ORDEN POUR LE MÉRITE

FÜR WISSENSCHAFTEN UND KÜNSTE

REDEN UND GEDENKWORTE

FÜNFUNDDREISSIGSTER BAND

2006 – 2007

WALLSTEIN VERLAG

2. VERVIELFÄLTIGUNG UND SELEKTION: DAS GRUNDPRINZIP DER BIOLOGIE

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THE EVOLUTIONARY ORIGINS OF HUMAN CANCER

I want to talk today about the origins of human cancer and how the disease of cancer intersects with the process of Darwinian evolution. Much of what we know about the disease of cancer comes from epidemiology, and I thought I would give you some insights into the origins of cancer through some epidemiological studies that will eventually converge on the issue of how Darwinian evolution affects the development of human tumors.

You should know on an optimistic note that the death rate from many kinds of common cancer has actually been progressively declining. So we start off on a positive note.

I.

Here you see certain cancers which were major killers 70 years ago (Figure 1). Their death rates have been declining progressively for the last 70 years. Stomach cancer in men and women, for example, used to be very common; it has been decreasing precipitously due to the effects of refrigeration of foods and of food preservatives. So the next time you hear »Die Grünen« telling you how evil food preser-

vatives are, think about the decline of stomach cancer. Note also the decline of cervical cancer because of the Papanicolaou smear test, and of colon and rectum cancer because of colonoscopy.

This is not, however, the trend for all kinds of human cancers. Figure 1, for example, shows also male lung cancer. It has gone up enormously over the last 60 years but has started to go down. In women lung cancer exceeded breast cancer in about 1990 as the most common cause of cancer-related death.

Many other kinds of cancers have been relatively constant. Figure 2 shows breast cancer in women (green line). The mortality from breast cancer was quite constant over a period of 70 years, when allegedly we were experiencing an epidemic of breast cancer among women. In saying this I make mention of the fact that these figures are age-adjusted, that is to say that these figures have been changed to take into account the fact that the population is getting older and that, as I will argue shortly, cancer is largely a disease of old people.

In Figure 3 the mortality from one of the most common cancers is shown. It is cancer of the colon. It is relatively constant, going down slightly, but not dramatically. This is a serious problem, because it is a common cancer in the West. Perhaps the most relevant issue for my logic today comes from these graphs, which indicate the ages at which people first are diagnosed with cancer. Figure 4 shows that, with the exception of breast cancer, cancer is largely a disease of old people. This in itself teaches us some very important lessons about how the disease develops. I will investigate this in much greater detail.

Figure 5 is an example of colon cancer in more detail. The risk of colon cancer in a 70 year old man is 1000 times higher than is the risk of colon cancer in a 10 year old boy. In other words, to state the obvious, it takes a very long time for these diseases to develop. When someone is diagnosed with cancer, it is not as if the cancer began 3 or 4 years earlier. Many kinds of cancers began 40 or 50 years earlier, but we did not realize their existence in our body, because they were so small for so many years.

An important issue to understand is the fact, as we all know, that the Western populations are getting older and older. Figure 6 is an ex-

ample from the United States, where the projection is that by the year 2050 there will be almost 80 million people over the age of 65, in other words, we're now living longer and longer and as a consequence the diseases of the elderly are more and more frequent This is also shown in Figure 7. This figure illustrates the number of cancer deaths in the American population from 1930 to 2000. Does this mean that each of us is at a greater risk for cancer? The answer is no. Instead, what is happening is that we are living long enough to get a disease of the elderly and therefore cancer is increasing in numbers, not because anyone of us has a greater risk, but because we are living long enough to be exposed to this disease. Therefore cancer, like Alzheimer's disease, will increasingly be an important public health issue in the West not because we are exposed to greater carcinogens, not because of environmental pollution, but simply because of the entropy, the disorder which occurs as the human body gets older and different components of the human body begin to malfunction. 60 or 100 years ago, cancer was relatively rare, because people did not live long enough to get cancer in the same way they did not live long enough to get, for example, Alzheimer's.

II.

We go now into issues of biology. You will excuse me if I enter into the elementary aspects of biology, but I know there are architects and film producers and philosophers and economists here, so I want to give some deference, pay some respect, to them.

Figure 8, left shows a normal human tissue and the architectural structure of this tissue at the microscopic level. There is great order here. These various cells are collaborating with one another in order to create an architecturally well-ordered structure, doing so in order to create a functioning tissue. In contrast, if one looks at a tumor under the microscope, all one sees is chaos (Figure 8, right). The normal cells are interested in collaborating with one another to construct a functional tissue, while the cancer cells have only one agenda:

to proliferate, to make more copies of themselves. They are not interested in creating normal structure and normal function. In this image we are looking at perhaps 100 cells, but in order to appreciate the scale, we have to understand that the human body at any one time has 3×10^{13} cells, in other words, 30.000 billion cells, all residing in a single adult human body. That gives one a feeling for the enormous complexity and the size of the human body.

Figure 9 (left) shows a normal retina, one of the most complex tissues of the human body. I show it to you to indicate the extraordinary structural elaboration of the retina that allows us to see. Given its complexity, it is an extremely improbable organ, yet we are looking at it right now using precisely this organ. And when one of these cells begins to grow uncontrollably, then once again one has this chaos, this disorder, which represents in this case a tumor of the eye. Figure 9 (right) shows such a tumor, which happens to occur largely in young people. Figure 10 left shows the lining of a normal stomach; once again – we see order. But in Figure 10, right there is the chaos that one begins to see when normal tissue becomes transformed into cancerous tissue. One uses the word »transformation« to indicate conversion from a normal growth state into a state of chaotic and runaway growth.

Now we arrive at the basic problem that I will be wrestling with today: If you look at how many times cells divide in the human body during the course of a life time, the number is about 10^{16}. I told you just before that we have 3×10^{13} cells in our body at any one time. What that means is that the number of cell divisions exceeds that by a factor of 300. That means that the body is turned over 300-fold during a human lifetime. In other words, there are constantly new cells formed and old cells killed at an enormous rate, and this explains why the number of cell divisions is vastly larger than the number of cells in the body at any one point in time.

Let us now look at other mammals: Figure 11 shows the smallest mammal, a bat from Thailand. It is so much smaller than we are, and it has a shorter life. It goes through only 10^{11} cell divisions in a life time. Figure 11 also shows the largest mammal – a whale. It goes

through, we imagine, 10^{20} cell divisions in a lifetime. By the way, something that is very remarkable about this: Human beings have the same number of genes and the same genes as the bat and the whale. We are actually very closely related to them, only about 85 million years apart. And so, from the same construction plan one can make all these organisms. However, when one constructs a large organism, such as humans, right away we encounter an enormous danger, because each time a cell in our body divides, there is the danger that something will go wrong. And that something that will go wrong may be, for example, the birth of a tumor.

Consequently, to refer to Darwin, you can imagine that during the course of our evolution, as we evolved from smaller organisms to larger organisms and as we came to live longer and longer (we live 60 or 80 times longer than a mouse, for example), the number of cell divisions increased and therefore there needed to be a compensatory co-evolution of defense mechanisms that would prevent the onset of cancer. Small organisms like the mouse have a far smaller risk of cancer because they experience 100.000 fewer cell divisions than we do in their lifetime. As a consequence, small organisms have far fewer anti-cancer defense mechanisms in their cells. Nobody really knows about the cancer risk of a blue whale, we really have not studied it, but we can imagine that it runs an enormous risk of cancer during its lifetime, because it goes through as many as 10^{20} cell divisions.

Another important concept in our discussion today is the fact that not only does cancer take a very long time to develop, but it develops as the endpoint of a complex series of steps, starting with a normal tissue which becomes progressively more and more abnormal. In Figure 12 the lining of a colon is depicted. The endpoint of many kinds of cancers is that cells in this localized primary tumor may eventually enter into the circulation and land in distant sites in the body (red arrow), where they form new colonies, the so-called »metastases«. These metastases are highly important, because, as I will indicate, they represent a frequent cause of cancer-associated death.

Figure 13 shows, in the context of the colon, how the tissues become progressively more and more abnormal. There is clear evidence that

each of these steps takes a very long time to occur, perhaps 10 or 20 years. You can accelerate this process. If, for example, you go to McDonalds every day or you eat Bratwurst every morning, then the steps may only take two or three years. Or if you are a vegetarian, you can extend the whole process of colon cancer development to a very long period of time, so it may take a 100 years and only reach completion long after you are gone from this earth.

III.

The reason why each of these processes, why cancer development takes so long, is that the human body is organized to erect a series of barriers to the forward progress of cancer development. Therefore, each time the next growth appears, it represents the successful surmounting of a barrier, of another defense mechanism. As you will notice from the figure, after one defense mechanism has been broken or breached, another defense mechanism will be breached and so force. And this indicates that our tissues are organized so that it is very difficult to go from here to here, or from Figure 13, left to Figure 13, right. If one could go from a normal lining of the intestine to a carcinoma in one step, we all would have colon cancer by the age of three. That is impossible, because our tissues have evolved to become extremely resistant and to erect multiple barriers against the forward development of cancer.

In Figure 14 we have one of the very few precise measurements of how long it takes to develop lung cancer. On the left is a plot of global cigarette consumption and on right is lung cancer incidence. (In the year 1900, when a doctor encountered a lung cancer patient, that patient was paraded in front of a medical school class as being a person whose disease was so rare that the medical students would be unlikely to ever see someone with this disease ever again during their careers.) What is interesting about these two curves (Figure 14) is that there is a very precise thirty year lag time between the onset of large scale cigarette consumption and the development of lung can-

cer; this probably represents the minimum period of time required for the disease to develop.

