



FDA *Consumer*

The Magazine of the U.S. Food and Drug Administration

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Prostate Health:

What Every Man
Needs to Know

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FDA Consumer

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10 Ensuring the Safety of Medical Devices

A quicker response to problems with medical devices is the goal of a new FDA effort.

16 'My Family Health Portrait' Available in English and Spanish

A free computer-based tool that tracks family health histories can help people determine whether they should be screened for certain illnesses.

Cover Story

18 Prostate Health: What Every Man Needs to Know

Most men will experience some type of prostate problem during their lifetime. Find out about FDA-approved treatments that help relieve common prostate conditions.

26 Treating Restless Legs Syndrome

The FDA has approved the first drug targeted specifically to treat Restless Legs Syndrome.

30 The FDA and Product Recalls

Take a look at the FDA process for removing or correcting products that don't follow the agency's regulations.

36 New Health Initiative to Improve Cancer Treatments

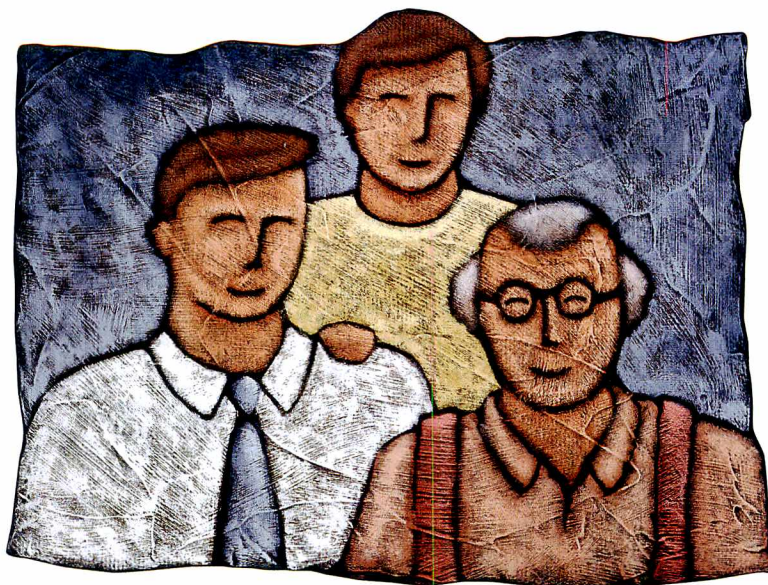
Three federal agencies collaborate on the Oncology Biomarker Qualification Initiative.

38 Keeping Up With Drug Safety Information

Here's how to keep up-to-date on drug warnings and other regulatory changes using FDA resources.



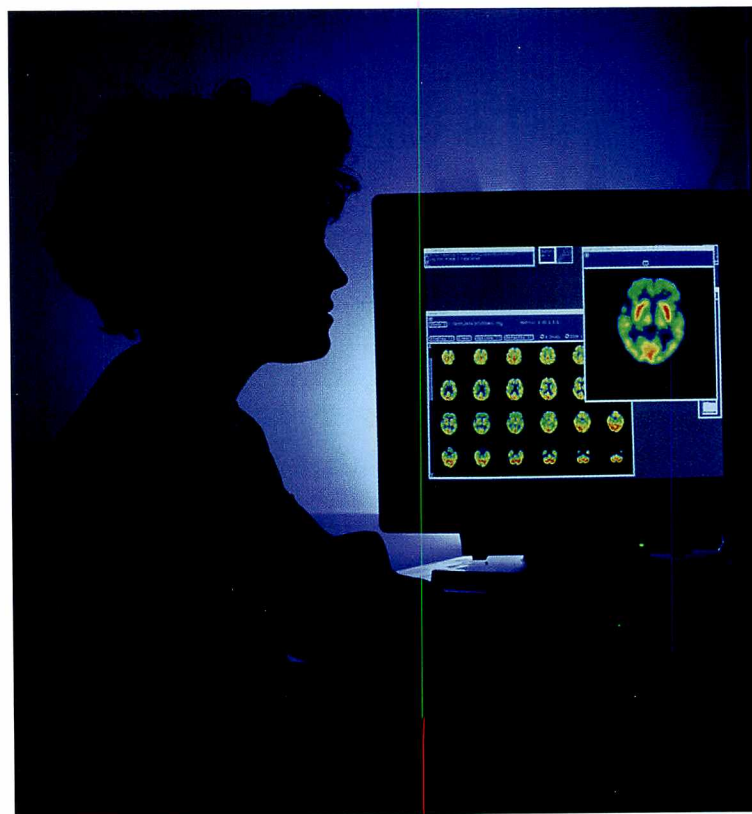
- 10** The FDA must act quickly to protect consumers from medical devices that fail to work properly.



- 16** Health care professionals know that many diseases, such as cancer, diabetes, and heart disease, can run in families.



- 30** The FDA handles recalls for all the products it regulates. A recall is a way to remove or correct products that violate laws enforced by the agency.



- 36** Three Department of Health and Human Services agencies are collaborating to improve cancer treatments.

DEPARTMENTS

- 2 Observations
- 2 Updates
- 9 Research Notebook
- 40 FDA Consumer Quiz

OBSERVATIONS

It's only about the size of a walnut, but if it becomes enlarged, inflamed—or worse—a man's prostate gland can be the source of enormous discomfort and worry.

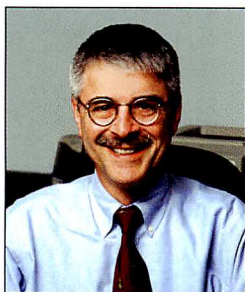
The prostate's main function is to produce semen, the fluid that helps to nourish and transport sperm. Located just below a man's bladder, the prostate surrounds the urethra, a tube that carries urine from the bladder, and semen during sexual climax.

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), prostate problems afflict young and old alike. For men younger than 50, inflammation of the prostate, called prostatitis, is the most common problem.

For men older than 50, it's prostate enlargement, called benign prostatic hyperplasia, or BPH for short. Experts at the Mayo Clinic in Rochester, Minn., say that prostate gland enlargement affects about half of men in their 60s and up to 90 percent of men in their 70s and 80s. Older men also are at risk for prostate cancer, a much rarer condition.

For more on the prostate and the importance of having regular prostate examinations, see our cover story titled "Prostate Health: What Every Man Needs to Know," beginning on page 18.

About 25 cents of each dollar spent by consumers in the United States involve products regulated by the FDA. Occasionally, a company discovers a problem or a potential problem with one of those products.



One way to deal with the situation is for the manufacturer to initiate a product recall in cooperation with the FDA. While recalling a product that has been widely distributed can pose significant challenges, compared to legal actions, a voluntary recall often can be the best method to handle a problem with a product.

The FDA handles recalls for all the products it regulates—human drugs; devices and radiation-emitting products; biologics such as vaccines and blood products; veterinary products, which include animal drugs and animal feed; cosmetics; and about 80 percent of the foods consumed in the United States. To learn more about recalls, see our feature story titled "The FDA and Product Recalls," beginning on page 30.

People with Restless Legs Syndrome (RLS) often feel an overwhelming urge to move their legs in an attempt to get temporary relief from the crawling, pins and needles, prickly, or painful sensations they experience. The National Institute for Neurological Disorders and Stroke says that RLS is a common neurological disorder for which there is no cure. Read more about RLS, and the only FDA-approved drug to treat it, in our feature story titled "Treating Restless Legs Syndrome," beginning on page 26.

We also take a look at a new FDA effort designed to ensure the safety of medical devices, a new health initiative by three HHS agencies aimed at improving cancer treatments, and advice on how to keep up with the latest drug warnings using FDA resources.

Raymond Formanek Jr.
Editor

UPDATES

New Treatment for Chest Pain

The FDA has approved Ranexa (ranolazine) to treat chronic angina. Ranexa is the first drug approved to treat this condition in over 10 years. Because Ranexa affects electrical conduction in the heart, it should be used only by people who have not responded to other anti-anginal drugs, such as long-acting nitrates, calcium channel blockers, and beta blockers.

People who have chronic angina have episodes of chest pain, pressure, or discomfort that occur during exercise because the heart muscle is not getting enough oxygen. The most com-

mon cause of angina is coronary heart disease, in which the coronary arteries that supply the heart with oxygen-rich blood become blocked with plaque deposits.

According to the American Heart Association, nearly 7 million Americans are diagnosed with angina every year. Acute attacks of angina are treated with nitroglycerin placed under the tongue, whereas treatments for chronic angina are given to increase the amount of exercise a person can do before angina occurs.

"Chronic angina limits people's activities," says Steven Galson, M.D., direc-

tor of the FDA's Center for Drug Evaluation and Research. "The approval of Ranexa provides a new treatment option for Americans who continue to suffer symptoms of angina despite using other angina drugs."

In clinical trials, Ranexa appeared to be less effective in women than in men. Common side effects included dizziness, headache, constipation, and nausea.

Ranexa is manufactured by CV Therapeutics Inc. in Palo Alto, Calif.

Reducing Risk of Entrapment in Hospital Beds

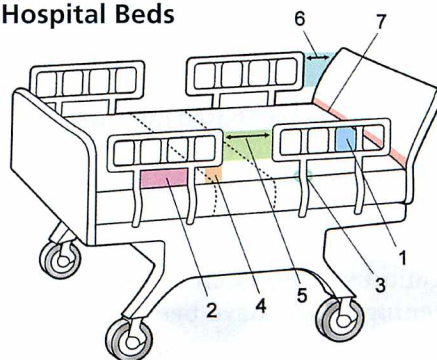
The FDA has published final guidance to reduce the risk of patients becoming entrapped in hospital beds. Entrapment can occur when part of a person's body gets caught between parts of the bed, such as in the space between the mattress and the side rail. This hazard can cause strangulation and death. Older people in hospitals and nursing homes, especially those who are frail, confused, restless, or who have uncontrollable body movement, are most vulnerable to entrapment.

The guidance provides design recommendations for manufacturers of new hospital beds. It also gives suggestions to facilities with existing beds, including hospitals, nursing homes, and private residences, on ways to reduce entrapment risk.

Key body parts at risk of entrapment are the head, neck, and chest. Potential zones of entrapment in a hospital bed are

- Zone 1: Within the rail
- Zone 2: Under the rail, between the rail supports, or next to a single rail support
- Zone 3: Between the rail and the mattress
- Zone 4: Between the rail, at the ends of the rail
- Zone 5: Between split bed rails
- Zone 6: Between the end of the rail and the side edge of the headboard or footboard
- Zone 7: Between the headboard or footboard and the mattress end.

"While not all patients are at risk for an entrapment, and not all hospital beds pose a risk of entrapment, this new guidance will help ensure that new hospital



beds are designed to reduce the potential for entrapment," says Larry Kessler, Sc.D., director of the Office of Science and Engineering Laboratories within the FDA's Center for Devices and Radiological Health. The guidance will also help caregivers identify entrapment risks that may exist with current hospital beds, adds Kessler.

The guidance results from the efforts of the Hospital Bed Safety Workgroup (HBSW). Formed in 1999, the HBSW is a partnership among the FDA, the Veterans Administration, other federal agencies, Health Canada's Medical Devices Bureau, national health care organizations and provider groups, patient advocacy groups, and medical bed and equipment manufacturers.

The FDA has received 691 reports of entrapment over a period of 21 years, from Jan. 1, 1985, to Jan. 1, 2006. The reports included 413 deaths, 120 nonfatal injuries, and 158 near-miss events where staff intervened to prevent serious injury.

See www.fda.gov/cdrh/beds/ for more information.

New Vaccine for Infants

The FDA has approved RotaTeq, a live, oral vaccine for preventing rotavirus gastroenteritis in infants. It is the only vaccine approved in the United States that can help protect against this viral infection that can cause diarrhea, vomiting, fever, and dehydration.

Approved in February 2006, RotaTeq is a liquid vaccine that is given by mouth in three doses between 6 and 32 weeks of age. It can effectively prevent an illness that the Centers for Disease Control and Prevention (CDC) says affects almost all children within the first few years of life. The CDC estimates that rotavirus infection results in about 55,000 hospitalizations annu-

ally for infants and young children in this country.

In 1998, the FDA approved a different live vaccine against rotavirus that was later withdrawn from the mar-



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ket because of its association with an increased risk of intussusception, a rare and life-threatening type of blockage or twisting of the intestine. The risk of intussusception for RotaTeq was studied in a large trial of over 70,000 children. Half of those in the study received the vaccine, and the remaining half received an inactive pill (placebo). RotaTeq was not associated with either an increased risk of intussusception or an increased risk of other serious adverse events when compared to the placebo.

Safety of this vaccine, manufactured by Merck & Co. Inc. of Whitehouse Station, N.J., will be closely monitored in additional studies conducted after licensing.

Stronger Warnings for Antibiotic Tequin

The manufacturer of the antibiotic drug Tequin (gatifloxacin) has announced labeling changes based on continued reports of serious cases of low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia) in people taking the drug. Since the FDA approved Tequin in 1999, rare cases of life-threatening events have been

reported around the world in people treated with the drug.

Tequin, made by Bristol-Myers Squibb Co., New York, is approved to treat people with pneumonia, bronchitis, uncomplicated gonorrhea, and various infections including urinary tract, kidney, and skin infections.

The labeling changes strengthen an existing warning on hypoglycemia and hyperglycemia, add a contraindication

for use in people with diabetes, and provide information identifying other risk factors for developing low or high blood sugar, including advanced age, kidney malfunction, and taking glucose-altering medications while taking Tequin.

The FDA will continue monitoring Tequin's safety to ensure that its benefits outweigh the risks to people who take the drug.

First Depression Patch Approved

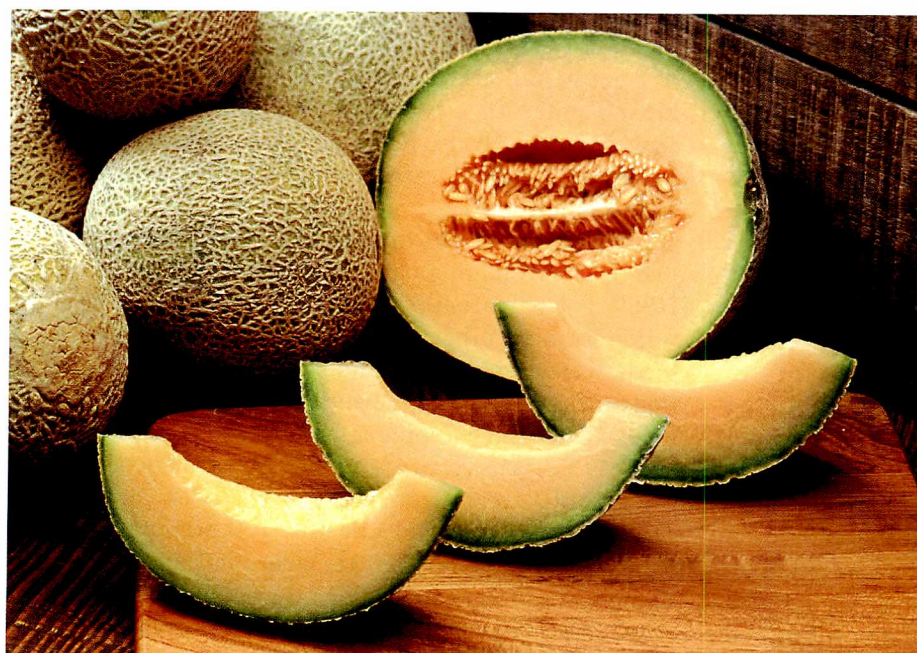
The FDA has approved the first skin (transdermal) patch, called Emsam (selegiline), for treating major depression.

Emsam is a once-a-day patch that delivers selegiline, a monoamine oxidase inhibitor, or MAOI, through the skin and into the bloodstream. Its three layers consist of a backing, adhesive drug layer, and release liner that is placed against the skin.

"Emsam provides a significant advance," says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research, "because at least in its lowest dose, patients can use the drug without the usual dietary restrictions associated with these types of drugs known as MAO inhibitors." The lowest dose of the MAOI patch delivers 6 milligrams (mg) of the medication over a 24-hour period.

MAOIs usually require specific dietary restrictions because when combined with certain foods, they can cause a sudden, large increase in blood pressure, or hypertensive crisis, which can lead to a stroke and death. Symptoms of a hypertensive crisis include sudden severe headache, nausea, stiff neck, fast heartbeat or a change in the way the heart beats, sweating, or confusion. Patients who have these symptoms must get medical attention immediately.

The Emsam patch, which will be distributed by the New York-based Bristol-Myers Squibb, will be available in three sizes that deliver 6 mg, 9 mg, or 12 mg of selegiline over 24 hours.



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Safer Fruits and Vegetables

The FDA has published draft guidance for food producers who work with fresh-cut fruits and vegetables, to minimize health hazards that may be introduced during processing.

Processing fruits and vegetables into fresh-cut produce increases the risk of bacterial contamination and growth. During processing, the natural exterior barrier of the produce is broken by peeling, slicing, coring, trimming, or mashing before being packaged for consumption. Examples of fresh-cut products are shredded lettuce, sliced tomatoes, raw vegetable salads, peeled baby carrots, broccoli florets, cauliflower florets, cut celery stalks, shredded cabbage, cut melons, sliced pineapple, and sectioned grapefruit.

The guidance discusses the production and harvesting of fresh produce and provides recommendations for fresh-cut processing.

Consumers can reduce their risk of illness from fresh-cut produce by following safe handling practices such as refrigerating the product after purchase; using only clean hands, utensils, or dishes in preparing the product; and discarding the product when the "use by" date has expired.

See portal.fightbac.org/pfse/toolsyoucanuse/phec/ and www.cfsan.fda.gov/guidance.html to find out more on how to safely handle food.

New Targeted Therapy for Rare Stomach, Kidney Cancers

The FDA has approved Sutent (sunitinib), a new targeted anti-cancer medicine to treat patients with gastrointestinal stromal tumors (GIST), a rare stomach cancer, and advanced kidney cancer.

The approval of Sutent is a major step forward in making breakthrough treatments available for patients with rare and difficult-to-treat forms of cancer, says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research. "New targeted therapies such as Sutent are helping FDA expand options for patients for whom there are limited alternatives."

The drug's approval in January marks the first time the agency has approved a new oncology product for two indications simultaneously.

According to the American Cancer Society, about 5,000 cases of GIST and 32,000 new cases of advanced kidney cancer are diagnosed each year.

Sutent was approved for patients with GIST whose disease has progressed or who are unable to tolerate treatment with Gleevec, the current treatment for GIST. Early data showed that Sutent delayed the time it takes for tumors or new lesions to grow in patients with this rare stomach cancer.

