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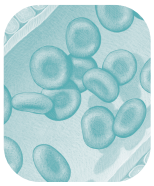

REPORT TO PHYSICIANS
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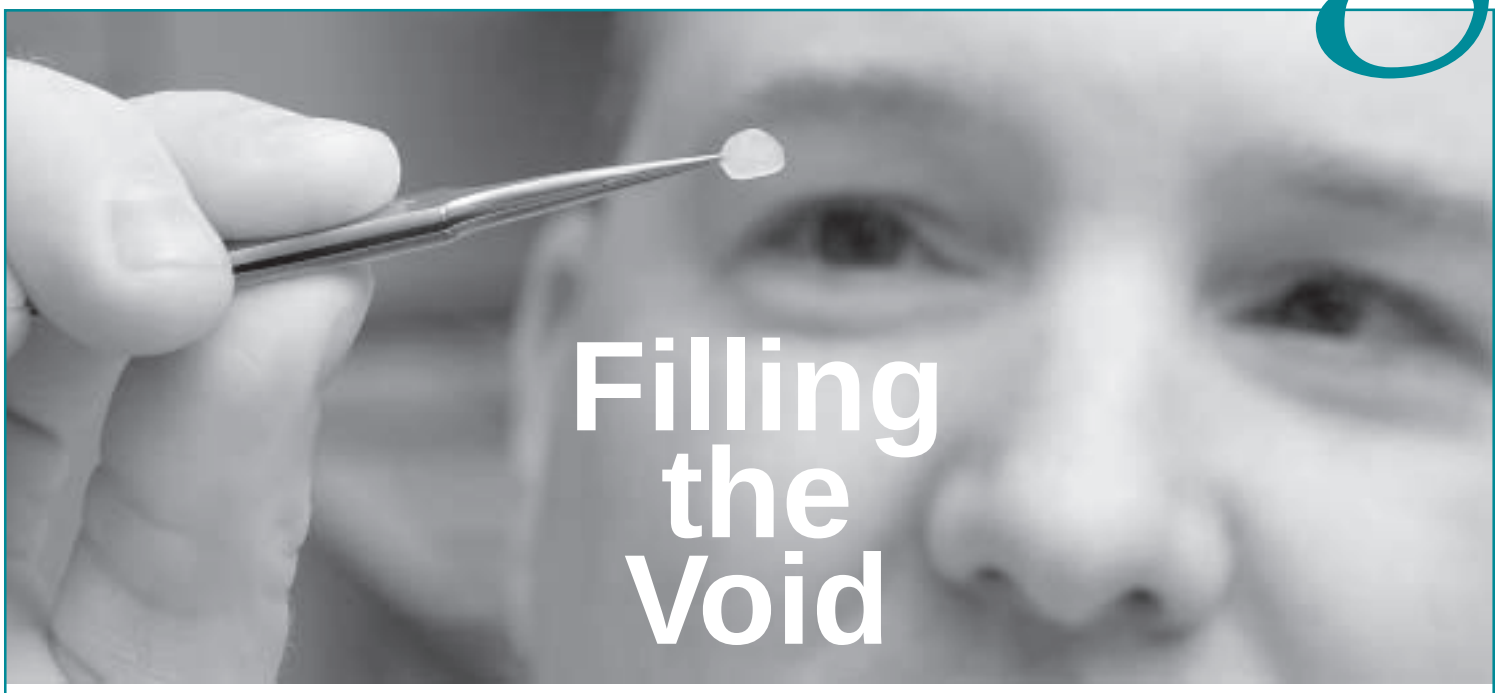

Filling the Void

Advances in tissue regeneration may soon mean new options for repairing postsurgical contour deformities, especially in the head, neck, and breast.

by Dawn Chalaire

Women who undergo surgery for breast cancer may soon have an alternative to reconstruction techniques that use artificial implants or autologous tissue transplants. It has been a long and difficult process—and much work remains to be done—but researchers are on the verge of engineering patient-specific breast tissue that can be grown ex vivo to a size and shape that precisely fits the deficit created by surgery.

"Our long-term goal is to apply tissue engineering to breast cancer rehabilitation and allow the patients to regrow their own breast tissue instead of having to take donor tissue from somewhere else in their body to reconstruct their breast. This would be a lot better from a tissue standpoint as well as better emotionally and psychologically for patients," said Charles W. Patrick, Jr., Ph.D., an associate professor in the Department of Plastic Surgery at The University of Texas M. D. Anderson Cancer Center and director of the department's Laboratory of Reparative Biology and Bioengineering.

