

**SERVICES OFFERED**

**GUIDE TO  
COMPREHENSIVE  
CANCER CARE**

**PATIENT / FAMILY  
RESOURCE CENTER**

**SELF CARE GUIDES**

**TESTS & PROCEDURES**

**COMPLEMENTARY /  
ALTERNATIVE CARE**

**HOME**

## *In the Know*

### **Connecting Patient / Family Library Patrons To Information, Ideas and Resources**

**February 2004**

from

**The Duke Patient/Family Resource Center**

The Duke Patient/Family Resource Center is:

- A lending library offering books, audio and video tapes, magazines and free brochures dealing with cancer and certain blood disorders and with issues of coping, survivorship, caregiving, and grieving
- Open 8:30 to 5:00 every day the Morris Clinics are open
- Located in the White Zone, first floor, of the Morris Cancer Clinic, Room 15123.
- Our phone number is 919-684-6955. Our email address is [FamilyLibrary@mc.duke.edu](mailto:FamilyLibrary@mc.duke.edu)

**Resource Center Coordinator:** [Harriet Whitehead, PhD](#)

**Cancer Patient Education Program Director:** [Kerry Harwood, RN, MSN](#)

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## **Introduction**

Several months back, curious about how our library could better serve patients and their families, we conducted a survey in the waiting rooms to

find out (among other things) the topics of greatest interest. The number one topic turned out to be “The nature of cancer and the sorts of research being done on it.” We were caught short on this one. Though we have hundreds of books in our library that are addressed to specific cancers, only a tiny few books in our entire collection specifically address cancer in general, and these few are getting a little dated. How did this situation come about?

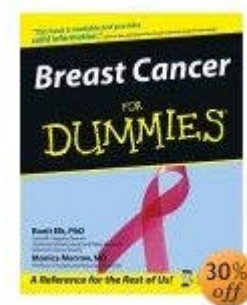
Well, for one thing, the topic is harder than most people realize. If you want to understand cancer research today, you have to understand something about molecular genetics, and molecular genetics is a tough read, even for the highly educated. Moreover, it seems that none of the experts who truly understand the subject has bothered to sit down and write a “Cancer for Dummies” book that might help us get started. I scanned Amazon.com for that title. After all, there's "Arthritis for Dummies," and "High Blood Pressure for Dummies" and "Diabetes for Dummies." Why not cancer?

Close but no cigar. I discovered “Breast Cancer for Dummies” and “Prostate Cancer for Dummies,” both of which seem eminently worthwhile. But like most of the books the Resource Center already has on specific cancers, neither of these “Dummies” books devotes more than a few paragraphs to the nature of cancer itself. Their real concern is explaining treatment options and how to manage your life situation. Fine. But many people don’t really understand their treatment options because they don’t really understand the nature of cancer.

The reason for wanting to get the big picture on cancer – and our survey responders must be feeling this – is to see why the doctors are making the often mystifying decisions that doctors make when it comes to dealing with the disease.

There may be another reason why no one has written the book we’re looking for. The molecular genetics of cancer field is developing so fast that by the time “Cancer for Dummies” were to hit the bookstores, half of its contents would be outdated and misleading. Experts don’t relish being the authors of such books. They envision their colleagues calling them up and saying things like “Man, are you still flogging that dead horse?” Or they envision getting half-way through the book, with tremendous labor, only to find they have to revise the whole thing. For all we know, there are dozens of half-written books out there right now that got left in the dust by some new research finding.

Well, guess what. If we can’t find someone else to do the job, we’ll have to do it ourselves. We don’t mind becoming outdated. After all, we put out a monthly newsletter and can update our perspectives every month! That’s why our next couple of installments will be entitled “Cancer for Dummies,” and will aim at providing a useful simple portrait of cancer that fulfills the following criteria: (a) you can understand it, (b) you will see, from this portrait, why doctors make the decisions they do, and (c) you will be able to appreciate some of the new treatment, prevention and screening possibilities

