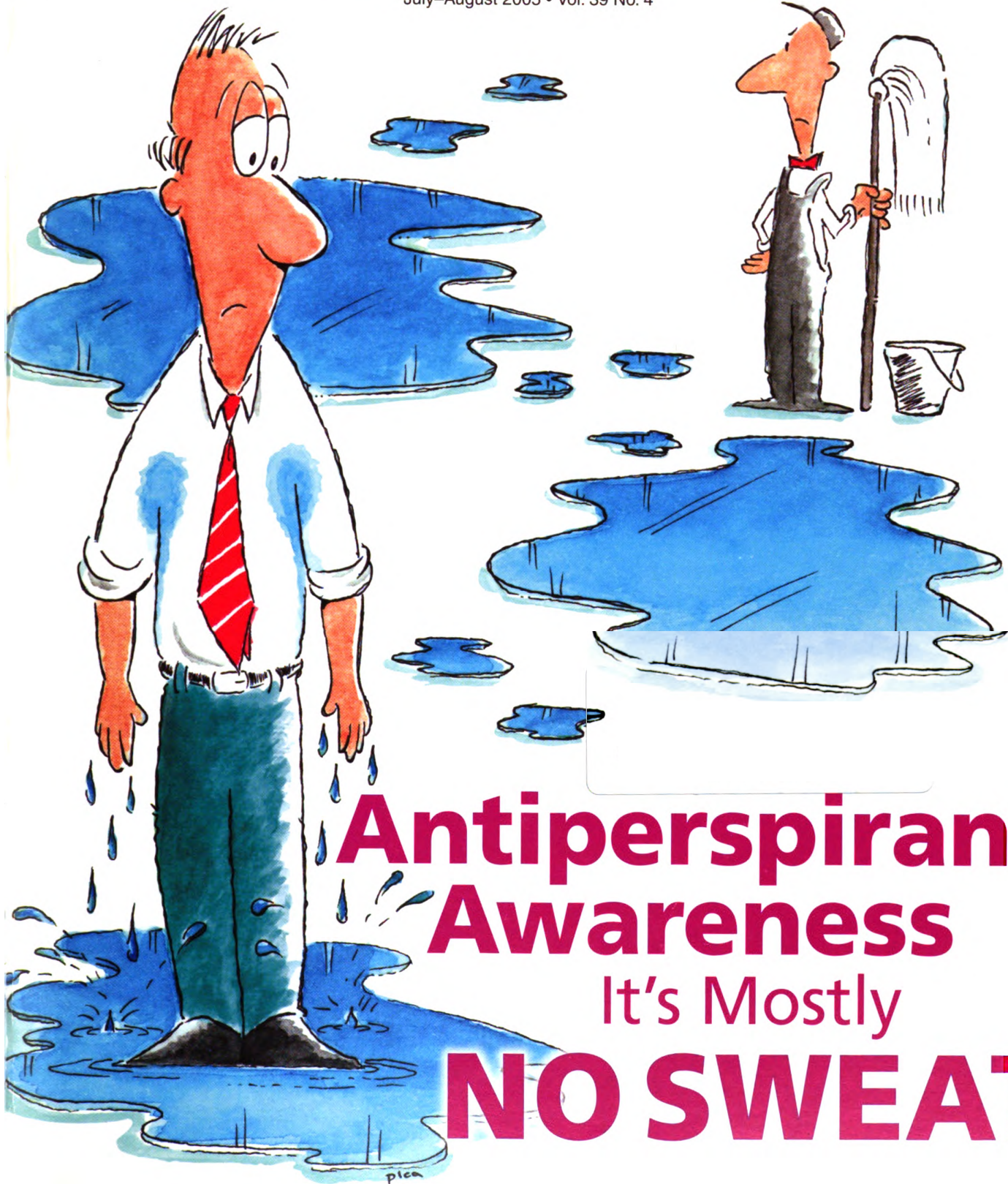


FDA Consumer

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

July–August 2005 • Vol. 39 No. 4



**Antiperspirant
Awareness**
It's Mostly
NO SWEAT



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FDA Consumer (ISSN 0362-1332) 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. Text of articles in *FDA Consumer* may be republished without permission. Credit to *FDA Consumer* as the source is appreciated. All photos, illustrations, and other graphic materials in *FDA Consumer* are covered under various copyright and usage restrictions. *FDA Consumer* is indexed in the *Reader's Guide to Periodical Literature*.

