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May 18, 1998

SECTION: SPECIAL REPORT: CURING CANCER; Pg. 48

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CANCER (General)
HER-2/neu protein ANTIBODY
Rituxan
RAS (rat sarcoma)
mice

HEADLINE: Molecular Revolution;
A new generation of drugs takes aim at the very heart of cancer--the abnormal genes that make cells malignant in the first place

BYLINE: Claudia Wallis, With reporting by Lawrence Mondi/New York and James Willwerth/Los Angeles

BODY:

Last week's miracle-in-mice may have launched a thousand premature hopes, but there's no doubt in the minds of cancer researchers today that a new era is dawning in the treatment of the U.S.'s No. 2 killer. Three decades ago, the Federal Government's "War on Cancer" underwrote basic discoveries about the ways broken-down genes lead to malignancies. Now that work is beginning to pay off. "The black box that was the cancer cell has been opened," says Dr. Bert Vogelstein, a world-renowned investigator of cancer genes at the Johns Hopkins University in Baltimore, Md. "As researchers, we feel a tremendous amount of hope, probably for the first time in the history of cancer treatment."

In pharmaceutical-company research departments and academic labs around the country, scientists are feverishly at work on drugs that target the products of specific genes--the very genes that make a cell cancerous. The hope is that these treatments will be more effective, longer lasting and far less toxic than traditional chemotherapy and radiation--treatments that inspire dread so deep that they are almost as feared as cancer itself.

"Because of the early success with chemotherapy in some forms of leukemias and lymphomas," says Dr. Dennis Slamon, of the Revlon/UCLA Women's Cancer Research Program, "we have been slugging at cancer that way for 25 years. We didn't make any significant inroads, and in some cases, we ended up killing people. Now we are beginning to look specifically at what's broken in a cancer cell and trying to target that."

What's broken in cancer cells is genes, usually genes that control some aspect of cell growth and division. Hundreds of genes play a role in this process, and more than three dozen have been identified as playing a role in cancer. Some are like accelerators, telling cells to grow, grow, grow. Others put the brakes on growth. Some regulate steps in cell division to make sure that DNA is copied correctly from mother to daughter cell. Some play executioner, killing mutant cells in which the copying has gone awry. Cancer is caused by errors in these genes, usually multiple errors. Though some of these errors may be inherited, most are acquired during years of living. Sunlight, cigarette smoke, environmental toxins and aging itself help these errors accumulate.

Since every gene holds the recipe for a vital protein, corrupt genes mean corrupt proteins: too much of one protein, too little of another, or a misshapen protein that doesn't function properly. The new generation of cancer drugs

takes aim at these defective proteins, blocking them, disrupting them in myriad ways. Unlike old-fashioned chemotherapy drugs, the new substances don't poison the tumor--an approach that usually causes collateral damage to healthy cells. Instead, they aim to halt the processes that make a cancer cell act like a cancer cell in the first place.

Barbara Bradfield, 55, is living proof that this can work. A teacher turned homemaker in La Canada Flintridge, Calif., Bradfield is one of the lucky cancer patients who have already benefited from the new generation of gene-based treatments. She was 47 years old when she discovered a large lump in her breast. Tests showed that the malignancy had spread to her lymph nodes. Bradfield got the works: a double mastectomy and six months of chemotherapy, followed by radiation and then more chemo. It bought her 18 months of symptom-free life. Then one hot August night, she recalls, "I went to rub my neck, and there was a tumor about the size of a marshmallow." Bradfield was already depressed--her daughter had just died in a car accident--and she never wanted to face chemo again. "I thought I was probably going to die, and I didn't want to die bald and throwing up."

As it happened, Bradfield's tumor cells had a characteristic present in about 30% of breast-cancer cells: too many copies of a gene known as HER-2/neu. This gene makes a protein that helps relay the signal telling cells to divide. Having too much of it is associated with an especially rampaging, hard-to-treat cancer. Once this form of breast cancer metastasizes, a patient typically has just six to 12 months to live.

Bradfield's doctor put her in touch with UCLA's Slamon, who was testing a brand-new antibody that targeted the HER-2/neu protein. Although Slamon was using the antibody in combination with chemotherapy--and Bradfield was loath to go back to chemo--the combined therapy proved miraculous in her case. Sixteen small tumors in her lungs melted away. By 1993 she was in remission, and still is. "I got to be at my son's wedding," she exults. "The gift is that I'm here!"

The antibody is not a panacea. It didn't work as well for Bradfield's fellow guinea pigs in the initial study. But results of a just completed trial with 470 women do show it to be a significant improvement over chemo alone for women with this awful form of breast cancer. The details of the study will be revealed by Slamon this Sunday at a meeting in Los Angeles of the American Society of Clinical Oncology. Manufactured by Genentech under the name Herceptin, the drug is on a fast track for approval by the FDA, perhaps before year's end.

Herceptin, if approved, will join the lymphoma drug Rituxan, also an antibody, as the first of the new gene-based therapies to make it to market. Rituxan, made by IDEC Pharmaceuticals, was approved late last year.

Other substances in the works may be further from the market, but they are in some ways even more exciting. Several of them take aim at a growth-signaling protein made by a gene called RAS (for rat sarcoma, the cancer in which it was first discovered). In about 30% of cancers, the RAS protein is stuck in an "on" position, mindlessly ordering the cell to divide again and again. It plays a role in 90% of pancreatic cancers, 50% of colon cancers and 25% of lung cancers. Dr. Edward Scolnick discovered the RAS gene in rats while working at the National Cancer Institute in 1978. Now president of Merck Research Laboratories, he is overseeing the development of a drug that stops the RAS protein from sending its malignant message. Several other big drug companies, including

Bristol-Myers Squibb, Johnson & Johnson and Schering-Plough, are testing similar drugs. "We think the odds are that if you treat people with a good RAS drug, you will produce some clinical benefit," says Scolnick. Finding a new kind of cancer therapy based on gene discoveries like his own is, Scolnick admits, "my fondest hope."

Other drug companies are targeting another common cancer gene: one that codes for a protein called the EGF (epidermal growth factor) receptor. This receptor, which takes in growth signals and relays them to the RAS protein, is found in abnormally high numbers on the surface of about 40% of tumor cells, including about 90% of lung-cancer tumors, some prostate tumors and other malignancies. Researchers at M.D. Anderson Cancer Center in Houston are testing an antibody to EGF receptors in patients with advanced head and neck cancers. But most other groups, including teams at drug makers Pfizer, Novartis and Zeneca, are using smaller molecules that, unlike antibodies, could ultimately be taken orally. "We have a very exciting tablet that is taken once a day," says Dr. George Blackledge, head of new cancer projects at the Zeneca Group. Testing on patients is still at a very early stage. "We have to be cautious," he says, "but potentially this could be an effective new treatment for the most common type of lung cancer."

At the Memorial Sloan-Kettering Cancer Center in New York City, Dr. Mark Malkin is working with a substance that targets a receptor for another growth factor called PDGF (platelet-derived growth factor). This receptor studs the surfaces of cells in certain ovarian, prostate, lung and brain tumors. Malkin has been testing the drug, SU101, on patients with an extraordinarily deadly brain tumor called glioblastoma. Median survival for a patient found to have this cancer is 14 months.

So far, the drug, manufactured by Sugen, appears to slow or arrest tumor growth in about a third of glioblastoma patients, but it's too soon to say how long the benefits will last. Side effects appear to be mild. "We have one patient who's been on it for two years and three months," says Malkin. "His tumor is still there, but it's stable. He's alive; he's at work. For someone with recurrent glioblastoma, that's remarkable."

Malkin is quick to point out that one growth-factor inhibitor isn't going to cure cancer. Cancer is a complicated disease. Tumors usually are made up of different types of cells, expressing different genes, sensitive to different growth factors and therefore responding to different drugs. "When you are trying to kill cancer cells, you're always likely to need combination treatment," says Merck's Scolnick. Like AIDS treatments, the new generation of cancer drugs will need to be combined with older drugs and possibly with one another to be most effective.

If the promise of these drugs holds up, however, cancer treatment in the 21st century will bear little resemblance to today's chemotherapy. Drugs will be precisely tailored to the individual tumor, and the cancers themselves will be described not by the site they attack--breast cancers, lung cancers, etc.--but by the genes they express. The National Cancer Institute is at work creating a DNA library of tumor types, a long-range project called C-GAP (Cancer Genome Anatomy Project). But it will be years before this library can be put to practical use. "It took 20 years to make testing for hormone receptors routine in breast-cancer patients," notes UCLA's Slamon. It will take at least a decade to make testing for HER-2/neu, RAS and other genes routine for cancer patients

in general.

It's also possible that the new generation of drugs emerging from the labs won't work very well, or that the much vaunted lack of major side effects will prove to be an illusion. All the enzymes and growth-factor receptors blocked by the new drugs play a role in normal cell division as well as in cancer. So disrupting them could cause harm. "Whether the therapy is going to be a major advance, a modest improvement or a disappointment is not clear," says Dr. J. Michael Bishop, molecular biologist at the University of California, San Francisco, who shared a 1989 Nobel Prize with Dr. Harold Varmus for their pioneering work on oncogenes. But Bishop is impressed that the field is moving so swiftly, and most researchers are convinced that they are at least on the right track. Says Joseph Schlessinger, a New York University scientist who helped develop SU101: "Early in the next millennium, we will significantly extend the life expectancy of cancer patients. I have no doubt about that."

Though patients long desperately for a "cure," extending life is the more realistic goal in treating cancer. The newer drugs, unlike chemotherapy agents, are "cancer stoppers," not "cancer killers," says Malkin. Chances are that they will have to be taken for many years, or even for the rest of a patient's life. But if such drugs can slow or stop the growth and spread of malignant cells, then cancer can be transformed from an acute and deadly disease into a chronic and manageable one. That doesn't make as sexy a headline as a cancer cure, but it's still the difference between life and death.

--With reporting by Lawrence Mondi/New York and James Willwerth/Los Angeles

BOX STORY:

KNOWING HOW CANCER CELLS MULTIPLY...

1 Normal cells begin to split in two when a substance called a growth factor binds to a receptor and triggers cell division. Cancer cells are different. Some have an excess of receptors, some produce their own growth factor, and some have both characteristics. That's why they divide uncontrollably

2 The stimulated receptor activates proteins inside the cell

3 One of these cellular proteins, called RAS, transmits the growth signal to the nucleus, using other messenger proteins. In certain types of cancer, the RAS protein is defective. Stuck in the "on" position, it transmits this growth signal even when not activated by a growth factor

4 When the message instructing the cell to divide reaches the nucleus, other proteins begin to replicate the cell's DNA

...MAY LEAD TO NEW TREATMENTS Researchers are trying to develop drugs that target specific steps in this process

1 Drugs that bind to the receptors could prevent the growth signal from reaching the cell

2 Substances called tyrosine kinase inhibitors can block the activation

3 Molecules that target RAS or other messenger proteins could short-circuit the growth signal before it reaches the nucleus

4 Drugs that penetrate the nucleus can block the proteins responsible for DNA replication.

BOX STORY:

IF YOU WANT MORE INFORMATION

On the Internet there are dozens of websites devoted to cancer research. Here is a selection:

--The National Cancer Institute's CancerNet (cancernet.nci.nih.gov)

--OncoLink, a site operated by the University of Pennsylvania's Cancer Center (oncolink.upenn.edu)

--The American Cancer Society (www.cancer.org)

--Cancer News on the Net (www.cancernews.com)

--CanSearch, a resource guide from the National Coalition for Cancer Survivorship (www.cansearch.org)

People who prefer using a telephone instead of a computer--or who want more detailed help with a specific problem--can call the National Cancer Institute information service at 1-800-4-CANCER.

GRAPHIC: COLOR ILLUSTRATION: TIME DIAGRAM BY JOE LERTOLA, [Diagram of ways in which new cancer drugs inhibit growth and multiplication of cancer cells]; COLOR PHOTO: AMY ETRA FOR TIME, [Barbara Bradfield]

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CANCER (General)
Same as Time

U.S. News & World Report

May 18, 1998
CORRECTION APPENDED

SECTION: CULTURE & IDEAS; COVER STORY; Pg. 56

LENGTH: 3295 words

HEADLINE: Killing cancer

BYLINE: By Shannon Brownlee; Nancy Shute; Laura Tangley

HIGHLIGHT:
New drugs can cure mice, thanks to advances in understanding the disease's basic biology. But cures for people are still years away

BODY:
Like any scientist whose work has been mired in controversy, Judah Folkman dreamed of proving his critics wrong. But he didn't plan on success unfolding quite this way. For two decades, he'd endured the ridicule of colleagues, who called him a clown and said his theory of cancer--that malignant tumors needed a blood supply in order to grow--was "dirt." The surgeon and cell biologist at Children's Hospital in Boston persevered nonetheless, spending mornings in surgery and afternoons hunched over a laboratory bench. Finally, after years of laborious and often frustrating research, Folkman, 65, had in hand two compounds that could wipe out large tumors in mice by cutting off their blood supply, proving his theory and opening the possibility of a revolutionary new way of treating cancer.

