

that I know a great deal about and have worked on in my lab for the last 17 years. It's a very important and very devastating disease. And we're going to try to give you an introduction to it. And you'll see that many of the approved by the Food and Drug Administration for the treatment of cancer today that are directed and in this more effective class is not great, but there are some. And that number will increase. So I think there's reason for optimism utilizing the information, next three lectures. So cancer, I think in some respects, needs no introduction. It's a disease that probably has less serious forms of skin cancer, basal cell carcinoma and squamous die in this country from cancer. That's more than 1,500 people per day. So in two days more people die of cancer than died in the World Trade Center disaster. It's a devastating disease. A major burden. Clearly something we need to do something about. So I'm going to show you some slides that introduce you to the disease. Cancer, as you know, is a generic term that covers a class of diseases that affect many, actually, almost all of your organs. You can get cancers in different places. They're all defined by one common property which is too many cells. Too many cells in a tissue causing a lump. Too many cells in the blood. Too many cells in lymph organs. So that's the common theme that relates to all cancers, but there are very important differences in cancers in different sites. This is a radiographic image of lung cancer. And this individual, you can see, has an opacity right here, a fairly large opacity that's probably about the size of your fist in this lobe of the lung. And that's fairly advanced lung cancer. This is a more precise diagnostic test called computed tomography, which is essentially a series of x-ray slices that get reconstructed. It gives better resolution. And you can see, again, a very large mass in the lung of this individual. Leukemia is also too many cells but here it's in the blood. This is a normal blood smear. These pale cells without nuclei are your red blood cells. These nucleated cells are white blood cells of different types. And you can see in this abnormal blood smear of a leukemia patient there is a vast increase in the number of white blood cells. So this is a diagnostic feature of leukemia, too many cells. And it's diagnosed by looking at blood counts. And the blood counts in leukemia patients of white cell counts can be elevated by thousands, if not hundreds of thousands of fold. You can also use other imaging techniques to detect and diagnose cancer. This is endoscopic examination, colonoscopy. they reach age 50 to detect tumors at an early stage so that they can be removed surgically which is, in fact, the most effective treatment for colon cancer. And, actually, for almost all cancers. The most effective treatment for cancer is the removal of the tumor. If you can get to the tumor at an early stage through some of these imaging techniques and eradicate it, remove it, you can greatly limit the mortality associated with the disease. So this is endoscopy. This is what a normal colon looks like, sort of a smooth structure. This is an early stage colon tumor. It's called a polyp at this stage. And I'll give you a little bit more nomenclature in a minute. This is actually not cancer. A polyp is not cancer. It's a benign tumor. This may or may not progress to a cancer, but if the doctor were to find a polyp like that they might follow it for one or two years. But if were to get bigger they would remove it. And they can actually do it endoscopically. to do surgery to remove polyps anymore. At some frequency these polyps do progress to colon cancer. And this is a true cancer, a carcinoma which has changed its shape and importantly changed its relationship to the tissue. Whereas, the polyp is sort of sitting up on top of the tissue, having grown out of the tissue, the colon cancer has invaded into the tissue. It has become much more destructive in that sense. And also, importantly, has the capacity to move outside of the colon through that process of invasion to other parts of the body, and thereby cause problems elsewhere. Usually, when these are diagnosed by endoscopy or other methods, they are removed. This is done by surgery where a portion of the colon is actually removed and then the two resected ends joined. One is that the cells have regular shape and a regular relationship to their neighbors. As you know, tissues are formed for normal function. They have particular genes expressed. They have particular structures inside them. They interact with their neighbors in order to perform their function. So the cells of the colonic epithelium line up like this touching each other, interacting with each other and interacting with the cells underneath them, as well as other material underneath them. otherwise known as the extracellular matrix. And this helps support the cells and provides the cells with certain nutrients and growth factors. There are also cells below these cells in the colon and in