The FDA also granted accelerated approval for Sutent in treating patients with advanced renal cell carcinoma (RCC). In contrast to the approval for GIST, which was based on the drug's ability to delay the growth of tumors, RCC approval was based on the drug's ability to reduce the size of tumors in patients.

Some common side effects reported with Sutent are diarrhea, skin discoloration, mouth irritation, weakness, and altered taste.

Sutent is distributed by Pfizer Labs of New York City.

Modernizing Medical Product Development Through Collaboration

Health and Human Services (HHS) Secretary Mike Leavitt and experts from the FDA announced in March 2006 the release of an opportunities list and the formation of a consortium to advance the FDA's Critical Path Initiative. The initiative is the FDA's premier effort to modernize medical product development so that new medical discoveries are brought to patients faster and at a lower cost.

The Critical Path Opportunities List outlines an initial 76 projects to bridge the gap between the quick pace of new biomedical discoveries and the slower pace at which those discoveries are currently developed into treatments.

"This Opportunities List enhances the health and well-being of Americans by fostering strong, sustained scientific advances in medicine to better public health," Leavitt said in announcing the list.

The Predictive Safety Testing Consortium was formed as a partnership between the Critical Path Institute (C-Path) and five of America's largest pharmaceutical companies. The consortium will share laboratory methods and tests to better understand the safety and side effects of potential new drugs before they are tested in humans. The FDA will assist the consortium in an advisory capacity.

C-Path of Tucson, Ariz., was established in 2005 as an independent non-profit research and education institute to facilitate collaboration among its founding partners: the FDA, The University of Arizona, and SRI International.

See www.fda.gov/oc/initiatives/critical-path/ for more information.

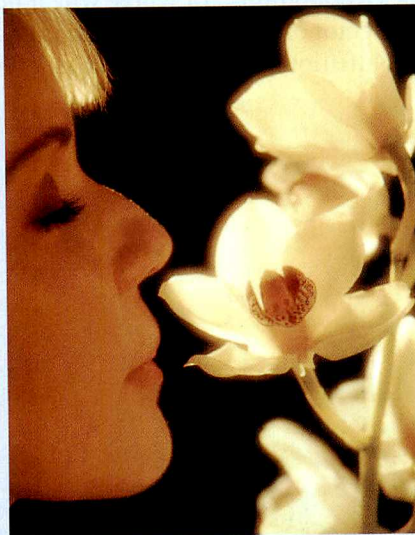
First Generic Flonase

The FDA has approved the first generic version of Flonase (fluticasone propionate), a drug that treats the nasal symptoms of seasonal and chronic allergies. The February 2006 generic approval gives Americans an additional, lower cost alternative when choosing prescription drug products.

Except for their price, which is much lower, generic drugs are in every way equivalent to their brand name counterparts, says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research. Offering consumers a safe, effective, and reasonably priced choice "is an extremely important priority for FDA," according to Galson.

Fluticasone Propionate Nasal Spray contains a synthetic, trifluorinated corticosteroid with anti-inflammatory capability. Like other corticosteroids, the generic nasal spray does not have an immediate effect on allergic symptoms. A decrease in stuffiness, runniness, itching, and sneezing nasal symptoms was noted in some patients 12 hours after initial treatment.

Common side effects of the new nasal spray, manufactured by Roxane Laboratories of Columbus, Ohio, are headache, sore throat, and nosebleed.



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Human Tissue Products Recalled

In February 2006, the FDA ordered Biomedical Tissue Services Ltd. (BTS) of Fort Lee, N.J., a human tissue-recovery firm, and Michael Mastromarino, D.D.S., the company's chief executive officer and executive director of operations, to immediately cease all manufacturing operations. All tissue products initially recovered from human donors by BTS were recalled, and the FDA is carefully monitoring these recalls to account for all of the tissue distributed.

The FDA order to cease manufacturing and to retain Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) requires BTS to suspend any and all manufacturing steps,

including but not limited to, the recovery and shipment of HCT/Ps.

The agency's inspection of BTS uncovered serious violations of the regulations governing donor screening and record keeping practices, as well as failures to follow the company's standard operating procedures, failure to recover HCT/Ps in a manner that does not cause contamination or cross-contamination during recovery, and failure to adequately control environmental conditions.

Despite records maintaining otherwise, the firm had inadequately screened donors for risk factors for, or clinical evidence of, relevant communicable disease agents and diseases. The FDA also found numerous

instances in which death certificates maintained in BTS' files were at variance with the death certificates the FDA obtained from the state where the death occurred.

After initially focusing efforts on assessing the safety of distributed tissues and on facilitating the appropriate recalls, the FDA has determined that these violations, because of their seriousness, constitute a health danger.

The FDA continues to investigate BTS' activities and to work cooperatively with tissue processors and appropriate federal, state, and local authorities, and will take further actions as needed.

Go to www.fda.gov/cber/compl/bts013106.htm for a copy of the BTS order.

Guidance on 'Whole Grain'

Consumers will now have help in making dietary choices based on a "whole grain" term that is consistent and reliable. The FDA has issued draft guidance for manufacturers on what the term may include.

"The food label is the best tool we have to help consumers choose a healthy diet, which includes whole grain products," says Robert E. Brackett, Ph.D., director of the FDA's Center for Food Safety and Applied Nutrition.

The draft guidance clarifies that the agency considers whole grain to include cereal grains that consist of the intact, ground, cracked, or flaked fruit of the grains whose principal components—the starchy endosperm, germ, and bran—are present in the same relative proportions as they exist in the intact grain. Such grains may include barley, buckwheat, bulgur, corn, millet, rice, rye, oats, sorghum, wheat, and wild rice.

The draft guidance states that although rolled and "quick oats" can be called whole grains because they contain all of their bran, germ, and endosperm, other widely used food products may not meet the whole grain definition. For example, the FDA does not consider

products derived from soybeans (legumes), sunflower seeds (oilseeds), and arrowroot (roots) as whole grains. And the draft guidance specifically recommends that pizza be labeled only as "whole grain" or "whole wheat" when its crust is made entirely from whole grain flours or whole wheat flour.

This guidance is part of the federal government's long-standing effort to advise consumers about healthy

food choices. The 2005 Dietary Guidelines for Americans recommend that half of the grain that consumers eat should be whole grains. Consumers, the guidelines say, should eat at least 3 ounces of whole-grain cereals, breads, crackers, rice, or pasta every day. One ounce is about one slice of bread, one cup of breakfast cereal, or 1/2 cup of cooked rice or pasta. Consumers also should look to see that grains such as wheat, rice, oats, or corn are referred to as "whole" in the list of ingredients.

Currently, manufacturers also can make factual statements about whole grains on food labels such as "10 grams of whole grains" or "1/2 ounce of whole grains."



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Another Option for Fungal Infections

The FDA has approved Eraxis (anidulafungin) to treat certain infections caused by *Candida*, a yeast-like fungus that can cause serious infections in hospitalized patients or patients with compromised immune systems.

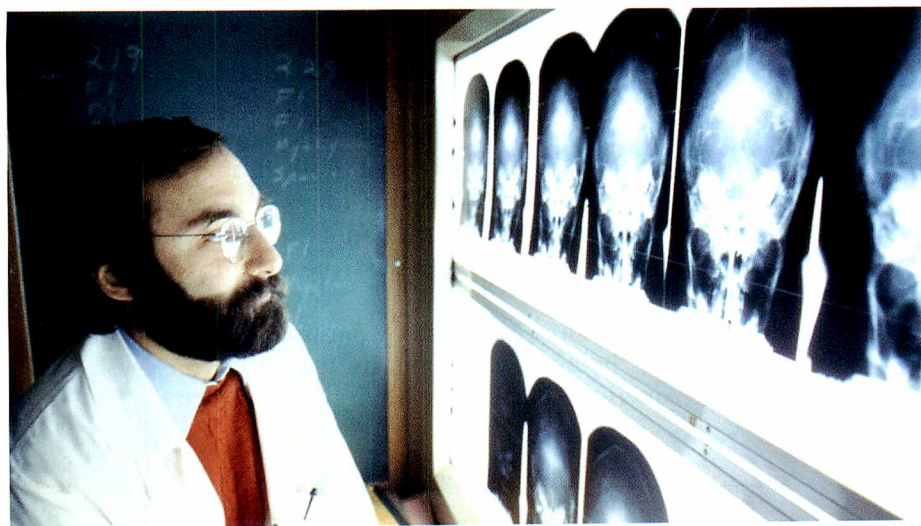
"This product offers a new alternative therapy for several types of infections associated with *Candida*," says Steven Galson, M.D., director of the FDA's Center for Drug Evaluation and Research. "It is a helpful addition to

the available antifungal medications that can be used in the treatment of these potentially serious fungal conditions."

Eraxis, a new molecular entity never marketed in the United States, is an antifungal drug that is administered intravenously. It is used to treat *Candida* infections in the esophagus (candidiasis), bloodstream (candidemia), and other forms of *Candida* infections, including abdominal abscesses and inflammation of the lining of the abdominal cavity (peritonitis).

Eraxis was generally well-tolerated in clinical studies. The most commonly reported adverse events were mild diarrhea, mild elevations in laboratory tests of liver enzymes, and headache. Some patients experienced infusion-related reactions, most of which were mild. In a few patients with significant underlying medical conditions who were on multiple medications, there were reports of serious liver abnormalities.

Eraxis is manufactured by New York City-based Pfizer Inc.



NCI

Treatment for Head and Neck Cancer

The FDA has approved Erbitux (cetuximab) for use in combination with radiation therapy to treat patients with squamous cell cancer of the head and neck (SCCHN) that cannot be removed by surgery.

The March 2006 approval is the first drug treatment for head and neck cancer that has shown a survival benefit. At the same time, Erbitux was also approved for use alone to treat patients whose head and neck cancer has spread, despite the use of standard chemotherapy.

"Patients suffering from all forms of cancer have a common goal—to treat the disease and prolong life," says Steven Galson, M.D., director of the

FDA's Center for Drug Evaluation and Research. "We consider this approval an important advance in the treatment of head and neck cancer because it has been shown to help some patients live longer. The approval of Erbitux monotherapy to shrink tumors in patients with metastatic disease who no longer respond to other forms of treatment is also important. Patients need as many effective treatment options as possible."

Erbitux, which received a priority review, is the first drug approved to treat head and neck cancer since methotrexate became available in the 1950s. Approval of Erbitux in combination with radiation therapy was based on a study that showed it prolonged survival by 20 months compared with radiation

treatment alone.

Approval of Erbitux monotherapy was based on evidence of tumor shrinkage in 13 percent of patients, lasting an average of six months. Standard cancer statistics databases estimate that there are about 29,000 new cases of head and neck cancer diagnosed every year in the United States.

The safety and effectiveness of Erbitux was established in two studies. The randomized clinical trial of 424 patients using Erbitux in combination with radiation therapy showed a survival time of 49 months versus 29.3 months on radiation therapy alone. In addition, delay in tumor growth was observed with the use of Erbitux and radiation, compared to radiation alone.

Since tumor growth is associated with pain and with difficulties swallowing, speaking, and eating, control of tumor growth as long as possible is important for a patient's well-being. In a second trial of 103 patients with recurrent or metastatic SCCHN, Erbitux helped to shrink the patients' tumors after the tumors no longer responded to platinum-based therapy, the current standard treatment for patients with this difficult-to-treat disease.

Erbitux is manufactured by ImClone Systems Inc., Branchburg, N.J., and will be distributed and marketed by Bristol-Myers Squibb Co., Princeton, N.J.

New Drug for Chronic Constipation

The FDA has approved Amitiza (lubiprostone), the first drug of its chemical type, for the treatment of chronic constipation of unknown cause in adults. Approved in January 2006, Amitiza is available as capsules for use by adults to treat "idiopathic" constipation cases not caused by other diseases or by use of medications.

Chronic idiopathic constipation is generally defined as infrequent and difficult passage of stool. It's one of the most common disorders suffered by Americans. This condition affects women more often than men and also affects people older than 65 more frequently. Symptoms of chronic idiopathic constipation are abdominal pain and discomfort, bloating, straining, and hard stools.

Amitiza increases the intestinal fluid secretion, which helps ease the passage of stool and helps alleviate symptoms. The FDA based its decision to approve Amitiza on results from two clinical trials, which were conducted in patients with, on average, less than three



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spontaneous bowel movements a week with symptoms of constipation for at least six months before entry into the studies.

The studies demonstrated that subjects treated with Amitiza had a higher frequency of bowel movements in the first week than the subjects who received a phony pill. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3, and 4 of therapy.

The most common adverse events reported in the trials included headache, nausea, diarrhea, abdominal pain, and distension. Whether these events are related to the drug is not known at this time. Amitiza should be

taken twice a day with food. Physicians and patients should periodically assess the need for continued treatment.

Amitiza is marketed by Sucampo Pharmaceuticals Inc., Bethesda, Md., and by Takeda Pharmaceuticals America, Lincolnshire, Ill. ■

We're eager to hear what you like and what you don't like. We also want to know the subjects you'd like to see covered.

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Making Multiple Lifestyle Changes Can Lower High Blood Pressure

Men and women with elevated blood pressure who make healthy lifestyle changes and sustain them for up to a year and a half can reduce their rates of high blood pressure and decrease their heart disease risk, a new study indicates.

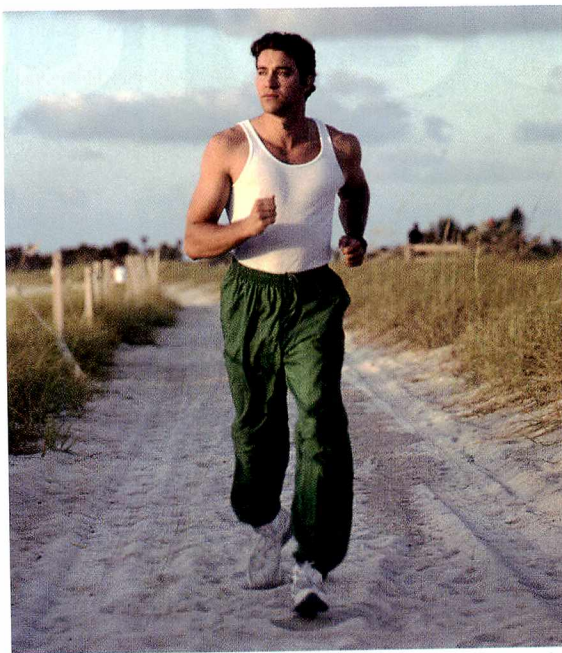
With behavioral counseling, increases in physical activity, and adoption of a healthy eating plan called Dietary Approaches to Stop Hypertension (DASH), rates of high blood pressure dropped from 37 percent to 22 percent among participants in a study conducted by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

High blood pressure is a major risk factor for heart disease and the chief risk factor for stroke. About 65 million American adults, one in three, have high blood pressure. An additional 59 million adults have prehypertension, a level that is above normal and that increases risk of heart disease and stroke.

Results of the study, called PREMIER, appear in the April 4, 2006, issue of *Annals of Internal Medicine*.

"This study underscores the value of lifestyle changes—namely improving diet and increasing physical activity—in reducing high blood pressure, an important public health problem," says NHLBI Director Elizabeth G. Nabel, M.D. "For the millions of Americans with prehypertension and hypertension, this shows that individuals can make healthy lifestyle changes to keep blood pressure under control without the use of medications."

A total of 810 men and women ages 25 and older with either prehypertension (120–139mmHg/80–89mmHg) or stage 1 hypertension (140–159mmHg/90–95mmHg), but who were not taking medications to control blood pressure, were randomly assigned to three groups. Participants in two of the groups attended 18 counseling sessions during the first six months—14 group meetings and four individual sessions. During the last 12 months, they attended 12 group



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meetings and three individual sessions. They were prescribed goals for weight loss, and physical activity, and were given sodium and alcohol intake limits.

One of these groups also received guidance on implementing DASH, which has been shown to lower blood pressure in other studies.

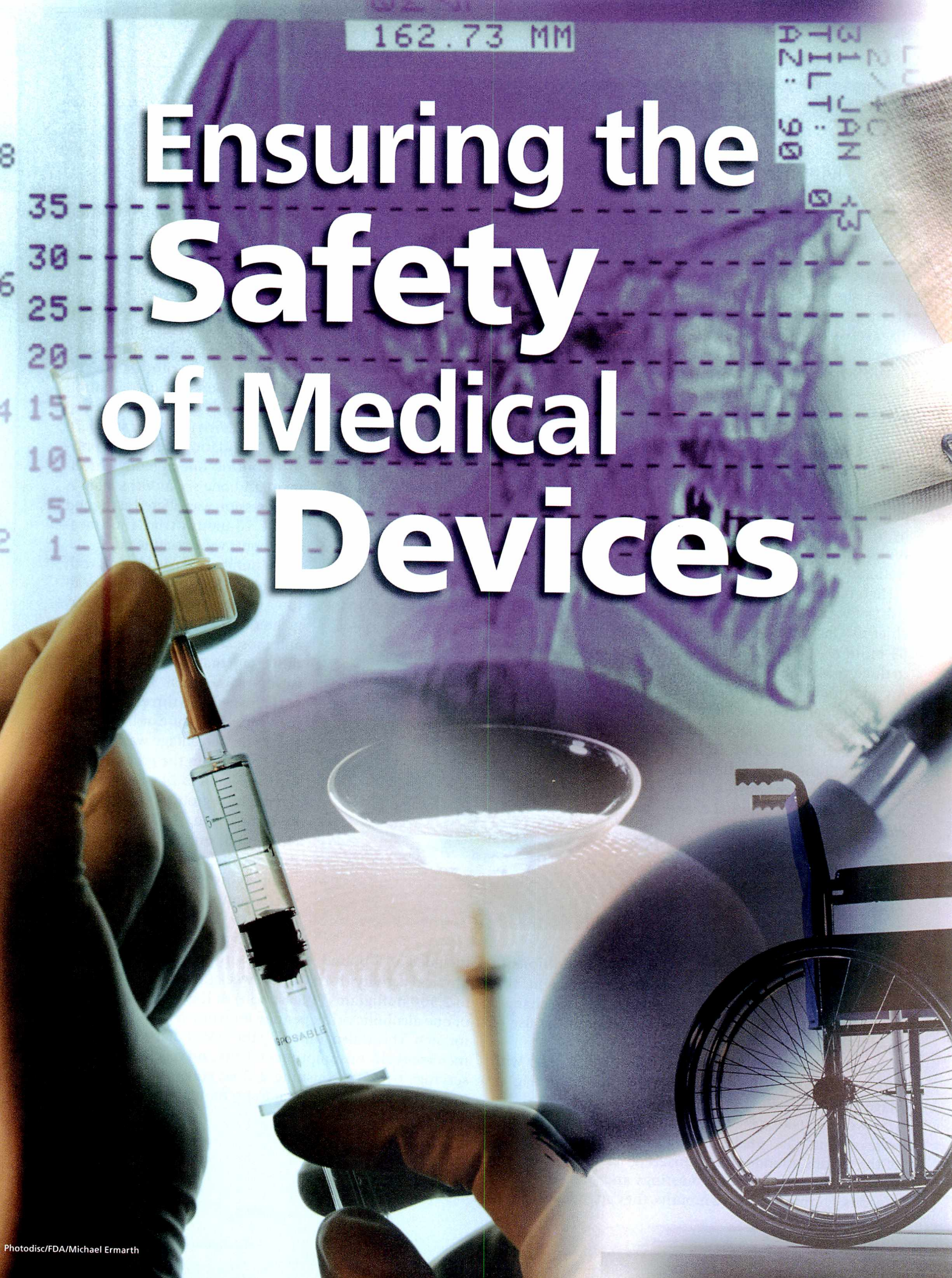
A third group served as a control, receiving only two 30-minute sessions of advice to follow standard recommendations for blood pressure control; one at study enrollment and one six months later. A third session was offered at the end of the 18-month trial after measurements were completed.