It turns out to be the case that this process of multi-step cancer development, sometimes called cancer progression, occurs in a wide variety of different tissues. Before, I was talking about the colon, but these multiple steps are found in many other kinds of human tissues as well (Figure 15), so this is not a peculiarity of the colon. Each of our tissues has evolved to erect multiple barriers against the forward progress of the tumor, against tumor development. In Figure 16, I'll show you the endpoint of tumor development, the metastases that I talked about before. These are not pretty pictures, I admit, but nonetheless they show vividly what can happen at the endpoint of cancer development. On the left of Figure 16 colon cancers have metastasized to the liver; on the right, breast cancers have metastasized to the brain. This is the last stage of cancer progression and these metastases are responsible for 90 % of cancer-associated death. In contrast, the primary tumors are only responsible for 10 % of cancer-associated death.

How do we know for example that these polyps, or adenomas (Figure 17) are the precursors of the carcinoma, of the actually invasive tumor? What scientific proof is there, or is this only a hypothesis or a theory?

In fact there is some very compelling clinical data. In Figure 18, the blue and yellow lines show the rate at which a population would be predicted over a period of 7 years to be diagnosed with colon carcinoma in a particular population. The red line shows the rate with which a population actually develops colon cancer if they went through colonoscopy and had polyps removed from their colon. In other words, if one removes the polyps from the colon by doing colonoscopy, then the actual rate of colon cancer incidence, of developing a carcinoma – an invasive tumor – is reduced by 90 % (Figure 19).

We can conclude from this if you get rid of the polyps, you never get the carcinomas (Figure 20). This represents a scientific proof that polyps are the obligatory precursors of carcinomas. It is no longer just a hypothesis or attractive idea.

Another important concept in cancer biology derives from how we

imagine tumors arise. There are in principle two logical alternative mechanisms one could imagine. They are shown in Figure 21: Here are normal cells, normal tissues. One could imagine in this scheme (right) that here are a series of normal cells, four of which crossed over the boundary from being normal to being cancerous. In other words, they passed through the process that I called transformation. The alternative is a scheme like this (left): that only one cell becomes the ancestor of all the cancer cells in a tissue. We now have very compelling proof that in fact the first theory is incorrect and that virtually all kinds of human cancers, all the cells in a tumor, derive from a single common ancestor (Figure 22).

Now, when I mention all the cells in a tumor, we must understand that a tumor of one centimeter diameter already has a billion cells in it. But they all descend from a single common ancestral cell, a founding cell, and therefore this focuses our attention on the biology of this founding cell (Figure 23). What made it grow abnormally and therefore, once it began to grow abnormally, how can we explain the biology, the behavior of all of its numerous descendants?

So, we pass through a bit more of a biology lesson to try to understand how the behavior of this single founding, ancestral cell is governed. Here is what a single human cell looks like (Figure 24). Obviously, there are many kinds of human cells. Here is the nucleus in the cell (dashed line). The nucleus is the control centre of the cell. Within the nucleus of every human cell there is a cluster of chromosomes and here is what the entire array, the entire repertoire of human chromosomes looks like (Figure 25). We have 46 of them. (For many years everybody thought that they were 48, because an expert said 48 and everybody else said it must be 48, until somebody actually had a look and it were only 46! We do just fine with 46!)

In the nucleus are the chromosomes, and within the chromosomes are the DNA molecules (Figure 26). The DNA molecules are organized schematically in the kind of plan shown in Figure 27. The different segments of the DNA molecule hold different distinct genes (red) and so we have now the hierarchy seen in Figure 28. There are a number of genes carried in the DNA molecules and each of these

genes, each of these red segments, is responsible for a distinct function inside a cell (Figure 29). Altogether in a single human cell there are about 20.000 genes and in a mouse cell there is the same number, and in a blue whale cell there is also the same number. That has not changed over the course of mammalian evolution. Our cells are almost identical to the cells of a blue whale or the cells of a tiny mouse or a tree bat.

These genes carried inside the cells control the behavior of the cell as a whole (Figure 30). In other words, these are not simply libraries of inert, inactive information. These genes have profound effects on how the cell around them behaves, when it proliferates, when it does not proliferate, when it grows larger, when it grows smaller. The genes within the cell control the behavior of that cell.

Another point is that each cell within a tissue, here they are about 10 cells (Figure 31), has the identical set of 20.000 genes. It is not as if there were different sets of genes, so there are 20.000 here, 20.000 there.

With that background I want to return to the issue of why tumor formation is so complicated, and to re-emphasize a theme that I described before, that each successful step represents the breaching, the break-down, of a pre-existing defense mechanism that is constructed in all of our normal tissues. If we look once again at the colon cancer, and here once again we have the names of each of these different kinds of intermediary growths, what we see is something interesting about the genes in these cells: Cells that have moved only a little bit on the way down through the first step have only one damaged, mutant gene (Figure 32). Cells that have moved down farther have two mutant genes. Cells that have moved down even further have three mutant genes etc. In other words, the further these cells advance, the more mutant, damaged genes they carry in their genomes. It is important to note one important fact: Each of these genes has the specialized function of controlling whether or not the cell will proliferate (Figure 33). These are not genes that determine hair color or skin color or how long fingernails are. Instead, these are genes whose focus is on governing whether or not the cell divides. Therefore, each

of these genes, once it becomes damaged and loses its proper information content, creates a degree of increasing disorder in the regulatory circuit that governs the life of the cell (Figure 34). And therefore, as one progresses in this direction to increasing degrees of biological, morphological abnormality, one accumulates increasing numbers of damaged genes. The cells on the right may have five or six damaged genes in them, whereas the cells on the left may only have a single damaged gene.

IV.

So now we arrive at Erwin Neher's »leitmotif«, Darwin. Figure 35 shows him before he grew a beard, probably when he went on the voyage of the Beagle. I would like to argue that tumor progression is indeed a form of Darwinian evolution. It goes like this: Figure 36 shows a whole group of normal cells. One of those cells sustains by accident a single mutation in a growth-controlling gene. And that single mutation, that red gene, confers an advantage on that cell. And so now this cell, this mutant, begins to proliferate more rapidly than all the grey cells around it. After a period of ten or twenty years it may have a million descendants, each of which will have proliferated more successfully than their fully normal neighbors. In one of those cells another mutation will accidentally occur. And now we have a cell that has two mutations, which grows even better than a cell with only one mutation. So these doubly mutated cells with two damaged genes grow more rapidly, and after another 10 or 20 years another mutation can happen. If this is in the colon and you eat bratwurst every day you can accelerate this process for reasons which are not totally clear. This is formally identical to the model of Darwinian evolution, mutation and selection. The mutations occur randomly, but if they happen to confer on the cell an increased ability to proliferate, you have the rapid expansion of those cells as shown in Figure 37. Here Darwinian evolution is occurring in the microcosm of, for example, a colon, rather than in the ecosphere. In other words, exactly these periods of mutation and selection back and forth create

cells that are more and more fit in the Darwinian sense. They have greater and greater competitive advantage (survival advantage), but of course, these cells are not necessarily compatible with the needs of the organism as a whole. These cells may be happy, but the organism around them clearly may not be happy because these cells will eventually end up killing the organism. So, Darwin was right in predicting how tumors arise.

Now we get to a little bit more complicated images, but we will not get into all of the details. In Figure 38 a single cell is depicted schematically with the names of various proteins that exist inside the cell. Each of these proteins acts like a resistor, or a capacitor, or a transistor inside a circuit board inside a computer. Each of these particular proteins is made by its own gene. There are 20.000 genes inside the cell, but I will only show the protein products of 100 genes. Each of these 100 proteins is made by its own gene, and each of these proteins has the specialized function of regulating cell proliferation (Figure 39). They collaborate together to form a decision-making network that ultimately decides whether the cell will grow or not. It is a mini-computer operating in all of our cells. Here is the way that some people are now hoping to study the way that our cells are organized (Figure 40). Each one of these is also a different protein, and researchers are trying to use computers to understand how these different proteins inside a single cell intercommunicate in order to converge on the decision of whether the cell should grow or not. In truth, at this stage, this attempt is »wahnsinnig«; it is much too early. We don't really understand enough about each of these components to seriously construct models that predict their behavior. But in 20 years, we will be able to use these depictions to understand and predict how a single cell grows. Right now it is vastly beyond our capabilities. Still this is the mindset of cancer biologists: trying to understand an individual cell as if it contained an electronic circuit.

Figure 41 contains another depiction of an individual cell, similar to the one I showed before. But now the individual proteins do not have names attached to them. But each of these circles is an individual protein, an individual signaling protein, that, as before, is intercom-

municating with other proteins in order to do the signal processing that will ultimately converge on the decision of growth or non-growth. And what we see here in Figure 42 is that, even if this is all one large circuit, there are multiple sub-circuits. Different groups of proteins are focused on one or another aspect of the life of the cell. The proteins in the green area are focused on cell survival. Each cell within us has a built-in suicide network – called apoptosis. These cells are involved in regulating whether or not a cell will commit suicide. The light brown proteins are involved in determining how fast the cell will grow. These proteins above are actually functioning as the brake to shut down cell proliferation when it is inappropriate. And finally, the proteins on top are focused on the motion of the cell, when does a cell move, or when does it stay quiet in one position.
Therefore, different sub-circuits have different functions. Here is one of those sub- circuits that serves as the breaking apparatus of the cell. Each of these proteins intercommunicates with one another to create the circuit as a whole, and mutations that damage each one of these different proteins can be found in various kinds of human tumors. In fact, we believe that in all human tumors one or another part of this sub-circuit is damaged. Now we can begin to rationalize the Darwinian evolution, because each time there is a mutation, one or another of these sub-circuits that regulates the life and the death of a cell is perturbed or disrupted. A normal cell will not grow as a cancer cell unless five of its sub-circuits are actually disrupted. In Figure 42 only four of these circuits are shown, but we know that there are actually five distinct regulatory sub-circuits in a human cell, all five of which must be disrupted or deregulated or damaged before a normal human cell will grow as a cancer cell. So this is not a problem of unlimited complexity. Instead, it can be understood with relatively simple ideas.