But when the New York Times featured his work on the front page last week, Folkman suddenly got far more attention than he'd ever bargained for--or wanted. In the next days, headlines across the country blared, "Cancer Cure." Share prices soared on the stocks of a dozen biotechnology companies hoping to bring Folkman's drugs and similar compounds to market (box, Page 64). Interview requests poured in to Children's Hospital from media outlets around the world. And phones and fax machines in Folkman's office were jammed by up to 1,000 calls a day, many of them urgent pleas from desperate cancer patients and their relatives, hoping for a chance to try the new drugs.

There was only one problem: Folkman's drugs, called angiostatin and endostatin, are not the "cure" for cancer--at least not yet. The drugs work spectacularly well in mice, shrinking cancers that would be the equivalent of a 1-pound tumor in a human being. But, as one doctor said, if curing mice were all that was needed, the war on cancer would have been won long ago. Folkman's drugs are the most potent among a throng of similar compounds discovered in the last decade, all aimed at choking off the growth of blood vessels around a tumor, causing it to shrink. But the new drugs have many hurdles to clear before they can begin helping patients--not the least of which is to be produced in quantities large enough to be tested in people. There is no guarantee they will work in human beings, or work as well as they do in mice. The road to eliminating cancer is littered with failed drugs that once were hailed as cures. And even if the drugs are found to be effective, it will be several years before doctors can prescribe them for their patients. As Folkman himself

wearily repeated over and over again last week, the only sure bet is: "If you are a mouse with cancer, we can take good care of you."

"Terrifically exciting." That said, most cancer researchers believe Folkman's discoveries truly are revolutionary and that they do in fact offer a novel strategy for curing cancer--though the "cure" may not come as quickly as the public would like. "This is terrifically exciting," says Helene Sage, a cell molecular biologist at the University of Washington. At a meeting in Bethesda, Md., late last year, Folkman presented data that prompted Richard Klausner, director of the National Cancer Institute, to give the drugs the highest priority for clinical testing. Even Folkman himself says, "I've been waiting for results like these my whole life."

Some of the enthusiasm among scientists stems from the fact that Folkman's drugs are helping to validate scientists' efforts over the last 30 years to understand cancer's basic biology. When Richard Nixon declared war on the illness in 1971, biologists knew precious little about how cancer worked on a cellular level, and oncologists had only the blunt tools of radiation, surgery, and chemotherapy to work with. Oncologists still don't have a lot of weapons at their disposal, but new understanding has spawned promising treatments, including gene therapy and monoclonal antibodies, the first of which went on the market late last year.

The insight that inspired Folkman to begin his search came long before biologists began to peer into the interior of a tumor cell. Clinicians knew that once a tumor grows beyond a few hundred thousand cells--no bigger than a BB--the cells at the center of the mass start to die. Folkman surmised that to grow, tumors need blood and send out an unknown substance that coaxes nearby blood vessels into sprouting new capillaries--a process known as angiogenesis, from the Greek angos, for vessel. But other clinicians, still wedded to the notion that the infiltration of a tumor by blood vessels was merely an unimportant side effect, scoffed at the idea.

Folkman proved the skeptics wrong in 1983, when two postdoctoral fellows in his lab purified a protein from a rat tumor that did precisely what he'd predicted, stimulating the growth of capillaries. There are now at least 14 known angiogenic factors. They cause blood vessels to sprout new branches and give tumors the double benefit of a rich supply of blood and proteins, produced by blood vessel cells, that also help cancer cells grow.

Folkman reasoned that if he could somehow block the tumor's blood supply, the cancer could be stopped. Soon after, he quit performing surgery and focused his attention full time on searching for a protein to do just that by inhibiting the growth of capillaries.

Serendipity. In 1985, he got a lucky break, when blood vessel cells being cultured in the lab were accidentally contaminated by a yeast that stopped the cells from growing but didn't kill them. Folkman's team isolated from the yeast a naturally occurring substance called fumigillin, which could slow down tumor growth when injected into mice, and which simultaneously proved Folkman's principle and transformed his critics into competitors. Synthetic versions of fumigillin have been shown safe in people and have a weak ability to slow tumors.

Since then, Folkman's lab and others have found dozens of antiangiogenic factors, some of which are already being tested in people, including thalidomide, banned in the 1960s after causing devastating birth defects, and alpha interferon, touted as a cancer cure in the late 1970s. Both these drugs, it turns out, have antiangiogenic properties and can inhibit blood vessel growth. Alpha interferon is now showing limited success battling slow-growing tumors of the bone and life-threatening hemangiomas, a childhood cancer. But the drug can't knock out tumors that are more malignant, says Folkman. "Breast cancer would laugh at interferon."

The scientist's new drugs, by comparison, are prizefighters. Their success rests upon a clinical observation that has baffled doctors for years: In some patients, the largest tumor in the body seems to stunt the growth of metastatic tumors, the tiny progeny of the original tumor that take up residence in far-flung sites in the body. Removing the largest tumor surgically in very rare cases allows the little tumors to spring to life, growing so rapidly they can kill the patient before doctors can suppress them. Folkman and his team realized that perhaps the main tumor was itself sending out antiangiogenic factors. These substances then traveled outward, blocking the blood supply to the little tumors and inhibiting their growth.

In the next years, this inspiration was fleshed out by the meticulous drudgery that makes up most of scientific research. A young doctor named Michael O'Reilly teamed up with the University of Washington's Sage and Yuen Shing, a protein chemist in Folkman's lab, and together they poured milliliter after milliliter of mouse blood through glass tubing, searching for a protein that might be a long-distance blocker of blood vessels. Eventually, they found two. O'Reilly then had the task of extracting from mouse urine, where the proteins are plentiful, a sufficient amount of them to treat a few mice. "He smelled so bad that his wife made him take his clothes off before he came in the door after work," Folkman recalls.

O'Reilly's efforts paid off. The proteins, angiostatin and endostatin, could shrink a mouse tumor size of an almond--much too big to be killed by chemotherapy--to almost nothing in a few days. Working in tandem, the drugs brought about a cure. Best of all, angiostatin and endostatin seem to home in on capillaries near cancer cells, leaving blood vessels in the rest of the body alone, and causing the mice no apparent side effects. Unlike traditional chemotherapy, which can make mice as well as human patients quite ill, endostatin, angiostatin, and vasculostatin, Folkman's newest find, appear benign. They are also, in contrast to standard chemotherapy, likely to keep on working even if they are given to patients for many years. Cancer cells mutate at a furious rate, and they can evolve the means to resist most chemotherapy drugs, requiring higher and more toxic doses to achieve an effect. Antiangiogenic factors do not seem to induce resistance in slower-growing blood vessel cells, but Folkman admits that no one knows precisely how they will work in humans.

Frantic calls. Last week's New York Times article is still reverberating in doctors' offices, where phones and faxes have been ringing with calls from patients begging for the new drugs. "These new drugs are all our patients want to talk about," says David Van Echo, an oncologist who heads drug development at the University of Maryland--Baltimore. "They are saying they want to get the new drugs and they don't want the treatment they're taking."

It is not a wish that will be granted anytime soon. For one thing, there is hardly enough angiostatin and endostatin in the world to treat a few mice, let alone millions of human patients suffering from cancer. And even if there were, the drugs must first run the gantlet of clinical trials--the careful, government-mandated tests that are the only way to determine if new medicines are safe and effective in people. At least 25 companies are racing to bring versions of antiangiogenic compounds to market, including pharmaceutical giants SmithKline Beecham, Merck, and Novartis, as well as biotech start-ups like Boston Life Sciences and EntreMed, the firm that was founded in order to commercialize angiostatin and endostatin. Some of the new drugs have already entered the early phases of clinical trials, which can take from five to seven years to complete. Endostatin and angiostatin are at least 1 1/2 years away from human tests, says an EntreMed spokeswoman, because the company has yet to work out the kinks to produce large amounts.

Many other obstacles lie between curing cancer in mice and battling tumors in human beings. Mouse tumors, says Martin Brown, a professor of radiation oncology at Stanford University Medical Center, grow extremely rapidly, and they are totally dependent on new capillaries. "I don't want to minimize Judah Folkman's work," he says. "There's a good chance these drugs will be active against human tumors. But it will not be as dramatic in humans as in mice, and human tumors will shrink more slowly." Other researchers warn that the drugs may cause side effects in people, like muscle inflammation. And antiangiogenics might cause birth defects if a woman takes them while she is pregnant, as other anticancer agents do.

If they finally come to market, the new drugs will join a variety of other new cancer treatments, many of which are already being tested in humans. In killing cancer, the key problem remains that standard cancer treatments such as radiation and chemotherapy damage many cells in the body, not just the cancerous ones. More recent experimental therapies tightly target newly identified molecular and genetic pathways within cancerous cells, rather than using the broad-spectrum attack of older therapies. Later this month, biotech giant Genentech will unveil the first evidence that a genetically engineered monoclonal antibody, to be marketed as Herceptin, mimics key components of the body's immune system and shrinks breast cancer tumors in women. Herceptin attacks the HER-2 gene, which generates a protein that boosts cancer growth in about 30 percent of patients.

Since the 1940s, researchers also have been trying with little success to stimulate the body's immune system to fight cancer by administering vaccines made of malignant cells. But in the past decade, researchers have devised vaccines, cobbled together from either whole cancer cells or pieces of cells, which boost an immune response against the tumor. In human trials at Jefferson Medical College in Philadelphia and elsewhere, the vaccines have proven as successful as aggressive chemotherapy against melanoma, but without the debilitating side effects. Dozens of similar vaccines are in the works targeting other cancers.

One of the most promising new cancer treatments is gene therapy. In the 1970s, scientists began to figure out that mutated genes are the triggers that turn normal cells into cancer cells, growing out of control. If the damage could be fixed, or the bad genes could be replaced with good copies, they reasoned, the cell proliferation could be stalled. Current gene therapy efforts are aimed at the three classes of genes that go bad in cancer: oncogenes, which

stimulate cell growth and division; tumor suppressor genes, which restrict cell growth; and another type of gene that controls DNA replication and repair. Gene therapy has generated huge interest and millions of dollars of funding, but until recently has been criticized as overhyped, because no one could find a method for delivering enough genes into cancer cells without producing toxic side effects.

Catch the bus. Later this month, however, researchers from the University of Texas M. D. Anderson Cancer Center in Houston will present results showing for the first time that gene therapy can in fact repair damaged genes and suppress tumors. The researchers drafted the adenovirus that causes the common cold into service as a bus, carrying the p53 gene into cancer cells. The p53 gene puts the brakes on cell growth and forces cells to commit suicide if their DNA is damaged, for instance by sun exposure or smoking. Last year, the adenovirus-p53 combo was tested in almost 100 patients with head and neck cancer, and tumors shrank in almost 50 percent of patients. "There was very little toxicity, even with monthly injections," says Jack Roth, the thoracic surgeon who led the study. "It was a little surprising." P53 gene therapy is also being tested on lung and prostate cancers, and is expected to go into clinical trials by the year 2000.

Another experimental treatment, anti-sense therapy, may not drive tumor cells to commit suicide, but it seems to slow them down. Anti-sense molecules are threads of nonsense DNA that derail oncogenes by jamming their message and canceling the order for growth-promoting proteins. Anti-sense drugs are in clinical trials in ovarian cancer and others. Research on still another substance, an enzyme called telomerase, isn't nearly as far along, but researchers are excited about its role in controlling the life and death cycle of all cells, including cancer cells. All DNA strands are capped by telomeres, extra bits of DNA that snap off piece by piece every time a cell divides. Once the telomeres are gone, the cell stops dividing and grows old. In January, researchers at Geron Corp. in Menlo Park, Calif., proved that the enzyme telomerase lengthens telomeres, enabling the cell to keep dividing. Cancer cells draft telomerase to keep themselves going. Geron and other firms are working on ways to block telomerase in cancer cells to force them to age and die like normal cells.

Old and new. At least a few of these new therapies are likely to make it to the market long before Folkman's antiangiogenic drugs become available. But none of the new treatments, including Folkman's, will put an immediate end to chemotherapy and radiation. Instead, old and new will be used side by side, delivering a one-two punch to tumors. "I'd love to put radiation and chemotherapy out of business, but it's not happening anytime soon," says John Mendelsohn, an oncologist and president of the M. D. Anderson Cancer Center. "We're still going to need all the help we can get, at least over the next five to 10 years."