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U.S. Department Of Health And Human Services *FDA Consumer* The Magazine of the U.S. Food and Drug Administration

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◀ **Inside Cover:** The foul odor of a spraying skunk is not the only reason to keep your distance. About one-third of the animal rabies cases reported in the United States are in skunks. For more on this serious disease, see page 25.

OBSERVATIONS

The heat and humidity of July have many of us paying more attention to our underarms.

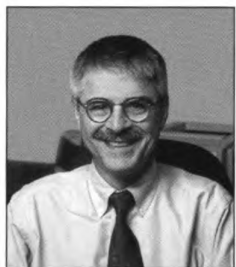
Concerns about body odor go back at least as far as ancient Arab and Roman civilizations, when frequent baths or sweet-smelling oils were used to keep offensive odors to a minimum. Today's higher-tech alternatives essentially use the tried-and-true fragrance method with the addition of agents that kill odor-causing bacteria that thrive in warm, moist areas such as the underarms.

Many deodorants and antiperspirants on the market keep odor to a minimum in much the same way. Antiperspirants, however, also contain aluminum salts that plug sweat glands to keep the areas on which they are applied comfortably dry.

The FDA regulates both deodorants and antiperspirants. Deodorants are considered cosmetics by the agency because they don't affect the body's structure or function. Antiperspirants are considered to be drugs because they affect the function of the body by reducing the amount of sweat that reaches the skin.

An antiperspirant that also is intended to be a deodorant must comply with the regulations covering both drugs and cosmetics. For more on how to keep your underarms dry and (nearly) odor-free, check out our cover story titled "Antiperspirant Awareness: It's Mostly No Sweat," beginning on page 18.

When it comes to men, women, and medicine, the differences are more than skin-deep. While many diseases affect both men and women, some may progress differently,



produce different symptoms, or respond differently to treatment, depending on the gender.

Ongoing research is looking into these differences and their potential causes, and FDA scientists are working to ensure that the drugs and medical devices regulated by the agency are safe and effective, regardless of the gender of the person being treated. For more on the differences between the genders when it comes to medical conditions and their treatments, see our feature article titled "Does Sex Make a Difference?" beginning on page 10.

In 1851, doctors came up with the name lupus erythematosus for a condition characterized by a facial rash. Lupus means "wolf" in Latin. Erythematosus means "redness." Those who came up with the name thought that the rash looked like the bite of a wolf.

Lupus is a disorder of the immune system known as autoimmune disease. In autoimmune diseases, the immune system turns against parts of the body it is designed to protect, leading to inflammation and damage to various body tissues. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, and brain.

At present, there is no cure for lupus. However, lupus can be effectively treated with drugs, and most people with the disease can lead active, healthy lives. For more on lupus, see our feature story titled "Battling Lupus," beginning on page 28.

We also take a look at how to protect yourself and your pet from rabies, at a new government program aimed at helping children develop healthy eating habits, and at the efforts to minimize the potential for confusion among drug names.

Raymond Formanek Jr.
Editor

UPDATES

First Whooping Cough Vaccine for Adolescents

In May 2005, the FDA approved the first vaccine for adolescents that provides a booster immunization against whooping cough (pertussis) in combination with tetanus and diphtheria.

Boostrix, a tetanus toxoid (T), reduced diphtheria toxoid (d), and acellular pertussis vaccine (ap) absorbed, will be marketed by GlaxoSmithKline of Philadelphia. Although booster vaccines for adolescents containing T and d are currently licensed and marketed for use in this age group, none contain a

pertussis component. Boostrix is indicated for use as a single booster dose to adolescents ages 10 to 18.

Adolescents who received Boostrix experienced pain, redness, and swelling at the injection site. The frequency of redness and swelling after Boostrix was similar to what is expected after the administration of a Td vaccine. Pain reactions at the injection site, however, were more frequent with those who received Boostrix. Other side effects included headaches, fever, and fatigue for a short period of time after injection.