Synthetic, natural, and hybrid hydrogels are being studied as scaffolds upon which preadipocytes—the precur-

(Continued on **next page***)*

It's not science fiction: **Dr. Charles Patrick, Jr.**, *and colleagues are growing patient-specific tissue in the laboratory to use in postsurgical reconstruction. Dr. Patrick holds up a hydrogel with a pair of tweezers.*

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Filling the Void

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sors of fat, or adipose, cells—can be cultured with human microvascular endothelial cells to form tissue similar to human breast tissue. The potential exists for breast tissue to be regenerated in vitro on a scaffold and then implanted into the patient.

Breast size and shape are different for every woman, so these breast tissue constructs must be designed individually. Dr. Patrick and his colleagues, Michael J. Miller, M.D., a professor in the Department of Plastic Surgery at M. D. Anderson, Mandri Obeyesekere, Ph.D., an associate professor in the Department of Biostatistics and Applied Mathematics at M. D. Anderson, and Mary F. Wheeler, Ph.D., director of the Center for Subsurface Modeling at The University of Texas at Austin, are developing mathematical models that take into account patient information such as age, ethnicity, and hormonal status and combining them with biomechanical and three-dimensional imaging data to create patient-specific virtual reality models of the breast.

Using three-dimensional measurements of the surface of the patient's breast, the model should be able to predict the exact shape and volume of a tissue construct needed to achieve the desired appearance. It could also show what the breast will look like after aging. "And it would help with patient education because we would be able to show a patient what her breast would look like after different surgery and reconstruction options," Dr. Miller said. The researchers have begun collecting data from patients to test a first-generation version of the model, which they estimate to be two to three years away from a clinical study.

ALTHOUGH GROWING BREAST TISSUE in a laboratory sounds a bit like science fiction, it is the result of a series of incremental steps in the science of tissue engineering. According to Geoffrey L. Robb, M.D., professor and chair of the Department of Plastic Surgery, the evolution of tissue engineering at M. D. Anderson has been "purposely and innovatively facilitated by our already strong foundation in advanced microvascular reconstructive techniques. These plastic surgery techniques," Dr. Robb continued, "have already immensely benefited cancer patients in their rehabilitation, recovery, and especially, their overall quality of life."

Researchers have been trying for years to develop a good method of repairing the soft tissue deficits that result from oncologic surgery, particularly in the head and neck and breast. These contour deformities, as they are sometimes called, are typically caused by the removal or scarring of the dermis and adipose tissue. Early attempts to replace soft tissue volume involved the use of waxes or oils, which were both ineffective and dangerous to the patient. More recently, substances such as reconstituted bovine collagen, silicone, gelatin powder, Teflon paste, and autologous collagen have been used to replace soft tissue, with mostly disappointing results.

For years, autologous fat transplants seemed like the perfect solution to soft tissue deficits. Autologous materials are biocompatible and do not cause allergic reactions or lead to tissue rejection. Unlike some types of tissue, adipose tissue can be harvested easily from many different parts of the body, and most people have enough excess fat that harvesting will not cause contour deformities at the harvest site. Autologous fat transplantation has not lived up to its potential, however. In studies, about half of the transplanted graft volume is reabsorbed by the body, probably because of inadequate vascularization. Regenerative tissues need a blood supply to remain alive and to control and maintain tissue growth.

