

FDA *Consumer*

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

July–August 2000 • Vol. 34 No. 4

Trying To Look
SUNsational?
Complexity Persists
In Using Sunscreens





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FDA Consumer (ISSN 00362-1332) is published bimonthly by the Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857, U.S. Public Health Service, Department of Health and Human Services.

Editorial Matters

Address for editorial matters is *FDA Consumer*, Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857. Articles in *FDA Consumer* may be republished without permission. Credit to *FDA Consumer* as the source is appreciated. *FDA Consumer* is indexed in the *Reader's Guide to Periodical Literature*. The current *FDA Consumer Index* is available on FDA's Website at www.fda.gov/fdac/index/conindex.htm.

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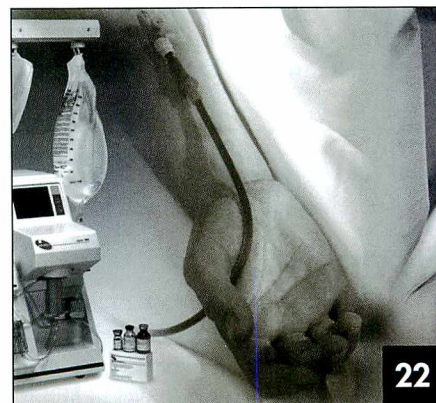
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◀ Inside Front Cover Photo:

A diabetes patient uses a spring-loaded device to insert a tiny catheter into his abdomen, allowing precise doses of insulin to be delivered from a pump about the size of a pager. For the latest on juvenile diabetes, see page 28.

OBSERVATIONS

The Food and Drug Administration frequently finds itself in the position of needing to make a public health policy decision even as it struggles with insufficient scientific information. Often, there is enough data to spot some of the dangers but not always enough to easily chart the safest course.

This theme—balancing the knowns and the unknowns of science with the need to regulate—runs throughout FDA's history. It's a challenge as old as the 40th anniversary of the Pill, the first medication approved for use in healthy people, that's recounted in the commentary on this issue's last page. And it's as contemporary as the cover story on current dilemmas about the best formulations and labels for sunscreens.

While debates are common within the agency, the public seldom hears much about FDA's deliberations until after the decision is made. Only then is there a notice in the *Federal Register*, and maybe a Talk Paper or Backgrounder. Sometimes the media pick up the story, sometimes not. Trying to understand a particular issue is often like following a baseball team's season when you only hear about an occasional score long after the game is over. You miss the drama of the competition in progress. Moreover, if you don't hear another score for several games, it's tough to know where the team places in the standings. Are they up; are they down? You can't tell. That kind of reporting makes it awfully difficult to follow the team—or a public health issue.

FDA Consumer won't report on the incremental advance of every important public health problem in every issue. But it will try to spend more time talking about work in progress. And that should make for interesting reading. Frequently, the story behind the outcome is as compelling



Larry Thompson, Editor

and fascinating as the decision itself.

So, future issues of *FDA Consumer* will try to pull back the curtain a bit and look at the process, not to reveal the bureaucratic machinations, but rather the very real human drama in which highly trained experts struggle with complicated information that has a profound impact on the public. FDA has a smart staff with unique skills and viewpoints. Future issues will bring you some of their stories and accomplishments.

The current issue contains plenty of examples of how FDA balances the risks and the benefits of medical products. For example, FDA recently approved the use of saline-filled breast implants. While the agency deemed them safe to use, it gathered considerable information about the side effects that a user can expect.

Pharmacy compounding is another risk/benefit balance. On one hand, this practice of customizing prescription pharmaceuticals in a private drug store can, for example, avoid problems with allergies to certain ingredients. But it also increases the risk of poor manufacturing controls. Only a well-informed consumer can make a well-considered decision about using this option.

I don't want you to get the impression that everything FDA does has a level of uncertainty. When dangerous problems arise, as in the medical gas industry, or when manufacturers make unsupported claims about a medical device as described in the Investigators' Report, the agency knows exactly what to do—and does it.

FDA remains a dynamic agency with a diverse portfolio of problems and challenges. And that makes for interesting stories.

Oh, and remember: Keep those cards and e-mails coming. Let us know how we are doing. If you have a story idea you think the magazine should consider—or an FDA staffer's story you think we should tell—send it along to the Letters to the Editor e-mail address, FDAC-letters@oc.fda.gov. We're always looking for ways to make this the most interesting magazine you read.

TO THE EDITOR

Safety of Soy

As the organization representing the infant formula industry, the International Formula Council is concerned that the *FDA Consumer's* discussion about potential effects of soy isoflavones on infants is unbalanced and may mislead consumers. (May-June 2000 *FDA Consumer*, "Soy: Health Claims for Soy Protein, Questions About Components.")

In particular, the article does not emphasize that isoflavones in soy foods are thousands of times weaker than natural

estrogens. There is no reference to the fact that there is no evidence, in the millions of infants who have consumed soy formula for over 60 years, that isoflavones have any estrogenic or other adverse effects. Additionally, extensive scientific data has demonstrated that infants fed soy-based infant formulas grow and develop normally.

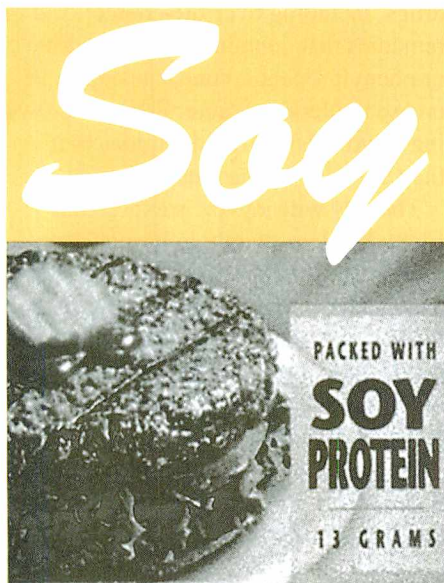
Also, the American Academy of Pediatrics (AAP) position statement on the use of soy infant formula was misleadingly qualified in the article. The article

incorrectly paraphrases the AAP statement by stating that only "in some cases" are soy formulas appropriate for use when cow's milk is not tolerated. The AAP statement clearly states: "In term infants whose nutritional needs are not being met from maternal breast milk or cow milk-based formulas, isolated soy protein-based formulas are safe and effective alternatives to provide appropriate nutrition for normal growth and development."

An infant's health may be put at risk if

parents change the feeding regimen because of unwarranted concern over the safety of soy-based infant formula.

Mardi K. Mountford, M.P.H.
Executive Director
International Formula Council



Your article on soy spoke of the possible risks of plant estrogens, but made no mention of the carcinogenic effects of protease inhibitors found in soy. McGuinness *et al.* report rats fed raw soya flour develop cancer of the pancreas ("The effects of long-term feeding of soya flour on the rat pancreas," *Scandinavian Journal of Gastroenterology*, 1980; 15:497-502). They say that pre-heating the flour protected the animals, but others have said that the high heat required (130 degrees Celsius) to deactivate the carcinogenic trypsin inhibitors in soya flour denatures the soy proteins to the point that they become virtually useless. If this is so, one either chooses less heating, resulting in more surviving trypsin inhibitors, or more heating, resulting in useless protein.

William Jarvis, Ph.D.
Department of Health Promotion
and Education
Loma Linda University
Loma Linda, Calif.

Labeling Genetically Engineered Foods

FDA has stated that it doesn't have the authority to require labeling of genetically engineered food based solely on the consumer's "right-to-know." (January-February 2000 *FDA Consumer*, "Are Bioengineered Foods Safe?") FDA has taken this position even though the Federal Food, Drug, and Cosmetic Act says it's meant to promote honest and fair dealing in the interest of consumers. In my view, refusing to label food as genetically engineered is not honest, is not fair, and is not in the interest of consumers.

To say that genetically engineered food needn't be labeled is like saying that ignorance is better than information. The Genetically Engineered Food Right-to-Know bills now in Congress, H.R. 3377 and S. 2080, are needed to do what FDA has never done: make sure that genetically engineered food isn't imposed on people without their knowledge or consent.

Marjorie Gallace
Camden, Maine

Misleading Health Fraud Example

In the November-December 1999 issue of *FDA Consumer*, the article "How to Spot Health Fraud" used the claims of an anonymous emu oil producer as an example of health fraud.

As president of the American Emu Association, representing more than 1,000 emu producers, I know that the company making these claims is not a member of the American Emu Association and your example is certainly not representative of our industry. In fact, our producers take every precaution against making claims about any emu product. We see the claims you used—of curing a wide range of unrelated diseases—as irresponsible, and the personal testimonial about Alzheimer's disease is abhorrent to us.

Our members understand that emu oil has not been evaluated by the FDA and they cannot print unsubstantiated claims on product labels. And the board of directors of AEA continues to convey this, both verbally and in written form, to each and every new member.

Our concern is that the examples you provided your readers painted a shoddy picture of a group of hard-working and conscientious professionals and presented only a portion of the picture of this industry as it exists today.

We see the behavior of the emu products company owner you quoted as irresponsible, negligent, and definitely not representative of our industry, as your article implies. Your readers should not take your article as an indictment of our entire industry.

Neil Williams
President, American Emu Association

FDA Consumer accepts letters to the editor. Letters can be e-mailed to FDAC-letters@oc.fda.gov, or mailed to *FDA Consumer*, Food and Drug Administration (HFI-40), 5600 Fishers Lane, Rockville, MD 20857. Letters should be 300 words or less, signed, and include a telephone number for verification. The editor reserves the right to edit letters for space and appropriateness.

Correction

The chart of newly approved medical products that appeared in the May-June issue of *FDA Consumer* contained an incorrect statement about the uses of Vioxx (rofecoxib). The drug is approved for the treatment of osteoarthritis, not rheumatoid arthritis, and for menstrual pain and acute pain in adults.



First Antibiotic in New Class of Drugs Fights Resistant Infections

The first in a new class of antibacterial drugs to treat serious infections resistant to other antibiotics has been approved by the Food and Drug Administration. Zyvox (linezolid) was approved April 18, less than a month after an FDA advisory committee reviewed study data and recommended its approval.

Zyvox treats infections, including bloodstream infections, associated with vancomycin-resistant *Enterococcus faecium* (VREF). Vancomycin has long been the drug of last resort in treating infections resistant to other antibiotics. Zyvox also was approved for the treatment of hospital-acquired pneumonia and complicated skin infections, including those due to methicillin-resistant *Staphylococcus aureus* (MRSA), for community-acquired pneumonia and for uncomplicated skin and skin structure infections.

Infections due to *Enterococcus faecium* and MRSA are a particular problem in hospital patients and in people with compromised immunity, such as people with AIDS or cancer. The first case of VREF was reported in this country in 1989. Since then, there has been a rapid increase in the incidence of VREF infections, as well as a dramatic rise in the incidence of MRSA infections.

Last fall, FDA approved Synercid, a combination of two older antibiotics, to treat infections resistant to vancomycin. Zyvox, however, is the first in a new class of synthetic drugs—the oxazolidinone class—approved for use in the United States and the world. It is also the first drug in over 40 years to be introduced into the U.S. market for treatment of MRSA infections.

The most frequently reported side effects attributed to Zyvox in clinical stud-

ies were headache, nausea, diarrhea, and vomiting. The most important laboratory test change was a decrease in platelet counts.

Zyvox may interact with certain other drugs, including over-the-counter cold remedies that contain pseudoephedrine or phenylpropanolamine, causing an increase in blood pressure. Patients receiving Zyvox should tell their doctors if they are taking such medications.

Therapy with Zyvox is expected to first take place mainly in hospitals or other institutional settings. Doctors have been advised to consider alternatives before prescribing Zyvox to outpatients, due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms.

Pharmacia and Upjohn, based in Kalamazoo, Mich., developed Zyvox and will market it in the United States.

Light Sabers Protect Sight of People With Age-Related Eye Disorder

A remarkable new Star Wars-like therapy that uses laser light to activate a drug within the blood vessels of diseased eyes has provided the first effective therapy for “wet age-related macular degeneration” (AMD). In April, the Food and Drug Administration approved Visudyne (verteporfin for injection) for treatment of the classic type of wet AMD. AMD is a form of degenerative nerve disease that destroys the eye’s retina, causing severe and irreversible vision loss. It is a major cause of blindness in people over 60 years old in the Western World. While 90 percent of AMD is the “dry” form and only 10 percent is the “wet” form, the “wet” form destroys vision more quickly.

Wet AMD is caused by the growth of abnormal leaky blood vessels in the eye. The leaking blood eventually damages the macula—the area of the eye’s retina responsible for central vision. Central

vision is essential for most visual activities, including reading, driving, and recognizing faces.

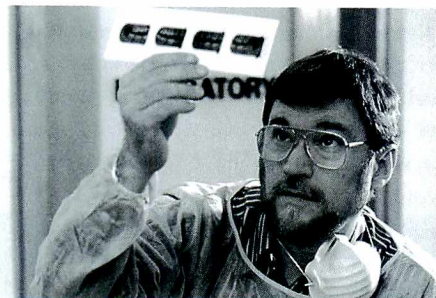
With AMD, the central field of vision is affected in varying degrees, while peripheral or side vision remains unaffected. Untreated, the majority of eyes with wet AMD will become functionally blind within two years. Visudyne therapy slows damage to the retina, but does not restore vision in eyes that have been damaged by AMD.

Visudyne therapy is relatively painless, takes about 20 minutes, and can be performed in a doctor’s office. First, Visudyne is injected intravenously into the patient’s arm. The drug travels through the body to the abnormal vessels in the eye. Next, the drug is activated by shining a laser light into the patient’s eye for about 90 seconds. The laser changes the drug’s molecular shape in such a way that the drug stops or slows blood leak-

age from the vessel, at least temporarily, slowing the rate of vision decline. Patients should be re-examined every three months to check for new leaks; if they occur, the treatment must be repeated. Because light activates the drug, the patient must avoid exposing skin or eyes to direct sunlight or bright indoor light for five days after treatment.

Fewer than 2 percent of the patients in clinical trials stopped therapy due to side effects. Unfortunately, within seven days of treatment, 1 to 4 percent of patients experienced a severe vision decrease equivalent to the loss of four or more lines of vision on a standard eye chart. The most common side effects included reactions at the injection site, passing vision disturbances, and increased sensitivity to light.

Visudyne therapy is manufactured by QLT PhotoTherapeutics Inc., the eye-care unit of Novartis AG, and is marketed worldwide by CIBA Vision.



See Your Dentist to Prevent Heart Attacks

Routine dental x-rays may be an early-warning system for the risk of dying from a heart attack or stroke, according to research conducted at the University of Buffalo. Researchers found that individuals with calcified plaque in their carotid arteries were twice as likely to die from heart attack or stroke as those with no plaque. The carotid arteries are large vessels on either side of the neck that carry blood from the heart to the brain. Plaque in these arteries, which can be seen on standard panoramic dental x-rays, increases the chances of the vessels narrowing or clots forming. Study results were reported on April 4 at the annual meeting of the International Association for Dental Research.

Serious Product Problem? Report It

Health professionals can report serious adverse reactions or other product problems to FDA's MedWatch program by:

- Mail: Use the postage-paid MedWatch form (available from the FDA Website)
- Phone: 1-800-FDA-1088 (1-800-332-1088)
- Fax: 1-800-FDA-0178 (1-800-332-0178)
- Internet: www.fda.gov/medwatch/
Call the 800 number or visit the Website for forms or for further assistance.

FDA encourages consumers to report through their doctors, but if they prefer, they may submit the MedWatch form themselves.

Contaminated Antiseptic Products Recalled

Antiseptic sterile skin products manufactured by Clinipad Corp. of Rocky Hill, Conn., were voluntarily recalled by the company in March because they could be contaminated by bacteria that cause serious—even life-threatening—skin, wound, or other infections. The products are frequently used at blood collection centers.

There have been no known instances of blood contamination traceable to the recalled products; however, the company confirmed bacterial contamination in some lots of its sterile products, one of which was recalled in December 1999, and could not assure the sterility of other products labeled and sold as sterile.

The swabsticks, prep pads, towelettes, ointments, pouches, and dressings are distributed under the tradenames Cliniswab, Clinipad, Clinidine, Cliniguard, EZ Prep, Cooper Instrument Corp., Moore Medical Corp., and Rauscher. Sold separately or packed in kits, they were distributed to blood banks, hospitals, clinics and retail pharmacies. Products in the recall were manufactured from January 1, 1997, to the time of the recall and include povidone iodine, tincture of iodine, benzoin tincture, acetone alcohol, and alcohol antiseptic products as well as Sterile Cliniguard Protective Dressing.

Products in the recall are labeled "sterile" or "sterile unless opened or damaged." They have lot numbers beginning with 7,8,9, or 0. Health professionals and consumers who have products with these lot numbers should destroy them.

Consumers and health professionals can get more information about the recall on the World Wide Web at www.fda.gov/medwatch. To help blood collection centers develop alternative skin preparations, FDA has also posted information on www.fda.gov/cber/infosheets.htm and www.fda.gov/cber/recalls.htm.

Clinipad Corp. has sent recall notices to 3,000 customers and 100 kit manufacturers. Consumers with questions may contact the Clinipad Corporation at 860-571-0100.



Medical Device Treats Female Sexual Arousal Disorder

A new medical device to treat female sexual arousal disorder (FSAD) has been cleared for marketing by the Food and Drug Administration. Available by prescription only, the Eros Clitoral Therapy Device consists of a small, soft, plastic vacuum cup attached by a tube to a palm-sized battery-operated vacuum pump. The cup is placed over the clitoris prior to sex and the pump draws blood into the clitoris through gentle suction, causing engorgement, which aids sexual arousal.

The device's effectiveness was studied in 25 women, 15 of whom had FSAD. Each of the women used the device during six sexual encounters. Of the 15 women with FSAD, all experienced more sensation; seven, more orgasm; 12, more satisfaction; and 11, more lubrication. Of the 10 women without FSAD, four experienced more sensation; four, more orgasm; two, more satisfaction; and three, more lubrication.

No adverse events from using the device were reported.

FSAD is a persistent or recurrent inability to attain or maintain adequate vaginal lubrication, expansion of the vagina and swelling of the external genitalia during sexual activity.

