MAY 18, 1998 $2.95 www.time.com

TIME

CANCER

How to tell the hype from the hope

A SPECIAL REPORT

The Hope & The Hype

Last week's breathless reports of an imminent cure were, of course, too good to be true. Still, these are exciting times in cancer research

By CHRISTINE GORMAN

UNLESS YOU HAVE GONE through the experience yourself, or watched a loved one's struggle, you really have no idea just how desperate cancer can make you. You pray, you rage, you bargain with God, but most of all you clutch at any hope, no matter how remote, of a second chance at life.

For a few heady days last week, however, it seemed as if the whole world was a cancer patient and that all humankind had been granted a reprieve. Triggered by a front-page medical news story in the usually reserved New York *Times*, all anybody was talking about—on the radio, on television, on the Internet, in phone calls to friends and relatives—was the report that a combination of two new drugs could, as the *Times* put it, "cure cancer in two years."

In a matter of hours patients had jammed their doctors' phone lines begging for a chance to test the miracle cancer cure. Investors scrambled to buy a piece of the action, turning the shares of a little company called EntreMed into the most volatile stock on Wall Street. Cancer scientists

PHOTO AND BORDER BY CNRI/MICROWORNS—PHOTOTAKE

UNDER ATTACK Magnified 29,000 times, an immune cell (yellow) targets a tumor cell (red) for destruction

BILL GREENE—THE BOSTON GLOBE

"I'm flattered, but it's mice, only mice. If you have cancer and you're a mouse, we can take good care of you."

—DR. JUDAH FOLKMAN, cancer researcher

raced to the phones and fax lines to make sure everyone knew about their research too, generating a new round of headlines and perpetuating the second major medical media frenzy in as many weeks. It was Viagra all over again, without the jokes.

The time certainly seemed ripe for a breakthrough in cancer. Only last month scientists at the National Cancer Institute announced that they were halting a clinical trial of a drug called tamoxifen—and offering it to patients getting the placebo—because it had proved so effective at preventing breast cancer (although it also seemed to increase the risk of uterine cancer). Then preliminary reports indicated that another drug, raloxifene, might prevent breast cancer without triggering new malignancies. Two weeks later came the *Times's* report that two new drugs can shrink tumors of every variety without any side effects whatsoever.

It all seemed too good to be true, and of course it was. There are no miracle cancer drugs, at least not yet. At this stage all EntreMed can offer is some very interesting molecules, called angiostatin and endostatin, and the only cancers they have cured so far have been in mice. By the middle of last week, even the most breathless TV talk-show hosts had learned what every scientist already knew: that curing a disease in lab animals is not the same as doing it in humans. "The history of cancer research has been a history of curing cancer in the mouse," Dr. Richard Klausner, head of the National Cancer Institute, told the Los Angeles *Times*. "We have cured mice of cancer for decades—and it simply didn't work in people."

Even that understates the scientific hurdles that lie ahead. No one knows yet whether angiostatin and endostatin will help people. Even if researchers do figure out how to make the compounds work, pharmaceutical companies estimate it would take as much as $400 million and at least 10 years—not two years—of thorough clinical trials to bring a drug to market.

So what happened last week? On one level this is a case of science journalism gone awry. Although the original story in the New York *Times*, written by influential science reporter Gina Kolata, was sprinkled with the necessary caveats, it distorted the significance of EntreMed's research in several important respects, and it exaggerated and romanticized the role of the drugs' discoverer, Dr. Judah Folkman, a researcher at Children's Hospital in Boston, in a way that surprised his colleagues and embarrassed Folkman.

But beyond the hype and confusion, something very real is going on. These are exciting times in cancer research, perhaps the most exciting since Richard Nixon declared war on cancer in 1971. Angiogenesis inhibition, the tumor-starving process that Folkman pioneered, is indeed a promising line of research. Dozens of labs are racing to perfect it, some of them doing work that is more advanced than Folkman's. But it's not the only field with potential. Just as exciting, say many researchers, is the revolution in cancer treatments made possible by what they've learned about how genes and cancer cells work at the molecular level, the fruits of which are already being delivered to human patients (*see following story*).

How did a story about preliminary data on laboratory animals spiral so completely out of control? The key is Kolata's piece in the *Times* and the prominent placement her editors gave it. "Within a year," she began, "if all goes well, the first cancer patient will be injected with two new drugs that can eradicate any type of cancer, with no obvious side effects and no drug resistance—in mice." It was a sentence that couldn't help grabbing readers' attention—despite those critical two words, "in mice"—and holding it throughout the rest of the story.

Apart from certain omissions, there was nothing factually inaccurate in what Kolata wrote. Folkman, in his statements, went out of his way to downplay his findings. But his carefully cautionary tone was completely overshadowed by the quotes Kolata attributed to a host of other scientists and the adjectives they used to describe Folkman's work. His results were "remarkable," "exciting" and "wonderful." Dr. James Pluda of the National Cancer Institute said he and his colleagues were "electrified" and "almost overwhelmed" by the data.

The quote that nailed the story, however, and put it on the front page, was the one attributed to James Watson, co-discoverer of DNA's double helix and one of the most famous scientists in the world. "Judah," he is supposed to have said, "is going to cure cancer in two years."