other tissues which replenish these cells when they get lost. These stem or progenitor cells exist probably in all adult tissues. They get recruited when cells turnover. slides, but we now think that these cells are probably very important in tumor initiation. We think that these are cells, these stem cells of the tissue are likely to be the place where the tumors initiate and then produce cells, like this brown cell here, which is already abnormal. Cells that have acquired a mutation which makes them different from their neighbors. Now, the first consequence of those early changes is that you get too many cells. And this is a process known as hyperplasia. adenoma. It's called other things in other places but let's say, just for the sake of simplicity, it's a benign tumor. And, again, this is an increase in the number of cells but the cells themselves don't look very different from their normal neighbors. And these tumors are not life-threatening yet. They sometimes will never be life-threatening but in this form they rarely cause problems. They're just a lump. Like a wart is a benign tumor, a lump that doesn't cause problems. And now, as you can see from this different shading, the cells take on different characteristics. And so they've become fundamentally changed in their appearance. Moreover, they have begun to recruit a blood supply. even if it's present in the tissue, the initial tissue alone, it would be recommended for removal. However, it rarely stays there. Tumors have the capacity to move from their original site through a process of invasion and then metastasis. This illustrates invasion, local invasion where the tumor cells are moving from the mass through the basement membrane and ultimately accessing the blood supply. Literally moving into blood vessels, the death of the cancer patient. It's the metastatic spread of the disease as opposed to the primary tumor that tends to kill cancer patients. And sadly it's this phase of the disease, metastatic spread that we know the littlest about. We actually know rather little about what allows cells to move from their primary site through the blood, establish themselves elsewhere and then grow there. And since it is the most deadly molecular biology, genetics and development, how things normally work, how cells normally function, how tissues are formed. how organisms are formed and function. And hopefully you've had an ample So up until

this point in the class you've learned basics about cell phase of the disease, it represents a clear need, clear opportunity to learn more. So let me just illustrate, or rather emphasize some of these bits of terminology for you. You have hyperplastic lesions, we call them, throughout your body. Most of them no problem at all. They're not going to do anything. It's just there are too few many cells in that particular place. These can progress to benign tumors which are non-aggressive. that much. They're not moving around. They have normal relationships with their neighbors. And with respect to the tissue that they reside in, they're nondestructive. They haven't breached the underlying basement membrane. They haven't changed their relationship with their normal neighbors. And they're also defined through a lack of spread. They haven't moved out into the local lymph nodes or to surrounding tissues. We actually only use the term cancer to refer to malignant tumors, not to benign tumors. These are true cancers. And these are proliferative capacity. They move around to a greater degree. They are destructive with respect to the tissue in which they reside. And they have the potential to spread. Not all diagnosed cancers have already spread, but the view of the pathologist is that they have the potential to spread and therefore they are typically removed. Now cancers in different places have different names. As I said, you can get cancer in virtually all tissues of your body. defined, and those are defined in part based on where they are and in what types of cells they occur. So there are tumors of epithelial cells, cells of the skin, lining of the intestine, mammary epithelial cells, epithelial cells of your brain. called carcinomas. And you might have heard, for example, a subset of carcinomas called adenocarcinomas. Adenocarcinoma is what I showed you with respect to the colon cancers. Adenocarcinoma of the breast. Adenocarcinoma of the lung. These are carcinomas that have a glandular appearance. And there are other kinds of carcinomas as well. And you've probably heard of myosarcomas. Those are tumors of the muscle. And there are different types of myosarcomas. And then there are tumors of the blood system. tumors are present, tumor cells are present within the blood itself. And I showed you an example of that. Or lymphomas. And here it's defined as tumors which stay within lymph organs like lymph nodes or spleen or thymus. They haven't made their way out into the blood, but they are still tumors of the blood cells. visual inspection. We also know what they look like based on histological analysis. This