V.

Leaving Darwin, I want to give you just some insights into where current cancer research is taking us. Figure 43 shows a human tumor. We used to think of a human tumor as only a collection of cancer cells, but now we come to realize that often in a human tumor the bulk of the cells may be normal cells that have been recruited into the tumor mass by the cancer. Why have they been attracted into the tumor? Because the tumor needs these normal cells for its own sustenance. They are sometimes called »stromal« cells. Often the bulk of the cells in a human tumor are not the cancer cells at all. Why does the cancer need normal cells? One explanation is given in Figure 44 left. It shows a human melanoma. It also shows a normal capillary made of normal cells, which has grown into the tumor mass. Why? Because the cells around the capillary are alive, but here and there are cancer cells have died, because they did not have close access to the blood (Figure 44, right). Figure 45 depicts this much more dramatically: It shows a tumor mass. Each of the light green things is a capillary, through which blood is flowing. Immediately around the capillary is a black area where there is a lot of oxygen; here the cells are thriving. In the red areas there is very little oxygen, because the cells are far away from the capillaries, and cancer cells out there are dying, because they do not have close access to the oxygen supplied by the blood.

In Figure 46 you see how the breast cancer cells (dark blue) have attracted a vessel to grow in here so that the breast cancer cells are provided with fresh blood and fresh nutrients in order to survive. Figure 47 shows a much more dramatic situation: To the right is a dark tumor mass. The tumor has attracted these normal blood vessels to grow in from the left and provide it with blood, with oxygen, to get rid of carbon dioxide, to bring in glucose and so on. In Figure 48 you can see what happens if you use a drug not to kill the tumor cells, but to kill the blood vessels that have been attracted to grow into a group of tumors, which appear red in the Figure. The animal bearing these tumors was treated with a drug that killed the blood

vessels that were attracted to grow into the tumor mass. The tumors then disappeared, illustrating a very attractive form of therapy.
One final idea: The endpoint of cancer development is the process of metastasis, which represents the successful completion of an extraordinarily complicated series of steps. There has always been a major puzzle about metastasis: How are cancer cells clever enough to figure out how to accomplish the complex steps that yield metastases? How do cancer cells learn how to spread throughout the body? The answer lies in the early embryo.
Figure 49 shows an early fly embryo of the fruit fly, Drosophila. Flies are not so distantly related to us as one may think. The early developmental mechanisms that have developed in a common ancestor of flies and us are still used by flies and still used by our cells. In fact, many of the important mechanisms of cancer development were not learned by cancer researchers who have dedicated their lives to curing cancer. Instead, these lessons were learned by the fly geneticists. They came to the cancer agencies and said: »Give us money, we will help you cure cancer.« And we said : »Ach, Quatsch mit Soße! We know that these people just want our money, but what they are doing has nothing to do with cancer research«. But we were wrong, because much of what we now understand about the development of cancer comes from the study of the genetics of flies and worms and even bakers' yeast. The brown cells at the bottom of Figure 49 start invading into the centre of the embryo. They invade not because they are malignant. Rather, this behavior is part of normal embryologic development, and cancer cells resurrect this early developmental program. They turn on a program of behavior that is normally active only early in the embryo, resurrecting this previously silent behavioral program. By turning it on, they acquire in one step many of the attributes, many of the powers that are required to initiate the process of invasion and metastasis.
In Figure 50 is another example of this behavior. This is a sea urchin. Believe it or not, they are more closely related to us than are the flies. Exactly the same thing is going on here. Cells in the outer layer of the embryo are not moving around, but at the bottom are cells that

have left the outer layer, rounded up, and begun invading into the center of the embryo. Once again, they use exactly the same genes and the same developmental programs that cancer cells use when they want to learn how to become invasive and metastatic.

So, cancer cells are not so clever. They don't invent or assemble this complex behavioral program on their own, Instead, they just reach back into the library of genes that they carry and turn on a gene or several genes that otherwise have been silent since early development of the embryo. Once they turn on such genes, they acquire this trait of being able to invade and to metastasize. The cancer cells are only exploitative, by resorting to cell biological programs that are usually operative in the normal development of the embryo. By studying biological development at the very beginning of life, we learn how the lives of many human beings are ended many decades later.

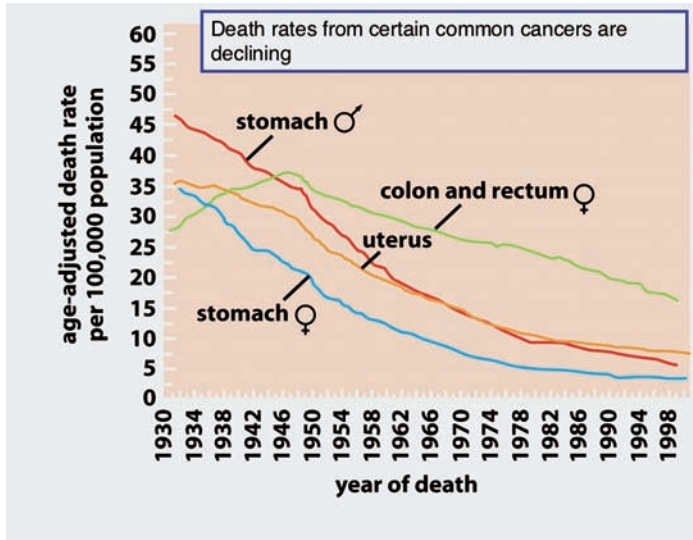
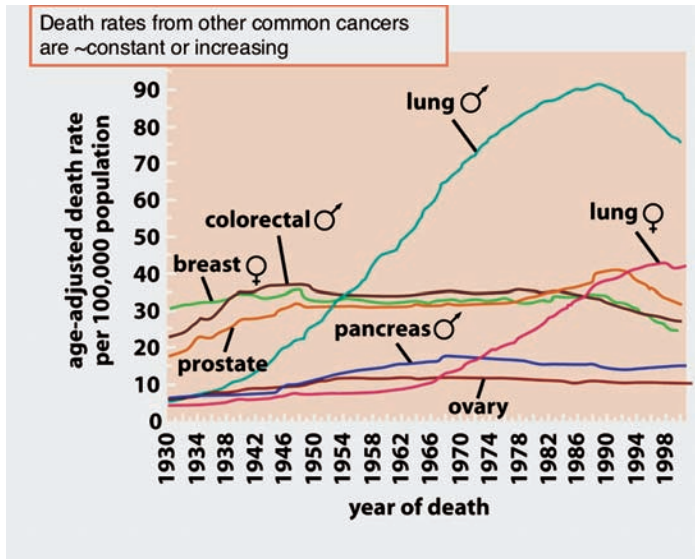


Figure 1: *The Biology of Cancer* (© Garland Science 2007)



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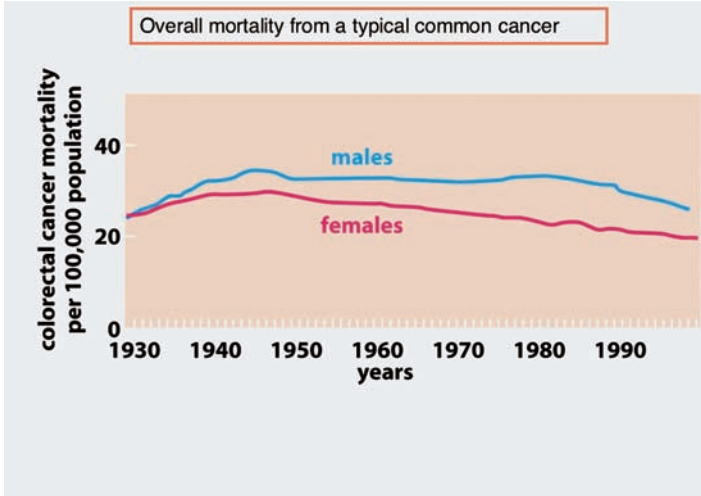
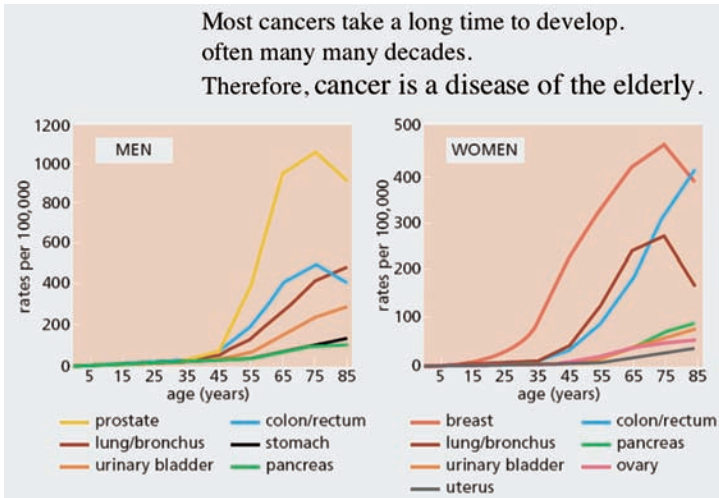


Figure 3: *The Biology of Cancer* (© Garland Science 2007)



