Subject: Missed Definitive Research on Colon Cancer Dietary Cause in Science Magazine 2003]
From: hopela@hopelausa.org
Date: Tue, December 27, 2005 4:59 am
To: kolata@nytimes.com
Priority: Normal
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Dear Ms. Gina Kolata:

As I specialize in sickness prevention your prevention of cancer series was impressive.

However, were you aware of the little known and ignored definitive research on the cause of the #2 killing colon-rectal cancer published in the Science Magazine, May 17, 2002, Volume 296 issue?

The culprit was found to be lithocholic acid the world's most carcinogenic substance which is a bile salt produced by the human liver from the digestion of fatty animal meat. Large amounts of Vitamine D at levels missing in most peoples diet or able to be produced by the sun in the skin inactivates it.

Your dietary prevention series article did not reflect this disturbing and significant research.

Please study this attached article and promulgate the public health significance of this overlooked research.

Thus one can better understand the 2003 National Cancer Institute research that found a correlation in human obesity and cancer incidences except for bladder, skin and brain cancers.

Since lithocholic acid is stored in tha adipose tissues of everyone who has eaten fatty animal meat, it is thus implicated in all other cancers except for perhaps bladder, skin and brain cancer.

The Science magazine article and press release of the researchers is attached for your convenience as a Adobe PDF file.

Keep up your excellent work.

Sincerely,

George W. Singleton

State of the World Forum Member # 20827
www.hopelausa.org

The New York Times
nytimes.com

September 27, 2005
Preventing Cancer

Which of These Foods Will Stop Cancer? (Not So Fast)

By GINA KOLATA

Leslie Michelson does not have prostate cancer, but as chief executive officer of the Prostate Cancer Foundation he knows all too well how bad the disease is. So Mr. Michelson, 54, changed his diet.

He used to avoid cruciferous vegetables, like cauliflower and brussels sprouts, hating their taste. Now he has them three or four times a week. He rarely ate fish, but now has it three times a week. He eats tomato sauce at least twice a week.

"I'm persuaded that with prostate cancer, diet makes a difference," he said.

Mr. Michelson is one of a growing number of people worried about cancer - because it is in their families or because they have seen friends suffer with the disease - who are turning to diets for protection. Cancer patients, doctors say, almost always ask what to eat to reduce their chances of dying from the disease.

The diet messages are everywhere: the National Cancer Institute has an "Eat 5 to 9 a Day for Better Health" program, the numbers referring to servings of fruits and vegetables, and the Prostate Cancer Foundation has a detailed anticancer diet.

Yet despite the often adamant advice, scientists say they really do not know whether dietary changes will make a difference. And there lies a quandary for today's medicine. It is turning out to be much more difficult than anyone expected to discover if diet affects cancer risk. Hypotheses abound, but convincing evidence remains elusive.

Most of the proposed dietary changes are unlikely to be harmful - less meat, more fish, more fruits and vegetables and less fat. And these changes in diet may help protect against heart disease, even if they have no effect on cancer.

So should people who are worried about cancer be told to follow these guidelines anyway, because they may work and will probably not hurt? Or should the people be told that the evidence just is not there, so they should not deceive themselves?

Dr. Barnett Kramer, deputy director in the office of disease prevention at the National Institutes of Health, said: "Over time, the messages on diet and cancer have been ratcheted up until they are almost co-equal with the smoking messages. I think a lot of the public is completely unaware that the strength of the message is not matched by the strength of the evidence."

But Dr. Arthur Schatzkin, chief of the nutritional epidemiology branch in the National Cancer Institute division of cancer epidemiology and genetics, said people wanted answers, even if they are not are not definitive.

"It is not enough to say that, well, this is complicated science and maybe in seven or eight years we will have new methods in place" that might resolve the issues, Dr. Schatzkin said. "We have a responsibility to give the best advice we can while pointing out where the evidence is uncertain and how we're working to improve the science."

That, however, is little consolation to cancer patients and family members who are terrified that cancer might strike them next. And there are more and more. As the population ages, the number of cancer patients is soaring. From 1997 to 2004, the number of Americans with cancer jumped, to 9.6 million from 9.4 million. Cancer strikes one in two men and one in three women in their lifetimes.

Most people want some sort of control, a way to prevent the disease from ever striking them or, if it does strike, to keep it from recurring. Many think of diet as a strategy.

Cassindy Chao, 36, of Oakland, Calif., said cancer runs in her family. Her mother has ovarian cancer and her grandmother died of the disease. "I am absolutely frantic about it," she said.

Ms. Chao has made substantial changes in her diet, for example, drinking carrot juice, loading up on green and leafy vegetables and switching to organic meats.

"Some people might want to wait for the evidence, but I've noticed it takes a while," Ms. Chao said. "I'm not going to wait." Dr. Tim E. Byers, a professor of preventive medicine at the University of Colorado Health Sciences Center in Denver, was convinced that up to 20 percent of cancers were being caused by diet and he wanted to be part of the exciting new research that would prove it.

"I felt we were really on the cusp of important new discoveries about food and how the right choice of foods would improve cancer risk," Dr. Byers sad.

That was 25 years ago, when the evidence was pointing to diet. For example, cross-country comparisons of cancer rates suggested a dietary influence.

"For prostate cancer, if you look around the world, there might be 50-fold or greater differences in rates; they're huge," said Dr. Meir Stampfer, a professor of epidemiology and nutrition at the Harvard School of Public Health. "There are also big differences, many-fold differences, around the world for breast cancer and colon cancer."

And when people move from low risk countries to high risk countries, they or their children acquire the cancer rates of their new countries.

At the same time, some cancers were inexplicably becoming more common or, just as inexplicably, fading away in the United States.

In 1930, for instance, stomach cancer was the second leading cause of cancer death in women and the leading cause in men. Now, Dr. Stampfer says, stomach cancer is not even listed in the American Cancer Society's 10 leading cancers.

"So people think, 'What's happened in the past 70 years to make that change?' " he said. "Diet comes to

mind."

There were also differences in diets in countries where cancer rates were high and in those with low rates. With breast cancer, for example, researchers could draw a straight line directly relating the amount of fat in the diet to the rate of breast cancer in the population.

"People looked at it and said, 'Here it is - fat causes breast cancer,' " Dr. Stampfer said.

Next came studies that compared the diets of people who developed cancer to the diets of those who did not. Those studies, Dr. Schatzkin said, tended to show that dietary fiber protected against colon cancer, that fruits and vegetables protected against colon and other cancers and that a low-fat diet protected against breast cancer.

There were, of course, a few nagging questions. For example, people who had cancer might remember their diets differently.

"Whenever people get cancer, the first thing they ask is, 'Why me?' " Dr. Stampfer said. "And then they try to answer that question."

If colon cancer patients heard that fiber protected against colon cancer, for example, they might recall eating less fiber than people without cancer.

Dr. Stampfer said evidence from one of his studies indicated that was occurring, at least with fat and breast cancer. But, he said, when he published a paper saying so, "a lot of people didn't believe it."

The best studies are the hardest to conduct: prospective studies that that follow healthy people for years instead of looking backward and relying on memory. Even better - and harder and more expensive - are studies that randomly assign people to follow a particular diet or not.