Folkman, for his part, envisions a time when doctors will hit tumors with an antiangiogenic drug to knock them down in size, surgically remove the tumors, then deliver more antiangiogenics along with chemotherapy or gene therapy to wipe out metastatic tumors. Long-term use of antiangiogenic drugs might be able to keep some tumors dormant so they never pose a threat. But that's all in the future. For now, the scientist just wants to get back to the lab and resume his search for even more powerful cancer killers.

EntreMed's new cancer-attacking proteins won't be tested on humans for at least a year, but patients can sign up for other promising treatments now in clinical trials. Learn how at www.usnews.com

Choking off tumors

Tumor cells stimulate the growth of new capillaries that fuel the tumor's own explosive growth. But large tumors also try to eliminate competition from other tumors in the body by sending out "inhibitor" that halt capillary growth. Researchers hope these inhibitors can be used to choke of tumors in people.

1. Once a tumor is the size of a BB, cells at its interior will start to die unless it can get a fresh blood supply. Angiogenic factors are proteins produced by the tumors that prod nearby blood vessels into sprouting new capillaries.

2. The new capillaries supply the tumor with oxygen and nutrients. The capillaries also provide a route for cancer cells to metastasize--to spread to distant parts of the body.

3. Antiangiogenic factors block the growth of new capillaries and shrink those supplying the tumor. Without a source of blood, the tumor cells die.

[Illustration labels]: Angiogenic factors; Tumor; Blood vessel; Capillaries; New capillaries; Metastasized tumors; tumor cells die; Capillaries shrink

Source: Judah Folkman--Boston Children's Hospital

From mouse to human

Discovering a drug that works in animals is only the first step in a lengthy process required before the Food and Drug Administration approves its use in humans.

Preclinical Testing

Before any trials in humans can begin, extensive screening tests in animals and test tubes are run to detect if a drug is toxic, causes birth defects, or poses other safety risks. The new anticancer drugs angiostatin and endostatin are in the early stages of this testing. Average duration in years: 6 1/2

Clinical Testing

Phase I. To verify safety in humans, a small group of healthy volunteers is given the drug, starting at low doses. Average duration in years: 1 1/2

Phase II. Researchers measure the effectiveness of the drug in treating a disease or condition in humans; precise dosage is established. Average duration in years: 2

Phase III. Full-scale human trials, often in several locations, are carried out to compare the effectiveness of the new drug with other standard treatments or placebos. Average duration in years: 3 1/2

FDA Review

FDA reviews all data and decides if the new drug can be released onto the market. Average duration in years: 1 1/2

Fast track. Cancer drugs are often put on what is known as a "fast track," during which clinical trials are shortened and FDA reviewers work faster. Safety standards are maintained, but testing of a drug's effectiveness can be less rigorous.

Sources: The Pharmaceutical Research and manufacturers of America, American Cancer Society

CORRECTION-DATE: June 29, 1998

CORRECTION:
In the search for cancer-fighting drugs, Phase I of clinical testing can include either healthy volunteers or cancer patients, not just healthy volunteers ["Killing Cancer," Cover, May 18].

GRAPHIC: Picture, A C57 black mouse like those used by Judah Folkman in his research (Photograph by George Steinmetz for USN&WR); Drawing, Choking off tumors (Rod Little--USN&WR); Chart, Choking off tumors (Judah Folkman--Boston Children's Hospital); Chart, From mouse to human (The Pharmaceutical Research and manufacturers of America, American Cancer Society); Picture, Antiangiogenic drugs like Folkman's work by cutting off the blood supply to tumor cells. (Photograph by George Steinmetz for USN&WR)

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CANCER (General)

ANGIOSTATIN
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October 5, 1998

SECTION: No. 3, Vol. 55; Pg. 8; ISSN: 1041-1410

IAC-ACC-NO: 21225847

LENGTH: 2156 words

HEADLINE: Cancer: the war heats up; includes related articles

BYLINE: Bregman, Mark

BODY:

For 14-year-old Janet Pendry of Lakeland, Florida, it began when she noticed a simple bump on her shoulder. The teen, who spends her free time hitting the piano, clarinet, and oboe in town bands, didn't think about the bump. It didn't hurt, though it didn't go away. Janet finally went to a doctor who diagnosed it as a cyst, a sac-like lump he believed was nothing to worry about. Other doctors told Janet the same thing, but after a year she decided to have the lump removed. Last February Janet was diagnosed with Ewings sarcoma, a kind of bone cancer found in children and young adults that can spread quickly through the body.

For Corey Wentworth, it started with a fever. The 14-year-old from Calais, Maine, who usually flies on his bike all over town, was suddenly laid low by aching flu-like symptoms in May 1997. His mom took him to a doctor, and later for blood tests at the Eastern Maine Medical Center. Corey remained in the hospital for a month, diagnosed with leukemia, a form of cancer that destroys healthy red blood cells.

Years ago, Corey's and Janet's diagnoses of cancer might have spelled quick death sentences. "When I first heard the news, I panicked," says Corey's mom Brenda Spear. "I thought I was going to lose him." A cure for most cancers still eludes scientists, because cancer isn't a single illness--it's a complex group of diseases marked by the uncontrolled growth and spread of abnormal cells (see inset, p. 9). Normal body cells grow and divide in a precisely controlled way; cancer occurs when cells keep dividing and multiply out of control.

But within the last decade, scientists have gleaned new insights into the workings of human cells. "For the first time, I feel confident we're getting a handle on the biology of cancer," says UCLA researcher Derek Raghavan. As a result, improved treatments have chipped away at cancer's deadly grip.

In fact, a recent barrage of news indicates science may be nearing a major breakthrough in the cancer wars. Researchers will soon begin human testing on a type of drug that has drastically shrunk and even eradicated cancerous tumors (a mass of cells) in mice--and left them cancer-free. But clearly the battle is far from over. About 560,000 Americans will die of cancer in 1998.

A LONG DEADLY WAR

The war against cancer has been long and deadly. This year alone, the American Cancer Society predicts about 1.2 million new cancer cases, 8,700 in children under 15. Four out of 10 patients now diagnosed with cancer will still be alive in five years (see chart, right). But the majority may not survive that long--unless the promising new treatments now slated for testing prove victorious.

Right now, Corey and Janet maintain normal lives. "What bothers me everyday isn't leukemia," says Corey. "It's 14-year-old stuff, like girlfriends who get mad at me."

What makes curing cancer so elusive? "Cancer cells are cunning," says Freda Stevenson, a scientist at the University of Southampton in England. The disease-fighting immune system is programmed to destroy abnormal cells, like cancer cells. "But tumor cells have developed ways of switching off the immune system to their presence, thwarting any possible attack," Stevenson says.

Scientists now know normal cells begin to split and produce copies of themselves through a complicated process. Cells produce substances called growth factors. These substances bind to receptors on the surface of cells, like keys fitting into locks. Growth factors trigger cell division.

Cancer cells flaunt the rules. Some have an excess of receptors; some contain their own growth factors; and some possess both. But all cancer cells share one trait in common--they divide uncontrollably. Hundreds of thousands of cancer cells combine to form a tumor. Once the tumor grows big enough, bits of it can break off and spread through the bloodstream to other body parts. There the bits seed, or sprout, new tumors.

Scientists have also begun to zero in on how genes, the cell parts that contain all inherited information, impact human cell division. They know hundreds of genes play different roles in the process.

One gene, for instance, produces a protein called p53 that works like a safety switch. If genetic information goes awry in any human cell, p53 commands the cell to stop dividing until damage is fixed; if the damage is beyond repair, p53 orders the cell to self-destruct. But p53 is often defective itself in people who develop cancer. So the safety switch that should stop damaged cells from ' dividing is "turned off." Then healthy cells reproduce furiously and turn cancerous. Researchers are trying to find ways to "turn on" defective p53, and halt wildly reproducing normal cells.

What factors trigger cancer cells in the first place? Researchers think most factors are acquired during life--like smoking and unhealthy diets (which together account for two thirds of all cancers!), over-exposure to sunlight, environmental toxins, viruses, and aging itself. But one in 20 cases of cancer may be inherited through mutations, defective genetic instructions passed down from parents to children.

STANDARD TREATMENT

Until recently, doctors had few weapons with which to fight cancer: mainly surgery, in which doctors cut out tumors; chemotherapy, one or more potent

drugs that stop cancer cells from growing or multiplying; and/or radiation therapy, which bombards cancer cells with high-energy x-rays.

Chemotherapy and radiation have been fine-tuned over the last four decades, but they can still destroy healthy cells as well as cancerous ones. Cancer cells also mutate so fast that they evolve strategies to resist chemotherapy. And side effects of chemo and radiation, such as the depletion of white blood cells and organ damage, are potentially life-threatening.

Corey takes chemo pills every day; once a month he travels to a Bangor clinic for an injection. "I get a little tired afterwards, but don't think about it much," he says. "Most of the time I feel fine." Janet receives monthly chemo shots and periodic intravenous drips (using a thin needle inserted directly in her veins) in the hospital. "I freaked out a little bit at first," she says. "I hated losing my hair," one of chemo's common side effects, along with nausea and vomiting. "But it's just a year of chemotherapy and I'm going to beat it."

ONE SCIENTIST'S WAR

Still in early stages of animal and human testing, the newest arsenal of cancer drugs aren't yet available to Corey or Janet. The most recently hailed advance in drug warfare has shined the spotlight on a scientist looking at cancer cells in a radical way.

For years Dr. Judah Folkman, a surgeon and cell biologist at Boston Children's Hospital, observed that in order to thrive, cancer cells find a way to signal nearby blood vessels to grow and feed them (see diagram, left). The process is called angiogenesis, the same process the body uses to produce new blood vessels to heal wounds.

Folkman and his colleagues decided to test whether choking off the blood supply to a cancerous tumor could destroy it. At first his experiments provoked ridicule among many colleagues. The traditional approach of cancer research was to seek methods to directly attack the tumor itself. For several years, Folkman tediously experimented with dozens of substances, and found several that did, in fact, partly block new blood vessels from forming in cancerous mice. Some even shrank small mouse tumors. But none of the substances were very effective against large or advanced tumors.

Then in a flash of insight Folkman recalled an earlier observation: extracting one massive cancer tumor-from a patient sometimes sparks a number of smaller tumors to sprout suddenly. Folkman formed a new theory: What if a large tumor actually blocks other tumors from growing by competing with them for a blood supply? And what if the substance he was searching for was actually a part of all large cancer tumors?

In other words, Folkman reasoned, a large tumor might secrete a sub stance that made sure only it was able to form new blood vessels--no other tumors could enlist their own blood supply. If this was true, and if he could discover a similar substance, he might find an answer to choking off the needed blood supply to all cancerous tumors. He could stop cancerous tumors from ever growing in the first place.

After another decade of seemingly endless experiments, Folkman found what he was looking for.

He eventually combined molecular fragments of proteins that he extracted from cancer-ridden mouse urine. The proteins prevented mouse tumors from stimulating blood vessels to feed them. He extracted enough of the proteins from mouse urine to make two drugs that he calls angiostatin and endostatin.

When combined, the two drugs shrink or totally destroy a wide range of tumors in mice. They do so without the side effects of chemotherapy and seem to cure cancer in mice. "I've been waiting for results like these my whole life," says Folkman.

Can enough angiostatin and endostatin be extracted from mouse urine to produce drugs for millions of humans? And will the drugs even succeed on humans? (See sidebar below.) A company called EntreMed is trying to manufacture the drugs, and the National Cancer Institute plans to launch human tests in 1999.

THE WAR'S OTHER FRONTS

As exciting as Folkman's treatment may be, it's only one of 300 new anticancer therapies currently being tested. Another drug is called AG-33-40. Early human tests suggest the drug might not only block angiogenesis, but also metastasis, the spread of cancer tumors to other parts of the body.

Meanwhile, British researchers have started the first human trials of a vaccine for the deadliest form of skin cancer, called melanoma.

The vaccine is made of DNA, or genetic material, from melanoma tumors. The idea is to trigger the immune system to attack the DNA as foreign and destroy it.

In the U.S., researchers are working on a treatment for lung cancer called photodynamic therapy (PDT), which relies on a combination of lasers and light-sensitive drugs. First, the drug is injected into the bloodstream. The drug settles in a cancerous tumor. Then, a laser-emitting tube is snaked into the lungs to the tumor. The laser sparks a chemical reaction in the drug, which inflames the tumor. Then the tumor sheds from the lung's lining, like someone scratching off a scab. PDT will soon be tested to treat intestinal, reproductive, and skin cancers.

Despite these advances, the war against cancer is far from over. But many scientists believe they've reached a turning point in the battle. For teens like Corey and Janet, these advances represent a sign of hope. "I'm going to be a video game designer," Corey says. "I want to be a music teacher," says Janet. Because of the army of new drugs already available and others almost ready for use, their goals may very well come true.

