Learning From Patients: The Science of Medicine (2003)
Lecture Two—Chaos to Cure: Bringing Basic Research to Patients
Bert Vogelstein, M.D.

1. Start of Lecture 2 (00:11)

From the Howard Hughes Medical Institute The 2003 Holiday Lectures on Science. This year's lectures Learning from Patients: The Science of Medicine will be given by Dr. Bert Vogelstein Howard Hughes Medical Institute Investigator at Johns Hopkins University School of Medicine and Dr. Huda Zoghbi Howard Hughes Medical Institute Investigator at Baylor College of Medicine. The second lecture is titled "Chaos to Cure: "Bringing Basic Research to Patients." And now, to introduce our program The Vice President for Grants and Special Programs of the Howard Hughes Medical Institute Dr. Peter Bruns.

2. Introduction by HHMI Vice President Dr. Peter Bruns (01:04)

Welcome back to Holiday Lectures 2003. These lectures are a product of the grants program at Hughes and that program actually focuses on science education across the educational spectrum and across the nation. And in the process of doing that we've created a network of educators of all sorts around the country who help us in a lot of different ways. For example, Tom mentioned earlier that these lectures end up on DVDs and to make sure that the DVD really is useful for teachers we actually activate our network of teachers and send them the DVDs and ask them what they would do with them to field-test the lectures and to create other supplemental materials that they can use educationally. Those materials end up, actually on another web site that we maintain called BioInteractive.org and you can go look there to see not only previous lectures but the other things that this network of teachers have added to it. You might go take a look on that web site. This is a commercial plug. On that web site, you'll find 3-D animations you can test your skills in interactive quizzes that we have on there and you can even do an experiment on the virtual labs that we have there. So there are a lot of other things that we do here educationally that come from these lectures. So now we're ready for the next lecture by Dr. Vogelstein. The second lecture is called "Chaos to Cure: "Bringing Basic Research to Patients..." and we'll have a short video to further introduce Dr. Vogelstein.

3. Introductory interview with Dr. Bert Vogelstein (02:44)

People in our lab come from all over the world. We're very lucky to have applicants from all over. We've had, I guess, over a hundred people who have trained in our lab over the past 25 years or so and the lab is run kind of like a family. You know, we consider everybody a lab family member. People socialize a lot while they're here. They work together as groups which helps them both scientifically and professionally. We have meetings a couple times a week where everyone gets together. We have some recreational activities so people generally remember it as a good time in their lives when they learned a lot and matured scientifically but also had a lot of fun. There are lots of different ways to be a scientist lots of different ways to enjoy science. The key thing is, I guess, underlying all of that is not being satisfied with the status quo. If you want to be a research scientist then you have to want to make things better. If you're a scientist, your homework is never done. There's always more to learn. You're never out of school. In addition to doing your own experiments you have to read about others, and there's lots to read. You have to be a bit skeptical about almost everything that is it really the way it seems? Is this explanation really the way it works? And one of the things that we try and teach our trainees is that sort of skepticism. The most fun part of what I do is seeing some young person make a discovery. That's by far the best part their first thing that they themselves have created have learned that no one else in the world right at that moment knows. It's an incredible feeling to have and it's a great thing to be able to watch. And that moment of discovery in a young person is a real is a real joy both to witness but as well as to help them

get there.

4. Three ways of using genetic knowledge to help cancer patients (05:06)

Welcome back. In this lecture we'll discuss some of the practical implications of the cancer revolution. And you'll recognize this slide which is a diagram of the genes that are responsible when mutated, for causing colon cancer. What the challenge is in the years ahead is to figure out how to use this information to actually help people and there are three ways that we envision this could be done: First, with risk assessment trying to test patients who have hereditary predispositions to see who does and who doesn't; early detection; and treatment. And all of these are at the experimental phase because most of the genes on this slide have just been discovered in the last few years. This is something that we hope some of you are going to help with in the upcoming years because we need good creative minds to work on these challenging problems.

5. Risk assessment and pedigree symbols (06:16)

Let's start with risk assessment. You'll remember that most colorectal cancers like most cancers in general are non-familial but there are a small fraction which are familial and the two syndromes we discuss. Just as a reminder the pedigree symbols are a square for male a circle for female. When the circle and the square get together if they're fruit flies they call it mating. The technical term that we scientists use is "hooking up." And if they're blocked in they're affected and I think you know the rest.