That was all the endorsement most journalists needed to hear. The *Times* wields so much influence as the paper of record—and has a reputation for being so conservative in its news judgment—that few reporters could justify holding their own stories while checking out all the details. And even those who did produce more balanced pieces only seemed to reinforce the impression that something really big had happened. Wire services ticked off the highlights. Television anchors and radio announcers provided the sound bites. And the tabloids dutifully served up the tearful stories of cancer patients desperate to try anything.

Most people thought they were hearing about a new breakthrough. In fact, Folkman's work on angiostatin and endostatin had been reported months before in scientific journals and just a few weeks ago in *Business Week*. A November article in *Nature* briefly boosted EntreMed's stock 28%, to $15.25 per share. But of course that was nothing compared with last week, when the stock rocketed past $80 before eventually dropping to $33.25 at Friday's close.

As the week wore on, further complications emerged. In a letter to the *Times*, Watson denied his remarks. "I sat next to [Kolata] at a meeting at UCLA six weeks ago," he told TIME. "She never took any notes." He says he did not tell her that cancer would be cured in two years, although he did communicate his excitement about Folkman's research.

Kolata stood by her story—as did the *Times*. "We are entirely comfortable with the coverage and the placement of the article," says Nancy Nielsen, a spokesperson for the newspaper. As for Watson's quote: "We don't wish to get into a quarrel with a respected scientist, but we are confident in the accuracy of our story."

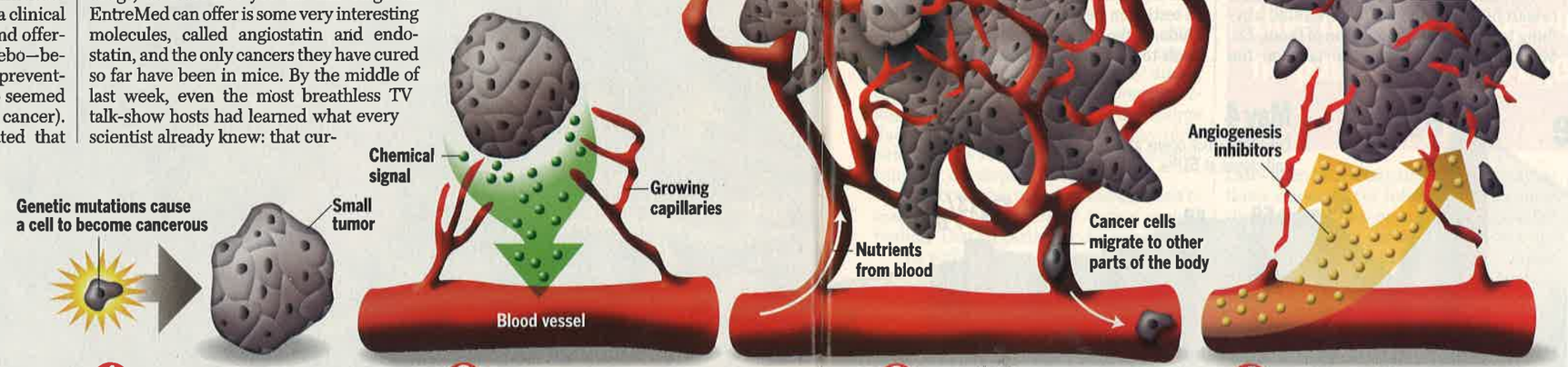
But things soon got worse for Kolata. On Wednesday the Los Angeles *Times* suggested that her enthusiasm for Folkman's work might have been influenced by a potential book deal. She had, in fact, at the urging of her agent John Brockman, dashed off an e-mail message that Brockman told her could, in the hands of the right publisher, be worth a cool $2 million. But after meeting with her editors on Tuesday, Kolata quashed any idea of writing a book. "I did not plan a book," she says. "I did not write anything that anyone could remotely consider to be a proposal, and any idea was immediately withdrawn."

Then the New York *Post* reported that Folkman would share in a $1 million book deal with Random House. Flat wrong, says Random House. It is true that the publisher has tapped science writer Robert Cooke of *Newsday* to produce a book about Folkman's life and cancer research and that Folkman has agreed to cooperate with the project. But the scientist won't get any money from the deal.

What he will get is some hard-won recognition for having single-handedly created the field of angiogenesis. Back in the 1970s, when conventional wisdom among cancer researchers was that most tumors are caused by viruses, Folkman was

HOW TO STARVE A CANCER CELL

The trick is to cut off the tumor's blood supply



1 A series of genetic mutations turns a normal cell into a malignant cancer cell that divides rapidly and grows into a tumor about the size of a pea. The tumor can't grow any larger unless it recruits its own blood supply

2 After a period that can range from months to years, another mutation triggers the release of a chemical that tells nearby blood vessels to grow new capillaries. Such growth is called angiogenesis

TIME Diagram by Joe Lertola

3 The capillaries invade the tumor, bringing it nutrients, stimulating its growth and providing a route for some of the cancer cells to spread to other parts of the body

4 Scientists have identified more than 300 substances that may inhibit angiogenesis by destroying newly formed capillaries or preventing their formation. As a result, the tumor may stop growing, shrink or, in some cases, disappear altogether

WHY DO I HAVE TO WAIT SO LONG?