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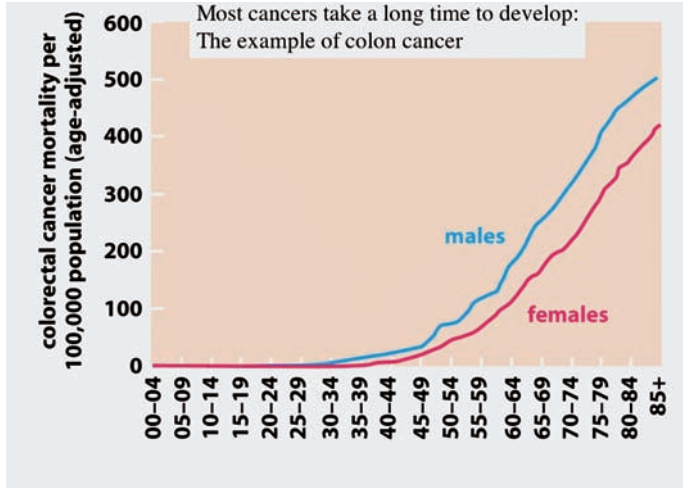

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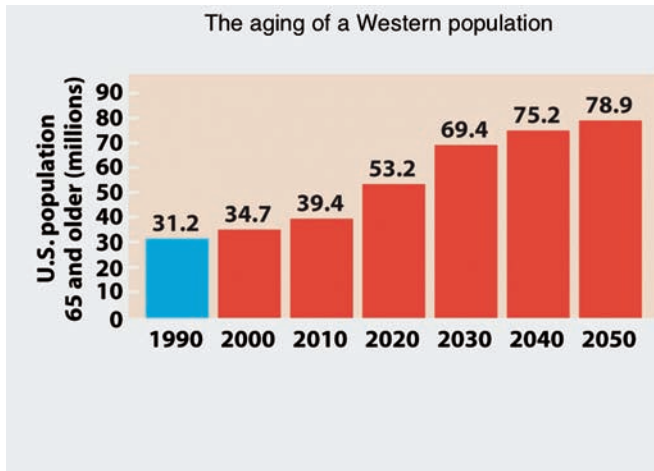

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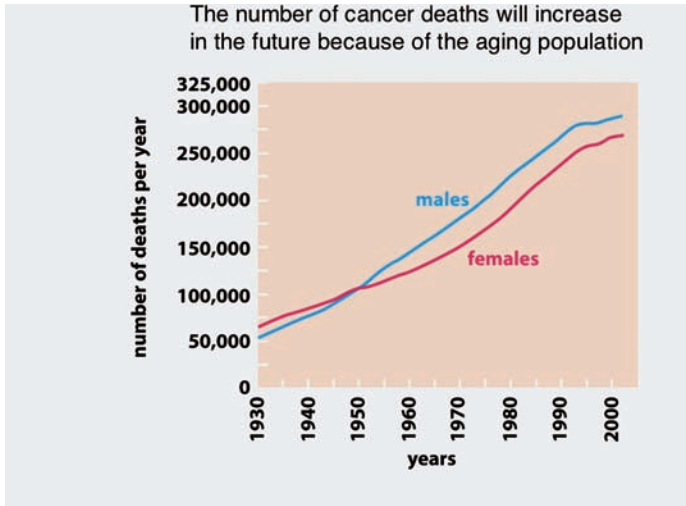

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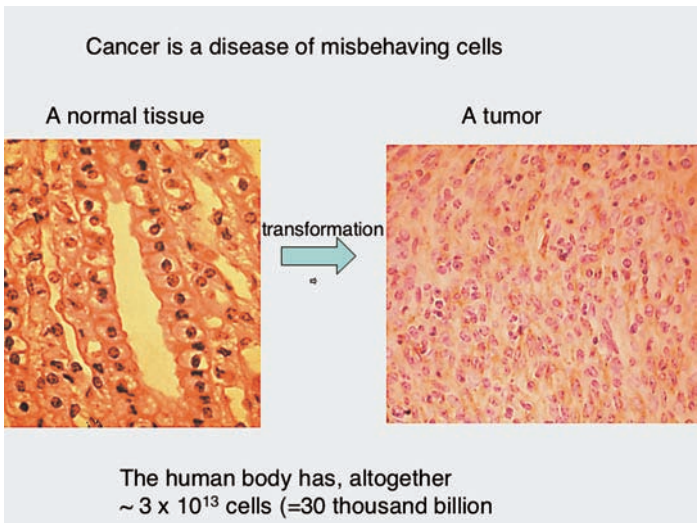

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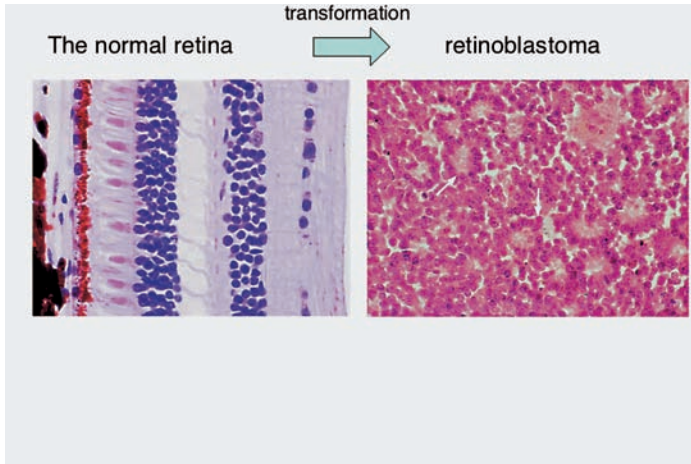

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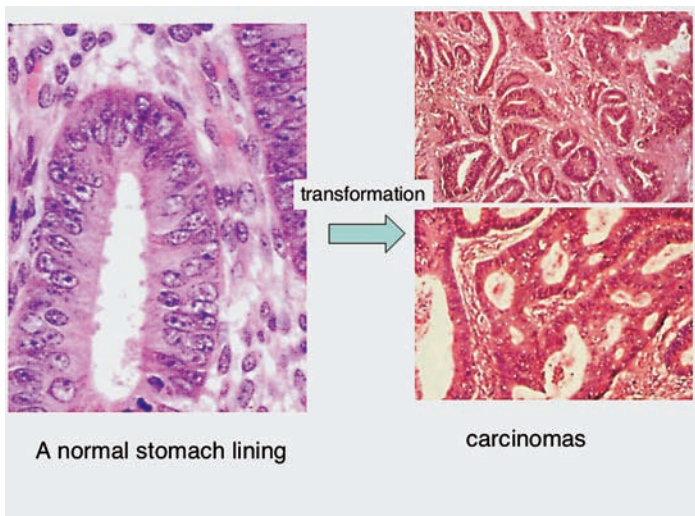
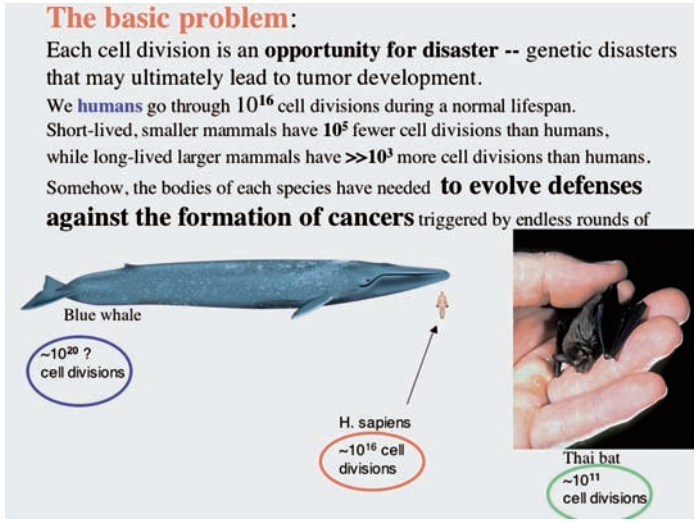


Figure 10: *The Biology of Cancer* (© Garland Science 2007)



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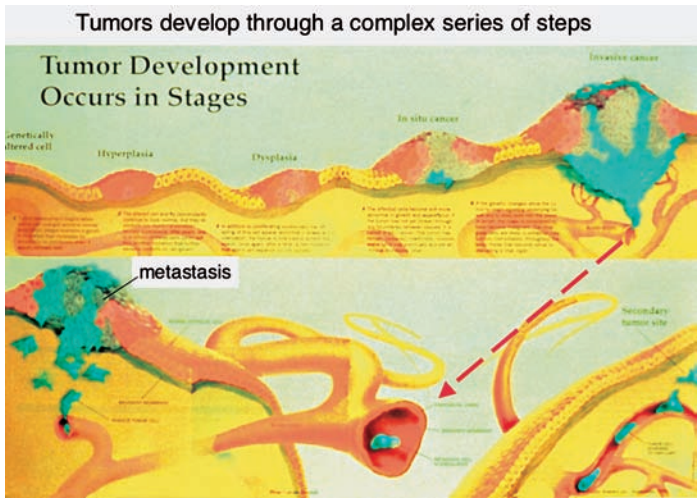
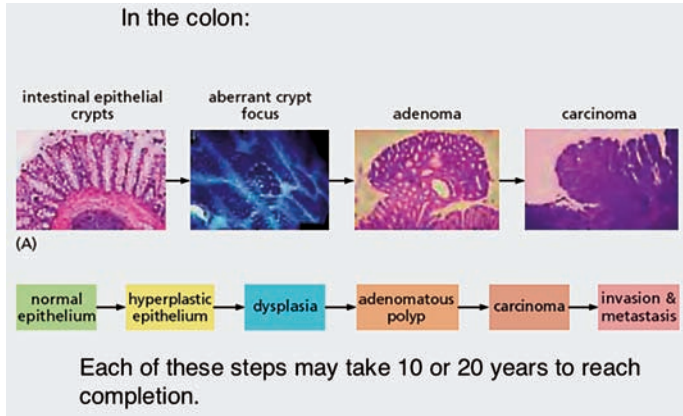


Figure 12: *The Biology of Cancer* (© Garland Science 2007)