But those more difficult studies were well worth doing, researchers said. And as more studies started, scientists hoped for definitive evidence that diet affected cancer.

The Fiber Theory

But as the results from those studies have begun to roll in, many researchers say they are taken aback. The findings, they say, are not what they expected.

Fat in the diet, the studies found, made no difference for breast cancer. "For fat and breast cancer, almost all of the prospective studies were null," Dr. Schatzkin said.

Fiber, in the form of fruits and vegetables, seemed to have a weak effect or no effect on colon cancer.

The more definitive randomized controlled trials were disappointing, too, with one exception. A study reported in May found that women with early stage breast cancer who followed a low-fat diet had a 20 percent lower risk of recurrence.

Even so, the effects were just marginally statistically significant. The study's principal investigator, Dr. Rowan Chlebowski of the Harbor-U.C.L.A. Medical Center, said it needed to be repeated before scientists would be convinced.

Nonetheless, the study contrasted sharply with those preceding it. Several involved beta carotene and antioxidant vitamins like C and E, substances that scientists thought were the protective agent in fruits and vegetables. The idea was that antioxidants could mop up free radicals in the body, which left unchecked could damage DNA, causing cancer.

Beta carotene was of special interest. People who ate lots of fruits and vegetables had more beta carotene in their blood, and the more beta carotene in the blood, the lower the cancer risk.

But a four-year study that asked whether beta carotene, with or without vitamins C and E, could protect against colon polyps, from which most colon cancers start, found no effect. People who took either beta carotene, vitamin C, vitamin E or all three had virtually identical rates of new polyps compared to participants taking dummy pills.

Another study, of 22,000 doctors randomly assigned to take beta carotene or a placebo, looked for an effect on any and all cancers. It found nothing. Two more, involving current and former smokers, found that those taking beta carotene actually had slightly higher lung cancer rates than those taking placebos.

Studies of fiber and colon cancer were similarly disappointing.

The fiber hypothesis had enormous appeal. Carcinogens from food can end up in stool. But when people eat a lot of fiber, their stool is bulkier and so carcinogens would be diluted. Bulkier stool is also excreted faster, reducing the time that the colon is in contact with cancer-causing substances.

Fiber also binds bile acids in the bowel, substances that can damage the colon and, possibly, result in cancer. And the intestines metabolize fiber into short-chain fatty acids that seemed protective against cancer.

Adding to the case for fiber was the fact that when researchers fed rodents carcinogens, the animals were protected against colon cancer if they also ate a lot of fiber.

Based on these indications, the cancer institute financed two studies on high-fiber diets and colon polyps. In one, 2,079 people were randomly assigned to eat low-fat high-fiber diets or to follow their usual diets. In the other, 1,429 people were assigned to eat high-fiber bran cereals or wheat bran fiber or to eat cereal and bars that looked and tasted the same but that were low on fiber. Fiber, the studies found, had no effect.

"We had high expectations and good rationale," Dr. Schatzkin said. But, he said, "we got absolutely null results."

Now, the largest randomized study ever of diet and cancer is nearing completion, involving 48,835 middle-age and elderly women. The women were randomly assigned to follow a low-fat diet with five servings a day of fruits and vegetables and two of grains or to follow their usual diet. The question was whether the experimental diet could prevent breast cancer.

The study is part of the Women's Health Initiative, a large federal project. When it began, the dietary fat hypothesis was ascendant. But after it was under way, other, less definitive studies failed to find any association between dietary fat and breast cancer.

The Women's Health Initiative diet study's results should be ready early next year, said its principle investigator, Ross L. Prentice, a biostatistics professor at Seattle's Fred Hutchinson Cancer Research

Center.

And if it fails to find an effect?

Dr. Prentice said he would still wonder. Maybe what matters is diet earlier in life, he said, or maybe the women in the study did not stick to their diets.

Others say they suspect they were simply naïve about the cross-country comparisons that persuaded them in the first place.

"People drew inferences that were in retrospect overenthusiastic," Dr. Stampfer said. "You could plot G.N.P. against cancer and get a very similar graph, or telephone poles. Any marker of Western civilization gives you the same relationship."

Because of the striking differences in daily life between people in countries with high cancer rates and those in countries with low rates, diet may have nothing to do with the incidence of the disease, Dr. Schatzkin said. Or diet may play a large role but the questionnaires used to measure what people were eating might have been inadequate to find it.

"That's the problem." Dr. Schatzkin said. "We just don't know."

As for Dr. Byers, who once had such high hopes for the diet and cancer hypotheses, he says he is sadder now, but wiser. "The progress has been different than I would have predicted," Dr. Byers said.

Specific food can affect general health, he added, but as for a major role in cancer, he doubts it. He now believes that it is the amount of food people eat, not specific foods or types of foods, that may make a difference. "I think the truth may be that particular food choices are not as important as I thought they were," Dr. Byers said.

Individual Approaches

Meanwhile, patients and those worried about cancer are adopting their own idiosyncratic dietary paths. Many know that the evidence is not solid, but they would rather take a chance that their diets will make a difference than wait helplessly for their fates to play out.

That is the view of John Napolitano, a New York graphic designer and marketer.

Three years ago, when he was 55, Mr. Napolitano found out that he had prostate cancer and that it had spread to his bones. Now, hoping to slow its progress, he avoids sugar and fat and almost never eats meat. He eats natural and organic foods. He drinks lots of water and green tea. He starts each day by whipping up a smoothie with a protein supplement and flaxseed.

"My diet is very different now than what it was three years ago," Mr. Napolitano said, adding that thinks that his new diet helped.

"Until recently, I was totally symptom free," he said. "I can't endorse anything I'm doing, but I've never had nausea, never had constipation" from his treatments.

Dr. Brad Efron, a professor of statistics at Stanford, has a different dietary approach. He does not have prostate cancer, but he had a couple of scares and he has friends who have it. So he is taking selenium, a

trace mineral found in plants.

A study that randomly assigned people to take selenium or not to see whether it protected against skin cancer found that it had no effect on that cancer, but that the men taking it had only a third as many prostate cancers. Now, the National Cancer Institute is conducting a study on whether selenium protects against prostate cancer. Dr. Efron chose not to wait. He even published a statistical analysis concluding that the prostate effect was likely to be real.

"One of my colleagues said, 'Why do you think something that people thought would work on skin cancer has anything to do with you?' " he said. "There's always a leap of faith. But I'm scared of prostate cancer and I wanted psychological reassurance."

The New York Times
nytimes.com

November 1, 2005
Preventing Cancer

But Will It Stop Cancer?

By GINA KOLATA

Bernyce Edwards's daughter was 42 in 1997 when she died of breast cancer. It was just 69 days from diagnosis to death. And through her shock and grief, Ms. Edwards had a terrible worry: what if she got breast cancer, too?

"That's my biggest fear," she said.

So, to protect herself, she has taken up exercise.

And not just any exercise. This 73-year-old woman has turned into an exercise zealot.

She walks, she runs, she leaves her house in Bellingham, Wash., as early as 5 a.m. and spends an hour every day, rain or shine, putting in the miles on the trails and around a lake.

But will her efforts help? Medical researchers agree that, at the very least, regular exercise can make people feel better and feel better about themselves.