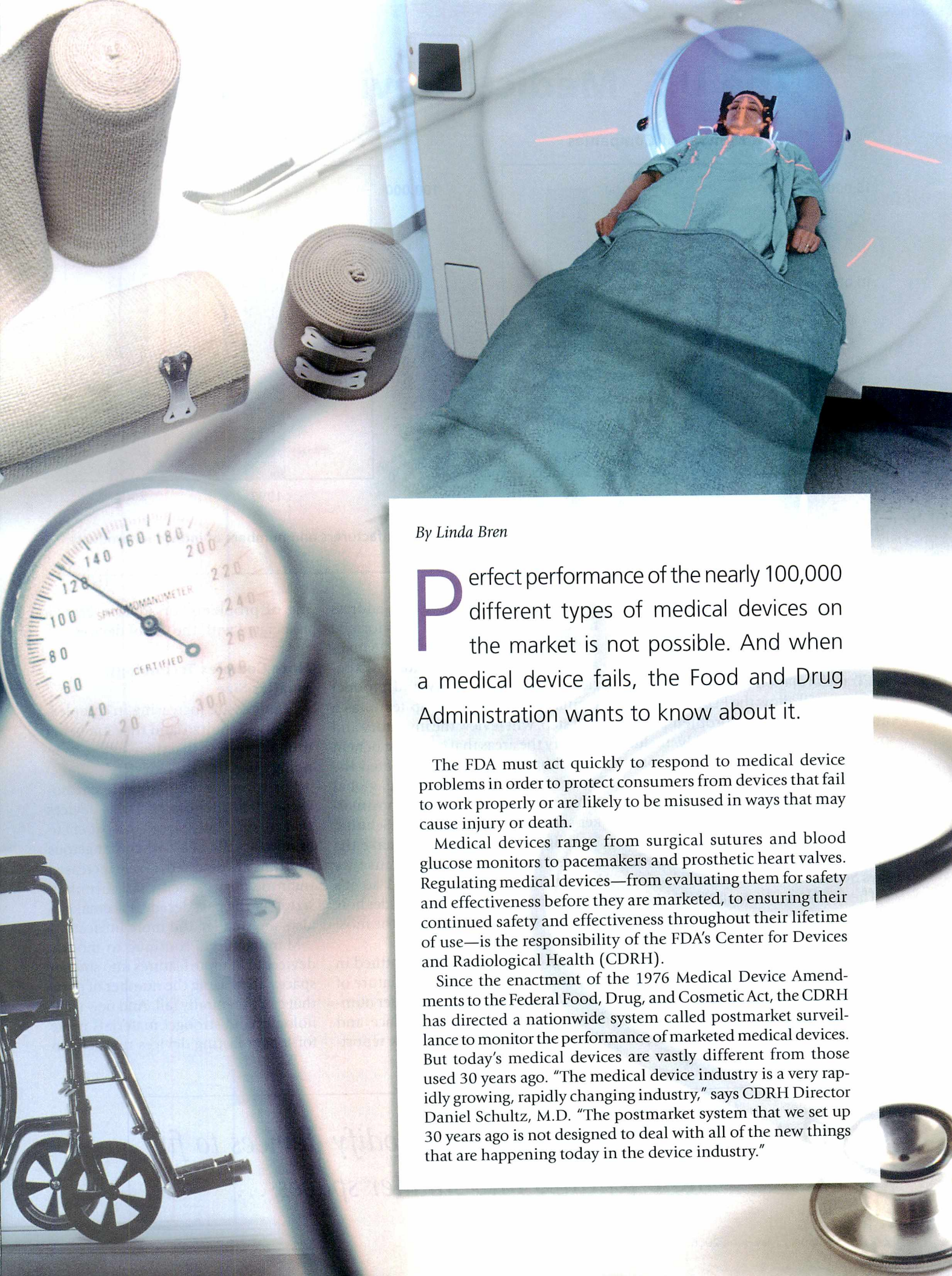
The numbers of participants with high blood pressure declined in all three groups, but the reduction was greater in the intervention groups and most striking in the intervention group that included the DASH eating plan. About 37 percent of participants in all three groups had high blood pressure at the study's start. The percentage was reduced to 22 percent in the group following DASH and to 24 percent in the intervention group without DASH. By comparison, the rate of hypertension fell only to 32 percent in the control group.

Ninety-five percent of the study participants were overweight or obese at the start of the study.

Goals for the intervention groups included a 15-pound weight loss, three hours of moderate physical activity three times a week, daily sodium intakes of 2,300 milligrams (1 teaspoon) or less of salt, and limits of one alcoholic drink per day for women and two per day for men. Those also following the DASH diet were asked to increase their consumption of fruits and vegetables to 9–12 servings per day, consume 2–3 servings of low-fat dairy products, and keep total fat to no more than 25 percent of total daily calories. ■

Ensuring the Safety of Medical Devices





By Linda Bren

Perfect performance of the nearly 100,000 different types of medical devices on the market is not possible. And when a medical device fails, the Food and Drug Administration wants to know about it.

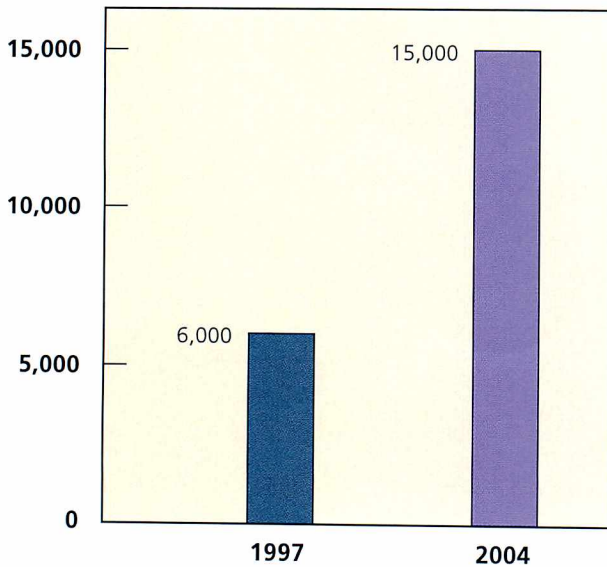
The FDA must act quickly to respond to medical device problems in order to protect consumers from devices that fail to work properly or are likely to be misused in ways that may cause injury or death.

Medical devices range from surgical sutures and blood glucose monitors to pacemakers and prosthetic heart valves. Regulating medical devices—from evaluating them for safety and effectiveness before they are marketed, to ensuring their continued safety and effectiveness throughout their lifetime of use—is the responsibility of the FDA's Center for Devices and Radiological Health (CDRH).

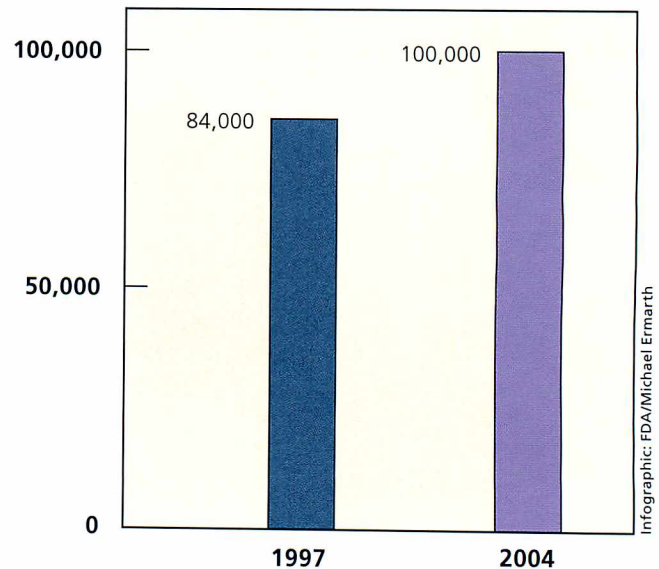
Since the enactment of the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, the CDRH has directed a nationwide system called postmarket surveillance to monitor the performance of marketed medical devices. But today's medical devices are vastly different from those used 30 years ago. "The medical device industry is a very rapidly growing, rapidly changing industry," says CDRH Director Daniel Schultz, M.D. "The postmarket system that we set up 30 years ago is not designed to deal with all of the new things that are happening today in the device industry."

The U.S. Medical Device Industry

Number of Companies



Number of Products



Infographic: FDA/Michael Ermarth

The medical device industry has grown rapidly in both numbers of manufacturers and numbers of individual products.

To respond to the growing and changing industry so it can better protect public health, the CDRH has launched the Medical Device Postmarket Transformation Initiative. This new program will allow the FDA to identify, analyze, and act on problems with medical devices more quickly, including alerting the public sooner of potential problems.

"With this initiative, we're going to improve the way we monitor the safety of medical devices and provide a stronger safety net to protect public health," says Schultz.

The CDRH undertook the initiative after completing a yearlong inventory in 2005 of the tools it uses to monitor medical device safety. The inventory identified many areas that are working well, says Schultz, but it also identified areas that challenge the FDA in its efforts to ensure device safety.

To guide the initiative and address the challenges, the CDRH has formed a special team of senior-level FDA managers and outside consultants experienced in device safety and product regulation. The leadership team, as a first step, will review the inventory and identify the areas that can most benefit from improvements. "We wanted the team to take a comprehensive, global look at the way we deal with postmarket safety information," says Schultz, "and figure out how we can make the process more effective. Of course we have limited resources, and so it's important for the team to consider how we can use those resources in the most cost-effective way."

Many of the challenges identified in the inventory arise from the nature of new device technology, the sheer numbers of devices in the marketplace, and the difficulties surrounding the report-

ing of problems, or adverse events, associated with the use of devices.

More Complex Technology, Smaller Size

"Devices are increasing in complexity," says Schultz, "and they are being miniaturized so that there's more technology in a tiny little device."

For example, implantable cardioverter defibrillators (ICDs)—devices that are surgically placed in a patient to jump-start the heart when dangerous rhythms are detected—have increased their memory capacity and shrunk in size over the past decade. Pacemakers, also, are smaller and more intricate.

Manufacturers continue to modify devices to fit more features into smaller spaces, increasing the number of parts that can potentially fail. And new technologies and stronger materials make for longer-lasting devices that remain

Manufacturers continue to modify devices to fit more features into smaller spaces ...

in use for a decade or more, extending the time for problems to arise.

Certain models of ICDs and pacemakers were recalled in 2005 because of malfunctions that could lead to heart failure and death. Schultz says that these device recalls did not trigger the postmarket transformation initiative, "but certainly those individual events strengthened my belief that this was something that the center needed to make its highest priority for the next year."

In addition to complexity, the numbers and types of devices on the market further challenge the FDA's monitoring efforts. Today's medical device industry consists of about 15,000 manufacturers producing nearly 100,000 individual products. The annual number of ICDs implanted, for example, increased from fewer than 10,000 implants in 1990 to close to 100,000 in 2002, according to an FDA analysis of manufacturers' annual reports. And the number of pacemakers implanted increased from about 95,000 in 1990 to more than 267,000 in 2002.

Reporting Device Problems

The FDA depends on reports it receives about adverse events involving medical devices in order to monitor the products and take actions to protect public health. Device manufacturers and distributors, hospitals, nursing homes, and other health care facilities are required by law to notify the FDA promptly about deaths and serious illnesses or injuries that a device may have caused or contributed to. They report these adverse events through the FDA's Medical Device Reporting (MDR) system.

The agency also relies on several other systems—MedSun and MedWatch—for adverse event reports. Through MedSun, about 350 hospitals and nursing homes around the country report not only injuries and deaths, but also close-call and near-miss events associated with medical devices. "If we know about a potential problem before someone is injured or dies, we can act to prevent these serious events," says Susan Gardner, Ph.D., director of the CDRH's Office of Surveillance and Biometrics. The FDA encourages

consumers and health professionals to use a voluntary system, MedWatch, to report any problems with medical products.

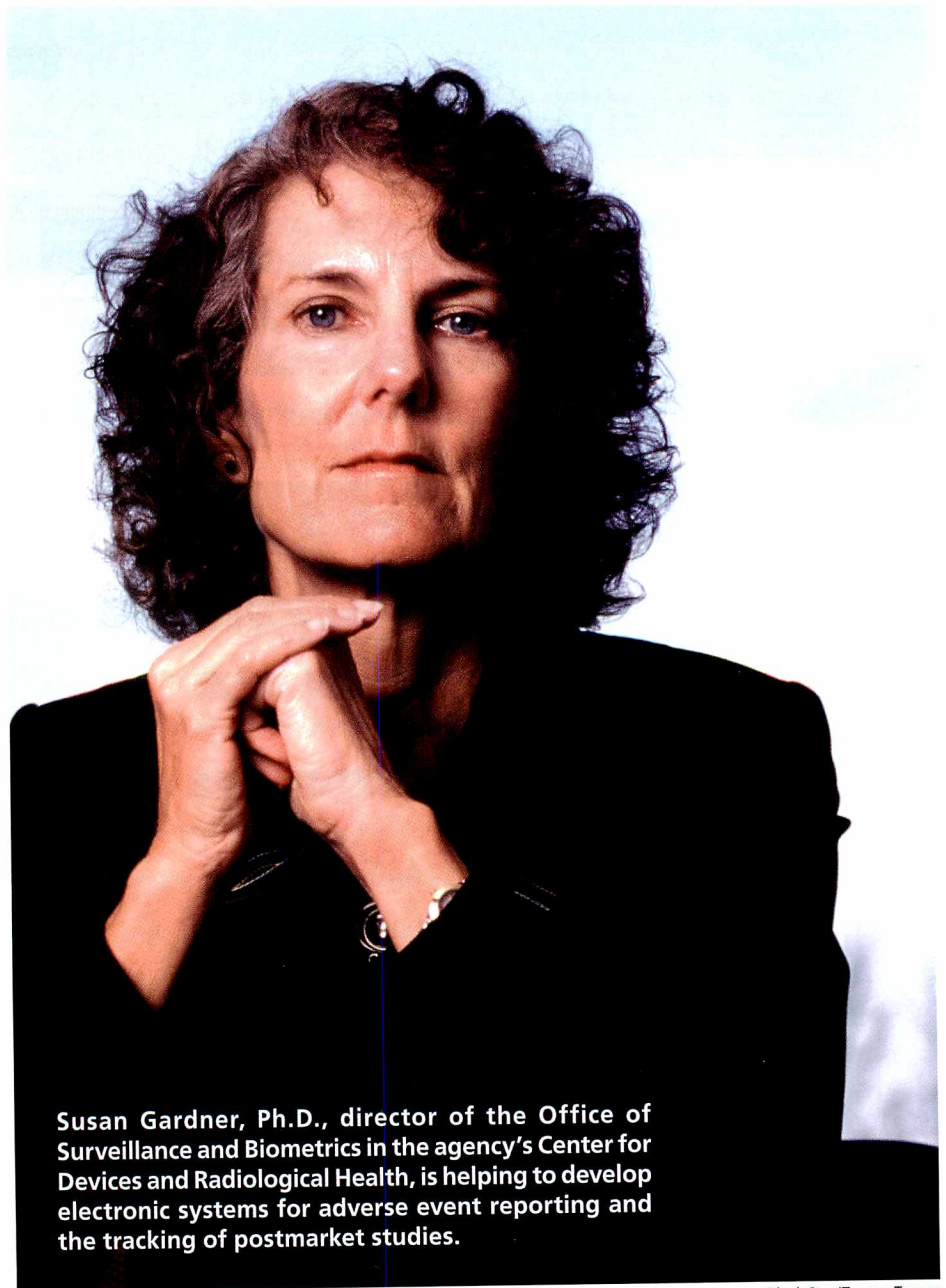
The FDA receives about 180,000 adverse event reports related to medical devices each year, yet congressional reports have estimated that perhaps as few as 1 in 100 medical device adverse events are actually reported. This under-reporting allows rare events to be missed. And even when a problem is detected, under-reporting makes it difficult to assess the true public health risk.

Many adverse event reports provide only sketchy information about how

the device was used and what may have caused the problem, says Gardner. "We have to do a lot of follow-up to get better information."

Those who report adverse events may not be able to identify the specific device involved because devices lack unique identifiers and because manufacturers continually produce modified versions of their products. Device firms often are purchased by other companies, compounding the problem of product identification.

And the gradual shift in the use of medical devices from hospitals and clinics to patients' homes presents yet another challenge. "More and more



Susan Gardner, Ph.D., director of the Office of Surveillance and Biometrics in the agency's Center for Devices and Radiological Health, is helping to develop electronic systems for adverse event reporting and the tracking of postmarket studies.

Black Star/Tyrone Turner



The monthly video show, "FDA Patient Safety News," promotes the safe use of FDA-approved products. It is available online and distributed to hospitals across the United States.

Collaboration

The CDRH has enlisted the help of professional medical organizations and the medical device industry to strengthen its postmarket device safety program.

In September 2005, FDA medical and scientific staff met with physicians, other health care providers, the medical device industry, and the public in Washington, D.C., at a conference on pacemakers and ICD performance sponsored by the Heart Rhythm Society. Participants discussed how to improve the quality of information that is made available to doctors and patients for making individual medical decisions about the use of those products. The CDRH has also formed a defibrillator working group to explore better ways to make information about the benefits and risks of defibrillators and pacemakers available to patients and health care providers.