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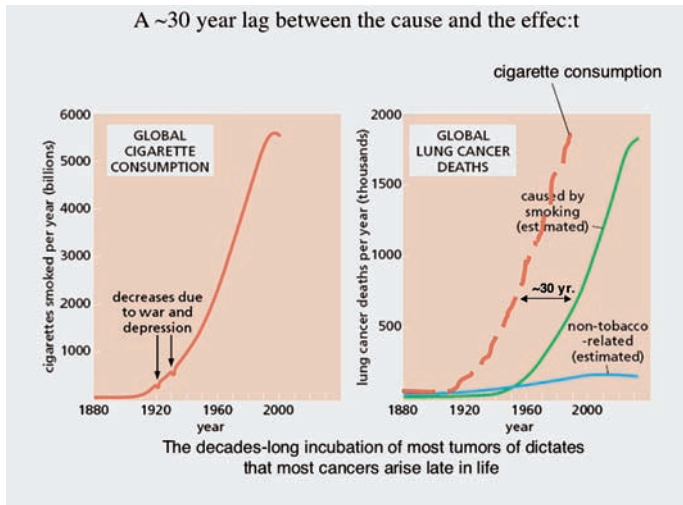
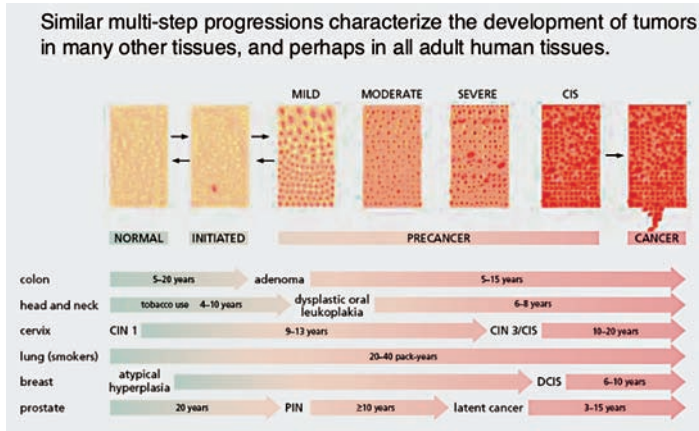


Figure 14: *The Biology of Cancer* (© Garland Science 2007)



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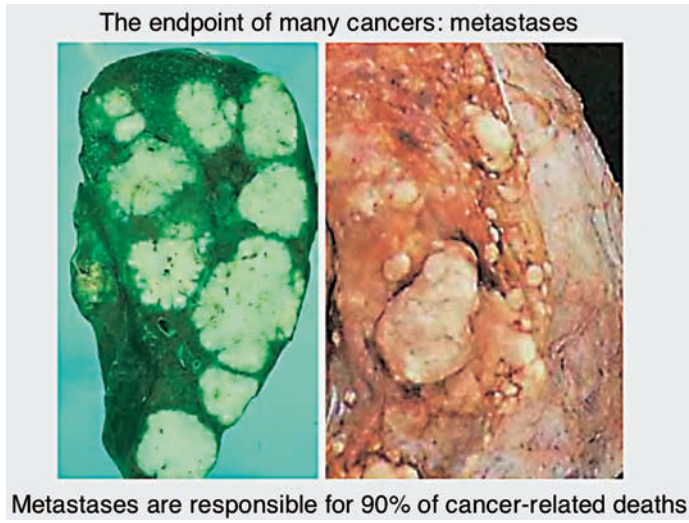

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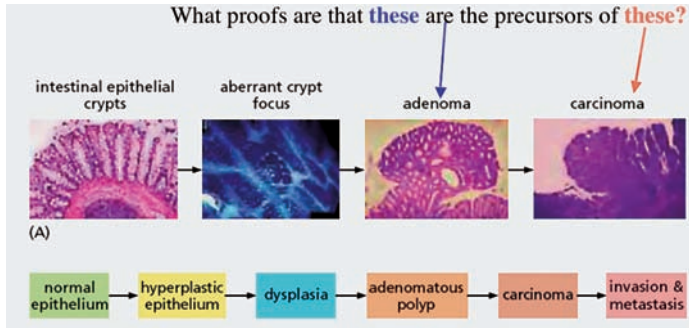

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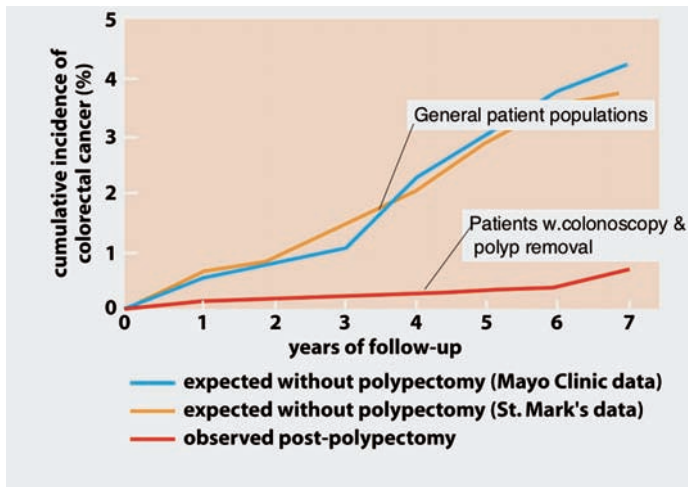

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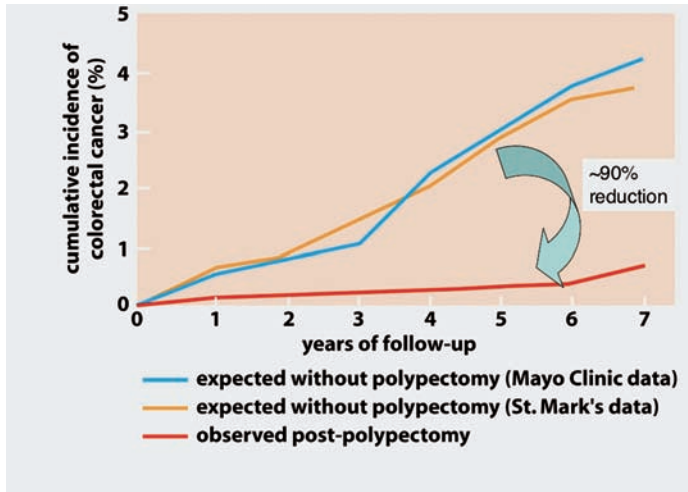

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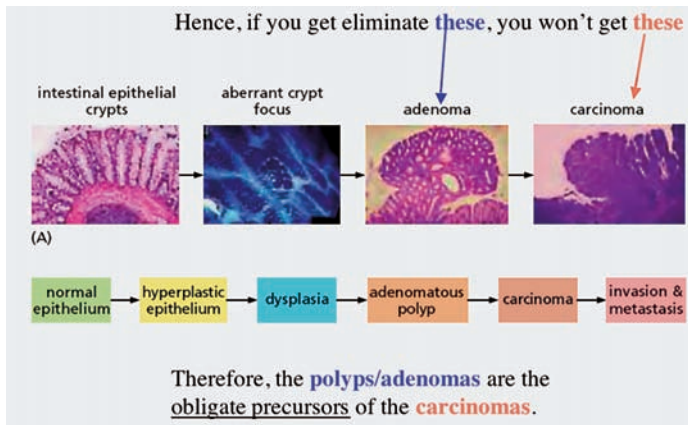

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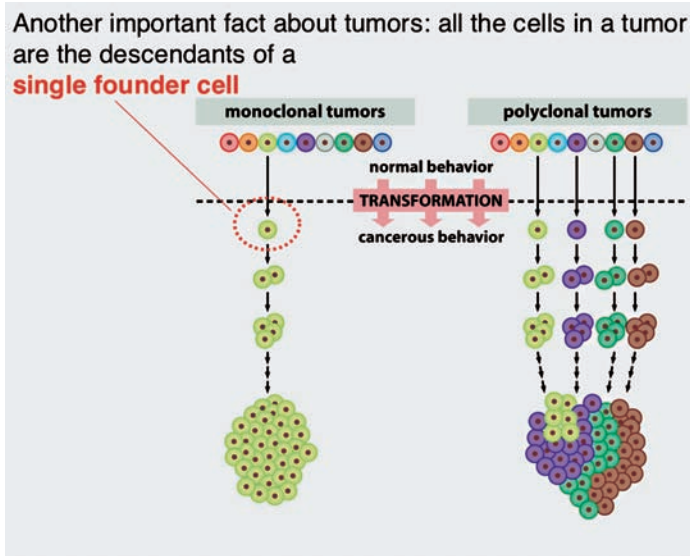

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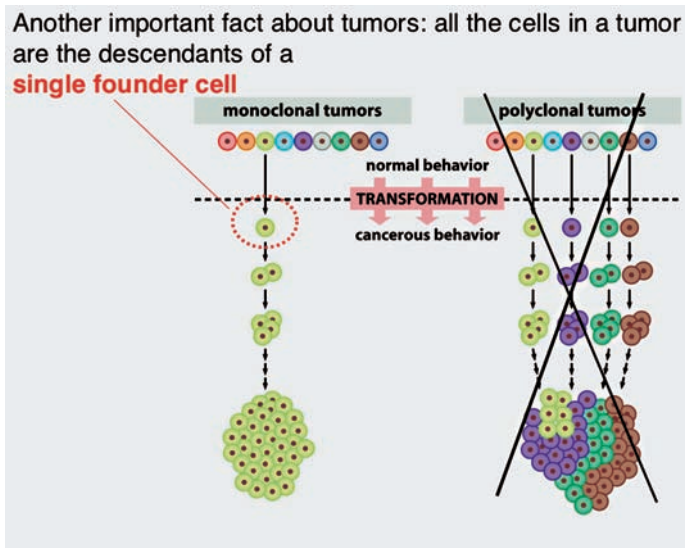

