December 29, 2009
FORTY YEARS' WAR

Old Ideas Spur New Approaches in Cancer Fight

By GINA KOLATA

Mina Bissell will never forget the reception she got from a prominent scientist visiting Lawrence Berkeley National Laboratory, where she worked. She gave him a paper she had just published on the genesis of cancer.

“He took the paper and held it over the wastebasket and said, ‘What do you want me to do with it?’ Then he dropped it in.”

That was 20 years ago, and ever since, Dr. Bissell and a few others have struggled for acceptance of what seemed a radical idea: Gene mutations are part of the process of cancer, but mutations alone are not enough. Cancer involves an interaction between rogue cells and surrounding tissue.

The idea seemed messy and unduly complicated. And cancer genes seemed comparatively clear-cut. So it was often ignored or dismissed as researchers focused on genes and on isolated cancer cells growing in Petri dishes in laboratories.

Now, though, more and more researchers are plunging into those murky depths, studying tumors in their cellular environments. And, once they do, they say, they can explain many anomalies of cancer. The new focus on a cancer’s

surroundings, researchers say, is a major shift in thinking about why cancer occurs and how to stop it.

As yet, the research has not led to cures, and scientists expect the real fruits of their efforts — if they occur at all — will be years in the future.

But as the war on cancer drags on, nearly 40 years after it began, scientists say new directions are urgently needed. The death rate has barely budged for most cancers, and the gene mutation strategy has so far had a limited effect. That is probably because cancer cells have so many genetic abnormalities. If one mutated gene is attacked, others take over.

So some researchers are taking a fresh look at ideas that were dismissed as folklore — a blow to the breast might spur cancer, an infection might fuel cancer cells, a weak immune system might let cancer spread. They also say the new approach may help explain mysteries, like why the breast cancer rate plummeted when women stopped taking menopausal hormones. One answer may be that hormone therapy changes normal cells of the breast and may allow some tiny tumors to escape from the milk ducts where breast cancer starts.

The basic idea — still in the experimental stages — is that cancer cells cannot turn into a lethal tumor without the cooperation of other cells nearby. That may be why autopsies repeatedly find that most people who die of causes other

than cancer have at least some tiny tumors in their bodies that had gone unnoticed. According to current thinking, the tumors were kept in check, causing no harm.

It also may mean that cancers grow in part because normal cells surrounding them allowed them to escape. It also means that there might be a new way to think about treatment: cancer might be kept under control by preventing healthy cells around it from crumbling.

“Think of it as this kid in a bad neighborhood,” said Dr. Susan Love, a breast cancer surgeon and president of the Dr. Susan Love Research Foundation. “You can take the kid out of the neighborhood and put him in a different environment and he will behave totally differently.”

“It’s exciting,” Dr. Love added. “What it means, if all this environmental stuff is right, is that we should be able to reverse cancer without having to kill cells. This could open up a whole new way of thinking about cancer that would be much less assaultive.”

Some companies are taking note. Genentech, for example, is investigating the way some skin, ovarian, colon and brain cancers signal surrounding cells to promote cancer growth. The company has an experimental drug that it hopes might block this signaling.

Others are studying drugs like statins or anti-inflammatory drugs that may act by affecting signals between surrounding cells and cancers. But, says Dr. Robert Weinberg, a cancer

researcher at M.I.T., “this is not a clearly articulated scientific agenda, in large part because we still know too little about these signals and how their release is controlled.”

The researchers are cautious. They, more than anyone else, know the blind alleys of cancer research over the past few decades. And no one is suggesting that controlling a tumor’s environment will, by itself, cure cancer.

And they are not discounting cancer-causing genes. But even some who have made their careers studying cancer genes say a tumor’s environment can no longer be ignored.

“I am an unabashed cancer geneticist,” said Dr. Bert Vogelstein, director of the Ludwig Center for Cancer Genetics and Therapeutics at John Hopkins. “The genetic alterations in the cancer cells are the proximate cause of the malignancy.”

But, Dr. Vogelstein said, “one cannot fully understand that disease unless one understands” the tumor’s environment.

It can be a reciprocal interaction, especially as cancers grow and become more advanced. The surrounding cells might let cancers start, but once they do, cancers appear to change the surrounding cells to help fuel the cancers’ growth.

“This notion is not a flash in the pan that will come and go,” said Dr. Weinberg, who, in 1981, discovered the first human oncogene, a naturally occurring gene that, when mutated, can cause cancer.

And Dr. Bissell is now hailed as a hero, with an award named after her.

“You have created a paradigm shift,” the Federation of American Societies for Experimental Biology wrote in a letter announcing that she had won its 2008 Excellence in Science award.