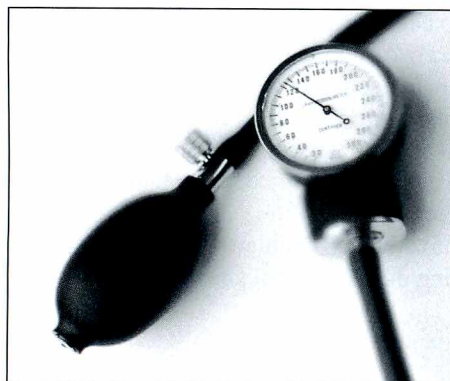
The Eros Clitoral Therapy Device is manufactured by UroMetrics, Inc., of St. Paul, Minn.

Mid-Life Tofu Consumption Associated With Mental Decline

Eating large amounts of tofu in midlife may be associated with mental deterioration in old age, according to the Hawaii Center for Health Research. An analysis of data from the Honolulu Heart Program found that men who ate the most tofu during their mid-40s to mid-60s showed the most signs of mental deterioration in their mid-70s to early 90s. The program began tracing the health of 8,000 Japanese-American men in 1965. Researchers said that both men and women eating tofu two or more times a week were up to twice as likely to show some signs of impaired mental function later in life than those who rarely ate tofu. The proposed link between eating tofu and decline in brain function is the isoflavones, chemicals in soy that affect an enzyme in the body that may block changes in the brain related to learning. (*Journal of the American College of Nutrition*, April 2000)

High Blood Pressure Linked to Breathing Disorders

Sleep apnea and other breathing problems during sleep are associated with high blood pressure, according to the results of a large multicenter study of individuals 40 years of age and older. Scientists from Johns Hopkins University and other research institutions found that the highest numbers of sleep-disordered breathing episodes each hour were more likely to occur in people with high blood pressure. (*Journal of the American Medical Association*, April 12, 2000)



High-Tech Hope For Heartburn Sufferers

The burning, bubbling, boiling sensation can last for minutes, hours, even days. It's often worse after eating. You can feel it, the sensation of stomach acid eating away at the esophagus. Heartburn. The American College of Gastroenterology estimates that more than 60 million Americans suffer heartburn at least once a month, and that more than 15 million Americans have the symptoms every day. If the heartburn is severe, or if it happens at least twice a week, you may have Gastroesophageal Reflux Disease, or GERD, a serious disorder that can lead to esophageal cancer.

Scientists believe GERD develops when the muscular valve at the lower end of the esophagus, where it connects to the stomach, malfunctions. The muscle relaxes too often and too easily, allowing stomach acid to flow up into the esophagus. Typically, GERD is treated with behavior modifications such as weight loss and dietary changes, antacids and other medications, and surgery.

But now, sufferers have available an entirely new approach. In April the Food and Drug Administration cleared for marketing two new medical devices that promise to control many of the symptoms related to gastric reflux. The devices, the Stretta System by Conway Stuart

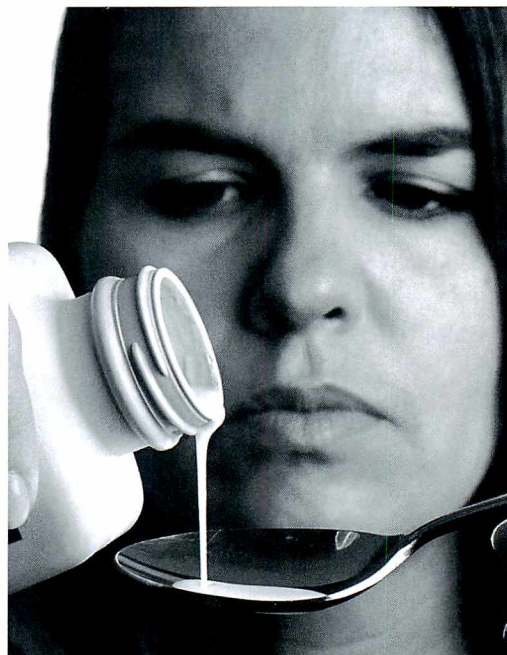
(now called "Curon") and the Bard Endoscopic Suturing System (BESS), provide potential alternatives to drugs and more invasive surgery for GERD by fixing the loosened muscle valve. Both use an endoscope, a tube with a built-in camera, inserted through the throat to provide the specific therapy to the area that joins the esophagus to the stomach. The two devices tighten the valve in different ways.

The Stretta System uses a radio-frequency energy generator to heat the tissue, shrinking the valve opening. The manufacturer, Curon, markets similar devices for tissue coagulation to treat snoring.

The BESS places small sutures, or "stitches," in the soft tissues of the esophagus and stomach. This tightens the valve, preventing stomach contents from flowing up into the esophagus.

Both procedures can be performed on an outpatient basis because they require no incisions and usually no general anesthesia. It's not known how long the benefits of treatment will last with either device, says Brian E. Harvey, M.D., the senior medical officer in FDA's Center for Devices and Radiological Health who reviewed the two device applications. Patients may need to be retreated if the acid reflux symptoms return.

The Bard Endoscopic Suturing System is manufactured by C.R. Bard, Inc., of Murray Hill, N.J. The SDM Stretta System is manufactured by Curon Medical, Inc., of Sunnyvale, Calif.



Plans for More Rigorous Review of Bioengineered Foods

Foods developed using genetic engineering will be subject to mandatory oversight before they reach the market, according to plans announced by the Food and Drug Administration in May. The new initiatives for bioengineered foods stem in part from input the agency received during public outreach meetings held throughout the country late last year. They also build upon procedures FDA has been following since 1994 for ensuring the safety of these foods. (See "Are Bioengineered Foods Safe?" in the January/February 2000 *FDA Consumer*.)

FDA's plans include a proposal to require developers of bioengineered foods and animal feeds to notify the agency at least 120 days before they intend to market the products. Such consultation with FDA has been voluntary since these foods were first marketed in the early 1990s.

Although FDA believes it has been consulted on all bioengineered foods and feeds currently on the market, it is proposing to strengthen the current process by requiring specific information from manufacturers. The agency will evaluate that information in terms of product safety, labeling, and adulteration issues, and then provide manufacturers its conclusions about the regulatory status of the food or feed. Posting these conclusions and manufacturers' information on FDA's Website (www.fda.gov) will give consumers easy access to information on individual bioengineered products.

In a related step, FDA will enhance the ability of its food and veterinary medicine advisory committees to address scientific questions related to bioengineered foods and animal feeds by adding members with agricultural biotechnology expertise.

FDA also plans to draft guidance that will assist manufacturers who wish to voluntarily label their foods as being made with or without bioengineered ingredients. The guidelines will help ensure that labeling is truthful and informative. To receive maximum consumer input, FDA will use focus groups to help develop the guidelines and will seek public comment on the draft guidance.



Increase in Beer Tax Lowers Gonorrhea Rate

When the beer tax increases, the rates of gonorrhea among young people drop, according to a national study of state alcohol policy changes from 1981 to 1995 by the Centers for Disease Control and Prevention. CDC researchers estimate that a state tax increase of 20 cents on a six-pack of beer could reduce U.S. gonorrhea rates by almost 9 percent. Two-thirds of the states that increased the beer tax were found to have decreased gonorrhea rates among teens aged 15 to 19 the year following the tax hike. Nearly three-quarters of the tax increases were associated with decreased gonorrhea rates among young adults aged 20 to 24. Gonorrhea rates among teens were also found to drop in states that increased their legal drinking age. These findings are consistent with other studies that link alcohol consumption to risky sexual behavior among youth. (*Morbidity and Mortality Weekly Report*, April 28, 2000)

Sharks Get Cancer Too

Cancer found in sharks casts doubt on the usefulness of shark cartilage pills to cure or prevent cancer, scientists from Johns Hopkins University and George Washington University reported April 5 at the annual meeting of the American Association for Cancer Research. Proponents of shark cartilage supplements have believed that since sharks did not appear to get cancer, their cartilage may block the growth of new blood vessels that supply nutrients to a tumor and cause it to spread. The new data challenge that belief. The researchers examined data in the National Cancer Institute's Registry of Tumors in Lower Animals and found 40 cases of tumors in sharks and related fishes. Researchers noted that their study can't rule out the possibility that scientists may one day find a useful cancer treatment in cartilage from sharks or other animals.

Moving a Step Closer to a Cancer Vaccine?

A vaccination aimed at an enzyme common to a number of human tumors might enable the body's immune system to attack and kill cancer cells. A team of scientists at the University of California, San Diego, working with colleagues at the Institut Pasteur in Paris, successfully used a vaccine in the test tube and in mice to activate a type of white blood cell to destroy cancer cells. The vaccine's target is telomerase, an enzyme key to the uncontrolled replication of cancer cells. Because telomerase is also essential to the functioning of normal cells, the scientists looked for negative effects of the vaccine on these cells—and found none. They predict that the telomerase levels in normal cells are low, causing little danger of the body attacking its own normal cells. The researchers do, however, acknowledge that this and other potential problems require further study. (*Proceedings of the National Academy of Sciences*, April 25, 2000)

Studies Show Antioxidants No Antidote for Disease

Consuming megadoses of dietary antioxidants does not prevent chronic diseases, concluded the experts on the Institute of Medicine's (IOM) Food and Nutrition Board. According to the April 2000 report on Dietary Reference Intakes, high doses of the nutrients vitamin C, vitamin E, selenium and beta-carotene do not protect the body from a variety of illnesses, such as cardiovascular disease, diabetes, and various forms of cancer, nor do they prevent basic nutritional deficiencies. In fact, the opposite may be true. Extremely high doses of antioxidants may lead to health problems, including diarrhea, bleeding, and the risk of toxic reactions.

In recent years, researchers have focused on the possible role that dietary antioxidants play in promoting and maintaining health. Antioxidants help neutralize potentially damaging molecules—byproducts of the body's metabolism—that may damage critical cellular components, including genes. Antioxidants can help prevent the damage.

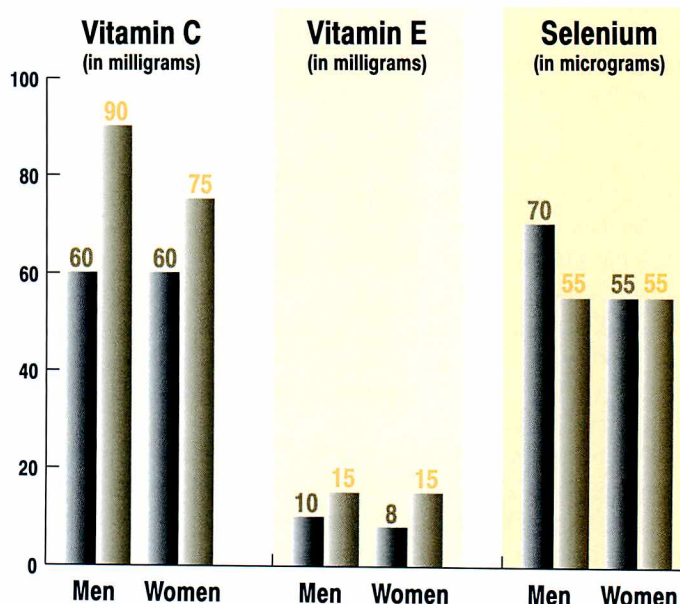
But after a comprehensive review of the scientific evidence, the IOM's Food and Nutrition Board, which is part of the National Academy of Sciences, concluded that although a large number of population studies reveal a link between a diet rich in foods containing antioxidants, such as fruits and vegetables, and a lower incidence of certain chronic diseases, they cannot be certain that antioxidants are the reason.

Since 1941, the Food and Nutrition Board has set Recommended Dietary Allowances (RDAs) for the types and quantities of nutrients that are needed for healthy diets. The board has updated and expanded the system over the past several years for determining these values—now called Dietary Reference Intakes, or DRIs. The 2000 report, “Di-

Daily Antioxidant Recommendations

The latest Dietary Reference Intake recommendations for several antioxidants by the National Academy of Sciences.

old recommendations
new recommendations



Source: Food and Nutrition Board

Infographic by Renée Gordon

etary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids,” is the latest in a series on DRIs.

“These IOM reports are a major source of scientific information for nutrition labeling,” says Elizabeth Yetley, lead scientist in FDA’s Center for Food Safety and Applied Nutrition. “They are an authoritative source, independent of the agency, and not influenced by regulatory applications.”

To determine how much of a specific nutrient one needs on a daily basis, the board considers two types of numbers: the RDA—a daily intake goal for healthy individuals, and the “tolerable upper intake level”—the largest amount of a nutrient that healthy individuals can take each day without risking adverse health effects.

Although this is the first time the science board has raised the daily recommended levels for the nutrients vitamin C and vitamin E (see accompanying chart), scientists continue to struggle with whether beta-carotene and other carotenoids are true dietary antioxidants. Laboratory tests show only that carotenoids have antioxidant properties, but the results of human trials searching for health benefits have been inconsistent. The only clear role of carotenoids, according to the board, is in the formation of vitamin A.

Norman I. Krinsky, Professor of Biochemistry at Tufts University School of Medicine, says that most North American adults get enough vitamin C, vitamin E, and selenium from their normal diets to meet current recommendations. Those who don’t, he adds, could get enough of these nutrients by simply improving their diets.

Saline Breast Implants

Stay On Market As Experts Warn About Risks

By Linda Bren

At the same time that Mattel's redesigned, smaller-busted Barbie doll was making its way onto the shelves of this nation's stores in 1998, a record number of the nation's women opted for a kind of surgery that would give them larger busts.

Breast augmentation has become the second most commonly performed cosmetic surgical procedure after liposuction, according to the American Society of Plastic Surgeons. In 1998 alone, more than 130,000 women in the United States underwent the procedure. This number grew to 191,000 in 1999—a 51 percent increase over the previous year and nearly a 500 percent increase since 1992.

Prior to 1992, two types of breast implants were available. Both had an outer silicone shell filled with either silicone gel or saline (sterile salt water). But since 1992, most of the breast implants have been of the saline variety because in that year, the Food and Drug Administration restricted the use of silicone gel-filled implants. This restriction was spurred by the concern that silicone gel leaking into the body could be harmful, and by the inability of the manufacturers to provide adequate safety data on their implants. FDA's decision eight years ago means that silicone-gel implants can only be used in controlled clinical studies for the purposes of reconstruction after mastectomy, correction of congenital deformities, or replacement of ruptured silicone-gel implants that were used for augmentation.

Saline-filled implants are believed to be safer than silicone because rupture or leakage will only release salt water—not silicone gel—into the body. Consequently, FDA has allowed these implants to remain on the market without evidence of safety until this year.

That evidence of safety was presented

by McGhan Medical Corporation and Mentor Corporation, both of Santa Barbara, Calif., to an FDA advisory panel on March 1-3. On May 10, following the panel's recommendation, FDA approved saline-filled breast implants made by these two manufacturers. The products are approved for breast augmentation in women 18 years or older and for breast reconstruction in women of all ages.

Reasonable Assurance of Safety

Breast implants had been on the market for more than a decade in 1976, when FDA was charged with regulating them as medical devices. While allowing the continued use of these "grandfathered" implants, FDA made it clear that manufacturers would be required to show their products to be safe and effective at some point in time.

FDA's approval of McGhan's and Mentor's saline implants acknowledges that these manufacturers have provided

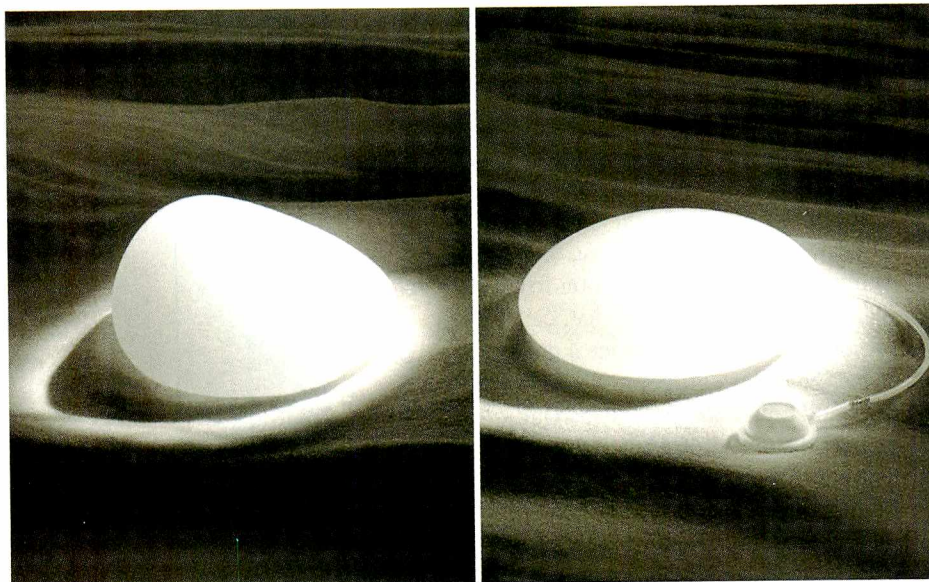
"reasonable assurance of safety and effectiveness" of their products.

Yet, these products do have risks. Breast implants are artificial medical devices—and no medical device functions as well, lasts as long, nor is as safe as the biological body part it replaces.

Like their silicone counterparts, saline breast implants can rupture, ripple, harden, change shape, and shift position. They can also cause infection, pain, and loss of feeling in the nipple or tissue of the breast. And they can interfere with breast-feeding and the detection of breast cancer.

Benefits and Risks

During the FDA advisory panel meeting, some women with breast implants, particularly those who had them for reconstruction after breast cancer surgery, reported that they had experienced significant improvement in their quality of life. Despite the complications that



Saline-filled breast implants come in different shapes and sizes, two of which are shown here. The implant is a sac of silicone elastomer (rubber), which is placed under the chest tissues. After the implant is inserted, the surgeon fills the sac with sterile saline (salt water) through a valve.

(Photos courtesy of Mentor Corporation, Santa Barbara, Calif.)

occurred in many women in the Mentor and McGhan studies, the majority of those still in the studies after three years reported being satisfied with their implants. These studies included both augmentation and reconstruction patients.

Even though breast implant surgery is well-established, there can be complications. "The most commonly occurring local complications reported for saline-filled breast implants are capsular contracture, implant rupture or deflation, and the need for additional breast implant surgeries," says Sahar M. Dawisha, M.D., a medical officer in FDA's Center for Devices and Radiological Health who reviewed the study data submitted by Mentor and McGhan.

