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March 2005

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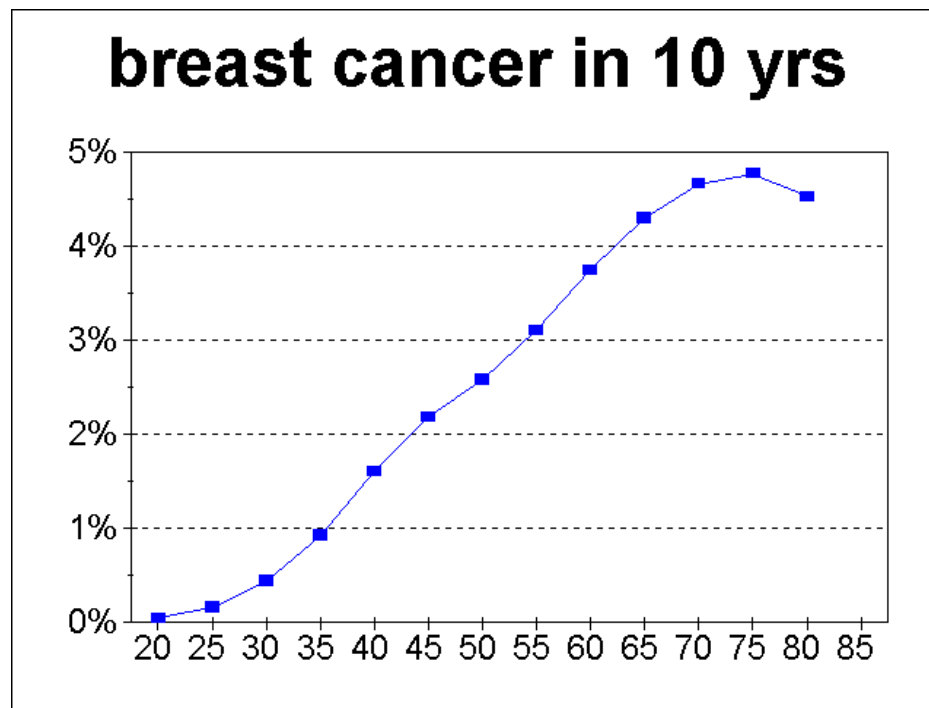
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Cancer and Aging



The enduring high correlation between age and cancer has produced the often heard generalization that "age is the single biggest risk factor for cancer." Of course, it's possible to get cancer at any age, including infancy. But the highest cancer rate occurs in decades 6-8. This is the age-range when the commonest cancers - lung, breast, prostate and colorectal - take their greatest toll. Even brain cancer, which is the main cancer that small children can get, is much commoner in older people.

The following chart shows the probability of a woman getting breast cancer in the next ten years, by age. The curve of the graph matches the curve of most cancer-by-age graphs. Bear in mind that if you see the rate suddenly tail off in the 9th and 10th decades of life, this doesn't disprove the relationship between cancer and age. Rather, it suggests that the minority of the population that is most resistant to cancer and other leading causes of death has now become the majority of the sample. These long-lived souls still show their hardiness in their late 80s and early 90s. In fact, it is claimed that a 94 year old has a better chance of living one more year than a 74 year old.



Graphic by permission of Tom Chester at
<http://la.znet.com/~schester/facts/index.html>

Why this close relationship between cancer and age? There are some simple answers which, while incomplete, are not wrong. One is that our immune systems, which have been holding some cancers in check, start to wear down with age. Ergo, more cancer. Another is that the longer we live in this world, the more carcinogens we are exposed to. Ergo, more cancer. A variation on this is that even when a carcinogen causes mutations early in life, it still takes a while for a tumor to grow to a detectable size, so the person will be older when diagnosed. A more refined variation on this is that cancer is a multi-step process; it usually takes up to 6 mutations before a cell acquires the ability to form a tumor. So again the process takes time, and this means the diagnosis will strike people in their later years.

