Is there ever going to be a meaningful defense against the scourge of breast cancer? Over the past 10 years, a host of innovations and insights have been hailed as The Answer: mammography, tamoxifen, chemotherapy, estrogen, low-fat diets. Yet during that same period, breast cancer rates have been steadily climbing. There were about 100,000 new cases diagnosed in 1985; last year that number was 180,000. Is it any wonder that women are skeptical that there will ever be a cure?

A group of geneticists, epidemiologists and molecular biologists have come to share the public's frustration with the lack of progress in breast cancer prevention, detection and treatment. These researchers have taken an audacious approach to the disease that appears to be on the verge of a spectacular payoff. With the aid of powerful new technologies, they have reached inside the unimaginably tiny cells of the human body to probe the very genes where, at the most fundamental level, the real action of breast cancer takes place. "All those studies about estrogen and other things are important but they don't go deep enough," says Anne Bowcock, Ph.D., a molecular geneticist at the University of Texas Southwestern Medical Center. "We're finally getting down to the root cause."

Gene hunters warn that breast cancer is a complicated disease and that it is important not to oversimplify.

Already, such genetic research has delivered stunning revelations about diseases as diverse as cystic fibrosis, sickle-cell anemia, retinoblastoma, Huntington's disease and colon cancer. Scientists are very close to a truly major breakthrough that will revolutionize our understanding of breast cancer and produce at least one practical benefit: a test to reveal an individual woman's exact risk of getting the disease. With this test, a 20-year-old woman might find out that it is a virtual certainty that she will contract the disease by age 40; another 35-year-old might learn she has only a 5 percent chance of developing the cancer by age 80.

The ramifications of being able to look into a crystal ball and foretell your fate are enormous, not just for individual women, but also for medicine and society. "It won't happen today, and it won't happen tomorrow," says Stephen H. Friend, M.D., a cancer researcher at Massachusetts General Hospital and Children's Hospital in Boston, "but a breast cancer test will eventually be available, and when it is, it's a whole new ball game."

The key to the mystery of breast cancer lies in a single reclusive gene, dubbed BRCA1, that researchers at the University of California at Berkeley have tracked to a short stretch of the long arm of chromosome 17, one of the 23 pairs of X-shaped bundles of DNA that all humans receive as part of their genetic inheritance. In what James Watson, Ph.D., the legendary codiscoverer of the structure of DNA, calls "the most exciting story in medical science," teams of scientists from around the world are engaged in a frantic high-stakes race to find BRCA1's exact location. In the conventional analogy, if a human cell were the planet Earth, and a single chromosome a nation the size of the United States, then scientists have tracked the gene to the equivalent of Chicago. It is now a matter of going house-to-house to find BRCA1's exact street address.

Even without actually locating the gene, however, scientists are already confident of its broad characteristics—and its implications for women. Most important, BRCA1 seems to be a tumor *suppressor* gene, whose function, as the name suggests, is to keep cancers from forming. As such, it is the opposite of the better-known oncogene, which *promotes* the development of cancer. This discovery alone is a major breakthrough, for it means that the fundamental cause of breast cancer lies within the cells of a woman's body. It does *not* lie in her diet, in her hormones, in any environmental toxins or in any of the many other explanations that have been proposed with such fanfare over the years. At best, such extracellular influences are only bit players in the drama of breast cancer, able to nudge the plot along but powerless to affect its essential shape. If they were all eradicated, the disease would still exist. In breast cancer, the evidence now suggests, a woman's genes hold her fate.

What happens to the BRCA1 gene to make it so lethal? There are two possible occurrences: Either it is defective from birth or it deteriorates later in life, probably due to an accident in cell division. It's the second possibility that can be affected by environmental events, but it should be remembered that these kinds of random changes in the genetic structure are also natural. They are the raw material of evolution, and as such would occur regardless of outside influences.

Everyone has two copies of all their genes, and in the case of BRCA1, both copies must be ruined before the cancer-suppressing function shuts down. (That is one difference between tumor suppressors and oncogenes—only one copy of the oncogene needs to be activated to spur on a cancer, whereas both copies of tumor suppressors have to be deactivated to start a cancer going.) Women whose breast cancers are inherited most likely are born with a defective version of BRCA1 in one of their two copies of chromosome 17. Their cancers develop when the other, good, copy is damaged during their lifetimes. These inherited cancers (that is, those in

(continued)