PATIENCE IS THE LAST THING YOU CAN REASONABLY ASK OF someone who's in the final stages of terminal cancer. For these people and their families, talk of safety and efficacy and extended double-blind trials are just so much noise. A treatment that may be available five years from now or next year or even in a few months amounts to no treatment at all. So what if angiostatin and endostatin work only in mice? If there's even a minuscule chance the compounds will cure cancer in humans too, why should the dying have to wait another minute?

Unfortunately, there are plenty of reasons. To start with, the substances are available only in tiny quantities at this point. When scientists first started making endostatin, it took 200 qt. of mouse urine to obtain less than a millionth of an ounce. Turning the compounds out in people-size doses will require entirely different manufacturing techniques. EntreMed claims it now has a way to make lots of endostatin, using yeast cells as tiny factories; angiostatin is proving a lot tougher to mass-produce.

Within a year or two, EntreMed and its partner in the project, Bristol-Myers-Squibb, will probably figure out how to make angiostatin in quantity. At that point the companies will have to apply to the FDA for permission to market them. But before the agency gives its blessing, the companies have to show that the medications work in humans, and that they don't have terrible side effects. Normally, that's a five- or six-stage process that can last 10 years or more.

Each stage takes money—to pay for the drugs, to pay the salaries of researchers and support staff—and while more money might speed things along, drug companies and universities don't always know in advance which medications will reach the market and therefore which ones to throw more money at.

Stumbling blocks lie all along the way. Sometimes the clinical trials are badly designed; a new medication may be given in the wrong dosage, or delivered to the wrong subset of patients. And even when everything's done right, chemicals that looked highly promising in laboratory animals often turn out to be dangerous or ineffective. Most experimental compounds never get out of the lab. And for every five drugs that do go into clinical testing, only one is eventually approved by the FDA.

pursuing his own, very different insight. He noticed that when cancer cells are still tiny—only a millimeter or two across—they don't need any blood vessels to survive. In order to grow to life-threatening size, however, they need blood. And they get that blood by persuading nearby capillaries to reach out and touch them.

Virtually alone in the scientific community, Folkman decided it would be easier to try to kill a tumor by destroying its blood supply than by attacking it directly. His reasoning was sound. Tumors are made up of rapidly dividing mutant cells that adapt quickly to almost any treatment thrown at them. Blood vessels, by contrast, are made up of normal cells that grow much more slowly and are nowhere near as difficult to outwit. Hoping to starve tumors through their supply line of nutrients, Folkman set out to find a drug that could block the construction of new blood vessels.

At first, he was almost too successful. Everywhere he looked—from cartilage to fungi to the notorious sedative thalidomide—Folkman found one compound after another that exhibited anti-angiogenic properties. But none of them was as effective as he wanted it to be. Then he remembered something that surgeons had often observed: that taking out one big tumor from a patient seems to trigger the growth of lots of smaller ones. Could it be that tumors secrete a substance that inhibits the growth of rival tumors' blood vessels?

It was such a crazy idea that none of the researchers in Folkman's lab wanted anything to do with it. Finally one of them, Dr. Michael O'Reilly, agreed to take on the project. Together he and Folkman eventually determined that various segments of a naturally occurring protein called plasminogen seemed to do the trick. They called the collection of molecular fragments angiostatin and found that each version of the compound differed slightly in its ability to stop a tumor from growing.

But no matter what its configuration, angiostatin could not make a mouse tumor disappear. Not, that is, until Folkman and O'Reilly added to the mix a second molecular fragment, which they called endostatin, from yet another naturally occurring protein. Together, the two compounds destroyed a range of tumors in mice. The results were startling enough that they merited testing in people—which is exactly what Pluda, at the National Cancer Institute, intends to do. How fast those studies can begin depends on how much angiostatin and endostatin EntreMed and its business partner, Bristol-Myers Squibb, can produce and whether they can figure out which fragment to focus on first.

At least Folkman doesn't have to spend all his time nowadays, as he once did, trying to persuade researchers that his approach to cancer treatment has merit. Scientists are currently investigating 300 different substances for their potential to block angiogenesis. Twenty of those compounds have already entered clinical trials in humans. Indeed, researchers suspect that some of the latest cancer treatments, like tamoxifen, may themselves work in part by blocking the growth of newly formed blood vessels.

There are risks involved in messing with the blood vessels. Sometimes angiogenesis is a good thing, especially during pregnancy. One potent anti-angiogenic being studied today is that old scourge thalidomide, which caused so many birth defects in the 1950s by cutting off the blood supply in developing fetuses.

The body also relies on angiogenesis to make new blood vessels during wound healing. That's a particular concern of people with diabetes, whose cuts and abrasions—particularly in their feet—often take a long time to close, leaving them vulnerable to infection. Fortunately they can use a new prescription cream, the first angiogenesis product to win FDA approval, that stimulates the body's repair processes and helps those tiny capillaries in their toes and feet to grow.

And although the newest angiogenesis inhibitors have relatively few side effects, at least compared with radiation or chemotherapy, they are not risk free. "Lack of toxicity in animals does not mean there is no toxicity to humans," says Dr. William Li, medical director of the Boston-based Angiogenesis Foundation, a nonprofit clearinghouse for information on the latest research.

Nor will angiogenesis inhibitors necessarily work equally well against all cancers. The Angiogenesis Foundation has analyzed 29 kinds of solid tumors and discovered that some rely much more heavily on blood-vessel networks than others.

