

# FDA *Consumer*

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

September–October 2004 • Vol. 38 No. 5

A detailed scanning electron micrograph (SEM) of cancer cells. The image shows several large, spherical cells with a highly textured, spiky surface, colored in a bright yellow-gold. These are surrounded by and interspersed with other cells that have a more irregular, flattened, and pinkish-red appearance. The background is dark, making the cells stand out prominently.

## Cancer Vaccines!

*Training the Immune System  
to Fight Cancer*







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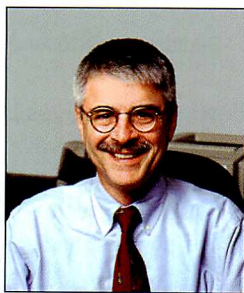
Surgery. Chemotherapy. Radiation. For decades, these have been the primary weapons used by physicians in the battle against cancer. And, while the battle is far from being won, there have been victories.

According to a recent report released by the National Cancer Institute (NCI) and the Centers for Disease Control and Prevention, there are about 10 million cancer survivors in the United States. The report defines a survivor as someone who has been diagnosed with cancer, from the time of diagnosis through the balance of his or her lifetime.

Currently, researchers are working to develop new therapies that use the body's own defenses, called the immune system, to fight or prevent cancer. According to the NCI, the immune system generally doesn't recognize cancer cells as dangerous or foreign. That's why tumors may not stimulate an immune response. Although as of August 2004 there are no vaccines licensed by the FDA to treat cancer, there is one vaccine licensed to be used to protect against hepatitis B, an infectious agent associated with liver cancer.

Scientists continue to evaluate several different vaccines in large human clinical trials to determine which may be an effective treatment for particular kinds of cancers. In an effort to improve the review of potential cancer vaccines and imaging devices used in cancer diagnosis and treatment, the FDA is creating a new Office of Oncology Drug Products to consolidate three existing areas within the agency.

For more on the development of cancer vaccines and the hope they hold, see our cover story titled "Cancer Vaccines:



Training the Immune System to Fight Cancer," beginning on page 20.

A chronic skin disease characterized by scaling and inflammation, psoriasis affects between 6 million and 7.5 million Americans, according to the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Psoriasis involves a type of white blood cell called a T cell, which is part of the immune system. The disease occurs when skin cells rise quickly from their origin below the surface of the skin and pile up before they have a chance to mature.

Typically, the result is patches of red, inflamed skin covered with silvery flakes that can appear virtually anywhere on the body. For more on this skin disease and the latest treatments, see our feature story titled "Psoriasis: More Than Cosmetic," on page 10.

Earlier this year, the FDA released a draft of its new guidelines for manufacturers of breast implants, identifying the type and amount of scientific data that will allow the agency to evaluate whether these products are safe and effective. The new recommendations include guidance on testing, modes and causes of rupture, clinical study information, and labeling.

To find out more about the risks and potential benefits of breast implants, read our feature story "Making an Informed Decision About Breast Implants," beginning on page 32.

We also take a look at the dangers of unpasteurized milk and explain the results of a new Institute of Medicine report that found no link between childhood vaccines, the preservative thimerosal, and autism.

*Raymond Formanek Jr.*  
Editor

## TO THE EDITOR

### Prescription Drug Information

Have you ever tried to read the patient information booklet enclosed with your medication? The print type is small, the letters are crammed in each line, and the medical information is like reading another language.

Just recently, I had to sit down with my mother to explain the dosing information regarding her heart medications. She couldn't read the patient information booklet or what was printed on the pill bottle. Not very

comforting if English isn't your first language or if your eyesight isn't the sharpest.

Drug labeling should consist of large letters, easy-to-read language (in different languages), comprehensive graphics, and simple layout and design. But is that what we see? Have we really made significant changes to drug labels and packages? And who exactly is policing this? If it's the FDA, has there been a recent report on the progress of drug labeling? Has there been progress with

pharmacies and pharmaceutical agencies?

As an average consumer and a concerned daughter, it would give me great comfort to see my mother read from her pill bottle, so that she knows how many times a day she should take her heart medication.

Linda Thrasybule  
Bronx, N.Y.



## TO THE EDITOR

### The FDA's Office of Drug Safety responds:

Thank you for sharing your concerns with the FDA. Understanding why a medicine has been prescribed and how to use it is essential to gaining the greatest benefit from the medicine while keeping any harmful or annoying side effects to a minimum. Information on how to use any medical product should be written clearly and in a format that is understandable to the consumer.

Recognizing the importance of useful written information for consumers who receive prescription medicines, Congress passed a law in 1996 requir-

ing that by 2006, 95 percent of all U.S. prescriptions be accompanied by information that is useful to the consumer. The FDA has the responsibility of monitoring how well pharmacies are progressing in meeting this goal.

A nationwide study done by the FDA in 2001 showed that, while 90 percent of all prescriptions are accompanied by some form of written information for consumers, the majority of this information does not meet the "useful" criterion. In many cases, as you point out, the letters are too small to read and the information is incomplete. The research report is available on the FDA

Web site at [www.fda.gov/cder/reports/prescriptioninfo/](http://www.fda.gov/cder/reports/prescriptioninfo/). The FDA is currently working with a broad coalition of pharmacy and consumer groups to improve this situation and meet the 2006 goal specified in the 1996 law.

However, the information that pharmacists put on the "amber bottle" that contains the medicine given to the patient is not regulated by the FDA.

We encourage you and other consumers to tell your pharmacist: "Please give me a label that I can read and written information about my medicine that I can understand." ■

## UPDATES

### New Drug to Treat Alcoholism

The drug Campral (acamprosate) has been approved by the FDA for treating alcohol-dependent individuals who want to continue to remain alcohol-free after they have stopped drinking. Campral is the first new drug approved for alcohol abuse in a decade.

Alcoholism, or alcohol dependence, is a disease. The consequences of alcohol misuse are serious and, in many cases, life threatening. Heavy drinking can increase the risk for certain cancers, especially those of the liver, esophagus, throat, and voice box (larynx). Heavy drinking can also cause liver cirrhosis, immune system problems, brain damage, and harm to the fetus during pregnancy. Chronic alcoholism continues to be a widespread and debilitating disorder that places a tremendous burden on society in terms of health care costs, lost wages, and personal suffering.

How Campral works is not fully understood, but the drug is thought to act on the brain pathways related to alcohol abuse. Campral was demonstrated to be safe and effective by multiple clinical studies involving alcohol-dependent people who had already been withdrawn from alcohol (detoxified). Campral proved superior to an inactive substance

(placebo) in maintaining abstinence. This was indicated by a greater percentage of people who were treated with the drug being assessed as continuously keeping off alcohol consumption throughout treatment.

The most common side effects reported for patients taking Campral in clinical trials included headache, diarrhea, flatulence, and nausea. Campral is not addicting.

Campral may not be effective in people who are actively drinking at the start of treatment, or in people who abuse other substances in addition to alcohol. Treatment with Campral should be part of a comprehensive management program that includes psychosocial support.

Campral is manufactured by Merck KGaA of Darmstadt, Germany, and will be distributed in the United States by Forest Laboratories Inc. of New York City.

### Botox Approved for Severe Underarm Sweating

After being approved for several other purposes since 1989, including improving the appearance of frown lines between the eyebrows, Botox now can treat severe underarm sweating (primary axillary hyperhidrosis) that

cannot be managed by topical agents.

Botox (botulinum toxin type A) is a protein produced by the bacterium *Clostridium botulinum*. When used to treat underarm sweating, small injected doses of the sterile purified botulinum toxin stop release of the chemical messenger acetylcholine, temporarily blocking the nerves in the underarm that stimulate sweating.

Before being treated for underarm sweating, patients should be evaluated for other potential causes of the problem. The most common adverse events associated with the new treatment included injection site pain and hemorrhage, sweating in other parts of the body, flu-like symptoms, headache, fever, itching, and anxiety.

Botox was first approved in December 1989 to treat the eye muscle disorders blepharospasm and strabismus. Since then, it has been approved to treat a neurological movement disorder causing severe neck and shoulder muscle contractions (cervical dystonia). In 2002, it was approved as Botox Cosmetic to improve frown lines.

The safety and effectiveness of Botox for sweating that occurs in other areas of the body have not been established.



### 'Take a Loved One to the Doctor Day'

Do you have a friend, neighbor, or family member who hasn't seen a doctor, nurse, or other health care professional in quite a while? The U.S. Department of Health and Human Services suggests that you take charge and "Take a Loved One to the Doctor" on Sept. 21, 2004.



Americans are encouraged to take charge of their health on that day—or any day—by visiting a health care professional, making an appointment for a visit, attending a health event in the community, or helping a friend, neighbor, or family member do the same.

Launched by HHS Secretary Tommy G. Thompson and Tom Joyner, a nationally syndicated radio personality and chairman of the event, the annual campaign is designed to reduce health disparities affecting racial and ethnic minorities by encouraging individuals to go to a doctor or health professional for a health screening.

Take a Loved One to the Doctor Day is part of "Closing the Health Gap," an ongoing campaign partner-

ship that combines HHS' medical expertise with the broadcast resources of ABC Radio Networks and the efforts of hundreds of national and community-based organizations. In 2003, 500 national and local organizations signed on as partners in the Take a Loved One to the Doctor Day campaign by organizing screening, health fairs, and other events promoting health and wellness.

"Because of Doctor Day, thousands of Americans are showing their family, friends and colleagues how much they care by taking someone to the doctor. This one preventive measure can help add years to your life," Thompson says. "Preventable diseases take a terrible toll on our nation, especially in minority communities. Doctor Day is about bringing people to health care early, when diseases can be prevented or treated successfully. It is also about creating awareness, providing information and motivating Americans to make healthier lifestyle choices."

For campaign information and materials on the Closing the Health Gap program or Take a Loved One to the Doctor Day, including a tool kit to help communities organize local health events, call (800) 444-6472 or visit [www.healthgap.omhrc.gov](http://www.healthgap.omhrc.gov).

### Chinese Infant Formula Not Safe

The FDA is warning consumers against using infant formula imported from China because the safety and nutritional adequacy of the products are unknown.

Although no illnesses or injuries associated with Chinese infant formula have been reported to date, an analysis by the New York State Department of Agriculture and Markets food laboratory found that a Chinese infant formula called Guan Wei Yuan contained less than 14 percent of the minimum amount of protein per serving required by federal regulations. The analysis also found the formulas contained only one-fourth of the required amount of fat per serving, and only minute amounts of the declared calcium and magnesium levels.

There is no guarantee that this product, as a potential sole source of nutrition, would provide adequate nutrients for an infant, FDA officials say. Infants

who are fed this formula according to instructions provided with the product could become severely ill or die.

Federal law requires that infant formula sold in the United States must be registered with the FDA at least 90 days before marketing. Manufacturers are required to provide assurances that they are following good manufacturing practices and quality control procedures and that the formula will allow infants to thrive. Such assurances have not been provided for any infant formulas from China.

Consumers are advised to report any adverse reactions related to infant formula immediately to health care providers as well as to the FDA and state and local agencies.

### Adverse Events Associated With 'Permanent Makeup'

The FDA has alerted the public to a number of reported adverse events associated with so-called "permanent

makeup," a form of tattooing called micropigmentation. The procedure is used to apply lip liner, eyeliner, or eyebrow color. The adverse events are associated with certain ink shades of the Premier Pigment brand of permanent makeup inks, which are manufactured by the American Institute of Intradermal Cosmetics, doing business as Premier Products of Arlington, Texas.

Reactions that have been reported include swelling, cracking, peeling, blistering, and scarring as well as formation of chronically inflamed tissue mass associated with an infection (granulomas) in the areas of the eyes and lips. In some cases, the effects reported caused serious disfigurement, resulting in difficulty in eating and talking.

In July 2003, the manufacturer reported to the FDA its intent to remove five of its ink shades from the market. However, the agency has obtained additional reports of adverse events involving ink shades not included



in the firm's removal effort. While the investigation continues, the FDA is alerting consumers to associated adverse event reports received about Premier Products ink shades identified on its Web site at [www.cfsan.fda.gov/~dms/cos-tat2.html](http://www.cfsan.fda.gov/~dms/cos-tat2.html).

The FDA considers tattoos, including permanent makeup, to be cosmetics. And the agency considers the pigments used in the inks to be color additives requiring premarket approval under the Federal Food, Drug, and Cosmetic Act. However, the agency traditionally has not regulated tattoo inks or pigments used in them. The actual practice of tattooing is governed by state and local regulations.

The FDA urges people to report adverse reactions from tattoos and permanent makeup to state and local health authorities. Adverse events also may be reported to the FDA's Emergency Operations Center at (301) 443-1240 or the Center for Food Safety and Applied Nutrition Adverse Events Reporting System (CAERS) at (301) 436-2405. People also may send e-mail to [CAERS@cfsan.fda.gov](mailto:CAERS@cfsan.fda.gov).

### New Anthrax Test

The first test approved for detecting antibodies to anthrax will soon be available in state and private labs. Before FDA approval of the Anthrax Quick ELISA test in June 2004, few laboratories other than those operated by the Centers for Disease Control and Prevention (CDC) and the U.S. Army could test blood for antibodies to anthrax.

The test helps confirm a diagnosis of anthrax in people by showing that a person's immune system has responded to a protein produced by the anthrax-causing bacteria—*Bacillus anthracis*. The test is quicker and easier to interpret than previous antibody testing methods. It can be completed in less than an hour, compared with about four hours for previous testing methods. Immunetics Inc. of Boston produced the test with funding from the CDC.

Anthrax is a serious infectious disease that most commonly occurs in wild and domestic cattle, sheep, and other herbivores. Humans can contract anthrax by handling products from infected animals or by breathing in or coming in close contact with *B. anthracis* spores from infected animal products, such as unprocessed hides and bones. Anthrax also can be transmitted to humans when anthrax spores are used as a bioterrorist weapon. Twenty-two people became ill and five died after letters containing anthrax were sent through the mail in 2001.

### Software System Detects Lung Nodules

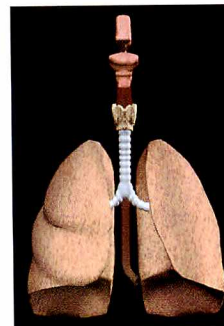
In July 2004, the FDA approved a new image analysis system designed to help radiologists detect solid lung nodules. Such nodules can indicate lung cancer.

The ImageChecker CT CAD software system uses computer-aided detection software to analyze computed tomog-

raphy (CT) images of the chest. The system, which is the first of its kind for use with CT chest exams, highlights areas in the images that appear to be solid nodules.

In a clinical study, 15 radiologists independently reviewed 90 cases from lung CT scans and then reviewed the cases again using the ImageChecker system. Radiologists were able to identify more nodules with the new system than they could without it, improving their ability to detect lung nodules that require further evaluation.

The software system is manufactured by R2 Technology Inc. of Sunnyvale, Calif.



TechPool Studios Inc.

### Company Ordered to Halt Sales of Unapproved Drugs, Reimburse Buyers

A New Jersey judge has found that two products sold as dietary supplements and another touted as a cosmetic are unapproved new drugs under federal law because they were being marketed as treatments for cancer and HIV without FDA approval. The three products are BeneFin, a purported treatment for cancer, MGN-3, marketed as an HIV treatment, and SkinAnswer, promoted as a treatment for skin cancer. BeneFin is produced from shark cartilage, MGN-3 is a rice bran extract, and SkinAnswer is a skin cream.

On July 9, 2004, U.S. District Judge William G. Bassler permanently enjoined the defendants, Lane Labs-USA Inc. and its president, Andrew J. Lane, from distributing drug products unless they are first approved for marketing by the FDA or are distributed under an Investigational New Drug application for purposes of conducting a clinical trial. Bassler also ordered the defendants to pay restitution to all purchasers of the products since Sept. 22, 1999.

"Today's action by Judge Bassler sends a strong signal that the promotion and sale of unapproved drug products, especially for the treatment of cancer and other serious diseases, will not be tolerated," said Dr. Lester M. Crawford, Acting FDA Commissioner.

The FDA issued a warning letter to the company and Lane in September 1997. Nevertheless, the promotions of BeneFin, MGN-3, and SkinAnswer continued through mass mailings, Internet sites, and employee statements.

The government's request for a permanent injunction was based on the defendants' demonstrated unwillingness to comply with the law.



### FDA Cautions Breast-Feeding Moms

Women who are breast-feeding should not use the unapproved drug domperidone to increase milk production due to safety concerns, the FDA says. The drug is excreted in breast milk and could expose a breast-feeding infant to unknown risks.

Published reports and case studies have cited cardiac arrhythmias, cardiac arrest, and sudden death in people receiving an intravenous form of domperidone, which has been withdrawn from the market in several countries. In areas where the oral form of domperidone continues to be available, labels for the product contain specific warnings against its use by breast-feeding women.