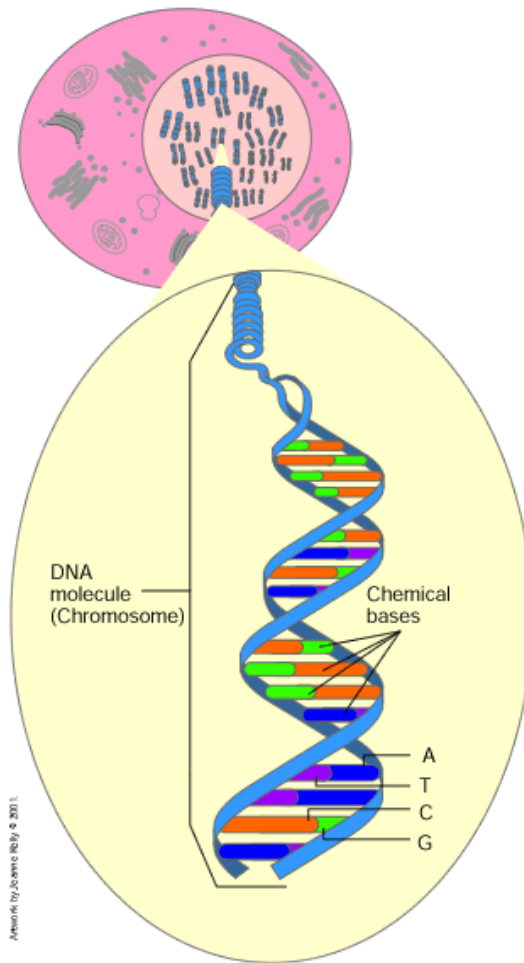


that lie on the horizon.

With no further ado, let us begin.

## Cancer for Dummies, Part I

**Cell trouble:** Cancer is a disorder of cells, so it is best to start with a brief word about these little guys. Cells are the microscopic building blocks of our bodies; about a million of them can dance on the head of a pin. The body contains several trillion. Within their infinitely tiny boundaries, an enormously complex orchestration of molecular activity is constantly going on, as the biochemical factors that sustain the cells and the life of our body are generated and sent into action. At the heart of each cell, its nucleus, sits the entire genetic code ("genome") for the body: those 23 chromosomes, along which are strung the clusters of DNA molecules called genes.

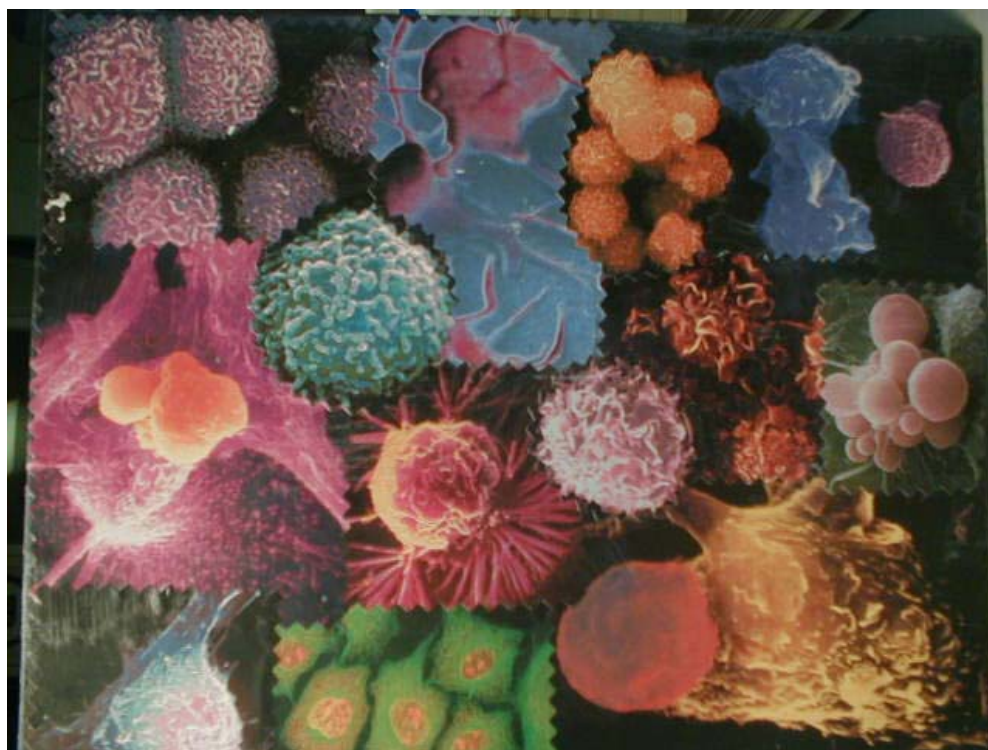


The field of molecular genetics is the study of these DNA molecules. (DNA is short for “deoxyribonucleic acid”, the organic acid out of which genetic molecules are constructed.)