The FDA, for its part, has tried to streamline the process. The agency recognizes that the terminally ill are a special case, and in recent years has come up with several shortcuts, including fast-track approval for some crucial medications and a "compassionate use" exemption that gives the dying access to promising but unapproved medicines.

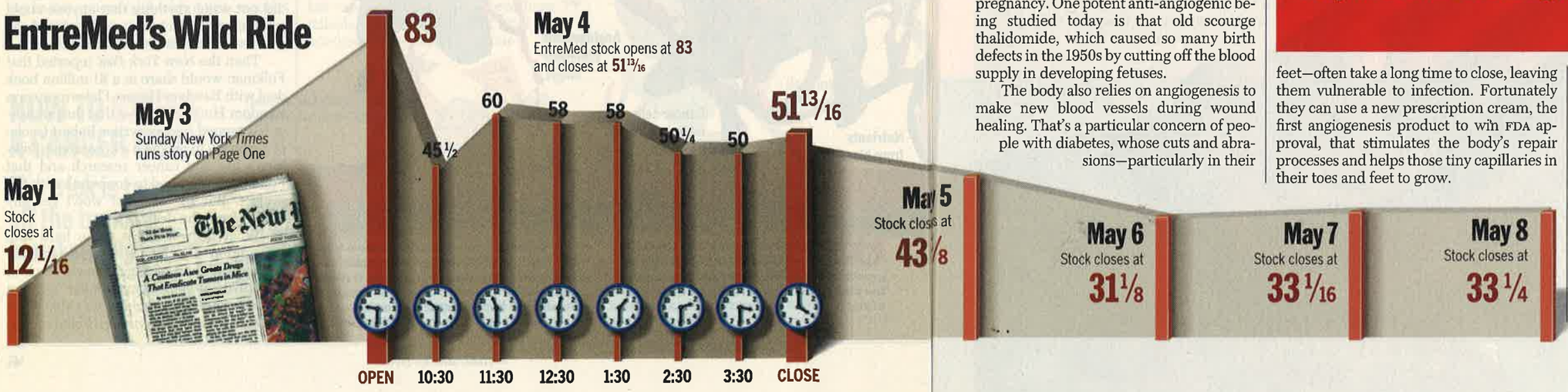
They get access, that is, if there is enough of the drug to go around, and that's not always the case. Beth Nocera of Medford, Mass., a 41-year-old mother of two, has terminal metastatic breast cancer. Nocera wants to try Herceptin, an anticancer drug now in clinical trials. But Herceptin is expensive, and the manufacturer, Genentech, isn't making much beyond what it needs for testing. It currently gives the extra Herceptin to a limited number of women, chosen at random by a computer, and Nocera's number hasn't come up yet. "My fear," she says, "is that it's all about money and that these companies don't need us if we don't meet their criteria."

The truth is that she's got a point. But the only way to give the drug to all the women who might want it would be to take some away from the trials. While that might save some people's lives (perhaps at the expense of someone else's), it could delay still further a process that's already slow enough. *—By Michael D. Lemonick. Reported by David Bjerklie/New York*

BROOKS KRAFT—SYGMA FOR TIME

"My biggest concern is the possibility that there is a drug out there that might help me and I won't get it in time."

—BETH NOCERA, cancer patient



Armed with such knowledge, younger researchers think they can improve on Folkman's techniques. They prefer a more targeted approach: selectively attacking the various molecules and biochemical signals involved in building a new blood vessel. For instance, researchers at Ixsys, a biotech company in San Diego, have developed an artificial antibody that dissolves the biochemical glue that holds a tumor's capillaries together. Indeed, one of the patients in their safety study exceeded all expectations when two of the tumors in his abdomen shrank 70%. "I've been on the drug now for over a year," says Barry Riccio, a college professor from Illinois who is suffering from a rare sarcoma. "I have more energy than I did just nine months ago, and I've gained back a lot of weight."

Other researchers are zeroing in on different targets. Some are looking at a specialized growth factor called VEGF (for vascular endothelial growth factor) that so far has been found only in the blood vessels that feed tumors. One synthetic molecule being tested at UCLA prevents VEGF from stimulating new growth by elbowing it aside and taking its place in the cell's receptors. Safety studies in more than 30 patients have so far not revealed any major side effects, although their tumors' growth was only slowed, not halted. Dr. Joseph Sparano, at Montefiore Medical Center in New York City, who is pursuing still another approach to anti-angiogenesis, says he doesn't need to stop tumor growth completely to judge his experiment a success: "If we can make patients with metastatic breast cancer live 20 years and not have symptoms, that may be as good as a cure."