There is less agreement on whether it can also prevent cancer. But for two types, the evidence is promising: breast cancer and cancer of the colon. Other cancers have not been studied, or the studies that have been done have yielded little evidence that exercise can help.

Even for breast and colon cancer, further confirmation is needed.

Researchers who are enthusiastic about a cancer-exercise connection also caution against too much enthusiasm.

Exercise is like a seat belt, says Dr. Anne McTiernan of the Fred Hutchinson Cancer Research Center in Seattle, a co-author of "Breast Fitness: An Optimal Exercise and Health Plan for Reducing Your Risk of Breast Cancer."

"It's not a guarantee, but it can reduce your risk," Dr. McTiernan said. "The negative side is when a person says, 'The reason I got cancer is that I didn't exercise.' That's the problem."

Dr. Brian Henderson, dean of the University of Southern California's Keck School of Medicine, knows just where the idea that exercise might prevent breast cancer came from. It was an extrapolation from an observation, and from the start it was filled with untested assumptions. He knows this, Dr. Henderson said, because it included work that originated with his research group.

He began with the observation that exercise could affect when girls started to menstruate. For

menstruation to begin, girls must be eating more calories than they burn, Dr. Henderson said. Adolescent girls who exercise strenuously often do not eat enough to make up for the extra calories they are using, and as a result, they may start menstruating later than more sedentary girls.

Researchers also knew that the older a girl was when she started to menstruate, the lower her risk of eventually developing breast cancer, Dr. Henderson said, and "that's where the idea came from that exercise might affect risk for breast cancer."

The question was whether they could document it. Dr. Henderson knew the problems with such studies.

"It's hard to measure exercise," he said.

Researchers can ask people to recall how much they exercised, but their answers may not be accurate.

And it is almost impossible to account for incidental activities, like walking up a flight of stairs, that can cause one person to get more total daily exercise than another.

"We all go around in circles: isn't there a better way to measure this?" Dr. Henderson said.

Another problem for researchers is the timing of exercise. Is it important throughout life? Only in young adulthood? Or is it as effective to start to exercise in middle age, when breast cancer risk rises?

The best test of the exercise hypothesis would be to assign thousands of people randomly either to exercise or not exercise and then follow them for years, keeping track of cancer diagnoses as they occur.

But, researchers say, not only would such a study be expensive - the exercise groups would need constant support, and researchers would have to monitor how much they were exercising - but volunteers would be unlikely to comply with their assigned regimens. Telling someone to exercise or to remain sedentary for years is not like telling her to take a pill.

The alternative is to look at populations of people who did or did not exercise and try to correct for factors that might be linked to exercise and to cancer. Exercisers might be thinner, for example, and if they had a lower incidence of breast cancer it might be body weight, not exercise, that was responsible.

Study after study was conducted: some found small protective effects of exercise on breast cancer; others found none.

Now, in Dr. Henderson's opinion, there is no point in continuing to ask the same question in the same ways.

"We've pretty much settled the issue that there is a small effect," he said. The effect, Dr. Henderson added, is so small, that even if it is real, it makes little difference to an individual woman. In one of his studies, the effect of exercise was so small that if he took into account alcohol consumption - which has been associated with a slightly increased breast cancer risk - the exercise effect went away.

"If you are going to exercise, there are other good reasons," Dr. Henderson says. "But protection from breast cancer is not one of them."

Dr. McTiernan has a different view. Instead of continuing to ask if there is a correlation between exercise and breast cancer, she said, she has been asking, "What are the biochemical changes that occur

with exercise and could they affect a woman's risk?"

In Dr. McTiernan's studies, she randomly assigned overweight postmenopausal women to exercise for an hour a day, six days a week, or not to exercise. And she kept track of the levels of sex hormones - estrogens and androgens - in their blood.

After menopause, women's estrogens and androgens are mostly synthesized by an enzyme in body fat. The more fat a woman has, the more hormones she makes. Exercise can reduce fat levels, and so it may reduce hormone levels and thereby lower breast cancer risk.

The results of the study were as Dr. McTiernan might have predicted: women who lost fat had lower hormone levels and those who did not lose fat did not.

On average, the exercisers lost about three pounds of fat over the yearlong study; the more fat they lost, the more their hormone levels dropped. Nearly a third lost at least 2 percent of their fat - about 4 pounds for a typical woman in the study, who weighed 180 pounds at the start and whose body was 47 percent fat.

That modest loss in fat was accompanied by a 10 percent drop in estrogen levels, nearly twice what would have been expected if they had lost the same amount of weight with diet alone, Dr. McTiernan said. That is enough of a hormone drop to be associated with a decreased breast cancer risk, she added.

Such studies, of course, do not prove that exercise prevents breast cancer. But, Dr. McTiernan said, finding biochemical changes that are consistent with a protective effect at least gives some plausibility to the findings from the population studies.

"It makes us more confident that exercise is working," she said.

While the link between breast cancer and exercise sprang from observation, the notion that exercise and colon cancer might be related came out of the blue. And epidemiologists and statisticians laughed when they first heard it.

The idea originated about 20 years ago when Dr. David Garabrant, now a professor of occupational medicine and epidemiology at the University of Michigan, was a young assistant professor at U.S.C.

Dr. Garabrant was interested in cancer epidemiology and, in particular, a cancer registry that Dr. Henderson had started and that kept track of all the cases of cancer in Los Angeles County.

"Our statisticians used to do computer runs, looking at cancer by age and ethnicity, and we used to look through these big computer printouts asking, 'Do we see anything interesting?' " Dr. Garabrant recalled.

"One day we were looking through the cancer risks for various occupations and we noticed that all the jobs where people sat around had higher rates," he said. "I said, 'Gee, that's interesting.' So we came up with a rating scheme and we grouped occupations according to how active they were - sedentary, moderately active or an active job."

Then, Dr. Garabrant said, he examined the colon cancer data. Sure enough, there was a direct relationship between exercise and illness. The more active the job, the less likely its holder was to have colon cancer.

"I presented it at a department meeting and they laughed at me; they hooted," Dr. Garabrant said.

He added: "This was a department made up of epidemiologists and statisticians. They just razzed me. 'Come on!' "

But it turned out that he was right. Now, Dr. Garabrant says, he knows of at least 50 studies, all of them showing the same relationship between exercise and colon cancer. "Everyone who has data that allows them to look for it finds it," he said.

Others researchers agree. In fact, said Dr. John Baron, an epidemiologist at Dartmouth Medical School, there have now been so many studies of colon cancer and exercise that the issue is no longer whether there is a correlation. There is.

Now, Dr. Baron said, the main issue is what does the correlation mean and why is it occurring.

He and others worry that the interpretation of such studies can be confounded, because people who exercise are often different from people who do not exercise in many other ways, as well.

"Who has very active jobs? Probably poor people who aren't making a lot of money. Who joins health clubs?" Dr. Baron said. "Well, these other characteristics may be important."

Researchers take into account every factor like this that they can think of. But, Dr. Baron said, "The problem is the things we're not smart enough to know about, the things we haven't even thought of."