Recognizing the immense health benefits that breast milk provides for a nursing infant, the FDA has issued the warning, not to discourage women from breast-feeding, but rather to inform them of the potential harm

from using this particular drug while breast-feeding. In fact, the U.S. Department of Health and Human Services' Office on Women's Health and the Advertising Council announced in June 2004 the launch of a new national campaign that encourages first-time mothers to breast-feed exclusively for six months.

The FDA has issued six warning letters to pharmacies that compound products containing domperidone and firms that supply the drug for use in compounding. Compounding, as it relates to pharmacies, includes the preparation, mixing, assembling, packaging, or labeling of a drug in response to a prescription written by a licensed health care practitioner. The letters state that all drug products containing domperidone, whether compounded or not, violate the Federal Food, Drug, and Cosmetic Act because they are unapproved new drugs and misbranded. Further violations may

result in enforcement actions, including seizure, according to the FDA letters.

In addition, the agency has alerted field personnel to watch for any attempts to import domperidone so that it can be detained and refused entry into the United States. Importation of domperidone-containing products also is a violation of the law.

### New Director at FDA's CDRH

Daniel G. Schultz, M.D., has been named director of the FDA's Center for Devices and Radiological Health (CDRH) by Dr. Lester M. Crawford, Acting FDA Commissioner.

Schultz leads the center that is responsible for the review of medical devices, as well as radiation-emitting products such as magnetic resonance imaging equipment and X-ray machines. He also will oversee implementation of the Medical Device User Fee and Modernization Act of 2002, which authorizes the FDA to collect user fees for its review of medical device marketing applications and sets performance goals for the reviews.

In April 1994, Schultz joined the FDA as a medical officer in the General Surgery Branch of CDRH. He went on to become chief medical officer in the Division of Reproductive, Abdominal, and Radiological Devices. He later served as director of the Office of Device Evaluation.

Schultz received a medical degree from the University of Pittsburgh in 1974. After entering the Commissioned Corps of the U.S. Public Health Service in July 1975, he worked as clinical director of the Tuba City Indian Hospital on the Navajo reservation in Arizona. He is board-certified in general surgery and family practice and is a Fellow of the American College of Surgeons.

Schultz has been acting director at CDRH since April 1, 2004.

### Robotic Device Cleared for Heart Surgery

A new use for a robotic device that assists surgeons in the operating room was cleared by the FDA in July 2004.

Now approved to assist in coronary bypass surgery, the da Vinci Endoscopic Instrument Control System allows a surgeon to perform heart surgery while seated at a console with a computer and video monitor. A fiber-optic instrument with a small video camera gives doctors a magnified internal view of the surgical site on a television screen.

The surgeon uses handgrips and foot pedals on the console to control robotic arms, which perform surgery with a variety of tools. A built-in "wrist" at the end of the tools helps the surgeon perform more exact and intricate motions.

The da Vinci surgical system is already cleared for general abdominal laparoscopic surgeries such as gall bladder removal and to treat severe heartburn, for general chest surgery using an endoscope that doesn't involve the heart, and for thoroscopically assisted heart procedures such as mitral valve repair. The system is manufactured by Intuitive Surgical Inc. of Sunnyvale, Calif.



W. Randolph Chitwood Jr., M.D.



## FDA, Alliance Work to Improve Health Information Access

Did you know that among all Americans with high blood pressure, Mexican-Americans are less likely than whites or African-Americans to know that they have it? Or that one-third of Hispanics with diabetes are undiagnosed?

Those statistics, prepared by the U.S. Department of Health and Human Services Office of Minority Health, highlight the need to reinforce the commitment to improve consumer access to health information, especially to Hispanic communities, according to Dr. Lester M. Crawford, Acting FDA Commissioner.

Crawford and Jane Delgado, Ph.D., president and CEO of the National Alliance for Hispanic Health, are working together to provide timely, accurate, and scientifically based health information to Hispanics to help them take active steps to prevent disease and stay healthy.

As part of that effort, the FDA and the Alliance are promoting National Hispanic Heritage Month, Sept. 15 through Oct. 15, 2004. The outreach effort promotes two sources of consumer health information:

- The FDA web site at [www.fda.gov/oc/Spanish/](http://www.fda.gov/oc/Spanish/) provides a wealth of consumer-friendly health information in Spanish and English on topics ranging from medicine and children to mammograms and breast cancer.
- *Su Familia*, a toll-free National Hispanic Family Health Helpline, offers free, reliable and confidential health information in Spanish and English. The Helpline—(866) SU-FAMILIA (783-2645) operates Monday through Friday, 9 a.m. to 6 p.m. EST. *Su Familia* is a program of the National Alliance for Hispanic Health and is made possible by support from HHS.

## Safeguards Strengthened Against Mad Cow Disease

The FDA and the U.S. Department of Agriculture (USDA) have taken three actions to strengthen existing safeguards that protect consumers against the agent that causes bovine spongiform encephalopathy (BSE), also known as "mad cow disease."

In July 2004, the FDA published an interim final rule (IFR) that prohibits the use of certain materials from cattle that could carry the BSE-infectious agent in human food, dietary supplements, and cosmetics. These high-risk materials, known as "specified risk materials" (SRMs), include the brain, skull, eyes, and spinal cord of cattle 30 months of age or older, and a portion of the small intestine and tonsils from all cattle, regardless of their age. Also prohibited are materials from non-ambulatory disabled cattle, material from cattle not inspected and passed

for human consumption, and mechanically separated beef.

This IFR, in conjunction with IFRs issued by the USDA in January 2004, will minimize human exposure to materials that may put people at risk for a disease similar to BSE called variant Creutzfeldt-Jakob disease (vCJD). Scientific studies have demonstrated that SRMs could contain the BSE agent when derived from cattle that are harboring the BSE agent. Consumption of products contaminated with the agent that causes BSE is the likely cause of vCJD in people. This rule was effective immediately, but the FDA is accepting comments until Oct. 12, 2004, for consideration before publishing a final rule.

In a second action, the FDA published a proposed rule requiring manufacturers and processors of human food, dietary supplements, and cosmetics derived from certain cattle

materials to maintain records showing that prohibited materials are not used in their products.

Finally, the USDA and the FDA jointly published an advance notice of proposed rulemaking (ANPR) requesting comments and scientific information on additional measures to help prevent the spread of BSE. In the ANPR, the FDA is requesting comments on potential new controls on animal feed, including:

- removing SRMs from all animal feed, including pet food, to control the risks of cross contamination throughout feed manufacture and distribution, as well as on the farm
- requiring dedicated equipment or facilities for handling and storing feed and ingredients that may contain prohibited material during manufacturing and transportation, to prevent cross contamination
- prohibiting the use of all mammalian and poultry protein in feed for ruminants (such as cows, sheep, and goats), to prevent cross contamination
- prohibiting materials from non-ambulatory disabled cattle and dead stock from use in all animal feed.

The FDA's current animal feed rule, which became effective in 1997, helps prevent the establishment and spread of BSE through feed in the United States. FDA and state investigators inspect animal feed firms to ensure compliance with the rule. According to the latest inspection results of July 17, 2004, among companies handling material prohibited in feed for ruminants, compliance rates remain greater than 99 percent.

For more information, visit [www.fda.gov/oc/opacom/hottopics/bse.html](http://www.fda.gov/oc/opacom/hottopics/bse.html) or [www.fsis.usda.gov/oa/topics/bse.htm](http://www.fsis.usda.gov/oa/topics/bse.htm). ■



## Report: Number of Cancer Survivors Increasing

There are 9.8 million cancer survivors in the United States, according to a recent report released by the Centers for Disease Control and Prevention (CDC) and the National Cancer Institute (NCI). A cancer survivor is defined as anyone who has been diagnosed with cancer, from the time of diagnosis through the balance of his or her life.

The findings in the report are based on incidence and follow-up data from the NCI's Surveillance, Epidemiology and End Results (SEER) program to estimate annual cancer prevalence—the number of people living following a diagnosis of cancer—and trends in cancer survivorship.

The data show that:

- 64 percent of adults whose cancer is diagnosed today can expect to be living in five years.
- Breast cancer survivors make up the largest group of cancer survivors, 22 percent, followed by prostate cancer survivors, 17 percent, and colorectal cancer survivors, 11 percent.
- The majority, 61 percent, of cancer survivors are age 65 and older.
- An estimated 1 of every 6 people over 65 is a cancer survivor.
- 79 percent of childhood cancer survivors will be living five years after diagnosis and nearly 75 percent will be living 10 years following diagnosis.

"The findings in this report have important implications for both the

public and health practitioners," says Loria Pollack, M.D., a CDC medical officer. "There is a growing need to promote health and ensure the social, psychological and economic well-being of cancer survivors and their families."



Getty Images

In the past, Pollack says, public health programs concentrated on early detection and prevention of cancer. However, the focus has now expanded to include cancer survivorship, transforming survivorship research into practice, and developing clinical guidelines to provide attentive follow-up and health promotion to survivors.

"Issues faced by cancer survivors include maintaining optimal physical and mental health, preventing disability and late-effects related to cancer and its treatment, and ensuring social and

economic well-being for themselves and their family," says Julia Rowland, M.D., director of the Office of Cancer Survivorship at the NCI. She adds, "NCI takes these factors into consideration when conducting research to identify, examine and prevent or control adverse effects associated with cancer. We are working to enhance survivors' quality of life."

The CDC's Division of Cancer Prevention and Control is supporting states, tribes, and tribal organizations to develop and incorporate survivorship priorities into their comprehensive cancer control plans. The CDC is also working with national organizations to promote education, awareness, and community programs that offer services and support for cancer survivors.

"Cancer is the second leading cause of death in the United States after heart disease. The number of cancer survivors in this country has increased steadily over the past 30 years for all cancers combined. We expect the number of survivors to increase as improvements are made in cancer detection, treatment, and care and as the population ages," says Health and Human Services Secretary Tommy G. Thompson.

The report was published in the June 25, 2004, issue of the CDC's *Morbidity and Mortality Weekly Report*.

To view the article, visit [www.cdc.gov/mmwr/PDF/wk/mm5324.pdf](http://www.cdc.gov/mmwr/PDF/wk/mm5324.pdf). ■

**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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**Mailing address:** Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857



# Beyond Bloodletting:

## FDA Gives Leeches a Medical Makeover

By Carol Rados

**F**or thousands of years, leeches have been worming their way in and out of medicine as a questionable cure for anything from headaches to gangrene, reaching their height of medicinal use in the mid-1800s. Today, the slimy aquatic creatures are making a comeback as a legitimate treatment that can help heal skin grafts and restore blood circulation. Their primary function is to drain blood. Pooled blood around a wound can threaten tissue survival.

In June 2004, the Food and Drug Administration cleared the first application for leeches (*Hirudo medicinalis*) to be used in modern medicine as medical devices. By definition, a medical device is an article intended to diagnose, cure, treat, prevent, or mitigate a disease or condition, or to affect a function or structure of the body, that does not achieve its primary effect through a chemical action and is not metabolized.

Surgeons who do plastic and reconstructive surgery find leeches especially valuable when regrafting amputated appendages, such as fingers or toes. Severed blood vessels in such cases often are so damaged that they lack the ability to clear the area of blood. In these cases, it is difficult for the surgeon to make a route for blood to leave the affected part and return to circulation.

"The idea behind the leeches is to cause blood to ooze so that the body's own blood supply will eventually take over and the limb can go on and survive," says Rod J. Rohrich, M.D., president of the American Society of Plastic Surgeons and chairman of the Department of Plastic Surgery at the University of Texas Southwestern Medical Center. Leeches apply the perfect amount of suction to get the blood flowing. But Rohrich also says he uses the leeches only when there's a compromised situation, such as fol-

lowing surgery, "when the patient's own blood supply isn't adequate."

Packing a one-two chemical punch, the benefit of leech therapy comes not from the amount of blood that is extracted, but in the powerful anti-clotting agent hirudin, contained in the parasite's saliva, which keeps blood flowing freely. At the same time, leeches emit a natural anesthetic that minimizes pain during their feast.

Having disk-shaped suckers on each end of their bodies helps leeches feed, as well as hang on. The number of leeches used varies with each patient—typically two or three leeches are applied to the body until they drop off after about 40 minutes, and then the process is repeated with a new leech "team." At \$7 to \$10 apiece, their expense won't break budgets of physicians or hospitals.

The FDA considered safety data as part of reviewing the marketing application for the leeches submitted by Ricarimpex SAS of Eysines, France. In addition, the agency studied published literature on the use of leeches in medicine, how the leeches are fed, their environment, and the personnel who handle them.

Leeches were already being used in hospitals. A 1976 law has allowed



Photo Researchers Inc.

**The saliva of medicinal leeches contains hirudin, a substance that prevents blood from clotting.**

companies that raised and sold medicinal leeches before that year to continue doing so. Newcomers seeking to market leeches for medical purposes, however, were required by the 1976 law to gain FDA approval.

You won't find the type of leeches approved for medical use in a lake, river, or swamp. Rudy Rosenberg, owner and vice president of Leeches USA Ltd., the initial importer and distributor for Ricarimpex in the United States, says the leeches are raised under optimum conditions in controlled basins and laboratories. The facilities are certified, and all lots are tracked. This, he says, protects patients from infection. Leeches drop off after "feeding," and must be treated as infectious waste material. Rosenberg says that he knows of no case of leech-borne infection having been reported.

How do people react to being treated with these slimy parasites? "Initially, they're repulsed by the idea of leeches as a treatment," says Rohrich, "but eventually, they come to terms with the fact that it may be saving their lives." ■







# Psoriasis:

## *More Than Cosmetic*

*By Linda Bren*

**I**t's not easy living in Leah Bird's skin. "The worst thing is when people just stare," says Bird. "I almost like it better if someone comes up to me and asks me what it is."

Then she'll tell them, "I have psoriasis. It's not contagious."

Bird, 51, of suburban Boston, has had flare-ups of this chronic skin disease since she was a teen-ager. The dry, red, scaly patches of skin that characterize psoriasis have covered as much as 85 percent of her body, she says. "It alarms people. It looks very scary to people who don't know what it is."

But psoriasis is more than cosmetic. "This disease is common, chronic, and costly, both in monetary terms and in quality of life," says Jonathan Wilkin, M.D., director of the Food and Drug Administration's Division of Dermatologic and Dental Drug Products.

More than 5 million Americans have psoriasis, and they spend between \$1.6 billion and \$3.2 billion each year to treat the disease, according to the National Psoriasis Foundation (NPF). Between 150,000 and 260,000 new cases are diagnosed each year, including 20,000 in children younger than 10.

"Psoriasis can be painful and can be profoundly disruptive to a person's life," says Jill Lindstrom, M.D., an FDA dermatologist. "People who don't have it don't understand how burdensome the disease can be. There is constant shedding of scales. There can be functional impairment, itching, and pain." And health complications, such as arthritis, accompany some cases.

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Leah Bird of suburban Boston has had psoriasis for more than 30 years. She says it's important for people who have the skin condition to "work on their emotional well-being."



There is no cure for psoriasis, but a broad range of treatments is available to reduce the symptoms, clear up the skin, and send the disease into remission. FDA-approved treatments range from creams rubbed into the skin, to lasers that aim ultraviolet rays at the skin, to the newest treatments—injectable drugs made from living cells.

### **What is Psoriasis?**

Psoriasis is an inflammatory skin disease in which skin cells replicate at an extremely rapid rate. New skin cells are produced about eight times faster than normal—over several days instead of a month—but the rate at which old cells slough off is unchanged. This causes cells to build up on the skin's surface, forming thick patches, or plaques, of red sores (lesions) covered with flaky, silvery-white dead skin cells (scales).

Rarely life-threatening, at its mildest, psoriasis can be itchy and sore. At

Skin Diseases, about 15 percent of people with psoriasis also get psoriatic arthritis, which can be progressively disabling if untreated.

### **Wayward White Blood Cells**

Scientists believe that certain white blood cells called T lymphocytes (T cells) play an important role in psoriasis. "And the disease has a genetic component," says Lindstrom. In about one-third of psoriasis cases, there is a family history of the disease.

T cells circulate throughout the body, orchestrating the immune system's response to foreign invaders like bacteria or viruses. In people with psoriasis, the defective T cells are overactive and migrate to the skin as if to heal a wound or ward off an infection. This process leads to the rapid growth of skin cells, triggering inflammation and the development of lesions.

Both the environment and genetics may play a role in the development of

ers used to treat high blood pressure, and antimalarial drugs.

### **Diagnosis and Treatment**

No single test exists to diagnose psoriasis, but a dermatologist can usually determine it by the appearance of the skin and by looking at an individual's personal and family medical history. In some cases, a specialist will confirm the diagnosis by examining a small piece of skin (biopsy) under a microscope.

Psoriasis treatments fall into three categories: medications externally applied to the skin (topical), ultraviolet light applied to the skin (phototherapy), and medications taken by mouth or injected (systemic).