RELATED ARTICLE: Choking off tumors

Cancerous tumor cells need blood cells to grow. And large tumors tend to hog the blood they need. Large tumors actually secrete a substance to stop other small tumors from getting blood supply. this substance could be choke off blood to all cancer tumors in humans.

1 Once a tumor reaches the size of a BB. its interior cells start to die unless the tumor can get a fresh blood supply. The tumor produces proteins called angiogenic factors and prods nearby blood vessels to sprout new

capillaries.

2 New capillaries supply the tumor with oxygen and nutrients. They also give the cancer cells a route to metastasize, or spread to distant body parts.

3 Drugs made of anti-angiogenic factors block the growth of new capillaries and shrink ones already supplying the tumor with blood. With no blood source, cancerous tumor cells die.

RELATED ARTICLE: From mice to men:

Testing new drugs

The field of cancer research is riddled with "magic bullets"--drugs that cure tumors in mice and fail to work in tests on humans. "We have cured mice of cancer for decades-and it simply didn't work in people," says Dr. Richard Klausner, head of the National Cancer Institute. One reason: researchers usually plant mice tumors just under the skin, which are far easier to attack than deep-seated human tumors.

First, several years of drug-screening tests in animals determine whether a drag poses safety risks. Then three phases of human tests follow, often lasting seven years. In Phase I, healthy volunteers take a new drug in low doses. In Phase II, researchers experiment with the exact dosage needed to treat a disease in ill volunteers. In Phase III, full-scale human trials compare a drug's effectiveness with other treatments or placebos, inactive drugs. Only then does the Food and Drug Administration review all data and decide whether a drug should be marketed to the public.

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BREAST CANCER

Pretty good for a People article - see pg. 15

34TH STORY of Level 1 printed in FULL format.

People

October 26, 1998

SECTION: SPECIAL REPORT/BREAST CANCER; Pg. 68

LENGTH: 2680 words

HEADLINE: Hope At Last;
Much remains to be done, but successful new drug therapies and improved surgical techniques raise the possibility that breast cancer may some day be safely and easily cured--even prevented

Tamoxifen
Herceptin
Raloxifene
+ new treatment

BYLINE: Written by: Anne-Marie O'Neill, Reported by: Giovanna Breu and Sheree R. Curry in Chicago, Linda Kramer in Washington, D.C., Patricia B. Smith in Houston and Lyndon Stambler in Los Angeles

BODY:

Elsie Anderson has never had cancer. But the 67-year-old grandmother of 12 knows the despair of it only too well. In 1984 the second of Anderson's five daughters, Gwen, died of breast cancer at 33. Three years later kidney cancer killed her oldest daughter, Debbie, at 37. Two of Anderson's sisters-in-law developed breast cancer, a brother has lung cancer, another has bowel cancer, and Anderson herself has had eight benign lumps removed from her breasts. So it was with good reason that, in 1992, Anderson signed up as a guinea pig when scientists set out to prove that the drug tamoxifen, long used in chemotherapy to treat breast cancer, could also be used to prevent it. "I watched what two of my grandchildren went through because they had no mom," says Anderson, a homemaker who lives with her husband, Arnold, 72, a retired bricklaying instructor, in Thunder Bay, Ont. "I don't want to see any more moms have to leave their children behind."

Considering the strides made in breast cancer research just this year, Anderson's wish may be more than a dream. Results released last month from the National Cancer Institute's tamoxifen trial in the U.S. and Canada show that the drug can cut the risk of breast cancer in half for women especially susceptible to developing the disease. And a new gene-based treatment called Herceptin that has surprised scientists by shrinking advanced breast-cancer tumors is available now--years earlier than expected.

Meanwhile, researchers across the country are working on techniques as diverse as ultrasound and breast cloning in their efforts to prevent breast cancer, detect and treat it, and deal with its aftereffects. Everyone knows there is far more to be done, but the news is encouraging. "Breast cancer is becoming more curable," says Dr. Marc Lippman, director of the Lombardi Cancer Research Center at Georgetown University in Washington, D.C. "This is the dawning of a new era of therapy in which we're not simply x-raying and cutting things out."

The most promising breakthroughs involve anti-cancer drugs. For years studies have indicated the preventive powers of such natural products as soy-based foods and broccoli. But until recently medical science has been at a loss to avert breast cancer, even as women have become more prone to it by menstruating as early as age 11, delaying childbirth and going through menopause later in

life. Over a lifetime these factors--products of a prosperous Western lifestyle--increase the body's level of estrogen, which is known to be one of the causes of breast cancer. "The bad joke is that we do know how to prevent most breast cancer: Delay puberty until a woman is 16," says Lippman. "But that would be social engineering."

So far tamoxifen, which works by blocking the estrogen that fuels breast-tumor growth, is the closest science has come to prevention in a pill. The Food and Drug Administration is expected to extend its approval of the drug--which was first passed in 1977 for patients with advanced breast cancer--for use in healthy but high-risk women later this month. But it is far from perfect. In the National Cancer Institute study postmenopausal women taking tamoxifen were twice as likely to develop uterine cancer during the five-year test as those on the placebo and were much more susceptible to developing blood clots in major veins and the lungs.

More promising is another estrogen-blocker called raloxifene, which is already prescribed to prevent osteoporosis in menopausal women and which might reduce the risk of breast cancer without tamoxifen's dire side effects. The NCI is launching a clinical trial with 22,000 women this fall. The drug "is one of the most exciting developments in breast-cancer prevention," says V. Craig Jordan, director of the breast-cancer research program at Northwestern University, who pioneered the development of tamoxifen in the early 1970s and will head the scientific team for the raloxifene study.

But if preventing breast cancer has captured the imagination of scientists, the prospect of curing it at the genetic level has blown them away. Herceptin, the first in a group of new gene-based drugs, represents a whole new approach to treatment. "Traditional chemotherapy and radiation are tantamount to throwing in a hand grenade and hoping it will kill more bad cells than good cells," says Dr. Dennis Slamon, director of the Revlon/UCLA Women's Cancer Research Program, who developed the drug. "New therapies like Herceptin specifically target what's broken in the cancer cell."

Combined with chemotherapy, Herceptin has been shown to shrink tumors in women with an aggressive type of breast cancer that accounts for 30 percent of all cases and involves a gene called HER2. The gene produces a protein which acts like an antenna on the membrane of a cancer cell, transmitting and receiving the signals that tell the cell to reproduce. Herceptin arrests the cancer by bonding to the protein that prevents the tumor from growing. And the side effects? A small fever at times, but nothing an over-the-counter painkiller can't fix.

Virginia Empey is living proof of the drug's potential. A nurse from Bakersfield, Calif., Empey, 54, discovered a lump in her right breast in 1993. Two different doctors told her there was nothing to worry about because the cancer didn't show up on her mammograms. A year later it had swelled to the size of a tennis ball. A mastectomy and chemotherapy failed to prevent the cancer from spreading to her liver, and by June 1995 her oncologist had lost hope, giving her less than six months to live. "Get your affairs in order," he told the thrice-married mother of two grown children. "Take a trip."

Unwilling to surrender, Empey pressed the doctor for more options until he mentioned the Herceptin trial. After establishing that her cancer involved the HER2 gene, researchers signed her up for the trial and for more than three

years she has received weekly Herceptin infusions. Today the spots on her liver, once the size of silver dollars, are as small as peas. And although Empey is not considered cured, her hope is restored. "I was supposed to be dead, and I'm not," she says. "Now I treasure every day."

For most women a diagnosis of breast cancer still means surgery plus chemotherapy or radiation. Of course, early detection remains the best way to avoid severe treatment. And although mammograms, recommended annually for women 40 and over, miss about 15 percent of cancers, a new digital scanner approved by the FDA in July could increase the accuracy of detection. Traditional treatments have also been improved. New antiemetic drugs developed in recent years have relieved much of the nausea associated with chemo. And these days about 45 percent of breast-cancer patients undergo a lumpectomy, a procedure used rarely until about 10 years ago, which targets only the malignant area of the breast. While doctors once removed many of the lymph nodes under a woman's arm to learn whether a cancer had spread, they are now able to test just one or two key, or so-called sentinel, nodes. Unfortunately, experts say as many as 35 percent of women who are eligible for lesser surgery still undergo a full mastectomy. "What that suggests," says Dr. Monica Morrow, a surgeon married to tamoxifen researcher V. Craig Jordan, "is that women are not being informed of the choice."

At the experimental stage are anti-angiogens that cut off a tumor's blood supply and have cured cancer in mice; vaccines that could work by "turning off" the cancer gene; and nonsurgical treatments that use ultrasound waves to zap away tumors without breaking the skin. Says Dr. Eva Singletary, chief of the Surgical Breast Service at the M.D. Anderson Cancer Center in Houston: "We are within 10 years of not even needing surgery to treat most breast cancer."

Still, for many survivors treatment is just part of the trauma. "It's a real roller coaster for most women," says Dr. Julia Rowland, codirector of the psycho-oncology program at the Lombardi Center. "Once a woman has been diagnosed with breast cancer, she isn't ever going to be the same person again. It will always be part of her life."

Body image is a major concern for many women. Three years ago, Kristina Pavlou had survived Hodgkin's disease and advanced breast cancer, but was left with only one breast and forced to use a prosthesis at age 22. Dating, says the former TV reporter from Chicago, was a daunting ordeal. "I wanted to feel whole again," she says. "I wanted to feel confident about dating and being intimate." A new reconstruction technique helped restore her breasts--and her self-esteem. In February 1995, using a microsurgery technique refined in the 1980s, Dr. David Hidalgo, chief of plastic and reconstructive surgery at Memorial Sloan-Kettering Hospital in Manhattan, replaced Pavlou's missing right breast with a cosmetic one fashioned from skin and fat from her buttocks. A few months later he repeated the procedure after Pavlou had her left breast removed to prevent further spreading of the cancer, which had already appeared in her lymph nodes. "Everyone thought I was nuts to go through it again," she says. "But I was happy I was getting my life back."

The 12-hour operation is among a host of new options for more natural-looking breasts. Surgeons at M.D. Anderson have helped perfect a new mastectomy procedure that preserves the patient's breast skin, creating a pouch that can be immediately filled with a saline implant. Alternatively surgeons can take a section of fat and muscle from the lower abdomen and--keeping it attached to

the blood vessels that feed it--tunnel the mass up between the skin and the rib cage and into the pouch.

At Anderson and elsewhere scientists are even experimenting with cloning breast cells and cultivating other body tissues to grow personalized, natural implants. "Some people are a little frightened that maybe we are learning too much," says Singletary. "But this could save a lot of suffering." Pavlou's new breasts certainly did. Now director of education for the national breast-cancer organization Why Me and dating Greg Chip, 30, a marketing consultant, she is no longer reluctant to show her naked breasts around women's locker rooms. "My breasts are a work of art," she says. "I'm proud of them."

Other aspects of breast cancer can't be surgically fixed, which is where the relatively new field of psycho-oncology--psychotherapy tailored specifically to cancer patients--comes in. "The vast majority of survivors have gotten on with their lives," says Rowland. "But a very small proportion of women find themselves drawn down through a spiral of despair." Some become obsessed with fear of a recurrence. Others overcompensate by running themselves into the ground at work. Mothers sometimes feel as if they've cursed daughters with a hereditary cancer. And single women may fear they'll never be able to date or have a child.

Some, like Angela O'Connell, a breast-cancer patient at Chicago's Rush Presbyterian St. Luke's Medical Center, simply needed a sympathetic ear. O'Connell, 51, began seeing the hospital's psycho-oncologist Suzanne B. Yellen almost three years ago after finding out that her cancer had spread. "She understands," O'Connell says. "She has assured me that this is not the end of the road." Most important, the experience is helping her toward the finish line that every woman with breast cancer hopes to reach--"to go back," she says, "to a normal life."

Written by: Anne-Marie O'Neill Reported by: Giovanna Breu and Sheree R. Curry in Chicago, Linda Kramer in Washington, D.C., Patricia B. Smith in Houston and Lyndon Stambler in Los Angeles

SIDEBAR:

HOLLYWOOD HELPS OUT Thanks to the efforts of a determined woman, a promising new drug arrives far ahead of time

It was the moment Lilly Tartikoff had been waiting for. Raising funds for Dennis Slamon, a scientist at UCLA researching a revolutionary treatment for breast cancer, Tartikoff for months had wanted to meet face-to-face with billionaire Revlon chairman Ronald Perelman, hoping he would contribute. Then, one night in 1989, she was dining in the chic Hollywood restaurant Spago when a friend spotted Perelman and introduced her. "Oh, my God," she blurted. "I thought you were going to be some old goat!"