But it may not be good enough for those millions of cancer patients whose hopes were stirred last week. Hope, for them, is a precious commodity, not something to be rationed or trifled with. Just ask Renee Smith of Dripping Springs, Texas, who three years ago found she has non-Hodgkin's lymphoma. She has a four-year-old daughter she'd like to see grow up and a husband with whom she'd like to grow old. When friends started calling excitedly last week with news of a possible cure, she resolved to maintain a philosophical calm. "I try to live in the moment because that helps level out the emotional roller coaster," she says. Still, the moment sometimes escapes her. "I am not perfect," she says. "I am not the Dalai Lama." Ironically, it's patients like Smith, the people most in need of a breakthrough, who were the most vulnerable to last week's false hopes. —***Reported by William Dowell and Alice Park/New York***

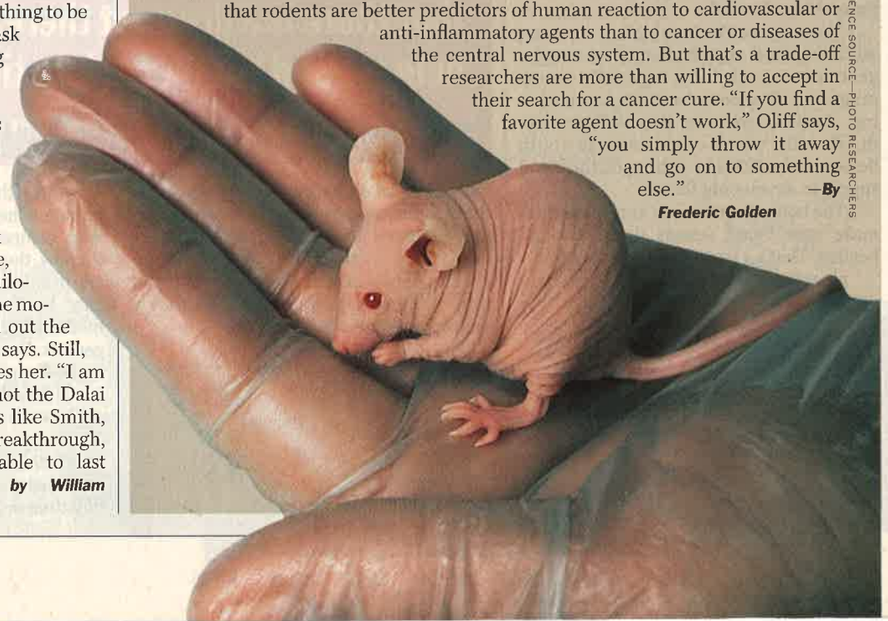
OF MICE AND MEN: DON'T BLAME THE RODENTS

WHEN DR. JUDAH FOLKMAN IS ASKED WHETHER HE CAN CURE CANCER, he invariably replies, "Yes, in mice." That's not entirely self-effacing whimsy. Like every good researcher—and every responsible science journalist—he knows all too well that most drugs that work in lab animals turn out to be duds in humans. The field is littered with "magic bullets" that failed, among them monoclonal antibodies, tumor necrosis factor, interferon and interleukin-2. While all were initially hyped as potential cure-alls, they have turned out to have only modest usefulness in the war on cancer. At best, says Dr. Allen Oliff, Merck & Co.'s chief of cancer research, no more than 10% or 20% of agents tried in mice succeed. (On the other hand, the treatments that are good for people are almost always good for mice.)

But don't blame that on the rodents. They are bred to spend their brief lives (about two years) as test subjects—a job they do pretty well. "As mammals with physical systems somewhat like our own, they give us a relatively quick, inexpensive way of getting at the causes of disease and possible therapies," says Dr. Kenneth Paigen, director of the Jackson Laboratory in Bar Harbor, Maine, the world's most famous mouse-breeding facility. Each year the lab ships out some 2 million mice from more than 1,700 stocks, including so-called designer mice with genes added or deleted so that they more closely "model" human disease. Among its customers is Folkman, whose lab relies on Jackson's best-selling C57BL/6J, or "Black 6" (cost: $8.15 to $10.85 apiece, depending on age).

Trouble is, Black 6 and kin often do their jobs too well. "Mice distort or exaggerate what you see in humans," says tumor biologist Robert Kerbel of Toronto's Sunnybrook Health Science Centre. Mouse tumors, which are usually planted just under the skin, grow much more rapidly than deep-seated human tumors. Also, as Nobel laureate J. Michael Bishop observes, too much breeding isn't always a good thing. In his labs at the University of California, San Francisco, he is genetically altering mice to provide better models for studying leukemia and neuroblastoma, the most common tumor in children under 3. But genetic alterations can go only so far. "How similar the mouse is to man," he concedes, "is still a legitimate issue."

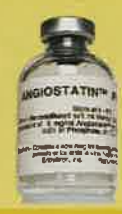
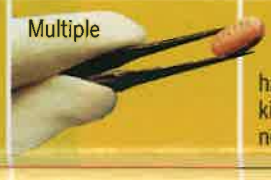
Similar or not, no one, except perhaps a few animal-rights activists, is about to chase mice out of the lab. Mice save lives. Because their tumors develop almost overnight, says Merck's Oliff, "we can do tests 10 or 100 times more quickly than in humans." Their usefulness varies with diseases, though. He notes that rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than to cancer or diseases of the central nervous system. But that's a trade-off researchers are more than willing to accept in their search for a cancer cure. "If you find a favorite agent doesn't work," Oliff says, "you simply throw it away and go on to something else." —***By Frederic Golden***



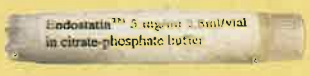
NIH/SCIENCE SOURCE—PHOTO RESEARCHERS

Checklist OF CANCER TREATMENTS

For years doctors and cancer patients had only three options: surgery, radiation and chemotherapy. But that's starting to change, as a new generation of more sophisticated treatments moves out of the lab