### **Topical Treatments**

Topical lotions, ointments, creams, gels, and shampoos for the skin and scalp are prescribed for mild-to-moderate cases of psoriasis or in combination

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## *Both the environment and genetics may play a role in the development of psoriasis.*

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its worst, it's painful, disfiguring, and debilitating. About two-thirds of the people with psoriasis have a mild form of the disease, says the NPF. About one-third have moderate or severe psoriasis. Psoriasis can affect people at any age, but it most often strikes those between the ages of 15 and 35.

There are five forms of psoriasis. Plaque psoriasis is the most common—affecting 4 out of 5 people who have psoriasis, says the NPF. Plaque psoriasis may start with small red bumps and progress to larger lesions.

The plaques of psoriasis occur most frequently on the elbows, knees, other parts of the legs, scalp, back, face, palms, and soles of the feet. Psoriasis can also affect the fingernails and toenails, causing pitting, discoloration, or tissue buildup around the nails. According to the National Institute of Arthritis and Musculoskeletal and

psoriasis. "In genetically predisposed children, psoriasis can be triggered by a strep or other infection," says Lindstrom. That's what happened to author John Updike. After an attack of measles at the age of 6, Updike developed psoriasis "in all its flaming scabbiness from head to toe," as he later described it in his memoir, *Self-Consciousness*.

### **Remission and Reactivation**

While the disease never goes away, the symptoms of psoriasis subside for a while (remission) and then return (flare-up, or reactivation). Remission can last for years in some people; in others, flare-ups occur every few weeks. Certain triggers, such as stress and seasonal changes, can reactivate psoriasis. "Certain drugs may also exacerbate it," says Lindstrom, including lithium, prescribed for bipolar disorder (also called manic-depressive illness), beta-block-

with other treatments for more severe cases. FDA-approved prescription topicals to treat psoriasis include corticosteroids, retinoids, calcipotriene, and coal tar products. These drugs slow down skin cell production and reduce inflammation.

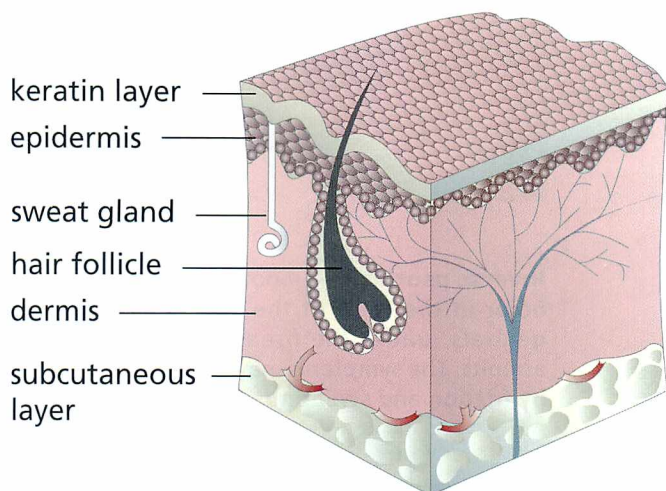
Corticosteroids are synthetic drugs that resemble naturally occurring hormones. Side effects may include thinning of the skin and stretch marks at the area where the topical is applied. Corticosteroids may also suppress the adrenal glands' production of natural steroids, which could leave the body susceptible to disease.

Retinoids are derivatives of vitamin A and calcipotriene is a synthetic form of vitamin D. Retinoids and calcipotriene are not the same as over-the-counter vitamin A and D supplements, which have no value for treating psoriasis, says Wilkin. "These topical creams on

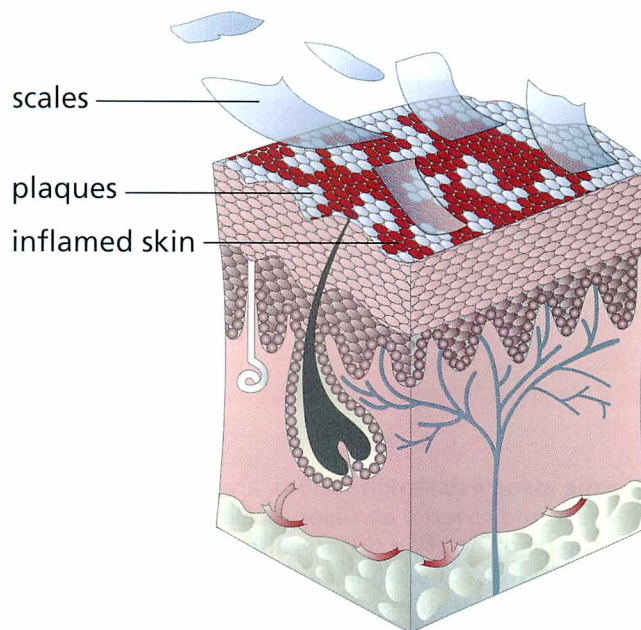


# Healthy Skin vs. Psoriasis

## Healthy Skin



## Psoriasis



In psoriasis, an activated immune system triggers the skin cells to reproduce every three to four days, building up on the outer layers (epidermis and keratin). The epidermis thickens, blood flow increases and reddens the skin, and silver-gray scales cover it.

Infographic: FDA/Renée Gordon

the skin deliver the vitamin-like chemicals right to where you want them," he says. Skin irritation where the topical is applied may be a side effect. Retinoids are also available by prescription as oral systemic drugs.

Coal tar products can help with scaling, itching, and inflammation but are not used as commonly as some other topicals, says Lindstrom. They are messy, can stain, and have a strong odor.

Carol Bentson of Washington, D.C., has had plaque psoriasis for more than 30 years, causing "major itching" all over and pain along the scalp line. She has treated it with topical corticosteroids, ultraviolet light, and cortisone injected into her scalp, elbows, toes, and legs. At times, "ointment wouldn't penetrate the areas of heavy plaque buildup, no matter how much I put on," she says.

Bentson has accumulated "sacks of lotions" to treat psoriasis. She would

find a topical treatment that worked for a while but then quit working, forcing her to switch to another one.

"With a potent topical steroid, there is a phenomenon called tachyphylaxis," says Craig Leonardi, M.D., associate clinical professor of dermatology at the Saint Louis University Medical School. "Prolonged use can cause down-regulation [decrease] of steroid receptors in cells. The net effect is that the skin becomes less responsive to steroids over time."

Wilkin adds that this unresponsiveness may be a temporary effect. "A patient may need to be off the steroid for a few days or a week and when put back on it, the responsiveness could come back."

### Light Therapy

Exposing the skin to ultraviolet (UV) light—either from the sun or an artificial source—sets off a biological process that kills T cells, which slows

the buildup of skin cells and reduces inflammation.

Light boxes that emit UV light to treat moderate-to-severe psoriasis and other skin diseases are medical devices that require licensing by the FDA. A person steps into the light box, which is about the size of a telephone booth, while lamps direct the light onto the body.

"Treatment with these devices is complex," says Richard Felten, an FDA chemist and senior medical device reviewer. The physician must determine an individual's sensitivity to UV and adjust the light emissions for the most effective treatment with the least risk of side effects, he says. Side effects may include burning, darkened skin, premature aging, and skin cancer. Three to five treatments per week for several weeks or months may be needed to get the psoriasis under control, followed by weekly maintenance treatments.

Light therapy, or phototherapy, is usually done in the physician's office or



# Types of Psoriasis



**Plaque psoriasis**—Skin lesions are red at the base and covered by silvery scales. They can appear on any skin surface, although the knees, elbows, scalp, trunk, and nails are the most common locations. About 80 percent of people with psoriasis have this type.



**Inverse psoriasis**—Smooth, red patches occur in the folds of the skin near the genitals, under the breasts, or in the armpits. The symptoms may be worsened by friction and sweating.

**Pustular psoriasis**—Blisters of noninfectious pus appear on the skin, particularly the hands and feet. Attacks of pustular psoriasis may be triggered by medications, infections, stress, or exposure to certain chemicals.



**Erythrodermic psoriasis**—Widespread fiery redness and scaling of the skin may be a reaction to severe sunburn or to taking corticosteroids (cortisone) or other medications. It can also be caused by a prolonged period of increased activity of psoriasis that is poorly controlled.

**Guttate psoriasis**—Small, drop-shaped lesions appear on the trunk, limbs, and scalp. Guttate psoriasis is most often triggered by upper respiratory infections, such as a sore throat caused by streptococcal bacteria (strep throat).





a medical facility that has the devices, says Felten. "The FDA has cleared some devices for home use under certain conditions and with a doctor's prescription," he says. Home devices include handheld devices for scalp psoriasis and stand-alone light boxes for other areas of the body.

Light therapy usually involves a short wavelength of ultraviolet light, called UVB. For people with resistant moderate-to-severe psoriasis, a combination of an oral or topical drug called psoralen and a longer wavelength ultraviolet A

tin, methotrexate, cyclosporine, and biologics, which are drugs made from proteins of living cells. Methotrexate, cyclosporine, and the biologic drugs are immunosuppressants, meaning they lower the body's normal immune response. "These drugs suppress the immune cells that cause psoriasis, but they don't distinguish these cells from the immune cells that protect our body from infections," says Elektra Papadopoulos, M.D., an FDA dermatologist.

Acitretin, a retinoid that is given orally for severe psoriasis, helps nor-

T-cell activation. Raptiva inhibits the activation of T cells and the migration of those cells across blood vessels and into tissues, including the skin.

Enbrel inhibits the action of an inflammatory chemical messenger in the immune system called tumor necrosis factor-alpha (TNF-alpha), which is believed to play a role in both the skin and the joint symptoms of psoriasis.

All three biologics are injected. The FDA has licensed Amevive to be given in a physician's office, either injected into the muscle or into a vein (intrave-

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## *'Biologics are an alternative treatment to some of the traditional therapies.'*

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(UVA) light is used. This treatment is called "psoralen plus UVA" (PUVA).

"Psoralen makes the patient more sensitive to the UVA," says Lindstrom, "so once they've taken a dose of psoralen, a smaller dose of UVA is needed to treat them." Patients must be very careful to protect both skin and eyes for 24 hours after psoralen use to prevent damage, she says.

The FDA has also approved a special type of laser, an excimer laser, as a phototherapy device to treat mild-to-moderate psoriasis. "These lasers can deliver a much more controlled beam of light to small areas of the affected skin," says Felten.

### **Systemic Treatments**

The FDA has approved oral and injected drugs that circulate throughout the body to treat psoriasis that is moderate, severe, or disabling. These systemic drugs are very powerful, and while some may be used continuously, others can only be used for a limited time because of their severe side effects. Once a drug is discontinued, the psoriasis may reactivate. The risk of birth defects prevents many systemics from being taken by pregnant women or women planning to become pregnant.

Systemic drugs that may be prescribed for psoriasis include acitre-

malize the growth of skin cells. One of the side effects is raised fat (lipid) levels in the blood, and people taking this drug must get regular blood tests to monitor their cholesterol and triglyceride levels.

Methotrexate and cyclosporine slow the growth of skin cells. Methotrexate, taken orally or by injection, is also a chemotherapy drug for cancer patients. Cyclosporine, taken orally, was first approved to prevent organ rejection in transplant recipients. People using either of these drugs must be closely monitored and should use them only for short periods of time because of serious, potentially fatal, side effects.

Biologics are the newest systemic psoriasis treatments. Since 2003, the FDA has licensed three biologics to treat moderate-to-severe plaque psoriasis: Amevive (alefacept), manufactured by Biogen Inc.; Raptiva (efalizumab), made by Genentech Inc.; and Enbrel (etanercept), marketed by Amgen Inc. and Wyeth Pharmaceuticals. Enbrel was first licensed in 2002 to treat the arthritis associated with psoriasis, and in 2004 to treat psoriasis itself.

"All are immunosuppressive and have different proposed mechanisms," says Papadopoulos. Amevive simultaneously reduces the number of immune cells, including T cells, and inhibits

nously). It's a once-a-week treatment for 12 weeks; further treatments may be given after a waiting period.

The FDA has licensed Raptiva and Enbrel for home treatment. People can inject themselves with Raptiva under the skin once a week or with Enbrel once or twice a week. Both drugs are recommended for continuous use to maintain results.

Since biologic drugs are immunosuppressants, they may carry an increased risk of infection and cancer. Rare but serious effects have also included blood abnormalities and autoimmune diseases such as lupus. Other side effects are flu-like symptoms and pain and inflammation at the injection site.

Some dermatologists prescribe biologics alone for psoriasis or in combination with topical treatments. Leonardi says when he prescribes biologics, "I don't have to resort to adding other systemic therapies such as methotrexate, cyclosporine, acitretin, or phototherapy."

"Biologics are an alternative treatment to some of the traditional therapies," says Papadopoulos.

"Now we need to get the expense down," says Leonardi, who has patients who pay \$30,000 per year on drugs to treat psoriasis.

Bird feels fortunate that her insur-



ance company covers most of the expense of Enbrel, which is prescribed for both her psoriasis and psoriatic arthritis. Because of the arthritis pain, she has used a cane to help her walk and has had surgery on her wrist to correct some of the arthritis damage. Although Enbrel has been less effective over time for the psoriasis, she says, it's reduced her arthritic pain by about 95 percent. "I can jog down to the corner to chase after the dog," she says. "And last summer, I went hiking with my children in Colorado."

### Reducing Treatment Risks

Biologics, other systemic drugs, and phototherapy are powerful treatments with increased risks, says Lindstrom.

Biologics may raise the risk for developing cancer and serious bacterial or fungal infections that spread throughout the body (sepsis).

Cyclosporine can damage the kidneys, methotrexate puts the liver and lungs at risk, and phototherapy can cause skin cancer. To reduce these risks, doctors often put patients on "rotational therapy." "The thought is by moving from one therapy to another therapy over time, the risk to any individual organ is reduced," says Lindstrom.

"We also try to choose a drug with an appropriate benefit-risk ratio," she says. For mild psoriasis, a topical steroid may be appropriate. For more severe disease, where it becomes impractical to apply topicals over a large surface area several times a day, a patient may need a systemic treatment.

Most of the highly effective treatments for psoriasis affect the immune

system in some way. For steroid drugs, which have been around for more than 50 years, the risks are well known. But less is known about the long-term side effects of newer drugs, such as the biologics. The safety and side effects of biologics and other immune-suppressing drugs to treat psoriasis continue to be monitored by drug manufacturers and the FDA.

### Emotional Impact

For many people, dealing with the emotional impact of psoriasis can be as challenging as treating the disease.

Bird says that mothers have pulled their children away from her on the subway, and some people, horrified by her skin lesions, have asked her if she has AIDS. As her disease has evolved over 30 years, so has Bird's way of dealing with these reactions. In her teens, she'd tell people she had leprosy just for the shock value, she says. Today, Bird is open about the disease but still relies on her defiant attitude to "steel myself for the experience" of going to the beach. "I love to swim," she says. But Bird knows that without covering herself up in a public place, she "runs the risk of people just rubbernecking."

"When I'm feeling forgiving, I try to ignore them," she says, "but when I'm angry, I think 'didn't your mother teach you not to stare?'"

Bird advises others with psoriasis to find out what works best for them to cope with the emotional effects of the disease. Going to therapy has helped her, she says. So has leading a support group for psoriasis sufferers. "It's important for people to work on

their emotional well-being," says Bird, "however they choose—whether it's meditation, yoga, or putting on long pants and going out dancing."

### The Future of Psoriasis Treatment

Researchers continue to look for reasons why immune cells overreact and what genes may be responsible for psoriasis, hoping to find better treatments, and eventually a cure. Psoriasis research is aided by the visibility of the symptoms on the skin.

"You can see the disease," says Leonardi. "You don't have to do invasive testing to see the effects of therapy." Psoriasis research has a "tremendous spillover into other fields besides dermatology," he adds. "There is a huge need for drugs to suppress the immune system without the side effects."

Multiple sclerosis, Crohn's disease, rheumatoid arthritis, and type 1 diabetes are just a few of the diseases that may also benefit from psoriasis research. ■

### For More Information

National Institute of Arthritis and Musculoskeletal and Skin Diseases  
Information Clearinghouse  
(877) 226-4267  
TTY: (301) 565-2966  
[www.niams.nih.gov/hi/](http://www.niams.nih.gov/hi/)

National Psoriasis Foundation  
(800) 723-9166  
[www.psoriasis.org](http://www.psoriasis.org)

American Academy of Dermatology  
(847) 330-0230  
[www.aad.org](http://www.aad.org)

## Sea, Salt, and Sun

Some psoriasis sufferers have tried salt water to relieve their itchy or painful skin. Some have even made pilgrimages to the world's saltiest lake, the Dead Sea.

"The Dead Sea is excellent for psoriatic treatment," says Lawrence C. Parish, M.D., clinical professor of dermatology and cutaneous biology at Jefferson Medical College of Thomas Jefferson University in Philadelphia. "But no one knows if the water itself has merit or whether the sun is the important part." As the lowest point on the planet, the Dead Sea region has unique weather and receives a distinctive spectrum of ultraviolet light from the sun.

Soaking in bath water containing Dead Sea salts or

Epsom salts may have limited value. "It can help remove the scales of psoriasis and make people feel better," says Parish, "but no one has shown these salts to have a therapeutic effect."