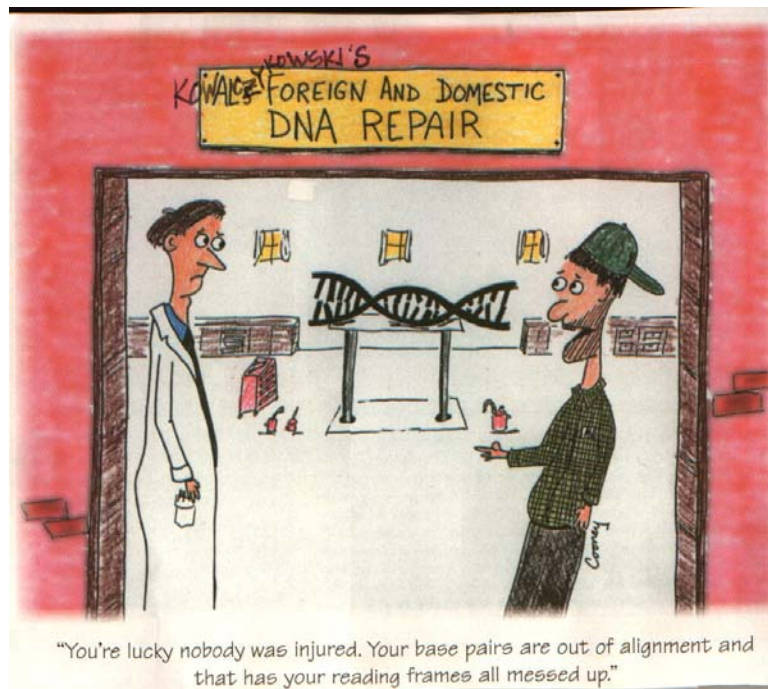
Bearing these perspectives out: autopsies done on men in their twenties who died of other causes have revealed that 9 percent of them have pre-cancer in the prostate gland; and 50% of autopsied deceased males in their 50s show actual cancer in their prostate gland. Yet *diagnosed* prostate cancer makes its greatest appearance among men who are 70 or older. Similarly, smokers, even heavy smokers, usually do not face the consequences until they have passed age 55. And cervical cancer may be preceded by years of disturbing pap tests. In other words, the cancer process often begins early, but is, by its nature, a process that generally takes years to blossom into detectable disease.

Cellular Aging and Cancer

It turns out that these simple answers, while being correct as far as they go, miss levels of the cancer-age relationship that are only lately coming to be

understood. Recent waves of research on cellular aging are bringing new insights into the origins of cancer. The relationship between age and cancer is even more intimate than thought, which is, admittedly, disheartening. On the positive side, new understandings of this relationship have opened the possibility that aging is a process that can be slowed. With a slowing of aging, comes a delay in the appearance of cancer.

Back to Cell School: Our readers learned quite a bit about cells and cancer in several of our earlier newsletters, such as the February, March and May 2004 issues. (For new readers, these issues can be accessed by clicking your Back arrow and going to "Previous Issues.") Here it will be necessary to expand on some of the concepts touched upon in these earlier discussions as well as introducing a new one. One concept concerns DNA repair; the other gene "expression." The new concept is that of the "telomere," that structure resembling a shoe-lace tip that sits on the ends of a chromosome and gets shorter each time the cell divides. All three concepts are necessary to our understanding of how cells age and why the aging process is conducive to the rise of cancerous cells.



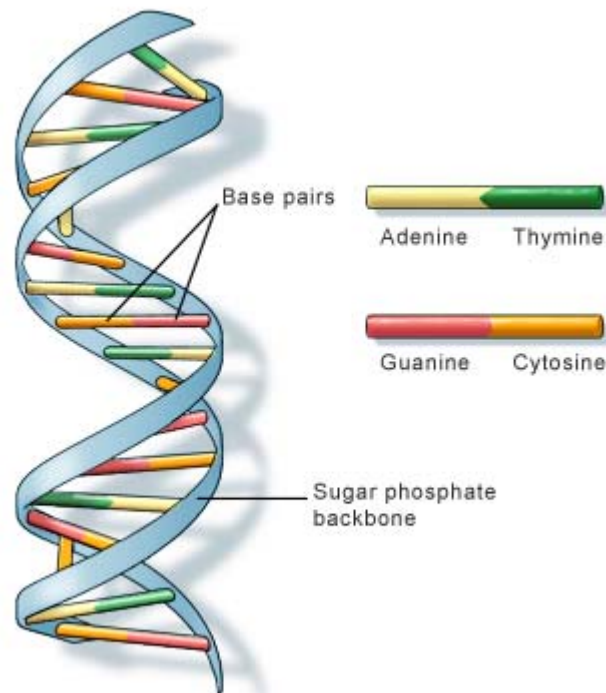
Graphic courtesy of the University of California, Davis, Microbiology Section

DNA repair - as natural as breathing. There are all sorts of insults to the DNA in our cells, beginning in the earliest stages of fetal development. You have probably heard of "oxidative damage" from "free radicals," those species of oxygen molecule set loose in our cells by external sources like radiation or internal sources like the metabolic processes of the cell itself. Indeed, every time we breathe, taking in oxygen, we are producing more reactive oxygen species in our cells. (But what's the alternative?) It is estimated that a cell, a single cell, will sustain 10,000 hits by free radicals *per day*. (This tidbit and much of what follows I have taken from Michael B. Fossel's, *Cells, Aging and Human Disease*.)