Because the implant is a foreign object, the body will typically form scar tissue around it. The tightening and squeezing of this scar tissue is called capsular contracture. 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 itself.

Breast implants have a limited life. A rupture can occur at any time. "I tell my patients that the implant is on loan," says Gregory O. Dick, M.D., a plastic and reconstructive surgeon and chief of surgery at Shady Grove Adventist Hospital in Rockville, Md. "They can enjoy it for 6 weeks or 6 years or 60 years."

Once the implant ruptures, surgery is required to remove or replace it. Surgery may also be necessary in the event of infection, shifting of the implant, or formation of calcium in the surrounding tissue.

Another potential complication from implant surgery is nerve damage, causing some women to experience a change in sensation or loss of feeling in their nipples and breast tissue. These symptoms may disappear eventually but can be permanent in some patients.

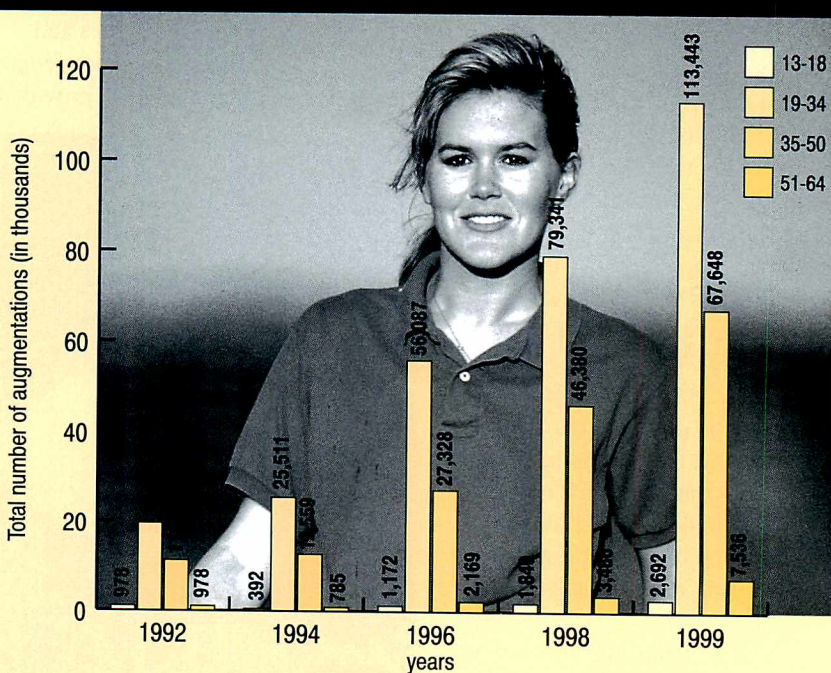
Additionally, says S. Lori Brown, Ph.D., an epidemiologist in FDA's Center for Devices and Radiological Health, "many women with implants are unable to breast-feed successfully." It is unclear whether insufficient milk production to breast-feed is due to damaged nerves or to other reasons, says Brown.

Factors to Consider Before Getting Saline-Filled Breast Implants

- Whether for augmentation or reconstruction, breast implantation may not be a one-time surgery. You are likely to need additional surgery for replacement or removal of the implants over the course of your life.
- Many of the changes to your breast following implantation are irreversible. If you later choose to have your implants removed, you may experience dimpling, puckering, wrinkling or other changes of the breast.
- Breast implants may affect your ability to produce milk for breast-feeding. Also, breast implants will not prevent your breasts from sagging after pregnancy.
- Routine screening mammography will be more difficult with breast implants. You will need to have additional views taken, which means more time, more radiation, and higher cost.
- For women who have undergone breast implantation either for augmentation or reconstruction, health insurance premiums may increase, coverage may be dropped, or future coverage may be denied. Treatment of complications may not be covered as well. You should check with your insurance company regarding coverage issues.
- Despite complications, most women who have received breast implants report they are satisfied with the results. ■

—L.B.

Breast Augmentation Surgeries on the Rise



The number of breast augmentation surgeries has increased steadily for all age groups in the United States since 1992. FDA's recent approval of saline-filled breast implants limits augmentation surgery to women 18 years or older.

Source: 1992-1998 data, American Society of Plastic Surgeons
1999 data, American Society for Aesthetic Plastic Surgery

Infographic by Renée Gordon

Making Cancer Harder to Detect

Breast implants can interfere with finding breast cancer during mammography. "The implant can hide breast tissue and, as a result, can hide lesions as well in the breast tissue," says Wendie Berg, M.D., director of breast imaging at the University of Maryland in Baltimore. In addition, extensive scarring and calcium deposits in tissue surrounding an implant can mimic cancer, Berg says, making them difficult to distinguish from tumors on a mammogram.

The process of taking a mammogram, which includes squeezing, or compressing, the breast, may increase the chance of rupture. But limiting the compression may compromise the quality of the picture.

When scheduling mammography, women with implants should ask for a comprehensive, or diagnostic, mammography instead of the regular screening mammography. They should request an x-ray technician who is experienced with mammography in women with breast implants. At the time of the appointment, women should inform the technician of the type of implant (saline or silicone) and its location (whether it is in front of or behind the chest muscle).

Making an Informed Decision

Women considering breast implant surgery need accurate information to help them make an informed decision. FDA requires breast implant manufacturers to provide printed information to help women with their decision, and has assisted manufacturers in developing this information. Women should ask their doctors for this "patient informed decision labeling" if they do not receive it.

For more information, request FDA's free consumer handbook, "Breast Implants, An Informational Update," by calling the agency's toll-free information line at 1-888-463-6332. (To get breast implant information, press 1, press 3, press 1, and then press 6.) The handbook, as well as copies of the Mentor and McGhan patient information on saline breast implants, is available at www.fda.gov/cdrh/breastimplants/. ■

Pharmacy Compounding: Customizing Prescription Drugs

By Tamar Nordenberg

Two thousand years ago, according to Christian belief, three wise men traveled to Bethlehem to worship the Christ child, bringing with them the gifts of gold, frankincense and myrrh. The aromatic resin myrrh, historically treasured for its medical and cosmetic usefulness, is still used in medicine today, mostly to treat inflammation of the mouth and pharynx.

Myrrh is not approved by the Food and Drug Administration to treat these or any other conditions. But the medical use of this unapproved drug may become legally acceptable under a new pharmacy compounding law that allows pharmacists and doctors to tailor-make some drugs for specific patients.

Considering the Alternatives

Health professionals are compounding when they prepare a specialized drug product to fill an individual patient's prescription when an approved drug can't fill the bill.

Compounding sometimes involves nothing more than crushing a pill into a powder with a mortar and pestle and then mixing it into a liquid, says Wayne Mitchell, an FDA regulatory counsel and member of the agency's internal pharmacy compounding steering committee. On the other hand, some types of compounding involve sophisticated scientific operations. Preparing sterile drug products, for example, can require complex steps to ensure a germ-free work environment.

The pharmacy compounding law, which is part of the FDA Modernization Act of 1997, defines the limits of legitimate compounding. By limiting the scope of the practice, the law aims to protect patients from the unnecessary use of compounded drugs, which carry intrinsic risks. Patients are often better served by taking commercially manufac-



tured drugs that have been scientifically tested, approved by FDA, and manufactured under controlled conditions.

Compounded drugs can be "a great alternative when nothing is commercially available," says Randy Juhl, Ph.D., dean of the University of Pittsburgh's pharmacy school and chair of FDA's pharmacy compounding advisory committee, a group that includes non-government doctors, pharmacists, and consumer advocates. "But," Juhl says, "as a rule of thumb, if there is a commercially available drug, that's always better because of the quality controls that we as pharmacists can't provide for something we make up as a single-patient batch."

No Seal of Approval

The pharmacy compounding law carves out a limited exception to the requirement that prescription drugs be approved by FDA based on studies demonstrating their safety and effectiveness. Because pre-approval drug studies are performed on a very specific drug formula and dosage, even relatively small compounding changes can convert an approved drug (a product tested as a tablet, for example) into an unapproved one (such as a liquid form made by the pharmacist).

The Law Laid Out

The pharmacy compounding law offers some protections against unsafe and ineffective compounded products, including the following main provisions:

- The compounded product must be individually prescribed for an identified patient.
- A bulk drug substance (basically, the chemical that becomes the drug's active ingredient) can qualify for use in compounding in any of three ways:
 1. It is found in an FDA-approved drug.
 2. It is listed in a book of widely used drug substances published by the United States Pharmacopeial Convention, an independent standard-setting organization.
 3. It is listed in an FDA rule as acceptable for pharmacy compounding (based on the agency's evaluation of the medical literature). A proposed rule, published in the Jan. 7, 1999, *Federal Register*, lists 20 acceptable bulk drugs (myrrh among them), and 10 others that are classified as "under consideration."
- Previously marketed drugs found to be unsafe or ineffective and removed from the market may not be compounded.
- Drug products listed in FDA's regulations as difficult to compound may not be compounded. FDA is making a list of difficult-to-compound drugs for discussion at a future advisory committee meeting.

Also, to protect consumers from the excessive use of these unapproved drugs and to prevent compounders from profiting from the research and development efforts of drug manufacturers, the law places limits on the compounding of copies of manufactured drugs.

"It's a hard line to draw between legitimate compounding and manufacturing," says recently retired FDA pharmacist Robert Tonelli, "but we want to draw that line so manufacturers can't use the guise of compounding to avoid the approval process." ■

—T.N.

As unapproved drugs manufactured without FDA oversight, compounded medications involve an extra risk factor compared to approved ones. "Any time you make a change to a drug, there is the potential for reactions between ingredients or other problems," says Fred Richman, an FDA compounding expert. "You could end up with something that is less effective and that, at worst, could harm the patient."

Patients have been injured and have even died after taking pharmacy-prepared drug products. Examples include three infants who died after receiving an intravenous solution incorrectly prepared in a pharmacy, and a patient who became blind in one eye from pharmacy-prepared eyedrops that weren't sterile.

Taking the Risk

So why would a doctor choose to prescribe a compounded drug for a patient despite the inherent risks? A doctor may determine, in his or her professional judgment, that the compounded drug's benefits over any approved alternative

justify the risk for a particular patient.

Drugs for certain conditions just aren't made by manufacturers. But even if a drug is mass-produced for a medical condition, patients might need a custom-made version for a variety of reasons.

Sometimes a patient can't use the standard version of a drug because of an allergy to one of its ingredients. If that ingredient is "inactive," meaning it has no therapeutic role, a compounder might make a similar drug minus that ingredient—say, without the dye used for coloring; or without lactose, a filler in many classes of drugs, from decongestants to antibiotics to chemotherapy medicines.

In other cases, the right dosage strength is not readily available for every patient. A child, for example, would usually need a smaller dosage than an adult. Commercial products are often not available in kid-sized portions, and sometimes it's not practical to break up the adult drug product.

And, commercially available drug products often need to be transformed into a different form for children and the

elderly. For people in these age groups who can't swallow tablets or capsules, compounders can make a drug in a powder, liquid, lozenge, suppository, or other form for them.

Children may refuse to swallow a medicine, even in a liquid form, if it tastes bad. Compounders can customize a drug in a kid's favorite flavor—cherry, orange, or raspberry, for example—to increase its appeal.

While flavoring a medicine may seem innocuous, it can alter a drug's makeup to the point of diminishing its effectiveness, scientists caution, so health professionals should not underestimate the potential downside of prescribing these drugs.

The risks of prescribing a compounded drug, along with the benefits, should be weighed in the context of a specific patient's medical condition, emphasizes the University of Pittsburgh's Juhl. It's "unfortunate," he says, that some pharmacists—including, for example, some makers of hormone replacement drugs—"are insisting that compounded drugs are better for you in all times and all places because they're 'all natural.' To generalize that these are necessarily best for everyone is, in my mind, a weak point in terms of credibility."

Proceeding With Caution

To encourage what quality control is possible for compounded drugs, the compounding law calls for certain federal requirements. (See "The Law Laid Out.") Some of these requirements, including a list of acceptable compounding ingredients, were developed by FDA's steering committee in consultation with Juhl and others on the external advisory committee.

Even with the law's restrictive provisions, however, pharmacist and former pharmacy compounding steering committee member Robert Tonelli cautions consumers, "Whenever possible, FDA would recommend that patients use an approved drug. We have more data and reporting requirements on those to assure us of their safety and effectiveness."

More information on pharmacy compounding is available on FDA's Website, at www.fda.gov/cder/pharmcomp/. ■

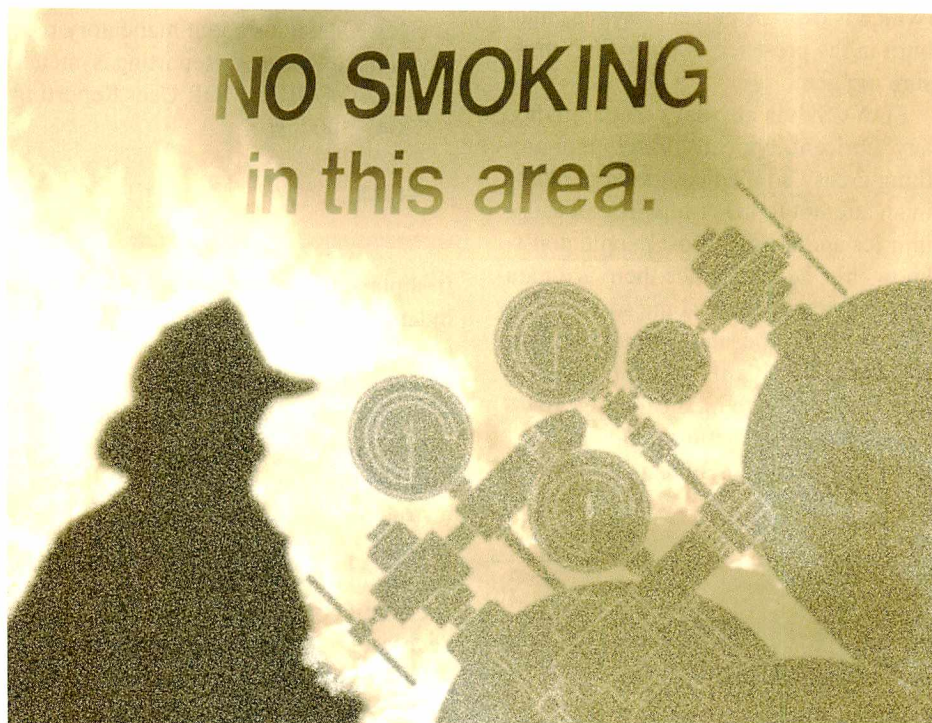
Avoiding The Hazards Of Medical Gases

By Carol Lewis

The popping sounds from the oxygen concentrator roused the elderly man from his sleep as fire engulfed his bed. With the help of his young granddaughter who was caring for him, the invalid managed to escape before two of the six high-pressure oxygen cylinders stored in a nearby closet exploded and burned the house down. The fire marshal investigation revealed that the oxygen concentrator malfunctioned, starting the blaze. Experts from the Food and Drug Administration, however, suspect that smoking also may have been a factor; both the man and his daughter, who lived with him, smoked cigarettes.

"My experience has been that smoking around oxygen may cause fires," says Duane Sylvia, a consumer safety officer in the Food and Drug Administration's Center for Drug Evaluation and Research. "Smoking anywhere near oxygen, even in the same room, can be extremely dangerous." FDA regulates medical gases, such as oxygen, as prescription drugs, and regulates the related delivery hardware, such as concentrators, tubing, and regulators, as medical devices.

Because of increasing reports about similar disasters involving medical gases, including some deaths, FDA is attempting to heighten both consumer and industry awareness about this specialty area of regulated products. Medical gases are the most frequently administered drugs in the United States, according to National Safety Technologies, Inc. The most commonly used include oxygen, nitrous oxide, carbon dioxide, medical air (which is used to provide a drug product to a patient), and nitrogen. These gases have a variety of medical uses, both in the home and in health-care facilities. For example, oxygen is usually administered at home to patients suffering from various respiratory conditions, such as emphysema. And surgeons use carbon dioxide to inflate the abdo-



men during laparoscopic surgery.

But in the last five years, FDA has received several reports of deaths and "near hits" (events in which the mistake of administering the wrong gas or contaminated gas was found in time to prevent injury), which have been traced to human error. For example, a patient died after receiving argon, a gas with a variety of industrial uses, instead of oxygen. Because maintenance personnel were

not properly trained, argon was inadvertently dispensed in the hospital's main oxygen supply.

In addition, FDA has received 16 reports of aluminum regulators (valves that control the flow of a gas) burning or exploding when used with oxygen cylinders. FDA and The National Institute for Occupational Safety and Health believe that the aluminum in oxygen regulators was a major factor in both the ignition

Medical Gas Terms

cylinder: metal container designed to hold compressed medical gases at a high pressure.

cryogenic vessel: metal container designed to hold liquefied compressed medical gases at extremely low temperatures.

compressed medical gas: any liquefied or vaporized gas alone or in combination with other gases.

concentrator: stand-alone unit that extracts oxygen from room air and delivers concentrated oxygen at a continuous flow rate.

regulator: mechanism that controls the flow of a medical gas.
—C.L.

and severity of these fires, although experts say there could have been other contributing factors. Brass regulators are believed to be safer than aluminum for use with high-pressure oxygen. And even though oxygen doesn't burn, it supports combustion. A material, such as the metal in oxygen regulators or cylinders, that will not burn in air (which is only 21 percent oxygen) may burn in the presence of pure, high-pressure oxygen.

FDA's Sylvia also says that applying any lubricant, typically Vaseline or anything greasy, to medical gas apparatus in an attempt to make repairs can cause injuries and deaths. Most people don't know this, he says, since there is a natural tendency to apply some sort of oil to appliances or household equipment that are mechanically difficult to operate. But, in fact, where medical gases are concerned, this practice could be deadly. "It's extremely dangerous in the

Reporting Problems

Since medical gases are prescription drugs, and a responsibility of the FDA's Center for Drug Evaluation and Research, report any problems with the drug product to FDA's MedWatch program at 1-800-332-1088. Reports can be submitted by fax on 1-800-332-0178, by mail to MedWatch, Food and Drug Administration (HF-2), 5600 Fishers Lane, Rockville, MD 20852-9787, or through FDA's Website at www.fda.gov/medwatch/.