Whether at the Dead Sea or anywhere else, sunlight can have a positive effect on psoriasis. "But be reasonable about it," Parish says. "A little bit of sun is fine." He advises wearing a wide-brimmed hat and applying sunscreen several times a day. "Anyone who wears makeup knows if you put it on at 8 o'clock in the morning, it doesn't last until 8 at night," he says, and neither does sunscreen. ■



By Carol Rados

**B**uying prescription drugs online from unknown foreign sources is risky business, and people are being advised by the Food and Drug Administration once again to use care when doing so. A recent analysis of three commonly prescribed drugs purchased by the FDA from a Canadian-advertised Web site showed that the “generics” were fake, substandard, and potentially dangerous.



“Consumers who believe they are getting equivalent products from reputable sources are being misled and putting their health at risk,” says Dr. Lester M. Crawford, Acting FDA Commissioner. “This firm shipped drugs that were the wrong strength, including some that were substantially super-potent and that pose real health risks as a result, drugs that didn’t dissolve properly, drugs that contained contaminants, and drugs that should not have been given because of potentially dangerous drug interactions,” he says.

The FDA purchased so-called “generic” versions of Viagra (sildenafil), Lipitor (atorvastatin), and Ambien (zolpidem). None of the drugs has a U.S.-approved generic version, so all of the purchased drugs were unapproved.

The “generic” Ambien, a controlled substance approved for short-term insomnia, contained too much active ingredient, including one tablet that

was nearly double the labeled potency. Taking super-potent Ambien puts patients at risk for central nervous system depression, especially in elderly or debilitated patients.

The “generic” Lipitor, a drug used for lowering cholesterol, was subpotent and failed to dissolve, providing on average only 57 percent of the active ingredient claimed on the label. It also failed the FDA’s purity testing. Subpotent products could present a long-term risk for the various complications of high cholesterol, such as heart disease. Further, the Lipitor product was furnished to the FDA’s online purchaser, even though the purchaser said that he was taking the antibiotic erythromycin. Lipitor’s label warns against taking these two drugs at the same time.

The “generic” Viagra, normally sold to treat impotence, contained too little of the active ingredient, failed to dissolve, and had an unacceptable level of impurities.

The FDA warns that, although a Web site may appear to be reputable and may look similar to other retail pharmacy Web sites, many of these are in fact operating from outside the United States and are providing unapproved drugs from unreliable sources. The National Association of Boards of Pharmacy (NABP) has established a program called Verified Internet Pharmacy Practice Sites (VIPPS), designed to certify Web sites that meet industry standards. Consumers should look for the VIPPS certification seal on the site or check with the NABP for a list of VIPPS-certified pharmacies at [www.nabp.net/vipps/](http://www.nabp.net/vipps/) to help minimize the risks of getting bad quality drugs from disreputable sources. ■



# IOM Report: No Link Between Vaccines and Autism

By Michelle Meadows

**T**here is no link between autism and the measles-mumps-rubella (MMR) vaccine or the vaccine preservative thimerosal, according to a report released by the Institute of Medicine's (IOM) Immunization Safety Review Committee.



Corbis

The report, released in May 2004, was prepared by a committee of independent experts established by the IOM in 2001 at the request of the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) to evaluate evidence on potential links between childhood vaccines and health problems. The agencies explored the issue because of growing controversy and questions from the public about vaccine safety.

Some parents have expressed concern because the symptoms of autism typically emerge in a child's second year of life, around the same time children first receive the MMR vaccine. Autism is a complex set of severe developmental disorders characterized by

repetitive behavior and impaired social interaction and communication abilities. Other concerns the committee looked at include the use of thimerosal, a mercury-based compound used as a vaccine preservative, because many forms of mercury are known to damage the nervous system in high doses.

## **Review of the Research**

This latest IOM report follows two reports on vaccines and autism published in 2001. The committee determined then that the evidence did not show an association between the MMR vaccine and autism, but that more evidence was needed regarding thimerosal. "The committee concluded that the evidence available at that time was

inadequate to accept or reject a causal relationship between thimerosal and neurodevelopmental disorders," says Marie McCormick, M.D., Sc.D., chairwoman of the immunization safety committee and a professor at the Harvard School of Public Health.

The committee revisited these issues because several studies exploring possible links between vaccines and autism have been published since 2001. Committee members concluded that the hypothesis about how the MMR vaccine and thimerosal could trigger autism lacks supporting evidence. Their conclusions were based on a careful review of well-designed studies and other information from researchers and parents.



Five large studies in the United States, the United Kingdom, Denmark, and Sweden done since 2001 found no evidence of a link between autism and vaccines containing thimerosal. And 14 large studies consistently showed no link between the MMR vaccine and autism. The committee also reviewed several studies that did report associations between vaccines and autism and found that these studies had limitations and lacked supporting evidence.

The committee reviewed potential biological links between vaccines and autism and found them to be only theoretical. Examples of some of the hypothesized links include a suggestion that the measles virus in the MMR vaccine might lodge in the intestines and trigger the release of toxins that could

vative in multi-dose vials of vaccines to prevent bacterial contamination. The active ingredient in thimerosal is ethylmercury.

Even though the risk of thimerosal is hypothetical, thimerosal began to be removed from childhood vaccines in 1999. The federal government, the American Academy of Pediatrics, and others agreed that thimerosal should be reduced and eliminated in vaccines as a precautionary measure. The FDA encouraged companies to comply with this recommendation. Currently, all routinely recommended vaccines manufactured for infants in the United States are either thimerosal-free or contain only trace amounts.

"We moved in this direction to address public concern and because it

preservative will increase as manufacturing capabilities expand. "To eliminate thimerosal as a preservative from flu vaccines, manufacturers will have to switch from multi-dose to single-dose preparations, which requires greater filling and storage capacity," Midthun says.

Based on federal guidelines on levels of mercury exposure, a child won't receive excessive mercury from vaccines, regardless of whether their inoculation against the flu contains thimerosal.

### **Recommendations**

The IOM's immunization safety committee did not recommend any changes with the MMR vaccine or with the current schedule of routine childhood

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## *The IOM's immunization safety committee did not recommend any changes with the MMR vaccine or with the current schedule of routine childhood immunizations.*

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lead to autism. Another hypothesis is that the MMR vaccine might stimulate the release of immune factors that damage the central nervous system. Yet another hypothesis is that thimerosal may interfere with biochemical systems in the brain, thereby causing autism. But according to the IOM report, no evidence has shown that the immune system or its activation play a direct role in causing autism, and autism has not been documented as being a result of exposure to high doses of mercury.

"There is no convincing evidence of serious harm from the low doses of thimerosal in vaccines," says Karen Midthun, M.D., deputy director for medicine in the FDA's Center for Biologics Evaluation and Research (CBER). CBER regulates vaccines in the United States and works with the CDC and the NIH to study and monitor vaccine safety and effectiveness.

### **Limiting Thimerosal Use**

Since the 1930s, small amounts of thimerosal have been used as a preser-

was feasible to eliminate mercury from vaccines," Midthun says. "We could eliminate thimerosal in vaccines as a way to reduce a child's total exposure to mercury, whereas other environmental sources of exposure are more difficult to eliminate."

In its latest report, the IOM's immunization committee reported that it does not dispute that mercury-containing compounds, including thimerosal, can be damaging to the nervous system. But the committee did not find that these damaging effects are related to the development of autism.

For the 2004–2005 flu season, the CDC is recommending that children ages 6 months to 23 months get vaccinated annually against the flu (influenza) with the inactivated flu shot. "The influenza vaccine is available both with thimerosal as a preservative and without it," Midthun says. "But the benefits of flu vaccination outweigh any theoretical risk from thimerosal."

According to the CDC, the amount of flu vaccine without thimerosal as a

immunizations.

"While the committee strongly supports research that focuses on achieving a better understanding of autism, we recommend that future research be directed toward other lines of inquiry that are supported by current knowledge and evidence, and that offer more promise for finding an answer," McCormick said at a media briefing. "Given the current evidence, the vaccine hypothesis doesn't offer that promise."

The IOM is part of the National Academy of Sciences. ■

### **For More Information**

*Immunization Safety Review: Vaccines and Autism*

Immunization Safety Review Committee, Institute of Medicine  
<http://books.nap.edu/catalog/10997.html>

Thimerosal in Vaccines  
[www.fda.gov/cber/vaccine/thimerosal.htm](http://www.fda.gov/cber/vaccine/thimerosal.htm)







# Training the Immune System to Fight Cancer

By Michelle Meadows

**V**accines traditionally have been used to prevent infectious diseases such as measles and the flu. But with cancer vaccines, the emphasis is on treatment, at least for now. The idea is to inject a preparation of inactivated cancer cells or proteins that are unique to cancer cells into a person who has cancer. The goal: to train the person's immune system to recognize the living cancer cells and attack them.

"The best settings are for treating people who have minimal disease or a high risk of recurrence," says Jeffrey Schlom, Ph.D., chief of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute (NCI). "But at this time, most therapeutic cancer vaccines are being studied in people who have failed other therapies."

Cancer vaccines are experimental; none have been licensed by the Food and Drug Administration. But there are about a dozen cancer vaccines in advanced clinical trials, says Steven Hirschfeld, M.D., a medical offi-

cer in the FDA's Center for Biologics Evaluation and Research. "Research has shown us that the fundamental approach to cancer vaccines is right; we are moving in the right direction," he says.

The three standard cancer therapies are surgery to remove tumors; chemotherapy, which modifies or destroys cancer cells with drugs; and radiation, which destroys cancer cells with high-energy X-rays. Immunotherapy, which includes cancer vaccines, is considered a fourth, and still investigational, type of therapy. Cancer vaccines are sometimes used alone, but are often combined with a standard therapy.

While standard treatments alone have proven effective, they also have limitations. Radiation and chemotherapy can wipe out a person's cancer cells, but they also damage normal cells. "We want to find treatment that is more targeted and less toxic," says Hirschfeld. "Cancer vaccines are designed to be specific, targeting only the cancer cells without harming the healthy ones."

The approach has made cancer vaccines generally well tolerated, allowing them to be used in outpatient settings. And they can be added to standard therapy with a low likelihood of causing further serious side effects.

## How Cancer Vaccines Work

Cancer is a term for more than 100 diseases characterized by the uncon-



Phototake

**A photograph taken through a microscope shows a cancer cell (red) being attacked by T lymphocytes (yellow).**

trolled, abnormal growth of cells. To the immune system—the body's natural defense system against disease—cancer cells and normal cells look the same. The immune system tends to tolerate the cancer cells, just as it tolerates the normal cells. That's because the immune system doesn't recognize cancer cells as something foreign, Hirschfeld says. Rather, cancer cells are once-normal cells that have gone awry. Cancer vaccines try to get the immune system to overcome its tolerance of cancer cells so that it can recognize them and attack them.

All cells have unique proteins or

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Gary Montgomery, a retired engineer from Redmond, Wash., flies to Georgetown University's Lombardi Cancer Center in Washington, D.C., every month. There, he receives a cancer vaccine to treat a rare form of abdominal cancer as part of a clinical trial.



bits of proteins on their surface called antigens. Many cancer cells make cancer-specific antigens. The goal of using cancer antigens as a vaccine is to teach the immune system to recognize the cancer-specific antigens and to reject any cells with those antigens. The antigens activate white blood cells called B lymphocytes (B cells) and T lymphocytes (T cells). B cells produce antibodies that recognize a particular antigen and bind to it to help destroy the cancer cells. T cells that recognize a particular antigen can attack and kill cancer cells. In 1991, the first human cancer antigen was found in cells of a person with melanoma, a discovery that encouraged researchers to search for antigens on other types of cancer, according to the NCI.

The two main approaches for cancer

vaccines are whole-cell vaccines and antigen vaccines. Whole-cell vaccines may take whole cancer cells from a patient or sometimes several patients, or use human tumor cell lines derived in a laboratory. "Some cell-based vaccines use tumor cells from the patient, some contain something that looks like a tumor cell but was created in a lab, and others are personalized vaccines that use some cells from the patient and some from the lab," Hirschfeld says. Cells that are taken from people with cancer are altered in a lab to inactivate them so that they are safe to re-inject.

Regardless of the exact source of the cells, whole cell vaccines potentially use all the antigens found on the tumor cells. Antigen vaccines try to trigger an immune response by using only certain

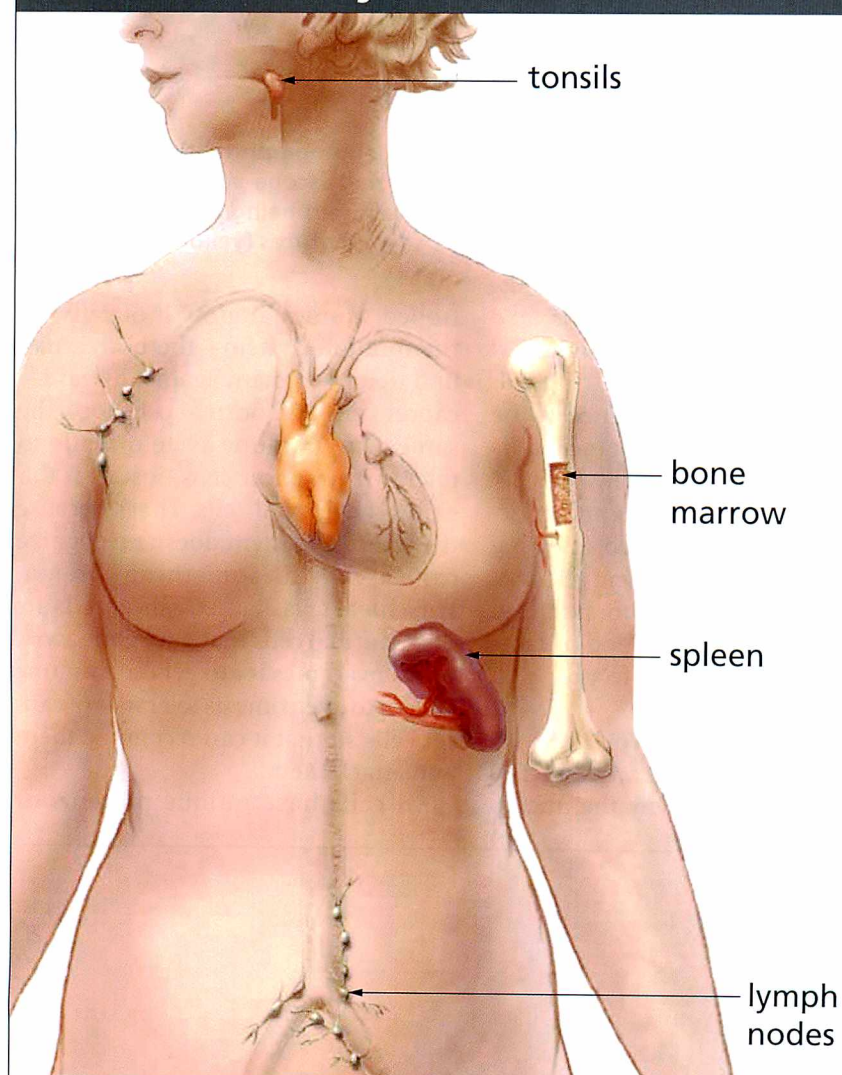
antigens from cancer cells. Hirschfeld says antigens may be particular to an individual, to a certain type of cancer, or to several types of cancers.

### Boosting the Immune Response

In the early 1990s, Steven Rosenberg, M.D., one of the pioneers of immunotherapy and chief of surgery at the NCI, wrote that trying to use the immune system to fight cancer is so difficult that it made him feel "like a dog trying to bite a basketball." Among Rosenberg's contributions was identifying the antigens that trigger an immune response, and cloning genes that look for, or "code for," those antigens.

Researchers have been working to develop cancer vaccines for more than 100 years in one form or another, and the main mission has always been to

## The Immune System and How It Works



Your immune system includes your spleen, lymph nodes, tonsils, bone marrow, and white blood cells. These all help protect you from getting infections and diseases. When your immune system works the way it should, it can tell the difference between "good" cells that keep you healthy and "bad" cells that make you sick. But sometimes this doesn't happen. Doctors are doing research to learn why some immune systems don't fight off diseases like cancer.

White blood cells are an important part of your immune system. When your doctor or nurse talks about your white blood cells, he or she may use words like:

- **Monocytes** (MON-o-cites) are types of white blood cells.
- **Lymphocytes** (LYM-fo-cites) are types of white blood cells.
- **B cells, T cells, and "natural killer cells"** are kinds of lymphocytes.



make the immune system's response to the cancer antigens as strong as possible.

One major strategy involves combining vaccines with additional substances called adjuvants, which act as chemical messengers that help T cells work better. An example of one type of adjuvant, called a cytokine, is interleukin-2. This protein is made by the body's immune system and can also be made in a lab.