But not to worry. A "hit" is only a problem if it causes lasting damage. In your typical robust, healthy cell, it does not. Mama Nature didn't raise no fool, and any living cell has a number of mechanisms that routinely deal with these hits. The first is that of sequestering the free radicals within the mitochondria of the cell where they cannot reach the nucleus that contains the cell's DNA and where they eventually degrade. There are "scavenging" molecules that patrol the cell specifically to find free radicals and turn them into "trapped" radicals. Secondly, there is a detection and repair process that takes place every time the cell divides. Lastly, if damage exceeds what the cellular repair crews are capable of fixing, a pattern of programmed cell death, "apoptosis," kicks in and the cell is eliminated from the body. Thus, those 10,000 daily chances for a cell to go wrong and start down the pathway to cancer, are essentially reduced to zero. Cellular defense mechanisms of this sort, far more than our germ-oriented immune systems, are our greatest bulwark against cancer.

The process by which a cell detects "mistakes" in its DNA sequence is quite an electrifying affair. An interview in the New York Times with Dr. Jacqueline K. Barton, who studies this process, hints at the cellular mysteries being unraveled in this research.

"What many people don't realize is how dynamic the structure of DNA is," said Dr. Barton, her fingers fluttering lightly over the (double-helix) model. "The base pairs are always moving and vibrating, electrons are migrating, holes are opening up and closing through the center of the DNA." It's like a kindergarten class," she said. "Nothing stays still for more than a femtosecond here or a millisecond there."



U.S. National Library of Medicine

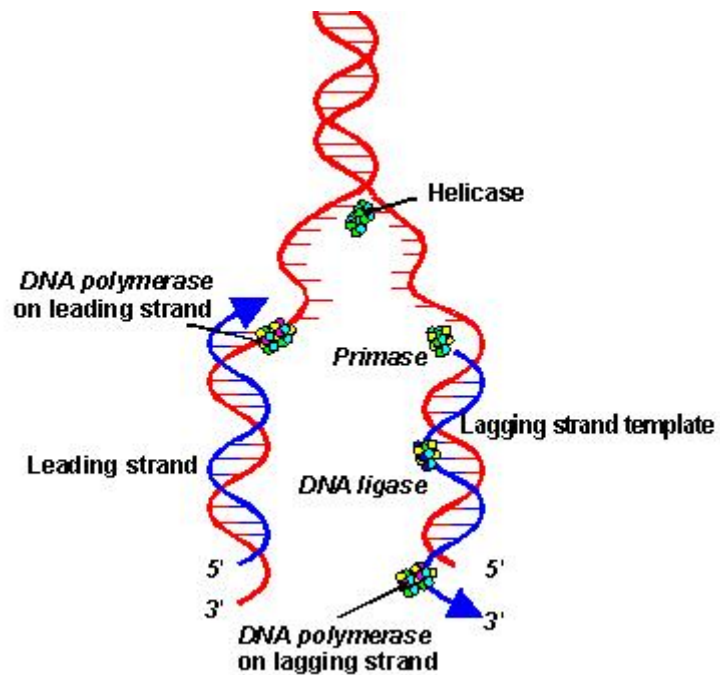
An important property of DNA is that it can replicate, or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell. [U.S. National Library of Medicine, *Genetic Home Reference Guide*.]

Dr. Barton and her colleagues are seeking to understand just how the double helix manages to be at once so twitchy and so reliable, capable of constant interchange with tens of thousands of proteins and other small characters in the cell, hammered at by blistering chemicals, ultraviolet rays and corrosive free radicals, and expected to split and split and split again, spawning numberless generations of daughter DNA molecules in the course of cell division; and all the while still staying sane and functional and relatively error-free.

Dr. Barton proposes that the DNA molecule polices itself electronically, periodically delivering a flow of charged particles from Point A to Point B to check for mutant, misplaced bases that might be skulking in the corridors. If the electrons proceed unimpeded, she suggests, all is well. But if there is a kink in the sequence, the smallest sign of a nascent mutation, the flow would short-circuit. That break would in turn sound an alarm, alerting the cell's DNA repair crew to fix the mess now, or at least sometime before lunch. [8]

DNA "repair crews" (there are apparently several) actually are a collection of genes that "switch on" when there is any signal of trouble from the detection process. These genes do what genes do - they instruct the cell to produce proteins, in this case proteins that collaborate in clipping out the mistaken

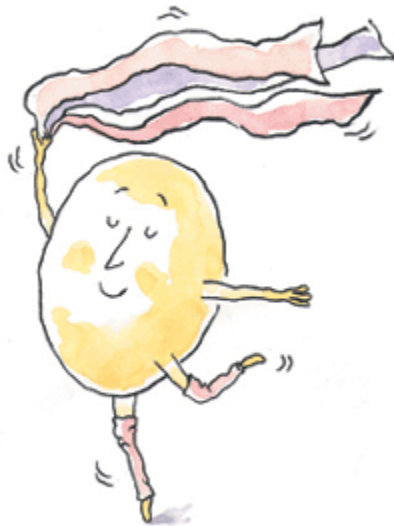
piece of DNA, generating a "good" new segment, and inserting it into the genome before the double helix "zips" itself back up. Below is a graphic of the unzipped double helix, and a brief explanation of how DNA is replicated.