In February 2006, the FDA and an industry advocacy group, the Advanced Medical Technology Association (AdvaMed), held the first in a series of public workshops to discuss postmarket device safety. The two-day workshop set the stage for further collaboration to improve postmarket device monitoring and follow-up.

Automated Systems

Better sources of data on device performance and better systems to allow the FDA to quickly collect and analyze reports of safety problems are needed. The CDRH is seeking a system of unique identifiers for devices to help associate adverse events with the right model and type of device. It is also exploring mechanisms and incentives for health professionals to include certain standardized information about devices in the health care records of patients who use the devices.

The CDRH is developing an electronic reporting system to replace the

devices that were originally intended for use by health professionals are now being used by consumers," says Schultz. Lay users often are not trained to recognize device-related problems, he says, nor do they all know the process for reporting adverse events.

Meeting the Challenges

The transformation initiative leadership team will recommend ways to improve postmarket device safety, but the CDRH has already begun to address some of the challenges through a number of actions. One of them is planning postmarket studies of devices even before they are approved.

The agency requires manufacturers of certain devices, such as long-term implants, to continue studying the devices after they are on the market.

"Premarket clinical trials are not 10 years long," says Gardner, yet many devices are going to be in the patient for a decade or longer, so it's important to continue studying them.

Gardner says that the CDRH has added to the premarket review team epidemiologists who can advise the manufacturer on how to study a device after it's on the market. "Early on, we want to think about what the possible postmarketing problems might be with a device if it is to be approved. Then by the time the product is on the market, the postmarketing study is already in place."

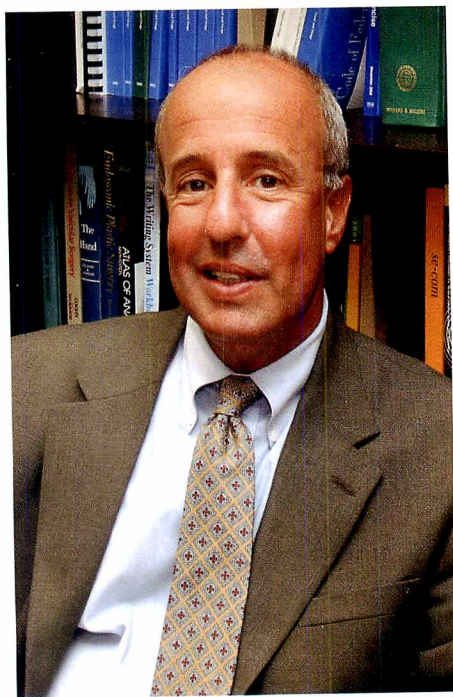
Other actions to strengthen the device postmarket safety program focus on four areas: collaboration, automated systems, communication, and enforcement.

current, "antiquated, paper-based system," says Gardner, which requires staff resources to be spent entering data into the system about adverse events reported by faxes, e-mails, and phone calls. "We're moving to an electronic MDR system that will allow us to get information to CDRH analysts more quickly," says Gardner, adding that a fully electronic system is expected to be in place within the next several years.

Communication

Once a medical device problem is identified and evaluated, the FDA must quickly inform health care professionals, patients, caregivers, and consumers of the device's risks and benefits.

As part of the Medical Device Postmarket Transformation Initiative, the CDRH is partnering with outside professional groups, using the media to help spread its messages, and creating easier access to CDRH device information. "We are using a lot of varied tools to make information flow better and reach the broadest audience possible," says Lynne Rice, director of the CDRH's Office of Communications, Education, and Radiation Programs.



FDA

Center for Devices and Radiological Health Director Daniel Schultz, M.D., says the FDA is increasing its efforts to respond more quickly to safety problems with medical devices.

The FDA encourages consumers, health professionals, and caregivers to report adverse events related to medical devices, drugs, or other medical products to MedWatch, the agency's voluntary reporting program. You can report by telephone, fax, mail, or online:

- Call (800) FDA-1088
- Fax report to (800) FDA-0178
- Mail to MedWatch, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787
- Log onto the MedWatch Web site at www.fda.gov/medwatch/

Patient identification is kept confidential and is protected from disclosure by the Freedom of Information Act. ■

Capitalizing on the Internet, the CDRH reaches out to consumers through electronic newsletters, mailing lists, and Web sites that provide information on new device approvals, device recalls, and benefits and risks of individual products. The center is increasingly using e-mail subscription services, says Rice. "It gives you the ability to sign up for very specific information, and you'll receive only new or updated information on that topic. You won't have to go searching for it—we are going to push the information out to you, and we're only going to send you the information you're interested in."

The CDRH also provides device information on a continuing basis to health care professionals through public health notifications and "FDA Patient Safety News," a monthly video news show available online and distributed across the United States via satellite to about 4,000 hospitals.

Enforcement

Under the Medical Device Postmarket Transformation Initiative, the CDRH is assessing the effectiveness of current enforcement strategies and is working to improve inspections of manufacturers, reporting of problems, and enforcement issues. One improvement already under way focuses inspection efforts on "risk-based inspections"—using the FDA's limited field resources to inspect manufacturers whose medical devices present the greatest risk to public health. The agency is also using accredited private firms to do some of the inspections of facilities that produce devices that have lower

safety risks.

The FDA is working with its counterpart agency in Canada on a pilot program to conduct joint inspections of facilities that market devices in the United States and Canada. The program would save resources for both agencies, says Schultz, as well as for the manufacturers who are required by law to be inspected by different jurisdictions. "Instead of having multiple inspections over a short period of time, manufacturers would have one inspection that would cover multiple jurisdictions." ■

For More Information

Medical Device Postmarket Transformation Initiative
www.fda.gov/cdrh/postmarket/mdpi.html

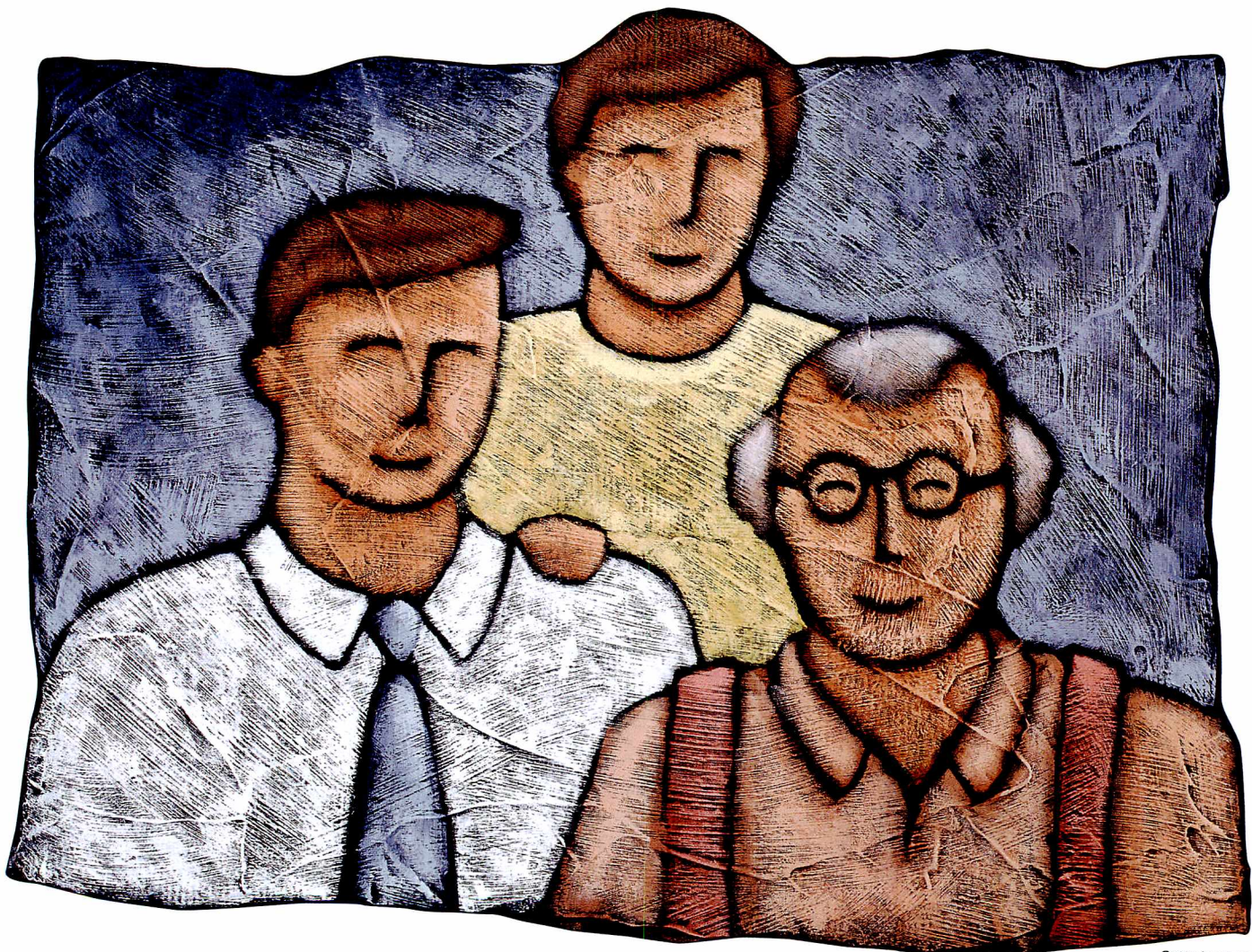
Medical Device Information for Consumers
www.fda.gov/cdrh/consumer/index.html

New Device Approvals
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/mda/mda-list.cfm?list+1

"FDA Patient Safety News"
www.fda.gov/PSN

Online Version of 'My Family Health Portrait'

Available in
English and Spanish



Getty Images

A revised and more convenient computer tool is available without cost, in English and Spanish, to help families gather their health information.

"I encourage all families to take time to collect important health history information that can benefit all family members," U.S. Surgeon General Richard H. Carmona, M.D., M.P.H., said in announcing the new tool in February 2006. "Even with all the high-tech tests, medicines, and procedures available in today's modern health-care setting, family health history remains the cornerstone of our efforts to prevent disease and promote personal health. It's clear that knowing your family history can save your life."

Health care professionals have known for a long time that many diseases, such as cancer, diabetes, and heart disease, can run in families. A detailed family history can predict the disorders for which a person may be at increased risk and can help to develop more personalized approaches to prevent illness or detect it early when it is most treatable.

Developed by the Office of the Surgeon General, the computer tool, called "My Family Health Portrait," is a revised version of one released last year that required downloading

to a user's computer. The new version is Web-based, which allows it to be operated on computers with Internet access running any one of several standard browsers. The tool organizes a family's health history into a printout that people can take to their health care professional to help determine whether they are at higher risk for disease. All personal information entered into the program resides on the user's computer only. No information is available to the federal government or any other agency.

The tool guides users to compile information for their family members on six common diseases—heart disease, stroke, diabetes, colon cancer, breast cancer, and ovarian cancer—as well as information about any other conditions that are of particular interest to the family. The tool focuses on these six diseases because a genetic link is known for each and because a preventive strategy can be developed to avoid illness.

"My Family Health Portrait" is part of a national public health campaign called the U.S. Surgeon General's Fam-

ily History Initiative, which encourages all American families to learn more about their family health history. The surgeon general launched the campaign in cooperation with other organizations within the U.S. Department of Health and Human Services (HHS), including the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH); the Centers for Disease Control and Prevention (CDC); the Agency for Healthcare Research and Quality (AHRQ); and the Health Resources and Services Administration (HRSA).

In unveiling the My Family Health Portrait tool, Carmona also praised the National Council of La Raza's Institute for Hispanic Health (NCLR/IHH) for developing its own family history consumer outreach program for Spanish-speaking Americans, based on the framework made available by the Family History Initiative. The NCLR is the largest national Latino civil rights and advocacy organization in the United States. ■

Web-based family history tool

<https://familyhistory.hhs.gov/> (English)

<https://familyhistory.hhs.gov/spanish> (Spanish)

U.S. Surgeon General's Family History Initiative

www.hhs.gov/familyhistory

Prostate Health:

What Every Man
Needs to Know

vention//We



By Carol Rados

To screen, or not to screen: that is the question. Whether men should get tested for prostate cancer when they have no symptoms is a long-running debate within the medical community.

There is good evidence, according to the Centers for Disease Control and Prevention (CDC), that the current prostate specific antigen (PSA) test approved in 1986 by the Food and Drug Administration to screen for prostate cancer can detect the disease in its early stages. Evidence, however, is mixed and inconclusive about whether early detection actually saves lives. A study published in the Jan. 9, 2006, issue of the *Archives of Internal Medicine* found that screening with the PSA test does not cut down on deaths from the disease. Moreover, it is not clear whether the benefits of screening outweigh the risks of follow-up testing and cancer treatments.

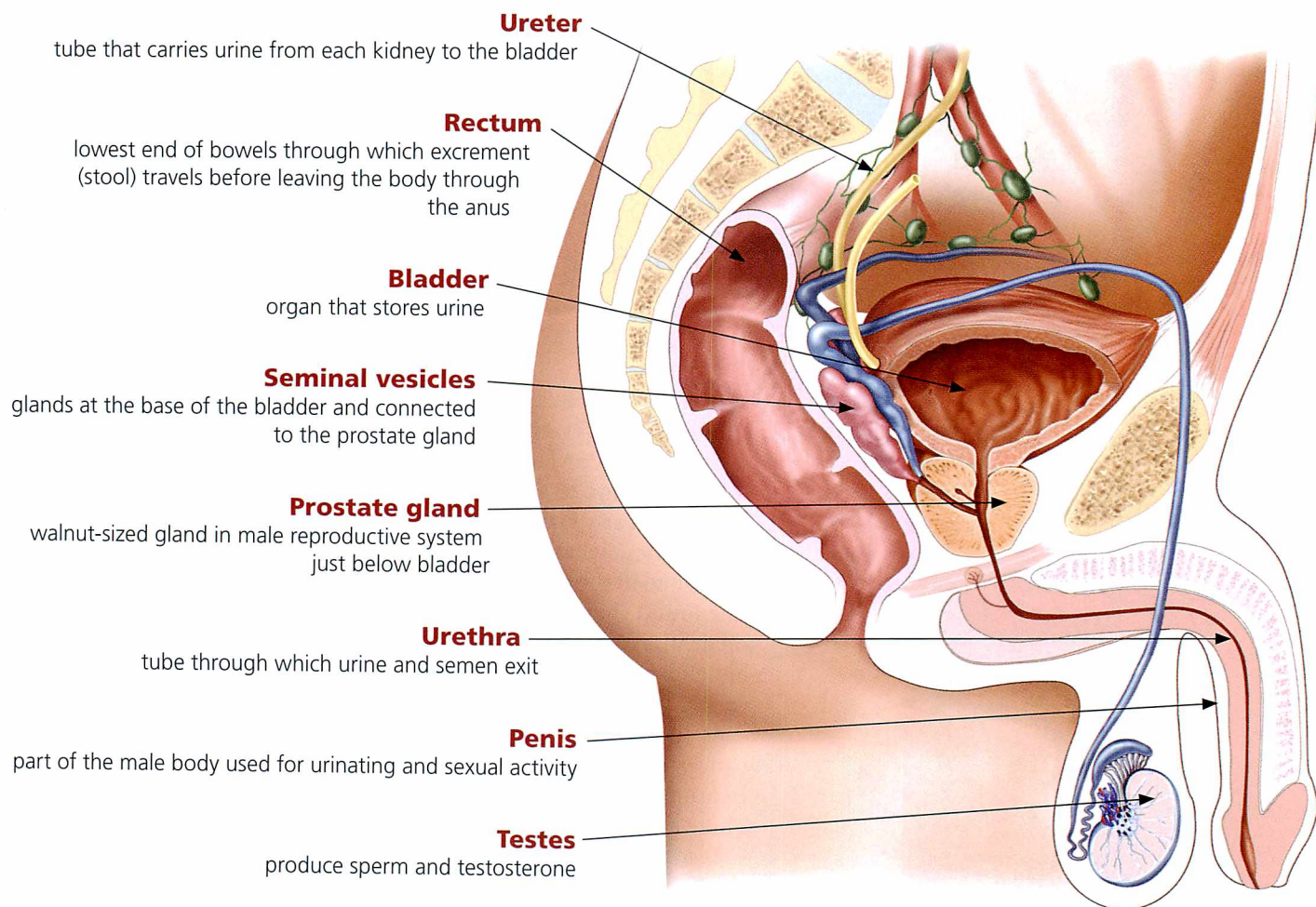
At the same time, evidence, such as a drop in the prostate cancer death rate—which some say could be due to improved treatments—suggests that early PSA testing may be saving lives. There are no definitive answers.

According to the National Cancer Institute (NCI), other than skin cancer, prostate cancer is the most common form of cancer and the second leading cause of cancer-related deaths among men in the United States. But doctors' recommendations on screening for the disease vary. Some encourage annual screenings for men older than age 50; others recommend against routine screening. American Cancer Society (ACS) Screening Director Robert Smith, Ph.D., says that the January *Archives of Internal Medicine* study "isn't strong enough to say definitively that prostate cancer screening isn't valuable."

The controversy, meanwhile, is contributing to a growing quandary for doctors and their patients: what's a man to do?

Until there is more evidence and, perhaps, a scientific consensus of the screening benefits, most doctors and medical organizations, including the NCI, the ACS, and the CDC, agree that men should learn all they can about what is known and what is not known of the benefits and limitations of early detection and treatment for prostate cancer, so that they can make their own informed decisions.

The Male Urinary and Reproductive System



NCI

Cancer screening is just one health concern related to the prostate—a very important part of the male reproductive system. As men age, the prostate may become a source of troubling, often inconvenient problems that can, but don't necessarily, include cancer. And since the symptoms of some noncancerous prostate conditions can mimic cancer, many men who learn they have a problem often assume the worst. In general, growing older raises a man's risk for prostate problems, including cancer.

For these reasons, it is important that men know and understand, in the earliest stages, the changes that can occur in the prostate and could, ultimately, affect their health.

Understanding Prostate Changes

The prostate is a walnut-shaped gland found only in men. It lies in front of the rectum, sits just below the bladder where urine is stored, and surrounds the tube that carries urine from the body (urethra). The gland functions as part of the male reproductive system by making a fluid that becomes part of semen, the white fluid that contains sperm.

Three main problems can occur in the prostate gland: inflammation or infection, called prostatitis; enlargement, called benign prostatic hyperplasia (BPH); and cancer.