Early in the life of the fetus, the fetal cells start to become specialized. Each

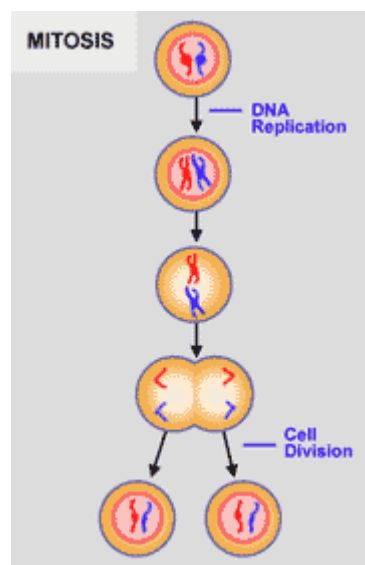
has the ability to become any part of the human body, these are the classic “stem cells,” but rather than persisting in this generalized state, the cells shut down large parts of their genetic material and confine themselves to being just liver cells, or stomach cells, or heart cells, or lung cells, or retinal cells, etc.

Each type of cell has its distinct appearance and character. Even when a cell becomes cancerous, it usually retains enough of that distinct appearance so that pathologists can identify its place of origin. Under the microscope, it is still a breast cell or a lung cell, for instance. It retains much of its distinctive character as well, such as its way of reacting to different chemotherapies and hormones. That is why when breast cancer cells migrate to the liver, they do not give rise to liver cancer. Rather, they are still breast cancer and must be combated with the chemotherapy specific to breast cancer, not to liver cancer. Below is a collage of cancer cells from different organs and systems constructed from images taken under the scanning electron microscope. You can see the diversity of appearance.



**Protein factories:** Cells have been likened to little factories because their main business in life is the production of the proteins that make up life. The role of each gene (each active gene) in the cell’s nucleus is to issue the “instructions” – the code – for the production of a certain protein. It is the biochemical interaction of proteins that then produces and renews physical structures. Proteins furnish the building material, but equally importantly, they operate as the signaling system that coordinates the building and the maintenance of structures. When signals go wrong, because a protein has gone wrong, because the gene for making that protein has suffered a “mutation,” then structures, in turn, start to go wrong. A cell is in trouble. Not all such trouble leads to cancer, but some does.

**Carcinogenesis: the “origins of cancer:”** Each cancer can be traced to a single transformed cell that set the cancer in motion. The transformation has to be of certain sort, however, and it typically requires an accumulation of genetic mutations within the cell. The most likely time for a mutation to occur is during cell division. Every cell must periodically undergo cell division to rejuvenate itself, entering a cycle where it expands, doubles and then splits its genetic material and forms into two daughter cells. This is called cell mitosis.



For an animated Web movie of cell mitosis, visit <http://www.cellsalive.com/mitosis.htm>

Every time cell division takes place, there is a chance for a genetic mistake to occur. Genetic material is being copied at this point and the copy system may malfunction. Instead of one copy, multiple copies of a certain gene might be made, as if from a stuck xerox machine. This gene can now start flooding the new daughter cells with its proteins, drowning out the input from other genes. Or the sequence of genes on the chromosome may be disrupted, so that their proteins no longer coordinate properly and the cell stops functioning properly. Often a whole

chromosome will drop out, leaving the cell bereft of a variety of genes with their attendant proteins.

But as the Australians say, “No worries.” At least not usually. Normal cells have repair mechanisms and are able to clean up much of this sort of damage before completing cell mitosis. Normal cells even have a process for committing cell death – called “apoptosis” (pronounced "a-puh-TOE-sis") if the damage is too severe. Last, but not least, normal cells have a limited number of divisions coming to them. Once they use these divisions up, they (or rather their descendants) expire. This is why we age. You may have noticed how thin the skin of elderly people becomes. Reason: many of their skin cells have checked out for good.

In other words there are a lot of safeguards, at the cellular level, against genetic mutation. But the soon-to-be cancer cell has mutated in a direction that evades these usual safeguards. Some geneticists speculate that the first and most crucial change is a mutation that guarantees the cell an infinite number of divisions. It can now spawn a whole line of “immortal” cells, any one of which may, with another genetic “accident,” progress further down the road to cancer, passing on its “immortality” to its even more dangerous daughters, and so on. The remaining mutations required to produce a true cancer are just, so to speak, a matter of time.