He said he remembered studies of colon cancer and dietary fiber. Some studies of populations found that the more fiber a person ate, the lower the risk for colon cancer. But two large studies that randomly assigned people to eat lots of fiber or stay away from it found no protective effect.

On the other hand, noted Dr. Robert Sandler, a gastroenterologist at the University of North Carolina, the finding that people who took aspirin on a regular basis had less colon cancer, also from population studies, was supported by a large study that he directed. In it, people were randomly assigned to take aspirin or not take aspirin. So is exercise like fiber or is it like aspirin? Medical researchers may never know.

There are animal studies, but it is hard to know what they mean. With cancer, Dr. Baron said, "sometimes animal studies are right on the money and sometimes they're not."

The problem, he added, "is that you don't know which is which."

Still, Dr. Baron said, with the possible exception of over-the-counter anti-inflammatory drugs like aspirin, nothing has been so strongly associated with reduced risk of colon cancer as exercise. And he said he thinks it makes sense to counsel patients who are at risk of colon cancer to exercise.

There, is, however, one problem: Doctors say that it is so hard to persuade most patients to exercise that many do not even try.

Dr. Sandler said he sees patients right after they have had a colonoscopy, a screening test for cancer that looks for small growths, polyps, in the colon. Although most polyps are not cancerous, most colon cancer starts with a polyp, and so patients with polyps are at increased risk.

Doctors cut polyps out in a colonoscopy but more can grow back. So patients with polyps are often frightened, and they ask what could have caused the polyps and how they can protect themselves from colon cancer. Dr. Sandler suggests aspirin and he suggests exercise.

"I'm pretty confident it will work," Dr. Sandler said of the exercise prescription. But, he adds, most patients dismiss that advice.

"They kind of blow me off," he said.

Dr. John Min, an internist in private practice in Burlington, N. C., loves exercise - he runs in marathons - and he believes it can improve health and possibly protect people from colon and breast cancer. But he does not even mention it to his patients as a way to protect against those cancers.

"Unfortunately, trying to get patients, even those who are very interested, to start exercising is very difficult," he says.

He said he has tried, and patients have left his office seeming excited about turning their life around. But they soon return to their sedentary ways.

"This is unfortunately what I have realized," Dr. Min said. "The ability for someone to significantly change their lifestyle, which they've lived with for years, is extremely difficult unless it is personally important to them. I can't make it personally important to them in the time of an office visit."

Once in a while, though, someone who never thought they wanted to exercise takes it up out of fear of cancer and discovers that they love it. That happened with Ms. Edwards, who worries about breast cancer but says her life is so much better now that she is active.

John Knudson, a 58-year-old mathematics instructor at Seattle Central Community College had a similar experience. Mr. Knudson had never really been a regular exerciser. He would sometimes play soccer on the weekends, he said, but "I would play one day and hurt for four days."

Then, about five years ago, Mr. Knudson had a colonoscopy. Mr. Knudson had polyps, lots of them.

"I remember my gastroenterologist, when he was doing it, said, 'Well, you're a regular polyp farm,' " Mr. Knudson said.

Soon afterward, he got a letter from his gastroenterologist asking him to be in another of Dr. McTiernan's studies - a one-year study at the Fred Hutchinson Cancer Center that would randomly assign people like him, with lots of polyps and so a high risk for colon cancer, to exercise vigorously for a year or to remain sedentary.

As in the breast cancer study, the idea in this research was to track biochemical changes with exercise to see if they were related to cancer. In the case of colon cancer, the researchers were looking for prostaglandins, insulin and insulin-like growth factor, all proteins that have been associated with colon cancer risk. And they were looking for small molecules that have been associated with cell growth, reasoning that excessive growth might indicate cancer risk.

Mr. Knudson agreed to participate in the study. He was assigned to the exercise group, and he discovered he loved running.

Dr. McTiernan says she and her colleagues are still analyzing their data from the study and so it is not clear yet whether there is a biochemical explanation for the colon cancer connection.

But Mr. Knudson has gone beyond his original reason for exercising. Running has become his passion. Years after the study ended, Mr. Knudson is now running in half marathons. His polyp problem has gone away, although, he says, he has no idea if it was the exercise or whether his doctor just cut out all the polyps the first time and they have not had a chance to grow back.

In any event, he said, "The polyp farm is kind of dormant."

Some of the other study participants had trouble with the exercise program, he noted. "It was a big commitment."

But not for him.

"I like the freedom I get running," he said. "I like the feeling that I can pick up and run somewhere. It's kind of exhilarating."

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nytimes.com

November 29, 2005
Preventing Cancer

Is There a Link Between Stress and Cancer?

By GINA KOLATA

Christina Koenig found out she had breast cancer on a Friday afternoon. She was just 39 years old.

On Monday, she thought she knew why the cancer had struck.

"I went in and talked to a team of medical professionals who ultimately performed a lumpectomy, and I said, 'How long has this been there?' They said, 'Five to ten years.' And immediately, my mind jumped to: 'Well, I did go through a divorce. I did have stress.' "

Ms. Koenig, who lives in Chicago, was divorced four years before her cancer was diagnosed. Was it just a coincidence, she wondered?

Now, four years later, she still wonders. So do many other women who get breast cancer. Ms. Koenig now works for Y-ME National Breast Cancer Organization, which gets 40,000 calls a year on its hot line. Over and over, she says, women ask, Did stress cause their cancer by weakening their immune system and allowing a tumor to grow?

"It's a widespread belief," Ms. Koenig said.

And it is not restricted to women with breast cancer.

Jim Kiefert of Olympia, Wash., is absolutely convinced that stress led to his prostate cancer. It was diagnosed in 1989, when he was 50. Mr. Kiefert was a school superintendent, and he was in the midst of difficult negotiations with teachers over their contracts. "I was stressed out," he says. "I know stress caused my cancer."

The question of whether there is a link between stress and cancer has puzzled and intrigued researchers as well as patients. Study after study has asked whether people who developed cancer had more stress in the years before the diagnosis, and conversely, whether people who experienced extreme stress were more likely to develop cancer.

Investigators have also explored possible mechanisms, asking, for example, whether stress might suppress the immune system cells that might be needed to squelch rogue cancer cells. And they have tried to determine whether the immune system, the body's defense system, protects people from cancer in the first place.

What has emerged is a tenuous connection between stress, the immune system and cancer, with a surprising new insight that is changing the direction of research: it now appears that cancer cells make proteins that actually tell the immune system to let them alone and even to help them grow.

As for whether stress causes cancer, the question is still open.

"I have no idea, and nobody else does, either," said Barbara Andersen, a psychology professor at Ohio State University who studies stress reduction in cancer patients. "If somebody suggested that they know, I would question them."

Polly Newcomb, the head of the cancer prevention program at the Fred Hutchinson Cancer Research Center in Seattle, decided to ask whether stress caused breast cancer, because women seemed convinced that it did.

The issue came up in her epidemiologic studies of what might be causing cancer. She used trained interviewers to ask women with cancer and healthy women who served as controls about their medical histories, their environments and the medicines they were taking.

Then the interviewers asked the women if they had anything to add. Repeatedly, the women with cancer would turn to their interviewers and say, "Why didn't you ask me about what really caused my cancer?"