is a progression series actually taken from a mouse model of cancer generated in my lab. appearance of the lung here. And this circle you can see hyperplasia, too many cells. Cells, if you were to see them up close, look pretty much like their neighbors, but there are just too this case. These are benign tumors. They don't have the features of the more aggressive malignant cells. And you can see them here. They all look pretty much the same. And if you saw them next to a normal cell they would look pretty much like those. more advanced tumors. These are true cancers. And you can tell that based on the fact that the nuclei, if you compare one cell to another, looks very different, and the cell shape looks very different from one to the other. So there's heterogeneity. And what you cannot see here is that the tumors are also much more proliferative. They are dividing. The cells are dividing much more frequently. So, again, histologically we can characterize what these tumors look like. the class is that we understand, at least to a degree, what these arrows represent, what happens to a normal cell on the way to hyperplasia or to an adenoma or to an adenocarcinoma. these transitions, allow a normal cell to develop into a cancer cell. And so in that sense we consider cancer as a genetic disease. Now, cancer actually is also a more traditional genetic disease in some instances. There are people who are genetically predisposed to developing cancer. And I'm actually going to tell you about them next time. the development of cancer in them is a genetic disease. How do we know that? Why do we think that? Well, we think that for a number of reasons. And one of them, which we've appreciated for more than a hundred years is that the chromosomes of cancer cells are screwed up. They look different than normal cells. I've actually shown you this slide before. This is a karyotype of a normal cell, 46 chromosomes, 23 pairs. These are highlighted by stains that allow us to distinguish one chromosome from another. So chromosome one stains yellow, chromosome two stains red, and so on and so forth. And this is the karyotype of a cancer cell. It's different in many ways. Name me two. I heard there was mumbling but I didn't hear anybody. Say again. many chromosomes. I didn't count them up, but there is more than double the proper number of chromosomes in this cancer cell. So chromosome number defects are quite common in cancer cells. But also structure, and I've boxed two of them here, the structure of chromosomes in cancer cells are different. This chromosome has undergone what we call a translocation in which a piece of one chromosome has been joined to a piece of a different chromosome. And we now know that when that happens it's reflective of a mutation that either is inactivating or activating a gene that's present at the point of translocation. And this chromosome has undergone a truncation, a deletion. Genetic material has been loss. And this, again, indicates that there was a gene present there that the tumor cell wanted to get rid of in the development of the cancer. So chromosomal abnormalities are quite common, which was a first clue that cancer is a genetic disease. which came along as early as the 1920s, is that many carcinogens, of an agent of interest. mice or rats. And one takes the animal and exposes it to agent X. It might be injected into the animal or it might be painted on the skin of the animal. And then one waits a period of time and asks the question did the animal develop a tumor? bacteria. So one takes a bacterial strain and asks whether the agent can cause mutations in that strain. And usually to do this one takes a bacterial strain that already has a mutation, a bacteria that is histidine deficient, which means that it's not able to synthesize its own histidine and amino acid. Petri dish that lacks histidine, you haven't added histidine to the media, will it grow? No. It's histidine minus, it cannot make its own, if you don't provide it, cells cannot grow, so you get no colonies. However, if I now add agent X, get is an indication of the strength of the mutagen. Lots of colonies, strong mutagen. Fewer, not so strong. And what I'm saying is that there's a strong correlation between things that pass this assay and things that pass that assay, another indication that cancer might be caused by mutations to DNA. Now some things that we know for sure are carcinogens. They pass this carcinogenicity test very, very strongly. They clearly are cancer-causing. But if you mix them with bacteria in isolation here you don't get any increased mutation frequency. What's different? What's different about this situation versus this situation? Yes? their native form are not mutagenic. We call them promutagens. However, when acted on by the body in the process of metabolism they become mutagens. The body senses that these are actually dangerous compounds and will try