What are these remaining mutations? The most essential of these involve the cell losing the genetic wherewithal to properly regulate itself. One type of dis-regulation results in the cell becoming unable to shut down its natural cycle of growth and division. The "on switch" for growth and division has been thrown, by one gene, but there is no longer any countervailing "off switch" to stop the process, as the gene responsible for the off switch has been damaged and is no longer functional. A key protein has dropped out of the system. Another mutation can result in the cell being unable to repair its own genetic damage as normal cells do. Another can erase the cell death (apoptosis) mechanism or raise the threshold of damage needed to set apoptosis off.

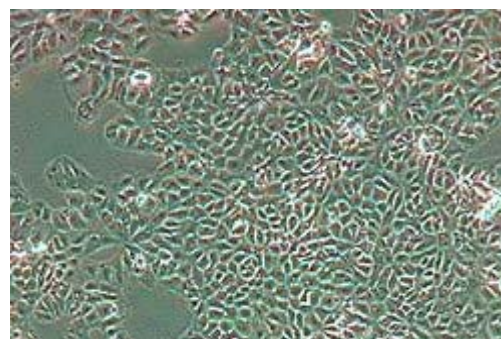
Below is an account from ABC's *News in Science* of a cancer genetics finding that will help illustrate the point about "on switches":

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## myc sends cancer cells out of control

Wednesday, 13 October 1999

Scientists have found a critical gene that, at the same time, takes the 'brakes' off and accelerates cell growth often leading to rapid growth of cancer.



Researchers at the University of Rochester Medical Center, US, in the October issue of [the Journal of the European Molecular Biology Organization](#) (EMBO), describe their finding that myc, one of the body's most potent cancer-causing genes, not only promotes cell growth but removes the inhibitions to cell growth.

"Myc is central to our cells' ability to grow, divide, and even die when they should," says Hartmut Land, director of the University's Center for Cancer Biology and lead investigator of the EMBO study. "Basically, myc is like the starter of an engine; it's responsible for making the whole cell go. It's a very potent gene, but one that's been slow to yield its secrets."

Land's team showed that myc controls another protein, cyclin D, known to play a big role in making cells grow; the EMBO paper marks the first time scientists have identified the 'brains' behind cyclin D's actions. Land's team

also found that cyclin D can not only accelerate growth, which has been known, but also knock out the proteins that a cell normally uses to put the brakes on growth, a surprising finding.

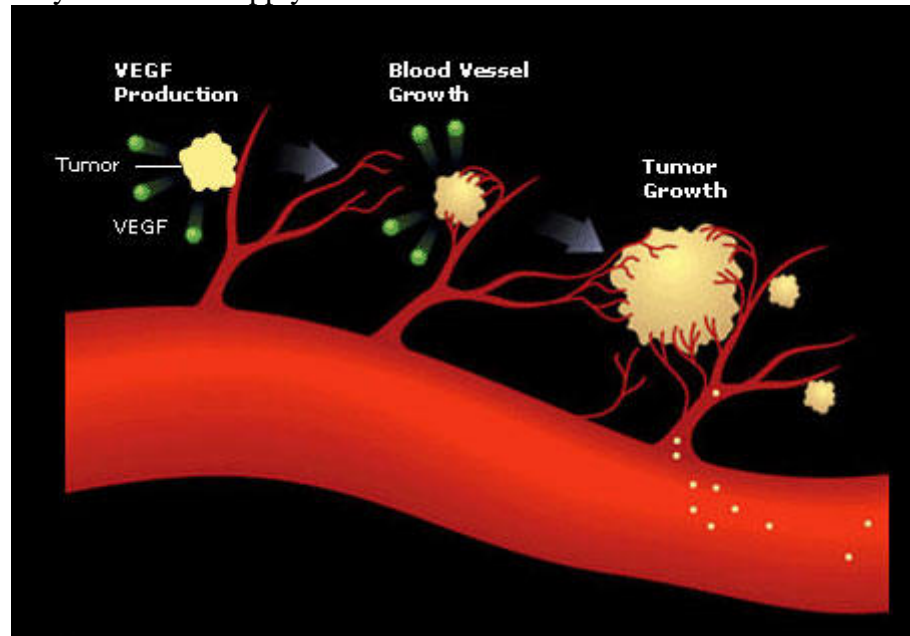
For more *News in Science*, visit <http://www.abc.net.au/science/news/>