If Perelman was offended, it didn't show. The gene-based breast cancer drug Herceptin was made available this year, a decade earlier than expected, thanks to Perelman's millions, Slamon's know-how and the nerve of Lilly Tartikoff, 45, whose husband, Brandon, onetime president of NBC Entertainment, died last year of Hodgkin's disease, which was first diagnosed in 1974. "Lilly is a very determined woman with a lot of energy" says Perelman, 55. "Combine those qualities with a big heart and you begin to understand how she has been able

to achieve so much."

The chain of events that brought the threesome together began in 1982 when Brandon, then 33, was struck with a recurrence of Hodgkin's. A friend referred him to Slamon, who administered an experimental chemotherapy that sent the disease into remission for 14 years. Lilly, a former dancer with the New York City Ballet, was determined to repay Slamon with funds for research. "I had never raised a dime," she says. "But I had the friendship of an industry in a town called Hollywood."

She made her pitch constantly, at premieres and parties. "She'd ask women, 'Do you have breasts?'" says Slamon, 50. "And remind the men, 'Your mother has breasts.'" But it was her meeting with Perelman that really paid off. Since he signed on in 1989, Revlon has donated more than $ 13 million to Slamon's research. (Nationally, over $ 20 million is raised for breast-cancer research each year from individuals and corporations, and from events like the Fire & Ice balls that Perelman and Tartikoff launched in 1990.) Still driven, despite her remarkable success, Tartikoff has no intention of slowing down. "Every time I'm really, really tired, I look at the girls," she says of her two daughters with Brandon, Calla, 15, and Elizabeth, 4, "and I realize I can't stop."

BOX STORY:

MEDICAL ADVANCES

Drug Therapies

Tamoxifen: Pros: Halves the risk of getting breast cancer. Cons: Doubles the risk of uterine cancer in menopausal women, heightens the risk of blood clots and early menopausal symptoms.

Herceptin: Pros: With few side effects, shrinks and delays the spread of tumors in women whose cancer cells overproduce the HER2 gene. Cons: Does nothing for the 70 percent of breast cancers without HER2.

Raloxifene: Pros: Could reduce the risk of breast cancer by up to 54 percent without tamoxifen's uterine-cancer effect. Cons: Yet to be proven, and can cause blood clots.

New Treatment Options

Sentinel Node Biopsy: Determines if cancer has spread by removing and dissecting just one or two key lymph nodes instead of stripping numerous nodes from the chest and arms.

Lumpectomy: Removes only part of the breast, which along with the sentinel node biopsy makes for less invasive surgery.

Antiemetic Drugs: New antinausea drugs reduce the debilitating sickness associated with chemotherapy.

In the Future

Ultrasound: Scientists are testing a device on humans that uses energy from ultrasonic sound waves to selectively heat and destroy cancer cells without

damaging adjacent tissue.

Anti-angiogens: Drugs that block the growth of the blood vessels that feed tumors have already been shown to cure cancer in mice and are now being tested in humans.

Gene Therapies: Tests have begun in which genetically engineered viruses have been used to invade cancer cells and replace damaged genes that promote the growth of the tumor with healthy ones.

Cloning: Breast cells harvested from a patient could one day be genetically engineered, then used to grow healthy breast tissue for use as an implant.

Early Detection

Fact: Most breast cancers detected early can be cured. Self-Exam: Recommended monthly for all women over 20. Mammograms: Recommended annually for women aged 40 and over.

GRAPHIC: COLOR PHOTO: KERI PICKETT, "I did it for my granddaughters," Elsie Anderson (with her family) says of the tamoxifen trial.; THREE COLOR PHOTOS: BLACK/TOBY (3), "We complement each other," tamoxifen researcher V. Craig Jordan (below) says of his marriage to breast surgeon Monica Morrow (operating, left, and with Jordan at home, right). [V. Craig Jordan; Monica Morrow and another surgeon performing surgery; work; Monica Morrow and V. Craig Jordan]; TWO COLOR PHOTOS: JAN SONNENMAIR/AURORA (2), "Herceptin has given me a reprieve on a death sentence," Virginia Empey (below, getting her weekly treatment) says of the drug that can shrink tumors and was developed by Dennis Slamon (above). [Woman administering treatment to Virginia Empey; Dennis Slamon observing lab results]; COLOR PHOTO: JAN SONNENMAIR/AURORA, "Never in my wildest dreams did I imagine we would come so far so fast," says Tartikoff (with a photo of her late husband, Brandon). [Lilly Tartikoff]; COLOR PHOTO: KERI PICKETT, Angela O'Connell (left) calls psycho-oncologist Suzanne B. Yellen, who helped her fight cancer's mental toll, "a source of hope."; COLOR PHOTO: KEVIN HORAN, After reconstruction, "I got a smaller butt but larger breasts," jokes Kristina Pavlou (with boyfriend Greg Chip).; COLOR PHOTO: ROBIN BOWMAN, David Hidalgo says breast reconstruction can aid "emotional recovery."

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PRESIDENT WILLIAM J. CLINTON
TALKING POINTS FOR
G&P CHARITABLE FOUNDATION
FOR CANCER RESEARCH EVENT
SHERATON HOTEL, NEW YORK CITY
October 12, 1998

Acknowledgments: Mother Denise Rich, Milton Berle, CBS President/CEO Leslie Moonves

Milton Berle is a record breaker in many ways. He's been in show business for 85 years, one of the longest careers in industry history. He's performed in drag more than just about any other entertainer, with the possible exception of the road show cast of La Cage a Folles. And, most impressive of all, he holds the Guinness Book of World Records for the most charity benefit performances of any entertainer ever.

Twenty five years ago, America declared war on cancer. Twenty five years from now, I hope that we will have won this war. Twenty five years from now, I hope that the war on cancer will have about as much meaning to school children as the War of 1812. Twenty five years from now, I hope those school children don't even know what the word "chemotherapy" means.

The progress we are now making against cancer is nothing short of stunning. We are closing in on the genetic causes of breast cancer, colon cancer, and prostate cancer, and testing medicines to **prevent** these cancers.

New tools for screening and diagnosis are returning to many patients the promise of a long and healthy life. And from 1991 to 1995, cancer death rates actually dropped for the first time in history.

For the last six years, my administration has made fighting this terrible disease a top priority. We've helped cancer patients to keep their health coverage when they change jobs. We've accelerated the approval of cancer drugs while maintaining safe standards. We've continually increased funding for cancer research.

And in just the last few weeks we've taken four crucial new actions. First, we have won from Congress the largest single increase in funding for cancer and other medical research in history. Second, I have directed the National Cancer Institute to expedite a new computer system that will give tens of thousands of cancer patients access to clinical trials of the kinds of cutting-edge cancer treatments that can save their lives.

Third, I have taken steps to ensure that by next year, cancer patients and advocates will have a seat at the table when the federal government sets the medical research agenda, because those who suffer from cancer know truths about this disease that even the experts don't understand.

And fourth, we have made $15 million available to study the long-term effects of cancer treatments and how to prevent cancer recurrence. These grants have a special significance for us tonight because as you know, Gabriella herself succumbed to cancer as a result of the treatment she received for Hodgkin's disease. So we give these grants, Gabriella, with you in mind.

But there is much more that we must do if we want to win this war as quickly as I believe we can. We must convince the next Congress to pass a strong patients' bill of rights to ensure cancer patients high-quality care, as this Congress failed to do.

We must convince the next Congress to help Medicare beneficiaries with cancer to take part in clinical trials. We must convince the next Congress to confirm the first oncologist, Dr. Jane Henney, to be commissioner of the FDA.

And finally, we must convince Congress to take strong action to protect our children against the number one cancer threat, tobacco. The current Congress has taken none of these steps. The next Congress must.

-30-

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FDA Press Release: Pfizer Updates Viagra Labeling

Focus On...
Olestra and Reduced-Fat Foods

A high-fat diet is associated with numerous adverse health conditions including obesity, cardiovascular disease, diabetes, and some cancers. High-fat snack foods are a major source of fat in the typical American diet. It seems logical that the availability of highly palatable, but fat-free snack foods could help Americans to reduce their dietary fat intake, but does this really happen?

Despite the availability and popularity of reduced-fat and fat-free foods and the assumption by consumers that these foods will help them to control their fat intake and body weight, very little is known about how reduced-fat and reduced-energy foods affect overall caloric intake.

These issues were investigated in a recent study of the impact of dietary restraint and food nutrition labels on the consumption of fat-free potato chips. Dietary restraint is the ability to restrict food intake to reduce body weight. The fat-free potato chips were manufactured with olestra, a sucrose polyester lipid that is not absorbed through the digestive tract and, consequently, contributes no fat and less caloric energy to the diet. These fat-free chips contain half the energy content of regular potato chips, but they posses the texture and flavor qualities associated with chips fried in fatty oils.

Continued...

For more information about olestra and its treatment see:

- DrugPR: FDA APPROVES FAT SUBSTITUTE, OLESTRA
- MSB Review: FDA NEWS: Olestra and Other Fat Substitutes
- MSB Review: FDA Approves Olestra, Fat-free "Fat"
- MSB Review: Olestra and Inflammatory Bowel Disease Symptoms
- MSB Review: Eating Fat-Free Potato Chips Reduces Your Caloric Intake -Regardless of How Many You Eat!
- OMR News: Doctor Argues That Olestra Should be Used With Caution

31ST STORY of Level 1 printed in FULL format.

November 16, 1998

SECTION: No. 221, Vol. 9; Pg. NA

IAC-ACC-NO: 53222659

LENGTH: 639 words

HEADLINE: FDA APPROVAL EXPECTED NEXT YEAR MONSANTO'S CELEBREX FOR RA PROVES EFFECTIVE IN PHASE III By Lisa Seachrist Washington Editor.

THIS IS THE FULL TEXT

BODY:

WASHINGTON - Pivotal Phase III studies of Monsanto Co.'s new non- steroidal anti-inflammatory drug (NSAID), Celebrex, indicate the compound works as well as commonly prescribed NSAIDs in relieving the signs and symptoms of rheumatoid arthritis (RA), but without gastrointestinal side effects.

Celebrex (celecoxib), one of a new class of NSAIDs, is currently under priority review at FDA and will be the first of this new class of drugs to be considered by the agency's ArthritisAdvisory Committee, on Dec. 1.

"We think this is a drug that has real benefit and meets and unmet medical need at the moment," said Nancy Tait, spokeswoman for G.D. Searle, the pharmaceutical division of St. Louis-based Monsanto. "And, assuming we do eventually get approval, we are prepared to have it on the market very quickly."

Tait said the company anticipates approval in the first or second quarter of 1999.

Prostaglandins are the main perpetrators of the pain in inflammation. Normally, these ubiquitous substances carry out housekeepingduties all over the body. When disease or trauma triggers inflammation, the body produces a flood of prostaglandins.

All NSAIDs ease pain and inflammation by inhibiting the enzymes that create prostaglandins from the fatty acid arachidonic acid. However, currently approvedNSAIDs indiscriminately block both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).

Present in most human tissues, COX-1 is vitalto protecting the gastrointestinal (GI) system, and to maintaining normal platelet and kidney function. COX-2, on the other hand, is turned on in response to inflammation. Blocking COX-1 can lead to gastrointestinal ulceration and bleeding, inhibition of platelet aggregationand dangerous interactions with other drugs. Upper gastrointestinal complications from NSAID use currently result in 107,000 hospitalizations and 16,500 deaths each year in the U.S. Unlike currently approved NSAIDs, Celebrex selectively blocks COX-2, allowing COX-1 to continue

to function normally and thus reducing potentially dangerous side effects. These results come from four Phase III studies presented at a meeting of the American College of Rheumatology, in San Diego.

Celebrex Causes Fewer GI Problems Than Naproxen A 12-week study involving 1,149 RA patients suffering flares demonstrated Celebrex was as effective as the commonly used NSAID naproxen in relieving joint pain and swelling. Celebrex, however, caused significantly fewer gastrointestinal problems. A 12-week study of 1,004 patients with osteoarthritis showed similar results.

A 24-week study of the drug in 600 RA patients showed that it worked as well as the NSAID diclofenac, but resulted in a four-fold decrease in ulcers that could be detected with endoscopy. In addition, far fewer patients receiving Celebrex dropped out of the study due to GI complaints.

Celebrex also proved compatible with two medications commonly prescribed to arthritis patients: methotrexate for the treatment of RA; and warfarin, a blood thinner prescribed for concomitant cardiovascular conditions, such as blood clots.

"It's like the old science brought us some great drugs, but theyhad some serious side effects," said Tait. "With the advances in molecular biology and screening, it lets the scientist specifically target a drug so you don't get all the collateral damage."

Searle and Pfizer Inc., of New York, will develop and commercialize Celebrex in all world areas except Japan, where Searle will develop the drug with Yamanouchi Pharmaceutical Co., of Tokyo.