TREATMENT	TARGET	HOW THEY WORK	STATUS
Anti-angiogenesis Factors	Multiple	A growing tumor requires plenty of nutrients, and to make sure it gets them the tumor secretes substances that stimulate the **growth of new blood vessels.** A number of agents can **block this process**—at least in animals. 	See chart below
Anti-metastatic Factors	Multiple	What kills most cancer patients is not the primary tumor but its metastatic spread. Scientists have identified a class of enzymes that enables cancer cells to enter the bloodstream by **dissolving tissue** and **boring holes** through capillary walls. New drugs could keep cancer cells confined to one spot.	Human tests have just begun
Anti-oncogenic Factors	Multiple, including breast, colon, pancreatic and lung	Tumors do more than pick up growth factors that circulate in the bloodstream; they also make them by **switching on "oncogenes."** Many cancers, for example, have been found to contain mutations in the **RAS oncogene,** and companies are racing to develop drugs that inhibit its growth-promoting activity.	Human tests are in early stages
Chemoprevention Therapies 	Breast, head and neck	Many breast cancers depend on the female hormone estrogen to stimulate their growth. **Tamoxifen,** which acts as an antiestrogen in the breast, has been shown to prevent the development of this form of cancer. Preliminary evidence suggests that a newer compound, **raloxifene,** may confer a similar benefit without serious side effects. Compounds know as **retinoids,** derivatives of vitamin A, can prevent recurrence of certain head and neck cancers.	✔ Tamoxifen has been approved as a treatment for breast cancer; raloxifene, as a treatment for osteoporosis
Gene Therapies	Multiple, including breast, ovarian and small-cell lung cancers	In tumors, genes that are supposed to serve as checks on runaway cell growth are often so damaged that they stop functioning. Scientists hope to correct this problem by engineering viruses that can "infect" cancerous cells with **healthy tumor-suppressor genes.** Preliminary evidence suggests that this approach can sometimes cause tumors to stop growing and even shrink in size.	Testing in humans has just begun 
Chemotherapy 	Multiple	New, more selective compounds and powerful but less toxic versions of older drugs are being added to the oncologist's arsenal. **Oral and wafer formulations** of injectable drugs have made the delivery of chemotherapy more convenient for patients. Enclosing cancer-killing toxins in a **protective lipid "envelope"** can increase their effectiveness while sparing normal tissues.	✔ In the past two years, the FDA has approved two dozen new chemotherapy agents
Monoclonal Antibodies	Non-Hodgkin's lymphoma, breast, colon, melanoma	Like **miniature guided missiles,** these biological constructs home in on specific proteins displayed on the surface of cancer cells. By blocking strategic sites, monoclonals can interfere with a tumor's ability to absorb growth factors from the bloodstream. They can also carry **radioactive and chemical toxins** that directly destroy malignant tissue.	✔ Rituxan won FDA approval last year; Bexxar and Herceptin could be on the market within a year
Radiation Therapies	Multiple: often prostate and solid tumors in internal organs; lymphomas	Radiation destroys cancerous cells but can damage healthy ones as well. Using **3-D computer images** and new delivery techniques like **radiation "seed" implants,** doctors can aim doses with microscopic precision, sparing healthy tissue.	✔ In use 
Surgical Procedures	Multiple	Doctors are always looking for ways to make this standard treatment more effective and less traumatic for the patient—for example, by removing part rather than all of a breast or preceding surgery with other treatments. One promising new technique is **lymphatic mapping,** in which surgeons use dyes and radioactive tracers to help them be more selective in removing nodes.	✔ Widely available; the newest procedures are performed at most large cancer centers
 **Vaccines**	Melanoma, breast, colon, ovarian, pancreatic and many others	Malignant growths have a deadly knack for skirting around the body's immune system. But scientists are finding that by vaccinating patients with **antigens derived from tumors,** they can sometimes goad white blood cells into attacking cancerous tissues.	Dozens of vaccines are being tested

WHO'S WHO IN ANGIOGENESIS



Dr. Folkman's approach is not the only one—or the most advanced

Drug	Who's Working on It	How It Works	Source	Status
Marimastat	British Biotechnology and the NCI; blocks the activity of enzymes	Needed to build tumor blood vessels; synthesized in the lab	Synthesized in the lab	Being tested in breast-cancer patients
SU5416	Sugen and UCLA	Prevents a tumor blood-vessel growth factor from binding to its receptor	Synthesized in the lab	Being tested for safety in patients
Neovastat	Aeterna Laboratories	Inhibits activity of enzyme involved in the growth of tumor blood-vessel cells	Derived from cartilage of spiny-dogfish sharks	Safety tested for lung, breast, prostate cancer
Combreta-statin	Oxigene	Destroys tumor blood-vessel cells	Originally derived from African bush willow	Human studies to begin this fall
THP-dox	University of Texas Southwestern and ILEX Oncology	Attaches to blood-vessel cells and delivers toxin to vessels and tumors	Synthesized in the lab	Still being studied in animals
Angiostatin and endostatin	Children's Hospital and EntreMed	Somehow blocks the growth of tumor blood vessels	Originally derived from mouse urine	First human trials expected within a year
Tamoxifen	Zeneca will evaluate	Mechanism unknown; may block growth of tumor blood vessels	Synthesized in the lab	New trials to block blood vessels may begin shortly
TNP-470	TAP Pharmaceuticals	Blocks enzyme that instructs tumor blood-vessel cells to divide	Originally derived from a fungus	Being tested in patients

THE BEST PREVENTION

Changes in life-style—chief among them quitting smoking—can remove risk factors that cause cancer in the first place. Other commonsense advice: exercise regularly, don't drink heavily, avoid overexposure to the sun, go light on fats, serve salmon instead of sirloin; and eat plenty of fruits and vegetables.