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**The perfect storm:** When four of the most essential mutations (“the perfect storm”) are present – infinite divisions, no repair mechanisms, no apoptosis, and no way to shut down growth - a cancer scenario begins to play out. The cancerously mutated cell divides into two daughter cells that have the same genetic defects, and these two instantly set about growing and dividing again. If they, or any of their offspring, should be hit with a later mutation, chances are no repair will be done on this because key repair mechanisms are broken. Instead, these even more mutated daughter cells will proliferate as well. So, as the descendants of the original cell increase in number, they also increase in genetic diversity. At an increasing rate, they stop being perfect clones of each other, and become more and more a motley collection of wild-haired relatives. “Clonal variants” is the more scientific term for them.

**The talented Mr. Cancer Cell:** We have a cancerous process launched now, but we’re not yet at a fully malignant state. The cells have lost important abilities and are multiplying like mice. But to get a full-blown malignancy, you have to have these impaired cells also “acquiring” new abilities. This makes it sound as if the cells are acquiring new genetic material they never had before, but this is impossible. More plausibly, one of two things is going on. The new “acquisitions” may really be just new losses. There are many abilities within normal cells that are *dormant* until called upon by special circumstances. If a mutation knocks out the process that usually keeps this ability dormant, the ability will suddenly turn on full-time. It will look as if the ability was suddenly “acquired” when in fact, it was always there, but held in check. In other words, genetic loss is still the key, but in these cases, the loss of an inhibiting component. This turns into gain for whatever was formerly inhibited. A second possibility is that a gene, by mutation, is now represented by multiple copies of itself, all of them instructing the cell to produce the protein associated with that gene. If overproduced at a sufficient rate, a protein can simply override the inhibiting component (another protein) and cause the formerly latent ability to turn on full time. There is evidence that this process too can cause a cancer cell to develop new “talents.”

An example of a cancer cell talent is the ability of cancer cells to exude a protein that signals nearby blood vessels to send out new branches that will bring nourishment to the signaling cell. (One such protein is labeled VEGF, see picture). Normal cells have this ability dormant, and are able to turn it on when a wound touches them that requires healing. As the injured cell begins to signal, newborn tiny blood vessels flock to the wounded area bringing nutrition and oxygen to speed wound healing. Cancer cells apparently have mutated so that this latent signaling ability is turned on

permanently. What an advantage to a budding tumor – it can now recruit its very own blood supply!



Another ability cancer cells “acquire” is the ability to invade the tissues around them by breaking through the walls of normal neighboring cells. This invasive ability distinguishes a malignant tumor from a benign growth like a fibroid or a wart. Benign growths such as warts contain cells with proliferative abilities but they cannot pierce surrounding tissue. Molecular geneticists are beginning to focus in on another “loss” to explain this piercing: the loss of a protein that normally enables neighboring cells to communicate with one another and abstain from mutual invasion.

Eventually too, given their genetic instability, some among the crowd of proliferating cancer cells will lose the genetic information that causes normal cells to cling together in their place of origin and to self-extinguish when cut loose from this matrix. With this loss, cancer cells now slip away from the original tumor and find their way, as single cells, into the blood or lymph vessels. From there they will be carried to distant parts of the body where they may embed themselves and start new malignancies – the “metastases” of cancer. This is a third distinguishing feature of the truly malignant cell.

In sum, the new truly malignant talents consist of (1) ability to recruit a blood supply (2) invasiveness, and (3) ability to escape into the blood or lymphatic system.

**The secret of cancer’s success:** The same steps that bring a cancer into being help to explain why it’s so hard to get rid of. Lets go back to the fact that cancer cells are genetically unstable (they aren’t correcting their new mutations), and that, as a result, the population of cancer cells in a person’s body will become genetically diverse - the cells are not perfect clones of one another. The fact is, if cancer cells were all perfect clones of each other, cancer would be far easier to treat. A treatment that could kill one of them, could kill all of them. But the genius of cancer, its ability to persist even in

the face of multiple treatments, rests upon its genetic diversity. You may kill millions of cells with your treatment, but it takes only one survivor, one with just enough genetic difference to make it resistant to treatment, to become the mother cell of a new spread that is now even better adapted to its environment – your body. Survival of the fittest! The population of diversely mutated cells in the body becomes an infernal evolution machine.