DNA replicates so that from one helix of DNA emerge two "daughter" helices. These daughter helices are exact copies of the parental helix. DNA creates daughter helices by using the parental strands of DNA as a template. The first step in DNA replication is the separation of the two DNA strands that make up the helix that is to be copied. An enzyme called DNA helicase untwists the helix to form a Y shape called a replication fork. The replication fork moves down the DNA strand, splitting it into two single strands. Next, an enzyme called DNA polymerase helps new nucleotides line up next to the two separated strands, according to the rules of base pairing: adenine and thymine pair with each other, and guanine and cytosine pair with each other. As new nucleotides line up at the appropriate spots along the original strand, they form the "rungs" on the new DNA molecule. Ultimately replication produces two new DNA molecules that are identical to the original molecule. Replication is complete when both of the new strands have formed and reword into their characteristic double helix shape. [Taken from Barnes & Noble's Sparknotes, at <http://www.sparknotes.com/testprep/books/sat2/biology/chapter6section4.rhtml>]

The idea that genes can switch on and switch off again, as the DNA repair genes do, leads us into our next concept, the concept of "gene expression."

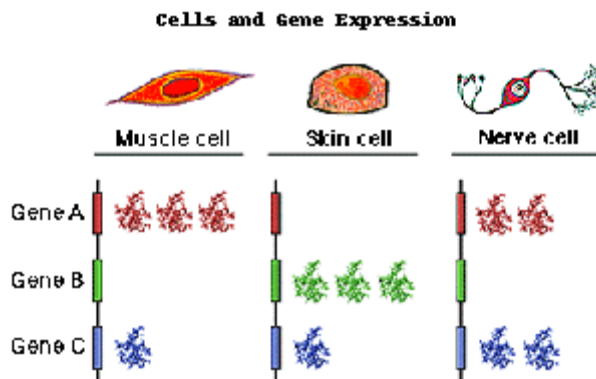
Gene Expression



© 2001 KF Dunn & Associates

Noisy genes and silent genes. Quick. How do you tell a muscle cell from a skin cell, genetically? After all, inside the nucleus of each is the double helix that contains our entire genome, all those 30,000 some genes that collectively produce our total body.

Answer. In any particular cell, not all of these genes are "switched on" or "expressed." A significant percentage are permanently silent, leaving only a particular pattern of "expressed genes" that is characteristic of whatever organ or tissue the cell came from - a nerve, the muscle, the skin, etc.



Graphic courtesy of the National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD

Furthermore, within the pattern itself of a particular cell type, there will be genes that are silent much of time, but that wake up and do their thing only when suitable signals from their environment arrive to prod them into action. The DNA repair crews are only one example.

- Every time we sustain a wound, silent genes inside the cells of all the tissues affected by that wound, wake up and blaze into action,

producing proteins that will set healing in motion. As healing progresses, the emergency signals diminish and the awakened genes gradually fall silent once again.

- As we grow, or simply put on weight, genetic "body building" kits switch on to produce more vasculature and tissue - muscle, nerve, fat! - to bring into being a larger body.
- At puberty, a master switch is thrown in our brain and pituitary gland that sets in motion a cascade of hormones. These hormones, acting as signals, pervade the tissues and organs of the body where sensitive cells in the right places respond - their relevant genes "waking up" and bringing about the appearance of secondary sex characteristics, overall physical growth and sexual thoughts and interests. A burst of development takes place, but in 6 years or less, the process is dialed back to a less aggressive, self-sustaining level.
- And ooh! Here's the fun part. Within limits, some genes are activated or silenced by events going on in the creature's environment, not simply by internal processes. For example, baby mice that receive a lot of licking and grooming from their mothers turn out mellow and stress-resistant, while youngsters whose mom's have been neglectful are nervous wrecks. The molecular silencer that sits astride a key stress-receptor gene in brain cells is apparently the key. Grooming sends signals that eventually remove the silencer and the gene does its beneficial thing. [6]

What if a molecular "silencer" were to latch onto a crucial DNA repair gene in the cell? Alternatively, what if a molecular silencer were removed when it shouldn't be, perhaps a silencer that normally keeps the cell from dividing excessively? What if silence were to fall over the genes that set apoptosis in motion when the cell's DNA is damaged beyond repair?