to detoxify them, typically by adding hydroxyl groups to them to make them more water-soluble so that they can be secreted or excreted by the body. But in the process of making them more water-soluble they go through an intermediate form which turns out to be highly mutagenic. benzo(a)pyrene. This is an agent found in cigarette And what happens is that the body, in an attempt to add hydroxyl groups different ring positions of this molecule, as an intermediate towards making it more hydroxylated. And these epoxides are very And the Ames Test takes the compound, the agent that you're trying to test the mutagenicity of, and rather than adding it directly back to bacteria it's mixed first with an extract of the liver. Many of the enzymes that do this detoxification are present in your liver. Cytochrome P450 enzymes, for example. And through that modification becomes mutagenic. And then the agent gets tested in the standard bacterial mutagenicity test. disservice in thinking it's actually trying to help you. There are still other agents which are not mutagens, even in the Ames Test, but are clearly carcinogens. Asbestos, for example. That stuff in packing material that's now been banned exposure to which gives people, or can give people mesothelioma, a tumor of the lining of the lungs. It's not a mutagen. However, you test it, it's not a mutagen. Alcohol, which is clearly associated with liver cancer, is not a mutagen. These agents we think act as irritants. They cause damage to tissue which causes the cells to have to increase their proliferation to repair the tissue, and that is inherently a mutagenic process. And so these things can act as carcinogens in that very indirect way. OK. Now there are many things in impose on ourselves. But what's the biggest carcinogen that we impose on ourselves? Smoke. Tobacco smoke. cancer in this country per year? Anybody want to hazard a guess? 10, 00? 100,000? 175, 00. 175,000 people per year die of lung cancer each year. And more than 150,000 of them it's because of smoking. this country than breast cancer, colon cancer and prostate cancer combined. And it's completely preventable, or almost completely preventable through a change of habit, failure to smoke. So let me just emphasize the importance of this. among men and women and the incidence of cancer, lung cancer in this country among men and women. You can see that early on, in the early part of the century smoking was uncommon and lung cancer was uncommon. But as people began to smoke this frequency increased and then years later the incidence of lung cancer increased dramatically. It takes a little while. You've got to expose yourself to these carcinogens for a period of time for this process to have its effect, but eventually that smoking exposure leads to the development of lung cancer. You can see that women started smoking a little bit later, but they quickly caught up. And now the lung cancer incidence in women is also extremely high. Lung cancer among women is the leading cause of cancer deaths. It's now surpassed breast cancer as the leading cancer killer of women. The statistics about smoking in this country, despite these facts, are remarkable. 47 million adults smoke. Roughly one in four men, and almost as many women smoke. statistics that, but in 2002 the percent of high school students who responded to a survey about whether they smoked was what? What do you think? High school students. 28%. So this is not just people who have been smoking a long time, who started when they didn't know any better. Kids who get exposed to the message about smoking and lung cancer from an early age are not paying attention. So the problem is not going away. These folks obviously have a dramatically increased risk of dying from lung cancer. heart disease, of stroke, of emphysema. I read a startling statistic when I was preparing this. Of all the people who are alive today on this planet, 500 million of them will die early due to tobacco usage. exposure to tobacco products. So if you learn nothing else from this class this year, if you now smoke, stop. If you don't smoke, don't start. OK. So carcinogens in our environment and carcinogens that we exposure ourselves to are important. No doubt about it, they can be a cause of cancer. founding in understanding normal biology. We're going to take a turn environmental mutagens. And, as I mentioned, sunlight and other forms of radiation, certain dietary things that we expose ourselves to fall into this category. And it's very important that you know that. In fact, more of the mutations that happen in cancer are due to indigenous processes, things that happen inside your bodies regardless of what you get exposed to, like DNA replication mistakes. DNA polymerases that duplicate your DNA are pretty good, they have proofreading functions, but they still make mistakes. lead to tumor development. cell during various processes. Sometimes it gets broken, and sometimes those breaks are not properly repaired. And this can lead to some of the defects that I've shown you on this slide like the translocations where different pieces get rearranged with the wrong other piece. the class and how the cells