Prostatitis is a clinical term used to describe a wide spectrum of disorders ranging from acute bacterial infection

to chronic pain syndromes affecting the prostate, says Regina Alivisatos, M.D., a medical officer in the FDA's Center for Drug Evaluation and Research (CDER).

There are four main types of prostate syndromes. Acute bacterial prostatitis, although the least common of the four types, is the easiest to diagnose and treat. This form, Alivisatos says, is caused by bacteria and comes on suddenly. "It's not something a doctor or patient would miss. It hurts, and there are a lot of white blood cells and bacteria in the urine," she says. Symptoms include chills and fever, pain in the lower back and genital area, and burning or painful urination.

Chronic bacterial prostatitis also is

caused by bacteria, but does not come on suddenly. The only symptom a man may have is bladder infections with the same bacteria that keep coming back. The cause may be a defect in the prostate that allows bacteria to collect in the urinary tract. Usually, the prostate is normal or somewhat tender on exam.

Chronic (nonbacterial) prostatitis—chronic pelvic pain syndrome is the most common, but least understood, form of prostatitis. Found in men of any age from the late teens on, the symptoms go away and then return without warning, and may be inflammatory or noninflammatory. In the inflammatory form, urine, semen, and other fluids from the prostate show no evidence of a known infecting organism, but do contain the kinds of cells the body usually produces to fight infection. In the noninflammatory form, no evidence of inflammation, including infection-fighting cells, is present.

Asymptomatic inflammatory prostatitis is the diagnosis when there are no symptoms, but the patient has infection-fighting cells in the semen. It is often found when a doctor is looking for causes of infertility or is testing for prostate cancer.

According to the NCI, prostatitis is not contagious, and the vast majority of cases are not spread through sexual contact. Only a doctor can tell one form of prostatitis from another.

BPH, or benign prostatic hyperplasia, is the second main problem that can occur in the prostate. "Benign" means "not cancerous"; "hyperplasia" means "too much growth." The result is that the prostate becomes enlarged. The gland tends to expand in an area that doesn't expand with it, causing pressure on the urethra, which can lead to urinary problems.

The urge to urinate frequently, a weak urine flow, breaks in urine stream, and dribbling are all symptoms of an enlarged prostate. Because the prostate normally continues to grow as a boy matures to manhood, BPH is the most common prostate problem for men older than 50. Older men are at risk for prostate cancer as well, but it is much less common than BPH.

A doctor will do a digital rectal exam (DRE) to check the size and condition

of the prostate by inserting a gloved finger into the rectum. The doctor also may need to do special X-rays or scans to check the urethra, prostate, and bladder. BPH can lead to urinary problems like those with prostatitis. By age 60, many men have signs of BPH. By age 70, almost all men have some prostate enlargement. At its worst, BPH can lead to a weak bladder, bladder or kidney infections, complete blockage in the flow of urine, and kidney failure.

It is true that some men with prostate cancer also have BPH, but the two conditions are not automatically linked. Most men with BPH do not develop prostate cancer. But because the early symptoms for both conditions could be the same, a doctor would need to evaluate them.

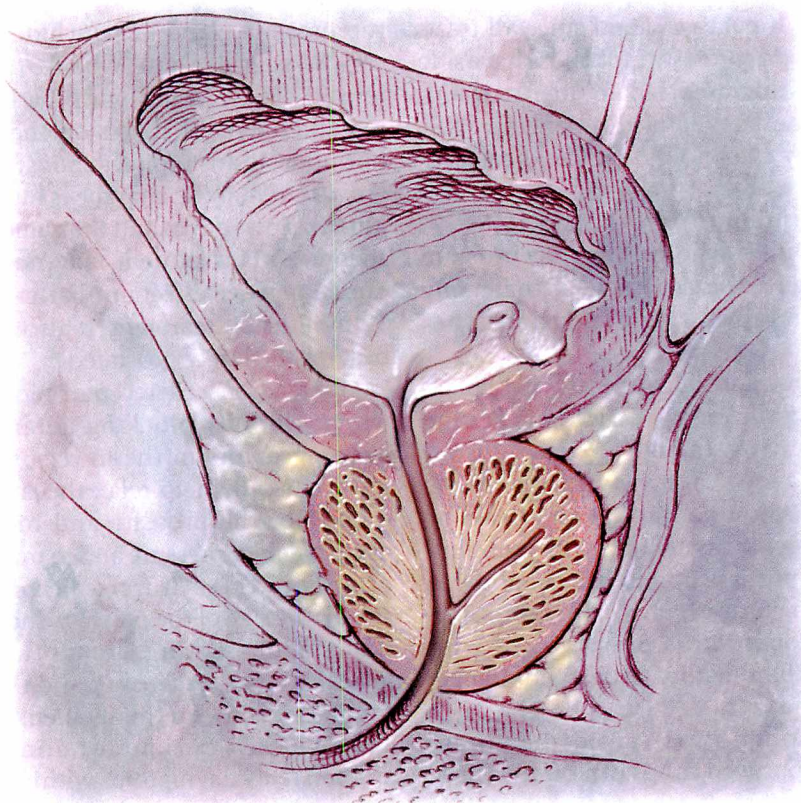
Different prostate problems sometimes have similar symptoms, according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). For example, one man with prostatitis and another with BPH may both have a frequent, urgent need to urinate. A man with BPH may have trouble beginning a stream of urine;

another may have to urinate frequently at night. Or, a man in the early stages of prostate cancer may have no symptoms at all.

But according to the NCI, one prostate change does not lead to another. For example, having prostatitis or an enlarged prostate does not increase the chance for prostate cancer. It is also possible to have more than one condition at a time. This confusing array of potential scenarios makes a case for the importance of all men, especially after age 45, to have a thorough medical exam that includes the PSA test and DRE every year.

Adam S. Kibel, M.D., associate professor of urologic surgery at Washington University in St. Louis, says that in his practice, the most common concerns of men with prostate problems include the frequent need to urinate (particularly at night), the inability to delay urination (urgency), and the inability to urinate at all.

"Getting up to go three, four, or even five times every night or having to get up in the middle of a movie—these things can interfere with a man's life-



Artville

Normal Prostate Gland

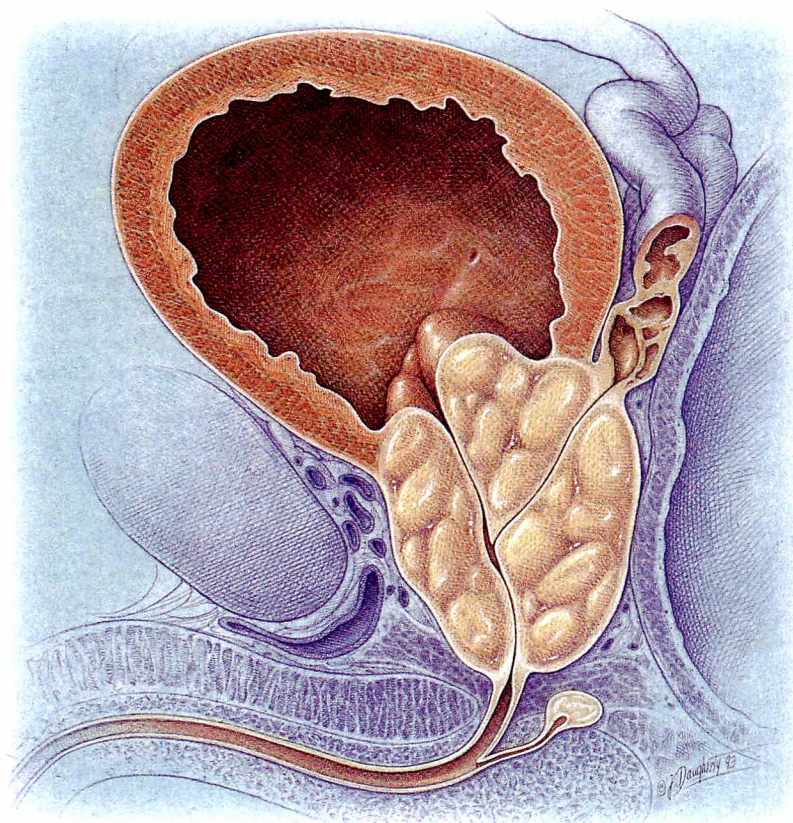


Photo Researchers Inc.

Enlarged Prostate Gland

style," Kibel says. "And since all treatments [for prostate problems] have side effects, it's important for men to evaluate the effects of the different therapies so they can know what to expect."

A Roundup of Treatments

For men who are having prostate problems, the good news is that many new and effective treatments are available.

For prostatitis, getting the right diagnosis of the exact type is key to getting the best treatment. George Benson, M.D., a medical reviewer in the FDA's CDER, says that prostatitis caused by an infection is treated with antibiotics, "but there are no drugs approved to treat chronic pelvic pain syndrome. This condition is often treated with anti-inflammatory drugs and analgesics," he says.

Although BPH cannot be cured, FDA-approved drugs can often relieve its symptoms. Such drugs to treat BPH currently include two major classes. The 5 alpha-reductase inhibitors shrink

the prostate gland and include Proscar (finasteride) and Avodart (dutasteride). These drugs work by blocking an enzyme that acts on the male hormone, testosterone, to boost organ growth. When the enzyme is blocked, growth slows down and the gland may shrink. This treatment may not produce a positive effect until after six to 12 months of treatment. It also works best for the larger prostate.

Alpha-adrenergic receptor blockers, which work by blocking adrenergic nerve receptors in the lower urinary tract, basically help relax the smooth muscle of the prostate and bladder neck to relieve pressure and to improve urine flow. These drugs, which do not shrink the size of the prostate, include: Cardura (doxazosin), Flomax (tamsulosin), Hytrin (terazosin), and Uroxatral (alfuzosin). For many men, these alpha-blockers can improve urine flow and can reduce symptoms within days. Possible side effects include dizziness, headache, fatigue, and a lowering of blood pressure.

Non-Surgical Treatments

Because drug treatment is not effective in all cases, and different surgeries are often associated with serious complications, researchers have developed a number of procedures, including transurethral—accessing the affected area through the urethra—using FDA-approved or cleared medical devices to relieve BPH symptoms. These procedures are considered minimally invasive, non-surgical treatments:

Transurethral microwave thermotherapy (TUMT). Uses microwaves sent through a catheter to heat and destroy excess prostate tissue. For most TUMT devices, a cooling system protects the portion of the urethra that goes through the prostate during the procedure. The TUMT procedure takes about one hour and can be an option for men who should not have major surgery because they have other medical problems. Microwave therapy does not cure BPH, but it reduces urinary frequency, urgency, straining, and intermittent flow. It does not completely correct the problem of incomplete emptying of the bladder. TUMT has limited long-term effects. Up to 40 percent of men treated may need re-treatment a few years later. Though rare, there have been cases reported of incontinence and impotence with this procedure. Although microwave thermotherapy has been demonstrated to be safe and effective, the FDA has been concerned in the past about unexpected procedure-related complications that occurred since these devices were marketed.

Water-induced thermotherapy (WIT). Uses a device to treat urinary symptoms of BPH. The device uses hot water circulated through an inflated balloon catheter to heat the inside of the prostate, causing adjacent tissue to die. Over time, some tissue is either expelled through urine or absorbed internally.

Surgical Treatments

A number of devices with different modes of action have been cleared by the FDA to perform transurethral surgery that usually relieves any obstruction and incomplete emptying of the bladder. Less tissue is removed in these

procedures, which is either ablated or vaporized, rather than cut. They are considered minimally invasive surgeries:

Transurethral needle ablation (TUNA). Delivers low-level radio frequency energy through twin needles to burn away a well-defined area of the enlarged prostate.

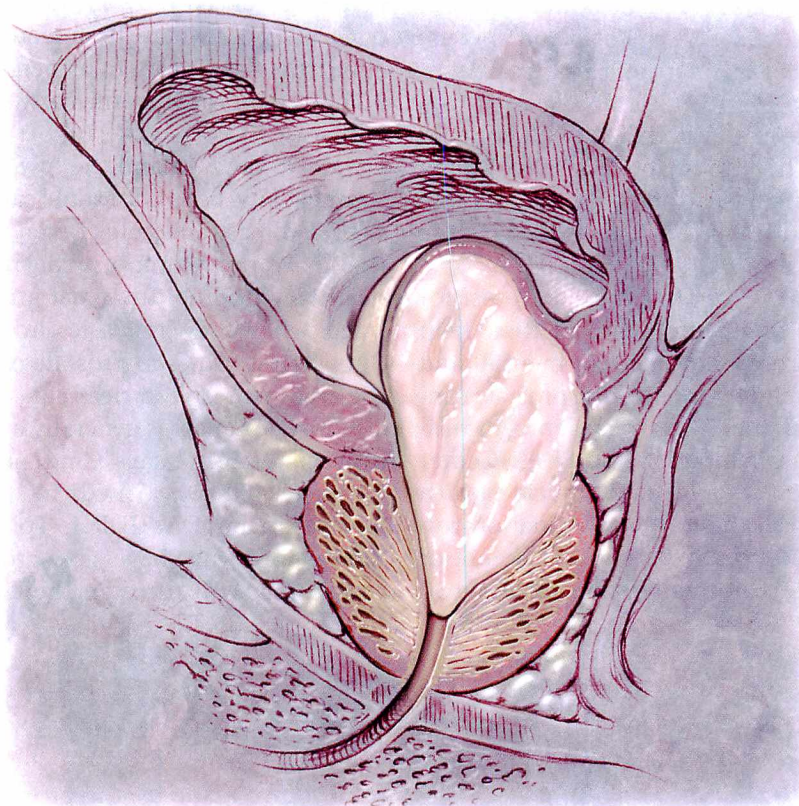
Transurethral vaporization of the prostate (TUVP). Uses electrical current to vaporize prostate tissue.

Laser surgery. Uses side-firing laser fibers to vaporize obstructing prostate tissue. The doctor passes the laser fiber through the urethra into the prostate and then delivers several bursts of energy lasting 30 seconds to 60 seconds. The laser energy destroys prostate tissue and causes shrinkage. Laser surgery requires anesthesia and a hospital stay. One advantage of this laser evaporating surgery may be that it causes little blood loss. It also allows for a quicker recovery time. This procedure may not be effective on large prostates. Its long-term effectiveness is unknown.

Transurethral resection of the prostate (TURP). Considered the gold standard for treating BPH, and accounts for 90 percent of all BPH surgeries. The doctor passes an instrument through the urethra and trims away extra prostate tissue. The tissue is sent to the lab to check for prostate cancer. This surgery requires anesthesia and a hospital stay. Recovery from TURP is much shorter than with open surgery, but TURP and other procedures for BPH remove only enough tissue to relieve urine blockage.

Transurethral incision of the prostate (TUIP). Similar to TURP but, instead of removing tissue, widens the urethra by making a few small cuts in the bladder neck, where the urethra joins the bladder, and in the prostate gland itself, which relieves pressure without trimming away tissue. This procedure is often done on smaller prostates. The NIDDK says that although people believe that TUIP gives the same relief as TURP with less risk of side effects, its advantages and long-term side effects have not been clearly established.

Open prostatectomy. Removes the



Artville

Inflamed Prostate Gland

prostate through a cut in the lower abdomen or between the anus and scrotum. This procedure is done only in rare cases when the prostate is very large with severe obstruction, or when other procedures can't be done. General or spinal anesthesia is used, and a catheter remains for up to seven days after the surgery. This surgery carries a higher risk of complications, such as incontinence and impotence, than medical treatment or less invasive surgeries. Removed tissue is sent to the lab to check for prostate cancer, and periodic follow-up is recommended.

All of these procedures, whether less invasive or not, often require patients to wear a catheter for three to four days after surgery, and carry some risk of urinary incontinence and impotence. The CDRH says that the more invasive the procedure, the more risks are involved. Because all of these procedures involve the removal of some, but not all, of the prostate, regular follow-ups are necessary to watch for cancer.

An alternative treatment that has become popular is an herbal pill—saw palmetto—used by millions of men in the United States to treat BPH. Saw palmetto, however, was recently found to have no effect in reducing the frequent urge to urinate or other annoying symptoms of an enlarged prostate. Published in the Feb. 9, 2006, *New England Journal of Medicine*, the year-long study found that the plant extract was no more effective than inactive pills (placebos) in easing symptoms of BPH.

Experts agree that the best protection against prostate problems is to have regular medical checkups that include a prostate exam.

Prostate Cancer and the PSA Tests

The third major problem that can occur in the prostate is cancer. It grows quietly for years, giving most men with the early disease no obvious symptoms.

"It's a silent killer," says J. Brantley Thrasher, M.D., chairman of urology at

the University of Kansas Medical Center in Kansas City, Kan., and spokesman for the American Urological Association (AUA). "So, most men with a nodule or elevated PSA aren't going to know it." That's why Thrasher and the AUA believe strongly in PSA testing. "It's an imperfect marker, but it's the best we've got."

The FDA approved the PSA test for use in conjunction with a DRE to help detect prostate cancer in men 50 and older, and for monitoring prostate cancer patients after treatment. According to scientists in the FDA's Center for Devices and Radiological Health (CDRH), the finger examination can detect cancer in the form of a nodule or hardness, normally when it is about 50

percent advanced and not curable. PSA detects cancer when the finger exam appears normal in about 35 percent to 40 percent of cases, in the early stages of disease.

Indeed, the NCI and the ACS agree that checking people for some cancers, such as breast and colon, even when they have no symptoms, can reduce deaths by finding tumors at an early stage, when they are easiest to treat. But when it comes to prostate cancer, the argument isn't so clear-cut.

"Prostate cancer is generally a slow-growing cancer," says Cmdr. James P. Reeves, Ph.D., a medical device reviewer in the FDA's CDRH. "For those men who do not have slow-growing cancer that will threaten their lives,

we do not have sufficient information that PSA or DRE testing prior to or after diagnosis would distinguish such men from those who will have cancer, but will not die from that cancer."

So what's the harm in being tested? Reeves says that screening for prostate cancer sometimes finds tumors that wouldn't cause any problems if left untreated. Many professional medical organizations agree. But there's no good way at this time to tell which cancers need treating and which don't. Therefore, many men who are diagnosed with prostate cancer likely will be treated, but also may experience unnecessary and harmful side effects that could lower their quality of life. About 15 percent to 50 percent of men treated for prostate cancer by surgery, radiation therapy, or hormonal therapy will have urinary incontinence and sexual impotence, and in extremely rare cases, scarring of the intestine.

"These percentages indicate that there is a risk for significant harm from over-treatment of prostate cancer," Reeves says. "Is the cure worse than the disease, especially if the cancer is not significant enough to threaten a man's life over 10 to 15 years of remaining life expectancy?"