You get the idea. Specific changes in the *pattern of gene expression* within a cell can set that cell on a cancer pathway. The study of this class of phenomena is called "epigenetics." "Epi" comes from the Greek word for "upon." The silencers referred to above are carbon or methyl tags that sit "upon" the gene. Patterns of gene expression are sometimes called *patterns of methylation*, and some speak of these patterns collectively as the "epigenome." We could think of our genome as a vast pipe organ constantly played upon by the secret fingers of the epigenome. There is an exciting science being born here.

The website of EpigenX Pharmaceuticals has a nice easy introduction to this subject, and contains the following thinking about cancer.

Methylation of cytosines in certain control regions in our genome causes genes to be inappropriately silenced. Up to 65% of all cancers appear to be related to such methylation abnormalities. It is believed that the inhibition of methylation can be used as a therapeutic strategy to fight such cancers.

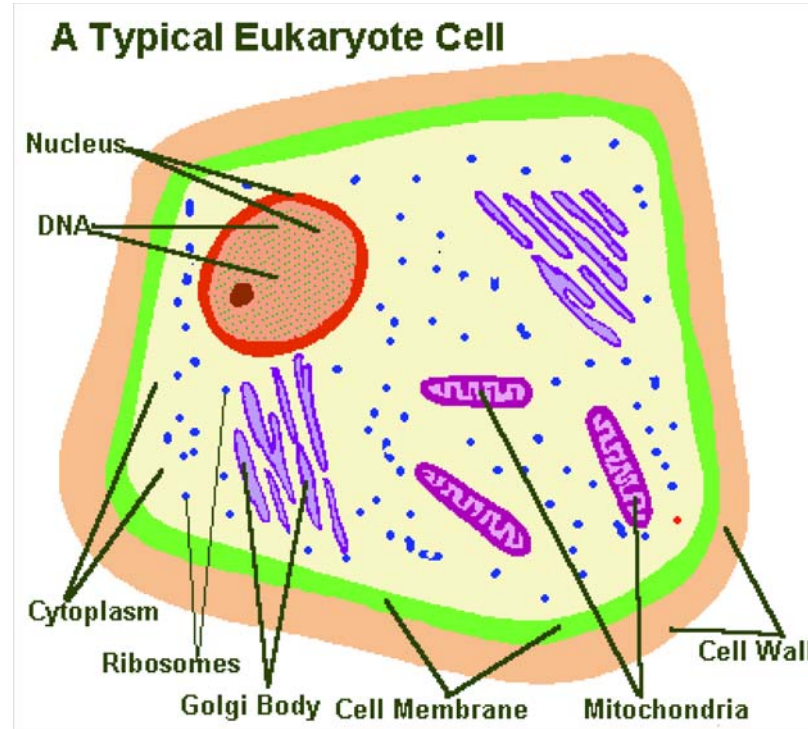
<http://www.epigenx.com/science.htm>

Coming soon to the Web, and to supplements shops near you, will

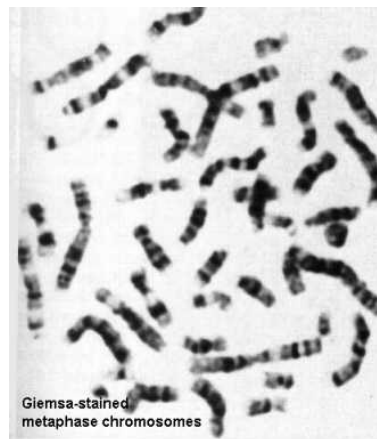
undoubtedly be a fresh batch of quack remedies featuring the concept of methylation! Oh well.

Telomeres and Telomerase: This discussion has been building up to the cumbersome new concept that we need to finally establish links between cancer and aging, or more specifically, between cancer and *cellular* aging. This concept is that of the telomere, and the protein required to produce it, telomerase. To show you what a telomere is, it will help to run through a series of pictures.

1. First the cell and its nucleus. While we're at this picture, notice those mitochondria where the "free radicals" will be sequestered.

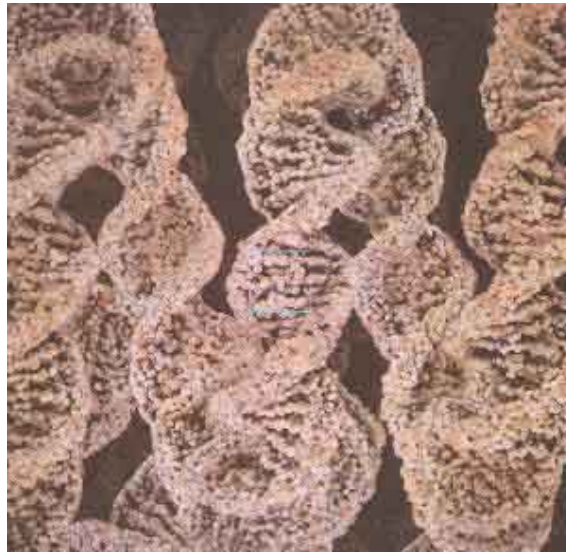


2. Next we see the little packages of genes, called chromosomes, that are found within the cell nucleus. Each chromosome is composed of a distinct collection of genes arranged in a characteristic sequence. Each of our somatic cells contains 46 chromosomes, while each of our germ cells (ova or sperm) contains half that number.