6. Genetic test for detecting FAP patients (07:00)

So let's start with a young woman named Jennifer who presented to our clinic a few years ago with pain and blood in her stool, in her feces and she turned out to have hundreds of polyps in her large intestine. And it turned out that her father had died in his forties of colon cancer, and in fact his mother Jennifer's grandmother, had also died from colon cancer. So it was very clear that she had polyposis familial adenomatous polyposis, a familial form of cancer. The real question was, what about her four siblings her two brothers and two sisters? Now, it's important to point out that these are not just symbols. These are real people and this sort of information is really important for them to manage their lives. Polyps, in this disease these benign tumors don't generally form until patients are in their teens or even twenties so it was impossible to tell whether her younger siblings she was the oldest in the family actually were going to get this disease. In the past, what physicians would have to do would be simply to wait and see whether patients got them and then advise them accordingly. But now that we know the gene that causes this disease we can do a simple blood test in families like this. And when we did that blood test on Jennifer and sequenced her *APC* gene we knew the *APC* gene is the only gene that causes this syndrome we found a mutation. And you can all see where that mutation is. This is just a standard sequencing result that we do in our lab every day. You can read off the bases A-G-A-A-A-T-A, *et cetera* And you can see there's one position that's mutant. It's "G," normally and Jennifer had both a "T" and a "G." The "T," the mutant base she inherited from her father, who had polyposis and the "G" she inherited from her mother, who was normal. Now, it's kind of awesome to think about the fact that there are six billion of these building blocks these As, Cs, Ts, and Gs in every one of our cells and a mutation of only one of them that is, this specific mutation in the *APC* gene just one out of the six billion that mutation alone is sufficient to guarantee 100% certainty, that a patient will get polyposis thousands of polyps and will eventually get cancer. Now, how do we use this information in this family? Well, we can then do the blood tests on the four siblings who were too young to have polyps. And when we did that we found that two of them Barbara and Matt actually had the syndrome and the other two didn't; had the mutation and were going to get the syndrome whereas the other two didn't. And that was very helpful because in the two siblings that didn't the brother and sister, they didn't have to worry. Their mother didn't have to worry and that was a

great relief to them. In Barbara and Matt we'll discuss in a minute what could be done for them.

7. Ethical issues in sharing genetic-testing information (10:34)

But this raises some other issues the fact that we can do simple blood tests and predict what's going to happen to patients in terms of diseases like this. You can clearly do it the technology for doing it is available it's done in labs every day but should we do it? And it raises a host of ethical issues. For example should Jennifer's test result or those of her brothers and sisters be given to insurance companies? She's going to be applying for jobs in a couple of years. Should they be given to her employer? And what do you think? Who thinks that it's permissible on ethical grounds to give genetic information like this to life insurance companies which would allow them to either give or not give insurance or raise the price? Who thinks it is permissible and reasonable to do that? Only one person whose father probably works for an insurance company. Who thinks it's not? Everybody else. That's the response we usually get. But think about it. Everyone who gets a life insurance exam gets a test lots of tests but including a test for blood pressure. Now, this is a low-tech way of predicting who's going to get heart disease. I'm not saying it's right that blood pressure results should be given to insurance companies but if that's right then genetic testing really isn't that much different. They're either both right or both wrong. They're just tests to predict disease. So questions like these have no simple answers. Here's another one. Suppose should these tests be given to every family member? Suppose Christa finds that Daniel's mutations aren't so bad and decides to marry him but Daniel unbeknownst to Christa, actually has polyposis. Does he have to tell Christa or should he tell, on ethical grounds his fiancé that he is going to have polyposis and that his kids at least half of them are likely to have it? Who thinks Daniel should tell Christa? And who thinks Daniel shouldn't tell Christa? Nobody. All right. Well, we've all seen movies of what happens if you don't tell your fiancé the truth. But, you know, if I asked you whether if Daniel had an infection with H.I.V would he have to tell Christa everybody, without doubt, would say yes. Nobody would say no. And for the same kind of reason I want to show you one pedigree of a gentleman in Baltimore who married six wives and had well over 100 grandchildren half of whom had polyposis a one-man epidemic of polyposis. So, both from a public health perspective not only from an ethical perspective who should get results about genetic testing distant family members, *et cetera* is not an easy one to answer and we'll discuss other ethical issues in a bioethics session this afternoon at 1:30 or 2:00.