The Safe Medical Devices Act of 1990 requires hospitals and other user facilities to report deaths, serious illnesses, and injuries associated with the use of medical devices. Questions about mandatory reporting can be answered by the Division of Surveillance Systems, Reporting Systems Branch, by phone on 301-827-0361, or write to FDA, CDRH, MDR User Reporting (HFZ-531), PO Box 3002, Rockville, MD 20847-3002. ■

—C.L.

For More Information

For more information on medical gas safety, contact:

Compressed Gas Association
1725 Jefferson Davis Highway
Suite 1004
Arlington, VA 22202-4102
www.cganet.com

National Fire Protection Association
1 Batterymarch Park
Quincy, MA 02269-9101
www.nfpa.org

American Society for Testing and Materials
100 Barr Harbor Drive
West Conshohocken, PA 19428-2959
www.astm.org

Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
Division of Safety Research
1-800-35-NIOSH (1-800-356-4674)
www.cdc.gov/niosh/firehome.html

first place for companies to deliver cylinders or equipment without proper instructions and precautions," which would provide these warnings, he says, but there is no specific requirement for health-care companies to do so. "People shouldn't accept the apparatus without instructions, or use medical gases from a company that isn't registered with FDA and licensed by the state."

Christy Foreman, a biomedical engineer in FDA's Center for Devices and Radiological Health, emphasizes the importance of having all at-home medical gas equipment properly installed and regularly maintained by professionals. Pam Schweikert, a compliance officer in FDA's Office of Enforcement, agrees. Some patient manuals indicate that oxygen concentrators should be serviced every 9,000 hours, yet Schweikert says that just last year FDA issued a warning letter citing a firm for waiting as long as 30,000 hours before servicing a unit.

"Part of the problem is that the small operations [firms that provide medical gases], as well as many of the welding supply companies, haven't been brought up to industry standards," Sylvia says, "and we need to educate these companies about the many risks involved."

It's not easy to tell if a company has delivered the right gas, or if the oxygen cylinder is made with the safest material. Most people rely on the experts to assure that equipment delivered to their homes is in good working order. But there are actions consumers can take to protect themselves:

- Always check the label on each high-pressure cylinder or cryogenic vessel be-

fore using a medical gas. The label should state for high-pressure cylinders, "Oxygen Compressed U.S.P.," or for liquid vessels, "Oxygen Refrigerated Liquid U.S.P." If the labels do not contain these drug names, do not use the product and call your supplier immediately.

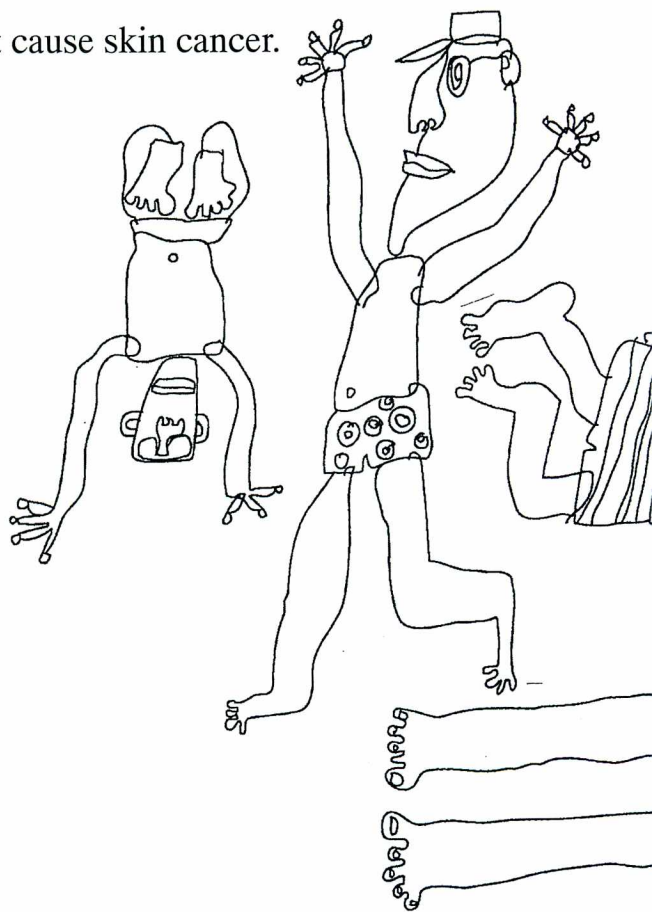
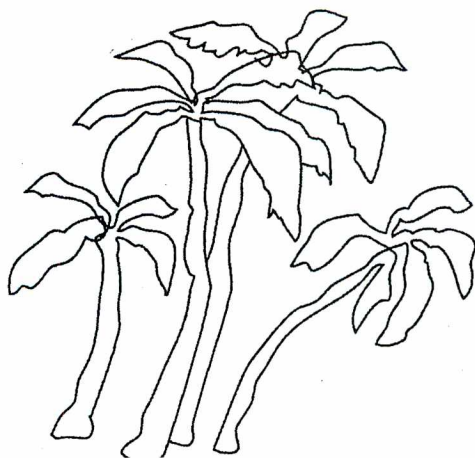
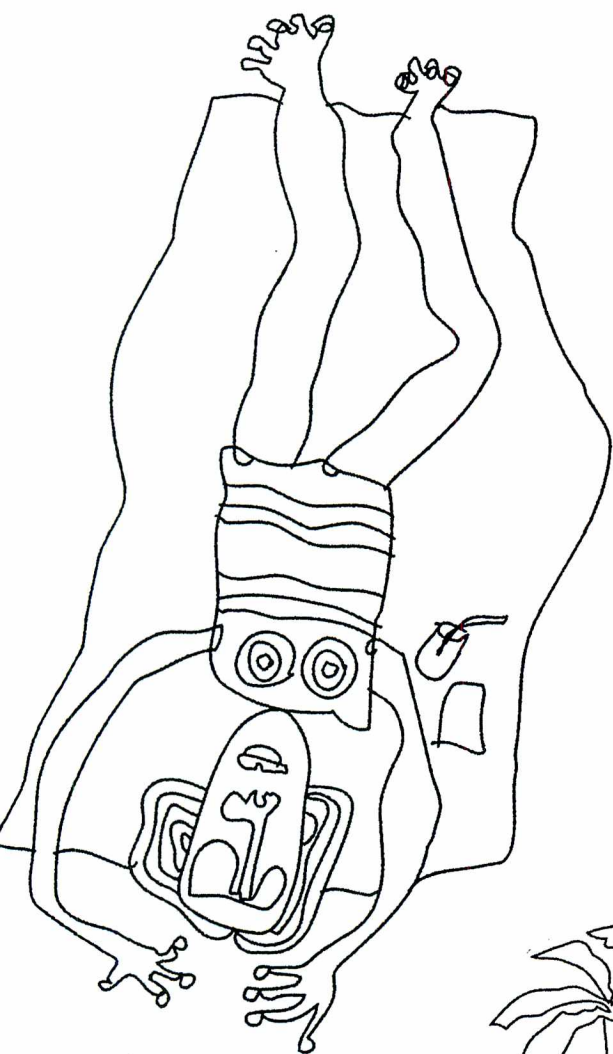
- Check to see that the high-pressure cylinders are secured in place, in an upright position, and in a well-ventilated area. Do not allow cylinders to be stored on their sides or loosely on the floor.
- Always turn or open cylinder valves slowly. Opening a valve quickly can cause the valve seal or "O" ring to ignite and release dangerous gases.
- Always place an oxygen concentrator in a well-ventilated area and not in a closet, back room, or garage where it might mix exhaust fumes with the medical gas.
- Do not leave the unit turned on when not in use. A cannula (nose tubing) that is left in contact with a synthetic comforter, for example, could spark a fire.
- Do not open an oxygen concentrator. If you detect a problem, contact your supplier immediately.
- If you are presently using an oxygen regulator that contains any aluminum, replace it with a regulator made of brass. Consult the manufacturer if you don't know what material the regulator is made of.
- If non-aluminum oxygen regulators are not available, contact the Center for Devices and Radiological Health, Office of Compliance, at 301-594-4659 for specific precautions when using aluminum regulators. ■

Trying To Look *SUN*sational?

Complexity Persists In Using Sunscreens

By Larry Thompson

You would think that all the questions about sunscreens have been answered by now. You slather it on before you go to the beach. It keeps you from being fried to a crisp. And, if you use enough, it helps prevent your skin from taking on that wrinkled, leathery look of photo-aged skin. Best of all, it protects you from the harmful ultraviolet rays that cause skin cancer.



SUNsational?

If that's your perception, you're mostly right, but that view is not complete. While all the basic information remains true—sunscreens do protect skin from sunburn—a scientific debate simmers about the importance of lower-energy ultraviolet light to skin damage and whether current sunscreens provide adequate protection.

Just recently, the Food and Drug Administration delayed until December 2002 the implementation of a so-called final monograph on sunscreens—the kind of rules that FDA publishes for the more than 100,000 over-the-counter (OTC) drug products currently on the market. OTC drug monographs—which cover 80 classes or therapeutic categories of OTC drugs, including sunscreens—are a kind of “recipe book” covering acceptable ingredients, doses, formulations, and labeling. Once a final monograph is implemented, companies can make and market an OTC product without the need for FDA pre-approval. New prescription drugs, on the other hand, require pre-approval before they can go on the market.

In 1997, Congress ordered FDA to issue regulations on the prevention and treatment of sunburn. The agency com-

pleted the sunscreen monograph in May 1999 to meet the congressional mandate, and it initially gave the industry until May 2001 to implement it. The new regulation established a list of 16 active ingredients that companies can use in sunscreen products and simplified the labeling so consumers will know how to use these products properly. The monograph also applied to sunscreen-containing cosmetics.

But questions about the harmfulness of a certain type of ultraviolet light and how to best label sunscreens led FDA to delay these regulations until further studies could be conducted.

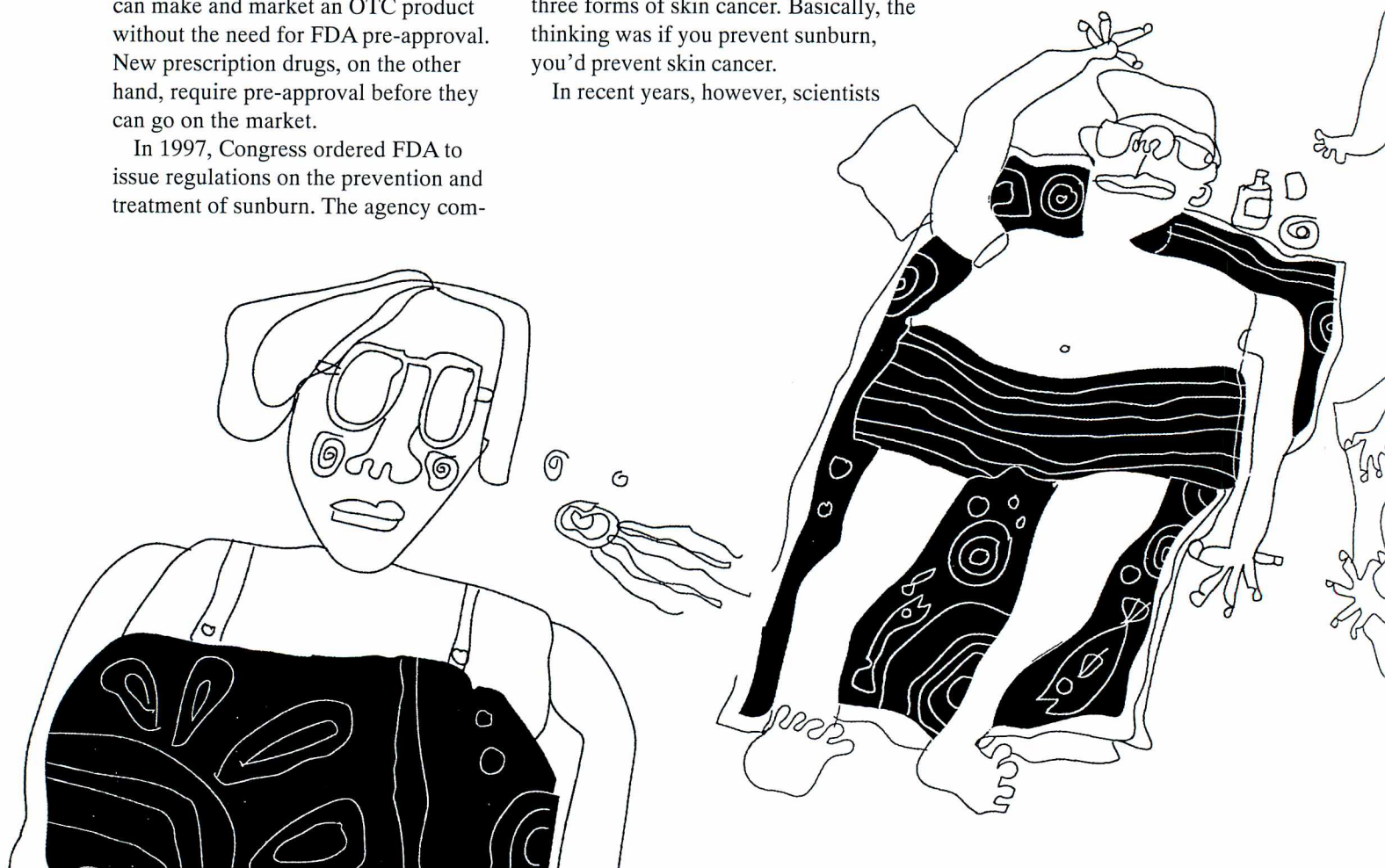
Sunburns and Suntans

Sunburn, which is caused by a type of ultraviolet (UV) light known as UVB, has served as a surrogate for more serious skin disorders, such as melanoma and basal and squamous cell carcinoma, three forms of skin cancer. Basically, the thinking was if you prevent sunburn, you'd prevent skin cancer.

In recent years, however, scientists

have come to appreciate that a different form of ultraviolet light, called UVA, may be just as, or even more, important in causing some skin disorders. Although experts still believe that UVB is responsible for much of the skin damage caused by sunlight—especially sunburn—UVA may be an important factor in other types of sun damage, including photoaging and the development of skin cancers. Most sunscreens do a good job blocking UVB but fewer filter out most of the UVA.

“Both laboratory and epidemiological studies indicate that sunscreens may not block the initiation or promotion of melanoma formation,” says Ronald D. Ley, Ph.D., at the University of New Mexico School of Medicine's Steve Schiff Center for Skin Cancer in Albuquerque, N.M. Studies using a fish model of melanoma induction “suggest



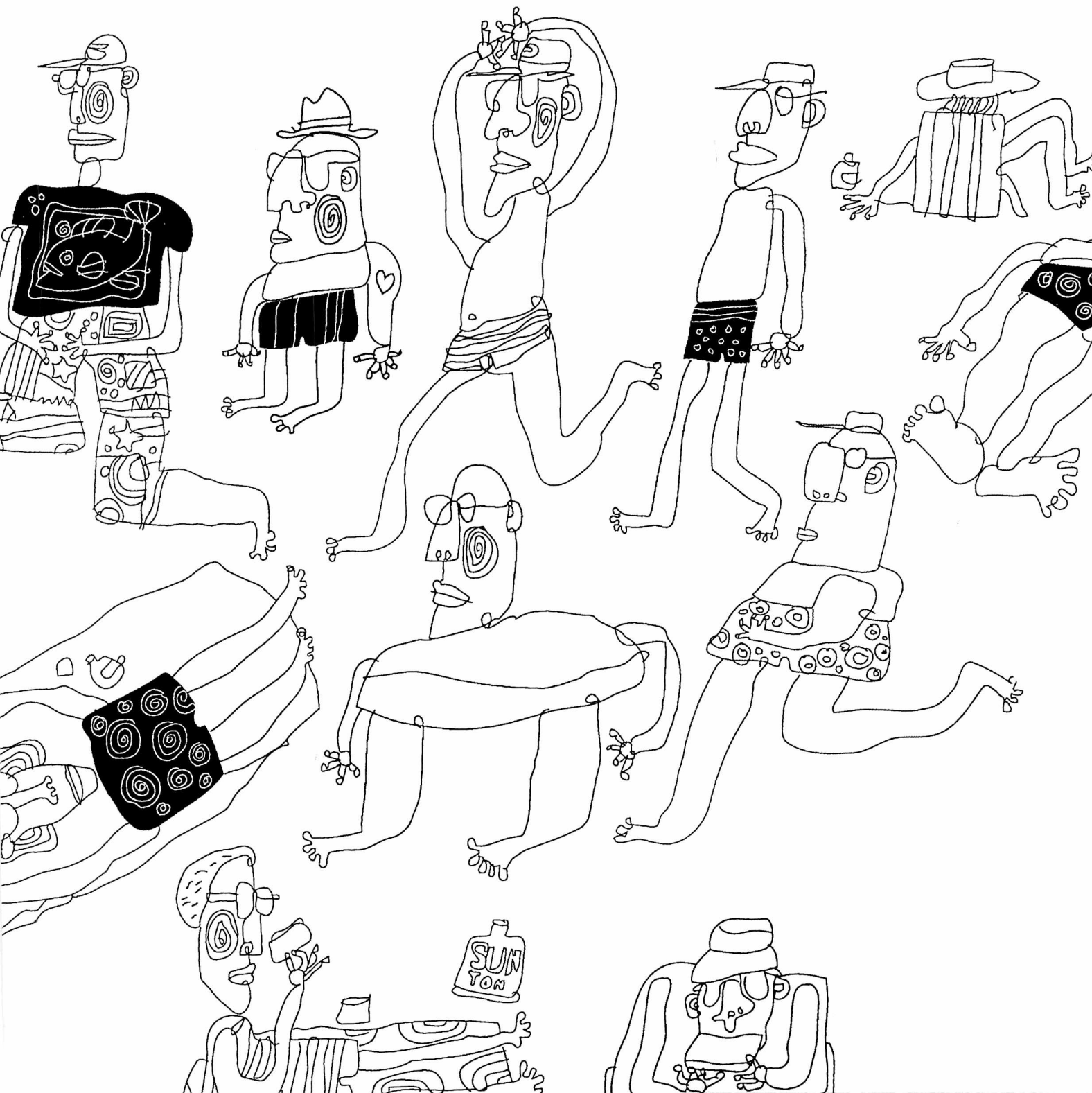
that the action spectrum [the defined wavelength of ultraviolet light that damages skin] for erythema induction is different than the action spectrum for the induction of melanoma." Erythema means red skin, that is, sunburn.