What really caused it, they would say, was stress. It was plausible, Dr. Newcomb reasoned. After all, stress could alter the functioning of the immune system, in turn altering susceptibility to cancer.

So Dr. Newcomb incorporated standard questions about stressful life events into her continuing study of nearly 1,000 women. Had family members or friends died? Had they gotten married or divorced? Had they lost a job or had they retired? Had their financial status changed? Were there stressful events not on the list that they would like to add?

The women did not know why the questions, incorporated as part of a longer interview, were being asked. And the interviewers did not know which women had had cancer.

But the results were clear: there was no association between stressful events in the previous five years and a diagnosis of breast cancer. Other studies had the same result.

Still, not everyone was convinced. Critics told Dr. Newcomb and her colleague, Dr. Felicia Roberts, that they had measured stressors, not stress. And Dr. Newcomb had to agree that they had a point. She chose stressful life events as a surrogate for experienced stress, but it is not easy to measure the actual physiological stress that people experience and then follow them to see if they got cancer.

Barrie Cassileth, chief of the integrative medicine service at Memorial Sloan-Kettering Cancer Center, suggested that there was another way to ask the question.

"These are what we call natural experiments in the real world," Dr. Cassileth said. "Look at situations of extreme stress or distress - being in a concentration camp, being a prisoner of war. How about a mother losing a child?

"People in all of those circumstances have been followed. And they have no higher incidence of cancer."

Many large studies of cancer and stress were done in Denmark, which has national records of illnesses. One looked at the incidence of cancer in 11,380 parents whose children had cancer, surely a stressful event, Dr. Cassileth said. The parents, though, had no more cancer than members of the general population.

Another study looked at the cancer rate among 21,062 parents who had lost a child. There was no increase in cancer among the parents for up to 18 years afterward. A third Danish study looked at cancer rates among 19,856 parents who had a child with schizophrenia. Once again, there was no increase in cancer.

It also is unclear whether stress reduction can improve the prognosis of people who already have cancer.

"If the question is, Have we established it?, the answer is, Absolutely not," said Sheldon Cohen, a psychology professor at Carnegie Mellon University who has studied the role of support groups and stress reduction in cancer. "If the question is, Would it work?, we don't know that, either."

The concern, Dr. Cassileth said, is that cancer patients, under enormous stress, often worry that they are hurting their own prognosis. And patients who look back over their lives and remember that they went through stressful times before their diagnosis often conclude they brought the cancer on themselves.

"People need answers," Dr. Cassileth said.

For many, a diagnosis of cancer is a complete shock. They thought that they were healthy; they were exercising and eating right. "They are at a loss to understand why that happened to them," she said.

And, she added, all people can find stress in their lives if they look for it.

"I tell them they did not cause their cancer. Absolutely not," Dr. Cassileth said.

The question for Dr. Drew Pardoll, director of the cancer immunology program at Johns Hopkins' Kimmel Comprehensive Cancer Center, was not whether stress causes cancer. It was how cancers can even exist.

The white blood cells of the immune system are always bumping into cancer cells. They should attack cancers as foreign bodies and destroy them. Why don't they? Is it that the immune system is too weak? Or is it something else?

As it turns out, Dr. Pardoll and others found, it was something else, and not at all what most scientists expected.

The old idea, Dr. Pardoll said, was that cancers arise every day but the immune system destroys them. Anything that weakens the immune system - stress, for example - could hinder this surveillance. The result would be a cancer that grows large enough to resist the body's effort to heal itself. "Nobody believes that anymore," Dr. Pardoll said.

Dr. Fred Applebaum, director of the clinical research division at the Fred Hutchinson Center, said that he and most other cancer experts believed the theory. But then they looked at mice that were genetically engineered to have no functioning immune systems.

"They really don't show a huge increase in the incidence of cancer," Dr. Applebaum said.

For example, researchers looked at people whose immune systems were suppressed because they were taking drugs to prevent rejection of a transplanted organ or because they had AIDS.

"There are small increases in certain types of cancers," Dr. Applebaum said, but those tend to be cancers

that are associated with infections - like stomach cancer, associated with ulcer-causing Helicobacter pylori; liver cancer, associated with hepatitis B and hepatitis C infections; Kaposi's sarcoma, associated with herpesvirus 8 infections; lymphoma, associated with Epstein-Barr virus; and cervical cancer, associated with human papillomavirus.

"The common types of cancer, the ones that cause the huge burden of suffering in humans, really aren't increased," he said.

What happens to the immune system in cancer patients? It should be protecting them. Every tissue of the body is larded with white blood cells, and cancers are no exception. In fact, Dr. Pardoll said, in some tumors, including melanomas and kidney cancers, white blood cells make up 50 percent of the cancer's weight.

And cancer cells are clearly foreign tissue. Their surfaces are studded with proteins that look very different from the proteins on normal cells. The T cells of the immune system, which should start the attack, are perfectly capable of recognizing the foreignness of the cancer cells. But for some reason, they do not.

Why not? The answer, Dr. Pardoll, Dr. Allison and others have found, is that proteins on the surface of cancer cells turn off the immune system's attack. At the same time, the tumor is excreting molecules that recruit immune system cells to help it metastasize, spreading through tissues and organs.

"We knew very little about what regulated these immune responses to tumors until very recently," Dr. Pardoll said. "We now are in a position to totally rewrite the book."

One immediate consequence of this line of thinking is a new idea for treatment: scientists could seal off the cancer cells' proteins that block the immune system and enable white blood cells to kill the tumor. Or they could make the immune system more aggressive. To do that, they can block a molecule on the surface of T cells, CTLA-4, that tends to dampen the immune response.

The first strategy is only starting to be investigated because the discoveries are so new. But the second strategy is well under way.

In mice, said James Allison, chairman of the immunology program at Sloan-Kettering, some cancers went away after just a single injection of an antibody to CTLA-4. Other cancers required a vaccine, as well, to bolster the newly unleashed immune attack. But then, Dr. Allison found, even the most intractable tumors in mice were destroyed.

Dr. Allison licensed the technique to Bristol-Myers Squibb, which is working with Medarex to see if the method will work in humans. But while the work showed that the immune system can destroy cancers, at least in mice, it leaves unanswered the question that plagues many patients: Did a weakened immune system, possibly weakened by stress, cause cancer in the first place?

Cancer immunologists are skeptical. "There is absolutely no evidence for that association," Dr. Pardoll said.

Dr. Allison agreed. "I can't rule it out," he said, "but I would be very skeptical."

Christina Koenig said that her group, Y-ME, is careful in its response to women who think stress caused their breast cancer. While Ms. Koenig said she thought it might have contributed in her case, she knows

what scientists say and she does not want to overstate the evidence.

When women ask, she said, Y-ME hot line peer counselors tell them, "We don't have scientific evidence" and focus on recruiting emotional support to help them now, when they are dealing with treatment and survival.

As for Mr. Kiefert, he is now chairman of the board of Us Too, an advocacy and support group for cancer patients, and he does not hesitate to tell men what he believes: that stress caused his cancer, that stress fuels the growth of the prostate cancer cells that are still in his body, and that stress may well have caused their cancer, too.

That is not what many men want to hear, he said.