STEVE WILLIAMS

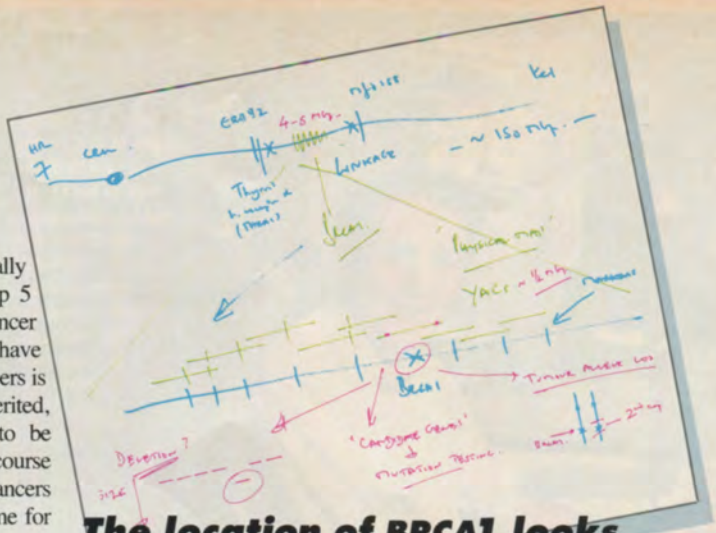
Dr. Bruce A. J. Ponder is one of the sleuths in search of the elusive BRCA1. He and his colleagues, Dr. Charis Eng (near right) and Dr. Mike Jackson, are conducting their research at Cambridge University.

solving the breast cancer mystery

Scientists are closing in on the gene for breast cancer. It's not a cure, but it's as close as we've ever come. By JOHN SEDGWICK

women who have a family history of the disease) generally strike before the woman is 45 years old and make up 5 percent to 10 percent of the total population of breast cancer victims. It is these kinds of cancers that geneticists have focused on because the genetic link among family members is so apparent. Women whose breast cancers are not inherited, by contrast, would require both copies of BRCA1 to be knocked out by separate, independent accidents in the course of their lives, and that may explain why noninherited cancers usually afflict older women. It simply requires more time for two separate accidents to occur.

BRCA1, then, plays a critical role in cases of inherited breast cancer. But, because it helps explain the mechanism by which cancers get started, it is also important for the remaining uninherited cases as well. That's why so many scientists are engaged in such a wild scramble to find it. "BRCA1 may not be the only gene," says Dr. Friend, "but its discovery will certainly make the biggest splash."



The location of BRCA1 looks straightforward enough when Dr. Ponder sketches it out. X marks the spot, but where's the spot?

How do I think of the search for BRCA1?" asks professor Bruce A. J. Ponder, M.D., Ph.D., a geneticist at Cambridge University who is one of the more prominent gene hunters in the chase. "I think of it as a helluva big fishing expedition." A slender, soft-spoken man with kind eyes, Dr. Ponder, 49, has a scholar's demeanor and a relaxed bearing that is unusual in the highly competitive world of "gene jocks." He began his medical career as an internist with the British National Health Service but switched to genetic research 10 years ago when he realized how little conventional medicine had to offer cancer patients. "The science behind the various drug treatments was lousy," he says, "so I decided to get into genetics because I thought it would at least provide a rational underpinning for treatment." By the time a patient's cancer has been diagnosed, the disease is too fully entrenched to be attacked by any but the most extreme methods. Ponder was determined to put potential treatments on a firmer footing by discovering the fundamental genetic contribution to the disease.

But how? The most sensible way to zero in on any cancer gene is to find cases where the cancers seem to cluster in families. Ponder's search for BRCA1, then, is proceeding in two directions—down into the mysteries of the cell and out into the world to collect patients with inherited breast cancer. Finding the patients is, in some ways, the task most critical to the entire enterprise, since the genetic analysis is only as good as the genes running through it.

The most efficient strategy is to find very large families in which there is a lot of breast cancer. To understand why that is so, picture each family member's genetic makeup as millions of dots scattered across a sheet of clear plastic. As you begin to lay all the sheets on top of each other, any dots that are exactly in the same place will become evident. The more sheets you have stacked up, the more likely you are to find the one common element among all the dots—namely the gene that causes breast cancer.

Once the scientists have put together a sample of patients they know are carrying the gene, they are still left with the task of distinguishing that gene from the trillions of other genes in the human cell, the vast majority of which are (as of now) also indistinguishable. There are a few genes whose locations and characteristics we know, and these serve as guideposts, or markers, to help investigators find their way through the seemingly endless strands of DNA in the chromosomes. Some of the more salient of these markers account for such familiar physical variations as eye and hair color. Because investigators know that, in most cases, two genes that lie close together on a chromosome are almost invariably going to stick together when the genes pass from parent to offspring, they try to find markers that consistently show up in their samples of breast cancer patients. Eventually, the relevant markers will move closer and closer together, which means they are very close, perhaps right next door, to BRCA1, and those that are farther away will fail to show up in some breast cancer patients because they don't get passed on with BRCA1.