There are some men who have ample reason to choose the cure. "My grandfather and my father had prostate cancer," says 54-year-old David Glunt from St. Louis. "And at 51 years old, I wasn't taking any chances." Glunt's younger brother tested positive for prostate cancer four years ago; Glunt tested negative. "But I was betting all along that I would get it," he says. A year later, he did.

Speaking on behalf of the AUA, Thrasher says that while a more specific and sensitive marker is needed, questioning the validity of early screening puts men at risk. "Physicians should discuss the risks and benefits of prostate cancer screening on a yearly basis with men 50 to 75 years of age, and earlier if they are African-American or have a family history of prostate cancer," Thrasher says. Screening, he adds, should include both a PSA test and DRE.

Because so much remains unknown about how to interpret the PSA test, its

The Science Behind Prostate Specific Antigen

Prostate specific antigen (PSA) is a substance made by the prostate gland. Although the substance is mostly found in semen, a small amount is also present in the blood. According to the American Cancer Society, most men have levels under 4 nanograms per milliliter of blood (ng/ml). When prostate cancer develops, the PSA level usually goes above 4ng/ml but in some cases, the cancer can be present at levels lower than 4. A PSA rise does not automatically mean cancer. PSA also rises when the prostate is enlarged because of benign prostatic hyperplasia, or BPH, and sometimes with prostatitis.

If the level is borderline range between 4ng/ml and 10ng/ml, a man has about a 25 percent to 35 percent chance of having prostate cancer. PSA higher than 10ng/ml could mean between a 40 percent and 50 percent chance for cancer, and the risk increases further as the PSA level increases. PSA is an ideal marker for prostate cancer because it is basically restricted to prostate cells.

Most PSA tests measure "total PSA," or the amount that is bound to blood proteins. But some tests measure not only total PSA, but another component called free PSA, which floats unbound in the blood. Free PSA above 25 percent is a stronger indication that cancer is not present. Comparing the two helps doctors rule out cancer in men whose PSA is mildly elevated from other causes.

The benefits of screening for prostate cancer are still being studied. Scientists are researching ways to distinguish between cancerous and non-cancerous conditions, those that are slow-growing and fast-growing, and potentially lethal cancers through new PSA methods and other tumor markers.

The National Cancer Institute and other medical organizations are conducting the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, or PLCO Trial, to determine whether certain screening tests reduce the number of deaths from these cancers. The PSA and DRE tests are being studied to see whether yearly screening will decrease a man's chance of dying from prostate cancer. ■

ability to discriminate between cancer and noncancerous conditions, and the best course of action if the PSA is high, the magnitude of the test's potential risks and benefits also is unknown.

Still, Kibel adds, "the PSA controversy should not stop men from discussing being tested with their doctors."

In its early stages, prostate cancer stays in the prostate and is not life-threatening. But without treatment, cancer eventually spreads to other parts of the body, often resulting in death.

Doctors have several ways to treat prostate cancer. The choice depends on many factors, such as whether or not the cancer has spread beyond the prostate, the patient's age and general health, and how the patient feels about the treatment options and their side effects. According to both the NCI and the ACS, approaches to treatment include: watchful waiting to see whether the cancer is growing slowly and not causing symptoms; surgery to remove the entire prostate and surrounding tissues; and internal and external radiation therapy, both of which use high-energy rays to kill cancer cells and shrink tumors. Hormone therapy and chemotherapy drugs are approved to treat the various advanced stages of cancer.

The gold standard for treating early, localized prostate cancer is radical retropubic prostatectomy. The whole prostate and seminal vesicles are removed. At Johns Hopkins Hospital in Baltimore, the surgery has improved over the years with the development of a nerve-sparing procedure. This procedure, says the CDRH, in most cases, avoids sexual impotence. The same technique has been used in the last decade by many urologists in the United States and throughout the world.

Computer- or robot-assisted surgery was cleared by the FDA in 2005 for use in all urological procedures, including the removal of the prostate (radical prostatectomy) because of cancer. Even though the prostate is surrounded by nerves and muscles that affect urinary, rectal, and sexual functions, doctors say that improved vision and flexibility of the instruments allow for magnification of the prostate during this procedure. "It's too early to tell if this

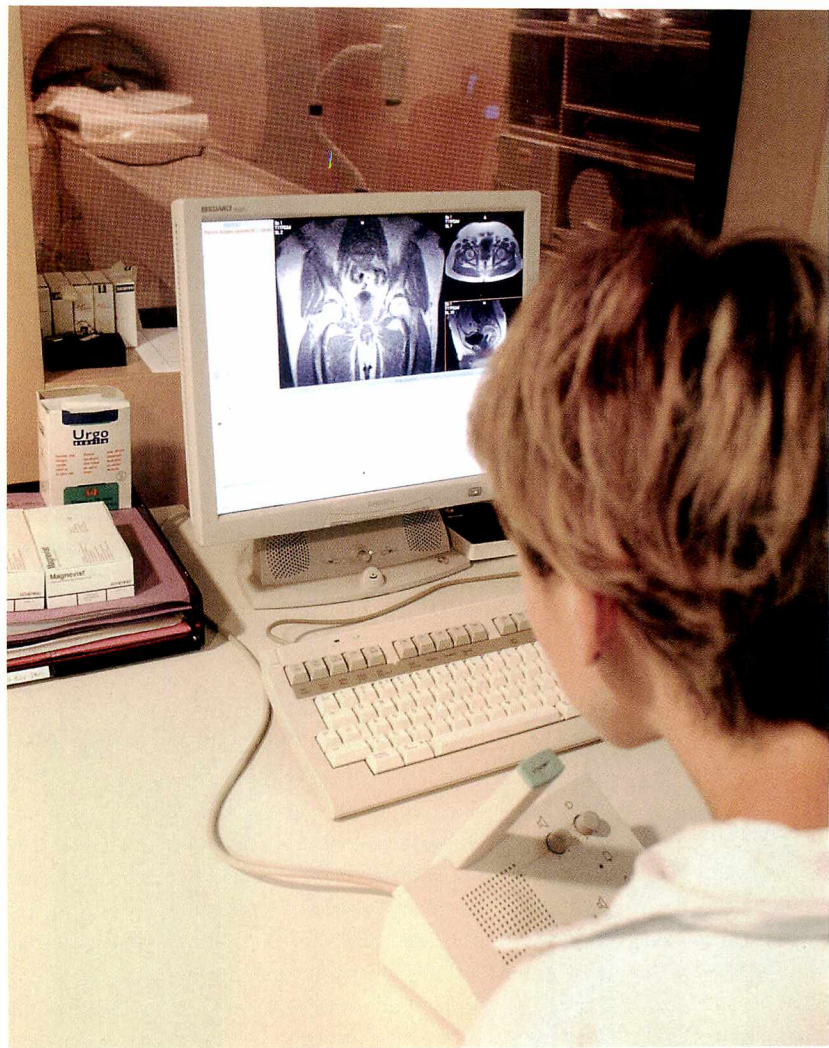


Photo Researchers Inc.

A medical technician monitors a patient undergoing an MRI of the prostate gland.

will equate to more precision and better outcomes," adds Thrasher.

Regular checkups are important even for men who have had surgery. BPH surgery does not protect a man against prostate cancer, because the prostate is not completely removed.

Research is under way to evaluate new approaches to finding even more effective treatments for prostate and urinary disorders. ■

For More Information

Food and Drug Administration
www.fda.gov

National Kidney and Urological
Diseases Information Clearinghouse
www.kidney.niddk.nih.gov/
(800) 891-5390

American Urological Association
www.auanet.org

National Cancer Institute
www.cancer.gov/prostate
(800) 422-6237

American Cancer Society
www.cancer.org
(800) 227-2345



Treating Restless Legs Syndrome

Restless Legs Syndrome (RLS) is a medical condition characterized by unpleasant sensations in the legs, including burning, tugging, and tightening, and feels “like insects crawling inside the legs,” according to the National Institute of Neurological Disorders and Stroke (NINDS).

Although experts have known about RLS for years, a broader lack of awareness appears to have severely limited diagnosis of the condition. A survey conducted by the Restless Legs Syndrome Foundation (RLSF) not only found that more than half of those who responded had never heard of RLS, but also found that many did not fully understand the impact that the condition can have on daily life.

“RLS is sometimes described as ‘the most common condition you’ve never heard of,’” says Georgianna Bell, executive director of the RLSF.

The abnormal sensations (paresthesias) or unpleasant abnormal sensations (dysesthesias) often range from uncomfortable to irritating and painful.

The NINDS says that some researchers estimate that RLS affects as many as 12 million people in the United States. However, others estimate a much higher occurrence because RLS is thought to be underdiagnosed, and, in some cases, misdiagnosed. There are a number of people who don’t seek medical attention, because they believe that their concerns will not be taken seriously, their symptoms are too mild, or their condition is not treatable.

In May 2005, the Food and Drug Administration approved the first drug treatment for RLS for which the cause is unknown (idiopathic). Called Requip (ropinirole), the drug is specifically labeled for the treatment of moderate-to-severe symptoms of the condition. According to the RLSF, the FDA’s approval of Requip represents a significant step forward in patient care. “It is our hope that the millions of people suffering from RLS will benefit from this increased awareness and will more easily find the help they need,” says Bell.

People with RLS feel uncomfortable sensations in their legs, especially when sitting or lying down, accompanied by an irresistible urge to move about. The NINDS says that these sensations usually occur deep inside the leg, between the knee and ankle. More rarely, they occur in the feet, thighs, arms, and hands. Although the sensations can occur on just one side of the body, they most often affect both sides.

Because moving the legs, or other affected parts of the body, temporarily relieves the discomfort, people with RLS often keep their legs in motion to minimize or prevent the sensations. They may pace the floor, constantly move their legs while sitting, and toss and turn in bed.

The most distinctive or unusual aspect of RLS is that lying down and trying to relax actually activates the symptoms. As a result, most people with RLS have difficulty falling asleep and staying asleep. The NINDS says that left untreated, the condition causes exhaustion and daytime fatigue. Many people with RLS report that their jobs, personal relations, and daily activities are affected as a result of their lack of sleep. They are often unable to concentrate, have impaired memory, or fail to accomplish daily tasks.

What Causes RLS?

The cause of RLS, in most cases, is unknown. A family history of the condition is seen in about half of these cases, the NINDS says, suggesting a genetic basis for the disorder. In some cases, RLS appears to be related to chronic medical conditions, including low iron levels, severe kidney disease, and peripheral nerve diseases—referred to as “secondary forms of RLS.” These secondary forms can also be associated with pregnancy and the use of certain medications.

Researchers also have found that caffeine, alcohol, and tobacco may aggravate or trigger symptoms in people who are predisposed to the development of RLS. The reduction or complete elimination of such substances may relieve symptoms, but the NINDS says that it remains unclear whether either can prevent RLS symptoms entirely.



Black Star/Tyrone Turner

Benjamin Brown, 34, of Bethesda, Md., first experienced Restless Legs Syndrome (RLS) when he was in college. Brown has not felt the leg sensations for more than seven years.

NINDS researchers are investigating the possible role of dopamine function in RLS. Dopamine is a chemical messenger that carries nerve cell signals in the brain that control body movement. When the dopamine system does not function properly, it may upset the normal communication of these signals. Researchers suspect that impaired transmission of dopamine signals may play a role in RLS.

RLS was first fully described in a paper published in 1945 by a Swedish neurologist. Although he did not call the disorder RLS, the neurologist characterized the condition as having sensory symptoms and motor disturbances of the limbs, mainly during rest.

difficult for me to fall asleep," he says, but only occasionally. Brown says that although a long walk would help alleviate the sensation, he remembers that "it wasn't easy to get rid of."

As he got older, the condition got better, to the point where "it just didn't seem like it was at the level where you'd see a health professional." Despite not seeking treatment for the disorder, Brown says the feelings gradually went away. In fact, he says he hasn't felt the leg sensations for more than seven years.

If such improvements do occur, the NINDS says it is usually during the early stages of the disorder. In general, however, symptoms become more

Who Has RLS?

Men and women experience RLS, but the incidence may be slightly higher in women, the NINDS says. The syndrome may begin at any age, even in infancy, but most people who are severely affected are middle-aged or older. In most cases, the severity of the disorder increases with age, but there are exceptions, like that of Benjamin Brown.

The 34-year-old Bethesda, Md., resident experienced much worse symptoms of RLS through high school and as an avid athlete in college. "Restless is the best word to describe the feelings," Brown says. "It felt like a tingling or tightening in my legs, like I needed to stretch or exercise them." Brown says that the sensations came on usually during sedentary periods in the evening, when he was watching TV or studying for school. "It may have made it more dif-

severe over time.

Older patients experience symptoms more frequently and for longer periods of time.

The symptoms of the condition vary in severity and duration from person to person. Mild RLS generally occurs episodically, with only mild disruption of sleep, and causes little distress. In severe cases, the symptoms of RLS occur more than twice a week and result in burdensome interruption of sleep and impairment of daytime function.

More than 80 percent of people with RLS also experience a more common condition known as periodic limb movement disorder (PLMD), according to the NINDS. PLMD is characterized by involuntary leg twitching or jerking movements during sleep that typically occur every 10 to 60 seconds, sometimes throughout the night. The symptoms can cause repeated awakening and severely disrupted sleep.

The difference between the two disorders is that PLMD occurs while people are sleeping and has no symptoms, while RLS keeps people awake because of the symptoms. Although many patients with RLS also develop PLMD, the NINDS says that most people with PLMD do not experience RLS. And like RLS, the cause of PLMD is unknown.

How Is RLS Diagnosed?

There is no single diagnostic test for RLS. It is diagnosed clinically by evaluating a person's symptoms and medical history. In 1995, the International Restless Legs Syndrome Study Group identified four basic criteria for diagnosing RLS: a desire to move the limbs, symptoms that are worse or present only during rest and are partially or temporarily relieved by activity, motor restlessness, and worsening of such symptoms at night. The NINDS says that most people with RLS have sleep disturbances, largely because of the limb discomfort and jerking.

Despite established standard criteria, the clinical diagnosis of RLS is often difficult to make. Doctors must rely on patients' descriptions of the symptoms and information from their medical history, including past medical problems, family history, and current medi-

cations. The NINDS says that blood tests to rule out anemia—a reduction in the number of red blood cells—as well as decreased iron stores, diabetes, and renal dysfunction, should be performed. Other tests that measure electrical activity in muscles and nerves also are recommended.

Other tests are important to determine whether the RLS is secondary to another disorder that requires treatment. The treatment of that disorder may, on its own, relieve the symptoms of RLS.

Most people find the symptoms to be less noticeable during the day and more pronounced in the evening or at night. For many, the symptoms disappear by

specifically approved to treat moderate-to-severe RLS last year, after it was found to be effective in three studies in adults. The studies measured effectiveness of the drug using a patient-rated scale that measures different aspects of RLS, including severity of muscle movement and discomfort, sleep disturbance, mood, and overall effect on quality of life, as well as an investigator-rated scale that scores improvement of symptoms after treatment. All three studies demonstrated a difference between the treatment group receiving Requip and the group receiving an inactive pill (placebo).

There has been a clinical impression that “drugs that help Parkin-

Prognosis

Although there is no cure for RLS, treatment with Requip can control the disorder, thereby minimizing symptoms and increasing periods of restful sleep. In most cases, RLS can be effectively diagnosed and treated by a primary care physician—in the more difficult cases, by a sleep specialist or a neurologist.

As distressing a condition as it is, some patients like Brown do experience remissions, or periods in which symptoms decrease or disappear. And the NINDS says that a diagnosis of RLS does not indicate the onset of another neurological disorder.

Currently, another medication for

Most people find the symptoms to be less noticeable during the day and more pronounced in the evening or at night.

early morning. Other triggering situations are periods of inactivity, such as long car trips, watching a movie, long-distance airplane flights, or relaxation exercises.

How Is RLS Managed?

Movement of the legs generally brings about temporary relief from RLS. And sometimes treating associated medical conditions, such as diabetes or Parkinson's disease, will often alleviate many symptoms.

While central nervous system depressants, anticonvulsants, dopaminergic agents—largely used to treat Parkinson's disease—and opioids have been commonly used by doctors to treat RLS, there have been no clinical studies conducted to support their safety and effectiveness in treating the condition. Finally, Requip was approved for RLS, based on scientific evidence from clinical trials.

First approved for Parkinson's disease in 1997, Requip is a dopamine agonist—it directly stimulates dopamine receptors in the brain. The drug was

son's disease seem to also help RLS,” says Norman Hershkowitz, M.D., the primary clinical reviewer for RLS in the FDA's Center for Drug Evaluation and Research. But Hershkowitz says that the physiological mechanism—or what's actually happening in the body when RLS occurs—isn't well understood.

Requip works to prevent the symptoms of RLS, so patients take the drug at the same time every day, rather than on an as-needed basis. Common side effects include nausea, headache, and vomiting. The drug's label also includes a caution that Requip has been associated with sedating effects, including sleepiness, and the possibility of falling asleep while engaged in activities of daily living. Fainting or low blood pressure also may occur, particularly during initial treatment or dosing.

The RLSF reports that some medicines can make RLS worse and that people need to make their doctors aware of all drugs they are taking, including herbal remedies and over-the-counter medicines.

treating the symptoms of the condition is under FDA consideration. Additional research should provide a scientific understanding of how RLS occurs, which is likely to lead to more effective treatments and even prevention of the disorder. ■

For More Information

The National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov
(800) 352-9424

Restless Legs Syndrome Foundation
www.rls.org

National Sleep Foundation
www.sleepfoundation.org

**RETURN TO
SENDER**



THE FDA AND PRODUCT RECALLS

By Michelle Meadows

Most recalls of products regulated by the Food and Drug Administration are voluntary. One way or another, a company discovers a problem or a potential problem and then initiates a product recall in cooperation with the FDA. A recall is a way to remove or correct products that violate laws enforced by the agency.

Compared to court actions, which can be time-consuming and costly, a voluntary approach to recalls is preferable. "It's the most efficient and effective way to get defective products off the market quickly and protect the public health," says David Elder, director of the FDA's Office of Enforcement.

The FDA handles recalls for all the products it regulates—human drugs; devices and radiation-emitting products; biologics such as vaccines and blood products; veterinary products, which include animal drugs and animal feed; cosmetics; and about 80 percent of the foods consumed in the United States. The Food Safety and Inspection Service, part of the U.S. Department of Agriculture (USDA), handles recalls for meat, poultry, and certain egg products.