"Men almost never like to admit that they are under stress," Mr. Kiefert said. "Our male ego says it is a sign of weakness. We have a tendency to keep it inside, we try to tough it out." Not him, he adds. He still has prostate cancer, and he has changed his life.

"I avoid stress," Mr. Kiefert says. "I know what happens when I'm under stress."

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Preventing Cancer

Environment and Cancer: The Links Are Elusive

By GINA KOLATA

When Mike Gallo learned he had cancer, a B cell lymphoma, two years ago, his friends and relatives told him that they knew how he got it.

His cancer, Dr. Gallo's friends said, was obviously caused by the dioxin that he had worked with for three decades in his laboratory. After all, the Environmental Protection Agency classifies dioxin as a probable human carcinogen. And among the cancers that it may increase the risk for, in high doses, is lymphoma.

Dr. Michael A. Gallo, director of the National Institute for Environmental Health Sciences Center of Excellence at the Robert Wood Johnson Medical School in New Brunswick, N.J., tells his well-meaning advisers that he does not think so.

"I say, 'No, I know my blood levels of dioxin,' " Dr. Gallo said, explaining that he measured them when he worked with the chemical. His levels, he said, are low. And there is no way to make a leap from such low levels of dioxin to his cancer.

Yet many of his friends and relatives remain convinced.

"That's the way people think," Dr. Gallo said. "If you get cancer, there has to be a reason."

And there may be a reason, he and other scientists say. But pinning cancer on trace levels of poisons in the environment or even in the workplace is turning out to be a vexing task. There has been recent progress in addressing the issue, but the answers that many people believe must be out there remain elusive.

"It's an area where there's certainly been a lot of heat and not a lot of light for some time," said Robert Hoover, director of the epidemiology and biostatistics program at the National Cancer Institute. For the most part, Dr. Hoover said, "we are down to speculations based on some data but without having the information we need."

Members of advocacy groups agree that there is much to learn, but they say the questions are too important to brush off by saying the research is difficult or the questions complex.

"Science is very specific," said Linda Gillick, a founder of Ocean of Love, a support group for children with cancer in Ocean County, N.J. "Sometimes you have to think outside the box."

Barbara Brenner, executive director of the Breast Cancer Action Coalition, an advocacy group in San Francisco, said that at the very least people should look for the least toxic alternative to chemicals in

common use that may cause cancer.

Having had breast cancer twice, Ms. Brenner is impassioned by the cause. "I have a firsthand experience, and I would do anything - anything - to keep someone else from having that experience," she said.

Researchers, for their part, say they have not given up the quest. In their search for answers, they are trying a variety of methods. They are looking for reliable ways to detect environmental exposures and determine whether they are linked to cancer risk. They are studying the bewildering array of factors that can determine a chemical's effects on individual people. And they are looking at cancer statistics and asking whether there are blips in cancer rates that may point to an environmental cause.

The effort is important, Dr. Hoover said. While most scientists think that only a tiny fraction of cancers might be caused by low levels of environmental poisons, these are cancers that could, in theory, be avoided.

"All it takes is the political will to ban them or impose regulations to minimize exposure, and the cancers are gone," Dr. Hoover said.

The problem is to decide which chemicals might be causing cancer, and in whom.

Some scientists, like Aaron Blair, an epidemiologist at the National Cancer Institute, see hints that environmental pollutants like pesticides, diesel exhaust in cities and workplaces and small particles in the air may instigate cancer.

But, Dr. Blair says, there is a huge problem in following up on these hints because scientists need to figure out who was exposed to what and when the exposure occurred. Asking people is not much help. Most people do not know what they were exposed to, and even if they think they know, they often are wrong, he said.

So Dr. Blair and his colleagues decided to try for the greatest possible rigor by focusing on one group, farmers, that is not only routinely exposed to pesticides that may increase cancer risk, but also keeps excellent records of exposure.

The effort, a collaboration involving the cancer institute, the National Institute of Environmental Health Sciences and the Environmental Protection Agency, began in 1993 and includes nearly every farmer and farmer's spouse in Iowa and North Carolina - 55,000 farmers and 35,000 spouses.

Investigators have been asking the farmers what pesticides and herbicides they used, when they used them and how much they used, and have been obtaining information on other risk factors like smoking. Then they use the medical records from tumor registries to determine who developed cancer and what type was developed.

"We're now just in the period of time where we can look at outcomes," Dr. Blair said. So far, the researchers have found a few associations, but nothing that is definitive.

"I would call it, at this stage, interesting leads," Dr. Blair said. "None are large enough for any regulatory agency to take action or to say they are a human carcinogen. They are leads." They include, for example, a slightly higher rate of lung cancer and leukemia in farmers who used the insecticide diazinon and a possible increase in prostate cancer among farmers who used methylbromide to fumigate

the soil.

The investigators looked for an association between pesticides and herbicides and breast cancer, but they did not find one, Dr. Blair said, adding that one pesticide, atrazine, was under particular suspicion because it causes breast cancer in rats and has estrogenlike properties.

Even if the study finds that some chemicals have increased farmers' cancer rates, it remains unclear what that means for the general population, where exposures are usually much lower. Also unclear is whether those chemicals should be banned.

Dr. Blair noted that such decisions were difficult because they were, in part, political, balancing the costs of getting rid of the chemical against the benefits. But, he said, regulatory decisions require reliable scientific data. "You can only make a decision if you know something," he said.

So the studies continue. "We want to know what to worry about, so at least we can make rational decisions," Dr. Blair said.

Gerald N. Wogan, a chemist at the Massachusetts Institute of Technology, takes a different approach. He, like most other scientists, worries that the public is overly concerned about cancer risks from the chemicals they are exposed to. But, he says, the question of how environmentally induced cancers arise is a puzzle that he would like to solve.

Dr. Wogan became interested in pollutants and cancer when he began studying the effects of aflatoxin, produced by mold on peanuts. The toxin caused liver cancer in rats and, Dr. Wogan and others showed, it also causes liver cancer in people. But exposure to aflatoxin was just part of the risk.

Dr. Wogan studied men in Shanghai who were eating foods with high doses of the toxic chemical. They ended up with four times the risk of liver cancer. Another cause of liver cancer, hepatitis B infections of the liver, increases the risk by a factor of seven.

Then Dr. Wogan noticed something that astonished him. The risk of liver cancer was increased 70 times in people who met both criteria; they ate contaminated foods and they were infected with hepatitis B.

"It was like a model system for the environmental causes of cancer," Dr. Wogan said.

The two cancer-causing agents were amplifying each other's effects. He went on to study the mechanisms of cancer causation and discovered that the more he looked at environmental pollutants the more complex and individualistic the biochemical pathways leading to cancer turned out to be.

"People differ very greatly in their response to chemical carcinogens," Dr. Wogan said. "Almost all chemicals, with relatively few exceptions, have to be converted from what they are into something more chemically active to be carcinogenic.

"If you encounter one of these compounds, most of it is converted to less toxic material that is excreted," he continued. "Only a tiny amount is converted to a form that could cause cancer. A small fraction of 1 percent gets converted. And people can differ enormously in their genetic ability to do these metabolic conversions."

Further complicating the issue is that a person's diet, or components of the diet, can increase the activity of enzymes that convert chemicals into carcinogens. And other dietary components can inactivate

enzymes that detoxify chemicals.