By exhaustive analysis of the hundred or so subjects in his sample, Ponder has been able to narrow his search to a stretch of the chromosome that includes about a dozen of these markers. All of the patients in his sample have all of the markers, which means that BRCA1 is probably somewhere among them. Unfortunately, none have fewer—or he would be able to home in on the cancer gene all the more tightly. That leaves him with a sequence of more than *5 million* base pairs of genes—a million miles by genetic standards. Other researchers may have gotten closer, depending on the genetic assortment of the breast cancer patients they started with. "This part of it is absolutely dependent on the size of the families you have [in your sample]," Ponder says. "And on luck."

Ponder thought that he had gotten a break last year when he chanced upon a seven-year-old copy of an obscure French medical journal and read about a case of breast cancer that happened to be linked to a rare inherited skin disorder whose gene, Ponder knew, lay "smack in the middle of this region" of chromosome 17. Could this be a marker that would lead him directly to BRCA1? The possibility thrilled him. "That's the sort of thing that sustains us in what is rather a slog," he says. "It makes you think you are going about the task intelligently, that you are going to arrive at a solution by force of reason and not simply by elbow power." With the aid of a French colleague, Ponder succeeded in tracking down the family in a small town in coastal Brittany, and he persuaded a family member to give a blood sample, something that is not always forthcoming. Unfortunately, the laboratory results have failed to yield anything useful so far.

So to find the gene, Ponder's lab has had to use a normal version of chromosome 17 and compare each bit of that million-mile stretch to samples of the same stretch from the breast cancer families. This is an enormously time-consuming process, yet one that could bring success at any moment. "It's not a race in the usual sense of the word," explains Friend. "It's more like hunting for a certain piece of mail hidden in a box at the post office. Once you find it, you're done. And you could find it at any time."

Perhaps the most important consequence of the search for BRCA1 is a broader understanding of what can—and cannot—be done about cancer.

It is tempting to focus on BRCA1 as if it alone holds the key to the mystery of breast cancer. The most captivating mysteries, after all, involve a hunt for a single elusive prize, the Maltese Falcon, say, or the Third Man. While that makes for a more satisfying drama, it is, alas, not true for breast cancer, and it is important not to oversimplify. Breast cancer is a complicated disease and, in the words of Ray White, Ph.D., a gene hunter at the Howard Hughes Medical Institute at the University of Utah, it is a "mortal certainty" that other genes are involved besides BRCA1. Ponder himself, drawing on the mathematical analysis of his colleague Douglas F. Easton, Ph.D., believes that only 40 percent of inherited breast cancers can be attributed directly to BRCA1 and that the remaining 60 percent involve a delicate interplay of BRCA1 and still other genes, which Ponder calls BRCA2, BRCA3 and so on, conceivably up to BRCA6 or even 7. "As to where the other breast cancer genes are," he says with a shrug, "who knows?"

They won't be easy to find either. One reason that researchers have zeroed in so keenly on BRCA1 is that its effects are the strongest. Genes with weaker effects are, like small distant planets, much harder to spot. Further blurring the picture, researchers are already aware of another group of genes that are involved in some fashion, but because none of them produce breast cancer exclusively, they aren't thought to be part of the BRCA series. P53, for instance, is a gene on chromosome 17 with tumor suppressor qualities like those of BRCA1; its absence or malfunction gives rise to lung and ovarian tumors, in addition to those in the breast. P53 could, therefore, be called a breast cancer gene. Another one is the gene for a degenerative disease called ataxia telangiectasia, or AT, which promotes breast cancer as well. To muddle things still further, even BRCA1 is, quite likely, responsible for other diseases besides breast cancer. It is already strongly implicated in combined breast and ovarian cancers and, according to Dr. White, it may well be involved in prostate cancer.

Even if all the genes could be found, understanding how they interact would still be no simple matter. Ponder suspects that, even in the cases where BRCA1 is largely responsible, the cancer will turn out to involve the complex interaction of a number of genetic factors, rather like the way that a nose is formed, and that the exact process is not going to be easy to disentangle. "One tends to think of the signaling pathways that control the growth of cells as being some sort of linear sequence, that A tells B to do this, which tells C and so on, so that if you crank up A, the signal goes all the way down the line," he says. "But I tend to suspect that it is a very intricate, crisscrossing network, so that if you perturb something over there, all sorts of things adjust in all sorts of ways across the system, and the response you get way over here bears only the most tenuous relation to the impulse you put in over there."