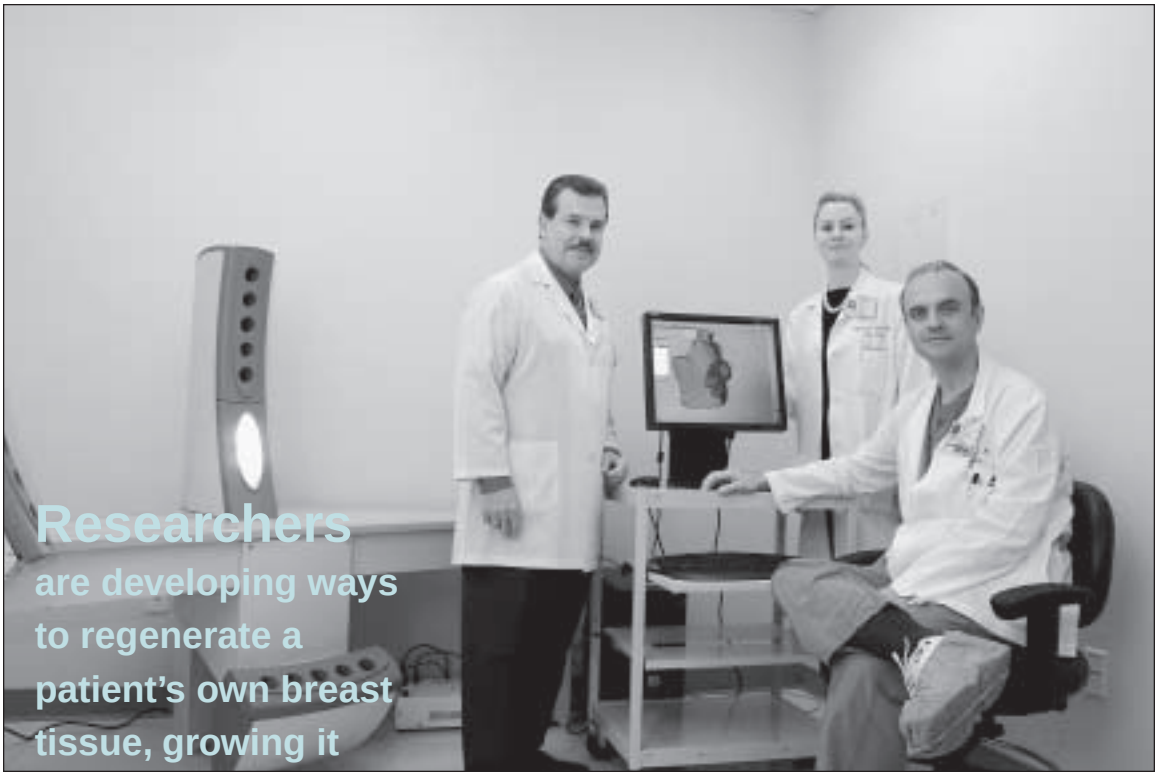
"What we do is kind of counterintuitive to cancer care, where you're normally trying to stop blood vessel growth," Dr. Patrick said. "We actually want them to grow, but in a controlled manner, with no systemic effect.

"You would think that we understood everything about blood vessels by now and about angiogenesis, but we don't—especially when trying to grow new tissue. You can't translate the information from wound healing and tumor environment to the regenerative environment. Different cells are involved, the extracellular environment is different, and the temporal genetics are different."

In addition to requiring a good deal of vascular support, mature adipose tissue cannot be grown in culture, and although the size of cells can change, their number remains constant. In contrast, preadipocytes proliferate freely, can be grown easily in culture, and can be expanded ex vivo. It is also possible to isolate preadipocyte cells from enzyme-digested adipose tissue or liposuction aspirates, and whereas mature adipose tissue is often damaged during aspiration, preadipocytes are able to maintain their cellular integrity during the process. In addition, adipose-derived stem cells could potentially be used to develop cultures of preadipocytes.

WHETHER USING PREADIPOCYTES or other types of cells, creating an engineered adipose tissue construct requires three essential components: adipose cells grown in a controlled environment, a three-dimensional scaffold to support and shape the formation of tissue, and a suitable microenvironment that includes an adequate blood supply.

In acellular tissue engineering, a tissue construct is implanted into the patient and either remains acellular or recruits host cells. The reconstituted basement membrane of a mouse tumor, or Matrigel, supplemented with basic fibroblast growth factor can induce the migration, proliferation, and differentiation of preadipocytes in vivo. Elisabeth K. Beahm, M.D., an associate professor in the Department of Plastic Surgery, and her colleagues have been studying the use of a vascular pedicle construct for adipose tissue engineering. In a recent study, silicone molds were sutured to the superficial inferior epigastric blood vessels of athymic nude mice. The molds were then filled with polyethylene glycol (PEG) fibers, and Matrigel and basic fibroblast growth factor were injected into the fibers, causing de



Researchers are developing ways to regenerate a patient's own breast tissue, growing it in the laboratory to the precise size and shape needed, then implanting it into the patient.