8. Using genetically engineered mice to find treatments for FAP (14:06)

Now let's go back to our family with Jennifer and Matt and Barbara. What can we do for Matt and Barbara and Jennifer? Well, we can take out their colon. That will prevent them from getting colon cancer for sure and you can do that. You don't need your colon. You need your small intestine but you don't need your colon. All the colon does is dehydrate the stool so it becomes solid. People can live without their colons. It's not pleasant, but it can be done. On the other hand many investigators, including us are trying to develop drugs that will prevent the onset of polyposis in such patients and to test such drugs, we use animal models. We obviously can't and don't want to use people to test experimental drugs. And through genetic engineering we can create a mouse with polyposis. In fact, we created a mouse that has exactly the same mutation that we found in Jennifer. This mouse gets polyps which you can see there highlighted in red and they look under the microscope the same as in a polyposis patient. We find these mice have lots of polyps indicated by those red dots and if we treat them with a drug called Sulindac this is a pretty harmless drug. It's the same chemical class as Advil. I'm sure many of you have taken Advil for aches and pains. But Advil actually can help with colon polyps and people who take Advil or aspirin actually have less polyps and colon cancer than people who don't. At any rate this reduces polyps in the mice by about 50%. Another drug an experimental drug not yet released to the public called EKI also can reduce them by 50%. When they're both used together they're dramatically reduced. The mice hardly get any polyps. Even if they're just treated for a couple of months they don't get polyps throughout their entire lives. A clinical trial of these drugs will probably be instituted in a couple of years in polyposis patients and

hopefully will at least delay the time when they need to get their colons removed if not precluding the need for colon removal at all.

9. Early detection of polyps to help nonfamilial cases (16:23)

Now, risk assessment can only be done in familial cases because then we're looking for changes in the blood with blood tests that are present in every cell in the body. Only those heritable mutations are the subject of risk assessment. Most cancers.. are not heritable not familial. What can we do for those patients? What we can do is try to detect their tumors early and the best way to do that now for colon tumors is through colonoscopy.

10. Video: *Today* host Katie Couric's colonoscopy (16:57)

And this video shows Katie Couric who's the host of the *Today* show and her colonoscopy at least, part of it. Hi, everybody. Here we are in my kitchen. It's about 18 hours-plus before I get my first colonoscopy and here's my cherry-flavored Nulytely. Looking forward to drinking this in the next several hours. Bottoms up, so to speak. The next morning, it was business as usual except my stomach was empty and my colon was ready. After the show I went directly to Columbia Presbyterian Hospital for my date with Dr. Ford. I heard you're a little light on the sedation. I'd like to request plenty o' sedation. No, I give you what you need. OK, good. I'm a little nervous. Is that normal? Normal. I have a pretty little colon. So Katie has a pretty little colon and also a normal colon. She's a wonderful lady whose husband actually died from colon cancer in his forties and she's been a great champion of colon cancer research.

11. Video: Polypectomy (18:16)

If she had had a polyp it could be removed through the colonoscope like this. The colonoscope is a fiber optic tube that's inserted through the anus and kind of snaked up through the colon the large intestine allowing the physician to view the inside of a colon. And if they see a polyp, like that this is how they remove it. Can you show the video? There's a little snare coming from the end of the colonoscope. It kind of catches the polyp like a little scissors snips it off, and then takes it out. And this procedure works.

12. Need for developing noninvasive techniques to detect cancer (18:55)

The colonoscopy works but most Americans don't get it. In part, they don't get it because it's uncomfortable. It's a bit painful and that has established a need for non-invasive techniques techniques where you don't have to insert things into people and where there's no dangers associated with the procedure. And we and others are trying to develop non-invasive techniques based on the knowledge of the genes that actually cause colon cancer. Colon cancer takes thirty to forty years to develop and that gives us a large window of opportunity to intervene in the process to try and uncover or identify mutations in patients who have cancers. Now, let me show you this slide this movie which I hope will be informative. *Early in the season dung is collected strictly for food. Later, when the hunger is satisfied these males gather even larger balls as gifts for females. It's the perfect engagement present. She rides on top while he searches for a patch of soft ground.* So I would not advise Daniel to give that gift to Christa for their engagement. What does this have to do with cancer research? Well, people think stool is not very valuable but some people think it's very valuable. Some insects do, like dung beetles but also people weird scientists like me, I guess and the members of my lab. Here's members of my lab. You might think we're weird but I think we're just well-dressed.

13. Using stool samples to detect mutations (20:56)

But at any rate the reason we think stool is valuable is because we can find mutations in it in patients who have colon cancer. These cells, cancer cells, are secreted into the stool and we can simply examine the stool looking for mutations in genes which we know cause the disease and this slide illustrates a typical example of that. Everybody see the mutation? Right? What is it? Just yell it out. Right, two bases missing a deletion which is a kind of mutation that will change the reading frame of a protein and cause it to be abnormal. And we can currently detect about 80% of cancers simply by doing a stool test which is obviously not a dangerous procedure and hopefully we'll get more people to undergo screening. So, in summary the knowledge about the genes that cause colon cancer have already led to advances in patient management particularly in risk assessment but hopefully in the future through early detection using the technique that I just showed you. Prevention is always the best way to go for managing diseases. We've learned that throughout history and I hope in the future this will become more and more of a reality. Now it's time to break for questions.