have an intricate ability to properly segregate their chromosomes, that each daughter cell gets the right number. Sometimes that process doesn't work properly so that one cell gets too many chromosomes or one cell gets too few. These chromosomal imbalances can also contribute to tumor development. Defects in DNA repair. that will try to find damaged DNA and fix it, but these enzymes themselves can be mutationally inactivated in the development of cancer. So now you've debilitated the cell's ability to fix the damage leading to an increased frequency of damage, increased frequency of mutation, increased cancer risk. And importantly -- oxygen radicals such as superoxide -- reactive to DNA, can cause DNA breaks and base changes, and cause mutation. And your body produces these naturally in the process of metabolism. You have enzymes that will kind of keep the concentrations of these down but, nevertheless, they're present and cause damage at a certain frequency in all cells. If that damage occurs in the wrong cell at the wrong time it can be cancer-causing. So there are lots of ways that the DNA of your cells can get mutated, which then overall contributes to the development of cancer. Now, this doesn't happen all at once, development from a normal cell to a more advanced cancer cell as a clonal evolution process. A clonal evolution process whereby abnormal cells arise in a population. These now have a selected advantage compared to their normal cells and will grow, for example, better than their normal cells, divide faster than their normal cells, make more of themselves. The mutation that took place is now present in all the daughter cells of that abnormal cell. And within that now-expanded clone of abnormal cells a second mutation takes place which increases the capacity of that cell to grow and divide, survive, move around compared to its neighbors. So now this cell and of its descendents have two mutations. And within that expanded clone a third mutation can take place and so and so forth. We now think that cancers, advanced cancers in human probably have five, ten, maybe twenty distinct mutations in genes controlling important processes. What are those processes? There are many. We're going to emphasis. in this class. iust proliferation and cell death. I'll sav a bit more about that in a second. But it's also

important for you to know that the cancer cells also regulate factors that increase the blood supply. today and for the next three lectures talk about abnormalities extracellular matrix to allow the cells to move around, and other factors. Factors, for example, that allow them to move into the blood vessels or move back out of the blood vessels in the process of metastasis. So we're going to emphasis proliferation and cell death in the next lecture, but I want you to know that many other aspects of cell biology are important in this process as well. there might be changes that lead to more cell division. And, indeed, the original cancer-associated genes did this. And many of the important cancer-associated genes that we know about are involved in promoting increased cell division. positive mutations that block apoptosis, loss of function mutations in genes that are normally required for apoptosis. And we think, therefore, that the balance, if you think of this as a scale where proliferation is on one end and cell death is on the other. Whereas, this process is well balanced in normal tissues, what we call normal homeostasis, you produce as many cells as you need, you kill off as many cells as you need in order to give rise to a normal, average cell number. In cancer this process is deranged. And this can happen in one of two ways, and typically in both. There can be an increase in proliferation and a reduction in cell death. And we'll talk about some of the factors that control those specifically next time. But the final way that we know that cancer is a genetic disease is by looking in the DNA of a tumor, by looking at the genes themselves. You know about genes. You know about gene sequences. You know how to figure out what the sequence of a gene is. mutations. And this is actually the very first cancer gene found in the context of human cancer. It was found here at MIT by Bob Weinberg's lab. And when its DNA was sequenced compared to the normal sequence shown above it incurred a mutation, a mutation which blocked the ability of this protein to be properly regulated leading to increased proliferation. that lead to disease. And, whereas, I have tried to keep things light for you in my lectures and try to be entertaining if possible, the subject of the next three lectures is not a light one. It's a very serious one. And it is cancer. It is a disease things that you've learned over the course of this class, up until this point, really prepare you to understand the details of cancer, cancer development, and hopefully also cancer treatment. And I'll say right up front that I'm actually quite optimistic that the progress that we've made over the last several years in understanding