Celebrex is also being studied in clinical trials for the treatment of Alzheimer's disease and prevention of colon cancer.

Monsanto's stock (NYSE:MTC) closed Friday at $ 38.562, up $ 0.562. Pfizer's stock (NYSE:PFE) ended the day at $105.375, up $ 1.062. *

LANGUAGE: ENGLISH

IAC-CREATE-DATE: November 16, 1998

LOAD-DATE: November 17, 1998

17TH STORY of Level 1 printed in FULL format.

Omaha World-Herald

November 23, 1998, Monday SUNRISE EDITION

SECTION: ;LIVING; Pg. 27

LENGTH: 1647 words

HEADLINE: Arthritis Advances Drugs recently approved by the FDA and others in development offer new hope to arthritis sufferers. Arthritis Facts

BYLINE: DOUG THOMAS

SOURCE: WORLD-HERALD STAFF WRITER

BODY:

Rheumatoid arthritis eventually snapped every tendon in Gary Duncan's hands, and surgery to rebuild the tendons hasn't restored the strength of his grip. Making a fist is out of the question.

But he no longer has to hold his wrists under running water for 15 minutes to get his fingers to function in the morning. This was the drill: five minutes in water as hot as he could stand, five minutes in cold water and five more in hot. Repeat if necessary.

The pain in his hands isn't quite gone, he says, but it's not nearly as bad as it used to be. And because the joints are less stiff and swollen, the 59-year-old former Nebraskan can type, button his shirt and tie his shoes.

"That doesn't sound like much," he says. "But for people with arthritis, that is a big deal."

So is the drug he credits for his progress, a new type of pain reliever called Celebrex. On track for federal approval in January, it's one of five new or forthcoming drugs that offer hope to millions of Americans with arthritis.

Whether the drugs will improve millions of lives is harder to say. They're expensive. Studies haven't ruled out the possibility of long-term health risks. And some physicians remain unconvinced that the new drugs are substantially better than old ones.

At a minimum, though, the new drugs should broaden the choices for patients and doctors in combating the stubborn and sometimes maddeningly unpredictable disorders known collectively as arthritis.

"This is really a very exciting time," says Dr. Art Weaver of Lincoln, past president of the American College of Rheumatology. "I can't remember any other time in the 30 years I've been in practice that we've had this many good new agents come on the market."

The new drugs:

Arava, Enbrel and Remicade, which are already on pharmacy shelves.

Celebrex and Vioxx, which are expected to gain federal approval next year.

The U.S. Food and Drug Administration approved Arava and Enbrel this fall for treatment of rheumatoid arthritis, the cripplingly progressive disease that afflicts Duncan. Remicade, approved in August to treat inflammatory bowel disease, also appears effective against rheumatoid arthritis. Some doctors are prescribing it for that purpose.

Celebrex and Vioxx come from a new class of pain relievers called Cox-2 inhibitors. They're designed to ease inflammation without the troubling side effects of current anti-inflammatory drugs such as ibuprofen (Advil, Nuprin, Motrin) and naproxen (Aleve).

Weaver, director of clinical research at the Arthritis Center of Nebraska, is leading studies of Celebrex, Vioxx, Enbrel and Arava. One person taking part in a Celebrex study is Duncan, a former Lincoln seed company executive who moved to San Antonio a year ago. He has driven the 1,700-mile round trip to Lincoln every three months to remain in the Celebrex trial.

"It's kind of exciting to be part of something that could do a lot of good for people," he says.

If approved by the FDA, Celebrex and Vioxx probably will end up in far more medicine cabinets than the new rheumatoid arthritis drugs. Rheumatoid arthritis accounts for just 2.1 million of the estimated 40 million arthritis cases in the United States. More than 20 million Americans have osteoarthritis, a degenerative joint disease associated with aging or injury.

Celebrex and Vioxx could help rheumatoid and osteoarthritis as well as other forms of arthritis such as fibromyalgia and gout.

Arthritis specialists hope patients don't expect too much.

Says Weaver: "I think perhaps the public has been misled a bit to expect a super amount of pain relief."

Celebrex and Vioxx relieve pain no better than current anti-inflammatory medications known as NSAIDs, or non-steroidal anti-inflammatory drugs.

But Weaver says the new drugs are much safer.

Complications from steady use of current anti-inflammatory drugs result in some 60,000 hospitalizations a year in the United States. They can cause digestive problems ranging from diarrhea and nausea to stomach ulcers. The drugs also can affect the kidneys, causing fluid retention, elevated blood pressure and sometimes kidney failure. And they impair the ability of blood platelets to form clots, which can be life-threatening for someone with a bleeding ulcer.

Celebrex and Vioxx don't inhibit blood clotting, Weaver says, and studies suggest they're less likely than current drugs to affect the kidneys.

Digestive problems appear less likely, too. Patients taking Celebrex or Vioxx in clinical trials have been no more likely to develop ulcers than people taking sugar pills, Weaver says. And the new drugs appear about half as likely

as current drugs to cause problems such as diarrhea and nausea.

Doctors sometimes refer to such problems as "nuisance" symptoms, but Weaver says that understates the concerns they raise.

"You wonder, 'Are they developing ulceration and the possibility of bleeding?'" he says. "With the newer agents, we can be pretty well assured it's not going to be a major catastrophe."

Dr. Harry Klein, an arthritis specialist with Alegent Health's Omaha Internal Medicine Physicians, says early evidence suggests that Celebrex and Vioxx might be good enough to make older anti-inflammatory drugs obsolete.

"Why take an agent that hurts the kidneys, stomach and platelet function," he asks, "when something is available that won't do any of these things - or at least not to the same extent?"

One reason might be expense. The companies making Celebrex and Vioxx haven't established prices, but Klein predicts that they will cost at least $ 100 a month. Prices for current anti-inflammatory drugs range from a few dollars a month to $ 80.

Enbrel and Arava are much more expensive. Arava costs $ 250 a month, and Enbrel costs $ 1,000.

Dr. James O'Dell, an arthritis specialist at the University of Nebraska Medical Center, suspects that most health insurers will cover Arava. He expects them to set tight restrictions on coverage for Enbrel. Medicare will not cover it.

The FDA approved Enbrel for patients with rheumatoid arthritis who have tried and failed standard medications. And failure is not rare.

While treatment of rheumatoid arthritis has improved dramatically in the past decade, O'Dell says, only 10 percent of patients see medication drive the disease into remission. He says about half of the others don't respond well.

Perhaps 5 percent to 10 percent find nothing that helps them, Klein says. They end up in agonizing pain.

The current drug of choice against rheumatoid arthritis is methotrexate (Rheumatrex), often used in combination with other drugs such as Plaquenil and Azulfidine.

"I think we have to emphasize that we can do pretty well with the drugs we have available," says Dr. Doyt Conn, a native of Gering, Neb., who now serves as national medical spokesman for the Arthritis Foundation. "Methotrexate is amazingly safe."

O'Dell says Arava seems to work about as well as methotrexate. "It's not a breakthrough," he says.

Enbrel and Remicade might be. They attack rheumatoid arthritis in a new way, neutralizing a powerful source of inflammation called tumor necrosis factor.

Early studies have been very promising, says Weaver, who has conducted Enbrel trials for three years. He says the drug has caused dramatic improvement in patients who were not responding to any other medications.

"This is truly a breakthrough," he says.

But because Enbrel and Remicade affect the immune system, doctors say, they could increase the risk of cancer and infection. Arava could, too.

Studies so far have shown no increased cancer risk, O'Dell says, but they've been too short to rule out the possibility.

Dan Duffy is willing to take his chances. The 56-year-old Lincoln man was diagnosed with rheumatoid arthritis 11 years ago, and at times the pain grew so intense that he couldn't walk.

He's been taking Enbrel for two years as part of a clinical trial. Now balky toe joints and swollen knuckles are the only signs of arthritis.

He used to take methotrexate, a cancer agent employed to treat rheumatoid arthritis for nearly 20 years. But it gave him persistent canker sores.

"My dad died of cancer 33 years ago, and he was on methotrexate," Duffy says. "This stuff can't be any worse than methotrexate."

Arthritis Facts

Arthritis cases are on the rise as Americans age, a trend likely to continue as baby boomers head toward retirement. There were 35 million Americans with arthritis in 1985, 37.9 million in 1990 and 40 million in 1995. There will be 59.4 million by 2020, according to projections by the U.S. Centers for Disease Control and Prevention.

Arthritis is the leading cause of disability among Americans older than 15. It ranks second to heart disease as a cause of work disability.

Arthritis refers to more than 100 diseases that affect areas in and around the joints. The disease also can affect other parts of the body.

Arthritis affects people in all age groups, including as many as 285,000 children with juvenile arthritis.

Common types of arthritis:

Osteoarthritis: 20.7 million Americans, most older than 45.

Fibromyalgia: 3.7 million Americans, mostly women.

Rheumatoid arthritis: 2.1 million Americans, mostly women.

Gout: 2.1 million Americans, mostly men.

Definitions:

Osteoarthritis: a degenerative joint disease causing deterioration of the cartilage that covers the ends of the bones, causing pain and loss of movement as bone rubs against bone.

Fibromyalgia: Widespread pain affects muscles and attachments to bones.

Rheumatoid arthritis: A disease of the immune system in which the joint lining becomes inflamed.

Source: The Arthritis Foundation

GRAPHIC: B&W Photo/2 DIGITAL DEXTERITY: Gary Duncan says a new pain reliever called Celebrex has helped restore flexibility in his fingers, which have been damaged by rheumatoid arthritis. Celebrex is expected to gain federal approval early next year.; JEFFREY Z. CARNEY/WORLD-HERALD/1sf
Knight-Ridder/World-Herald/1

LANGUAGE: ENGLISH

LOAD-DATE: November 27, 1998

2ND STORY of Level 1 printed in FULL format.

The San Francisco Chronicle

DECEMBER 2, 1998, WEDNESDAY, FINAL EDITION

SECTION: NEWS; Pg. A4

LENGTH: 537 words

HEADLINE: New Kinds of Pain Drugs on Way -- Hopes for Fewer Side Effects

BYLINE: Carl T. Hall, Chronicle Science Writer

BODY:
Pain sufferers may be getting some new drug options that appear to bring relief with fewer side effects than most other treatments.

One drug, called gabapentin, is already on the market as a treatment for epileptic seizures. Two new studies, appearing today in the Journal of the American Medical Association, show the drug is an effective painkiller in hard-to-treat cases of nerve damage from diabetes or shingles.

Separately, a panel of experts advising the U.S. Food and Drug Administration endorsed the first in a potential new line of pain relievers, known as Cox 2 inhibitor drugs.

The new medications are designed to reduce inflammatory pain from arthritis, without the stomach distress and other gastrointestinal side effects of widely used painkillers.

The Cox 2 inhibitors are being widely touted as potential blockbusters, likely to generate at least $1 billion a year in sales during their first year on the market. Estimates for worldwide sales of all analgesics run as high as $12 billion a year.

But many experts doubt the new drugs will live up to their early billing as "superaspirins." The evidence does suggest they cause fewer side effects than ibuprofen and aspirin, even with daily use for many years. But the Cox 2 inhibitors don't seem to control pain much better than current treatments.

The FDA-sponsored advisory panel voted to recommend approval of Celebrex, G.D. Searle & Co.'s Cox 2 inhibitor, for both osteoarthritis and rheumatoid arthritis. The vote paves the way for full FDA approval sometime next year. Meanwhile, Merck & Co. has its own Cox 2 inhibitor awaiting approval, and other drugmakers are said to be close behind.

Patients with pain from nerve damage will not need to wait to try gabapentin -- it's now sold as an anti-convulsant under the brand name Neurontin by Parke-Davis, a unit of Warner-Lambert Co.

Because the drug is already on the market, doctors are free to start prescribing it immediately for pain patients. Many already have been using it as a pain remedy, in fact, although they have had little besides rumor and first-hand experience to suggest that it works.

The new studies were carried out by independent teams of clinical researchers across the country, including doctors at the University of California at San Francisco.

Results showed that the drug works at least as well and probably better than other treatments for neuropathic pain, but with far fewer side effects.

Although the tests were conducted only in diabetes and post-herpetic neuralgia, or shingles, experts said it might also help alleviate nerve pain suffered by people with cancer and AIDS.

"It's a very important advance in pain management," said Dr. Edgar Ross, director of the pain management center at Brigham and Women's Medical Center in Boston, who participated in one of the two studies.

"This is the first time we have a drug reasonably well-tolerated by most people and effective for a problem that has been resistant to most treatments."

A Warner-Lambert spokeswoman said the company is evaluating the new evidence, and may seek FDA permission to start promoting Neurontin as a pain remedy. But no decision has been made, she said.