Treatment of cancer, if it is to be curative, must - in theory - extinguish every cancer cell in the patient's body. Obviously, the larger the population of cancer cells in the patient's body and the greater their genetic diversity, the harder this task becomes. I say, "in theory" above, because there is still a role for the immune system to play in mopping up microscopic amounts of a remaining cancer after treatment is done. We will turn to the question of cancer and immunity in a future newsletter.

**Some reflections on prevention and treatment:** With just this simplified portrait of cancer, we can begin to make sense of certain medical advice and treatment decisions. Let us consider, from this new vantage, the problem of mutation, the importance of early detection, and certain increasingly common treatment approaches.

*Keeping those mutations down:* Obviously, we wouldn't need to worry about treatment at all if the causes of cancer – those lethal types of mutation – could be prevented. Unfortunately, this isn't so easy. Cell mutation is a regular fact of life. Some of us are born with certain cancer-predisposing genetic abnormalities, "germ line mutations" these are called. And all of us, far too easily, encounter things in the environment that cause cells to mutate – things like tobacco smoke or industrial chemicals or the UV rays of the sun. Lastly, our very processes of metabolism set loose "free radicals" in our bodies that have the power to mutate cells.

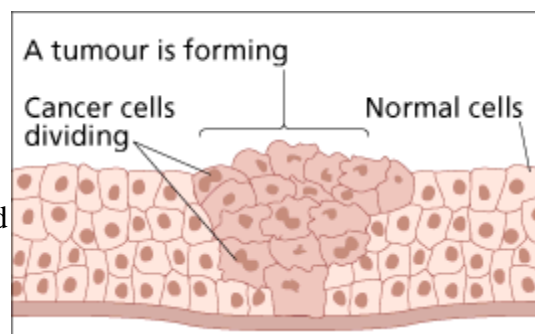
Fortunately, the vast majority of mutations are harmless because they damage parts of the genetic material not involved in cell regulation. Thus the affected cell retains its ability to self-repair, shut down growth, or, if worse comes to worst, commit apoptosis. Another fact of great importance is that it takes more than one mutation to set a cell on the cancer pathway. Even those people unlucky enough to be born with a "germ line mutation" are not guaranteed to develop cancer, because usually at least one more mutational hit is required to produce that lethally transformed cell. In fact, for many cancers, multiple mutations seem to be required. As anyone who bets the trifecta knows, the odds on getting the first three horses in order are much longer than the odds on getting any one horse. Comparably, the odds on getting most cancers early in life are reassuringly long.



But in the end, like horse racing, it is a game of chance. The longer we live, the more of our cells take mutational hits – from internal sources like free radicals or from external mutagens like sunshine - and the greater our chances of having one cell win the trifecta and undergo a malignant transformation. That is why age itself is the single greatest risk factor for cancer.

There's another factor at work in these statistics that's sort of like aging but a little different. This is that many natural functions cause the cells in some part of our bodies to rapidly proliferate, usually for short intervals. The linings of the stomach, bronchial passages, intestines, throat, and mouth to mention just a few organs are constantly shedding and regenerating. The cells of the prostate gland and the cells lining the ovaries are constantly called upon to divide and replenish, as the normal reproductive cycle repeats itself. Similarly, the cells lining the milk ducts of the breast proliferate with every menstrual cycle as do the cells of the endometrial lining of the uterus. These proliferations raise the statistical chances that something can go wrong in these populations of cells. Recall that every cell division carries with it the possibility of a genetic mistake. When there's a lot of division going on in an area, over time that area becomes a likelier locus for the appearance of cancer. Most of the common cancers classified as "carcinomas" are, in fact, cancers that arise in "linings," the growthy areas of the body.

Of course the aging body, with its greater accumulation of partially transformed cells – cells that need just one or two more changes to become cancerous – is not the kind of body one would want to artificially stimulate into further proliferating its cells. And yet



proliferation is what many of our popular lifestyles choices induce!

Hormone replacement stimulates cell proliferation in reproductive tissues; consumption of fatty foods stimulates cell proliferation in the lining of the colon; continued smoking not only pours more mutagens onto our lung cells but stimulates cell proliferation in our bronchial passages as the linings of these passages struggle to repair themselves from the smoke damage. We can't stop aging itself, true. But there are certainly things we can do, or refrain from doing, to keep from adding insult to injury.