14. Q&A: How do you determine what drugs to give FAP mice? (22:25)

How do you determine what drug to give the like, the mice with like you said, the polyp, or whatever it's called? How do you determine what drug to give them to make them better? How do we determine what drugs to give them? The one drug was discovered serendipitously by a surgeon many years ago. He was treating a patient with polyposis with Sulindac a drug like Sulindac because the patient had tennis elbow. That's what it's used for. And noticed that when he performed a colonoscopy on that patient about six months later all of the polyps had disappeared. And he wrote a paper about this in the scientific literature and nobody believed him because it just seemed so extraordinary. It seemed like a mistake. When we see a dramatic result like that in the lab we think maybe you mixed up samples. Maybe people thought he'd mixed up colons or something. I don't know. I also wanted Wait a minute. I'm not finished. So anyway, that's how that drug started. The other one was developed as an inhibitor of a growth factor. It was developed through a knowledge-based approach.

15. Q&A: How do you explain the effects of Sulindac and EKI (23:53)

Other questions? I'm Jamie Worlich from St. Alban's School. How do you explain the effects of Sulindac and EKI and more importantly can we harness these effects in maybe a more effective way? Sulindac works through is an inhibitor of an enzyme called cyclooxygenase which is known to produce certain small chemicals that stimulate the growth of cancer cells. That's the best guess for how it works. EKI is an inhibitor of a kinase we'll talk about kinase inhibitors later a receptor kinase that's important for the growth of cancer cells. And lots of people throughout the world are working on doing just what you said improving these drugs making them work better and more specifically.

16. Q&A: Do different cancers develop in different age groups? (24:42)

Yes. In the back. I remember my name is Sandra Katz from Winston Churchill High School. I remember the beginning of this presentation began with a little girl and my question is relating to the age of onset of cancers. Are we fighting different cancers depending on what age a person is getting them or is this more of a reflection of the different, varying immune systems from one person to another? In general, it has nothing to do with the immune system. Cancers most cancers appear in people who are middle-aged or older and the reason for that is because it takes many years to accumulate all of the mutations that are required to get to a cancer. Mutations are not common events and even cancer cells have lots of repair systems which are still active to guard them against these mutations. So that's why, in general cancer is a disease of older age. However, some cancers, particularly leukemias don't require as many mutations as tumors like colon cancers. They may require only one or two mutations and those are the kind that develop in childhood. So conceptually they're the same but the numbers of mutations that are required are

different.

17. Q&A: What are the body's defenses against cancer? (25:53)

My name is Alexander. I'm from Good Council High School. Where are the body's defenses against cancer? Are there any mechanisms the body uses other cells in the body to fight against cancer? Yes. In fact, the suppressor genes, the brakes are one sort of protective mechanism. Remember, there are two brakes in every cell two genes, one from the mother and one from the father so it's a redundant system, just like on the space shuttle. You want to build in redundancy. Both those brakes have to be altered for any suppressor gene. The repair systems are a kind of safeguard to protect against mutations carcinogen-induced mutations as well as naturally occurring mutations. And the fact that you need five or six mutations to get to a metastatic cancer is an excellent protective mechanism. It means it's only going to happen rarely to get that many mutations. So cells are pretty well protected. Remember, even patients who get cancer there are thirteen billion cells at risk but only one cancer forms from one cell.

18. Q&A: Do different populations have resistance to cancer? (27:01)

Have scientists witnessed any populations that seem to have developed any resistance to various forms of cancer? There are definitely geographic differences in incidences of cancer but largely, they're thought to be environmentally determined. For example, Japanese historically have had a low incidence of colon cancer compared to Americans but over the past twenty or thirty years their incidence of colon cancers have gradually gone up. People think that's due to Westernization of their diet perhaps because there are so many more McDonald's in Japan now than there were thirty years ago. Similarly, we're getting more gastric cancers stomach cancers than we used to even though that was high in Japan to start with. Maybe that's due to sushi. So, don't geographic differences but perhaps due to environmental causes not so much differences in genes.

19. Q&A: Can cancers be detected before they are metastatic? (28:08)

I'm Anne Carr from Holinars High School and it has been said that cancer cells will secrete certain toxins throughout the body. Is early detection ever dependent on the discovery of these toxins or mainly just the cancer cells that are found throughout the bloodstream and stool samples? Canwell, I think your question was can cancers be detected before they're metastatic? Is that basically the question? Yes. In fact, it really wouldn't do too much good to be able to detect a cancer that was metastatic because by then it's too late. All of the cancers that I showed you that were detected by analysis of the stool they were all curable cancers early stages prior to metastases. And the reason they could be detected because those cells are shed into the stool those DNA molecules are also shed into the blood and we can detect some just by a blood test. Soand that's true in general, not just colon cancers.