Dr. Geoffrey Robb *(left)*, **Dr. Elisabeth Beahm**, *and* **Dr. Michael Miller**, *in the Department of Plastic Surgery's Digital Simulation Laboratory, work with the 3D Torso System (background), a device that captures a three-dimensional computer image of the patient for use in planning surgery and assessing outcomes in cancer treatment.*

novo adipogenesis. Dr. Beahm and her colleagues next plan to study this technique in a large animal model.

Cellular tissue constructs are grown ex vivo in a bioreactor microenvironment and then implanted into the patient, as in the breast cancer model mentioned earlier, or they are implanted first, with the patient serving as a bioreactor. Preadipocytes can be seeded onto a scaffold, where they will proliferate and differentiate into adipose tissue. Several different types of tissue engineering scaffolds have been studied for adipose tissue growth, but hydrogels are thought to be the most promising. Hydrogels are three-dimensional viscoelastic structures that contain mostly water. They are sometimes used for controlled drug release or tissue augmentation but can be "decorated" with bioactive peptides that mimic cell adhesion to the extracellular matrix. They can also be designed to be degraded by enzymes released from the cell.

Dr. Patrick and colleagues have developed an injectable, biodegradable polymer that can be seeded with stem cells or precursor cells and injected into a subcutaneous soft tissue deficit in the face or breast. The polymer is a liquid when injected, but exposure to ultraviolet light causes it to change to a hydrogel in a matter of seconds. With time, the cells proliferate and form new tissue at the same rate that the polymer degrades, restoring the subcutaneous contour with the patient's own adipose tissue. This strategy should eventually be clinically useful for small-volume defects.

"For some applications that we want to translate into the clinic, we're not talking about regrowing a whole new breast. If there is a large dimple or divet caused by tumor resection, we want to restore that contour," Dr. Patrick said. "In addition to small tissue augmentation, it could be useful for repairing the breast following a lumpectomy."

In preliminary studies, the hydrogel system supported the viability of cells and allowed them to proliferate. The next step is to test the system in a small animal model.

Additional strategies for soft tissue augmentation include (1) implanting a thin, flexible fabric or felt made of biodegradable polymer that has been seeded with preadipocytes harvested from the patient using liposuction or fat biopsy and expanded ex vivo and (2) injecting biodegradable polymer microspheres filled with adipogenic and/or angiogenic factors and coated with preadipocytes.

MAINTAINING ENGINEERED TISSUE over the long term is a major area of concern for tissue engineering researchers worldwide. The effects of age, menopausal status, radiation therapy, and chemotherapy on engineered adipose tissue are not known. What is known is that engineered fat must be reliable, biocompatible, and able to maintain its shape over time. Most important, adipose tissue constructs must have an adequate blood supply. Vascular support for the tissue construct is probably the most critical factor limiting the size, maintenance, and quality of engineered constructs.

"Many tissue engineering applica-

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Patient-specific virtual reality models of the breast should be able to predict the exact shape and volume of tissue needed to achieve the desired appearance.

tions work well short term and in small-animal models," Dr. Patrick said. "The challenge is to get it to work well in humans or a large-animal model, where you have clinical-size defects, over a long period of time. This is largely a blood supply issue. We need to enhance the growth of blood vessels at the same time we grow the tissue to achieve long-term stability.

"One of the things we and a lot of other people are working on is understanding what controls blood vessel persistence. We can create large amounts of capillary networks … but for some reason, they tend to regress and go away after a short time. So we're obviously missing some cellular or molecular cue that tells them 'I need that network to stay there.' Whoever can solve that problem first will open up tissue engineering tremendously to other clinical applications."

According to Dr. Patrick, who has the distinction of being the first engineer in the nation to work in a plastic surgery department, it takes the collaborative efforts of life scientists, bioengineers, and physician-scientists to make advancements in the challenging field of tissue engineering.

"I came to M. D. Anderson to work on the frontline with the clinical faculty on developing clinically translatable tissue engineering strategies. I really wanted to apply my engineering fundamentals to help patients, and this is one great way to do it." ●

For more information, *contact Dr. Charles Patrick at (713) 563-7567.*

IN BRIEF

Unexpected Benefits: Treating HER-2 Breast Cancer With New Preoperative Drug Combination

A new use of the drug Herceptin appears to offer a much more powerful treatment advantage than expected for patients with HER-2-positive breast cancer, say researchers at The University of Texas M. D. Anderson Cancer Center.