*Catching it early:* The more cancer cells in a person's body, the more formidable the problem becomes, as we have seen. A tumor caught early not only is more operable, not having poked fingers so deeply into surrounding tissue; it is also less genetically diverse than an older, larger cancer. The chances of being able to deliver a knockout punch with chemo or other treatment substances are thus much better. Also, nowadays, thanks to molecular genetic research, a new form of early detection is beginning to

become available. Remember those proteins? Cancer cells manufacture a configuration of proteins different from the configuration produced by normal cells. This is because they are themselves genetically different. As it turns out, many of these cancerous configurations can be detected in the blood stream – very early. Promising new blood tests will soon appear for the early detection of prostate and ovarian cancers. We will tell you more about “proteomics” tests in a future newsletter.

*Swallowing that cocktail:* The drug of choice for many newly diagnosed cancers nowadays is actually a cocktail of several drugs, delivered in close succession or, when feasible, all at the same time. Some of the cancer cells may be more vulnerable to one drug, the others to another, and so on. The strategy is to whack them from every direction and, hopefully, get them all. The best opportunity to get them all is right at the start of medical intervention before the patient has become worn down by treatment itself and before the cancer has had time to greatly diversify.

*Starving the little devils:* The classic line about cancer treatment, delivered, I believe, by Dr. Susan Love, is that after all these years we still rely on mainly three forms of treatment: surgery, radiation and chemotherapy, or as she put it, “slash, burn, and poison.” In fact, there is now a fourth workhorse of treatment, especially for the hormone sensitive cancers. This is starvation. The more molecular genetics reveals the inner workings of the cancer process, the better researchers have been able to home in on ways to deprive cancer cells of the substances that keep them going. Examples abound:

- Cancer cells may require a certain hormone to stimulate their growth cycle. The prime examples are estrogen, progesterone (and testosterone) for breast cancer cells, and testosterone for prostate cancer cells. Block the particular hormone and the population of cells crashes. Many well-known treatment drugs are devoted to this: tamoxifen (Nolvadex®), letrozole, (Femara®), anastrozole (Arimidex®), leuprolide (Lupron®), bicalutamide (Casodex®), to name a few.
- Coming at starvation from another angle, all cancer cells need that blood supply. What if we could medically shut down the protein that cells exude to attract new blood vessels? This is precisely the function of many new drugs coming onto the market, such as the recently hailed bevacizumab (Avastin®) first pioneered in the treatment of colorectal cancer, by - among others - Dr. Herbert Hurwitz at Duke. Many researchers envision a day when blood vessel growth blockers are a common part of every treatment cocktail. **Dr. Hurwitz**---->
- Certain cancers have one key genetic component that makes them aggressive, or that enables them to proliferate. A targeted drug, such as imatinib



mesylate (Gleevec®) for chronic myelogenous leukemia, or trastuzumab (Herceptin®) for certain breast cancers, can deprive the cells of this key principle and turn the cancer off. The more the genetics of each type and sub-type of cancer is understood, the more these targeted forms of starvation will enter into cancer treatment.



**Where do we go from here?** We have to stop for now as we're just about out of space. But answering one set of questions inevitably raises others. For instance, what role, if any, does our immune system play in controlling cancer and how might it be harnessed for better control? What is a "precancerous" condition and how should one deal with it? Who would be helped by "genetic counseling" for cancer risk? Could each specific cancer have a drug targeted just for it? These are all matters we hope to touch upon in future newsletters.

### Our Recent Email Questionnaire

We are hoping that all of you who received our recent email questionnaire in your mailboxes in January will send in your responses and enter our drawing for four exciting gift certificates - two for A Southern Season (the gourmet store) and two for Amazon.com (the online bookstore). Your names and phone numbers will be held in strictest confidence. If you have deleted the questionnaire in haste and would like to see it again, or if you are a new reader and missed the mailing, just notify us at our email address at the top of this newsletter. Our drawing will take place the first week in March.

You may also send in an evaluation of this, the February 2004 newsletter, by filling out the small questionnaire in the announcement you just received. To qualify for the drawing, however, you must fill out the longer earlier questionnaire. Those of you who've sent in your responses already are already eligible.

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