20. Q&A: What parts of the body tend to develop metastatic cancers? (29:08)

All the way in the back. I had two questions. And I'm Sheila Agigapal from Montgomery Blair High School. I was wondering, first off, what places in the body are more likely to develop metastatic cancers? Yes. I think the first question is all we'll have time for and that's a good question. The most likely places are liver because all the cancers that occur in the gastrointestinal system their bloodstream is connected to the liver through the portal circulation. So the liver is the common site for stomach cancer colon cancer, pancreatic cancer gastrointestinal. Other forms of cancer say, breast cancers and bladder cancers often metastasize to the lung predominantly because their blood supply and the tumor cells that invade blood vessels go first to the lung and are trapped there. So they're the two major sites, but no organ is spared. People who have cancer often die from brain metastases or bone metastases so it really can go anywhere and once that happens, they are generally incurable. That is why people are trying to develop systemic

therapies that can be injected intravenously rather to help produce better results than are achievable by surgery. And that's a perfect place to begin our last session which is on treatment.

21. Current treatments for cancer and direction for future (30:41)

How do we use this information to develop new treatments? Certainly one of the most difficult issues in current cancer research. The conventional forms of treatment include surgery. That's the mainstay and that's great when the cancers are confined locallythat is when they're malignant but they're not metastatic. It works. Patients are cured. Unfortunately, by the time cancers are detected often the tumor has metastasized and can't be removed by surgery so then patients are irradiated with x-rays or high-energy electrons. That works to a certain extent but generally doesn't cure patients. It just shrinks the tumors and allows them to live for a longer time. And the same with chemotherapy. These are chemicals that are used. The problem with conventional chemotherapeutic agents is that they're not really specific for the tumor cells. The first chemotherapeutic agents were, in fact agents used for chemical warfare in the first world war. They were only then later modified to be used for cancer treatments. They kill all cells, including cancer cells. They kill cancer cells a little bit better than normal cells for reasons which aren't really known. But because they kill normal cells, too they cause lots of side effects. That's why anyone treated with these drugs that you know probably they've lost their hair they're nauseous, they feel terrible. They're very toxic. So one challenge for the future is how to develop agents which are less toxic and more specific and for that we resort to our knowledge of what's wrong with a cancer cell. And really, there are only three basic things that are wrong. One is, there are altered chromosomes two is, there are altered DNA sequences and three is, there is an altered blood supply.

22. Cancer cells have altered chromosomes (32:41)

Now, altered chromosomes are virtually ubiquitously present in cancers. Here's a normal karyotype. Each chromosome is colored differently through a technique called chromosome painting and you can see each member of each pair looks the same. It's a perfectly normal karyotype. But in cancers the karyotype often look like thiswildly abnormal. For instance, chromosome 4 You can see there are three copies instead of two and only one of those three copies looks normal. In chromosomes 2 and 11 there is one normal copy and one abnormal copy and here what's happened is one end of chromosome 2 has fused with one end of chromosome 11 containing a fusion chromosome. And virtually every chromosome even the sex chromosome is abnormal in these cases.

23. Chromosome translocation generates Philadelphia chromosome (33:35)

This leads to an abnormal DNA sequence these chromosome translocations and this slide of the Philadelphia Chromosome which I showed you before illustrates one such example. Here, part of chromosome 9 has been translocated to part of chromosome 22. The bottom segments of those two chromosomes have been switched leading to two new abnormal chromosomes a translocated chromosome 9 and a small chromosome called the Philadelphia Chromosome. Now, this chromosome was first seen by investigators in Philadelphia. That's why it's named the Philadelphia Chromosome. Many years later it was identified at the molecular level. Remember chromosomes consist of DNA so when you have a translocated chromosome it means you've translocated DNA sequences. And in this case half of the chromosome 9 sequence encoded a gene called *abl* a-b-l which is an oncogene and the chromosome 22 sequence encoded a different protein called bcr. and the result of this translocation is a fusion gene half made of *bcr* half made of *abl*. The important thing about this particular chromosome is that it has led to a new form of therapy which is shown in the following animation.

24. Animation: Gleevec inhibiting the activity of BCR-ABL protein (35:04)

Normally The BCR-ABL protein that fusion protein functions in a cancer cell to phosphorylate a substrate or target protein and the way it does that is it takes a phosphate group from ATP which binds to it and transfers that phosphate group to its target substrate protein. The target substrate protein then changes its shape and goes on to stimulate cell growth of the leukemia cells. This abnormal chromosome Philadelphia Chromosome is found in leukemia cells a particular form of leukemia called CML. Now, Gleevec a drug which many of you may have heard of, mimics ATP. It binds to the site within the BCR-ABL that's normally bound by ATP and it prevents ATP from binding. It thereby prevents phosphorylation of the substrate target protein and prevents cell growth.