Until the mechanism is understood, it will not be clear how medical science might intervene to prevent a cancer or to stop one from progressing. Hard as it is to identify the genes, it can be just as hard, or harder, to put that knowledge to use. Although geneticists have now found genes for more than a dozen diseases, they have come up with few treatments based on their discoveries. It may be that it will prove especially difficult to reverse defects in a tumor suppressor like BRCA1. Marc E. Lippman, M.D., a cancer researcher at Georgetown University, argues that it would be much easier if BRCA1 were an oncogene. "You can think of many more ways to turn something *off* than to turn something *on*," he says.

Right now, the most practical genetic work involves the

(continued on page 200)

MYSTERY

(continued from page 169)

oncogene HER-2/*neu* at the Revlon/UCLA Women's Cancer Research Program. HER-2/*neu* is overproduced after tumors are formed and encourages their growth, much as gasoline feeds a fire. For now, HER-2/*neu* is only good for gauging the ferocity of the disease, and thus in helping decide on the intensity and, ultimately, the efficacy of treatment. But it is entirely possible that scientists will soon figure out how to disarm it, which would mean that the growth of tumors could be slowed dramatically.

When BRCA1 is located, its most immediate use will be in identifying women who have an inherited predisposition to breast cancer; later on, it could be used as a screen, much as mammography is today, to tell women if either copy of their BRCA1 gene is defective and, therefore, puts them at greater risk of developing the disease. Later still, the genetics might serve as a basis for what Mary-Claire King, Ph.D., a pioneering breast cancer geneticist at the University of California at Berkeley, terms "molecular mammography," a kind of early-detection system that could possibly spot a tumor when it is still the size of a few atoms. Such perspicacity could work wonders in targeting treatments and in limiting the ravages of the disease.

For the near term, however, researchers can picture doctors providing predictive genetic screening as commonly as they now perform Pap tests. Yet that will place medical science in a terrible dilemma, as it will enable doctors to tell who will get the disease but not how to help them do anything about it—short of removing their patients' breasts entirely in prophylactic mastectomies, hardly a satisfactory treatment given that the disease may not actually strike for many years. "Genetics is opening up a terrible gap between diagnostics and therapeutics," says Robert Cook-Deegan, M.D., a policy analyst who is a member of the Human Genome Project's working group on the ethical, legal and social implications of genome research. "And there is going to be a very painful interlude until the therapeutics catches up."

For now, there is at least one clear benefit from such a test: It will dispel the anxieties of women born into breast cancer families who have seen their mothers, sisters or cousins die of the disease and fear they will be next. Although the test will not be ready for the general public for some time after the BRCA1 gene is found (and researchers caution that its development may take years), a type of test is already available for some breast cancer families who share one of the marker genes that are known to be linked to BRCA1. Francis Collins, M.D., Ph.D., director of the National Center for Human Genome Research at the National Institutes of Health, set up such a program in 1992 at the University of Michigan. One of his first patients was a 32-year-old housewife identified only as Susan M. Terrified of the breast cancer that had swept through her immediate family, she had gone so far as to schedule prophylactic surgery on both breasts when Dr. Collins' team informed her that, based on the blood sample she had provided, she did not carry the gene. Susan M. burst into tears at the news, relieved not only for herself but also for her infant daughter. Since she didn't have the gene, there was no chance she had passed it on to her child. When word of her results got out to her family, others wanted to find out, too, and for some, inevitably, even the good news was bittersweet. In one case, a cousin who had had her breasts amputated five years earlier discovered that she did not carry the breast cancer gene either.

Perhaps the most important consequence of the search for BRCA1 is a broader understanding of what can—and cannot—be done about cancer. For years we have spoken of a "cure," as though cancer was an infection that might clear up with an antibiotic. Although there is some hope for intervention that will limit cellular damage after it starts, nothing is being contemplated that would actually undo cancer in the manner of a conventional cure. The real cure is prevention. If the problem lies in our genes, then the solution lies in them as well—most likely through a preemptive strike in the form of gene therapy.

While its common use is still many years away, gene therapy made its debut last spring when three newborn babies were treated with altered genes to ward off the onset of Severe Combined Immunodeficiency—the hereditary immune disease known widely as the condition that afflicts "bubble boys." Such a therapy for breast cancer would be far more complicated. Among other problems, it would have to be delivered perfectly to every last cell in the breast, and it would have to be completely safe before it was tried because the patients would be in good health when they were treated. But a piece of luck might still turn up, as it has in cystic fibrosis, where researchers discovered that gene therapy would have to be delivered to only one cell out of 50 and the beneficial effects would automatically spread.

Despite these difficulties, Ponder remains optimistic that genetics will lead to new therapies, or he would have bailed out of the gene hunt years ago. "I would be rash to say that gene therapy can never happen," he says. He looks around the lab at all his technicians and their remarkable technology. "After all, things are happening now that I wouldn't have dreamed of when I started."