the molecular basis of cancer has put us into position to treat the disease differently than we've done in the past and more effectively. The number of drugs that have been the kinds of information, the strategies that we'll cover in the affected some of you already in your lives personally. Certainly everybody knows a family member or friend who has developed the disease. It is a remarkably common disease. In this country alone -- -- more than a million people are diagnosed every year with cancer. And this does not include another million who are diagnosed with the cell carcinoma. So, in that respect, more than two million people get the diagnosis of cancer every year in this country. Moreover, each year -- -- more than half a million people Half of the men in this room and a third of the females -- -- will be diagnosed with cancer in their lifetimes. And overall more than a quarter of all deaths are attributable to cancer. A major problem. What you're looking at here is a standard chest x-ray. So that's a solid tumor imaged by radiography. This is leukemia. It's now recommended that everyone undergoes this exam every year when They can remove it using a surgical endoscope. They don't actually have And you can see the colon cancer right here. If the cancer is detected at an early enough stage, surgery is curative for colon cancer. Unfortunately, it's often too late when it's diagnosed. It looks like that. Because it's already moved outside of the colon and tumor cells have found their way to other parts of the body. So surgical removal of the primary tumor, while helpful, may actually not be curative. So I want to go through in diagrammatic form some of the points that I've just made. Cancer develops in states. It doesn't happen all at once. As I showed you in the normal colon polyp to colon cancer series, things happen in stages. It's actually best worked out in the colon. But we believe the same phenomena hold true for other cancers in other places. It doesn't happen all at once. It happens in stages. And these slides illustrate the basic principles of that. This illustrates a normal tissue. It could be anywhere, but let's say that it's in the colon. And there are certain important features to pay attention to. Here is a material called the basement membrane, And we now think, and it's not illustrated on these Hyperplasia simply means hyper, too many, plasia, division, cell division. So there are too many cells. But the cells that are present there look pretty normal. They don't histologically, by looking at the tissue, appear different from their normal neighbors. There are just too many of them. This process continues until you can actually see a discernable lump, a mass, and that is a formation of a benign tumor. In the colon that tumor, that benign tumor is called an At some frequency these tumors can progress further. They look different from their normal neighbors. Their cyto architecture, the cell shape looks different. The nucleus often looks different from the normal cells. The presence of these blood vessels which were not present up here is another indication that things have progressed. And tumors require a blood supply of their own to feed the tissue, this abnormal growing tissue. As soon as they get to a certain size they need to recruit a new blood supply. This tumor at this stage has changed enough that we now call it cancer. This is based on these histological changes, the appearance of the cells, as well as the cells' relationship to one another. And this is now considered dangerous. If you're diagnosed with a cancer, traveling through the blood, and then moving out of blood vessels and beginning to proliferate, expand in other tissues. And this is the process of metastasis. And the tumor cells can literally go anywhere. Certain tumors have preferences to go to certain tissues than others. And when they get there they begin to grow again and turn, become actually more advanced, more dangerous, cause local tissue damage, organ failure. And it's usually this that causes Hyperplasia is simply too many cells. That is the cells are relatively well-behaved. They're not dividing These can progress to malignant tumors. And these are true cancers. aggressive. The cells have changed shape. They have much greater There are probably 250 or 300 different types of cancer clinically And these tumors are called carcinomas. These cancers are Those are the cancers. And the benign tumors of these tissues, especially of the class that gives rise to adenocarcinomas are called adenomas. There are also tumors of your connective tissues like you cartilage or your muscles or your tendons. These are called sarcomas. These are called leukemias if the OK. So we know a lot about what these tumors look like based on It's a tumor of the lung. You might be able to see the lacev manv of them. These progress into lumps. masses called adenomas in But these