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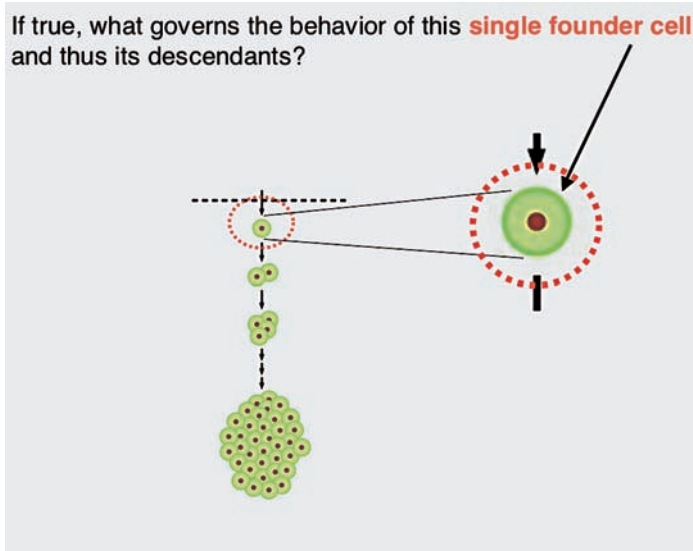

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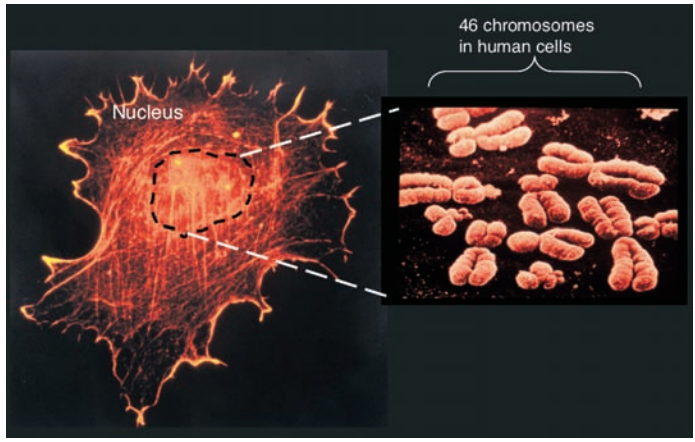

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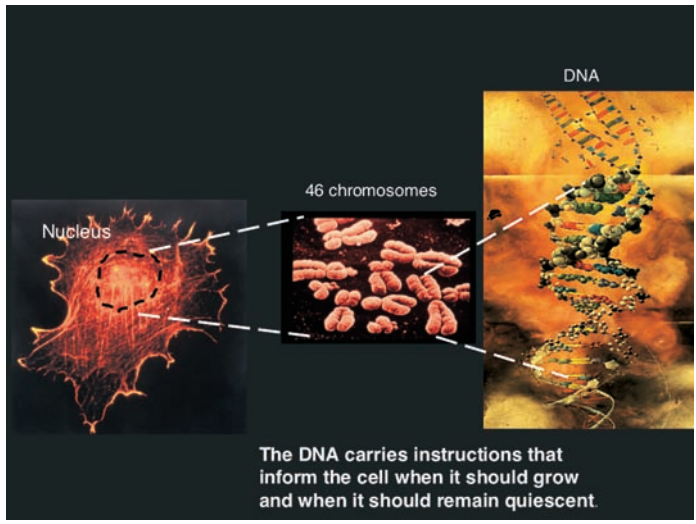

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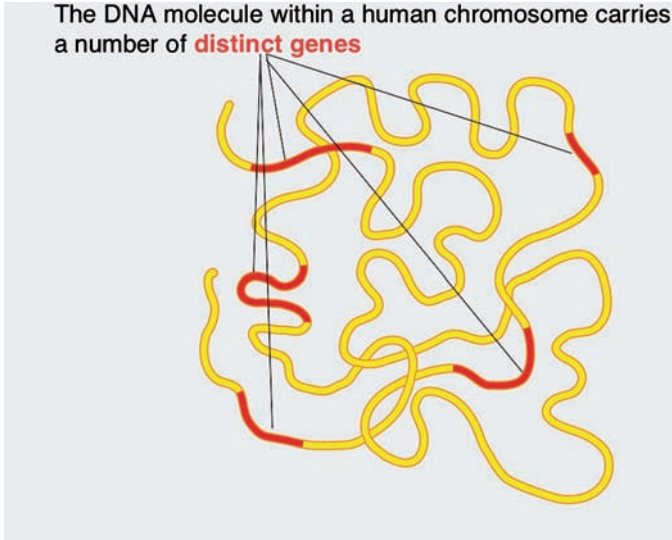

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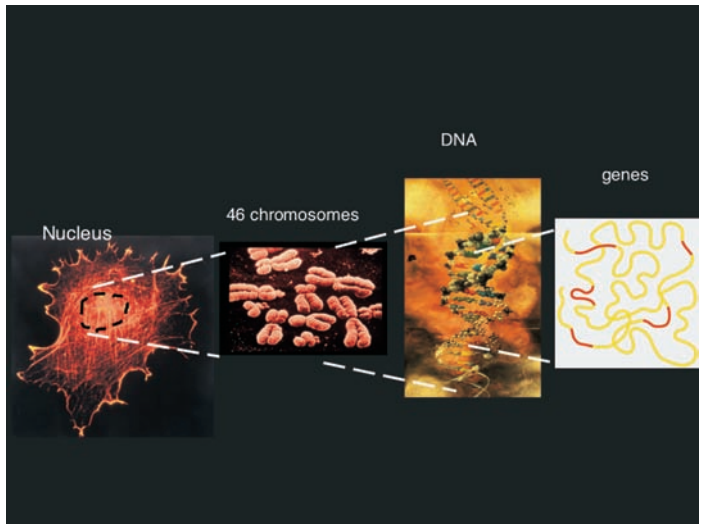

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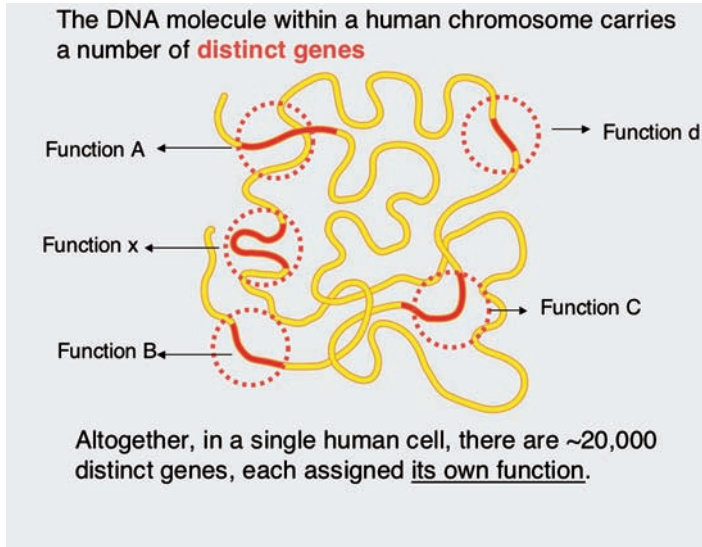

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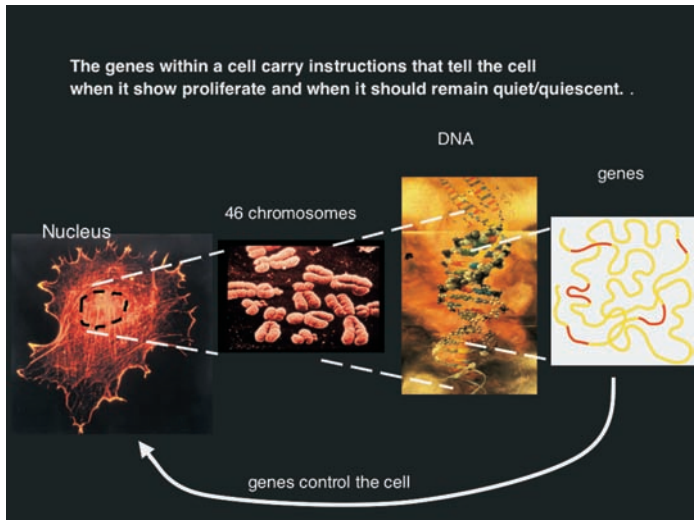

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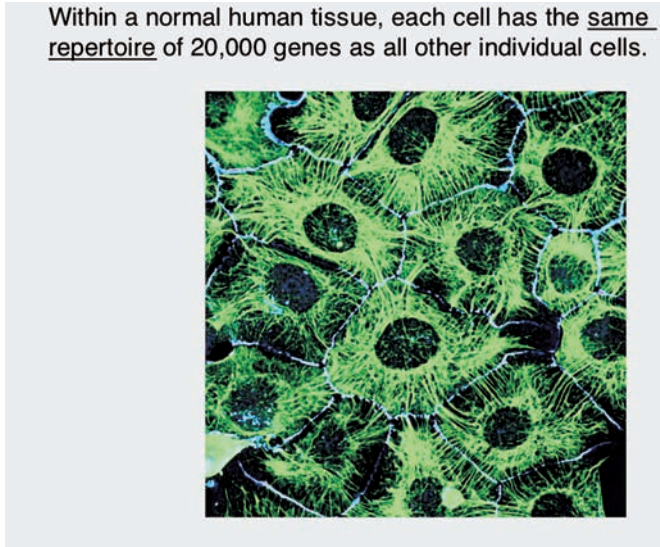