TIME chart by Lawrence Mondi, J. Madeleine Nash and Alice Park

CLOCKWISE FROM TOP: RICHARD ELLIS—SYGMA FOR TIME; JAMES KING-HOLMES/SPL—PHOTO RESEARCHERS; K. GLASER & ASSOCIATES—CUSTOM MEDICAL STOCK; NO CREDIT; A.B. JOYCE—PHOTO RESEARCHERS; RICHARD ELLIS—SYGMA FOR TIME; DAVID PARKER—PHOTO RESEARCHERS; A.P. CUSTOM MEDICAL STOCK

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

By CLAUDIA WALLIS

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 Cañada 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."

AMY ETRA FOR TIME

"I thought I was probably going to die, and I didn't want to die bald and throwing up."

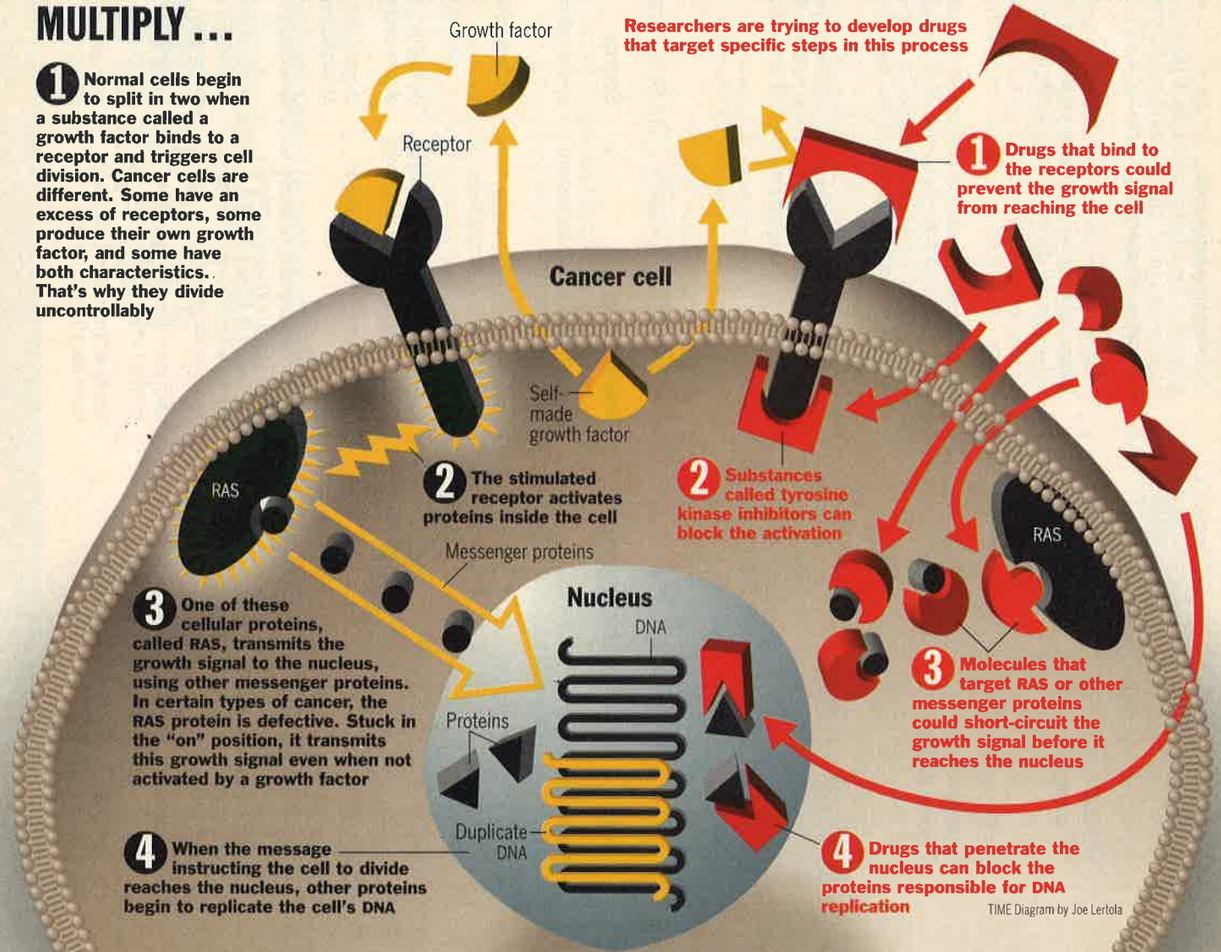
—BARBARA BRADFIELD, cancer survivor

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

KNOWING HOW CANCER CELLS MULTIPLY . . . . MAY LEAD TO NEW TREATMENTS



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*

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 service at **1-800-4-CANCER.**