Types of Voluntary Recalls

Sometimes, a company discovers a problem with a product and then contacts the FDA. That's what happened in a highly unusual recall announced in February 2006 by Mead Johnson, based in Evansville, Ind., for a batch of its 24-ounce cans of GENTLEASE powdered infant formula.

Mead Johnson informed the FDA that metal particles were found in lot number: BMJ19, with a use by date of July 1, 2007. About 41,464 cans of this lot of recalled product were distributed beginning in December 2005 through retail stores nationwide. No illnesses had been reported at the time of the recall, but officials were concerned that the particles could damage the baby's respiratory system and throat, causing coughing, difficulty swallowing, or difficulty breathing.

In other instances, a company recalls the product after the FDA raises concerns. This action could occur after the agency inspects a manufacturing facility or evaluates reports of health problems. For example, the Cold Stone Creamery, in Arizona, removed all of

and changes in blood pressure and in other circulatory functions.

The FDA has received reports of a serious eye injury called Toxic Anterior Segment Syndrome (TASS), as well as complaints relating to injuries in more than 300 people who were given BSS. An estimated 1 million units of BSS products manufactured by Cytosol were distributed between December 2003 and December 2005.

In response to the FDA's request, Cytosol voluntarily recalled the following products: AMO Endosol, distributed by Advanced Medical Optics Inc., Santa Ana, Calif.; Cytosol Ophthalmics, distributed by Cytosol Ophthalmics, Lenoir, N.C.; and Akorn, distributed by Akorn Inc., Buffalo Grove, Ill.

what risks apply to various segments of the population, including children, pets, and surgical patients; the degree of seriousness of the health hazard; and the volume of product involved and the distribution.

"Based on all of this information, the experts assign the recall a classification to indicate the relative degree of the health hazard, with Class I being the most serious," says Pete Cook, an FDA recall coordinator.

Here's a look at the classes of recalls:

Class I: A Class I recall involves a situation in which there is reasonable probability that the use of or exposure to the product will cause serious health problems or death. After a physician reported confusion over

For any product regulated by the FDA, a recall is handled by the appropriate FDA product center.

its "cake batter" ice cream products from store shelves in July 2005 after the FDA told the company that several cases of *Salmonella Typhimurium* infection occurred among people who had eaten the cake batter products. This type of salmonella can cause abdominal pain, high fever, nausea, and vomiting in healthy people and can cause serious and sometimes fatal infections in small children, older people, and in those with weakened immune systems.

In rare cases, the FDA "requests" a recall. An example of this type of recall occurred in February 2006, when the FDA asked Cytosol Laboratories Inc. of Braintree, Mass., to recall all brands and sizes of its Balanced Salt Solution (BSS), which health professionals use to irrigate patients' eyes, ears, nose, or throat during cataract surgery and other procedures. The FDA requested the recall because product lots were found to have elevated levels of endotoxins, substances found in certain bacteria that can cause fever, shock,

Whatever the reason for a voluntary recall, the FDA's role is to oversee the company's recall strategy. In 2003, the agency released guidance for industry on managing all aspects of a recall. "The guidance assists the firm in recall strategy development, and encourages firms to provide the information FDA needs to evaluate and classify the recall," Elder says.

Evaluating the Health Hazard

For any product regulated by the FDA, a recall is handled by the appropriate FDA product center. A recall of a blood product, for example, would be addressed by the FDA's Center for Biologics Evaluation and Research. A recall of a drug for dogs would fall with the FDA's Center for Veterinary Medicine.

Once a recalled product is referred, the center convenes a board of experts who evaluate the health hazard associated with the recall. Scientists evaluate factors such as whether any diseases and injuries have already occurred;

a dosing syringe, the Perrigo Co. of Allegan, Mich., initiated a voluntary recall in August 2005 of lots of liquid concentrated infants' oral drops that were packaged with a dosing syringe bearing only a 1.6-milliliter mark. The products included pain relievers containing acetaminophen and cough and cold drops. The drops were recalled because the dosing syringe could be confusing in determining the proper dose for infants younger than 2 years and could lead to overdosing, which could be fatal.

Class II: A Class II recall means that the use of or exposure to the product may cause temporary or medically reversible health problems or that the probability of serious health problems is remote. McNeil Consumer & Specialty Pharmaceuticals of Fort Washington, Pa., was involved in a Class II action when it recalled 4-ounce bottles of Children's Motrin Dye-Free Berry Flavor Liquid in September 2005. Some of the products intended for destruction because of "black specks" and

FDA-Regulated Products Recalled in 2005

Biologics	Human Drugs	Devices	Foods	Veterinary Products
Class I: 1	Class I: 18	Class I: 77	Class I: 354	Class I: 16
Class II: 1,848	Class II: 314	Class II: 1,351	Class II: 243	Class II: 25
Class III: 601	Class III: 170	Class III: 170	Class III: 82	Class III: 68
Total: 2,450	Total: 502	Total: 1,598	Total: 679	Total: 109

In 2005, there were recalls for 5,338 products regulated by the FDA. Each recall is assigned a classification to indicate the degree of the health hazard. Class I recalls are the most serious.

“foreign organic material” were possibly sent to retail stores.

Class III: A Class III recall is the least serious and indicates that exposure to the product is not likely to cause health problems. The American Bottling Co. of Ottumwa, Iowa, had a Class III recall in August 2005, when it recalled certain cases of A & W Sparkling Vanilla Cream Soda that were labeled as caffeine-free. The bottles of soda actually contained caffeine.

In 2005, more than 5,300 products regulated by the FDA were recalled. Of these products, 466 were Class I, 3,781 were Class II, and 1,091 were Class III. Most Class I recalls in 2005 were in the food category.

Notifying the Public

An evaluation of the health hazard helps companies determine the strategy for communicating risks associated with a recalled product. As part of reviewing a company’s proposed recall strategy, the FDA looks at the depth of the recall, the extent of public warnings needed, and whether the recall is being extended to the wholesale, hospital, pharmacy, retail, patient, or consumer levels.

“If companies sell directly to consumers and can identify them easily, a letter could work,” Elder says. “But if we’re talking about a can of soup—a situation where only consumers know whether they bought a product or not—then the approach has to be much

broader so that we can reach as many people as possible.”

Class I recalls almost always warrant a release to the media, Elder says. “When a recalled product has been widely distributed, the media is a very effective way to reach large numbers of consumers,” Elder says.

Many other recalls aren’t announced in the media, but they go into the FDA’s weekly Enforcement Report, posted at www.fda.gov/opacom/Enforce.html on the agency’s Web site. This document lists each recall according to classification, with the specific action taken by the recalling firm.

Companies must report to the FDA whether the recall will be posted on the company’s Web site, what customers are being instructed to do, and how products should be returned, if applicable. Key information should be communicated clearly to consumers, including the name of the product being recalled, the lot numbers, serial numbers, or other identifying information, and the reason for the recall.

“Consumers need to take any recall communication seriously and determine whether they are impacted,” Elder says. “In some cases, it may be that only a small portion of the product is actually affected. But to be on the safe side and to operate within current good manufacturing practice regulations, the entire product line, lot, or model may be recalled.”

An example of a case in which con-

sumers were instructed to return the recalled product was when RC2 Brands of Stoughton, Mass., recalled certain teething rings in January 2006. The liquid contained in the rings is contaminated with bacteria that may cause serious illness if swallowed by babies, if it enters the lungs, or if it is absorbed through a cut in the mouth. The risk of illness is especially high in infants whose immune systems are compromised by malnutrition, by blood problems, or from cancer therapy.

The teething rings were sold nationwide between July 2005 and January 2006 at major retail, grocery, and specialty stores. About 352,000 were distributed in the United States. Products included six types of teethers, including the Disney Soft Cool Ring Teether—Styles #Y1470 and #Y1490 and Sesame Beginnings Chill & Chew Teether—Style #Y3095. As of February 2006, the firm had received 105 complaints of fluid leakage, 14 reports of sharp edges that resulted in nine incidents of cuts, and two reports of babies biting through rings.

“For this recall, the firm asked consumers to place the teethers in a plastic bag and return it to the company, but consumers should be aware that some recalls don’t involve returning products,” says Jay Rachlin, associate director of the Division of Device User Programs and Systems Analysis in the Center for Devices and Radiological Health (CDRH). Sometimes,

the recall doesn't involve a removal, but rather a correction. This solution is a way to address a problem with the product where it's sold. For example, a medical device in a hospital might need a new label or some kind of reprogramming.

A recall also may be issued when a company has released new warnings and instructions for a device. In June 2005, Vail Products Inc. of Toledo, Ohio, recalled about 5,000 enclosed or canopied bed systems because patients could become entrapped or suffocate. An alternative to physical or drug restraint, padded beds are used to enclose patients with cognitive impairment, unpredictable behavior, spasms, seizures, or other disorders.

At the time of the recall, the FDA was aware of 30 entrapments, of which eight resulted in death. The company did not retrieve or replace the beds; they couldn't be returned to the company. But the company provided new instruction manuals and warning labels, and stopped manufacturing, selling, and distributing the bed systems.

"With an implanted device," Rachlin says, "a recall may mean that doctors and patients should discuss the risks of removing the device compared to the risk of leaving it in place." That is what happened when Guidant Corp. of St. Paul, Minn., announced a voluntary Class I recall in July 2005 of certain pacemakers that were manufactured between Nov. 25, 1997, and Oct. 26, 2000.

A seal within the devices can leak, allowing moisture to affect the electronic circuits. This defect can prevent the pacemaker from providing pacing or can cause a rapid heart rate. The problems could occur without warning and lead to loss of consciousness,

heart failure, or death. As of July 2005, Guidant had received reports that 69 pacemakers may have failed because of the leakage.

In a letter to physicians, Guidant gave physicians recommendations about how to identify a leak-related malfunction and other advice for minimizing the risk of pacemaker failure.

Preventing Future Problems

Companies should work with the FDA to identify the root causes for a recall and to prevent the problem from recurring. "The FDA's role is to oversee the recall and verify that the firm's steps reflect the right conclusions about the problem and how it should be corrected," says Mel Szymanski, senior recall coordinator for the FDA.

In December 2005, Diamond Pet Food, Meta, Mo., traced the cause of injuries and deaths of dozens of dogs to a potent toxin called aflatoxin, which was found in some of the pet food manufactured at the company's facility in Gaston, S.C. The aflatoxin came from a fungus found on corn that was used to make the food. Experts say that severe drought followed by high moisture contributes to the growth of this fungus.

Animals that consume aflatoxin may experience severe liver damage. Signs of illness in pets include sluggishness, lethargy and reluctance to eat, a yellowish tint to the eyes and gums, and severe or bloody diarrhea.

"From the first week of the recall, we have been working with FDA to get the word out to potentially affected households and improve our food safety procedures and protocols," says Mark Brinkman, chief operations officer of Diamond Pet Food.

Testing showed that the products

affected with the toxin were Diamond Professional for Adult Dogs, best by date of Jan. 29, 2007; Diamond Maintenance Dog Food, best by dates of April 3 and 5, 2007; and Diamond Premium Adult Dog Food, best by date of April 11, 2007.

The company recalled product date codes several weeks before and after the suspected dates out of precaution. "Far below one percent of what we recalled contained toxic levels," according to Brinkman, who says his company acknowledges the tragic situation for its customers. "We had a breakdown in quality control that cost the lives of customers' pets, and we are working to make things right for the families as best that we can."

Diamond Pet Food has taken several actions to prevent oversights from happening again. "First, we've implemented sampling and testing protocols for corn that require two signatures throughout the chain of custody—that of the employee and the immediate supervisor," Brinkman says. "The USDA requires four probes per load of corn. Diamond is conducting 12 probes per load."

He says that Diamond also has added aflatoxin testing to the finished product and is working with the USDA to source corn from areas that are less likely to have aflatoxin-tainted supplies.

Evaluating Effectiveness

Companies carry out the recall, and the FDA acts as a monitor, Szymanski says. The FDA encourages companies to make sure that recall notification letters reached the target audience, that the letter was read, and that instructions were understood.

Classification of the recall helps the FDA determine the number of audits needed to check on a recall. An audit check, whether done by personal visit, phone call, letter, or a combination, is made so that the FDA can verify who has been notified about the recall. Check levels range from A to E. A "Level A" check means that 100 percent of those targeted were contacted about the recall. A "Level E" check means that no effectiveness checks were needed.

The FDA requests that recalling firms submit periodic status reports indicat-

Sign Up for Recall Alerts

News releases about recalls of products regulated by the FDA can be delivered directly to an e-mail account. Go to the FDA's free e-mail lists page at www.fda.gov/lemaillist.html and click on "FDA Recalls."

After the FDA issued warnings in 2001, several companies voluntarily recalled mini-cup gel candies that contain the ingredient "konjac" because of a choking hazard. The FDA also issued an import alert to keep the candies out of the country.



FDA

ing how many people are responding to the recall. "The recall is considered complete after all of the company's corrective actions are reviewed and deemed appropriate," Szymanski says. "The FDA evaluates whether all reasonable efforts have been made to remove or correct the product, and whether all outstanding product is recovered or destroyed."

When the Recall Is Not Voluntary

Though most recalls are voluntary, there are times when the FDA mandates a recall. The FDA can "order" a recall in some cases involving infant formulas, biological products, and devices that present a serious hazard to health. In 2002, the FDA ordered CryoLife Inc., Kennesaw, Ga., to recall and prevent further use of human tissue that was processed from October 2001 to August 2002.

During an inspection in 2002, the FDA found significant violations of FDA regulations and issued a Warning Letter. The FDA issued the recall order after determining that CryoLife had failed to take adequate measures to address possible infectious disease contamination of tissue. Tissue from a donor processed by CryoLife was associated with the Nov. 7, 2001, death of a patient who

received a soft tissue implant during reconstructive knee surgery.

If FDA experts determine that a recall wouldn't be effective or if a recall proves ineffective, or if the violation is continuing, then the agency can take legal action such as injunctions and seizures. An injunction is a civil action taken to stop production or distribution of a product that violates the law. A seizure involves removing a product from the market by requesting a court to direct a U.S. Marshal to take possession of the goods.

The FDA conducted a seizure in May 2002 of New Choice Food mini-gel candies at the company's facility in Irwindale, Calif. In 2001, the FDA had issued warnings against consuming mini-cup gel candies that contain the ingredient "konjac," also known as conjac, konnyaku, yam flour, or glucomannan. The FDA and the Consumer Product Safety Commission considered this product a choking hazard, especially to children and older people. The candy, which was sold under various brand names and distributed by different companies, doesn't readily dissolve in the mouth.

At the time of the seizure, six deaths had been reported from choking in the United States, and deaths were also

reported in other countries. The FDA issued an import alert in 2001 to keep the candy out of the country. Other firms voluntarily recalled the gel candies, but New Choice Food did not.

"When companies are unwilling to comply with the law, we take decisive action to protect consumers," Elder says. "This sends a strong signal that the agency doesn't tolerate harmful products in the marketplace." ■

For More Information

The FDA's page on recalls
www.fda.gov/opacom/7alerts.html

Listing of recalls by six federal agencies
www.recalls.gov/

The FDA's Enforcement Report
www.fda.gov/opacom/Enforce.html

The FDA's MedWatch
www.fda.gov/medwatch/index.html

Standardizing and evaluating imaging technologies are part of the Oncology Biomarker Qualification Initiative.

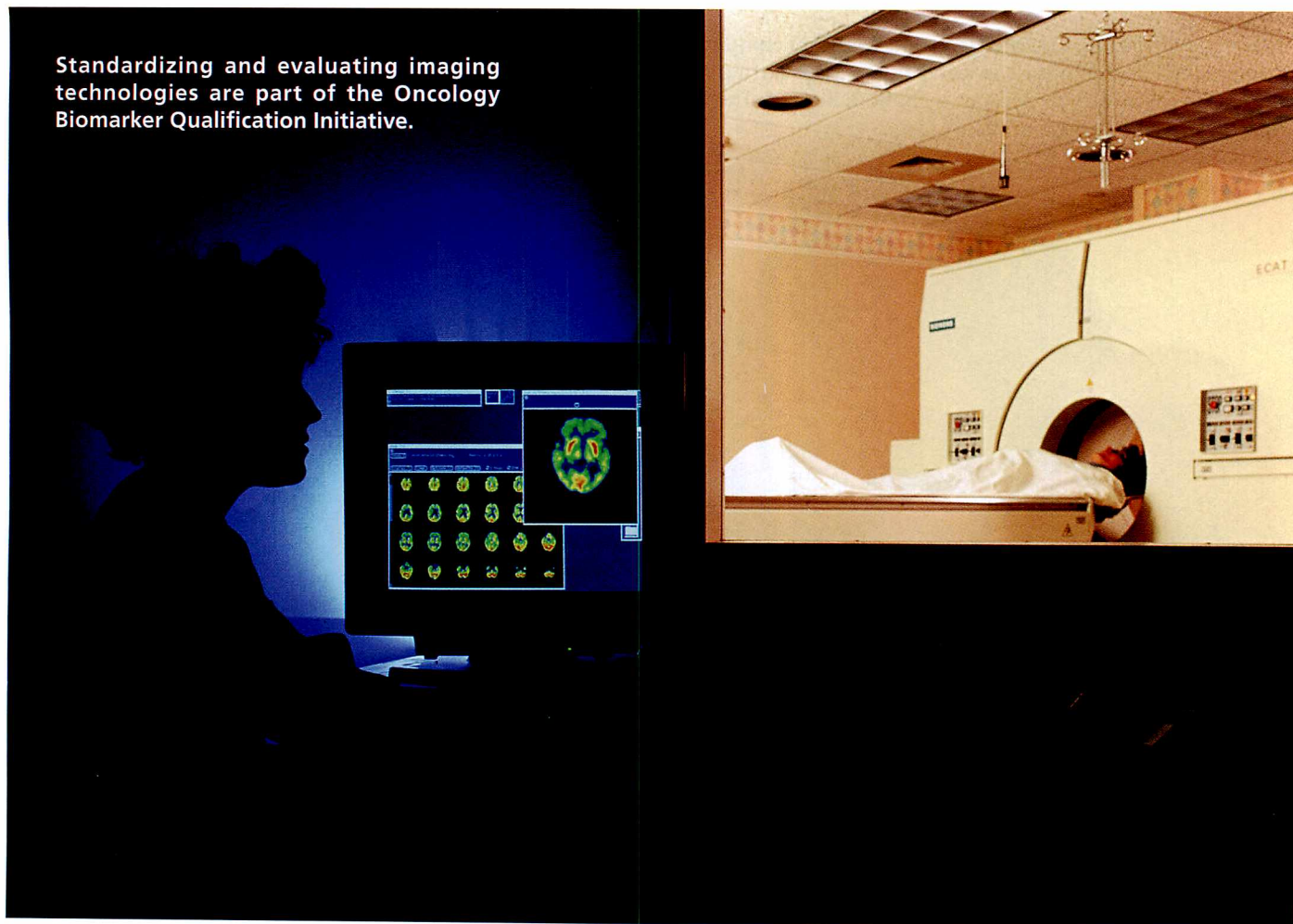


Photo Researchers Inc.