The calculus grows so complex that it can be virtually impossible to predict what will happen in an individual person exposed to low levels of a possibly toxic chemical. For example, Dr. Wogan said, "The same food, broccoli, can affect both types of enzymes."

Added to this are the effects of chronic infections, like hepatitis B, in which the immune system releases chemicals that can magnify the effects of carcinogens.

In theory, Dr. Wogan said, there is hope for untangling the mess.

"If we knew how to identify exactly which factors or agents or dietary factors were responsible and if we were able to identify their effects in people, then, in principle, cancer is preventable," he said. But, he added: "It's so tough. It's so very tough to do."

In the meantime, he and others say they take comfort in cancer statistics that do not indicate a cancer epidemic. Rates of cancer have been steadily dropping for 50 years, if tobacco-related cancers are taken out of the equation, said Prof. Richard Peto, an epidemiologist and a biostatistician at Oxford University.

What appear as increases in cancers of the breast and prostate, Dr. Peto added, are in fact artifacts of increased screening. When healthy people are screened, the tests find not only cancers that would be deadly if untreated, but also a certain percentage of tumors that would never cause problems if let alone.

His analysis of cancer statistics leads Dr. Peto to this firm conclusion: "Pollution is not a major determinant of U.S. cancer rates."

Advocates for cancer patients, like Ms. Gillick, of Toms River, N.J., do not agree. They say they have heard it all - scientists' insistence that the risk of cancer from environmental chemicals is very low, that it is almost impossible to ascribe cancer in any individual to an environmental exposure, that most cancers are just a result of unlikely genetic draw or spurious mutation.

But Ms. Gillick and other advocates are not convinced.

Her son Michael, 26, was given a diagnosis of neuroblastoma when he was 3 months old. Ms. Gillick had never heard of that cancer, a pediatric cancer of the sympathetic nervous system. But she soon learned how devastating it could be.

Over the years, as Michael spent time in hospitals in New York and Philadelphia, she noticed something striking. Child after child in those cancer wards came from her town and surrounding Ocean County.

"You start talking to the other parents," Ms. Gillick said. " 'Why? How could that have happened?' "

She found what she thought was the answer: trace levels of industrial chemicals in the drinking water.

But the cancer institute and the E.P.A. investigated and said that they saw no particular danger in the water and that what looked like an increase in childhood cancer was just a statistical fluke.

Dr. Gallo was sent to talk to Toms River residents. Although Ms. Gillick said that she respected him and his views and that she found him likable, she did not like his message.

"Scientists," Ms. Gillick said. "They think it was random bad luck or whatever.

"We can't sit back and say, 'O.K., it happened.' If we could find the cause of a lot of these cancers, we wouldn't have to worry about the cure."

That is also the message of the Breast Cancer Action Coalition. "We think there is something going on, and we'd like to find out what it is," said Ms. Brenner, the executive director. "The scientists who say these kinds of environmental exposure are the smallest contributors, I'd like to know how they know that. If we haven't done the research, how can they say with assurance what is the contributor to anything?"

And, she adds, there are now so many chemicals in the environment that the task of figuring out what effects they might have is dizzying.

"Nobody can keep up," Ms. Brenner said. "And we don't know the health effects. I think it is not an irrational response to say our environment is making us sick."

That is not Dr. Gallo's view. Even though he had cancer, he is not blaming environmental exposures.

"If I were to take that tumor that came out of me and grind it up and run it through a mass spectrometer, I could find every persistent organic chemical I've ever been exposed to," he said. "Is that cause and effect? No, it's an association."

Still, he understands the concerns. "We, the scientific community, should take the blame for this," Dr. Gallo said. "Toxicologists, and I'm one of them, have perpetuated the idea that if 100 molecules are going to kill you, then one molecule is going to kill 1 percent of somebody. And that's the problem. We have a tremendous ability to analyze anything and everything, and the scientific community has said: 'Oh, by the way, we ran this chemical in rodents and found cancer. And therefore ... .' "

Dr. Gallo added that cancer was a complex disease. "There is a gene and environment interaction, and the environment is much broader than just chemicals," he said. "The challenge is to figure out what is the role of the gene and how does the lifestyle and environment overlay that gene."

And science, he said, is just not there yet.

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Preventing Cancer

Slowly, Cancer Genes Tender Their Secrets

By GINA KOLATA

Jay Weinstein found out that he had chronic myelogenous leukemia in 1996, two weeks before his marriage.

He was a New York City firefighter, and he thought his health was great.

He learned that there was little hope for a cure. The one treatment that could save him was a bone marrow transplant, but that required a donor, and he did not have one. By 1999, his disease was nearing its final, fatal phase. He might have just weeks to live.

Then, Mr. Weinstein had a stroke of luck. He managed to become one of the last patients to enroll in a preliminary study at the Oregon Health & Science University, testing an experimental drug.

Mr. Weinstein is alive today and still taking the drug, now on the market as Gleevec. Its maker, Novartis, supplies it to him free because he participated in the clinical trial.

Dr. Brian Druker, a Howard Hughes investigator at the university's Cancer Institute, who led the Gleevec study, sees Mr. Weinstein as a pioneer in a new frontier of science. His treatment was based not on blasting cancer cells with harsh chemotherapy or radiation but instead on using a sort of molecular razor to cut them out.

That, Dr. Druker and others say, is the first fruit of a new understanding of cancer as a genetic disease. But if cancer is a genetic disease, it is like no other in medicine.

With cancer, a person may inherit a predisposition that helps set the process off, but it can take decades - even a lifetime - to accumulate the additional mutations needed to establish a tumor. That is why, scientists say, cancer usually strikes older people and requires an element of bad luck.

"You have to get mutations in the wrong place at the wrong time," Dr. Druker says.

Other genetic diseases may involve one or two genetic changes. In cancer, scores of genes are mutated or duplicated and huge chunks of genetic material are rearranged. With cancer cells, said Dr. William Hahn, an assistant professor of medicine at Harvard Medical School, "it looks like someone has thrown a bomb in the nucleus."

In other genetic diseases, gene alterations disable cells. In cancer, genetic changes give cells a sort of superpower.

At first, as scientists grew to appreciate the complexity of cancer genetics, they despaired. "If there are

100 genetic abnormalities, that's 100 things you need to fix to cure cancer," said Dr. Todd Golub, the director of the Cancer Program at the Broad Institute of Harvard and M.I.T. in Cambridge, Mass., and an oncologist at the Dana-Farber Cancer Institute in Boston. "That's a horrifying thought."

Making matters more complicated, scientists discovered that the genetic changes in one patient's tumor were different from those in another patient with the same type of cancer. That led to new questioning. Was every patient going to be a unique case? Would researchers need to discover new drugs for every single patient?

"People said, 'It's hopelessly intractable and too complicated a problem to ever figure out,' " Dr. Golub recalled.

But to their own amazement, scientists are now finding that untangling the genetics of cancer is not impossible. In fact, they say, what looked like an impenetrable shield protecting cancer cells turns out to be flimsy. And those seemingly impervious cancer cells, Dr. Golub said, "are very much poised to die."