When combined with chemotherapy and used before surgery in early-stage breast cancer, the drug proved so beneficial—eliminating 42% more tumors than chemotherapy alone—that the clinical trial testing of this new treatment plan was halted early, researchers reported.

"This is a far better result than we had anticipated and seems to suggest that simultaneous use of chemotherapy and Herceptin offers a much more potent treatment than use of these drugs sequentially or alone," says lead investigator Aman Buzdar, M.D., professor in the Department of Breast Medical Oncology at M. D. Anderson. "This is the best treatment result we have seen in this patient population. It shows that we can potentially change the natural history of a disease that is associated with a high risk of recurrence and death."

Researchers also found that it did not matter whether the patients' tumors were estrogen-receptor positive or negative—a distinction that usually demarcates which patients will respond to hormonal therapy. And, to date, serious heart problems have not been observed in the patients.

Buzdar cautions, however, that although this combination of therapies seems to show better efficacy, as well as less risk of heart damage, than has been seen before with Herceptin treatment, "the jury is still out on the long-term safety and outcome. As in all such studies, we will need to wait years to follow the progress of our patient participants," Buzdar said.

Study Shows Long-Term Decrease in Risks of Radiation Treatment

The risk of ischemic heart disease and, ultimately, cardiac death following radiation treatment for breast cancer has steadily declined over the last quarter century. That was the conclusion of researchers at M. D. Anderson Cancer Center based on results of a new study, the largest and most comprehensive prospective study of its kind.

The study offers scientific evidence of what was long thought to be true but never proven: that improvements in radiation techniques and delivery have greatly impacted radiation-associated cardiac mortality.

"Before now, there were no studies that looked at the effects of radiation to the heart over time," says Sharon Giordano, M.D., the study's lead author and an assistant professor in M. D. Anderson's Department of Breast Medical Oncology.

Giordano and her colleagues analyzed information from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database and found that in women diagnosed in the 1970s, those who had breast tumors on the left side had a higher ischemic heart disease mortality rate after 15 years (13.1%) compared with those who had tumors on the right side (10.2%).

However, in women diagnosed from 1980 to 1984 and from 1985 to 1989, there was no such difference in cardiac mortality. The researchers concluded that each year after 1979, the risk of death from ischemic heart disease declined by 6% annually in women with left-sided breast cancer compared with those with disease on their right side.

Giordano cautions that death from ischemic heart disease may not occur until 15 years after treatment, so longer follow-up will be needed. Nevertheless, she believes that the study will encourage patients in need of radiation therapy for breast cancer to proceed with treatment without fear. ●

HOUSE•CALL

Understanding Your Blood Counts

Blood counts refer to the number of blood cells circulating in the bloodstream. Cancer treatments like chemotherapy and radiation can temporarily lower blood counts, causing fatigue, easy bruising or bleeding, and susceptibility to infection.

Your doctor will monitor your blood counts closely as you go through treatment, so having a little background information will help you be a more knowledgeable partner in your health care.

What types of blood cells do I have?

There are three main types of blood cells:

- White blood cells
- Red blood cells
- Platelets

White blood cells fight infection, and there are several different kinds, each with its own function in protecting the body from germs. Three major types include neutrophils, monocytes, and lymphocytes. Neutrophils kill most bacteria. Monocytes kill unusual bacteria such as tuberculosis. Lymphocytes are responsible for killing viruses and for overall management of the immune system. Lymphocytes recognize foreign material and increase the body's resistance to infection. Infections are therefore more likely to occur when there are too few normal white blood cells in the body.

Red blood cells, the major component of blood, carry oxygen throughout your body. The most important part of the red blood cell is hemoglobin, the protein that carries oxygen. All body tissues need oxygen to function properly.

What is a CBC?

A complete blood count (CBC) is a simple laboratory test used to monitor blood counts. Your doctor will explain the findings on your lab report, but knowing some of the key concepts will help you sort through the numbers and lingo more easily.

Normal values for the following blood counts are

White blood cell count: 4 - 11 K/UL
Hemoglobin:
Male: 14 - 18 G/DL
Female: 12 - 16 G/DL
Platelets: 140 - 440 K/UL
Absolute neutrophil count:
(ANC) 1.70 – 7.30 K/UL

What causes low blood counts?