There have also been improvements in vaccine delivery. For example, Schlom developed a vaccine in which genes for tumor antigens are put into a weakened virus called a "vector" that delivers genetic materials to cells. This makes the tumor antigen more visible to the immune system. The CEA-TRICOM vaccine was developed at the NCI through a cooperative research and development agreement with Therion Biologics in Cambridge, Mass. Researchers use the vaccinia virus, the same virus in the smallpox vaccine, as the vector. The carcinoembryonic antigen (CEA), which is found on most breast, lung, colon, and pancreatic tumors, is added to the virus. Researchers also add three molecules, called "costimulatory molecules," which serve as signals that make the vaccine more potent than it would be if the antigen were used alone. A similar vaccine developed under the NCI agreement with Therion is the PANVAC vaccine, which has now entered advanced study as a treatment for pancreatic cancer.

In addition to studying this type of virus-based technique, researchers at Duke University's Cancer Center in Durham, N.C., have been studying vaccines that mix white blood cells called dendritic cells with genetic material from a person's tumor.

Dendritic cells, which can activate T cells, work by looking around, finding antigens, and showing them to the fighter T cells. Researchers have found ways to increase the number of dendritic cells in a vaccine. "Employing millions of 'pumped up' dendritic cells can help elicit a strong immune response," says H. Kim Lyerly, M.D., director of the Duke cancer center.

Recent work by Lyerly and Duke

investigators Michael Morse, M.D., and Timothy Clay, Ph.D., has focused on modifying dendritic cells with viruses so that they activate even stronger T cell responses against cancer antigens.

"This is an evolving area, and it's exciting to be able to make progress," says Lyerly. "For decades, people thought it wasn't even fundamentally possible to develop cancer vaccines, and here we are. The science behind cancer vaccines is leading us to believe that we will find the answers."

### **Promising, But Still Early**

As with any new treatment, cancer vaccines must be first studied in lab animals and then tested for safety and

NCI's Cancer Therapy Evaluation Program, it's too soon to say which cancers will be treated with vaccine therapy. The types of tumors that have proven most susceptible to vaccines so far, he says, are: skin cancer (melanoma); kidney cancer (renal cell); a group of cancers that affect the lymphatic system (lymphoma); a malignant tumor of the bone marrow (myeloma); and solid tumors, such as lung cancer. The most work has been done in the area of melanoma, a type of skin cancer in which treatment options are limited when the disease is in advanced stages.

"After having a tumor removed, about half of patients with stage III

## **Cancer Vaccine Facts**

- Cancer vaccines are intended either to treat existing cancers (therapeutic vaccines) or to prevent the development of cancer (prophylactic vaccines).
- Therapeutic vaccines, which are administered to cancer patients, are designed to treat cancer by stimulating the immune system to recognize and attack human cancer cells without harming normal cells. Prophylactic vaccines, on the other hand, are given to healthy individuals to stimulate the immune system to attack cancer-causing viruses and prevent viral infection.
- The only cancer vaccine licensed by the Food and Drug Administration is a prophylactic vaccine against hepatitis B virus, an infectious agent associated with liver cancer.
- Scientists are currently evaluating several different vaccines in large human trials to determine which approaches are most effective for particular kinds of cancers.

Source: National Cancer Institute

effectiveness in three phases of human studies, called "clinical trials," before they can be approved by the FDA. In Phase 1 clinical trials, cancer vaccines are used alone and studied for safety and to determine the proper dose. In Phase 2 trials, they are tested for effectiveness and may be used alone or in combination with another therapy. Phase 3 trials are large-scale studies testing effectiveness and usually comparing a vaccine with some standard therapy. Researchers are testing vaccines using various adjuvants, delivery methods, and types of antigens.

Cancer vaccines have shown promise in clinical trials with many types of cancer. According to Howard Streicher, M.D., a senior investigator with the

melanoma may have a recurrence, and we want to prevent that," Streicher says. "Chemotherapy doesn't work in this area, so our hope is that this could be just the right place for a vaccine."

James Mulé, M.D., Ph.D., associate director of the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Fla., says, though some early studies have shown that some people's tumors shrank or even disappeared in response to a cancer vaccine, it's still early. Mulé was an investigator on the first study that tested dendritic cells in children. In the Phase 1 study, one 16-year-old with cancer that had spread to her lungs and spine showed significant shrinkage of tumors.

"There is promise in the sense that



# *With a cancer vaccine, there may be fewer signs of tumor shrinkage, but a person might live longer.*

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some of these vaccines can illicit a powerful immune response in some patients, but I think we have to be careful about getting too excited over early studies that can't be reproduced," Mulé says.

Jeffrey Weber, M.D., Ph.D., director of the Norris Melanoma Center at the University of Southern California, says there is also still a lot of work to be done in discovering new antigens and adjuvants and more sophisticated strategies to overcome the immune system's tolerance of cancer cells. "We are still discovering molecules that regulate the immune system such as CTLA-4, so we're still in the dark in some areas," Weber says. Recent research has found that inhibiting CTLA-4 can help the immune system attack some tumors.

Experts say that no therapeutic cancer vaccine has been licensed yet because few Phase 3 studies have been completed, and those that have been completed did not meet their goals of demonstrating safety and effectiveness of the vaccine. "We are still working with industry to define the characteristics, including potency," says the FDA's

Hirschfeld. "So a trial may look promising early on, but our job is to make sure it can be reproduced. We have to ask: 'Will this treatment work in the larger population?'"

One of the challenges is that cancer vaccines may produce different effects than those caused by cancer drugs. With cancer drugs, experts ask whether there is an objective, measurable response, such as tumor shrinkage. A cancer drug may cause tumors to shrink, but a person still may not live longer. With a cancer vaccine, there may be fewer signs of tumor shrinkage, but a person might live longer.

There aren't the same landmarks that you would see with traditional therapies, says Natalie Sacks, M.D., medical director in the clinical research division at San Francisco-based Cell Genesys, which is studying its vaccines, called GVAX, in people with prostate cancer, pancreatic cancer, leukemia, and myeloma. These whole-cell vaccines all use a hormone that stimulates immune response, called granulocyte macrophage colony stimulating factor (GM-CSF).

"As sponsors, we want to develop treatments and get them out to the market and help patients," Sacks says. "In the case of cytotoxic chemotherapies, the traditional endpoints used in drug development are shorter-term outcomes, such as tumor response and progression-free survival. Where I expect immunotherapy to be successful is in longer-term outcomes and increased survival. Because of the mechanism of action, the patient may not show an immediate response as is generally observed with standard chemotherapies, and the trial may take longer."

## **Finding a Clinical Trial**

Cancer researchers say their work won't mean much if more people don't enroll in clinical trials. According to the NCI, less than 3 percent of U.S. adults with cancer participate in clinical trials.

If there is a standard treatment available for a type of cancer, the NCI recommends choosing it over an experimental therapy. Cancer vaccines show the most promise at preventing a recurrence of cancer after surgery, radiation, or chemotherapy because the immune system will need to recognize and attack a smaller number of cancer cells. Cancer vaccines are also being tested as a treatment for advanced cancer.

Gary Montgomery, 66, of Redmond, Wash., enrolled in a cancer vaccine trial in 2002 to treat a rare form of abdominal cancer called pseudomyxoma peritonei. According to the National Organization for Rare Disorders, the disease is characterized by the accumulation of mucus-secreting tumor cells in the abdomen and pelvis. As the mass of tumor cells grows, the abdomen swells and digestive function becomes impaired.

Montgomery first had the standard therapy of surgery to remove the tumors in 2000. "They opened me up like a sardine can—from the sternum to the abdomen—and took out as

## **The Role of FDA and NCI**

After conducting preclinical research in lab animals, drug companies or clinical investigators submit an investigational new drug application to the Food and Drug Administration, requesting permission to move forward with testing in humans called clinical trials. The agency and the sponsors continue to communicate throughout the three phases of clinical trials, and the FDA ensures that treatments are safe and effective before they can be marketed.

The National Cancer Institute (NCI) is the main federal agency that supports and conducts cancer research. The NCI funds studies conducted by hospitals, universities, and businesses. The institute also supports a network of cancer centers across the country.

Both agencies are part of the U.S. Department of Health and Human Services, and they share responsibility and oversight for clinical trials. In 2003, the FDA and the NCI entered an agreement to enhance the efficiency of clinical research and the evaluation of new cancer medications. An NCI-FDA Oncology Task Force involves senior staff from both agencies and oversees the agreement. The agencies collaborate on developing the markers that show whether a treatment is effective, such as survival time, tumor shrinkage, and time to relapse. ■



many tumors as possible," Montgomery says. Then they inserted a tube into the abdomen, which delivered chemotherapy for six months. He experienced no tumor growth for about a year, but then the tumors came back. "It's known as a relentless form of cancer that wears you down," he says. "The doctor said that with the exception of another surgery, there was really nothing else they could do."

So Montgomery started with the Internet and found one NCI study that involved surgery and chemotherapy with an agent different from the one he had before. But the trial was closed. Taking advice from a friend, he checked at the Lombardi Cancer Center at Georgetown University in Washington, D.C. "I was feeling pretty low at this point," he says. He found out the one vaccine study he was interested in had just ended. But a nurse told him that another trial with newer versions of cancer vaccines developed at the NCI was about to start. "There were two slots left," he says. "Luckily, I met the criteria."

Montgomery received a "prime-boost regimen" of Therion Biologics' TRICOM vaccine. He first received an injection in the upper leg of a modified version of the smallpox vaccine to prime the immune system. Then he received monthly boosters of a vaccine called fowlpox CEA (carcinoembryonic antigen), an antigen found on most colorectal and pancreatic cancers. He also received a shot of the hormone GM-CSF, which helps stimulate the cells of the immune system. He had to give some of the injections to himself when he arrived back home in Washington state.

He says he experienced minimal side effects, such as soreness at the site of injection and mild flu-like symptoms. Though most cancer vaccines have been well-tolerated, in other trials some people have experienced autoimmune problems such as inflammation of the thyroid gland, skin disorders, and colitis. Autoimmune conditions are those in which the immune system mistakenly attacks the body's tissues and organs. Before he began the trial, Montgomery signed an informed consent form acknowledging that he was



National Cancer Institute

**A researcher prepares the carcinoembryonic antigen (CEA) vaccinia vaccine.**

aware of all the risks.

Montgomery continues to participate in the trial and flies to the nation's capital every month to receive treatment because it's been working. "It hasn't cured the cancer," Montgomery says, "but it seems to be keeping it in check.

And that's good enough for me."

Those interested in finding out about clinical trials to treat cancer should talk with their doctors and contact the NCI at (800) 4-CANCER (422-6237) or on the Web at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). ■

## New Cancer Office and Program

In July 2004 the FDA announced plans to create the Office of Oncology Drug Products, which will be housed in the agency's Center for Drug Evaluation and Research (CDER). The new office will consolidate three existing areas within CDER that are responsible for reviewing drugs and biologics used to prevent, diagnose, and treat cancer. The creation of this office will improve the consistency of review and policy toward oncology drugs and bring together oncologists who will help develop new therapies.

"Biomedical research in the United States is second to none, and it is our responsibility to see that patients reap the fruits of that research," says Health and Human Services Secretary Tommy G. Thompson. "We are committed to creating the most effective and efficient review process possible to ensure life-saving treatments are made available to cancer patients."

The FDA also is creating a new oncology program within the office, which will coordinate cancer-related work performed throughout the FDA. The program will promote cross-agency consultation and discussion and the development of regulatory policy and standards, and will serve as a focal point for agency interactions with the National Cancer Institute and other stakeholders. ■



# The Critical Path: Accelerating the Development of Medical Products

*By Carol Rados*

**D**rugs recently approved by the Food and Drug Administration help children with rheumatoid arthritis walk, prevent or halt heart disease, slow the progression of multiple sclerosis, and cure infectious diseases. New medical devices improve the heart's blood-pumping ability in patients with heart failure, and the latest vaccines protect against the threat of bioterrorism.

Advances in medical products ultimately can shorten hospital stays, lengthen life expectancies, and reduce overall health care costs. New classes of drugs—a few pills, for example—have virtually replaced major surgery for treating ulcers.

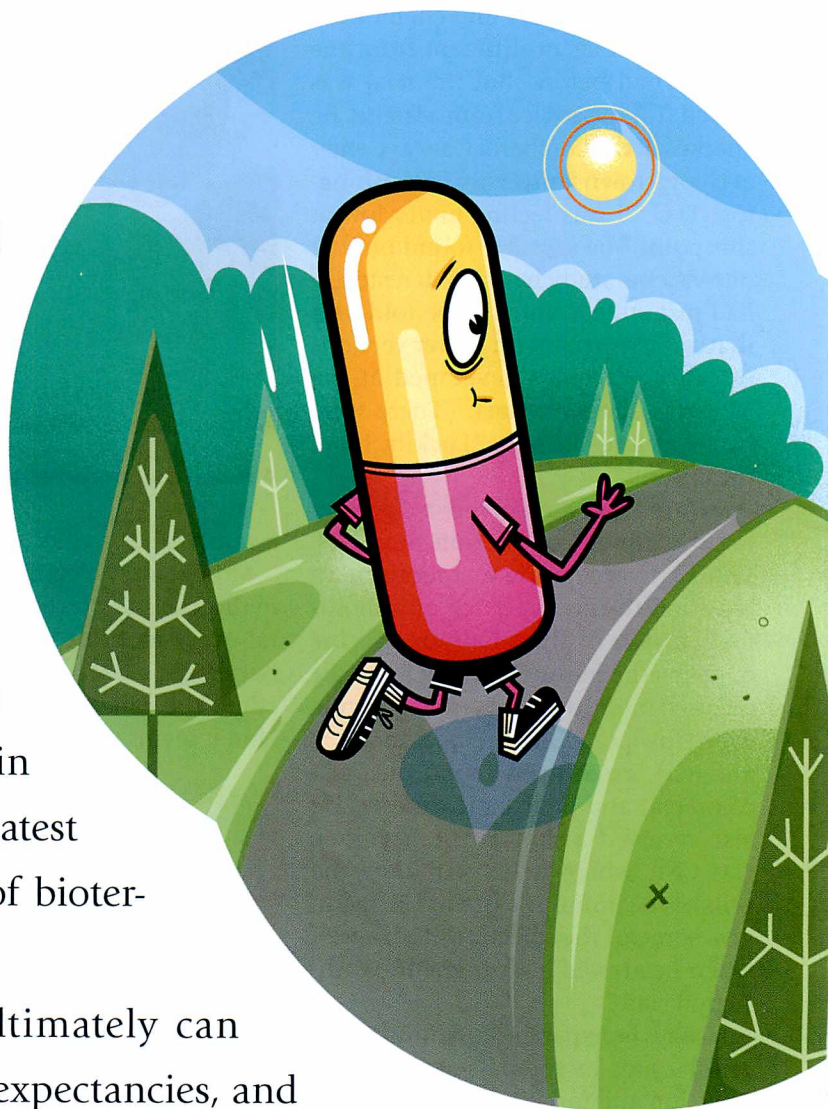


Illustration: Jack Hornady



But the recent slowdown—instead of the expected acceleration—of new medical treatments actually reaching patients concerns the FDA. Products fail before they reach the market because they could not be proved safe or effective, or they could not be manufactured commercially at a consistently high quality.

Despite recent innovations, many serious and life-threatening diseases still lack effective treatments. In the agency's view, the scientific tools needed to develop medical products have not kept pace with the rapid advances in product discovery. As a result, fewer of the sound ideas spawned in medical

whether and how quickly a discovery leads to a reliable treatment for patients.

The report, which looks at the development processes for drugs, biologics, and medical devices, calls for a joint effort of industry, academic researchers, product developers, patient groups, and the FDA to identify key problems and to develop solutions.

### The Problems

Despite notable advances in basic biomedical research, such as the studies of gene structure (genomics), proteins in living cells (proteomics), and of miniaturized equipment (nanotechnology), there has been a downward trend in the number of new drug and biologic marketing applications being submitted to the FDA for review. This means that the new sciences are not yet having a substantial impact on patient care.

"We can see from our reviews that these products aren't being moved along," says Kathy Carbone, M.D., acting associate director for research in the FDA's Center for Biologics Evaluation and Research.

She adds, "Sometimes candidate medical products get presented to us where we simply lack the tools to easily determine the safety and effectiveness of these products that are based on exciting, but edge-of-the-wedge, technologies."

As a result, many of the investigational products that enter clinical trials fail. And sometimes product development programs must be abandoned after extensive investment of time and resources. This high rate of failure can drive up costs, and the critical path to market—even for successful product candidates—is costly, timely, and unpredictable. And researchers are forced to rely on cumbersome, often imprecise assessment methods.

For example, product developers use scientific tools, such as laboratory tests,

computer models based on past experiences, and animal studies, to predict a high probability of safety and effectiveness. Other tools for making these predictions include knowledge of blood markers that accurately predict disease remission or the benefits of devices, or that can be used in early human trials to indicate effect and guide dose and regimen decisions. Developers also use scientific tests to demonstrate the biocompatibility of implanted devices.

But in many cases, product developers have no choice but to use the tools and concepts of the last century to assess this century's potential products.