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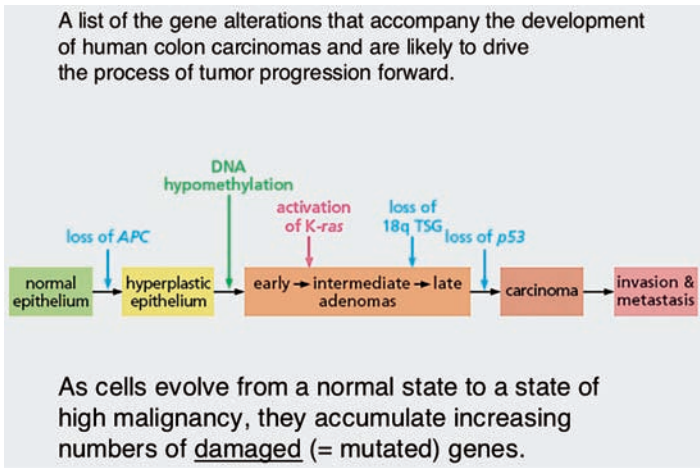

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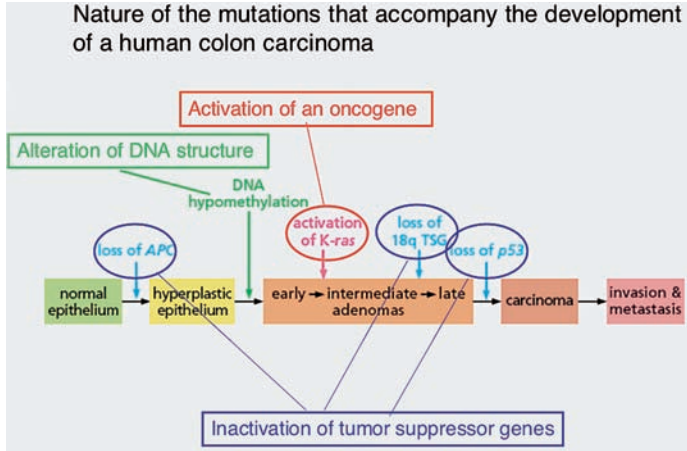

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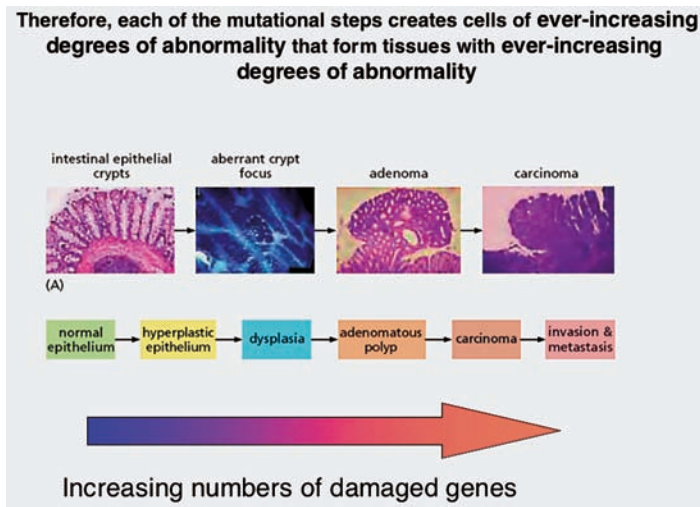

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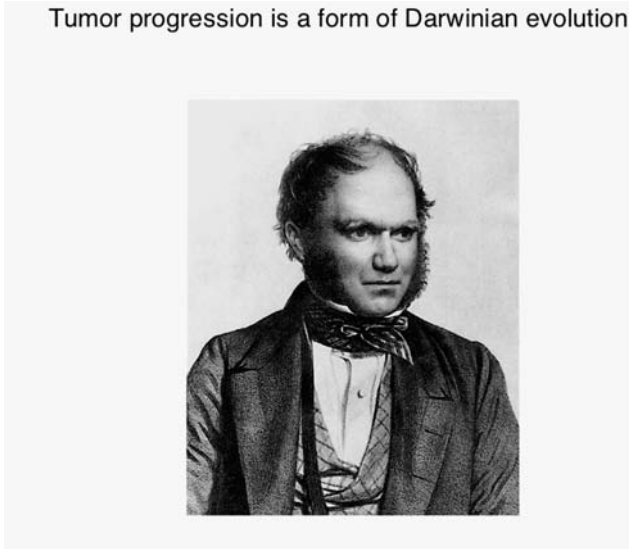

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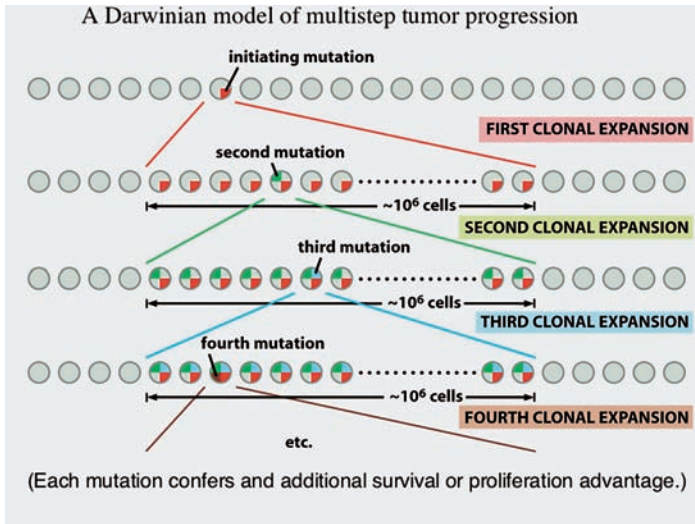

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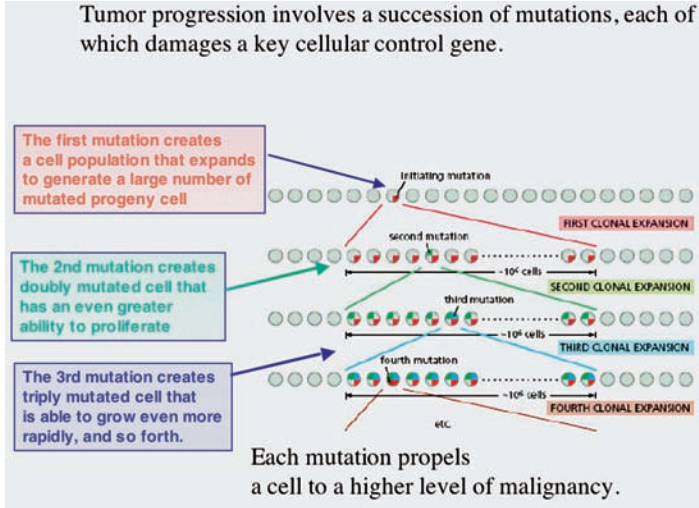

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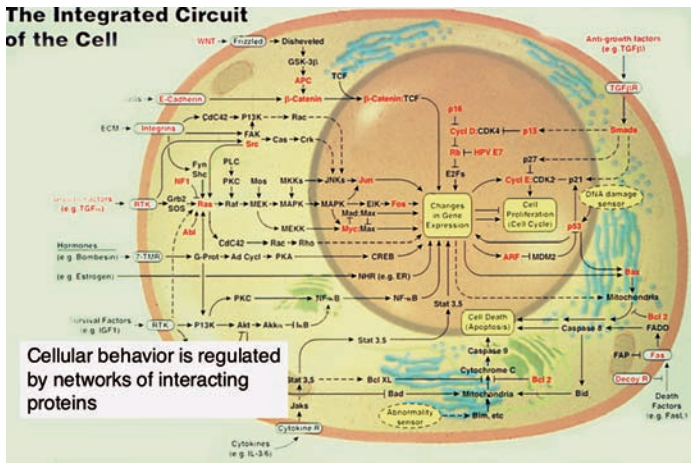

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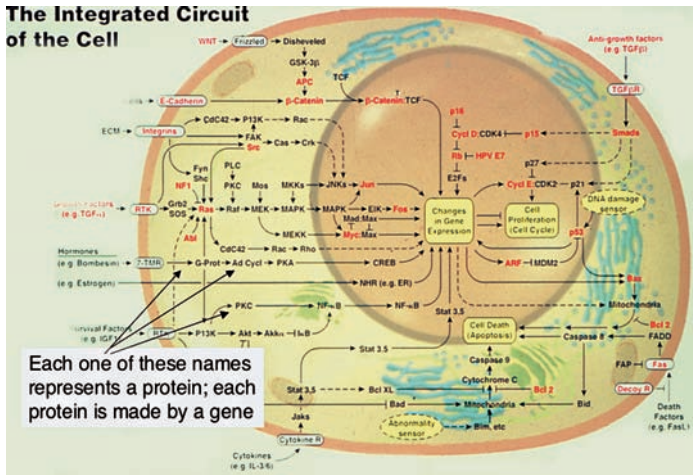

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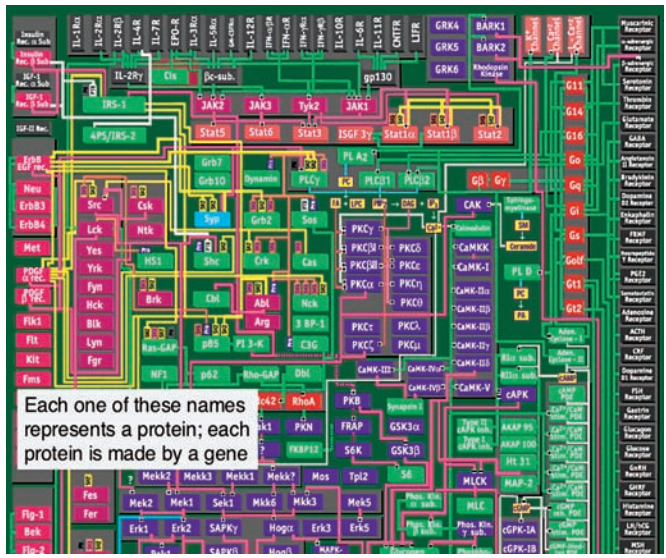