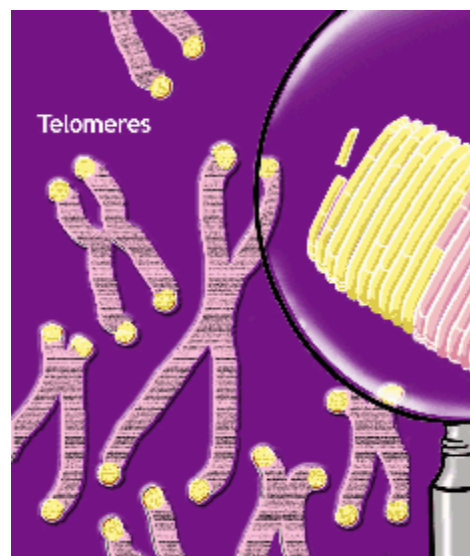
The chromosomes' appearance will vary according to whether or not the cell is dividing. Often they are depicted as little worm-like X's, as in a later picture below.

3. Next, the famous DNA "double-helix" which is the structural arrangement of the genetic material inside the chromosome. It really does look sort of like the models. Here it is under the electron microscope. Scroll up to see our earlier picture of two graphic models showing the ladder-like base pairs circling down like a spiral stair-case.



This picture, originally published in Philip and Phylis Morrison's, *The Power of Ten*, was taken from the Eye Design Book website with permission (<http://www.eyedesignbook.com/ch4/eyech4-cd.html>)

4. Finally, a picture of chromosomes illustrating that feature we've been leading up to: the telomere ("TELL-uh-mere"). Here the chromosomes are depicted in the X structure formed just after DNA replication is complete but before the cell has physically divided.



Graphic by Joanne Nova

As the picture illustrates, the chromosomes come "tipped" with a cap called the telomere. Telomeres are not genes, but they are composed of DNA base pairs just as genes are. Their function has been variously described as

- keeping the chromosomes from unraveling
- providing that extra stretch of DNA needed to make cell replication possible
- keeping the genetic sequence inside the chromosome from getting scrambled
- keeping the genetic sequence inside the chromosome from being mistakenly "repaired" by the DNA repair crews

Why the chromosome always needs to "waste" a few base pairs of DNA each time the double helix zips itself back up again, I can't explain to you. (The explanation is a bit too mathematical for me). But it does. And if there were no neutral supply of DNA to use, it would have to use a piece of a whatever gene sits nearest the tip. Well, that won't do! So, undoubtedly one of the most important functions of the telomere, in the list above, is that of providing a supply of neutral DNA base pairs to waste during cell replication. Notice in the picture above that a little snippet of substance is detaching itself from the telomere. That would be a few base pairs of neutral DNA.

It also happens to be the case that when a telomere is missing (i.e. removed by scientists in the lab) bad things do happen to the exposed ends of the chromosome. They glue to each other inappropriately, resulting in scrambled gene sequences; they get attacked by the DNA repair crews, etc. The protective functions of the telomere become apparent when it is absent. But normally, it would never be absent, UNLESS...

You guessed it. *Unless, it's been all used up by cell replication.* As you can deduce, there is a ticking clock inside this chromosomal design. Unless the cell can renew its length of telomere each time it divides, the day will come when there is none left and the tips of the chromosomes have no protection. Then the cell has to make some really tough decisions. Cancer, from degraded and scrambled genes, is one such decision.

But let's not rush the story.

Certain cells throughout their lifetimes express the gene that codes for the protein that renews telomeres, called telomerase ("tell-AH-meraze"). When this gene is "expressed," telomerase will replenish the telomere and the cell can then go on and on like energizer bunny. In the lab at least, any cell, even one approaching death, if fiddled with in a way to wake up the telomerase gene, will promptly become a healthy functioning cell again. Cell mortality is thus reversible.