"We are dealing routinely with novel products—novel technology," says Carbone, and part of the difficulty is predicting ultimate success with a novel candidate. If industry and the FDA could make these predictions more accurately, fewer products would fail on the critical path from laboratory to consumer. Similarly, new tools to measure product quality in process would mean more efficient, higher quality manufacturing.

"We think we have a way to fix it," says Carbone, "and we're asking industry, academia and others to help us focus on the gaps."

### The Solutions

To meet the challenge, the FDA is calling for a new focus on modernizing the tools that researchers and product developers use to assess the safety and effectiveness of potential new products and to mass-produce high-quality therapies. New scientific and technical tools—including assays (tests), standards, computer modeling techniques, biomarkers, and clinical evaluation techniques—will improve predictability and efficiency of products along the development path, more likely resulting in safe products that benefit patients.

For example, the FDA rapidly developed standards and calibration tools that enabled product developers to design and produce test kits to screen donated blood for the presence of West Nile virus. This work involved extensive collaboration with public health laboratories, industry, and U.S. blood banks, as well as using applied



laboratories are becoming safe and effective treatments.

In the interest of public health, the FDA says that action is needed to modernize the product development process.

In March 2004, the agency issued a major report that identifies both the problems and the potential solutions for bringing more breakthroughs in medical science to patients as quickly and efficiently as possible. The report, "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products," examines the crucial steps that determine



research. During 2003, roughly 8.6 million blood donations were tested. Of these, more than 1,000 donations confirmed positive for West Nile virus were identified and removed from the blood supply.

The FDA also developed and implemented a more flexible and innovative approach to the clinical trials needed to evaluate medical screening devices. This new trial design allows small companies, which often cannot afford the large trials needed to evaluate screening devices, to use common protocols so that their data can be pooled for

to maximize patient benefits with a minimum of risk.

### **The Opportunities**

The FDA is uniquely suited to take a major role in these efforts because of its experience overseeing medical product development, its vast clinical and animal databases, and its close interactions with all the major players in the critical path process. The agency sees the product development problems industry-wide.

Building on the agency's proven "best practices" for expediting the availabil-

by smart, articulate AIDS activists in the late 1980s." Much work, however, still needs to be done on clinical trial design and patient response measures to ensure that new therapies accurately reflect patient needs and values.

Binita Ashar, M.D., acting clinical deputy director for the FDA's Center for Devices and Radiological Health, says that, while medical devices don't seem to be experiencing the product development delay to the degree that drugs and other products have, the concerns about improving product development tools still apply.

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## *The FDA believes that patients have an important role to play in this effort.*

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analysis. The design currently allows manufacturers to test the effectiveness of digital mammography for screening use.

Such success stories can only be accomplished through a concerted and joint effort by industry, academia, patient groups, and the FDA. Key to this effort will be the development of a "Critical Path Opportunities List" that will identify and prioritize the most pressing development problems and the areas that provide the greatest opportunities for rapid improvement and public health benefits.

To create this list, the FDA is consulting and soliciting suggestions from all interested parties to identify and address specific defined critical path opportunities to make product development more efficient and predictable. The agency will publicize the list and encourage collaborations to address the problems and create new product development tools.

In addition, the FDA intends to refocus its own activities and take on new partnerships, as needed, to fulfill these priority opportunities. These actions promise not only to bring medical breakthroughs to patients more quickly, but also to do so in ways that ensure greater understanding of how

ity of promising medical technologies, there is an urgent need, for example, to develop tools to accurately assess the risk that a new drug will cause heart rhythm abnormalities. Ongoing international efforts include developing, testing, and validating nonclinical tools such as computer models that may be useful in predicting human risk. Examples of tools that the FDA says are urgently needed include better predictors of human immune responses to foreign substances, methods to further enhance the safety of transplanted human tissues, and new techniques for assessing drug-induced liver toxicity.

The FDA believes that patients have an important role to play in this effort.

"The FDA's critical path initiative now encourages patients and their advocates to join us as we roll up our sleeves to identify the difficult problems in drug development," says Theresa Toigo, the FDA's assistant commissioner for special health issues. This, she says, "may uncover a promising treatment or technology that otherwise might not be developed." The critical path to the development of effective therapies for HIV and AIDS, Toigo adds, "was cleared of overgrowth and underbrush

"There doesn't necessarily have to be a problem to support the innovation process that critical path promotes," she says. Ashar sees the critical path initiative working together with the goal of providing the "least burdensome" path to market—a provision of FDAMA (the Food and Drug Administration Modernization Act of 1997) that applies only to devices.

For example, scientists involved in reviewing medical devices at the FDA report an urgent need for predictive software to model the human effects of design changes for rapidly evolving devices. Ashar adds, "There's a learning curve with devices, and we have to try to anticipate the problems users might encounter."

Thanks to the enormous growth in research, the FDA is dealing with more complex and innovative products struggling in development. As discoveries made in the laboratory begin the transformation toward effective medical products consumers can safely use, both the FDA and industry seek a new and better set of tools to accelerate that development and better predict the performance of these new products. ■



# Got Milk?

## Make Sure It's Pasteurized

By Linda Bren

**P**asteurization, since its adoption in the early 1900s, has been credited with dramatically reducing illness and death caused by contaminated milk. But today, some people are passing up pasteurized milk for what they claim is tastier and healthier "raw milk."

Public health officials couldn't disagree more.

Drinking raw (untreated) milk or eating raw milk products is "like playing Russian roulette with your health,"

says John Sheehan, director of the Food and Drug Administration's Division of Dairy and Egg Safety. "We see a number of cases of foodborne illness every year related to the consumption of raw milk."



Jack Lefkowitz



More than 300 people in the United States got sick from drinking raw milk or eating cheese made from raw milk in 2001, and nearly 200 became ill from these products in 2002, according to the Centers for Disease Control and Prevention.

Raw milk may harbor a host of disease-causing organisms (pathogens), such as the bacteria campylobacter, escherichia, listeria, salmonella, yersinia, and brucella. Common symptoms of foodborne illness from many

killing disease-causing bacteria, pasteurization destroys bacteria that cause spoilage, extending the shelf life of milk.

Milk can become contaminated on the farm when animals shed bacteria into the milk. Cows, goats, and sheep carry bacteria in their intestines that do not make them sick but can cause illness in people who consume their untreated milk or milk products.

But pathogens that are shed from animals aren't the only means of con-

is barely perceptible.

"Milk is a good source of the vitamins thiamine, folate, B-12, and riboflavin," adds Sheehan, "and pasteurization results in losses of anywhere from zero to 10 percent for each of these, which most would consider only a marginal reduction."

While the major nutrients are left unchanged by pasteurization, vitamin D, which enhances the body's absorption of calcium, is added to processed milk. Vitamin D is not found in signifi-

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## *Research has shown that there is no significant difference in the nutritional value of pasteurized and unpasteurized milk.*

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of these types of bacteria include diarrhea, stomach cramps, fever, headache, vomiting, and exhaustion.

Most healthy people recover from foodborne illness within a short period of time, but others may have symptoms that are chronic, severe, or life-threatening.

People with weakened immune systems, such as elderly people, children, and those with certain diseases or conditions, are most at risk for severe infections from pathogens that may be present in raw milk. In pregnant women, *Listeria monocytogenes*-caused illness can result in miscarriage, fetal death, or illness or death of a newborn infant. And *Escherichia coli* infection has been linked to hemolytic uremic syndrome, a condition that can cause kidney failure and death.

Some of the diseases that pasteurization can prevent are tuberculosis, diphtheria, polio, salmonellosis, strep throat, scarlet fever, and typhoid fever.

### **Pasteurization and Contamination**

The pasteurization process uses heat to destroy harmful bacteria without significantly changing milk's nutritional value or flavor. In addition to

tamination, says Tom Szalkucki, assistant director of the Wisconsin Center for Dairy Research at the University of Wisconsin-Madison. Cows can pick up pathogens from the environment just by lying down—giving germs the opportunity to collect on the udder, the organ from which milk is secreted. "Think about how many times a cow lays down in a field or the barn," says Szalkucki. "Even if the barn is cleaned thoroughly and regularly, it's not steamed. Contamination can take place because it's not a sterile environment."

### **The Health Hype**

Raw milk advocates claim that unprocessed milk is healthier because pasteurization destroys nutrients and the enzymes necessary to absorb calcium. It also kills beneficial bacteria and is associated with allergies, arthritis, and other diseases, they say.

This is simply not the case, says Sheehan. Research has shown that there is no significant difference in the nutritional value of pasteurized and unpasteurized milk, he says. The caseins, the major family of milk proteins, are largely unaffected, and any modification in whey protein that might occur

cant levels in raw milk.

"Pasteurization will destroy some enzymes," says Barbara Ingham, Ph.D., associate professor and extension food scientist at the University of Wisconsin-Madison. "But the enzymes that are naturally present in milk are bovine enzymes. Our bodies don't use animal enzymes to help metabolize calcium and other nutrients."

"Enzymes in the food that we eat and drink are broken down in the human gastrointestinal tract," adds Ingham. "Human bodies rely on our own native enzymes to digest and metabolize food."

"Most of the native enzymes of milk survive pasteurization largely intact," says Sheehan, "including those thought to have natural antimicrobial properties and those that contribute to prolonging milk's shelf life." Other enzymes that survive are thought to play a role in cheese ripening.

Ingham says that pasteurization will destroy some bacteria that may be helpful in the fermentation of milk into products such as cheese and yogurt, "but the benefit of destroying the harmful bacteria vastly outweighs the supposed benefits of retaining those helpful microorganisms. Plus, by add-



ing the microorganisms that we need for fermentation, we can assure a consistently high quality product."

Science has not shown a connection between drinking raw milk and disease prevention. "The small quantities of antibodies in milk are not absorbed in the human intestinal tract," says Ingham. "And there is no scientific evidence that raw milk contains an anti-arthritis factor or that it enhances resistance to other diseases."

Fans of raw milk often cite its creamy rich taste, says Szalkucki, who adds that it may be creamier because it is not made according to the standards for processed milk. "If you go to a grocery store and buy fluid milk, it's been standardized for a certain percentage of fat, such as 2 percent," he says. "Raw milk is potentially creamier because it has not been standardized and it has a higher fat content."

### The Law

It is a violation of federal law enforced by the FDA to sell raw milk packaged for consumer use across state lines (interstate commerce). But each state regulates the sale of raw milk within the state (intrastate), and some states allow it to be sold. This means that in some states dairy operations may sell it to local retail food stores, or to consumers directly from the farm or at agricultural fairs or other community events, depending on the state law.

In states that prohibit intrastate sales of raw milk, some people have tried to circumvent the law by "cow sharing," or "cow leasing." They pay a fee to a farmer to lease or purchase part of a cow in exchange for raw milk, claiming that they are not actually buying the milk since they are part-owners of the cow. Wisconsin banned cow-leasing programs after 75 people became infected with *Campylobacter jejuni* bacteria in 2001 from drinking unpasteurized milk obtained through such a program.

### Raw Milk Cheeses

The FDA allows the manufacture and interstate sale of raw milk cheeses that are aged for at least 60 days at a temperature not less than 35 degrees Fahrenheit. "However, recent research

## A Sampling of Raw Milk Incidents

- **July 2004**—The Indiana Public Health Department advised consumers to check their refrigerators and freezers for raw milk cheese that may be contaminated with salmonella. Routine product sampling found the bacteria in lot number 139 of "Natural Raw Milk Cheese" made by Meadow Valley Farm after the cheese was distributed to farmers' markets and specialty food stores in parts of Indiana and Wisconsin.
- **2002–2003**—Two children were hospitalized in Ohio for infection with *Salmonella enterica* serotype Typhimurium. These children and 60 other people in Illinois, Indiana, Ohio, and Tennessee developed bloody diarrhea, cramps, fever, chills, and vomiting from *S. Typhimurium* tracked to consuming raw milk. The milk producer voluntarily relinquished its license for selling raw milk upon recommendation of the Ohio Department of Agriculture.
- **2000–2001**—In North Carolina, 12 adults were infected with *Listeria monocytogenes* linked to homemade, Mexican-style fresh soft cheese produced from contaminated raw milk sold by a local dairy farm. Ten of the 12 victims were pregnant women, and infection with the bacterium resulted in five stillbirths, three premature deliveries, and two infected newborns.
- **1998**—In Massachusetts, 66 people received injections to protect against potential exposure to rabies after drinking unpasteurized milk from a local dairy. A cow that died at the dairy was found to be infected with rabies. Transmission of the rabies virus through unpasteurized milk, although not the common route of infection, is theoretically possible, according to the Centers for Disease Control and Prevention. ■

Sources: CDC, Indiana State Board of Animal Health

calls into question the effectiveness of 60-day aging as a means of pathogen reduction," says Sheehan.

The FDA's Center for Food Safety and Applied Nutrition (CFSAN) is currently examining the safety of raw milk cheeses and plans to develop a risk profile for these cheeses. This information will help FDA risk managers make future decisions regarding the regulation of these products to protect public health.

### Ensuring Milk Safety

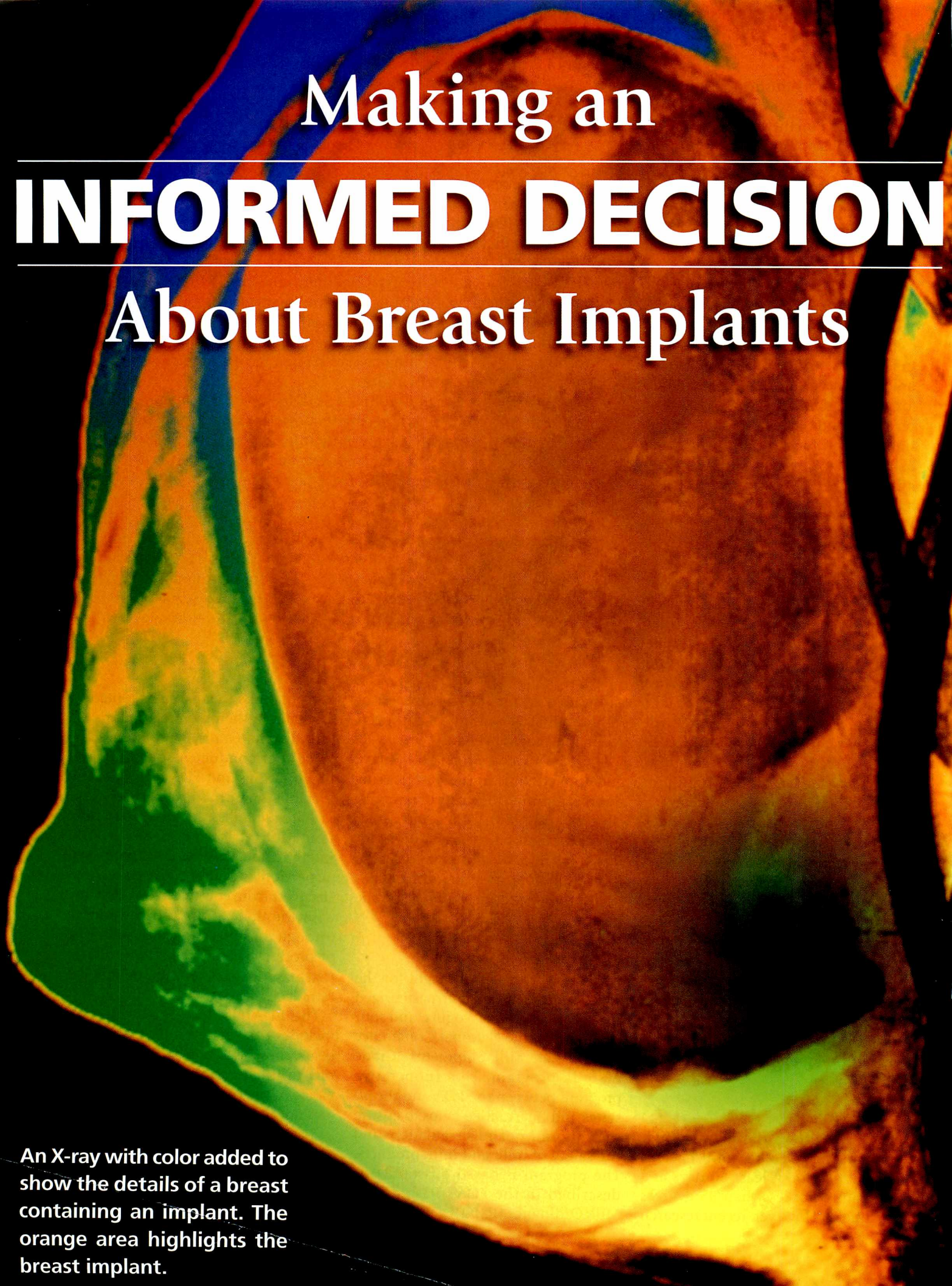
The FDA provides oversight for the processing of raw milk into pasteurized milk, cottage cheese, yogurt, and sour cream under the National Conference on Interstate Milk Shipments "Grade A" milk program. This cooperative program between the FDA and the 50 states and Puerto Rico helps to ensure the uniformity of milk regulations and the safety of milk and milk products. The program is based on standards described in the FDA's Pasteurized Milk Ordinance (PMO), a model code

of regulations that can be adopted by the states in their own regulations.