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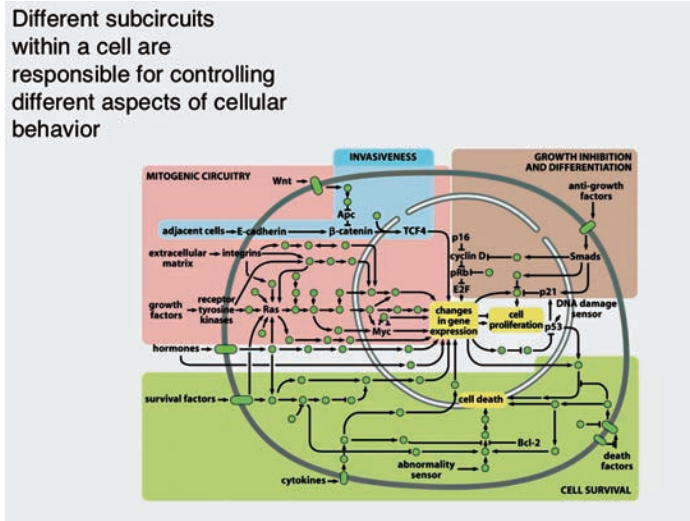

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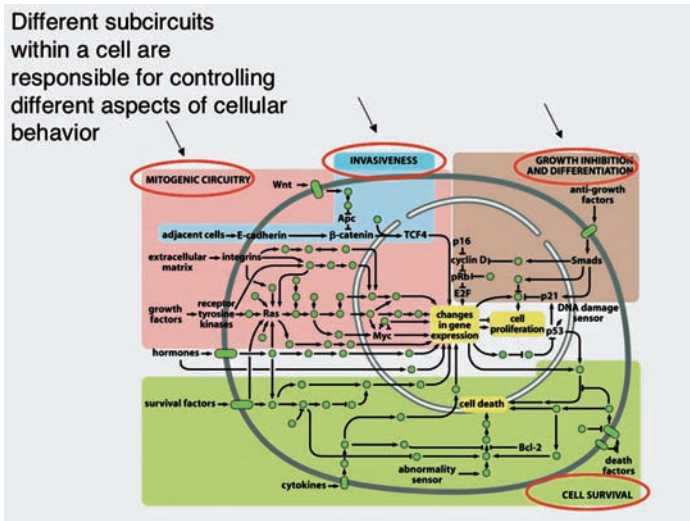

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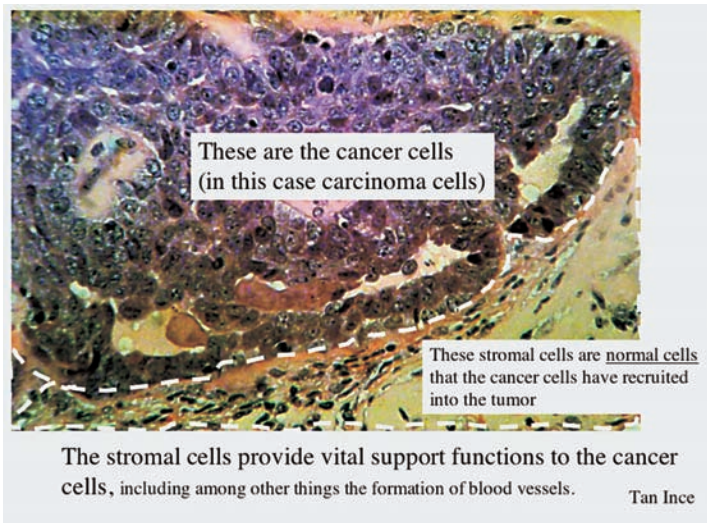

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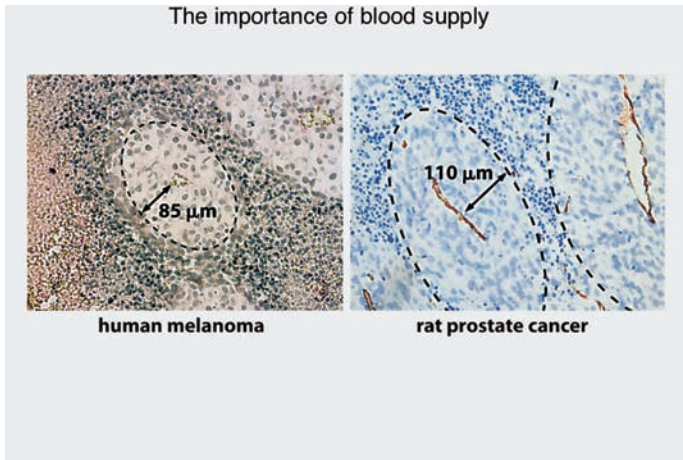

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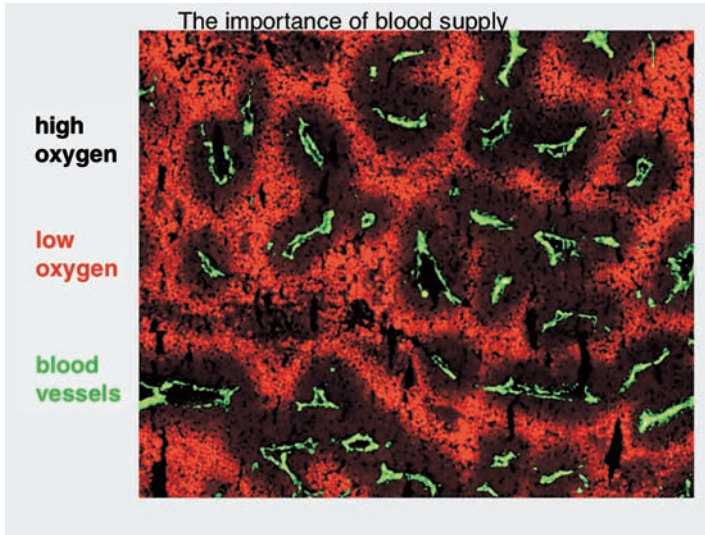

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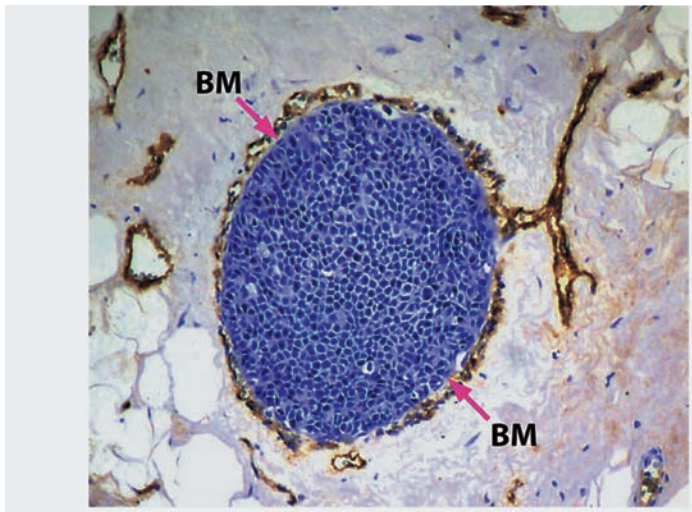

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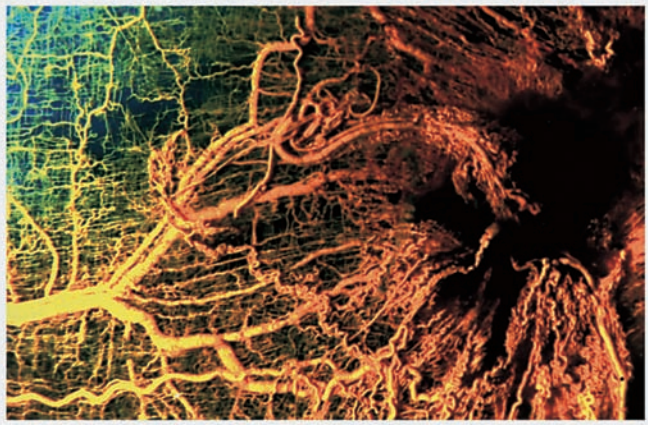

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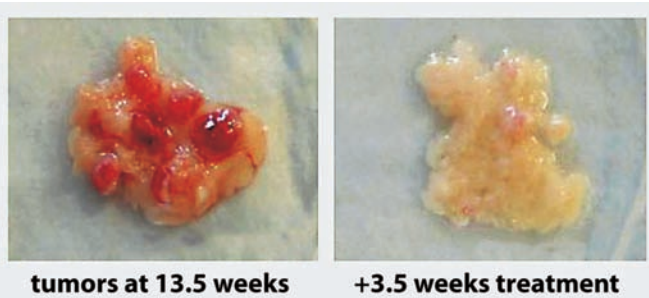

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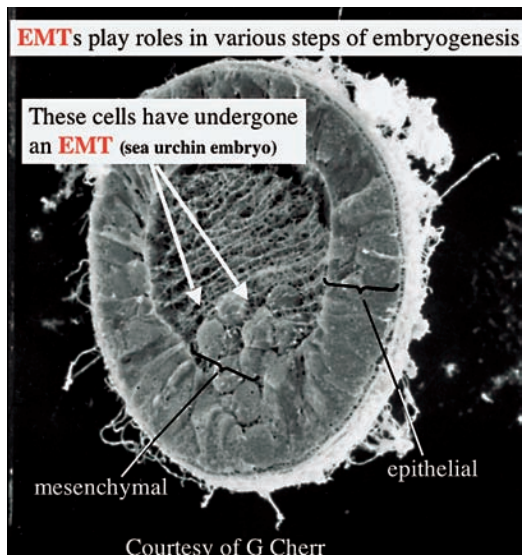

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