25. Treating leukemia patients with Gleevec (36:09)

If you look in the blood of a patient with leukemia you'll see cancer cells filling it up as I showed you in the first lecture in this case, with chronic myelogenous leukemia. It's just one of the many forms of leukemia. Fortunately, this disease can now be treated. On the "x" axis, we've plotted days of treatment with Gleevec; on the "y" axis the white blood cell count in the blood. Normally it should be less than 10,000 cells per microliter or ten million cells per cubic centimeter. In leukemia patients it's often 30,000-80,000 cells. Treatment with Gleevec results in a rapid decrease of cells for the normal range and produces remissions of the disease for at least a year. So this is the first example of a specific chemical inhibitor a new drug based on a very specific understanding of what's wrong with a cancer cell.

26. Animation: Using a virus to kill cancer cells with defective p53 (37:16)

Let me show you another good idea based on another cancer gene, *p53*. This is a tumor suppressor gene unlike *abl* which is an oncogene. And this movie shows a strategy which uses viruses that target cancer cells. The virus is derived from a typical cold virus called an adenovirus. It infects or begins to infect all cells. If the virus infects a normal cell the DNA from the virus will get out of it and go to the nucleus. But then this cell has an antidote *p53*, in fact, the tumor suppressor gene which then prevents that viral DNA from replicating and the cell lives. On the other hand if the same virus infects a cancer cell the DNA will get out from the virus, travel to the nucleus and there's no p53 around because the p53 is mutant; it's defective. Therefore, the viral DNA will continue to multiply will eventually burst the cell release lots of viruses into the environment. They will infect both normal and cancer cells but the normal cells are kind of immune to the virus whereas the cancer cells will continue to be killed by it because they have no p53. So, this is a very clever way to exploit a defect in a tumor suppressor gene. It works reasonably well in animals and it's now being tested in humans.

27. Animations: Cancer cells recruit blood vessels to grow (38:51)

Let's talk about the third major defect, which is blood vessels. Blood vessels are different in tumor cells. This video, which you've seen before shows how when even a benign tumor arises it needs to recruit blood vessels. If it doesn't recruit blood vessels it can't get the oxygen and the nutrients that it needs to grow to a clinically significant size. It can't even grow more than 1/10 of an inch or so. And blood vessels are needed throughout the process.

28. Animations: VEGF released by tumors recruits blood vessels (39:34)

The way that the tumors recruit blood vessels is through secreting a hormone called VEGF as you'll see in this video. It's a hormone V-E-G-F stands for Vascular Endothelial Growth Factor. It's a fancy name for a kind of growth hormone that is a growth factor for blood vessel cells. Blood vessel cells have receptors for this growth factor on them and when that happens going back when that happens, the blood vessels are stimulated to grow.

29. Using antiangiogenesis drugs to treat cancer (40:19)

Now, investigators have recently developed an inhibitor of this growth factor. This inhibitor can turn a bloody tumor most tumors are bloody to start with because they have recruited lots of blood vessels into a non-bloody tumor, shown here. It's white because there are no or there are fewer blood vessels in it. The question asked me before about Judah Folkman's work that's this kind of therapy. It inhibits the process of blood vessel recruitment and growth. And again, it works well in animals and the first clinical trial of this form of therapy was just released last month and it is showing some good effects in patients with colon cancer so this looks to be perhaps a real gain in therapy.

30. Using engineered anaerobic bacteria to treat cancer (41:11)

And the last treatment scenario I'll show you is also based on abnormal blood vessels in tumors but it's based on the fact that even though there are lots of blood vessels tumors grow so fast sometimes they outpace the blood vessels. And as a result tumors are not only composed of the tumor cells themselves which are shown here the cancer cells but cancers also have.. these supporting cells which contain the blood vessels which can't always keep up and often lead to dead cells which don't have enough oxygen and nutrients to grow and often die. The only place in the body that has no oxygen is in these areas of dead cells within the middle of tumors that have outgrown their blood supply. That environment hostile environment does not exist in any normal tissue and this observation has stimulated investigators like us to try to develop new methods that target that defect. And in particular, one that we're working with now is a strain of anaerobic bacteria. These bacteria are found ubiquitously in the environment. If you look at dirt outside you'll find lots of these bacteria. They can only grow when there's no oxygen. If you expose them to oxygen even for a few seconds, they die. And we've engineered one such strain of bacteria called *C. novyi-NT*, for "non-toxic..." because we've removed one of its major toxin genes and made spores out of it. All of you are familiar with spores. Bacteria often make spores which allow them to live for even millions of years. You've heard of it in connection with the anthrax outbreak but this is a medical use of a different bacteria. If we make spores and inject them into a mouse then the spores germinate only within the tumors because they can only germinate where there's no oxygen and they become this hairy beast. And, in fact, when they germinate within the tumor they actually eat the tumor. They use it to provide nutrients. This series of slides shows what happens when you treat a mouse with a tumor with these bacteria. This is a nude mouse. It has no hair that's why it's called nude but more importantly, it has no immunity so you can put human tumor cells into it. If you put human tumor cells into a regular mouse it will reject them as foreign. At any rate 6 hours after injection of the bacteria a little black spot can be seen on the tumor which gradually expands and, within a day or two occupies the whole tumor mass. Over the next few days to weeks the tumor rots out because the bacteria have completely essentially, eaten it. And then the tumor falls off and many of the mice are cured. Now, this works well in mice. Again, it's another thing about whether it will work in patients but hopefully clinical trials in the next couple of years will show results that are similar to what has been achieved in animals and it represents another way to exploit the defects in cancer. So there are lots of ways which we can think of to use the information gained from the cancer revolution to help people with cancer to prevent them from getting cancer or to treat cancers once they arise. Will it be easy? Well, look at this movie. I can't imagine doing any of the things in that movie at my age, anyway but if you guys can do that stuff you guys can cure cancer, but you just have to try. Thank you.