New Health Initiative to Improve Cancer Treatments

Three Department of Health and Human Services agencies are working together for the first time to find biologic markers that could help improve cancer treatments.

In February 2006, the Food and Drug Administration; the National Cancer Institute (NCI), part of the National Institutes of Health (NIH); and the Centers for Medicare & Medicaid Services (CMS) announced the Oncology Biomarker Qualification Initiative (OBQI)—an agreement to collaborate on biomarker development and evaluation.

Biomarkers are biologic indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests and tests on blood, tissue, and other biologic samples.

"An enhanced understanding of clinical biomarkers will help make the development of diagnostics and treatments more targeted, one of our most pressing goals under the Critical Path Initiative, FDA's program to modernize the medical product development process," says Acting FDA Commissioner Andrew C. von Eschenbach, M.D. "We believe

partnerships that help us standardize the use of new technologies are essential to refining the drug development process so we can bring personalized medicines to patients more quickly and ultimately improve outcomes."

The collaboration will develop scientific understanding of how biomarkers can be used to assess the impact of therapies and better match therapies to patients. For instance, OBQI will address questions such as how particular biomarkers can be used to

- assess after one or two treatments whether a patient's tumor is responding to treatment
- determine more definitively whether a tumor is dying, even if it is not shrinking
- identify which cancer patients are at high risk of their tumor coming back after therapy
- determine whether a patient's tumor is likely to respond at all to a specific treatment
- efficiently evaluate whether an investigational therapy is effective for tumor treatment.

The goal of OBQI is to validate particular biomarkers so that they can be used to evaluate new, promising technologies in a manner that will shorten clinical trials, reduce the time and resources spent during the drug development process, improve the linkage between drug approval and drug coverage, and increase the safety and appropriateness of drug choices for cancer patients.

"Almost four years ago, NIH set out to create a 'roadmap' for 21st century medical research," says NIH Director Elias A. Zerhouni, M.D. "Programs like OBQI will be central to that vision, not only because they will lead to vital discoveries about the biology of disease, but because they will be models for scientific collaboration."

Under OBQI, biomarker research will be focused in four key areas: standardizing and evaluating imaging technologies to see in more detail how treatments are working, developing scientific bases for diagnostic assays to enable personalized treatments, instituting new trial designs to use biomarkers, and pooling data to ensure that key lessons are shared from one

trial to another. By working with academic and industry scientists, as well as with professional organizations, the OBQI teams can foster the development of key information on biomarkers through clinical trials.

"By identifying biomarkers for specific cancers and clinically evaluating them, researchers will have an evidence base for their use in targeted drug development and to determine which therapies are likely to work for patients before treatment selection," says NCI Deputy Director Anna D. Barker, Ph.D. "Rather than waiting weeks to months to determine if a specific drug works for a patient, biomarkers could be used to monitor real-time treatment responses."

The first OBQI project will serve to validate and standardize the use of Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) scanning. PET scans are used to characterize biochemical changes in a cancer. Under the collaboration, researchers will use FDG-PET imaging technology in trials of patients being treated for non-Hodgkin's lymphoma to determine whether FDG-PET is a predictor of tumor response. Data resulting from this type of evidence-based study

will help both the FDA and the CMS work with drug developers based on a common understanding of the roles of these types of assessments.

"There are many steps between a novel scientific idea with tremendous promise and a new drug reliably benefiting patients," says CMS Administrator Mark B. McClellan, M.D., Ph.D. "This collaboration will produce evidence that will help people with Medicare and Medicaid get better care more quickly, as a result of better-targeted treatment decisions for cancer patients."

Over the next several months, the OBQI team will design a number of initiatives to identify and clinically qualify other cancer biomarkers. The new initiatives will bring together scientists from many sources and will address agency priorities identified through the FDA's Critical Path and the NIH's Roadmap Initiatives.

OBQI also represents the work of the NCI-FDA Interagency Oncology Task Force (IOTF). The IOTF is a collaboration between the NCI and the FDA to enhance the efficiency of clinical research and the scientific evaluation of new cancer treatments. ■

The FDA's Critical Path

Critical Path is the FDA's premier initiative to identify and prioritize the most pressing medical product development problems and the greatest opportunities for rapid improvement in public health benefits. Its primary purpose is to ensure that basic scientific discoveries translate more rapidly into new and better medical treatments. New tools will lead to answers about how the safety and effectiveness of medical products can be demonstrated in faster timeframes with more certainty and at lower costs. Visit www.fda.gov/oc/initiatives/criticalpath/ for more information on the FDA's Critical Path. ■

The NIH Roadmap

The NIH Roadmap is a series of new initiatives designed to pursue major opportunities and gaps in biomedical research that no single NIH institute could tackle alone, but which the agency as a whole can address. The goals include making the biggest impact possible on the progress of medical research, and catalyzing changes that will transform new scientific knowledge into tangible benefits for public health. See www.nihroadmap.nih.gov for more on the NIH Roadmap. ■

Keeping Up With Drug Safety Information



Black Star/Tyrone Turner

Douglas C. Throckmorton, M.D., deputy director of the FDA's Center for Drug Evaluation and Research, serves as chairman of the Drug Safety Oversight Board. The board makes recommendations on how complex safety issues should be managed and communicated to the public.

By Michelle Meadows

The Food and Drug Administration approves a drug for marketing after determining that the drug's benefits outweigh the risks for the intended user. But even with a rigorous evaluation process, some safety problems surface only after a drug is used in the wider population.

"No amount of study before marketing will ever reveal everything about a new drug's effectiveness or risks," says Sandra Kweder, M.D., deputy director of the Office of New Drugs in the FDA's Center for Drug Evaluation and Research (CDER). "This is why post-marketing surveillance is extremely important and serves to complement the pre-marketing assessment."

After a drug is on the market, the FDA evaluates reports of safety problems on an ongoing basis. Experts consider such factors as the frequency and seriousness of the problems reported, as well as the seriousness of the disease the drug is meant to treat and whether alternative therapies are available.

"As we find out more about the potential risks or benefits of a drug," Kweder says, "the label may be revised so that it better reflects information on appropriate use of the drug."

The Drug Safety Oversight Board

The FDA's Drug Safety Oversight Board (DSB) was formed in 2005 to make recommendations to the CDER about the management of emerging drug safety issues and to assist in communicating those issues to patients and physicians.

CDER Deputy Director Douglas C. Throckmorton, M.D., serves as chairman of the board. Susan Cummins, M.D., M.P.H., who worked previously in the FDA's Division of Pediatric Drug Development, is the board's executive director. The DSB also includes members from throughout the CDER, as well as experts from other parts of the FDA, the Department of Veterans Affairs, and the National Institutes of Health.

"The board adds an independent perspective to the decision-making process," Kweder says. "It's made up of FDA experts who were not involved in

the initial review of the drug, as well as medical experts from other federal agencies." Where appropriate, the DSB can also consult with experts outside of government and representatives of patient and consumer groups.

The DSB is charged with conducting timely and comprehensive evaluations of complex safety issues and with making recommendations to the CDER on how they should be managed and communicated to the public. Members meet roughly every six weeks to discuss emerging drug safety issues and to assist in developing safety policy in the CDER.

An important aspect of their work is weighing the impact of adverse drug reactions against the benefits of a drug, and how best to communicate that balance around emerging safety concerns—even when the FDA is still evaluating data and has not reached a conclusion. "All of these activities help the CDER communicate emerging safety concerns effectively to patients and physicians," Throckmorton says. Some examples of drugs that the DSB has discussed include

Tequin (gatifloxacin). In February 2006, after reports of patients who developed abnormal blood sugar levels from the use of Tequin, labeling changes were made to this antibiotic. The changes strengthened warnings about serious cases of low blood sugar and high blood sugar in people taking the drug. Also, a new contraindication was added; Tequin should not be used in people who have diabetes.

Trasylol (aprotinin injection). Trasylol is a drug used to prevent blood loss during surgery. In February 2006, the FDA issued a public health advisory alerting doctors who perform heart bypass surgery that Trasylol has been linked in two scientific publications to a higher risk of kidney problems, heart attacks, and strokes in those who undergo artery bypass graft surgery. The DSB agreed with this course of action, and the FDA has undertaken a full review of the available data before considering what additional steps, if any, are necessary.

Paxil (paroxetine). In December 2005, the FDA's patient information sheet for the antidepressant Paxil was

Quick Information

When a new warning, label change, or other regulatory action occurs, how can you find out about the information quickly? You can find the latest FDA actions at www.fda.gov, the FDA's Web site. Web pages of interest to both consumers and health professionals include

- An index to drug-specific information: Visit www.fda.gov/cder/drug/drugsafety/DrugIndex.htm to access a list of hundreds of drugs. Click on a specific drug and pull up information sheets with the latest warnings about the drug, related press announcements, and other fact sheets.
- The MedWatch Home Page: MedWatch is the FDA's Safety Information and Adverse Event Reporting Program. The home page at www.fda.gov/medwatch/ lists safety alerts for all products regulated by the FDA. To receive safety alerts by e-mail, click on "Join the E-list." The MedWatch site also links to the monthly "FDA Patient Safety News," a video news show that is carried on satellite broadcast networks shown in hospitals and other medical facilities. ■

updated to indicate that early results of new studies show the drug increases the risk of birth defects, particularly in the first three months of pregnancy. Because of the risk of untreated depression, it was important to recommend that for some women who have already been taking the drug, the benefits of continuing the drug may be greater than the potential risks to the baby.

Biaxin (clarithromycin). The FDA's patient information sheet for this antibiotic was updated in December 2005. A preliminary analysis of a study in Denmark of people with heart disease showed that clarithromycin use was associated with a higher chance of death from heart problems. After extensive internal analysis and discussion with the DSB, the FDA agreed with the conclusions of the Danish Medicines Agency and has not recommended any changes to the use of the drug at this time.

Evaluating Communication Tools

As part of the agency's commitment to improving communications, the FDA held a public hearing on "CDER's Current Risk Communication Strategies for Human Drugs" in December 2005, in Washington, D.C.

"The purpose of the meeting was to obtain public input on our current risk communication tools and identify partners for collaboration," says Paul Seligman, M.D., director of the FDA's

Office of Pharmacoeconomics and Statistical Science.

Panels of FDA officials heard testimony from 28 individuals and organizations, including physicians, pharmacists, experts from academia, representatives of consumer groups, and the pharmaceutical industry. Seligman says, "We asked questions such as: Are the current communication tools user friendly and timely? Does the risk information that's communicated help health professionals make decisions?"

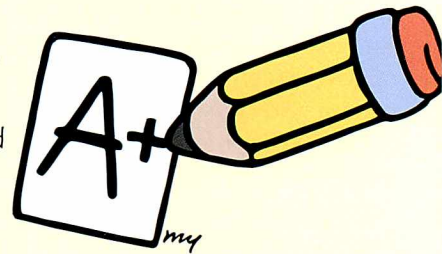
Meeting participants suggested that the FDA engage health professional organizations, simplify its risk communications, improve provider and consumer access to the Internet site, develop consistent communication approaches, and address people who have limited health literacy and English skills. Some also recommended that the FDA maintain a benefit-risk balance so as not to scare people away from what may be effective therapy for them.

Seligman says, "Feedback from the meeting will give us a greater understanding of the strengths and weaknesses of CDER's existing communication strategies, so that we can evaluate which approaches work best and whether additional tools are needed." ■

Take the FDA Consumer Quiz

What are the three most common problems men experience with their prostate glands? How do doctors diagnose restless legs syndrome? How many reports of problems, or adverse events, related to medical devices are received by the FDA each year? To find out how much you know about these and other health-related topics, take our quiz.

Hint: The answers to all of these questions can be found in the May-June 2006 issue of FDA Consumer (and at the bottom of this page).



1. Other than skin cancer, prostate cancer is:
 - a. the most rapidly spread cancer
 - b. the most common form of cancer
 - c. the deadliest form of cancer
 - d. the mildest form of cancer
2. The prostate gland is:
 - a. round
 - b. pear-shaped
 - c. walnut-shaped
 - d. oval
3. What are the three main problems that occur in the prostate gland?
 - a. inflammation, enlargement, and cancer
 - b. thickening, thinning, and cancer
 - c. stretching, inflammation, and cancer
 - d. shrinking, enlargement, and cancer
4. Which sensation typically describes restless legs syndrome?
 - a. burning
 - b. tugging
 - c. tightening
 - d. like insects crawling inside the legs
 - e. all of the above
5. How many individual products make up today's medical device industry?
 - a. about 3,500
 - b. nearly 5,000
 - c. about 50,000
 - d. nearly 100,000
 - e. more than 200,000
6. How many reports of problems, or adverse events, related to medical devices are received by the FDA each year?
 - a. nearly 50,000
 - b. about 150,000
 - c. about 180,000
 - d. more than 200,000
 - e. nearly 270,000
7. A free computer-based tool can help people organize their family health histories related to what common diseases?
 - a. multiple sclerosis, lung cancer, hepatitis, alcoholism, and asthma
 - b. heart disease, stroke, diabetes, colon cancer, breast cancer, and ovarian cancer
 - c. heart disease, diabetes, lung cancer, arthritis, lupus, and clinical depression
 - d. obesity, diabetes, osteoporosis, hypertension, leukemia, and Crohn's disease
8. How many FDA-regulated products were recalled in 2005?
 - a. about 580
 - b. about 1,450
 - c. about 2,200
 - d. more than 5,300
9. Class I recalls are the most serious type. Most Class I recalls in 2005 concerned:
 - a. drugs
 - b. veterinary products
 - c. food
 - d. devices
10. Which of the following statements is false?
 - a. All recalls involve returning the product to the place of purchase.
 - b. Most recalls of FDA-regulated products are voluntary.
 - c. The FDA can take legal action against companies that don't carry out a recall effectively.
 - d. The FDA requests that recalling firms submit status reports.
11. What is the name of the FDA's initiative to advance the development of new and better medical treatments?
 - a. The Product Push
 - b. The Main Roadmap
 - c. The Fast Track
 - d. The Critical Path

Answers:

1. b 2. c 3. a 4. e 5. d 6. c 7. b 8. d 9. c 10. a 11. d



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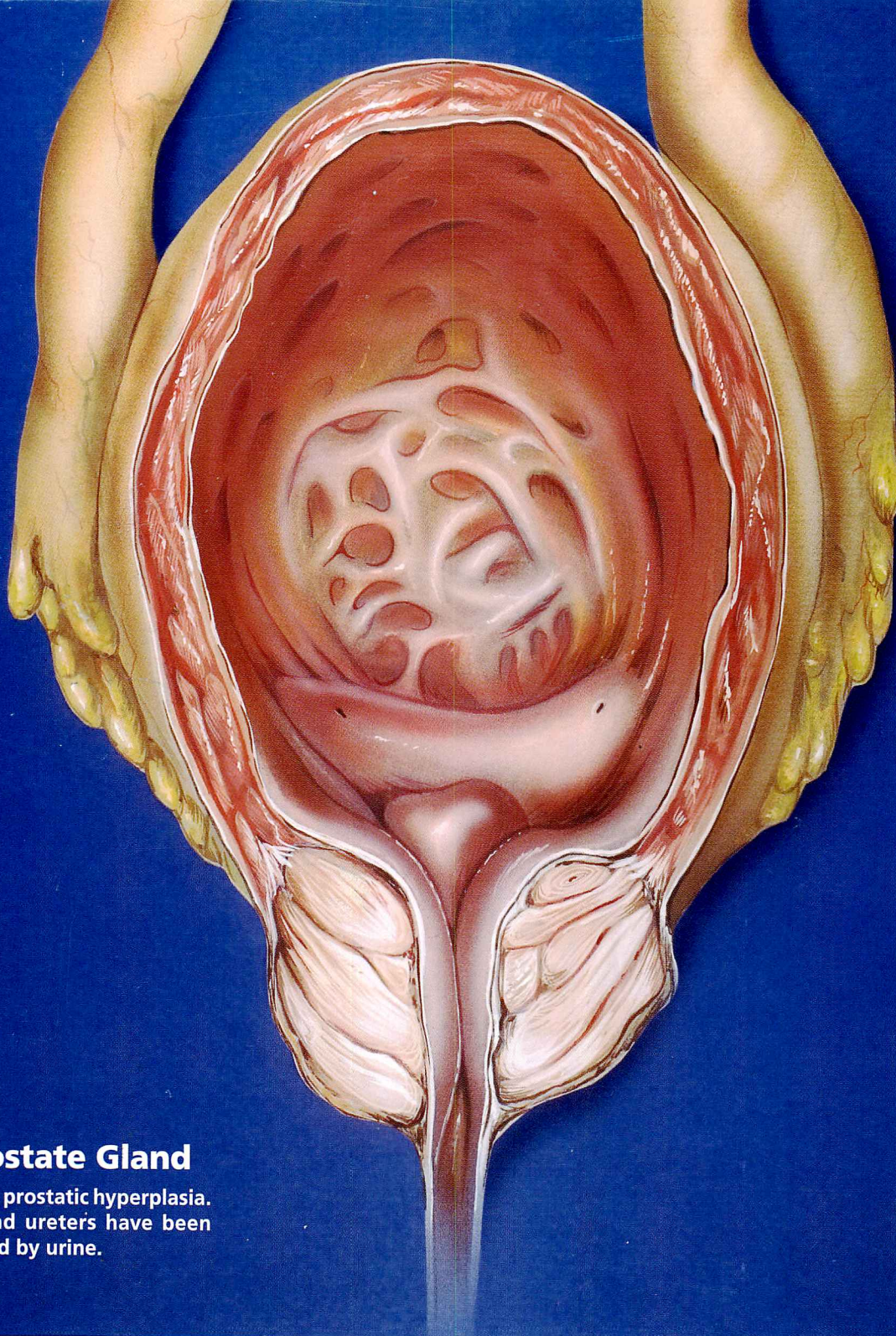
Food and Drug Administration

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The Center for Information and Study on Clinical Research Participation

1-888-CISCRP3 www.smartparticipant.org



Enlarged Prostate Gland

Illustration of benign prostatic hyperplasia. The bladder wall and ureters have been abnormally distended by urine.

Phototake

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