LOAD-DATE: December 2, 1998

About the Program

The National Breast and Cervical Cancer Early Detection Program

You may also download a PDF version (283K) for Adobe Acrobat Reader or a PostScript version (578K).

The National Breast and Cervical Cancer Early Detection Program

AT-A-GLANCE
1998

"As we move into the 21st century, public health organizations, private agencies, and professional and voluntary organizations must form partnerships to support and enrich services to the public."

David Satcher, MD, PhD, Director
Centers for Disease Control and Prevention

Breast and Cervical Cancers

An estimated 2 million American women will be diagnosed with breast or cervical cancer in the 1990s, and half a million will lose their lives from these diseases. A disproportionate number of deaths will be among women of minority and low-income groups.

Many of these deaths could be avoided by making lifesaving screening services available to all women at risk. Such screening measures could prevent approximately 15%-30% of deaths from breast cancer among women over the age of 40 and virtually all deaths from cervical cancer.

Excluding skin cancer, breast cancer is the most common cancer among American women and is second only to lung cancer as a cause of cancer-related death. An estimated 178,700 new cases of breast cancer among women will be diagnosed in 1998, and 43,900 women will die of the disease.

The incidence of invasive cervical cancer has decreased significantly over the last 40 years, in large part because of early detection efforts. Still, an estimated 13,700 new cases of invasive cervical cancer will be diagnosed in 1998, and 4,900 women will die of the disease.

CDC's National Breast and Cervical Cancer Early Detection Program

"This initiative will remove many of the financial barriers women face in getting timely mammograms and Pap tests."

--Donna E. Shalala, Secretary
U.S. Department of Health and Human Services

Recognizing the value of screening and early detection, Congress passed the Breast and Cervical Cancer Mortality Prevention Act of 1990. This act authorized CDC to establish a national program to ensure that women for whom screening is recommended receive regular screening for breast and cervical cancer, prompt follow-up if necessary, and assurance that the tests are performed in accordance with current recommendations. CDC conducts many of these activities through partnerships with state and territorial health agencies, American Indian/Alaska Native organizations, and national organizations.

In fiscal year 1998, CDC entered into the eighth year of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), a landmark program that brings critical breast and cervical cancer screening services to underserved women, including older women, women with low income, and women of racial and ethnic minority groups.

Fiscal year 1998 appropriations of $145 million enable CDC to establish greater access to screening and follow-up services, increase education and outreach programs for women and health care providers, and improve quality assurance measures for mammography and cervical cytology.

The legislation for NBCCEDP mandates lifesaving screening for the early detection of breast and cervical cancer. Although funding cannot be used to pay for cancer treatment, participating programs have shown creativity and determination in ensuring that treatment services are available for women diagnosed with breast cancer or cervical abnormalities.

The availability of these treatment sources reflects the extent of state and local government support, medical provider generosity, and community commitment.

The National Breast and Cervical Cancer Early Detection Program

Comprehensive Screening Programs

- All 50 states
- American Samoa
- District of Columbia
- Northern Mariana Islands
- Republic of Palau
- U.S. Virgin Islands
- American Indian/Alaska Native organizations
  - Arctic Slope Native Association, Alaska
  - Cherokee Nation, Oklahoma
  - Cheyenne River Sioux Tribe, South Dakota
  - Consolidated Tribal Health Project, California
  - Eastern Band of Cherokee Indians, North Carolina
  - Hopi Tribe, Arizona
  - Maniilaq Association, Alaska
  - Native American Community Health Center, Inc., Arizona
  - Native American Rehabilitation Association of the Northwest, Oregon
  - Navajo Nation, New Mexico and Arizona
  - Pleasant Point Passamaquoddy Tribe, Maine
  - Poarch Band of Creek Indians, Alabama
  - South East Alaska Regional Health Consortium, Alaska
  - South Puget Intertribal Planning Agency, Washington
  - Southcentral Foundation, Alaska

Capacity-Building Program

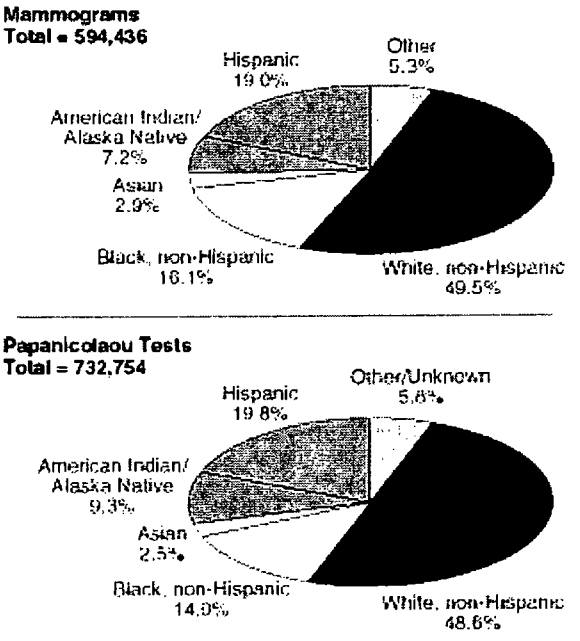
- Puerto Rico

Screening and Follow-up Services

Benefits of Screening

Mammography is the best way to detect breast cancer in its earliest, most treatable stage. Mammography detects cancer an average of 1.7 years before the woman can feel the lump herself and locates cancers too small to be felt during a clinical breast examination. Generally, the earlier breast cancer is detected, the better the survival rate. When breast cancer is diagnosed at a local stage, the 5-year survival rate is 97%. When breast cancer is diagnosed after it has spread, the 5-year survival rate decreases to 21%.

CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP): Percent Distribution of Mammograms and Papanicolaou Tests Provided to Participants, by Race/Ethnicity, Fiscal Years 1991–1997

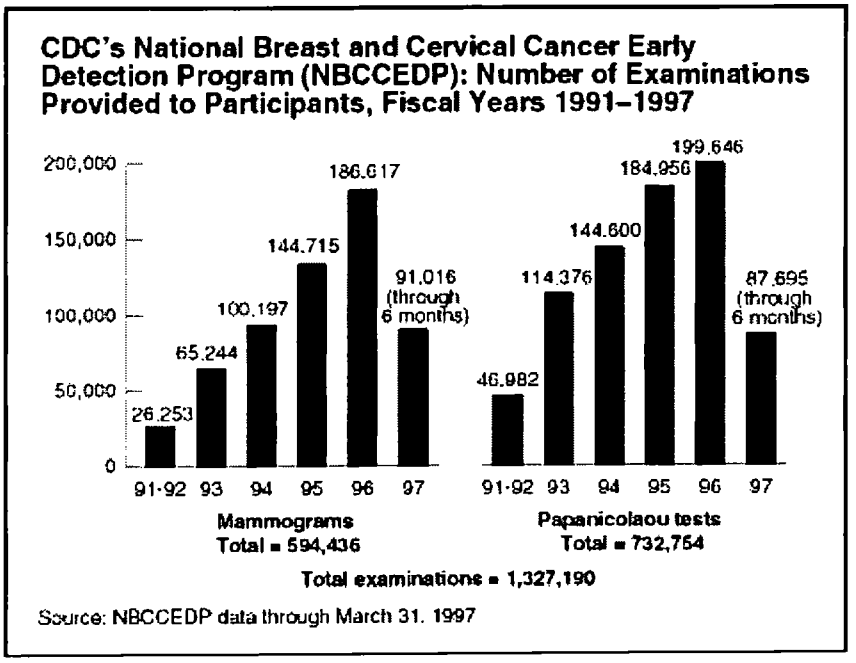


Source: NBCCEDP data through March 31, 1997

The purpose of cervical cancer screening differs from that of breast cancer screening: the goal is not to find cancer, but to find precancerous lesions. Detection and treatment of precancerous cervical lesions identified by Papanicolaou (Pap) screening can actually prevent cervical cancer. Additionally, if cervical cancer is detected while in its earliest stage, the likelihood of survival is almost 100% with timely and appropriate treatment and follow-up.

Common Barriers to Screening

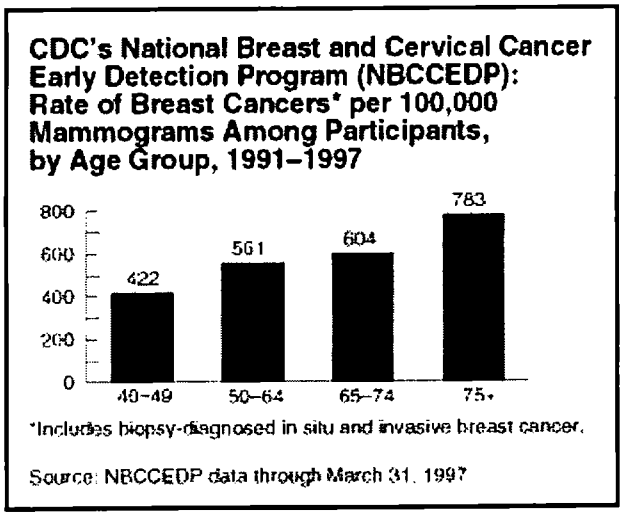
- **Fear.** Women may be afraid to discover that they have cancer.
- **Cost.** Many women cite cost as the reason they do not use early detection programs. Many are not aware of the availability of low-cost programs.
- **Transportation.** Because many women lack transportation, convenient location of screening facilities is important.
- **Communication Barriers.** Communication styles and methods appropriate for one group may be inappropriate for another.
- **Lack of Physician Referral.** Studies have shown that women are more likely to be screened if their physician recommends screening.
- **Lack of Child Care.** Some women need assistance with arranging child care to be able to use screening.



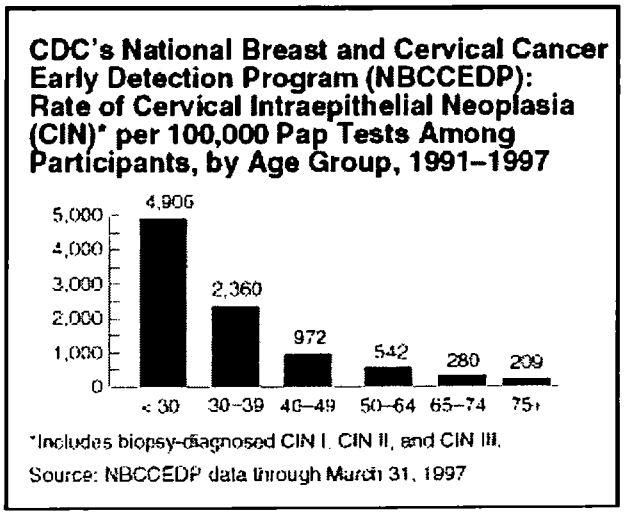
Surveillance

How the Program Has Helped

Through March 1997, more than 1,300,000 screening tests were provided by NBCCEDP. Of the 576,408 mammograms provided to women aged 40 and older, 39,516 (6.8%) were abnormal, and 3,409 breast cancers were diagnosed. As depicted below, the rates of breast cancer increased with increasing age.



Of the 732,754 Pap tests provided, 22,012 (3%) were abnormal. A total of 23,782 cases of cervical intraepithelial neoplasia (CIN) I, II, or III, precursors of invasive cervical cancer that can be successfully treated, were diagnosed. A total of 303 cases of invasive cervical cancer were diagnosed, representing an age-adjusted rate of 37 diagnoses per 100,000 Pap tests. As depicted below, the rates of CIN decreased with increasing age.



Public Education and Outreach

"Comprehensive strategies will be needed to educate and motivate women to seek screening services."

--Donna E. Shalala, Secretary
U.S. Department of Health and Human Services

NBCCEDP has made significant progress in building state and community partnerships to serve women. Various outreach activities have been designed to educate women and motivate them to be screened. The following programs are examples of such activities.

- Arkansas builds on the concept of the lay health worker by recruiting African American breast cancer survivors to serve as witness role models. These women "witness," or give oral testimony, about their breast cancer experiences to African American churches and community groups.

- Minnesota has developed outreach efforts for Native Americans in the Fond du Lac Tribe. Coordinators developed a home visiting program after observing that Native American women in this region are generally not receptive to large group activities. Because it was also learned that most of these women prefer discussing their health with public health nurses, the program hired these nurses to visit eligible women. To further meet this audience's needs, the screening message emphasizes that women must take care of themselves to take care of their families.

- New Mexico's Pass It On program uses home health parties to deliver breast and cervical cancer screening information in a volunteer's home. This structured but familiar setting helps participants be more receptive to, and less fearful of, discussing these sensitive topics. The program targets rural areas and relies on word of mouth to recruit hosts for additional parties.