31. Q&A: Do bacterial and viral therapies have side effects? (46:08)

So, we have some time for some final questions. The cancer or the viral and bacterial therapy that you mentioned could that potentially have any harmful side effects like causing the virus or the bacteria to develop mutations which might make it harmful to the person it's being used on? I think it's fair to say that any therapy for a serious disease like cancer is going to have side effects. There's no drug known to

humans that doesn't have some sort of side effects. What they are can only be told once people are treated but it would be unrealistic to expect that they won't have side effects. Hopefully, the therapeutic effects will be greater than the side effects but that can't be told until clinical trials are done.

32. Q&A: Can you poison cancer cells with excess oxygen? (45:57)

My name is Christina Hawkins. I'm from Northwestern. And I was wondering since these tumor cells undergo angiogenesis to get more oxygen is it a way to give them more oxygen to poison them? Because if our normal cells get too much oxygen they die from poisoning and since the tumor cells want more oxygen is there a way to give them an elevated level of it to the point where they die, but not our normal cells? It's an interesting idea but the problem, the challenge with that kind of idea is how to deliver something specifically to tumors. That's really one of the major challenges for gene therapy for example, as well as other forms of therapy is how you get whatever agent you're using just to go to the tumors and kill only the tumor cells. Now, the bacteria that I showed you only will germinate in tumor cells so they're tumor-specific. The virus that I showed you only will replicate in tumor cells without p53 so that's specific. In order to implement your idea you'd have to figure out a way to get oxygen just to tumor cells. If you can do that, it would be a great thing but I don't know how. Maybe you'll be able to think of a way.

33. Q&A: Which treatment do you prefer? (48:13)

Over there. I'm Calvert Coley from Episcopal High School. Considering side effects and extended lifetime which treatment do you prefer? Which treatment do I I prefer not to have cancer. If I do have to have cancer, I prefer detecting it early so that all I'll need to have is surgery. But I'm not sure that's what you mean. Do you mean which of the experimental therapies? The experimental therapies really are just that they're experimental. At this point, no one would prefer any of them because you don't know whether they're really going to work in humans. That therapies work to a certain degree in mice are encouraging, but we'll have to wait until they're really tested in humans to decide whether any human patients deserve to get them on a routine basis.

34. Q&A: How do you make the new therapies available to everyone? (49:09)

Jay Levin from Colonel Zadok Magruder High School. It sounds like you guys are so close to treating cancer and to detecting it early to possibly prevent it but how would you go and make all these treatments available to the mass public when so many Americans don't have insurance which may or may not even cover this all these revolutionary procedures? So I guess, how would you make it available to the public? That way, you could go and possibly eradicate cancer in our lifetime. Yes, your question is very good and I'll give you a T-shirt. And others who have asked questions who I haven't thrown T-shirts to can come up afterwards. That's obviously a big problem for society and it's not only with new cancer treatments it's treatments for all diseases and how to make sure people who don't have the means can get them. And those of you who don't go into science but I hope some of you will try to answer that question. That may even be a harder one than curing cancer.

35. Q&A: How does hormone therapy to treat cancer work? (50:15)

I'm Miriam Bravi from High School of Technology, Edison and my question was, how can we use hormone therapy to help us treat cancer? I have heard of cases that it actually stimulates the growth of the cancer. How is that? Question about hormone therapy. Interestingly, hormone therapies are one of the best forms of therapy and the oldest. For breast cancers, the standard form of therapy is with antiestrogens because cancers don't lose all their normal controlling mechanisms. They lose enough so that they can grow abnormally and invade but they still have some remnant. You can look at them under the microscope and still tell that they're from breast, for example. And they still are inhibited by antiestrogens

because breast cells normally require estrogenic hormones female hormones to grow so that's a standard treatment for breast cancers. For prostate cancers, it's antiandrogens are used. Most of those treatments don't actually stimulate cell growth when they don't work. It's just some cancers most cancers, in fact eventually become immune to them. So it doesn't help but they often can put people in remission for years and are part of conventional therapy for cancers now.