The story of genes and cancer, like most in science, involves many discoveries over many years. But in a sense, it has its roots in the 1980's, with a bold decision by Dr. Bert Vogelstein of Johns Hopkins University to piece together the molecular pathways that lead to cancer.

It was a time when the problem looked utterly complicated. Scientists thought that cancer cells were so abnormal that they were, as Dr. Vogelstein put it, "a total black box."

But Dr. Vogelstein had an idea: what if he started with colon cancer, which had some unusual features that made it more approachable?

Colon cancer progresses through recognizable phases. It changes from a tiny polyp, or adenoma - a benign overgrowth of cells on the wall of the colon - to a larger polyp, a pre-cancerous growth that, Dr. Vogelstein said, looks "mean," and then to a cancer that pushes through the wall of the colon. The final stage is metastasis, when the cancer travels through the body.

"This series of changes is thought to occur in most cancers, but there aren't many cancers where you can get specimens that represent all these stages," Dr. Vogelstein said.

With colon cancer, pathologists could get tissue by removing polyps and adenomas in colonoscopies and taking cancerous tumors in surgery.

Colon cancer was even more appealing for such a study because there are families with strong inherited predispositions to develop the disease, indicating that they have cancer genes that may be discovered.

So Dr. Vogelstein and his colleagues set out to search for genes "any way we could," Dr. Vogelstein said. Other labs found genes, too, and by the mid-1990's, scientists had a rough outline of what was going on.

Although there were scores of mutations and widespread gene deletions and rearrangements, it turned out that the crucial changes that turned a colon cell cancerous involved just five pathways. There were dozens of ways of disabling those pathways, but they were merely multiple means to the same end.

People with inherited predispositions to colon cancer started out with a gene mutation that put their cells on one of those pathways. A few more random mutations and the cells could become cancerous.

The colon cancer story, Dr. Druker said, "is exactly the paradigm we need for every single cancer at every single stage."

But scientists were stymied. Where should they go from there? How did what happens in colon cancer apply to other cancers? If they had to repeat the colon cancer story every time, discovering genetic alterations in each case, it would take decades to make any progress.

The turning point came only recently, with the advent of new technology. Using microarrays, or gene chips - small slivers of glass or nylon that can be coated with all known human genes - scientists can now discover every gene that is active in a cancer cell and learn what portions of the genes are amplified or deleted.

With another method, called RNA interference, investigators can turn off any gene and see what happens to a cell. And new methods of DNA sequencing make it feasible to start asking what changes have taken place in what gene.

The National Cancer Institute and the National Human Genome Research Institute recently announced a three-year pilot project to map genetic aberrations in cancer cells.

The project, Dr. Druker said, is "the first step to identifying all the Achilles' heels in cancers."

Solving the problem of cancer will not be trivial, Dr. Golub said. But, he added, "For the first time, we have the tools needed to attack the problem, and if we as a research community come together to work out the genetic basis of cancer, I think it will forever change how we think about the disease."

Already, the principles are in place, scientists say. What is left are the specifics: the gene alterations that could be targets for drugs.

"We're close to being able to put our arms around the whole cancer problem," said Robert Weinberg, a biology professor at the Massachusetts Institute of Technology and a member of the Whitehead Institute. "We've completed the list of all cancer cells needed to create a malignancy," Dr. Weinberg said. "And I wouldn't have said that five years ago."

The list includes roughly 10 pathways that cells use to become cancerous and that involve a variety of crucial genetic alterations. There are genetic changes that end up spurring cell growth and others that result in the jettisoning of genes that normally slow growth. There are changes that allow cells to keep dividing, immortalizing them, and ones that allow cells to live on when they are deranged; ordinarily, a deranged cell kills itself.

Still other changes let cancer cells recruit normal tissue to support and to nourish them. And with some changes, Dr. Weinberg said, cancer cells block the immune system from destroying them.

In metastasis, he added, when cancers spread, the cells activate genes that normally are used only in embryo development, when cells migrate, and in wound healing.

But so many genetic changes give rise to a question: how does a cell acquire them?

In any cell division, there is a one-in-a-million chance that a mutation will accidentally occur, Dr. Weinberg notes. The chance of two mutations is one in a million million and the chance of three is one in a million million million million.

This slow mutation rate results from the fact that healthy cells quickly repair damage to their DNA.

"DNA repair stands as the dike between us and the inundation of mutations," Dr. Weinberg said.

But one of the first things a cell does when it starts down a road to cancer is to disable repair mechanisms. In fact, BRCA1 and 2, the gene mutations that predispose people to breast and ovarian cancer, as well as some other inherited cancer genes, disable these repair systems.

Once the mutations start, there is "a kind of snowball effect, like a chain reaction," Dr. Vogelstein said.

With the first mutations, cells multiply, producing clusters of cells with genetic changes. As some randomly acquire additional mutations, they grow even more.

In the end, all those altered genes may end up being the downfall of cancer cells, researchers say.

"Cancer cells have many Achilles' heels," Dr. Golub says. "It may take a couple of dozen mutations to cause a cancer, all of which are required for the maintenance and survival of the cancer cell."

Gleevec, researchers say, was the first test of this idea. The drug knocks out a gene product, abl kinase, that is overly abundant in chronic myelogenous leukemia. The first clinical trial, which began seven years ago, seemed like a long shot.

"The idea that this would lead to therapy was something you wrote in your grant application," said Dr. Charles Sawyers, a Howard Hughes investigator at the University of California, Los Angeles. "It wasn't anything you believed would happen soon."

But the clinical trial of Gleevec, conducted at the Oregon Health & Science University, U.C.L.A. and M. D. Anderson Cancer Center in Houston, was a spectacular success. Patients' cancer cells were beaten back to such an extent that the old tests to look for them in bone marrow were too insensitive, Dr. Sawyers said.

Gleevec is not perfect. It is expensive, costing about $25,000 a year. It is not a cure: some cancer cells remain lurking, quiescent and ready to spring if the drug is stopped, so patients must take it every day for the rest of their lives. And some patients are now developing resistance to Gleevec.

Still, Dr. Sawyers says, "Seven years later, most of our patients are still doing well." Without Gleevec, he added, most would be dead.

As for the future of cancer therapy, Dr. Golub and others say that Gleevec offers a taste of the possible.

Dr. Golub said he expected that new drugs would strike the Achilles' heels of particular cancers. The treatment will not depend on where the cancer started - breast, colon, lung - but rather which pathway is deranged.

"It's starting to come into focus how one might target the problem," Dr. Golub said. "Individual cancers are going to fall one by one by targeting the molecular abnormalities that underlie them."

And some cancer therapies may have to be taken for a lifetime, turning cancer into a chronic disease.

"Seeing cancer become more like what has happened with AIDS would not be shocking," Dr. Golub

says. "Does that mean cure? Not necessarily. We may see patients treated until they die of something else."

That is what Mr. Weinstein hopes will happen with him. The cancer is still there: new, exquisitely sensitive tests still find a few cells lurking in his bone marrow. And Gleevec has caused side effects. Mr. Weinstein says his fingers and toes sometimes freeze for a few seconds, and sometimes he gets diarrhea.

But, he said, "Certain things you put out of your mind because life is so good."