Struggle for Acceptance

Dr. Barnett Kramer, associate director for disease prevention at the National Institutes of Health, recently discovered a paper that startled him. It was published in the medical journal The Lancet in 1962, about a decade before the war on cancer was announced by President Richard M. Nixon. In it, Dr. D. W. Smithers, then at Royal Marsden Hospital in London, argued that cancer was not a disease caused by a rogue cell that divides and multiplies until it destroys its host. Instead, he said, cancer may be a disorder of cellular organization.

“Cancer is no more a disease of cells than a traffic jam is a disease of cars,” Dr. Smithers wrote. “A lifetime of study of the internal-combustion engine would not help anyone understand our traffic problems.”

Dr. Kramer said: “I only wish I had read this paper early in my career. Here we are, 46 years later, still struggling with issues this author predicted we’d be struggling with.”

Others say the time was just not right for such ideas. They

know, they say, because they were excoriated when they advanced them.

Dr. Bissell said she had struggled for decades to find acceptance for her ideas.

She was not alone. In 1975, not long after Dr. Bissell started her work, another scientist published a hard-to-refute seminal experiment that seemed to indicate that cancer cells could become normal in the right environment.

The scientist, Beatrice Mintz of the Fox Chase Cancer Center in Philadelphia, inserted mouse cancer cells into early mouse embryos. The embryos grew into mice with cells from the cancer, a teratocarcinoma, and cells from the original embryo. The cancer cells had certainly been incorporated into the mouse embryo, but they were defanged, developing normally. Yet the same cancer cells will spread and kill an adult mouse if they are injected under the skin or into the abdomen.

“It was a sensational experiment,” Dr. Mintz said.

Dr. Bissell also thought the experiment was sensational. But she wanted to know why cells would become deadly tumors in one location and not another.

At the time, she was working with Rous sarcoma virus, or R.S.V., which causes fatal tumors in chickens when inserted into cells. Then, one of her postdoctoral fellows, Dr. David Dolberg, unearthed papers suggesting that the cancer virus

would behave differently in chicken embryos.

They injected the virus into embryos. The old papers were correct.

“That meant that if you put the virus in cells in an embryo, you don’t get cancer,” Dr. Bissell said. “And if you put it in a chicken, you do.”

Dr. Bissell and Dr. Dolberg’s paper — the one the visiting scientist dropped into a wastebasket, thinking it ridiculous and clearly wrong — was published in the journal Nature in 1984. The scientist was not the only one who scoffed, Dr. Bissell said.

She interprets the response to the sociology of science.

“The people who are successful become vested in their ideas,” Dr. Bissell said. “It becomes extraordinarily difficult for new ideas to find their way.”

But, to her, the R.S.V. experiments were a clarion call.

Sleeping Cells Awakened

Next, Dr. Bissell did an experiment that gave some credence to an old idea oft dismissed.

Over and over, doctors and patients tell stories of injuries that seemed to spur a cancer. A blow to the breast, an operation, and suddenly cancer takes off. It may mean nothing, just an effort to explain the seemingly inexplicable.

Yet some stories end up in publications. For example, says Dr. Michael Baum, emeritus professor of surgery at University College London, there is a report of eight men with advanced testicular cancer who had surgery to remove the tumors, followed by "a sudden and dramatic exacerbation of the disease." Animal studies find similar effects, Dr. Baum says.

And in breast cancer, he says, observations of women whose cancer accelerated after breast surgery as well as mathematical modeling indicates that surgery at the site of a dormant tumor can spur it to grow. In some unusual cases, chronic inflammation, as can happen with hepatitis B and C viruses, for example, is thought to lead to cancer. The current hypothesis is that chronic liver inflammation can disrupt the normal architecture of cells, allowing cancers that might have lain dormant to thrive.

Most likely, if wounding or inflammation has an effect, it happens only under unusual conditions and if tiny cancers are already present at the site of the wound.

That is what happened when Dr. Bissell did an experiment in chickens.

She knew that when she injected a chicken with R.S.V., the cancer-causing virus, the bird would develop a huge tumor at the site of the injection. But Dr. Bissell had injected the virus into the bird's blood. Why weren't there tumors everywhere?

She reasoned it through.

“What do we do when we inject?” Dr. Bissell asked. “Well, we make a wound. We injected the virus in one wing and got a huge tumor. What would happen if we injected the virus in one wing and wounded the other wing?”

She tried it. A huge tumor grew where she had injected the virus and another grew on the other wing where she had made the wound.

Researchers are not saying that infections or simple cuts or most cancer operations will cause cancer or make an existing cancer spread. Most likely, if there is an effect, it happens only if tiny cancers are already present at the site of the injury.