36. Q&A: How do anaerobic bacteria survive after eating dead tissue? (51:30)

I'm Rachel Brown from Northwest High School and I was wondering you said that the tumors that have outgrown the blood vessels are the ones that form a dead section inside of the tumor so when you insert the *C. novyi* and it eats away at the dead part wouldn't it die as soon as it touches the live part of the tumor and therefore not eliminate the entire tumor? Yes. That's a very insightful question. You definitely should get a T-shirt. And, in fact, the bacteria, once they eat up the dead part come to the live part, and importantly and delightfully, I guess around even the live part there's a small area of hypoxia where the cells are metabolizing so rapidly that it's anoxic and the bacteria can grow. So that's one way the bacteria kill the rim. Another way is, in some forms of this therapy we combine it with conventional drugs that kill, actually the outside live tumors better than the inside so the combination actually generally works better than either agent alone. It's a very good question.

37. Q&A: Isn’t an adenovirus treatment limited by immunity (52:45)

I'm Nirisha Dawn from Northwest High School and you mentioned adenoviruses with tumor cells. I'm familiar with the fact that adenoviruses can be used via genetic engineering to exploit some weaknesses and cure diseases. However, once an adenovirus is used, isn't it possible I mean, it's a fact that that can't be used again; that you should incorporate as many possible cures into one adenovirus as possible because an immunity is developed after that? Yes. One of the problems with adenoviruses is that immunity will develop, if it isn't already there so patients can only be treated once. In general, there's a wider answer to your question which is, most investigators feel that no single therapy will ever work to eradicate a metastatic cancer and that the best hope for actually treating cancers will be to combine things combine anti-angiogenesis with agents that target anaerobic parts of bacteria with conventional agents with new agents. Many of you are probably aware of the successes for treating AIDS and those successes, in general have come from treating AIDS with multiple different agents, not single agents. Single agents don't work so well and it's the same for cancer. The more ways you attack it at once the more likely you'll be able to handle it.

38. Q&A: Shouldn’t stool or blood testing for cancer be made routine? (54:10)

The gentleman with the green light. You were saying how, with a stool sample we can identify most forms of cancer that we might have. No, only colon cancer. Only colon cancer? I thought you said all. Other investigators have looked at the blood to find evidence of those mutations because the cancers not only leak DNA out into the stool but they also leak DNA into the bloodstream so investigators have been able to detect, say kidney cancers, stomach cancers, some colon cancers by looking at the blood as well. Then why wouldn't we have it as a normal physical? Like, you go to the doctor to get a physical. Would they look at your blood and tell you you're going to have cancer or not? Well, that's my hope. I mean, my hope, you know, in twenty years remember, in *Star Trek*, they have that little gizmo where you scan up and down on people and you tell exactly what disease they have? That's the idea with a drop of blood that you can tell what disease people have simply by looking at what mutations there are. But it's going to require a lot of technical development to do that. It's not simple.

39. Q&A: How do you treat people with multiple cancers? (55:21)

Either anybody. Good morning. I'm Deirdre Degeneres and I'm from Bishop McNamara High School and I was wondering, if multiple cancers develop in one person how do they go about treating that? Do the drugs have a good effect for one type of cancer but have a bad effect on another type? What are you going to do in those types of situations? Multiple cancers generally don't develop in people. Because people are so well protected against cancers most people only develop one cancer at once. The only people who develop multiple cancer are those who have a hereditary mutation and are predisposed, like with polyposis they develop thousands of tumors. And there, the only way to treat it, really is to remove their whole colon. Last question. Thank you very one more, or that was it? Thank you very much for your attention.

40. Closing remarks by HHMI Vice President Dr. Peter Bruns (56:18)

Thank you, Bert, for two really exciting lectures. They were really wonderful. And unfortunately, there were lots more questions. There were so many good questions and we know we can't answer all of them here now and certainly the people who are watching this on the Web can't ask their questions here and those people who are going to be watching DVDs in the future can't ask questions here but we have an answer. We have a prescription, which is on that other web site that we have www.BioInteractive.org we have a feature called "Ask a Scientist..." and this is useful to know for other parts of science, as well. We have a group of volunteer scientists who will custom-answer your questions. So go to the web site and there's a way you can e-mail us your questions if you have them and we will answer. So, we hope you join us tomorrow for more stimulating lectures that join basic science with medicine. Tomorrow, Dr. Huda Zoghbi will take us on a journey from the clinic to the lab and back to the clinic to deal with disorders of the nervous system. So, thanks for coming.