But which cells express telomerase? Germ line cells (ova & sperm) express it and are usually the only truly immortal cells in our bodies. Embryonic stem cells express telomerase, but once they start differentiating, the story changes. And cancer cells have re-acquired the ability to express telomerase,

thus "immortalizing" themselves. On the other hand, our somatic stem cells, which are in charge of replenishing the body's supply of cells, seem to start out expressing telomerase, but gradually, the relevant gene *falls silent*. Then the clock starts to tick. Over the course of many replications, the telomere shortens and *the pattern of gene expression* for the whole cell begins to change. It is as if the shortening telomere casts a shadow ahead of itself, silencing genes that were previously expressed, and causing other genes, previously held in check by an active counterpart, to wake up and express themselves inappropriately. The actual mechanisms involved in this are still poorly understood. [1]

Could cancer therapies be based on these findings about telomerase? Many people think so, but answer me this question. Would you rather flood your cells with telomerase in the hopes they would all convert back to healthy, normal, youthful cells - thus presumably delaying the appearance of cancer and other age-related disease? Or would you rather shut down telomerase everywhere it's still found in your system so that the cancer cells lurking in your body would age and die? Both approaches have their advocates. Both approaches have their problems. We'll see. Meanwhile, you can be sure that coming soon on the Web, or in a supplements shop near you, will be a fresh batch of quack remedies based on the concept of telomerase.

Cellular aging as replicative exhaustion. We can now look at aging in a rather new light. It is a process that unfolds over time, but is not strictly correlated with the passage of time. Rather, it is correlated with the shortening of the telomeres as our cells replicate. The symptoms and appearances of aging in our bodies are a function of the various outcomes of replicative exhaustion that our cells will eventually manifest.

There are three main outcomes to this pattern of replicative exhaustion. One is apoptosis, or programmed cell death. Aging thus involves losing a lot of our cells. Another is something called *cellular senescence*. Here the pattern of gene expression produces a cell that is much reduced in functioning and has a characteristic flattened appearance. Its cycle of growth and division is greatly slowed. The proteins it previously exuded in abundance, and the hormones and other signaling substances that depended upon these proteins, decline in the body. Its cellular repair mechanisms begin to fail. As far as free radicals are concerned, the cell is producing more of them, through inefficiency, but its mitochondria are beginning to leak, allowing the trapped ones to escape. Its DNA repair slows because its ability to produce the substances that go into making "replacement parts" has slowed. Its ability to respond to internal or external signals telling it to commit apoptosis also diminishes. The senescing cell becomes less and less able to pull its weight in the cellular neighborhood and this puts stress on its neighboring cells, which then may be required to exhaust themselves in replication. Michael Fossel writes:

Senescing cells drag down other cells. Extracellular effects may start locally as a subtle change in the function of a neighboring cell or a subtle change in the extracellular matrix, but the effects progress to neighboring tissue planes, to entire organs, to

downstream parts of the vascular bed in which they lie, and ultimately, throughout the organism. What begins as cell senescence ends as age-related disease. [1. p 55]

The third, and least welcome response to this downward spiral is, of course, cancer. The risk should in theory be rising in proportion to the changing genetic patterns in our senescing cells, and when we look at cancer in general, and people in general, that is exactly the way the statistics play out. About 1/3 of the people in the U.S. population will face cancer in their lifetime. The remaining 2/3 will die of other causes before ever hearing the fateful word. The greatest portion of these other causes will be other age-related chronic diseases.

Different strokes for different folks and different cells. Bear in mind that, in the age game, not everybody has the same genetic starting point. Some people appear to either age more slowly or age in a more cancer-resistant fashion. Some studies have shown that these slow agers have longer telomeres than their compatriots who are dying around them. But there are many other factors in the mix, including life-style and medical history. Studies of the extremely long-lived have shown that while they usually followed no specialized diet, they report no history of being over-weight and very little contact with doctors [10]. Interesting. Other studies have revealed that some people, presumably for genetic reasons, have the ability to more rapidly eliminate environmental pollutants from their bodies. These people prove to be more cancer resistant. [7]

On the cellular level once again, each cell type in our body has its particular replicative quotient. Heart cells, for instance, virtually never divide. This means they conserve their telomeres. Have you ever heard of heart cancer? There is such a thing, but it is quite rare. Similarly for the neuron cells in our brains. Most brain cancer originates in the replicating glial cells, not in the seldom-dividing neurons. By contrast, the epithelial cells that form the "linings" of organs and interior spaces, are great replicators and are also the main source of "carcinomas" - the commonest family of cancers, which includes all the reproductive cancers, as well as lung and colorectal. People whose lifestyle and/or medical choices involve doing things that cause their high proliferation cells to proliferate even further have been shown to have an elevated risk of cancer in the areas where proliferation was boosted. Hormone replacement therapy, or indeed any hormone boosting later in life, is ill-advised for this reason.