"There are a lot of data on both sides of the question about the tanning link to melanoma," says John Lipnicki of FDA's Center for Drug Evaluation and Research (CDER).

Now, with extra time before the monograph will be implemented, FDA and the scientific community have gone back to wrestling with the thorny questions that were not resolved in the initial document. Researchers will further study active ingredients and test methods to measure how well products block UVA's effect on the skin. The agency will also work to make the labeling clearer.

Risks and Reality

These questions transcend academic curiosity. The death rate from melanoma in the United States has been going up about 4 percent a year since 1973, according to the Centers for Disease Control and Prevention in Atlanta. Although melanoma represents only about 47,000 of the nearly 1.8 million cases of skin cancer diagnosed each year, according to the American Cancer Society, it will



cause 79 percent of skin cancer deaths. While cancer treatments continue to improve, melanoma recovery rates remain disappointing. Prevention is the better solution.

As prevention, however, sunscreens alone appear to be imperfect. In the first study to test the protective effect of sunscreens on people—not just the hairless mice or other models used in laboratory studies—researchers at the Queensland Institute for Medical Research in Brisbane, Australia, reported in September 1999 that sunscreen use reduces the risk of developing squamous cell carcinoma by 40 percent. But using sunscreen did not reduce the risk of developing melanoma or basal cell carcinoma. The Australian study followed 1,383 adults for five years.

FDA believes sunscreens are an important part of a person's total sun protection strategy, but that sunscreen use alone will not prevent all of the possible harmful effects due to sun exposure, according to agency statements. (See "Safe Sunning" on page 21.) Borrowing the "Slip, Slop, Slap" slogan from an Australian skin cancer prevention campaign, the American Cancer Society recommends that anyone out in the sun *slip* on a shirt, *slop* on sunscreen and *slap* on a hat.

The education campaign's benefits in Australia have been promising, says Robin Marks, M.B., of the University of Melbourne. "Suntans are out of fashion, especially deep tans. We can measure sunburn rates, and they have gone down." Most importantly, the epidemiological studies show the rates of skin cancer, including melanoma, are going down in the younger groups, says Marks, but not in the older groups whose skin already has been damaged by prior exposure to the sun.

As FDA ponders adjustments to the sunscreen monograph before its implementation, the agency finds itself in the familiar position of needing to make regulatory decisions about important public health issues in the face of scientific uncertainty.

UVA vs. UVB

The complexities of light quickly overwhelm freshmen physics students, but some basic principles can be readily

*Sunscreen should not
be used to prolong
time spent in the sun.*

understood. In one model of how light works, the electromagnetic radiation can be thought of as a series of waves, like ocean waves at the beach, steadily marching toward shore. At the beach, the wind makes the waves by transferring kinetic or mechanical energy into the water. The harder the wind blows, the more energy in the water and the higher and closer together the ocean waves. On a calm summer day, widely spaced waves lap mildly against the shore. During a hurricane, the wave action intensifies, pounding the sand with closely packed wave after wave of crashing white foam strong enough to wipe away the beach.

The electromagnetic energy in sunlight works much the same way: The higher the energy of the light, the closer together its waves. Some types of light have waves that are far apart—like ocean waves on a calm day. Other types of light have waves that are packed closely together, like ocean waves on a windy day.

This difference in closeness of a

light's waves, its wavelength, gives different parts of the electromagnetic spectrum its characteristics, such as the colors of visible light and the destructive capabilities of x-rays and ultraviolet light.

Physicists classify ultraviolet light into three types, by its wavelengths: UVA, UVB and UVC. The dimensions of their wavelengths are roughly 400 to 320 nanometers (nm) for UVA, 320 to 290 nm for UVB, and 290 to 200 nm for UVC. Although it may seem backwards, the shorter the wavelength and the lower the number, the greater the energy level of the light and the more damage it can do. For example, direct exposure to UVC for a length of time would destroy the skin. Fortunately, UVC is completely absorbed by gases in the atmosphere before it reaches the ground.

The longer wavelengths of UVB and UVA, however, pass right through the atmosphere, even on a cloudy day. That's why you can still get sunburned on a cloudy or hazy day. The molecules in sunscreens absorb most UVB and prevent it from reaching the skin just as the molecules of the atmosphere absorb UVC and prevent it from reaching the ground.

UVA, however, is another story.

According to a 1998 review article, most sunscreens do not protect the skin from the longer UVA wavelengths. And that may be critical to the creation of skin cancer. Approximately 65 percent of melanomas and 90 percent of basal and squamous cell skin cancers are attributed to UV exposure.

The precise wavelengths of ultraviolet that contribute to the formation of skin cancer still need to be sorted out. And scientists must still figure out how best to formulate sunscreens to provide effective protection against these wavelengths.

Scientists use a number of techniques to measure the UV-blocking ability of a sunscreen. Some rely on electronic laboratory equipment, some on living tissue or live animals. Some testing procedures even use human volunteers.

"We have a good way of measuring UVB protection with a sunburn or erythema test in humans," says Sharon Miller, an optical engineer in FDA's Center for Devices and Radiological



Health. But scientists lack a simple measure of UVA's impact on the skin, she says. That makes it difficult to determine how much UVA protection a sunscreen provides.

That leaves FDA with an unresolved technical dilemma that it is trying to resolve through additional research. "We are trying to determine a testing method that will demonstrate that a sunscreen is providing UVA protection," Lipnicki says. A claim such as "broad spectrum" on a sunscreen label needs to be supported by evidence that the product provides significant and meaningful protection across the entire UVB/UVA spectrum.

To Australia's Robin Marks, however, the issue is not UVA vs. UVB or even UVA combined with UVB. "The most common skin cancers seen in humans are related to sunlight, not to a limited band of the solar spectrum," Marks says. "It is the whole of all light coming from the sun. Don't concentrate on one band, but the entire spectrum. Keep it off the skin."

The SPF Debate

To figure out how much protection a sunscreen provides, most consumers turn to a simple number: the SPF, or sun protection factor, listed on the label. Studies show that most consumers understand that the higher the number, the more the product protects the skin.

Unfortunately, studies also show that people often have the mistaken notion that the higher the SPF number of the sunscreen they use, the longer they can stay—and will stay—in the sun. In August 1999, the *Journal of the National Cancer Institute* published a study showing that use of higher-SPF sunscreens led to increased sun exposure. Two groups of French and Swiss volunteers used unlabeled sunscreen during their vacations. One group used SPF 10 and the other group used SPF 30. The group using the higher-SPF sunscreen spent 20 percent more time in the sun (72.6 hours vs. 58.2 hours) than the group using the lower-SPF sunscreen.

"Because of variations between individuals, products, exposures, and conditions of use, there is no really easy way to explain SPF in a few words," says FDA's Lipnicki. "In the past, it was ex-

plained in terms of the amount of time you could stay in the sun longer with sunscreen than without it before getting 'burned'. We have gotten away from that. Sunscreen should not be used to prolong time spent in the sun. Even with a sunscreen, you are not going to prevent all the possible damage from the sun. Some of the newer research in the last several years shows that the sub-erythema doses [exposure to the sun that does not cause reddening of the skin], as little as one-tenth the energy needed to get a sunburn, start the process of skin damage of one sort or another."

In the final monograph completed last year, FDA proposed limiting SPF values on sunscreen labels to 30. Products with higher SPFs would be labeled "30+" (or "30 plus"). The agency took this action for two reasons: inadequacies in the testing methodologies for higher-level SPF formulations, and concern that the high SPF labeling may lead consumers to spend more time in the sun than they should.

The SPF portion of FDA's monograph immediately produced opposition from both industry groups and consumer organizations. The National Coalition for Sun Safety, an organization supported by the American Academy of Dermatology, advocated "a floor rather than a cap

on SPF," wrote coalition co-chairmen Rex Arnonette, M.D., and Roger Ceilley, M.D. The organization wants a minimum level of SPF to ensure that all products provide some protection.

Industry, primarily represented by the Cosmetic, Toiletry and Fragrance Association (CTFA), opposed the 30-plus cap for several reasons, including consumer confusion, fear that manufacturers would remove effective sunscreen protection in their products to avoid misbranding, and unresolved scientific issues about UVA. With the deferral of the monograph's implementation, the industry, along with the agency, will have additional time to resolve the issues.

The Labeling Controversy

The questions surrounding labeling, which may have less to do with science and more to do with motivating human behavior, may prove to be the thorniest of all. Everyone agrees on the goal: Create a simple label that consumers can easily understand.

In addition to recommending the SPF limit on labels, FDA has proposed further label changes to help clarify the risks and benefits of sunscreen use and how to use the products properly. For example, FDA wants the label to avoid *(Continued on page 21)*

A Label Caution



Although the Food and Drug Administration delayed implementation of its new rules on sunscreens, one new requirement in the monograph for over-the-counter sunscreen products went into effect on May 22, 2000, as originally scheduled. The new regulation requires all tanning products that **do not** contain sunscreen to bear the following warning statement on the label:

"Warning—This product does not contain a sunscreen and does not protect against sunburn. Repeated exposure of unprotected skin while tanning may increase the risk of skin aging, skin cancer, and other harmful effects to the skin even if you do not burn."

Tanning products that do not contain sunscreens and do not protect against the harmful effects of UV light are regulated as cosmetics. FDA requires this warning statement so that consumers are fully informed that such products do not provide protection from the sun. ■

—L.T.

How Sunlight Ages Skin

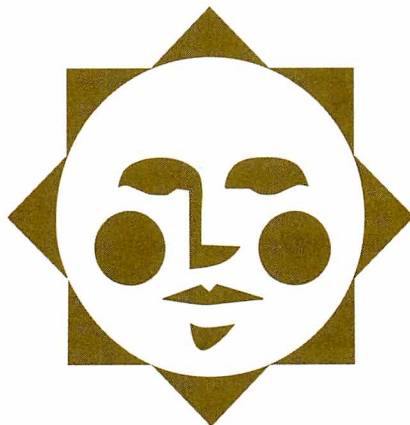
Take a look at a long-haul trucker sometime, a guy who's been driving for decades. Look closely at his face. One side will have more wrinkles than the other. Guess which one? The left side, the side of his face most exposed to the open window. Do you know why it has more wrinkles? Because it absorbs more direct sunlight than the right side of his face that's shaded inside the truck cab.

Look at the face of a long-haul trucker from a country like Great Britain, where people drive on the left side of the road. The right side of his face has more wrinkles because that's the side that faces the open window.

We're not talking lying in the sun here. We're not talking sunburn. We're talking chronic, long-term exposure to micro-doses of ultraviolet light that never overtly damages the skin, but over the years causes a collection of micro-scars that leaves a telling impression: wrinkles.

The epidermis, the outer layer of skin, "is as thin as a sheet of paper," says John J. Voorhees, M.D., chairman of dermatology at the University of Michigan Medical School. "Ninety percent of the mass of the skin is collagen," a large protein composed of three intertwined chains of amino acids that contributes to the form, function and strength of the skin. That also makes collagen the principal recipient of ultraviolet light damage.

But the pathway to aged skin is not straightforward. Sunlight itself does little direct damage to the collagen protein. A growing body of research shows, instead, that ultraviolet light



turns genes "on" and "off"—and which genes get turned on can make all the difference.

Normal skin maintains a dynamic collagen exchange. A common type of skin cell called a fibroblast exudes new layers of collagen when collagen genes are turned on. When collagen is damaged, skin cells produce enzymes that digest and liquefy the large collagen proteins into gelatin for disposal.

Voorhees' group discovered a complex genetic pathway through which sunlight can suppress collagen production by turning off the collagen-producing genes. At the same time, sunlight activates collagen digestion by stimulating production of the destructive enzymes.

Damaged skin results. The skin now carries a wound, and it needs to heal. "Anytime you cut yourself more than superficially, there is always a little bit of a scar," Voorhees says. "Our claim is that wound healing is never perfect. It could be 99.9 percent perfect, but never

perfect. And that 99.9 percent [healing after sun damage] is going to lead to the slightest imperfection that is not visible to the human eye, but after thousands of these over a lifetime, the micro-scars become macro-scars. This is the UV-induced aging we call photo-aging, and it is piled on top of natural aging that has nothing to do with the sun."

Prematurely wrinkled skin results. Although FDA has approved retinoic acid to treat chronic photo-aging, prevention remains the more effective approach.

Here's the really tricky part: Most of the genetic changes and resulting photo-aging appear to come from so-called UVA, the wavelengths of ultraviolet light in the A band of the spectrum. Most sunscreens currently on the market provide excellent protection against UVB, but not all provide equally good protection against UVA. "If you put on gobs of sunscreen, it blocks" the damage, Voorhees says. "But if you don't use much, it does not block [the damage] at all."

Moreover, sunlight turns on the genetic destruction quickly, but it also stops quickly when you get out of the sun. The level of collagen production is completely back to normal in two days.

"The average person thinks, 'I didn't get pink so I have no photo-aging,'" Voorhees says. "Our data suggest that is not true. You are going to be getting the photo-aged signals [that turn genes on and off] and develop the micro-scars without getting any pinkness at all. You can get photo-aged damage long before you get pink or sunburned." ■

—L.T.

Sunscreens are an important part of a person's total sun protection strategy, but sunscreen use alone will not prevent all of the possible harmful effects of sun exposure.

(Continued from page 19)

unsupported, misleading or confusing terms such as “sunblock,” “waterproof,” “all-day protection” and “visible and/or infrared light protection.” And when the label says the product is “water resistant,” or “very water resistant,” it must mean that the product provides the stated SPF level after water resistance testing for a specified length of time. FDA and the industry also are wrestling with what it means to claim that a sunscreen is “broad-spectrum,” that is, protective against both UVA and UVB.

Complexity is the problem because consumers want simplicity. Industry already has conducted studies that test the effectiveness of different ways to present information on the label. For example, Schering-Plough Health Care Products of Berkeley Heights, N.J., tested a label that contained another number in addition to the SPF to indicate the degree to which the product protected against UVA. “The second protection number created unnecessary complications and confusion for the consumer,” says Patricia Agin, Ph.D., Schering-Plough’s photobiology research director. “UVA should complement and not distract from SPF on the label. A descriptive approach better conveyed to consumers the added benefit of UVA protection and did not distract from the SPF number.”

“SPF should remain the primary index of efficacy,” agrees Jay Nash, Ph.D., of Procter & Gamble Pharmaceuticals Inc., of Mason, Ohio, “and any additional descriptor should be independent and commensurate with this information. Simplicity is the key to public policy.”

Simple or not, the labeling issue is not trivial because studies already show that consumers may not use sunscreens correctly. The public under-applies sunscreens by as much as half of the recommended amount, concluded a study published in the *Archives of Dermatology*. Consequently, the study argued, consumers are receiving only half of the SPF protection they believe the product provides.

Couple that with prolonged periods of baking in the sun and you have a recipe for future disease. ■

Larry Thompson is the editor of FDA Consumer.

Safe Sunning



The basic advice about protecting yourself from the harmful effects of the sun remains sound, according to the Department of Health and Human Services. The department continues efforts, launched in 1998 with its “Choose Your Cover” public education campaign, to help all Americans, but especially the young, prevent skin disorders associated with excessive exposure to the sun.

The recommendation is simple: To prevent premature aging, sun damage, and skin cancer, you need to protect yourself and your family from the harmful ultraviolet (UV) rays of the sun. And sunscreen alone will not protect you. You need to use a total program to reduce the sun’s harmful effects, including:

- Lavishly apply a sunscreen with a sun protection factor (SPF) of at least 15 and reapply it every two hours according to the directions on the label.
- Reapply sunscreen as needed after swimming, sweating or towel drying. And use sunscreen even on cloudy days.
- Avoid the sun during the middle of the day, especially between 10 a.m. and 4 p.m., when the atmosphere absorbs less of the harmful UV rays of sunlight than earlier or later in the day.
- If you have to be out in the midday sun, avoid long periods of direct sun exposure. Stay in the shade.
- Wear a wide-brimmed hat, protective clothing, and sunglasses.
- Never leave children exposed to the sun without adequate protection. Because of the long time it takes for cancer to develop, studies suggest that over-exposure early in life may lead to skin cancers later in life.

Although industry studies show that consumer use of sunscreen products continues to improve—up 13 percent in 1999—the American Academy of Dermatology (AAD) says that consumers still do not apply the correct amounts of sunscreen to achieve the full benefit.

A study sponsored by *Seventeen Magazine*, Beiersdorf Inc.’s Nivea brand, and the AAD found an increase in the use of sunscreen by teens, but also found problems: Eighty-eight percent of teens spend a significant amount of time in the sun, but only 72 percent say they use sunscreen at least some of the time. Only about 40 percent of the teens say they use sunscreen often or all of the time. Young women use sunscreen more than young men (46.2 percent compared to 30.5 percent), and the reasons given for not using it include the belief that they never burn (30 percent), inconvenience (17 percent), and the desire for a dark tan (6 percent).

The difficulty, of course, is that teenagers won’t see the effects of sun damage until they reach their 40s and 50s or later. By then, however, the damage already is done.

For more information on the DHHS education campaign, go on the Internet and connect to www.cdc.gov/ChooseYourCover. ■

—L.T.

Bone Marrow Transplants Come Of Age

New
Hope For
Deadly
Diseases

By Michelle Meadows

When Judge Morris was diagnosed with leukemia 10 years ago, doctors told him he would need a bone marrow transplant to survive.

"It gave me hope for a cure, but the big question was whether I'd ever find the right donor," says Morris, 47. The odds of finding a marrow donor in the general population are typically 1 in 20,000. Because of a rare genetic makeup, Morris' odds were 1 in a million.

For the next four and a half years, the Tulsa, Okla., resident underwent chemotherapy treatments and waited. He prepared his family for the possibility that he might not be around to see his two children grow up. "Then an angel named Mike Giglio came into our lives," Morris says. The National Marrow Donor Program found Giglio through its network, and Morris received a bone marrow transplant from Giglio in March of 1993.

"The leukemia is gone, I'm off medication, and not a night goes by that I don't thank Mike for saving my life," Morris says. At seven years post-transplant, the chance that the leukemia will return, experts say, is less than 5 percent.



