
36. Q&A: Why aren't growing children affected more by cancer?
37. Q&A: Do cancer cells have multiple mutations in apoptosis factors?
38. Closing remarks by HHMI President Dr. Thomas Cech

Lecture Two
Chaos to Cure: Bringing Basic Research to Patients
Bert Vogelstein, M.D.

1. Start of Lecture 2
2. Introduction by HHMI Vice President Dr. Peter Bruns
3. Introductory interview with Dr. Bert Vogelstein
4. Three ways of using genetic knowledge to help cancer patients
5. Risk assessment and pedigree symbols
6. Genetic test for detecting FAP patients
7. Ethical issues in sharing genetic-testing information
8. Using genetically engineered mice to find treatments for FAP
9. Early detection of polyps to help nonfamilial cases
10. Video: *Today* host Katie Couric's colonoscopy
11. Video: Polypectomy
12. Need for developing noninvasive techniques to detect cancer
13. Using stool samples to detect mutations
14. Q&A: How do you determine what drugs to give FAP mice?
15. Q&A: How do you explain the effects of Sulindac and EKI?
16. Q&A: Do different cancers develop in different age groups?
17. Q&A: What are the body's defenses against cancer?
18. Q&A: Do different populations have resistance to cancer?
19. Q&A: Can cancers be detected before they are metastatic?
20. Q&A: What parts of the body tend to develop metastatic cancers?
21. Current treatments for cancer and direction for future
22. Cancer cells have altered chromosomes
23. Chromosome translocation generates Philadelphia chromosome
24. Animation: Gleevec inhibiting the activity of BCR-ABL protein
25. Treating leukemia patients with Gleevec
26. Animation: Using a virus to kill cancer cells with defective *p53*
27. Animation: Cancer cells recruit blood vessels to grow
28. Animation: VEGF released by tumors recruits blood vessels
29. Using antiangiogenesis drugs to treat cancer
30. Using engineered anaerobic bacteria to treat cancer
31. Q&A: Do bacterial and viral therapies have side effects?
32. Q&A: Can you poison cancer cells with excess oxygen?
33. Q&A: Which treatment do you prefer?
34. Q&A: How do you make the new therapies available to everyone?
35. Q&A: How does hormone therapy to treat cancer work?
36. Q&A: How do anaerobic bacteria survive after eating dead tissue?
37. Q&A: Isn't an adenovirus treatment limited by immunity?
38. Q&A: Shouldn't stool or blood testing for cancer be made routine?
39. Q&A: How do you treat people with multiple cancers?
40. Closing remarks by HHMI Vice President Dr. Peter Bruns

Lecture Three
A Healthy Nervous System: A Delicate Balance
Huda Zoghbi, M.D.

1. Start of Lecture 3
2. Introduction by HHMI President Dr. Thomas Cech
3. Introductory interview with Dr. Huda Zoghbi
4. The importance of balance and coordination in everyday life
5. Cerebellum is important for coordination and balance
6. Cell types found in cerebellum, particularly the Purkinje cell
7. The story of an extended family with ataxia
8. Video: A patient with spinocerebellar ataxia type 1 (SCA1)
9. Cellular, clinical and genetic facts about SCA1
10. Anticipation: Later generations have earlier onset of disease
11. CAG trinucleotide repeat expansion causes SCA1
12. Animation: Trinucleotide repeat expansion
13. Number of CAG repeats influences the age of disease onset
14. CAG repeat produces polyglutamine, causing many diseases
15. Benefits of identifying disease-causing genes
16. Q&A: How does the change in protein affect the cell?
17. Q&A: Does the disease affect other involuntary functions?
18. Q&A: What are the differences among the 22 types of SCAs?
19. Q&A: How do the nerve cells express specific genes?
20. Q&A: Are African-American families more vulnerable to SCA1?
21. Is SCA1 caused by a loss-of-function mutation?
22. Is SCA1 caused by a gain-of-function mutation?
23. How do you tell that a mouse is ataxic?
24. Video: Balance test for SCA1 mouse
25. Purkinje cells degenerate in SCA1 mice
26. Ataxin-1 accumulates in both SCA1 mice and patients
27. Mutant ataxin-1 resists protein degradation and accumulates
28. Ubiquitin acts as a marker for proteins targeted for degradation
29. Animation: Ubiquitin and proteasome
30. Protein accumulation occurs in many neurodegenerative diseases
31. Using chaperones to counteract protein accumulation
32. Using an SCA1 model in *Drosophila* to find disease modifiers
33. Inhibiting protein kinase AKT can suppress the effects of SCA1
34. Q&A: Are chaperones specific? Do they degrade other proteins?
35. Q&A: Why do cells degrade proteins?
36. Q&A: Does mutant ataxin interfere with proteasome function?
37. Q&A: Does a mutation affect all cells?
38. Closing remarks by HHMI President Dr. Thomas Cech

Lecture Four
The Strength of Families: Solving Rett Syndrome
Huda Zoghbi, M.D.

1. Start of Lecture 4
2. Introduction by HHMI Grants Program Director Dr. Dennis Liu
3. Introductory interview with Dr. Huda Zoghbi
4. Rett syndrome introduction
5. Video: Normal child development
6. General description of Rett syndrome
7. Video: Julia Roberts describes Rett syndrome
8. Rett syndrome is typically rare and sporadic
9. Rare cases of families with inherited Rett syndrome
10. Video: Woodcock family's story
11. Four family pedigrees shed light on the pattern of inheritance
12. X-chromosome inactivation
13. Animation: X-chromosome inactivation
14. X-chromosome inactivation can explain asymptomatic carriers
15. How sporadic cases of Rett syndrome can arise
16. Challenge of mapping genes from small number of samples
17. Animation: Exclusion mapping strategy
18. Discovering the Rett syndrome gene
19. Q&A: What happens to the males who inherit this gene?
20. Q&A: Why don't symptoms appear until 6-18 months of age?
21. Q&A: What causes the mutations in the specific gene?
22. Q&A: Why don't cells inactivate the mutant gene?
23. Q&A: Can you remove genes that cause disease?
24. Q&A: How can you distinguish different neurological diseases?
25. What does methyl-CpG-binding protein 2 (MeCP2) do?
26. How MeCP2 regulates gene expression
27. Animation: MeCP2 regulation of gene expression
28. X-chromosome inactivation causes various phenotypes in girls
29. Different *MECP2* mutation causes various phenotypes in boys
30. *MECP2* gene is expressed during neuronal maturation
31. Designing a mouse model for Rett syndrome
32. Video: Rett mouse phenotypes
33. Rett mouse revealed anxiety as a Rett syndrome phenotype
34. Using DNA microarray to find genes regulated by MeCP2
35. Finding other genes may explain mechanisms of other diseases
36. Q&A: Why is MeCP2 not needed until neurons are fully mature?
37. Q&A: Does sporadic Rett worsen in each generation?
38. Q&A: How far away are you from improving patients' condition?
39. Q&A: How is Rett syndrome turning some genes off?
40. Closing remarks by HHMI President Dr. Thomas Cech