“Obviously it’s more than just surgery,” Dr. Love said. “The majority of people who have surgery don’t have a problem.”

But, she said, the findings tell her that if people have a choice of more or less invasive surgery — laparoscopy versus open surgery, for example — they might want to choose the less invasive.

“And I say this as a surgeon who likes to put her hands in and muck around,” Dr. Love added.

Dr. Kramer said that made sense, but added: “Would I avoid operations? No. I don’t think the evidence is good enough.”

A bigger risk than wounding, Dr. Bissell says, is simply aging, in which cell architecture crumbles, which is why

people get wrinkles, for example. And it may be why most cancer occurs in older people.

“I think that this is unfortunately a fundamental problem in cancer,” Dr. Bissell said. “Unfortunately, we haven’t discovered what to do about aging.”

One of the great mysteries about breast cancer is what to make of tiny tumors known as ductal carcinoma in situ, or D.C.I.S. They are so small they cannot be felt and so common they account for about a quarter of tumors found with mammograms. But, studies show, most stay in the milk ducts, where they originate, never spreading to the rest of the breast where they can become lethal.

The problem is that doctors cannot tell the dangerous D.C.I.S. tumors from the harmless ones, so they treat all such tumors as if they were dangerous.

Dr. Kornelia Polyak of Harvard Medical School, like many others, thought she could solve the problem. From the start, she thought, dangerous D.C.I.S. might have genes different from those of D.C.I.S. that remains harmlessly enclosed in milk ducts. Dangerous D.C.I.S. would look like invasive breast cancer cells and harmless D.C.I.S. would not.

But, she found, D.C.I.S. cells looked just like cells from aggressive breast cancers — gene expression patterns, mutations and cell maturation patterns were all the same.

“It’s just that one tumor is inside the duct, and the other is

outside the duct," Dr. Polyak said.

"That was surprising," she added. "Why is it D.C.I.S. if it looks like invasive cancer?"

She looked at cells surrounding D.C.I.S.

The first thing she noticed was that when D.C.I.S. broke free of a milk duct, the duct's outer layer had broken down. It could be that the duct falls apart because the cancer is bursting out. Or it could be that the cancer is escaping the duct because the outer layer disintegrated — which is what her research showed. As long as the milk duct is intact, D.C.I.S. cells cannot escape.

She also found that when breast tissue is injured, wound healing can destroy the crucial outer layer of ducts, allowing D.C.I.S. to escape. That is what happens in animals, and it is her hypothesis that it happens in humans.

It made her ask about biopsies. They are unavoidable, as she knows, because she recently had one herself. And they cannot be a huge factor in causing cancer or millions of women would be getting breast cancer at the site of their biopsies — and they are not.

Still, she worries. "Frankly, this has not been studied extensively," Dr. Polyak said. "People don't like to bring it up."

A Nudge Over Time

The dream of many cancer researchers is to find a way to prevent a cancer cell's environment from allowing it to grow. They could then prevent cancer.

And in one situation, they might have accidentally stumbled upon a possible method.

The discovery began with a surprise in 2003, when breast cancer rates in women 50 and older suddenly fell 15 percent, after the rates for all women had steadily risen since 1945. The pattern held in 2004.

The drop was traced to the release of a large federal study in 2002 that reported that Prempro, a hormone therapy for menopause that was supposed to keep women healthy and protect them from heart disease, actually made heart disease more likely and slightly increased the risk of breast cancer.

Sales plunged after the report was released, as millions of women stopped taking the drug.

But cancer is supposed to take years, even decades, to develop. How, some asked, could cancer rates drop so quickly?

Could it be possible that the hormone treatment somehow changed the environment of naturally occurring cancer cells and let them progress?

Dr. Karla Kerlikowske, professor of medicine, epidemiology and biostatistics at the University of California, San

Francisco, now believes that is a possibility. A combination of estrogen and progestin, like that in Prempro, may change the structure and activity of breast tissue, Dr. Kerlikowske finds, making breast tissue denser, a condition that has nothing to do with how breasts look or feel. Breast density is a cellular structure seen on mammograms and has long been associated with higher cancer risk.

Her hypothesis is that hormone therapy can give "that little bit of nudge over a long enough period to promote breast cancer," Dr. Kerlikowske said.

For some cancers destined to be aggressive, she suggests, it probably makes no difference if a woman takes hormones because the cancer will spread anyway. But she thinks that "for the average person, it becomes very important."

That, of course, makes it even harder to figure out cancer.

"If it was easy," Dr. Polyak said, "we would have done it already."