- New Jersey collaborates with the Women's Wellness Center of the University of Medicine and Dentistry of New Jersey and the YWCA of New Jersey to reduce physical access barriers by combining outreach and portable screening. Program staff

make monthly visits to senior housing complexes and other settings, such as beauty parlors and supermarkets. The site visits include an educational program targeted to women of color who are over 50 years of age. During the visit, the staff schedules mammography appointments for a portable mammography unit that comes to the site two weeks later.

Partnerships

Partnerships are critical to CDC's cancer control efforts. A successful national program to control breast and cervical cancers depends on the involvement of a variety of committed partners. CDC actively collaborates with state and local governments, health care professionals and organizations, social service and voluntary organizations, and academia. Through partnerships, CDC assists private and public nonprofit organizations in

- Developing, implementing, and evaluating national, community-based interventions for cancer prevention and early detection.
- Testing new methods and replicating proven strategies to educate their constituents about breast and cervical cancers.
- Increasing access to breast and cervical cancer screening among underserved women.

Partnerships for Cancer Control in Priority Populations

Deaths due to breast cancer are decreasing among white women, but not among African American women. The death rate from cervical cancer is more than twice as high among African American women as among white women. Both mammography and Pap tests are underused by women who are members of racial and ethnic minority groups, who have less than a high school education, are older, or live below the poverty level.

To address these differences in the burden of cancer and in the use of cancer prevention services among different populations, CDC funds a strong and effective network of partners that are well-positioned in the communities at risk. Projects sponsored by these partners include the following:

- **The U. S. Conference of Mayors' Research and Education Foundation** is conducting a 5-year national campaign, the Mayors' Coalition and Initiatives for Breast Cancer Early Detection and Control. This program is designed to reach underserved low-income women in cities with populations greater than 30,000.
- **The National Center for Farmworkers Health, Inc.,** has developed the National Comprehensive Cancer Program for Farmworkers to increase knowledge and awareness of breast and cervical cancers and to promote screening for the early detection of these cancers among Latina migrant and seasonal farmworkers.
- **The American Social Health Association** has formulated a national model for the primary and secondary prevention of cervical cancer. Piloted in two counties in North Carolina, this program targets economically disadvantaged women, Hispanic and African American women, and women living in hard-to-reach urban and rural areas.
- **The Association of Asian Pacific Community Health Organizations** disseminates education campaigns such as the Witness Project and the Waianae Cancer Research Project to promote screening for the early detection of breast and cervical cancer among low-income, medically underserved women in Asian and Pacific Islander communities.

- **Baylor College of Medicine** sponsors the Salud en Accion program, which combines research with public education and advocacy to promote risk reduction, screening participation, and improvements in cancer related services and policies in designated Hispanic communities.

- **The Institute for the Advancement of Social Work Research** has established a strategic team of experts to formulate a plan---Implementing Effective Breast and Cervical Cancer Health Education Interventions for High-Risk Women Across Diverse Populations and Service Systems---to improve rates of screening and adherence to follow-up among low-income women.

- **The Mautner Project for Lesbians with Cancer** has developed an intervention that strengthens the skills of health care providers in encouraging lesbian women to participate in breast and cervical cancer screening services.

- **The National Asian Women's Health Organization** offers professionals and community members a cultural competency training program for health, Communicating Across Boundaries: A Cultural Competency Training on Breast and Cervical Cancer in Women.

- **The National Association of Community Health Centers,** along with the E. Roybal Institute on Gerontology, promotes Project Vision, its successful breast cancer education, early detection, and intervention program for Hispanic women older than age 50, and has expanded it to include cervical cancer screening.

- **The National Education Association Health Information Network** uses Project REACH, a program developed by and for school employees, to provide training and advocacy for the early detection of breast cancer. The program specifically targets retired school personnel, education support personnel, minority school personnel, and lesbian school employees.

- **The National Caucus and Center on Black Aged, Inc.,** sponsors Circle of Friends: Women Telling Women About Health Issues, a culturally appropriate breast and cervical cancer education and early detection program for low-income, mature African American women, especially those who live in public housing.

- **The Witness Project** disseminates and implements a breast and cervical cancer education intervention that recruits, trains, and provides resources to African American witness role models and lay health advisors who will provide culturally appropriate educational messages to African American churches and community groups.

- **World Education** uses the program Health and Education Adult Literacy: Breast and Cervical Cancer to train and develop materials for adult educators to assist them in diffusing critical information to low income and minority women who have less than a high school education.

CDC and the American Cancer Society

CDC collaborates with the American Cancer Society (ACS) to develop and disseminate comprehensive information on cancer prevention and early detection. Through CDC, ACS divisions have formed partnerships with state health departments to increase screening services to medically underserved women. CDC and ACS collaborate in all programmatic areas, including establishing early detection programs, providing professional development, and conducting special demonstration projects.

Professional Education

Professional education activities in the states have reached a wide range of health care professionals. Of those trained, 49% have been nurses, 18% physicians, and 15% radiology technologists.

CDC's National Training Center provided three training programs in 1997: Effective Outreach Strategies for Older Medically Underserved Women, Enhancing Training Design and Developing Skills Using Clinical Breast Exam as a Model, and Case Management: Sharing the Tools of the Trade. The next three training programs will focus on community health workers, quality assurance, and evaluation. Training will be skills-based and will use creative new approaches, including live, interactive satellite courses. The targeted audience will include health professionals working in state and territorial agencies and tribal organizations.

Quality Assurance

Quality assurance is essential if the early detection of breast and cervical cancer is to be an effective tool for controlling cancer. CDC has supplied all NBCCEDP-funded programs with screening and diagnostic guidelines, has assisted the Food and Drug Administration in conducting quality assurance training programs, has teamed with the American College of Radiology to improve and ensure the quality of mammography screening, has developed guidelines on evaluating common breast problems, and has issued recommendations to develop a public health response to the regulatory closure of cervical cytology laboratories.

For more information, please contact the Centers for Disease Control and Prevention,
National Center for Chronic Disease Prevention and Health Promotion,
Mail Stop K-64, 4770 Buford Highway NE, Atlanta, GA 30341-3717, (770) 488-4751.

E-mail to cancerinfo@cdc.gov

World Wide Web at http://www.cdc.gov/nccdphp/dcpc

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You may also download a PDF version (283K) for Adobe Acrobat Reader or a PostScript version (578K).

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Breast and Cervical Cancer

National Breast and Cervical Cancer Early Detection Program

The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) provides breast and cervical cancer screening services to underserved women, particularly low-income women, members of racial/ethnic minorities, and older women. In 1997, 50 states, 5 territories, the District of Columbia, and 15 American Indian/Alaska Native organizations participated. NBCCEDP programs focus on

- Screening and follow-up
- Public education
- Provider education
- Quality assurance measures
- Surveillance and evaluation
- Coalition building

Impact of Breast and Cervical Cancer

Breast cancer is the most common cancer among American women and the second leading cause of cancer deaths

- 180,200 new cases of breast cancer were expected in 1997
- 43,900 women were expected to die of breast cancer in 1997
- Mammography is the most effective method for early detection of breast cancer

Although deaths from cervical cancer have decreased approximately 70% in the past 40 years

- 14,500 new cases were expected in 1997
- About 4,800 women die of cervical cancer each year
- Virtually all cervical cancer deaths are preventable through early detection and appropriate follow-up

The National Breast and Cervical Cancer Early Detection Program: At-A-Glance

Breast Cancer Rates Among Participants in National Breast and Cervical Cancer Early Detection Program, By Age (graph)

CDC's Cancer Prevention and Control Program

CDC's Office of Women's Health

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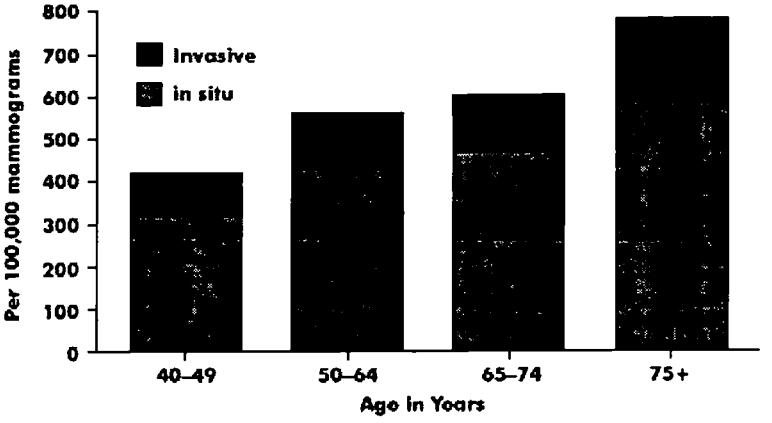
Breast Cancer Rates Among Participants in the National Breast and Cervical Cancer Early Detection Program, by Age



Source: Minimum data elements for mammograms through March 1997

Stories

Last Modified: October 14, 1998

People are what matter to the National Childhood Cancer Foundation.
We support the work of the wonderful people who are treating children with cancer and finding new cures for childhood cancer.
And daily we meet the patients, survivors and parents who have had their lives disrupted by childhood cancer, it reminds us that it is our mission to help these people by eradicating childhood cancer.

When you read these 'people stories' you will find out what the future holds for infants, children, teenagers, and young adults with cancer.

Meet These Patients -- You will be inspired when you meet these young survivors of childhood cancer

- Erin, who visited the White House
- Amy, a cheerleader with much to cheer about
- Brandon, who has been through a lot
- Hadley, beautiful Before and After
- Becky, the Air Force Kid
- Mandy, who writes poetry
- Jenee, who helps others find the bone marrow they need
- Megan, who looks up to Golfer Greg Norman
- Mark, once the patient, now the doctor
- Kristi Beat the Odds

Meet These Researchers -- You will be filled with hope when you read about the exciting progress being made by the medical researchers of the Children's Cancer Group

- Gregory Reaman, M.D.,pursues new agents
- Paul Meyers, M.D., says children with bone cancer now get chemotherapy before and after surgery
- Ernest Katz, Ph.D., studies the psycho-social effects of childhood cancer
- Stuart E. Siegel, M.D., points out how research into childhood cancer helps in the treatment of adults with cancer
- Roger J. Packer, M.D., predicts great advances will be made soon in treating children with brain tumors
- Louise C. Strong, M.D., describes the hereditary factors which could lead to a child having cancer
- Katherine Mattay, M.D., seeks the ideal intensity of chemotherapy for children with neuroblastoma
- C. Patrick Reynolds, M.D., removes cancer cells from bone marrow
- Richard Lemons, M.D., Ph.D., wants to know why broken genes cause leukemia
- Fatih Uckun, M.D., seeks a new anti-cancer agent from a common roadside plant

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Patient Story

Federal Employee Uses Her Leave Time To Battle Child's Cancer

It was over eight years ago when U.S. Justice Department attorney Sandra Schraibman learned that her two-year-old daughter Erin had leukemia. But she still remembers the "two years, two months, and two weeks" of chemotherapy that followed. The child suffered 13 fevers, and was hospitalized for some 80 inpatient days during her treatments.

Sandra - the daughter of a career Army M/Sgt. -- defends the Treasury, Transportation, Commerce and Labor Departments against lawsuits involving such issues as economic sanctions laws, the assault weapons ban, the Brady Act, and the Census Act. But those issues suddenly seemed less important than "family matters."

Sandra made use of "Voluntary Leave Transfer," which allowed fellow employees to donate 600 hours of their leave time for the medical emergency. Her husband Julian, a high school teacher, was then able to spend more time in the classroom and with Erin's older sister Jessica, then 6.

"It hit me at the time," Sandra says. "We were told 70-75% would eventually be considered cured of the kind of cancer she had. That's great. But not good enough. I suddenly realized 25-30% were going to die."

But today Erin is a confident, athletic little girl, at ease with her peers. "She has blossomed, and there are no real lingering effects that hamper her," Sandra says. She is a competitive swimmer, and her ambition is to swim in the Olympics.

While she was being treated for cancer, Erin came to love the staff at the Children's National Medical Center in Washington D.C. In fact, her mother remembers, "If she got mad at us she would say she was going back to the hospital." She told her parents, "They think I'm cute."

Erin's mother would tell a parent hearing a cancer diagnosis today: "It isn't an experience anyone would opt for, it may seem bleak at the beginning, and you have to go through a lot. But you can live through it, and your kids can turn out great."

Many federal employees and members of the U.S. military are donors to the Combined Federal Campaign, and have designated their contribution for the National Childhood Cancer Foundation. They are supporting vital medical research work. Sometimes that work benefits one of their own, such as the little leukemia survivor Erin Schraibman you have just read about, who is the daughter of a federal employee and the granddaughter of a career M/Sgt. in the U.S. Army. Or such as young Becky, the Air Force kid you will also find profiled in our "survivor stories."

Those federal employees wishing to donate to National Childhood Cancer Foundation during the year ahead should look for "CURE CHILDHOOD CANCER!" under Health and Medical Research Charities. The agency code is #2582.