Under the Grade A program, state personnel conduct inspections and assign ratings and FDA regional milk specialists audit these ratings, says Richard Eubanks, M.P.H., a senior milk sanitation officer on CFSAN's Milk Safety Team. "It's a rigorous process of inspection and auditing," he says, and "it covers from cow to carton," starting with the dairy farm and continuing through the processing and packaging of products at milk plants. Products that pass inspection may be labeled "Grade A."

The FDA Grade A milk program includes pasteurized milk from cows, goats, sheep, and horses. Raw milk and raw milk cheeses cannot be labeled Grade A, since they are not pasteurized and not covered under the program. ■



The background of the entire page is a color-enhanced X-ray of a breast. A large, irregularly shaped area in the upper right portion of the breast is highlighted in a bright orange color, indicating the presence of a breast implant. The rest of the breast tissue is shown in various shades of green and yellow, representing different densities. The text is overlaid on the top half of the image.

# Making an **INFORMED DECISION** About Breast Implants

An X-ray with color added to show the details of a breast containing an implant. The orange area highlights the breast implant.



**D**espite more than a decade of controversy over their safety, breast implants are more popular than ever among women who want to build upon what nature gave them or who want to restore what disease has taken away. Whatever the reason, opting for breast implants is a personal decision that should be made only after a woman fully understands and accepts the potential risks of the devices and the importance of follow-up evaluations with her physician.

Some people see an enormous benefit to getting implants and are willing to accept associated risks. They say that using breast implants to rebuild the breast (reconstruction), or change its size and shape (augmentation), significantly improves the quality of life for many women. Advocates of breast implants also say that a woman's consent to the surgery should be considered valid as long as she weighs the risks and benefits of the procedure.

implant surgeries in 2003, nearly twice the number done in 1998. Another 68,000 women received breast implants for reconstruction following mastectomy due to cancer or other disease.

But also in 2003, 45,000 augmentation patients and 17,000 reconstruction patients had their breast implants removed. The medical community and others, including the Food and Drug Administration, would like to better understand why.

vary in shape, size, and shell texture.

At this time, there are two manufacturers with approved saline-filled breast implants. No manufacturer has yet received FDA approval to market a silicone gel-filled breast implant.

#### **The Silicone Controversy**

Breast implants were first marketed in the early 1960s, before the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic

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*While every surgical procedure has potential risks, such as infection, bleeding, and scarring, there are risks that are specific to breast implants.*

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While every surgical procedure has potential risks, such as infection, bleeding, and scarring, there are risks that are specific to breast implants. Learning about them is key to being properly informed about the procedure.

#### **A Primer on Breast Implants**

According to the American Society of Plastic Surgeons (ASPS), there were nearly 255,000 breast enhancement

Breast implants are designed for augmentation, a cosmetic procedure; reconstruction; and replacement of existing implants, called revision. There are two primary types: saline-filled and silicone gel-filled. Depending on the type of implant, the shell is either pre-filled with a fixed volume of solution or filled through a valve during the surgery to the desired size. Some allow for adjustments of the filler volume after surgery. Breast implants

Act required a reasonable assurance of safety and effectiveness to be shown for certain medical devices. The 1976 law gave the FDA authority over such devices, but breast implants were "grandfathered" into the regulatory scheme, meaning that manufacturers were not required to provide the agency with scientific evidence of product safety unless questions arose about the safety and effectiveness of these already-marketed devices. Silicone was



initially assumed by manufacturers to be biologically inactive and, therefore, to have no harmful effects.

But over the years, questions did arise about the effects of silicone on the body. In 1991, the FDA published a regulation that required manufacturers of silicone gel-filled breast implants to submit premarket approval applications (PMAs). This requirement meant that the FDA needed to agree that the manufacturer has presented data showing a reasonable assurance of safety and effectiveness in order for the devices to remain on the market.

In January 1992, the FDA called

cone gel-filled implants, claiming the devices had caused serious ailments, such as connective tissue diseases, neurological diseases, and cancer. Consumer groups repeatedly filed petitions urging more studies on the implants. But many women said they were pleased with their implants, including cancer patients who had pleaded for the opportunity to choose silicone gel-filled implants for reconstruction.

#### **A Turn of Events**

In October 2003, the FDA held a two-day advisory panel meeting to discuss a manufacturer's PMA for a silicone

As a panel member, Benjamin O. Anderson, M.D., voted with the majority to recommend that the FDA approve the new PMA, but only with specific conditions. Anderson says he wants to avoid getting into the business of determining how a woman defines the value of breast reconstruction or augmentation.

"The use of implants and augmentation conjures up some social judgments that may well be unfair," says Anderson, a professor of surgery and director of the University of Washington's Breast Health Center. Rather than deciding that no woman can have access to silicone gel-filled implants because a small number may be at risk for certain illnesses, he says, "I believe the better approach is to make the devices available and inform all women of the degree of risk involved."

That, according to Anderson, "is reasonable informed consent."

In January 2004—contrary to the recommendation of the agency's advisory panel—the FDA determined that the new silicone gel-filled breast implant PMA was "not approvable" at that time. This meant that the implants were not approved for marketing pending additional information, but that women would continue to have limited access to them by enrolling in clinical studies.

"The public scientific process that has been used to consider these devices is fully consistent with the FDA's mission—to use the best available science to protect and promote the public health interests of the American people," says Linda Kahan, deputy director of the FDA's Center for Devices and Radiological Health (CDRH).

Also in January 2004, the agency released a draft of its new guidelines for companies submitting breast implant PMAs, explaining the scientific issues that the FDA recommends be addressed as part of their applications. The guidance document reflects the FDA's current thinking about new scientific information that the agency, manufacturers, and the clinical community have gained over the last 10 years, including information learned at the October 2003 advisory panel meeting. Consistent with the FDA's

## **Questions to Ask a Surgeon About Breast Augmentation**

- What are the risks and complications associated with having breast implants?
- How many additional implant-related operations can I expect over my lifetime?
- How will my breasts look if I choose to have the implants removed without replacement?
- What shape, size, surface texturing, incision site, and placement site is recommended for me?
- How will my ability to breast-feed be affected?
- How can I expect my implanted breasts to look over time?
- How can I expect my implanted breasts to look after pregnancy? After breast-feeding?
- What are my options if I am dissatisfied with the cosmetic outcome of my implanted breasts?
- What alternate procedures or products are available if I choose not to have breast implants?
- Do you have before-and-after photos I can look at for each procedure and what results are reasonable for me? ■

Source: FDA

for a voluntary moratorium—a delay on the use of these implants—until new safety information could be thoroughly reviewed. The moratorium was not intended to "ban" the implants, but instead to allow time to review the new safety information.

In April 1992, the agency decided that no PMA yet submitted contained sufficient safety and effectiveness data to support approval. However, access to these silicone gel-filled breast implants would continue for women enrolled in certain clinical studies.

In the years that followed that decision, thousands of women filed lawsuits against the manufacturers of sili-

cone gel-filled breast implant. Some people complained that the meeting was premature in light of the fact that long-term studies had not been completed, but the FDA proceeded because the agency was required by law to consider the pending PMA within a specified time frame. The meeting also provided patients and others with timely access to information and expert analyses on the issue. The issues before the panel reflected much of the decades-long debate over the implants. Moreover, the meeting provided a valuable public forum for discussing the issue from many diverse perspectives and for raising important additional questions.



good guidance practices, the agency has asked for public comments on the breast implant guidance. The guidance is not intended for implementation until it is finalized.

"Current testing doesn't reflect reality," says Michael A. Choti, M.D., an associate professor of surgery and oncology at the Johns Hopkins University School of Medicine in Baltimore, and also an FDA advisory panel member. The implants, he says, are extremely durable when tested outside the body. "You can virtually run a truck over them and they'll hold up. But the question is, what happens when implanted long-term in a woman's body?"

The FDA's draft guidance document says that two to three years of follow-up data may not be enough to allow the agency to evaluate the safety and effectiveness of breast implants. The agency recommends the use of tests that can predict clinical outcomes, such as how long breast implants will last before rupturing in the body, as well as tests that explain how and why the breast implants rupture. In addition, the agency recommends that more data be gathered regarding the rate of rupture over time, as well as the health consequences of rupture.

### Breast Implant Risks

In 1999, the Institute of Medicine (IOM) issued a report on a review of information related to health effects associated with silicone breast implants, both gel-filled and saline-filled, in humans. An important goal of the IOM was to provide women with detailed information about the potential risks of silicone breast implants.

One risk is capsular contracture, which is a tightening and squeezing of the scar tissue that naturally forms around the implant. This contracture may result in hardening of the breast tissue, rippling of the skin, and changes in breast shape. It also may cause pain, which, if severe, can require surgery to remove the scar tissue or replace the implant.

In addition, a rupture can occur at any time. While saline-filled breast implants leak only salt water when they rupture, the health effects of leak-

ing silicone gel-filled implants remain controversial. Women sense a change more easily when saline-filled breast implants rupture. But the silicone gel-filled implants are more likely to maintain their shape after they rupture, which can make it more difficult to detect a break.

Called "silent ruptures," these breaks involving silicone gel implants may occur without a visible change. And a woman may not feel any sensation, says Sahar M. Dawisha, M.D., a medical officer in CDRH who has reviewed

of whether it is saline-filled or silicone gel-filled.

Another potential complication of implant surgery is nerve damage, which can cause some women to experience a loss or increase in sensation in their nipples and breast tissue. These symptoms may disappear eventually, but can be permanent in some cases. It is unclear at this time whether insufficient milk production to breast-feed—another reported problem—is due to damaged nerves or to other reasons.

Women should know that, regardless

## Questions to Ask a Surgeon About Breast Reconstruction

- What are all my options for breast reconstruction?
- What are the risks and complications of each type of breast reconstruction surgery and how common are they?
- What if my cancer recurs or occurs in the other breast?
- Will reconstruction interfere with my cancer treatment?
- How many steps are there in each procedure? What are they?
- How much experience do you have with each procedure?
- What is the estimated total cost of each procedure?
- How long will it take to complete my reconstruction?
- Do you have before-and-after photos I can look at for each procedure and what results are reasonable for me?
- What will my scars look like?
- What kind of changes in my reconstructed breast can I expect over time?
- What kind of changes in my implanted breast can I expect with pregnancy?
- What are my options if I am dissatisfied with the cosmetic outcome of my implanted breast?
- How much pain or discomfort will I feel and for how long?
- How long will I be in the hospital? Will I need blood transfusions, and can I donate my own blood?
- When will I be able to resume my normal activities? ■

Source: FDA

data submitted by implant manufacturers. Magnetic resonance imaging (MRI) with equipment specifically designed for imaging the breast may be used for evaluating women with suspected rupture of their silicone gel-filled implant. The FDA considers MRI to be the best method at this time. There are no standards on how often to screen for silent rupture with MRI, and the costs of this procedure must be considered when choosing a silicone gel-filled breast implant. Physicians usually recommend removal of the implant if it has ruptured, regardless

of the type of implant, it is likely they will need to have one or more additional surgeries (reoperations) over the course of their lives, because of complications from breast implants. Reasons for reoperations include any of the potential complications, such as capsular contracture, wrinkling, asymmetry, rupture, or implant malposition.

The IOM committee also found that women with silicone breast implants are no more likely than women without implants to develop the life-threatening systemic illnesses that some people have claimed might be related



to the implants.

But many women disagree. They have reported health problems related to their immune systems or neurological symptoms that they believe are caused by ruptured or intact breast implants. And some women who have received breast implants claim they weren't fully informed of the risks.

Lynda Roth, who was diagnosed with breast cancer in 1990, says she was forced to make a quick decision, based on very little information, about getting breast implants following a mastectomy.

"I trusted what my highly respected doctors were telling me was true," says the 63-year-old social worker in central Colorado. "You're in shock, you think you're going to die, so what kind of informed decision can you possibly make about what you want your breasts to look like if you're lucky enough to survive?"

Roth did survive—both breast cancer and two silicone breast implants gone bad. But the ruptured devices, she believes, caused her to lose her good health, her job, and eventually her health insurance over the next 11 years. "I found out the hard way," she says. "There were many risks with the implants that I didn't know about."

Other women are pleased with their implants. Clara Filion underwent reconstruction in 1993 after having a breast removal that included the lymph nodes under the arm (modified radical mastectomy) due to cancer. The 67-year-old Bedias, Texas, resident says she's thrilled with the outcome of her saline-filled implant, as well as with her surgeon, even though her original implant will need replacing soon due to scar tissue—a local complication that Filion says she always

knew could occur. Filion has experienced no other complications related to the implant in 11 years.

### Other Considerations

"My doctor told me that these implants would go with me to my grave," says 44-year-old Patty Faussett of Henderson, Nev., who chose to aug-

to believe."

Experts caution that breast implants do not last a lifetime. Women should be prepared for long-term follow-up and additional surgeries to treat complications. They also should be prepared for the accompanying additional costs. One of the biggest problems Faussett says she hears from women

in her breast implant support group is that "most don't plan for the money it takes to fix what goes wrong."

In addition, women should be aware that hard pressure on the breast (compression) during mammography may cause implant rupture. Breast implants also can interfere with finding breast cancer during mammography. Doctors say the implant can hide breast tissue and, as a result, hide lesions as well. Extensive scarring and calcium deposits in tissue surrounding an implant can mimic the appearance of cancer, making the deposits difficult to distinguish from tumors on a mammogram.

Another consideration is the choice of a surgeon. Patient advocates, professional groups, and others agree that it's important to choose a plastic surgeon who has been trained in breast implant surgery and who has performed it successfully on many women.

After switching to a new, firmer silicone gel-filled implant through a clinical study only a year after experiencing rippling with her saline implants, Kathy Bracy says it's important that women who are considering breast implants do their homework.

"I love my breast implants, but I also spent six months researching the devices, which included picking the best doctor for me," says Bracy, a 38-



Black Star/Lee McDonald

**Patty Faussett of Henderson, Nev., says she regained her good health after she had her saline breast implants removed.**

ment her breasts with saline breast implants in 1997, after years of breast-feeding distorted their shape.

Faussett had her implants removed a year after implantation because she believes they caused a mixed bag of health problems, including disturbed vision, heart palpitations, muscle twitching, and an autoimmune thyroid disease. She says, "The risks were much greater than my surgeon led me



year-old self-employed bookkeeper from Tampa, Fla. "It's not necessarily the product, but who is doing the surgery." The key to breast implant satisfaction, she says, is to "find a doctor who is willing to answer all your questions and take all your concerns seriously. And the relationship with your doctor doesn't end after the surgery."

Experts also advise women to have realistic expectations about breast implants. There is no guarantee that the results will match those of other women. Overall health, age, chest structure, the shape and position of the breast and nipple, skin texture, the

surgery, the college student from Ennis, Texas, was a 34B—a breast size she thought would be with her for life.

Teen-agers who are dissatisfied with their bodies see breast implants as a harmless—and, according to Long, "fun"—thing to do to improve their self-image. Long says she felt that her body was too "bottom heavy" for her breasts and wanted to "even out" her figure. "But I never thought about my implants being dangerous," she says. A friend's mother worked for a plastic surgeon for 12 years and told Long she knew of no problems with patients who had gotten the implants. "I really thought that I had inside information, and that these devices were completely safe and maintenance-free."

Following implantation, Long went to a 34D. But complications convinced her to have the implants removed a short time later. "I had shooting pains in my arms, excruciating pain in every joint, bone, and muscle of my body, I was exhausted all the time, had no energy, lost my hair, and had pains in my chest, heart, and ribs. I had trouble remembering things and thinking clearly, and the list goes on," she says. "Before the implants, all I had was allergies."

Many of the changes to the breast that occur with an implant cannot be undone. If a teen chooses to have her implants removed, she may experience dimpling, puckering, wrinkling, or other cosmetic changes.

Three years later, Long's breasts measure 36C—one size larger than before she was implanted—suggesting that her own breasts continued to develop even after the implants were removed. "When you're making a decision that can impact your life at 19," Long advises other young women, "you need to research the subject like you're 50 years old."

Ongoing clinical studies for unapproved saline-filled and silicone gel-filled breast implants do not allow for

those younger than 18 to receive the implants for augmentation purposes. Some of these clinical studies even limit reconstruction and revision uses to women 18 and over.