can progress into adenocarcinomas, What I'm going to tell you about from this point really to the end of And the answer is defects to genes. Defects to many genes underlie But even for people who are not genetically predisposed to cancer, I didn't hear anybody. The number and shape of chromosomes. Good. So clearly there are too The second indication, and what I mean by that is agents that cause cancer. Many carcinogens are mutagens, agents that cause what? Yeah? Not all. But there is a very high correlation between things that will cause cancer and things that will cause mutation in simple mutation assays. And you can do assays to determine the carcinogenicity or mutagenicity Carcinogenicity assays are done typically in experimental animals, And if so the agent is a carcinogen. And you can actually determine how strong a carcinogen is, how strong a carcinogen it is by determine the dose, the amount of the agent needed to produce a tumor. There are also mutagenicity tests. And this is typically done in That means that if you take that bacteria strain and plate it onto a which I think might be a mutagen, to these bacteria, if it is a mutagen it might mutate the defective histidine gene and turn it into a normally functioning histidine gene such that if I now plate these bacteria that have been treated with the mutagen I may get some colonies. And you're still using a his-minus plate here. And the number of colonies that I Fail in this simple mutagenicity test. Why? How can that be? Excellent. Precisely correct. There are certain agents which in And that's illustrated here for a very powerful carcinogen known as smoke, for example. This agent is not highly mutagenic on its own, but in this type of test it is highly carcinogenic. to make it more water-soluble, will actually introduce epoxides in interactive with DNA and therefore mutagenic. So the body turns something that actually wasn't mutagenic into something that is mutagenic. And therefore this test, this mutagenicity test has been modified, principally based on the work of a bacteriologist at Berkeley named Bruce Ames. And so we now call it the Ames Test. In which case the compound becomes modified, or might become modified. OK. So we can now expand our list of things that are mutagenic through exposing them to some of the body's own enzymes. In this sense, the body is actually doing you a our environment that are carcinogens -- -- that we get exposed to either passively or deliberately. Sunlight, for example, is a carcinogen and a mutagen. It causes damage to DNA, causes mutation, increases your risk of skin cancer. Other things that we do to ourselves. Certain dietary carcinogens we And obviously tobacco smoke is associated with one particular type of cancer, although it's not limited to lung cancer. Any idea how many people die of lung Lung cancer is the number one cancer killer. It kills more people in These are curves that show the smoking frequency in this country Even more amazing to me than that, in 2002, I don't have more recent And it's not just lung cancer. Smoking increases your risk of 500 million people who are alive today would live longer if not for I call these exogenous or But they're not the only thing that causes cancer. And these mistakes can be then in critical genes which can ultimately Your DNA can sometimes get broken. It gets moved around inside the Defects in chromosome segregation. We talked about mitosis early in Your cells have all sorts of enzymes -- production of indigenous mutagens in contrast to exogenous mutagens. Your body actually produces things that are mutagenic. And the biggest class of these are -- or hydrogen peroxide. And these radicals are highly as I've tried to indicate to you. It doesn't happen from normal cell to cancer cell in a single step. We think that this process happens over time. And in humans over decades of time. Cancers often initiate maybe in mid-life, but they don't present themselves as a clinically advanced tumor until late in life. and that's because the process requires lots of steps that require lots of time to accumulate. And so we now consider tumor Cancer cells turn on growth factors that recruit blood vessels. If they didn't do so they would never be able to progress. You cannot actually make a solid tumor bigger than two millimeters in diameter without recruiting a new blood supply. And so the tumor cells turn on these factors to deal with angiogenesis. They also turn on factors that allow them to move around to a greater degree or separate themselves from their neighbors to invade into the basement tissues, the basement membranes. To turn on proteases, for example, that chew up the So proliferation, it's kind of obvious that in cancers But we also know that cell death or apoptosis, which I briefly introduced you to in an earlier lecture, is important in tumor development. And do you find more apoptosis or less apoptosis during tumor development? Less. There's decreased amounts of cell death in tumor cells compared to normal cells. And this is due to mutations in genes that regulate apoptosis, When this is done in a cancer cell compared to a normal cell one finds And I'll tell you that story next time.