Cancer itself—especially blood cancers like leukemia or myelodysplasia (MDS)—can cause cells in the bone marrow to stop growing for some time, as can the chemotherapy or radiation used to treat cancer. When this happens, mature cells may no longer leave the bone marrow and enter the bloodstream, causing your blood counts to be low during this period. Depending on your particular situation, your doctor may prescribe medications that can help improve your anemia and/or boost your immune system. If your blood counts fall below a certain level, you may need to have a transfusion of red blood cells or platelets. The good news is that, today, a transfusion is a relatively simple and safe procedure.

Are there precautions I should take when my blood counts are low?

Although you cannot always prevent an infection while your counts are low, the following precautions may help.

- Wash your hands frequently.
- Avoid getting cuts or breaks in the skin. Promptly apply antibiotic ointment and a bandage to any cuts so bacteria cannot get in.
- Wear disposable gloves while working in the garden, doing housework, or cleaning up after pets.
- Contact your doctor or nurse immediately if you have a temperature of 101°F (38.3°C) or above. If it is after regular clinic hours, go to the nearest emergency room.

When your platelet count is low, you can help yourself by following these guidelines:

- Avoid vigorous or rough activity, such as contact sports.
- Use an electric razor.
- Go to the nearest emergency room if you cough up blood or if you have bleeding that will not stop.
- Don't take aspirin-containing products or dietary supplements without your doctor's permission; they can further lower your platelet count.

When your hemoglobin is low, oxygen isn't circulating through your body efficiently, which can make you feel exceptionally fatigued. Consider the following tips:

- Stand up slowly to avoid becoming lightheaded.
- Avoid strenuous activity and heed your body's warning signals, such as an unusually high pulse rate or becoming short of breath easily.
- Get plenty of rest, and take rest breaks during the day. ●

For more information, contact your physician or contact the M. D. Anderson Information Line:

(800) 392-1611, Option 3, *within the United States, or*

(713) 792-3245 *in Houston and outside the United States.*

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R. Williams

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DiaLog

Celebrex Trials Resume

Jonathan M. Kurie, M.D.
Professor, Department of Thoracic/ Head & Neck Medical Oncology

Lung cancer continues to be the most lethal cancer in the United States. Most patients diagnosed with it die, and surgical resection is the only means of cure. Because treatment for advanced disease has proven unfruitful, efforts to prevent lung cancer have become a high priority.

While 90% of all patients with lung cancer are either active or former smokers, currently we have no effective way to identify those individuals at high risk to develop lung cancer. Further, we have no effective lung cancer preventive agents.

Laboratory studies have shown that the enzyme cyclooxygenase-2 (COX-2) is expressed at high levels in lung cancer and appears to be required for lung cancer cell survival and metastasis. For that reason, in 2001, we began a clinical trial with the COX-2 inhibitor celecoxib, a drug commonly used to treat arthritis, to examine the activity of COX-2 inhibitors in the lungs of smokers and former smokers.

Patients underwent bronchoscopy with biopsies at six predetermined sites to measure genetic and biologic evidence of damage to the lung caused by cigarette smoke. The endpoint of the study was bronchial epithelial proliferation, a surrogate marker of cigarette smoke induced damage.

However, in December 2004, review of recently completed colon cancer prevention clinical trials with Celebrex and other drugs with COX-2 inhibitory activity revealed an unexpected toxicity. A small but statistically significant proportion of patients experienced myocardial infarction and cerebrovascular accident. For that reason, the Food and Drug Administration and National Cancer Institute recommended that all clinical trials in cancer patients using this class of agents be halted pending further review of the toxicity data.

Recently, after further review by an external advisory panel, the FDA and NCI have recommended that trials with Celebrex be resumed using revised entry criteria. New exclusion criteria include a known history of myocardial infarction or stroke and uncontrolled risk factors for these events, including uncontrolled high blood pressure, hyperlipidemia, and diabetes mellitus. Further, more stringent follow-up of patients to measure changes in these risk factors during treatment is recommended.

Based on these new criteria, our clinical trial at M. D. Anderson Cancer Center was given permission in April 2005 to reopen. We have resumed the study and are now actively enrolling current and former smokers. To date, patients enrolled on this study have experienced primarily grade I toxicity; no serious cardiac or cerebrovascular toxicities have been observed.

Anyone interested in participating in this study should contact us at (713) 745-2784. ●

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