Can we put the brakes on replicative exhaustion? Perhaps. This is the buzz surrounding caloric restriction, as mentioned in the February 2005 newsletter ("Lifestyle Update"). Caloric restriction consists of carefully maintaining nutrient balance while cutting one's total calorie intake by 30-40%. It has been shown to increase the lifespan, and delay the appearance of cancer, in all tested mammals. The mechanism involved is still not well understood, but it apparently changes the pattern of gene expression, just as aging itself does, but in the reverse direction [9]. There is no re-lengthening of telomeres, however. Rather, Dr. Fossel speculates that caloric restriction, the equivalent of semi-starvation, increases protein turnover in one's cells

and this enables cell repair processes to speed up, and thus catch up, with the ongoing damage. The cell is not immortalized, but it is given a tonic.

Practical Applications

Humans are not among the mammals that have been tested on caloric restriction. No surprise there. Notes Fossel, "Human patients are notoriously resistant to permanent dietary change, let alone a 30% reduction in caloric intake." [(1) p.10] A more promising approach, medically, would be to work out the mechanisms that are involved in the benefits of caloric restriction and see if they can be triggered through some other means. Drugs that inhibit glycolysis or enhance insulin action are now being assessed [3]. Another research team working with mice reports that intermittent fasting has an even greater anti-aging benefit than daily caloric restriction [5]. If that proves to be true, do-it-yourselfers might start reviving the lost art of fasting. In fact, despite what Fossel claims, there are already websites for caloric restriction enthusiasts touting various diets that these enthusiasts claim will limit calories while providing sufficient nutrition.

What is the take-home advice from all of these researches? At present, we are reluctant to recommend caloric restriction approaches. There are dangers. One is that people will malnourish themselves despite their best researches into what is a nutritionally adequate diet. Even more seriously, severe dieting is associated with the appearance in dieters of *anorexia nervosa*. This is a psychopathological condition characterized by loss of appetite and aversion to food. It is difficult to treat and can prove fatal. Another thing to consider is that, except for the weight one might have lost through the caloric restriction diet, its anti-cancer benefits rapidly screech to a halt and reverse themselves shortly after the diet is violated. Cells that have perked up because of the diet lapse back into their "old" ways.

Researches into the fate of the aging cell do, however, lead us to reemphasize certain approaches already in use.

- First, it seems reasonable to start or continue one's use of dietary anti-oxidants, as these presumably have some modulating effects on the amount of oxidative stress one's cells undergo.
- Get screened. Age 50 through the early 70s define the age range in which cancer screening has its greatest life-prolonging benefit. The mammogram for women, the PSA test for men, the pap smear (which should start even earlier), the colonoscopy, and perhaps other tests indicated by family history, all are able to bring to light the early and more treatable cancers and pre-cancers. The patient too, in this age range, is usually vigorous enough to endure and rapidly recover from cancer treatment.
- Avoid, when possible, any diets, medications, and treatments that rely on hormones to achieve their effects since these cause cell proliferation in the reproductive system. High fat diets produce cell proliferation in the lining of the colon, while smoking causes a "wounding" of the lungs and bronchia that necessitates new cell growth. (This is over and above its directly mutational effects.)

- Finally, there is one "age retardant" that might be more easily controlled by the individual. This is reducing psychological stress. Some recent studies have shown that stress, as we rather darkly suspected, does indeed speed up aging. Specifically, women who were long-term caregivers of ill children, and who reported high levels of perceived stress, were found to have shorter telomeres than women in the control group. It is theorized that stress hormones are producing this cellular response. [2]

These three fronts on which to wage the anti-aging, anti-cancer battle are especially applicable to women and men caught in the "sandwich" generation: still dealing with children at home or college, while trying to be there for aging parents as well. Our library has numerous titles on coping, caregiving and taking care of the caregiver that might be helpful in this regard. I have listed several below.

- Always on Call: When Illness Turns Families into Caregivers*, by Carol Levine (Editor)
- Another Country: Negotiating the Emotional Terrain of Our Elders*, by Mary Pipher
- Caregiver's Rollercoaster: A Practical Guide*, by Billie Jackson
- How to Care for Aging Parents*, by Virginia Morris, Robert M. Butler
- Taking Time for Me: How Caregivers Can Effectively Deal with Stress*, by Katherine L. Karr
- Be Sick Well: A Healthy Approach to Chronic Illness*, by Jeff Kane
- Dancing in Limbo: Making Sense of Life After Cancer*, by Glenna Halvorson-Boyd, Lisa K. Hunter
- Expect Good Things*, by Lynne Gerard
- Fire in the Soul: A New Psychology of Spiritual Optimism*, by Joan Borysenko
- Grace and Grit : Spirituality and Healing in the Life and Death of Treya Killam Wilber*, by Ken Wilber
- Surviving Cancer Emotionally*, by Roger Granet

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