Bone marrow donor Mike Giglio (left) with recipient Judge Morris.

Bone marrow transplants give patients a chance to beat diseases once believed to have no cure.

Each year, bone marrow transplants give patients a chance to beat diseases once believed to have no cure. Although the first successful bone marrow transplant didn't take place until 1968, the discovery of human leukocyte antigens (HLA) in 1958 was a major breakthrough because it allowed recipients to be matched with donors.

Since then, the procedure has steadily advanced as research uncovered ways to improve transplant techniques. Donor registries have grown significantly and drugs that prevent rejection and infection have improved. The Food and Drug Administration reviews new drugs used to prepare patients for bone marrow transplants, and drugs that aid in recovery. The FDA also reviews so-called growth factors, genetically engineered substances that stimulate growth of the transplanted cells.

Treating a Spectrum of Diseases

Bone marrow, a jelly-like substance in the cavities of our bones, contains hematopoietic (blood-forming) stem cells, commonly referred to as simply "stem cells." These cells are critical for life because they continually produce red blood cells, which carry oxygen; white blood cells, which help fight infections; and platelets, which act as clotting agents to stop bleeding.

Bone marrow transplants may help cure diseases that interfere with the production of any of these types of cells. These include cancers such as leukemia, Hodgkin's disease and other lymphomas. For Judge Morris and others with chronic myelogenous leukemia (CML), a common form of leukemia, abnormal white blood cells fill up the bone marrow, enter the bloodstream, and can invade organs and tissues. Transplants also may help patients with non-cancerous conditions characterized by a deficiency in blood cell production, such as aplastic anemia and inherited immune disorders.

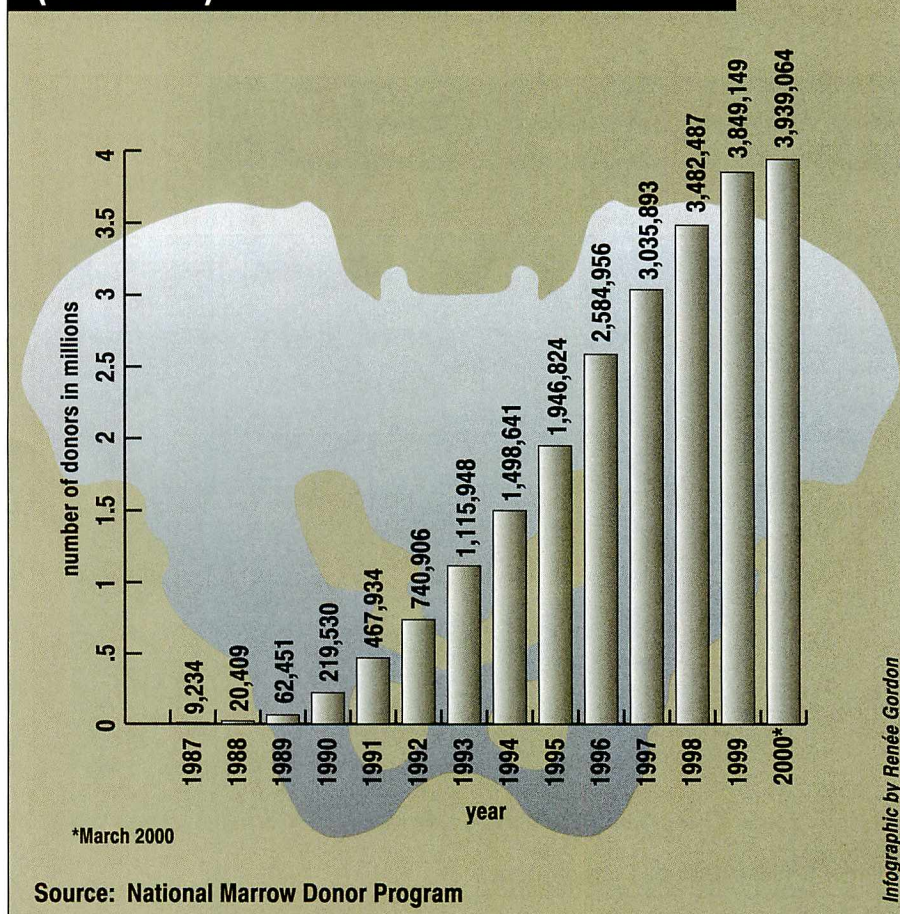
Diseases of blood-making cells in the marrow are hard to cure because tradi-

tional treatment—chemotherapy or radiation—destroys not only abnormal cells, but also normal cells. A bone marrow transplant allows doctors to treat patients with high-dose therapy—effectively killing all the cells in the bone marrow—and then replace the damaged marrow with healthy marrow. Craig Mullen, M.D., a member of the pediatric bone marrow team at the University of Texas M. D. Anderson Cancer Center, likens the situation to having a weed in your garden. "You have to kill it, but in doing so, you'll kill the other plants around it," he says. "The only way to get a new garden is to plant new seeds and repopulate it."

In earlier years, transplants were more commonly performed in the late stages of disease. But the 1970s marked a shift toward performing transplants during remission from disease, a change that improved patient outcomes.

Doctors have also used bone marrow transplants in experimental treatments of patients with solid tumor cancers (breast and testicular, for example) that require aggressive treatment with high doses of toxic drugs. Transplants are used to try to "rescue" the patient from the high doses of chemotherapy needed to destroy the cancer, which also destroys the marrow. Werner Bezwoda, Ph.D., a South African researcher, gave the

Donors in the National Marrow Donor Program (1987-2000*)



Unlike heart or lung transplants, bone marrow transplants don't involve surgery.

scientific community and cancer patients hope for this experimental procedure through his studies of breast cancer patients. Dating back to 1990, the studies showed an overall survival advantage for high-dose chemotherapy and transplant in women with breast cancer and stimulated a wide acceptance of this treatment. But in February of this year, Bezwoda's work was discredited after an external audit and his own admission to falsifying data. Many scientists, however, think the procedure may still have merit. "You can't rule the treatment out just because we didn't find evidence of it working in limited trials," says Grant Williams, M.D., an oncologist in FDA's Center for Drug Evaluation and Research. "We need further data before we can know whether it works or not."

Two Types of Transplants

Transplants usually are categorized as

allogeneic or autologous. Allogeneic transplants use bone marrow cells from another person who is genetically similar. The transplant is called syngeneic if the donor is an identical twin, which makes for a perfect match. Autologous transplants, the most common type, use the patient's own cells, which are removed, frozen, and reinjected later. In 1998, there were approximately 37,000 autologous bone marrow transplants and 17,000 allogeneic transplants worldwide, according to the International Bone Marrow Transplant Registry.

FDA reviews devices used in the collection, processing, purging and storage of stem cell products. In July 1999, FDA approved two cell separation devices that can select stem cells and decrease the number of cancerous cells that may be inadvertently re-infused into a transplanted recipient. "With autologous transplants (in which a patient uses his

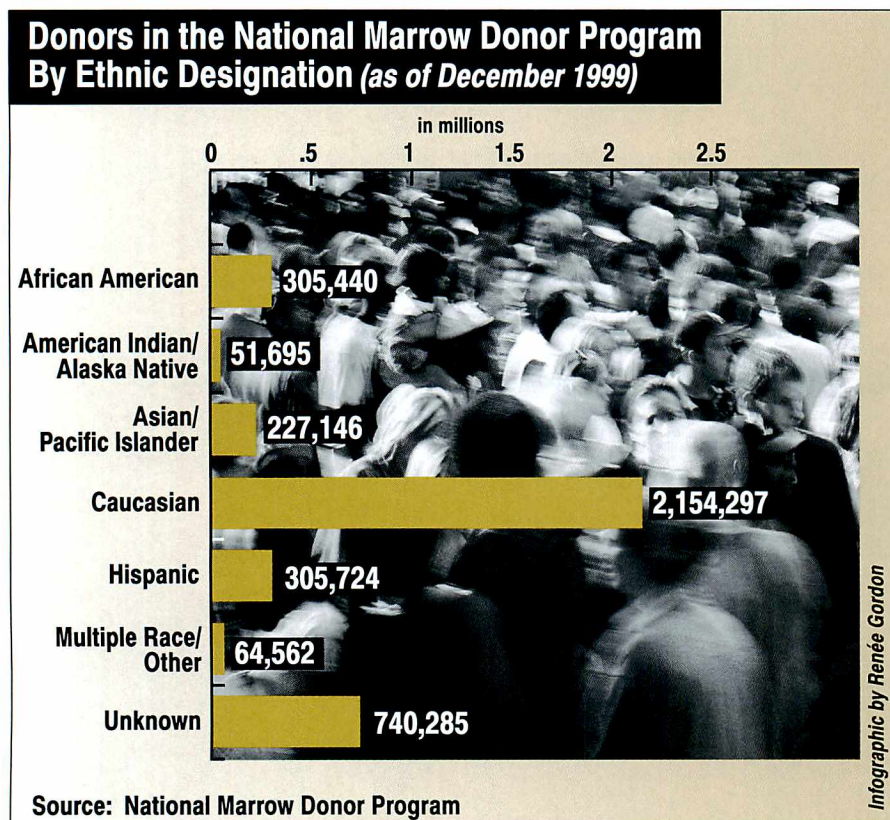
For More Information

National Marrow Donor Program
3433 Broadway St., N.E., Suite 500
Minneapolis, MN 55413-1762
1-800-MARROW2 (1-800-627-7692)
www.marrow.org

International Bone Marrow
Transplant Registry
Medical College of Wisconsin
PO Box 26509
Milwaukee, WI 53226
414-456-8325
www.ibmtr.org

The American Bone Marrow
Donor Registry
Information for donors:
American Bone Marrow Donor Registry
Headquarters
PO Box 8841
Mandeville, LA 70470-8841
1-800-745-2452
www.abmdr.org

Information for patients:
Caitlin Raymond International Registry
University of Massachusetts Medical
Center
55 Lake Ave., N.
Worcester, MA 01655
1-800-726-2824
www.crir.org



Although the first successful bone marrow transplant didn't take place until 1968, the discovery of human leukocyte antigens (HLA) in 1958 was a major breakthrough because it allowed recipients to be matched with donors.

Becoming a Donor

Mary Halet of Minneapolis, Minn., says that being a bone marrow donor was one of the most important events in her life. After giving bone marrow in 1993, she arranged for a donor center coordinator to pass along an anonymous note to the recipient. "I wished her well and told her that this is a small part of me that I hope can be a big help to her," Halet says.

Unlike heart or lung transplants, bone marrow transplants don't involve surgery. Doctors remove marrow with a needle that is inserted into the hip bones in the pelvis, the most marrow-rich site in the body. The sternum, the bone in the middle of the chest, is another possible site. Marrow is then delivered intravenously to the recipient like a blood transfusion.

The removal of marrow for transplant is usually an outpatient procedure that takes about an hour and is performed under general or regional anesthesia. "It's important for donors to know and understand the risks," Halet says, "but many safety precautions are taken." Donors may experience back discomfort for three to five days. "I had the procedure on a Friday, and I was out riding my bike on Monday," Halet says. "If the goal is to help someone have a chance at life, then I can endure a few days of discomfort." Lost bone marrow replenishes itself in a few weeks.

In accordance with confidentiality rules, Halet only knew that her recipient was a 23-year-old female with chronic myelogenous leukemia. "Even though we never met, I have a kindred connection with her," says Halet, a former bone marrow researcher who now works as a search coordinator for the National Marrow Donor Program. Her recipient died 11 months after the transplant, and Halet still keeps in touch with her family. One year after a transplant is performed, donor and recipient families are allowed to meet. ■

—M.M.

or her own stem cells), there may be tumor cells circulating in the bone marrow or blood that we don't want to give back," explains Stephen Litwin, M.D., a medical officer in FDA's Center for Biologics Evaluation and Research. Cell separation devices allow doctors to separate healthy stem cells from tumor cells. Litwin notes that the long-term

benefits of this tumor "purging" have not been proven in clinical trials.

The Transplant Process

"One misconception about bone marrow transplants is that the bone marrow is the only important part of this process," says Richard Jones, M.D., director of the bone marrow transplant unit at

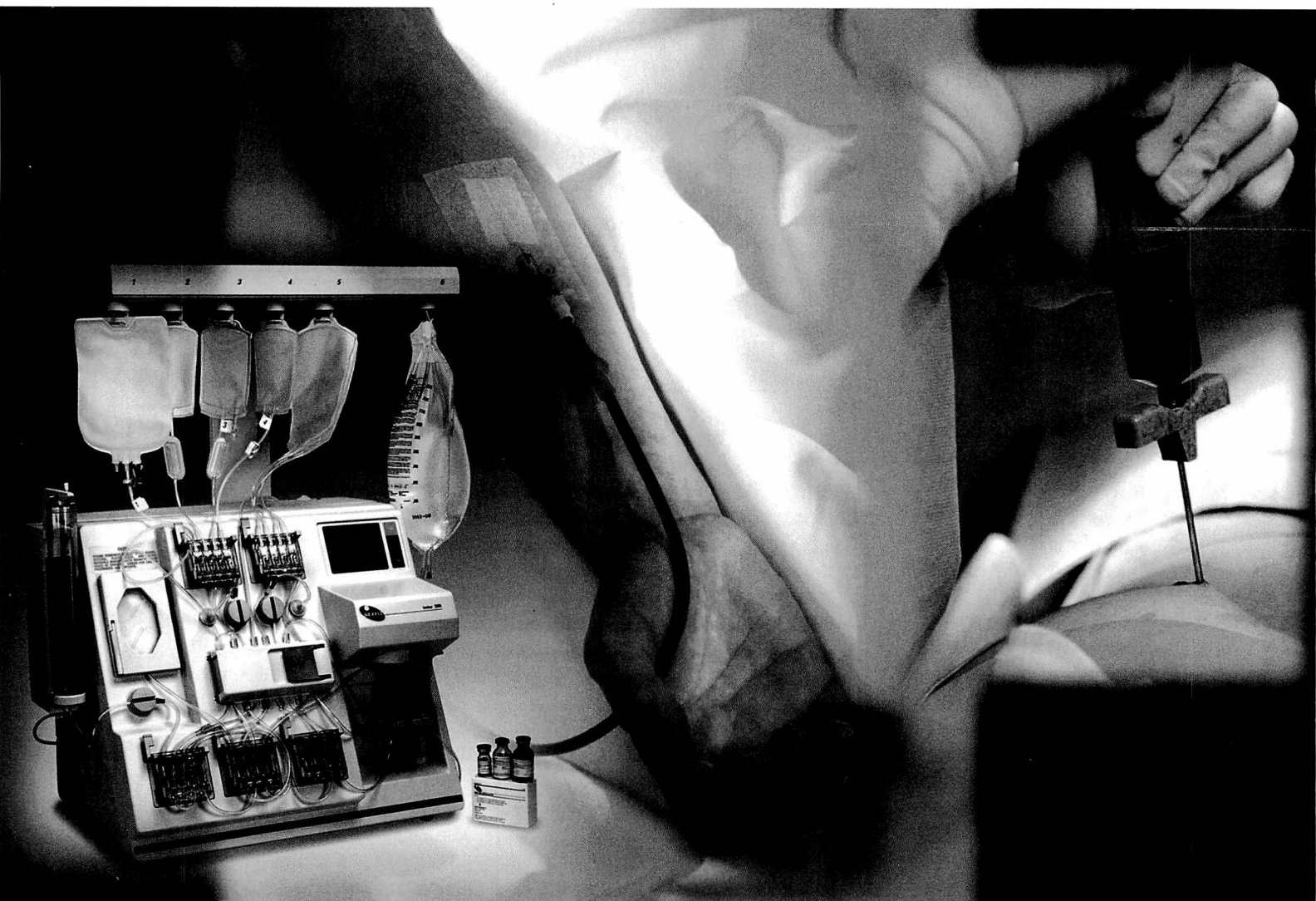
The Johns Hopkins Oncology Center. Bone marrow is certainly important, Jones says, but so is the chemotherapy or radiation treatment that precedes a transplant. "In many cases, the preparative therapy is the most important part" of the overall treatment. Therapy destroys cancer cells and defective marrow and makes room for new marrow.

This preparative regimen can be either high-dose chemotherapy or high-dose chemotherapy combined with total body irradiation, an x-ray procedure that exposes the whole body to radiation and penetrates all the body's cells. "The chemotherapy is about 10 times higher than doctors normally would give," Jones says. The anti-cancer drugs used for chemotherapy depend on the protocol of the treatment center and the type and stage of disease, but busulfan and cyclophosphamide are the most common. In February 1999, FDA approved an injectable form of busulfan. Previously used only in pill form, it's meant for use with cyclophosphamide as a conditioning procedure before allogeneic bone marrow transplants for CML.

Because side effects include severe nausea and vomiting, M. D. Anderson's Mullen says some researchers are rethinking the basic approach to transplants as it was laid out 30 years ago. "That approach was: Let's put together as toxic a drug regimen as we can and hope that the patient will survive," Mullen says. "Now some are asking whether such toxic doses are really necessary." He adds that some transplants in the adult program at the Anderson Center have been effective with lower doses of chemotherapy than were previously thought necessary. But the level needed depends on the stage and nature of the patient's disease.

Post-Transplant Recovery

After the transplant, it takes two to four weeks for engraftment—the process by which the new stem cells find their way to the bone marrow space and begin producing blood cells. Because the preparative regimen wipes out the patient's immune system, warding off infections during the recovery period is critical. Patty Clark, 41, of Baltimore, says her father served as a lymphocyte donor during her transplant. That means he



gave her white blood cells to bolster her immune system, a common way to boost immunity. Her father's donated white blood cells helped protect her against infections while the new bone marrow took root and began producing its own white blood cells. Other precautions include practices such as having visitors wear a mask and gloves to protect patients from infection. Clark received an autologous transplant in spring 1999 as part of ovarian cancer treatment.

Other potential complications include organ damage from chemotherapy, bleeding problems, and two types of rejection related to the bone marrow transplant. "You're not only replacing the organ, but you're also bringing a whole new immune system with it," explains Dennis Confer, M.D., chief medical officer at the National Marrow Donor Program. One type of rejection occurs when the residual immune system of the person receiving the transplant rejects the

donated marrow; a second, scarier form of rejection occurs when the donor marrow rejects the body of the patient, in what's known as Graft Versus Host Disease (GVHD). According to Confer, if the recipient rejects the marrow, blood counts will stay low. In GVHD, immune cells in the new marrow recognize the recipient as foreign and attack tissues in the body. Blood counts will come up, but the patient will experience symptoms such as a loss of appetite and energy, diarrhea, and a skin rash. If uncontrolled, GVHD will be fatal.