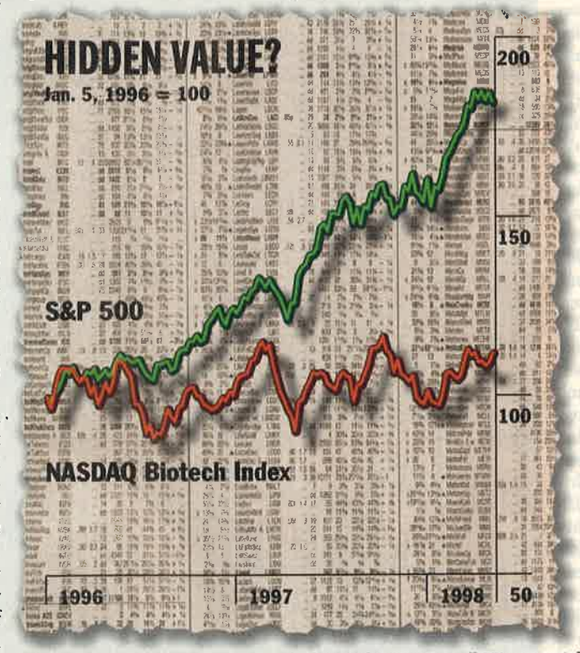
Daniel Kadlec

Why Biotech Stocks Are Cheap

EntreMed's "rally" points up the big risks, but now they may be worth taking

WHEN ALL IS SAID AND DONE, THERE MAY HAVE BEEN more losers than winners in last week's bizarre "rally" in the shares of the cancer-drug firm EntreMed. The stock began the week at $12 and ended at $33¼, a tidy 177% runup. But in the process, the company's 12 million shares outstanding changed hands an average of four times each—at prices up to $85. Sure, anyone who bought the stock more than a week ago received a windfall. But, in theory, there are three times as many people who got creamed. Cancer could well be eradicated before some of those latecomers get even with this stock.

The episode is typical of how individuals can get burned when they rush into a stock on a hunch, rumor, hope or partial information. With EntreMed, many placed buy orders for last Monday morning "at the market," with no inkling that the market price had swelled sevenfold without a posted trade. The pros knew. They saw the backlog of buy orders that had built up over the weekend.



Another information edge the pros enjoy is "real-time" stock quotes. You may not know it, but the NASDAQ quotes you get from CNBC, and quotes on most free Websites, are delayed 15 min. That delay can kill you when a stock is falling a point every 60 sec. And, let's be frank, a story in the New York *Times* or TIME can't take the place of in-depth analysis, although journalists can add valuable information.

The risks are especially acute in the complex world of biotechnology, where each of some 300 public companies, including EntreMed, claims to have one or more wonder drugs in research. Those claims make terrific investment pitches, and on the heels of a successful new drug launch—Pfizer's impotence pill, Viagra, in this case—investors can get, uh, excited. The reality, though, is that maybe 10% of today's biotech companies will ever bring a blockbuster drug to the market. Those that do will enrich shareholders. But casual investors face long odds trying to be in the right stocks.

That said, there are reasons to invest in the wonder-drug business. A potential huge payoff certainly is one. Last July, MedImmune's infant-pneumonia drug, Synagis, passed a significant clinical hurdle, and the stock shot from $15 to $55. More fundamentally, though, biotech stocks as a group have been woeful laggards for three years, and may represent the broadest base of value in today's sky-high stock market.

In the past, I've written about biotech investing with far more pessimism, mainly because of the risks, which haven't changed much. But some other things have changed, a lot. The overall market has roared ahead while biotech stocks barely budged, creating a vastly wider gap in value, and the biotech industry has had more time to mature. It will probably turn net profitable next year, and, notes money manager Stephen Flaks in Scottsdale, Ariz., "there are now hundreds of drugs that will be on the market within two years." Companies with such drugs are among Flaks' favorites: Matrix Pharmaceuticals (cancer), Neurocrine Biosciences (Alzheimer's) and Imclone Systems (cancer).

This new-product cycle has a number of pros bullish on the sector. Sensing opportunity, New York investor Stuart Wiesbrod founded Merlin Biomed, a private health-care fund, just three months ago. He estimates that the entire biotech industry has a stock-market value of about $110 billion. That's less than the market value of one big drug company like Merck or Pfizer, each with market values around $140 billion. Yet the biotech industry has 600 drugs in advanced development, vs. maybe 20 for each big drug company.

Biotech companies are notorious for moving ahead with tests too quickly. But, Weisbrod notes, "that still doesn't account for this huge discrepancy." His top picks, too, expect to have drugs approved within two years: Biochem Pharma (hepatitis) and Centocor (blood clots). Another fan of companies with late-stage drugs is Evan Sturza, editor of *Sturza's Medical Investment Letter*, whose top picks are Aviron (flu), Gilead Sciences (HIV, hepatitis) and Sepracor (side effects from Prozac, Claritin and others).

The safest approach to biotech is via mutual funds. Vanguard Health, Fidelity Select Health and Putnam Health Sciences have the best three-year returns, according to Lipper Analytical Services. But if you're playing with the speculative part of your portfolio, which is appropriate here, individual stocks pack the big thrill. Naturally, there's no telling if biotech stocks will break out of their slump anytime soon. But if you want to be there when they do, start nibbling now. ■

Daniel Kadlec can be reached at **kadlec@time.com**