Why Cancer Comes Back:
A controversial theory argues that stem cells lie at the heart of recurrence
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It's probably not an overstatement to say that everyone who's been diagnosed with cancer worries that it might one day return. But only some people have their cancer recur. The question is, why? Why do some cancers come back and others don't?

According to one theory, it's all about stem cells—not the ones being debated in Congress, but the so-called cancer stem cells. These unique cells, which got their name because they behave in ways that are similar to their healthy cousins, have the ability to produce new tumor cells. No one is certain where cancer stem cells come from or where they reside in tumors. But if even a few of these renegade cells are left behind during surgery to remove a tumor, they can cause cancer to recur.

The idea that stem cells might be responsible for initiating tumor growth has been around since the 1950s. But many researchers doubted that only a few cells were responsible for tumor growth, believing instead that each tumor cell had roughly the same ability to divide and produce more tumor cells. In fact, it wasn't till the last decade that the theory started to be taken seriously, in large measure because of experiments that provided evidence of cancer stem cells. As Philip Pizzo, M.D., dean of the Stanford Medical School, puts it, "There is good evidence that there may be cancer stem cells."

See How They Grow

Like their healthy counterparts, cancer stem cells appear to be able to make identical versions of themselves for many years. They also seem to be able to create other kinds of cells with a variety of shapes and functions. Just as important, though cancer stem cells stimulate cell growth initially, they become inactive once the tumor cells they've made begin reproducing. This quiet state makes them resistant to chemotherapy and other treatments, which are designed to kill rapidly dividing cells.

Because of their ability to reproduce themselves, cancer stem cells must be entirely removed to keep them from producing more tumors. "It's like trying to kill a dandelion in your backyard. You keep whacking the tops off the dandelion but it will still keep on growing," says John E. Dick, Ph.D., a stem cell biologist at the University of Toronto. "But if you can actually sever the root then you've eradicated the weed."

Finding the Roots

So far, scientists have had the greatest success in understanding the role of cancer stem cells in the blood disease leukemia. In a 1994 study published in Nature, Dick and his colleagues identified leukemia stem cells by their biomarkers (specific molecules that identify individual cells). They then tagged the biomarkers and used them to separate ordinary cancer cells from stem cells. When Dick and his team

transplanted the different cell groups into mice, they found that cancer stem cells gave rise to leukemia. These stem cells, Dr. Dick believes, are extremely rare, only about 1 in 250,000.

As in leukemia, cancer stem cells can initiate tumors in breast tissue, according to Michael F. Clarke, M.D., at the University of Michigan in Ann Arbor. He believes he has found a biomarker that can be used to separate human breast cancer stem cells from other tumor cells. In a study published in the April 1, 2003 issue of the Proceedings of the National Academy of Sciences, Clarke injected mice with several breast cancer cell samples, each having only one biomarker. While most of the breast cancer cells were unable to spur tumor growth, the cells in one sample did. They were the cells Clarke had identified as stem cells.

Because it's difficult to locate a small number of stem cells that may be embedded in a solid tumor like those found in breast cancer, researchers must continue to develop more effective methods to do this in order to study stem cells in isolation. If they are successful, it may be possible to design new drug therapies that target stem cells. "The hope," says Clarke, "is that we will be able to figure out a way to selectively kill or eliminate these cells."

The most fervent supporters of the cancer stem cell theory, including Dick, believe that such cells may be the root cause of every form of cancer. Other researchers aren't so sure. But for cancer patients the idea that stem cells may be the engine behind cancer helps to put a name and explanation to one of the most frightening aspects of cancer—the possibility that it will come back.—Caitlin E. Cox

Should Older Women Have Chemotherapy?

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Although nearly half of all breast cancers occur in women 65 and older, little is known about how women respond to chemotherapy as they age. This information gap is so extreme that oncologists have to follow their best instincts when deciding how to treat women in this group, often choosing to prescribe less chemotherapy than they would to younger women out of concern over the treatment's toxic effects. Research in the March 2, 2005, issue of JAMA, however, shows that reasonably healthy women between 65 and 70, and perhaps even later in life, can tolerate standard chemotherapy just as well as younger women.

The study combined four preexisting trials to look at nearly 6,500 women who had received adjuvant chemotherapy for lymph node–positive breast cancer. In all age groups, more rather than less chemotherapy decreased the risk of recurrence and death from breast cancer.

"We shouldn't decide not to offer chemo to older women who are really healthy and have a long life expectancy just because of their age," says Sharon Giordano, M.D., a

breast medical oncologist at the M.D. Anderson Cancer Center who is not connected to the study. She stresses that, in this case, "older" means ages 65 to 70, since only two percent of the study's participants were over 70.

The decision is less clear for women in the latter age group. "Some of my patients are very adamant that they want the most aggressive treatment possible," says Dr. Giordano. "And some say, 'Look, I'm 80 years old. I've had a good life. I don't want to go through chemotherapy. Even if my risk is higher, I don't want it.'"

According to Dr. Giordano, it is important to consider whether women have other health conditions, such as diabetes or heart disease, which might be worsened by chemotherapy.—Caitlin E. Cox

Sentinel Lymph Node Biopsy Comes of Age
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If you've just been diagnosed with a breast cancer more invasive than DCIS, your oncologist will check to see if the disease has spread to your lymph nodes. For years, this was done with a procedure called axillary dissection, but now there's a more recent technique—sentinel lymph node biopsy.

"Ten years ago, sentinel lymph node biopsy was considered highly experimental, with very few surgeons doing it," says Richard Bold, M.D., an associate professor of surgical oncology at the UC Davis Cancer Center. Now, he says, it has evolved into the standard of care at some medical centers.

Sentinel lymph node biopsy (SLNB) is far less invasive than axillary dissection. In the latter method, surgeons remove a section of fat from the armpit that contains around 10 to 15 lymph nodes. These nodes are then tested for cancer cells. The procedure leaves the nearby arm vulnerable to infection, muscle or nerve damage, as well as lymphedema.

SLNB is more precise. Radiologists inject either blue dye or a radioactive tracer (and sometimes both) near the tumor. These substances drain from the tumor site into the lymphatic system, following the same path that cancer cells would if they were spreading beyond the breast. Surgeons then remove only one to three lymph nodes, known as the "sentinel nodes," along that drainage path for testing. If those are cancer-free, nodes further down the path are likely to be cancer-free. If the test is positive, an axillary dissection is done.

Because SLNB is less invasive than dissection, it causes fewer side effects. According to England's ALMANAC trial, released at the 2004 San Antonio Breast Cancer Symposium, women who have SLNB experience fewer arm and shoulder problems than those who have axillary dissection. Despite its advantages, some oncologists don't think the test is as accurate as dissection, so SLNB may not be a

good choice for everyone, especially women with previous breast surgery, or those who have breast lumps in more than one area.

Finding A Surgeon
Make sure that your surgeon has experience with the SLNB procedure by asking the following questions:

* How many times have you done the procedure? Surgeons should go through a training period of at least 20 SLNBs, according to the American Society of Breast Surgeons.

* How often have you diagnosed a sentinel lymph node as cancer-free, but later found that cancer cells had spread to other lymph nodes? (This number is called the false negative rate.) The number should be five percent or lower.

* Did you learn the procedure along with the other doctors involved, such as the radiologist? Even if a surgeon is an expert at removing the node, several physicians work together to diagnose your cancer's stage. "Make sure that the whole team is on board," advises Dr. Bold.—Caitlin E. Cox