The immunosuppressive drug cyclosporine plays a major role in the success of an allogeneic transplant because it can help prevent GVHD and interstitial pneumonia, a lung infection caused by cytomegalovirus. "If you've had this virus and you undergo a marrow transplant, there's a high chance that it will reactivate," Confer says. Sometimes doctors also give patients growth factors,

Gathering bone marrow stem cells has become a much simpler process with the development of technologies used in the Isolex 300i Magnetic Cell Selection System. The machine (left) separates bone marrow stem cells from other cells circulating in the bloodstream. Blood is removed, as in a blood donation, passed through the machine so the stem cells can be collected, and then returned to the individual. Doctors return the stem cells to the bone marrow transplant recipient as a simple transfusion. Previously, the only way to get stem cells was for surgeons to suck bone marrow out of the hip bones using a large syringe (right) that they punch through the skin and the bone to reach the marrow.

*Left photo (Isolex) by Nexell Therapeutics Inc.
Right photo by Corbis/Leif Skoogfors*

A bone marrow transplant allows doctors to treat patients with high-dose therapy—effectively killing all the cells in the bone marrow—and then replace the damaged marrow with healthy marrow.

genetically engineered substances that stimulate a faster return of white cells. Examples are granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF).

As for success rates of bone marrow transplants, experts generally agree there is no clear-cut answer. These rates depend on many factors, including the type and stage of disease, the condition of the patient at the time of the transplant, the donor, and the age of the patient. Success can range from 80 to 90 percent for children with inherited abnormalities of the immune system to as low as 10 percent for patients with aggressive, resistant diseases.

Alternative Sources of Stem Cells

Researchers realized in the late 1980s that stem cells are not only found in bone marrow, but also in the bloodstream. When stem cells are collected from the bloodstream, they are called peripheral blood stem cells. “The challenge is that stem cells don’t generally circulate in large numbers in the peripheral blood,” FDA’s Litwin says. Growth factors—also known as mobilizing agents—are given to stimulate the bone marrow to produce more cells, which are then released into the bloodstream. To collect these cells, blood is circulated through a cell separator that removes peripheral stem cells and returns the rest of the blood—including hemoglobin-containing red cells—to the body. The process is called apheresis.

FDA and the National Marrow Donor Program are studying peripheral blood stem cells as an alternative to bone marrow for initial transplants. This procedure has been most widely used as a follow-up transplant to supplement the marrow transplant, Confer says. The research aims to document the safety of this collection method and compare how donors view bone marrow transplants vs. peripheral stem cell transplants. “As we

learn more,” Confer says, “I anticipate we’ll find out that there are some diseases for which peripheral blood is superior and others for which bone marrow is superior.”

In the last decade, doctors have also used stem cells collected from umbilical cord blood for bone marrow transplants. This new field is expected to widen the donor pool, but it is still considered experimental. One limitation is that the number of stem cells found in cord blood is small because babies are small. “As a result, engraftment is slower than if you obtain stem cells from the bone marrow or the peripheral blood,” Litwin says. Again, growth factors can help increase the number of cells. Under another FDA-sponsored study, the National Marrow Donor Program has invited cord blood banks to apply for membership to its registry. The program receives federal funding from the Health Resources and Services Administration to manage the registry.

FDA and the National Heart, Lung, and Blood Institute, part of the National Institutes of Health, have co-sponsored a series of workshops on stem cells over the past several years. With the discovery of alternative sources, FDA proposed in 1997 to regulate stem cells collected from peripheral and umbilical cord blood. The proposed approach centers on preventing the transmission of communicable diseases and assuring that stem cell procedures are safe and effective. FDA continues to work on developing the best methods and practices to prevent contamination of tissue and preserve stem cell integrity.

The newest alternative source of stem cells involves taking existing cells—from either the bone marrow, peripheral blood, or cord blood—and expanding them in a lab. This procedure is already being used but is highly experimental and challenging. “So far, it’s been easier to get stem cells to mature than to self-replicate,” Confer says, “but the potential is

tremendous. We want to be able to turn a million stem cells into 10 million.”

Increasing the Donor Pool

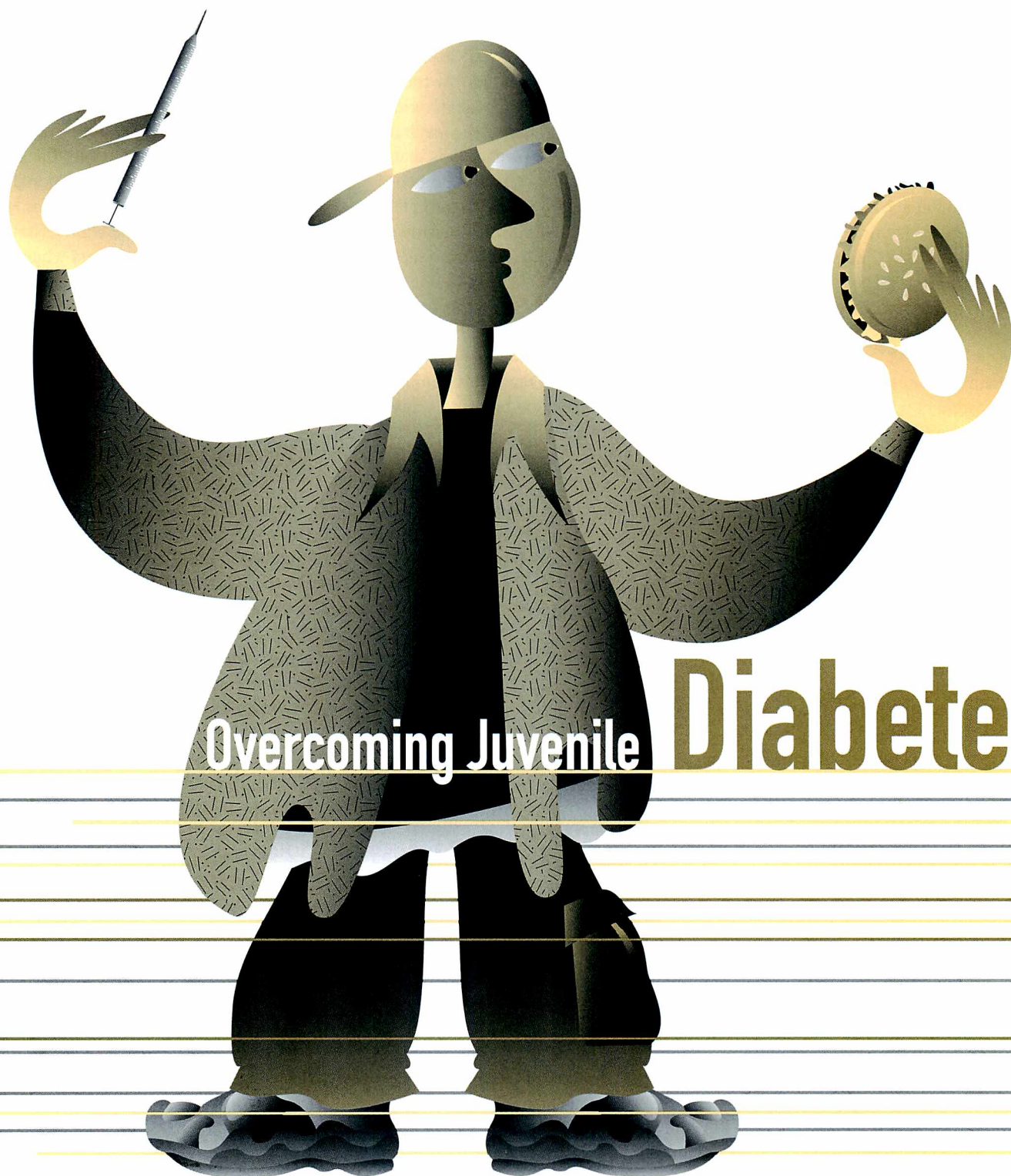
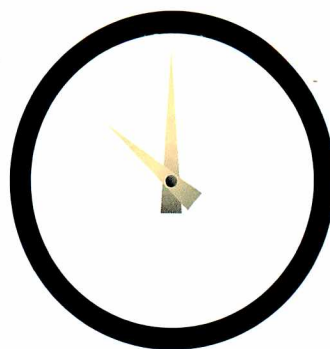
About 30 percent of people who need a transplant have siblings who, because they are a tissue match, are suitable donors. But many people must look to registries of unrelated donors in order to survive. Increasing the donor pool has been a key part of advancing the search process, Confer says. The National Marrow Donor Program, which helps locate unrelated donors in the United States, had 8,000 registered donors when the program began in 1987. Now the registry is up to about 4 million.

Global cooperation has also been key, giving patients access to donors wherever they reside. “No one could have guessed 10 years ago that there would be 6 million international donors today,” Confer says.

Donor shortages, however, do exist in racial and ethnic minority populations, including African Americans, Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives. “It’s not that an African American has to have an African American donor,” Confer says, “but the best chance [for a match] would be within your group.” The National Marrow Donor Program continues to conduct outreach and recruitment strategies for these populations. The program receives funds from the U.S. Navy for advancing the science of human leukocyte antigens and increasing diversity of the donor pool.

The National Marrow Donor Program is looking at ways to make the search for donors faster and more efficient. A search takes 100 days on average, but it can be as short as 20 to 30 days or as long as years, Confer points out. “But too many people have diseases that just won’t stand for a long search.” ■

Michelle Meadows is a writer in Laurel, Md.



Overcoming Juvenile **Diabetes**

By Damian McNamara

The challenges of being a teen with Type 1 diabetes are many. Forget the junk food at the mall or pigging out at a party. You can't sleep late, because your blood sugar (glucose) levels can drop dangerously during an extended snooze. It can be tough to find a safe and private place to monitor your glucose levels and inject yourself with insulin while at school.

It is possible, however, to stay on top of the condition and still do most things a typical teenager does. But "don't disregard it," advises Ryan Dinkgrave, a 16-year-old Michigan high school student with Type 1 diabetes. "Control the diabetes; don't let it control you."

Sticking to your doctor's recommendations is essential to leading a healthy life, says Robert Goldstein, M.D., vice president of research for the Juvenile Diabetes Foundation. "If you go by the book, you will handle it extremely well."

A Diabetes Diagnosis

Most people are first diagnosed with Type 1, or juvenile, diabetes during the teen years. Although this is a time when fitting in with your friends can be important, "don't think you're different because of it," Ryan says. More than 400,000 new cases are reported in children and adults up to age 24 in the United States each year. And more than 1 million Americans currently live with the condition.

There is much to learn after a diabetes diagnosis, particularly how important it is to take insulin regularly, eat a

With A Little Planning And High-Tech Tools

More than 400,000 new juvenile diabetes cases are reported in children and adults up to age 24 in the United States each year.

proper diet, and monitor blood sugar levels. Failure to keep what doctors call “tight control” over the disease can be very serious. This means being more responsible for your well-being than most teenagers.

“For teens newly diagnosed with Type 1, I tell them that there is good news and bad news,” Goldstein says. “The bad news is that, yes, you have this disease. The good news is that we know an extraordinary amount about it.”

“It was a real shock, because I knew nothing about diabetes,” says Ryan, recalling his diagnosis at age 10. “It was a lot to take in—they hit me with a lot of information.” At the University of Michigan, where Ryan goes for medical care, doctors now give most information to patients on a follow-up visit, not at the time of diagnosis.

The diet for teenagers with Type 1 diabetes resembles what health experts consider a healthy diet for anyone. Goldstein points out that many teenage Americans don’t watch their diets closely or live a healthy lifestyle. So those with diabetes tend to be more aware of nutritional requirements than other teens. “There is a big trend in this country to eat right and exercise, but it’s not something that catches on in general until you’re in your 30s,” Goldstein says.

The Importance of Insulin

Medical experts say Type 1 diabetes develops when the immune system turns against the body, or, more specifically, against the cells in the pancreas—called islet cells—that produce insulin.

Insulin is a hormone that helps break down glucose in the blood. Children and teens with diabetes typically monitor their blood levels and inject insulin three times a day, and some may need to do it as many as five times a day. Although insulin from outside sources—animals or genetically engineered

cells—does not cure diabetes, it can help people avoid some serious consequences of the condition, including blindness, heart attacks, seizures, strokes, limb amputations, and kidney failure.

A major drawback to injecting insulin is that glucose levels can “swing”—up high right after an injection, down low before the next. And injections have to be timed with meals. Ryan says he considers keeping up the blood testing and shots to be very important. Other teens with diabetes “might forget how serious it is because the day-to-day insulin shots become so routine. I’ve had three seizures from low blood sugar,” he says.

“It’s hard to improve on insulin,” says Robert Misbin, M.D., a medical officer in the Food and Drug Administration’s division of metabolic and endocrine drug products. “It’s a very powerful drug. The problem is that many injections a day are required. What would be better is an infusion that could be regulated to match food intake.”

The emphasis in Type 1 diabetes research is to find a more convenient and effective way to administer insulin. One way to do this is with the insulin pump, approved by FDA in the early 1990s. The pump, which contains 6 to 8 ounces of insulin, delivers it through a tiny needle stuck under the skin on the left side of the abdomen. The bloodstream absorbs a small, continuous dose of insulin throughout the day. A hand-held telemetry unit, similar to a TV remote, is used to signal the pump to give a little extra insulin, if needed. A different kind of pump that is implanted in the body is being tested in clinical trials now.

To help maintain tighter control on his insulin levels, Ryan switched to an insulin pump in 1998. When doctors first told Ryan about the pump, he was reluctant to try it. But when he learned that he would have to add another insulin injection to his daily routine—for a total of four—he decided to give it a try. “It

Juvenile diabetes patient Ryan Dinkgrave, 16, prepares a spring-loaded insertion device that will inject a tiny catheter into his abdomen. The catheter delivers measured doses of insulin to his bloodstream throughout the day from an exterior pump that is worn like a pager. Patients typically move the catheter to a new location in the abdomen every two to three days to avoid infection and buildup of scar tissue. This insulin delivery system, approved since the early 1990s, has given diabetic patients increased flexibility and freedom from insulin injections.



PHOTOGRAPH BY SANTA FABIO / BLACK STAR INC.



grants you a whole new freedom,” Ryan says. “You can eat whatever you want. With injections, you have to plan ahead.” He added that with more freedom comes more responsibility, such as calibrating and refilling the unit, but “it’s definitely worth it.”

Before Ryan switched to an insulin pump, like many teens with diabetes, he had to find a safe and private place at school to measure his blood sugar and inject insulin. “It was an issue with the school for me,” he explained. “Where I would do it became the issue. They set me up in a staff bathroom with a locked cabinet in it, but it was broken into. It was a struggle for a while.”

Ryan says some people at his school were reluctant to help him with his injections for fear that they would be sued if something went wrong. “People especially don’t want to give you an injection of glucagon when you pass out from low blood sugar. [Emergency Medical Services] just started doing it in my area.” Glucagon is a hormone that raises the level of sugar in the blood.

Most diabetics still use a needle and syringe to inject insulin. Also available are insulin pen injectors, which resemble a ball point pen. Researchers are studying inhaled insulin, which could be taken using a device similar to an asthma inhaler. One drawback to this approach is that it still requires many doses per day.

Other researchers are investigating a patch that would deliver insulin through the skin. One hurdle that remains is that insulin does not cross through the skin as easily as other molecules, for example, the nicotine in the patch that smokers wear when they want to quit using tobacco products.

In June 1999, FDA approved the first device to continuously monitor tissue glucose levels. The device has a tiny needle that is inserted under the skin of the abdomen and connected to a unit about the size of a pager that records the numbers. Although the device takes readings every five minutes for up to three days, it doesn’t replace the usual blood glucose readings, so people with diabetes still must perform daily finger sticks to check their blood glucose. The sensor provides trends rather than actual glucose levels, and the patient doesn’t

Type 1 diabetes develops when the immune system turns against the body, or, more specifically, against the cells in the pancreas—called islet cells—that produce insulin.

see the glucose information while wearing the device because it is not displayed on the device's monitor. The data are stored and transmitted to a computer to be evaluated only by a doctor. One reported drawback is that these devices have to be calibrated often to remain accurate.

Future Treatments

There are several promising pathways in diabetes research, says Goldstein. For example, some researchers are working on a vaccine for diabetes, which might someday prevent the disease in newborns much the same as shots for measles or hepatitis B.

"I would also like to find the cause, or trigger, that makes the immune system go haywire," Goldstein says. "Like other autoimmune diseases, there may be a genetic predisposition to getting diabetes, but the trigger is environmental, such as a virus." He added that there is a generation of drugs in development aimed at blocking such triggers.

Genetic engineering may be used someday to convert certain cells into islet cells—stem cells, for example, which the bone marrow uses to make blood cells. These specially designed cells would also resist rejection. Rejection is a concern in any patient because the body's immune system recognizes any transplanted cells as foreign and destroys them. In a person with diabetes, there is the added challenge of stopping the rejection of islet cells in the pancreas that caused the disease in the first place. In other words, before a diabetes patient's islet cells can be replaced, researchers want to make sure these cells won't be rejected a second time.

"The major change we've seen in the last 15 years or so is the ability to do home blood sugar monitoring. That has had a major impact," says Misbin. "The future will hopefully bring [new] ways of mea-

suring blood sugar levels noninvasively."

Making Progress

"Our greatest challenge is to find a way to make [juvenile diabetes] go away," says Goldstein. Ryan is optimistic about a cure being found soon. "I don't picture myself having a pump 10 to 20 years from now. We're at a point where I think all it will take is a little extra push to get a cure."

Ryan's positive outlook is due in part to attending the first-ever Juvenile Diabetes Foundation Children's Congress. The foundation's delegation of 100 children and teens with Type 1 diabetes from around the country appeared before legislators last year. Led by Juvenile Diabetes Foundation international chair Mary Tyler Moore, the delegates asked lawmakers to increase research spending for diabetes.

"It was interesting, too, to see how the government works when it comes to raising money for research," Ryan says. "I came back with a new motivation for working on [my] Website [for juvenile diabetes patients], and with a new sense of urgency for a cure."