Consumers can get a copy of the "FDA Breast Implant Consumer Handbook 2004," which provides in-depth information on both saline and silicone breast implants, by visiting [www.fda.gov/cdrh/breastimplants/](http://www.fda.gov/cdrh/breastimplants/), or by writing to: FDA, Office of Device Evaluation, Division of General, Restorative, and Neurological Devices, 9200 Corporate Blvd., HFZ-410, Rockville, MD 20850. ■

#### For More Information

Food and Drug Administration  
[www.fda.gov/cdrh/breastimplants/](http://www.fda.gov/cdrh/breastimplants/)

FDA Center for Devices and Radiological Health  
Consumer Affairs Staff  
(800) 638-2041

National Women's Health Information Center  
[www.4woman.gov](http://www.4woman.gov)  
(800) 994-9662

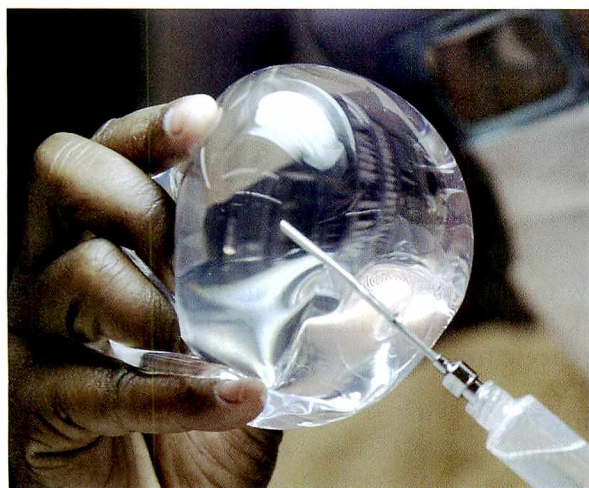
Institute of Medicine  
[www.iom.edu](http://www.iom.edu)

National Cancer Institute  
[www.nci.nih.gov](http://www.nci.nih.gov)  
(800) 422-6237

Office of Research on Women's Health  
[www4.od.nih.gov/orwh/](http://www4.od.nih.gov/orwh/)

American Society of Plastic Surgeons  
[www.plasticsurgery.org](http://www.plasticsurgery.org)  
(888) 475-2784

American Society for Aesthetic Plastic Surgery  
[www.surgery.org](http://www.surgery.org)  
(888) 272-7711



Corbis

**A laboratory worker at a silicone breast implant manufacturing plant does a product check.**

tendency to bleed, prior breast surgeries, and the surgical team's skill and experience all figure into the outcome of breast implant surgeries.

#### The Teen Scene

In addition to safety issues, there is concern about the growing use of breast implants among teen-agers. Health officials worry that teen-agers and their parents may not realize the relative permanence of the changes caused by the devices. They also want to be sure that teens are physically ready—that is, they're finished developing—and that they are psychologically mature enough to handle the outcome of surgery.

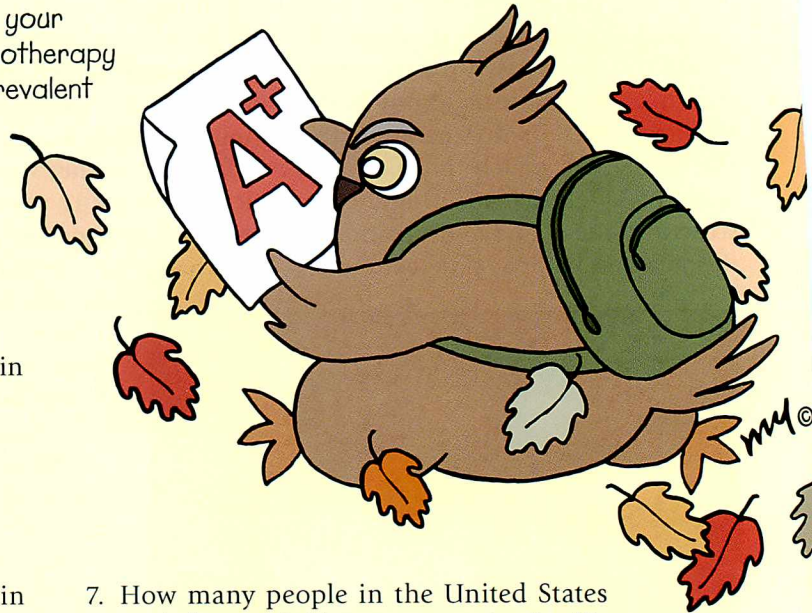
"I didn't know my breasts were still growing when I signed up for the surgery," admits Kacey Long, who got saline-filled breast implants in July 2001, when she was 19. Prior to her



# Take the FDA Consumer QUIZ

Are breast implants a safe and effective way to enhance your appearance? Will cancer vaccines someday replace chemotherapy and other treatments in the war against cancer? How prevalent is the skin disease psoriasis, and is it fatal? 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 September–October 2004 issue of FDA Consumer and at the bottom of this page. Good luck!



1. What percentage of U.S. adults with cancer participates in clinical trials?

- a. less than 3 percent
- b. 25 percent
- c. 10 percent
- d. 50 percent

2. About how many cancer vaccines are being studied in advanced clinical trials?

- a. none
- b. 5
- c. 12
- d. 25

3. How long have researchers been working to develop a cancer vaccine?

- a. for the last 5 years
- b. for the last 10 years
- c. for the last 50 years
- d. for more than 100 years

4. Psoriasis most often strikes people between the ages of:

- a. 6 and 10
- b. 15 and 35
- c. 35 and 55
- d. 55 and 70

5. How many new cases of psoriasis are diagnosed each year in the United States?

- a. nearly 10 million
- b. between 150,000 and 260,000
- c. 1 million
- d. 500,000

6. A health complication that occurs in about 15 percent of people with psoriasis is:

- a. arthritis
- b. asthma
- c. glaucoma
- d. lupus

7. How many people in the United States got sick from drinking unpasteurized milk or eating cheese from unpasteurized milk in the years 2001 and 2002?

- a. nearly 70
- b. about 100
- c. 300
- d. nearly 500

8. Symptoms of foodborne illness from drinking unpasteurized milk may include:

- a. diarrhea, stomach cramps, fever
- b. headache, vomiting, exhaustion
- c. kidney failure
- d. miscarriage
- e. all of the above

9. Medicinal leeches are raised in:

- a. swamps
- b. controlled basins and laboratories in certified facilities
- c. lakes and rivers
- d. special mud

10. Buying prescription drugs online from unknown foreign sources is:

- a. safe in some cases
- b. risky business
- c. safe in all cases
- d. a good way to save money on prescription drugs

## Answers

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



By John Henkel

## Magnets Attracting You? Read This

For centuries, magnets have been used in attempts to treat pain. And though scientific evidence so far doesn't support a conclusion that magnets can ease pain, some patients using them do experience relief.

So what's the story on magnets?

To help sort out fact from hype, the National Center for Complementary and Alternative Medicine has posted questions and answers that should give consumers the tools to make informed choices about using magnets. View the list at <http://nccam.nih.gov/health/magnet/magnet.htm>.

Note: The FDA has not approved the marketing of magnets with claims of benefits to health (such as "relieves arthritis pain"), and the agency, along with the Federal Trade Commission, has taken action against unscrupulous magnet marketers.

## Some Great Advice for Girls

Today is a great time to be a girl ... You have many possibilities and choices ... You can make goals for yourself and develop your talents ... All these choices are exciting, but they can be a little confusing.

So reads a page about self esteem found on *Girl Power*, a Web site created by the Department of Health and Human Services to promote positive values in girls ages 9 to 13 by targeting health messages to their unique needs and interests.

The site, at [www.girlpower.gov](http://www.girlpower.gov), is colorful and interactive, with loads of fun ideas for wholesome activities. Looking for a neat outdoor activity? Try one of more than 30 of *Girl Power's* ideas. Like to surf the Net? Check out *Girls Allowed* or *White House Kids* or any of the site's other suggestions. The site also has a guest page with upbeat messages from folks such as singer Brandy, astronaut Ellen Ochoa, author Judy Blume, and even cartoon character Lisa Simpson.

Mom and Dad can get in on the act, too, with a special section containing advice on better sleeping, keeping children drug-free, and getting involved with your community.

## An Easy Way to 'Get the Facts'

Did you know that about 12 percent of women in the United States suffer from depression, but that 80 percent of them get better with treatment? Or that most health plans won't cover the cost of LASIK eye surgery? Are you aware that dietary supplements such as vitamin pills should not be used as a substitute for eating a variety of foods?

These are a few of dozens of useful health tidbits that you'll find in a series of fact sheets called "Get the Facts," available online in graphical (PDF) form or in a printer-

friendly text format. Produced by the FDA Office of Women's Health, the series offers reliable background on nearly 30 topics, some of interest just to women, but many of value to all consumers. Among them:

- diabetes
- allergies
- tattoos and permanent makeup
- infertility
- heart disease

The fact sheets are brief and written in an easy-to-understand style. To "Get the Facts," go to [www.fda.gov/womens/getthefacts/](http://www.fda.gov/womens/getthefacts/).

## Our World is Dangerous Now—Are You Ready?

There was a time not long ago when disaster preparedness in the United States focused on natural calamities: bracing for a predicted tornado or creating structures to withstand earthquakes. But events in recent years have put America on notice that disaster preparation now must include dealing with catastrophes created by human actions rather than nature. The Department of Homeland Security (DHS) points out that terrorists are working to obtain biological, chemical, nuclear, and radiological weapons and that the threat of an attack is real.

On its Web site *Ready.gov* ([www.ready.gov](http://www.ready.gov)), the DHS offers much helpful advice on how to prepare yourself and your loved ones for natural and man-made emergencies. Tactics such as assembling a kit of basic survival items and developing a family communications plan can give an edge should a disaster occur. The site contains detailed instructions and supply checklists.

Also on *Ready.gov* are tips on what to do in the event of an attack if you are in a moving vehicle, a high-rise building, or at work or school. Though the DHS cautions that there's no way to predict what will happen in an attack, it says that "with a little planning and common sense, you can be better prepared for the unexpected."

The FDA also has an online gateway to other helpful information on its counterterrorism Web site: [www.fda.gov/oc/opacom/hottopics/bioterrorism.html](http://www.fda.gov/oc/opacom/hottopics/bioterrorism.html). ■

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*John Henkel is a member of the FDA's Website Management Staff.*



# Living with Psoriasis

By Michael Paranzino



When that very first patch of psoriasis appeared on my elbow during 10th grade, I was actually happy. It gave me a sense of solidarity with one of my older brothers, who had been living with substantial psoriasis as long as I could remember. It was not until eight years later, sitting in the hospital covered head to toe in psoriasis, that I realized the absurdity of welcoming that first patch. Now,

I would not wish it on my worst enemy.

Psoriasis is a disease driven by the immune system that typically manifests itself as patches of incredibly dry, flaky skin. For many people with psoriasis, it never moves beyond some annoying patches on places like the elbows, knees, or scalp, but I am not so lucky. I am part of that one-third of patients with what the experts call “moderate-to-severe” psoriasis.

Psoriasis, because it is so unsightly, can be emotionally taxing—I have psoriasis on my hands and face, for example, so hiding it is not an option. Everyone who sees me sees it, and everyone who shakes my hand feels it. But psoriasis can also be physically draining—walking, bending, even sitting can be painful because of psoriasis on the feet, legs, arms, or on the folds of the skin. I am one of those psoriasis patients whose skin bleeds—somewhere—almost every single day, and it itches constantly and ferociously.

In short, psoriasis is dreadful. And the kicker is that the treatments for moderate-to-severe psoriasis offer a choice among unpalatable potential side effects, including risks of liver damage, kidney damage, cancer, and serious infections. And this is just to minimize, not eliminate, my psoriasis.

But many new options are now becoming available. Three new psoriasis drugs have recently hit the market, and others are on the way.

And not a moment too soon. You see, I now have a 3-year-old son. So while I have grown more or less accustomed to bleeding, and itching, and looking strange, every day of my life, I do not want my child to face that same fate. I pore over the statistics suggesting that I have given him a 1 in 4 chance of developing psoriasis. I have met several psoriasis patients who elected not to have children for this reason. I worry every time he gets a scrape, which, for a 3-year-old,

means every day, because skin trauma can trigger psoriasis in those susceptible to it. I stare at the computer printout showing that the federal government spends one dollar per patient per year researching psoriasis, and I fret that he deserves more. I read that the pharmaceutical industry now considers the psoriasis market promising, and I am thrilled. It sure beats being ignored.

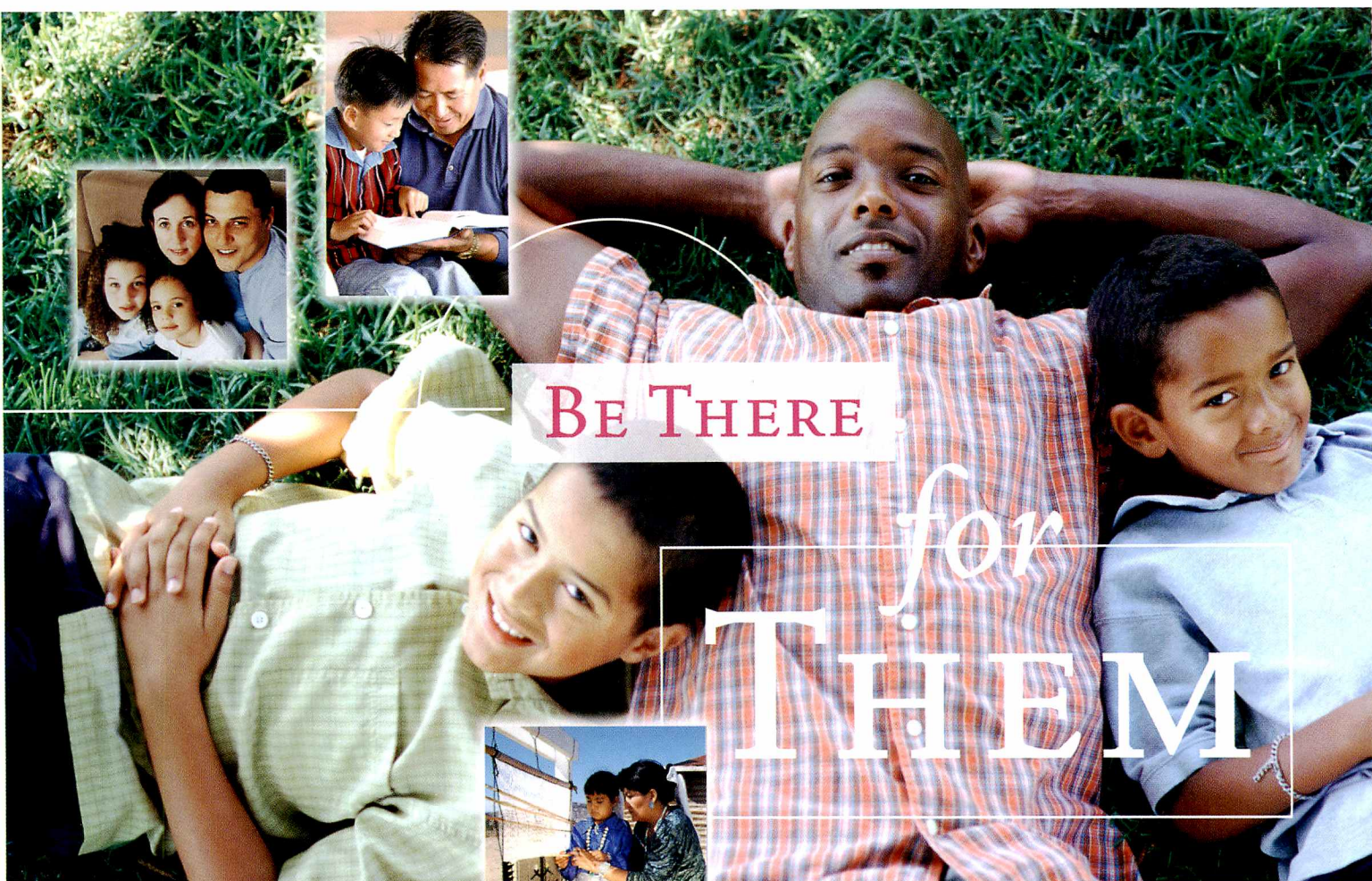
Comparing myself to other psoriasis patients, I consider myself lucky. While I have a more severe case than most, at least I have never been thrown out of a pool by a misguided lifeguard, like some other psoriasis patients I have met. I have not yet had the arthritis symptoms that make activity so painful for many others. And I did not have psoriasis in elementary school, when the teasing might have been horrible. But every day, some 50 American kids under age 10 are diagnosed with psoriasis. What about them?

While seeing psoriasis on my 8-year-old niece, or just imagining it on my son, can bring tears to my eyes, I remain optimistic, because the treatment options are rapidly improving beyond what I was offered during my first hospitalization in 1990. We’re not out of the woods yet, by any means—my leg psoriasis bled, in fact, as I wrote this piece—but scientific ingenuity is bringing us closer to that scenario we are all looking for: better treatments with fewer side effects.

In the end, those of us with incurable diseases draw hope from scientists. Perhaps that’s why I married a neurobiologist. She won’t cure psoriasis, but someday, maybe somebody else’s spouse will. ■

*Michael Paranzino is a government affairs consultant in Bethesda, Md. His clients include the National Psoriasis Foundation.*





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