"I've found that teenagers with diabetes are extraordinary," Goldstein says. "They become really, really smart—the implication being that they are role models to fellow teens who don't have diabetes, teaching them how to handle something like this." The added responsibility of sticking to a daily regimen of insulin injections, blood glucose monitoring and a healthy diet makes teens with Type 1 diabetes grow up faster than other teens, he adds.

"The everyday effort it takes is worth it," says Ryan. "You learn that you have to be prepared in case something happens. It makes you more mature, I think." ■

Damian McNamara is a writer in New York City.

For More Information

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301-654-3327
[www.niddk.nih.gov/health/diabetes/
ndic.htm](http://www.niddk.nih.gov/health/diabetes/ndic.htm)

American Diabetes Association
ATTN: Customer Service
1701 N. Beauregard St.
Alexandria, VA 22311
(Or write to your local affiliate)
1-800-DIABETES (1-800-342-2383)
For catalog of materials:
1-800-232-6733
www.diabetes.org

The Family's Guide to Diabetes
Ryan Dinkgrave, Webmaster
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By John Henkel

Drug Info at Your Fingertips

Easy-to-read information about more than 9,000 brand-name and generic drugs, both prescription and over-the-counter, is available on the National Library of Medicine's consumer Website, MEDLINEplus. Located at www.nlm.nih.gov/medlineplus/druginformation.html, the site gives information provided by the United States Pharmacopeia about side effects, dosing, drug interactions, precautions, and storage for each drug. Also included are links to information about newly approved drugs and drugs currently in clinical research studies. Consumers who want to delve deeper into a drug's background can search MEDLINE's huge database for research articles on specific drugs. The site also links to medical dictionaries, lists of doctors and hospitals, and "health topic" pages with background on diseases, fitness, and nutrition.

A Century of Health Improvements

Twenty-five years. That's how much was added to the life expectancy of people in this country during the 20th century. The last hundred years saw killer diseases wiped out and other deadly or debilitating disorders reduced to treatable conditions. Though the list of public health improvements between 1900 and 1999 is huge, there are standouts, according to the federal Centers for Disease Control and Prevention. On its Website at www.cdc.gov/od/oc/media/tengpha.htm, CDC has compiled a roster of the greatest 20th century health achievements. Included are immunizations, control of infectious diseases, safer foods, and declines in deaths from heart disease and stroke. Each item on the list is linked to an article that gives the historical perspective along with a view of where things stand now.

Some Mammography Basics

When being screened for breast cancer, how can a woman be sure that her mammogram is of high quality? Because federal law requires that all mammogram facilities meet quality standards, and FDA inspects these facilities regularly. The standards apply to the technician who takes the mammogram, the radiologist who interprets it, and the medical physicist who tests the equipment. An FDA Website dedicated to mammography has more information about the procedure, including a list of questions and answers to help women understand how mammography works. At www.fda.gov/cdrh/mammography, the site explains provisions of the Mammography Quality Standards Act of 1992, amended in 1998, including the requirement that mammography facilities must send a report in lay language that summarizes exam results to all patients within 30 days. Also found on the site are *Mammography Matters*, a quarterly newsletter published by FDA's Center for Devices and Radiological Health, and an article that explains improved breast cancer treatments. For more information about breast cancer prevention and treatments, go to the National Cancer Institute's Website at www.cancernet.nci.nih.gov/cancertypes.html.

Keeping Your Food Safe

You've likely heard the advice before about food safety: clean, cook, chill and separate. It's a blueprint for helping ensure that what you eat won't make you sick. Now you can learn more about these food safety measures and take a quiz to see how well you've absorbed the fine points. The Partnership for Food Safety Education, as part of its "Fight Bac!" campaign, has a Website that asks questions like "At what temperature should you set your refrigerator?" The site also has a special section on egg safety and a chart with safe cooking temperatures. To get up to speed on food safety, go to www.fightbac.org/tools/brochures. By the way, the answer to the refrigerator question is 40 degrees Fahrenheit.



How to Choose a Health-Care Plan

Savvy consumers try to seek out the best prices and quality for cars, houses, computers, and just about every other product or service. But when it comes to health-care, the process can be a bit more difficult than simply comparing car models. Like any commodity, health plans are not all created equal, and quality does vary. The Quality Inter-agency Coordination Task Force, a consortium of federal agencies involved with health-care, has created a Website at www.consumer.gov/qualityhealth/index.html to help consumers navigate through the sometimes tricky process of choosing a suitable health-care provider. First, it answers the question, "What is quality?" by showing scientific ways to measure health-care quality. Then the site explains choosing a health plan, buying smart, and patient rights. Also included is a special page devoted to ensuring personal privacy and the confidentiality of health information. More information on quality health-care also is available on the Department of Health and Human Services' "healthfinder" site at www.healthfinder.gov/smartchoices/qualitycare/default.htm.

John Henkel is a member of FDA's web management staff.

SUMMARIES OF COURT ACTIONS



Summaries of Court Actions are prepared by the Office of the Chief Counsel, Food and Drug Administration.

SEIZURE ACTIONS

Food/Contamination, Spoilage, Insanitary Handling

PRODUCT: Straw Mushrooms, 2,216 cases, more or less, at Jersey City, N.J. (D. N.J.); Civil Action No. 99-4012.

CHARGED 8-25-99: While held for sale after shipment in interstate commerce at Well Luck Co., Inc., in Jersey City, N.J., the article of food was misbranded in that its labeling was false and misleading because the invoice falsely represented that it had been packed by Kepper Food Processor Co.—403(a)(1). The article of food was adulterated in that it had been prepared and packed under conditions whereby it may have been rendered injurious to health because of inadequate processing—402(a)(4).

DISPOSITION: The article was destroyed. (F.D.C. No. 67274; S. No.122-0141337-9; S.J. No. 1)

Medical Devices

PRODUCT: Surgical steel instruments, 10 cases, more or less, at Alexandria, Va. (E.D. Va.); Civil Action No. 97-CV-2088.

CHARGED 12-30-97: While held for sale after shipment in interstate commerce at Matrix International Logistics, Inc., in Alexandria, Va., the articles of device were adulterated in that their quality fell below that which they were purported or were represented to possess because they contained rust, pits, and corrosion, and they lacked the ease of movement required by surgical steel instruments, which caused the instruments to fall below the quality expected of surgical steel instruments — 501(c). The articles of devices were misbranded in that their labeling was false and misleading since it stated that the devices were made in the United States and some of the devices had the word “Pakistan” etched into them—502(a).

DISPOSITION: The articles were destroyed. (F.D.C. No. 67213; S. No. 97-645-979; S.J. No. 2)

Drugs/Human Use

PRODUCT: Oxygen, U.S.P., at Nashville, Tenn. (M.D. Tenn.); Civil Action No. 3:98-1148.

CHARGED 12-11-98: While held for sale after shipment of one or more of their components in interstate commerce, the articles of drug were adulterated in that the methods used for their manufacture, processing, packing, and holding did not conform to and were not operated and administered in conformity with current good manufacturing practice to assure that such drugs met the safety requirements of the Food, Drug, and Cosmetic Act and had the identity and strength, and met the quality and purity characteristics which they purported, and were represented to possess—501(a)(2)(B). The high pressure cylinders were misbranded in that their label failed to bear an accurate statement of the quality of the contents; and the cryogenic home units’ labeling failed to bear, at a minimum, the

symbol “Rx only.”—502(b)(2) and 503(b)(4)(A).

DISPOSITION: The United States Marshals Service executed the Warrant for Arrest In Rem issued by the Court and seized the articles on December 22, 1998. During settlement negotiations, Medical Homecare Services, Inc.’s counsel informed the United States that Gayle Sensing had removed the “Restricted Area” tape and the USMS’ “No Trespassing” seal, taken the cylinders and vessels, vented the oxygen into the atmosphere, and sent the empty containers to another oxygen transfiller. Following an inspection at Medical Homecare Services by FDA investigators, the government filed a Motion for Show Cause Order, which the Court granted, and a hearing was held on the contempt issue on September 30, 1999. (F.D.C. No. 67252; S. No. 98-679-508; S.J. No. 3)

PRODUCT: Various Topical Products (Corticosteroids), at Miami, Fla. (S.D. Fla.); Civil Action No. 99-0912.

CHARGED 3-30-99: While held for sale after shipment in interstate commerce at Fontastic Products, Inc., in Miami, Fla., the articles were misbranded in that their labels failed to bear adequate directions for use and they were not exempt from such requirement under 21 C.F.R. Section 201.115, since the articles were unapproved new drugs—502(f)(1); and that they had not been duly listed as required by 21 U.S.C. Section 360(i)—502(o). The articles were further misbranded in that their labels failed to bear, at a minimum, the symbol “Rx Only.”—503(b)(4)(A).

DISPOSITION: Pursuant to a final default judgement entered on July 26 1999, the articles of drug were destroyed. (F.D.C. No. 67206; S. No. 41113; S.J. No. 4)

MISCELLANEOUS ACTIONS

ACTION: Mylan Pharmaceuticals, Inc. v. Shalala, at Washington, D.C. (D. D.C.); Civil Action No. 1:99CV02995.

CHARGED 11-10-99: This action challenged the Food and Drug Administration’s refusal to grant immediate approval of Mylan’s abbreviated new drug application No. 75-140 to market pharmaceutical products containing terazosin hydrochloride as generic versions of HYTRIN capsules, marketed by Abbott Laboratories, Inc.

DISPOSITION: On January 4, 2000, Judge Richard W. Roberts declared invalid 21 C.F.R. Section 314.107(e), an FDA regulation defining “court” in 21 U.S.C. Section 355(j)(5)(B)(iv) to the “the court that enters final judgement from which no appeal can be or has been taken.” At issue was what type of “court decision” could trigger the start of a 180-day period of exclusivity for the first generic drug applicant to assume the risk of patent litigation. FDA argued that the statutory reference to “court” was ambiguous so the agency had discretion to define the term as it did in its regulation. The Court disagreed, finding that FDA “confuse[d] generality for ambiguity” and promulgated an unduly narrow interpretation of a clear statutory term. Although the Court declared FDA’s regulation invalid, it refused to grant Mylan the relief it requested—immediate approval of its drug—because it found that Mylan’s competitor relied in good faith on the FDA regulation it thought to be valid. FDA has not determined whether it will recommend appeal of this decision. (Misc. 1235; S.J. No. 5)



Scheme To Sell Gas Grill Igniters For Pain Relief Backfires

By Tamar Nordenberg

A lucrative enterprise selling gas grill igniters as pain-relief devices went up in smoke recently when an appeals court ruled that two companies broke the law by marketing the devices without Food and Drug Administration approval.

In September 1999, the appellate court upheld a lower court's ruling that prohibited the two Akron, Ohio, companies, Universal Management Services Inc. and Natural Choice Inc., and their managers, Paul M. Monea and his son Paul A. Monea, from making or selling the "Stimulator" devices. The court also ordered the Moneas to offer full refunds to customers.

The companies made the Stimulators by simply outfitting gas grill igniters with finger grips. Users were instructed to apply the tip of the Stimulator to so-called accupressure points on the body and press on a plunger to send an electric current into the body. The companies also sold an accessory called the "Xtender" to help consumers reach otherwise hard-to-reach areas of the body, such as the spine.

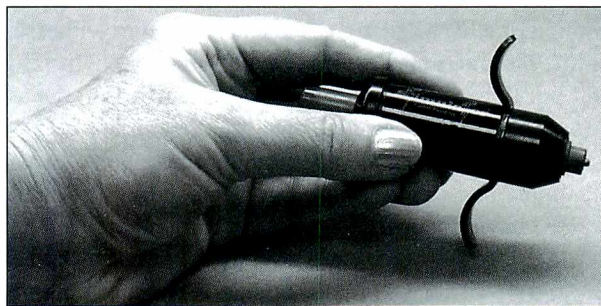
Advertisements for the Stimulator claimed that the device could relieve many kinds of pain, including migraine headaches, painful swollen joints, allergies, sciatica, and carpal tunnel syndrome. Starting in 1994, promotions for the product appeared in *USA Today*, *The New Yorker*, and other magazines and newspapers, as well as in national TV "infomercials" that featured celebrities such as daredevil Evel Knievel and actress Lee Merriweather.

According to court documents, between 1994 and 1997 the companies sold a total of 800,000 of the gas grill igniters—which cost them one dollar each—for about \$88 apiece. All told, the profits from the Stimulator sales exceeded \$65 million, according to an FDA estimate.

FDA's interest in the devices was sparked when complaints began coming in to the agency in 1994 from disappointed purchasers of the device. There were no reports of injuries more serious than simple stinging, says Lawrence E. Boyd, a compliance officer with FDA's Cincinnati district. But, Boyd says, "Some people did say the devices caused more pain than they solved. And, you could say the Stimulators were a pain to people's wallets. They were sold mostly to older people with aches and pains, those who could least afford to be targeted."

In May 1995, U.S. Marshals seized about 16,000 Stimulators, worth more than \$1.2 million, from the companies'

Akron offices. Even after the seizure, the Moneas continued to flout the law by selling the Stimulator and Xtender, Boyd says, which is why FDA went to court seeking an injunction against them and their companies.



The issue for FDA was not whether the devices worked, Boyd says, but more basically that the Stimulator hadn't been demonstrated to work, or even to be safe, and the companies didn't have the FDA approval needed to market it as a medical device.

In December 1997, the U.S. District Court for the Northern District of Ohio ordered a permanent

halt to the sale of the unapproved Stimulators and Xtenders, and told the companies to refund the purchase price to those who had bought the devices after the date of the May 1995 seizure.

The court rejected the sellers' claim that the Stimulator fell outside the definition of a medical device. Specifically, the court found that the device did not work primarily through chemical action, as the company argued, and that it was intended to affect the structure or function of the body, as evidenced by the pain-relief claim.

On Sept. 13 of last year, the Sixth Circuit U.S. Court of Appeals agreed with the lower court that the Stimulator and Xtender were medical devices being sold illegally and ruled that the companies could not resume making and selling the unapproved products. Also, the appellate court held, despite the companies' claim otherwise, that it was within the lower court's authority to order a refund of purchasers' money "to make the consumer whole."

In rejecting the companies' buyer-beware, "they-got-what-they-bargained-for" philosophy, the court said, "The approval process exists to protect consumers' health and their pocket-books ... To circumvent the law by marketing illegally without approval is to deceive the public both as purchasers and users of the device."

To FDA's knowledge, the Stimulator and Xtender are no longer on the market. The Moneas have asked the U.S. Supreme Court to revisit the issue of refunding customers' money and are awaiting the Court's decision on whether it will hear the case. ■

Tamar Nordenberg is a staff writer for FDA Consumer.

The Pill At 40

By Suzanne White Junod

In a century of astonishing scientific achievements, I imagine that the computer dominates the mind of most people in these (still) lucrative dot com days. And while there may have been impressive singular moments of technological triumph over the last 100 years, few have had as much impact on society as the development of a tiny tablet, the Pill.

This summer marks the 40th anniversary of the day the Food and Drug Administration approved, on June 23, 1960, the first oral contraceptive, Enovid by G.D. Searle. It may not have rocked the ground like the 1945 detonation of the first atomic bomb or energized an industry, like the first time current flowed through a transistor in 1947, but Enovid did more than just provide a technological tour de force. It transformed the very fabric of modern society.

Physiologically, the birth control pill simply prevents ovulation. Though an important scientific achievement, the real revolution began when millions of young women began to use it.

Searle's first marketing campaign showed its understanding of the Pill's revolutionary potential. One marketing logo featured the dramatic, colorful image of a sensuous Greek goddess freed from her bondage. This concept, however, proved too potent for the general public. Marketing for the Pill quickly switched to themes of domestic tranquility, portraying cozy couples, newly married and merely wishing to postpone their children.



Searle's original Pill icon

Sexual liberation did not appeal to the U.S. government, either. When the Eisenhower administration released a report suggesting that family planning be included in a European aid program, opposition by Catholic bishops killed the plan. The government thereafter said little about the Pill. It was treated as merely another drug, its approval deemed a medical decision best dealt with by the pharmacology experts. So it was sent to the bureaucratic hinterlands, to a smallish agency just refining its scientific foundation: The Food and Drug Administration.

The Pill presented FDA with several dilemmas. Commissioner George Larrick, the last agency commissioner to rise up through the ranks, worried about potentially medicating half the population for something that wasn't a disease. What would its side effects be in healthy women? Some experts

feared that it might cause cancers, which might not be seen for decades. This proved not to be the case, and, in fact, the Pill has proven to protect women from certain kinds of reproductive cancers. More significantly, however, some women developed severe blood clots while on the Pill and died. It took a decade to conclusively link the Pill with these adverse events, but early reductions in the drug's estrogen component substantially cut the risk.

Commissioner Larrick pondered the medical pros and cons, and according to witnesses, finally concluded that young couples might benefit from the ability to plan their families more carefully. But, the agency remained cautious. The Pill was the first and only drug approved with an imposed time limit. Women were not to be prescribed the Pill for more than two years until more data came in showing that it was safe to take it for longer periods. Many women, though, skated around the time limit by changing doctors and contraceptive brands. The restriction proved unenforceable.

Whatever its scientific issues, the Pill took the country by storm. Its extreme efficacy in preventing pregnancy opened up many new worlds. Young women with access to the Pill experimented with sex on college campuses. Mothers limited their families, both with and without their husbands' approval. Catholics in the United States, who were largely expected to reject the Pill, split with Rome over the issue.

A physician friend credits the Pill, in fact, with paving the way for many of the advances in late 20th century medicine. He vividly recalls that almost all of the physicians in the class ahead of him in medical school already had children by the time they graduated. They hurried into practice to support them. His class, however, was the first whose wives had access to the Pill, and virtually none of them had children at graduation. This allowed some to pursue advanced training and altered the very course of their careers.

New reproductive choices unleashed not only new professional energies, but new social energies as well. The women's movement and even the civil rights movement were fueled by some of these new energies.

But for many, the revolution was more personal, as country-western singer Loretta Lynn crooned in her musical tribute to the Pill:

*This incubator is overused because you kept it filled,
The feeling good comes easy now since I've got the Pill!
It's gettin' dark, it's roosting time,
tonight's too good to be real,
And Daddy, don't you worry none,
'cause Mama's got the Pill.*

Suzanne White Junod, Ph.D., is an FDA historian.

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