New Warning on Antipsychotic Drugs Used to Treat Older People

The FDA has issued a public health advisory on the unapproved use of several antipsychotic drugs to treat behavioral disorders in older people.

The drugs, which include Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Risperdal (risperidone), Clozaril (clozapine), and Geodon (ziprasidone), are approved only for the treatment of schizophrenia and mania. Clinical studies of these drugs to treat behavioral disorders in older patients with dementia have

shown a higher death rate associated with their use, compared with patients receiving an inactive substance (placebo), according to the FDA.

The April 2005 advisory also applies to such antipsychotic drugs as Symbyax (olanzapine and fluoxetine HCl), which is approved for treatment of depressive episodes associated with bipolar disorder.

The FDA is requesting that the manufacturers of the drugs add a boxed warning to their drug labeling describing this risk, and noting that the drugs are not approved for the treatment of behavioral symptoms in older people with dementia. Older people receiving these drugs for this particular treatment should have their treatment reviewed by their health care providers.

The agency also is considering a warning for the labeling of older antipsychotic medications because limited data also suggest a similar increase in the risk of death for these drugs. The review of the data on the older antipsychotic drugs is ongoing.

Visit www.fda.gov/cder/drug/advisory/antipsychotics.htm for additional information concerning the advisory.

New Drug Extends Lives of Brain Cancer Patients

The FDA has granted approval of a new indication for Temodar (temozolomide), a drug already being used concurrently with radiotherapy and as maintenance therapy after radiotherapy. Temodar now can extend the lives of adult patients newly diagnosed with the most common form of malignant brain cancer, glioblastoma multiforme (GBM).

The new approval of Temodar for GBM in March 2005 was based on data from a large controlled study in patients newly diagnosed with the often fatal disease. Temodar was previously granted accelerated approval—a regulatory mechanism that allows approval of certain drugs to treat serious or life-threatening illnesses—in 1999, for treating adult patients with

another form of brain tumor, anaplastic astrocytoma, who had relapsed after chemotherapy with two other cancer drugs.

Temodar is manufactured by the Schering-Plough Corp., Kenilworth, N.J.

Final Rule on Albuterol Inhalers

After December 31, 2008, albuterol metered-dose inhalers (MDIs) using chlorofluorocarbon (CFC) propellants must no longer be produced, marketed, or sold in the United States. By that date, sufficient supplies of approved, environmentally friendly albuterol inhalers will exist, according to a final rule published in the Federal Register in March 2005.

The production of ozone-depleting substances is being phased out under the terms of an international agreement called the Montreal Protocol on Substances that Deplete the Ozone Layer. Since most MDIs available in the United States contained ozone-depleting CFCs, many of them have been reformulated. Several non-CFC products are already approved and others are in development. The FDA has developed a regulatory strategy to ensure that consumers in the United States who rely on MDIs have continuing access to safe and effective treatment options.

The final rule published in March addresses only albuterol MDIs. It is important that patients who use albuterol MDIs talk with their doctors about the phaseout of CFC products to establish the timing and manner of their move to non-CFC inhalers.

The U.S. Department of Health and Human Services sought and received public comment on a proposed rule in June 2004. This public comment, feedback from a Pulmonary-Allergy Drugs Advisory Committee meeting, and consultation with other federal agencies helped the FDA develop the final rule.

Visit www.fda.gov/cder/mdi/default.htm for more information.

New Treatment for Chronic Hepatitis B

Baraclude (entecavir) tablets and oral solution have been approved to treat chronic hepatitis B in adults.

Chronic hepatitis B is a serious disease caused by the hepatitis B virus (HBV) that attacks the liver. The virus can cause lifelong infection, scarring of the liver, liver cancer, liver failure, and death. According to the Centers for Disease Control and Prevention, about 1.25 million Americans are chronically infected with the HBV virus.

Baraclude slows the progression of chronic hepatitis B by interfering with the reproduction of the virus. The FDA based its approval on the results of three studies in which Baraclude



CDC

was compared to another antiviral drug, lamivudine. In all three studies, people treated with Baraclude showed significant improvement in the liver inflammation caused by HBV and an improvement in the degree of liver scarring. In addition, more people treated with Baraclude showed significant improvement than those treated with lamivudine.

The major side effects of Baraclude in the studies were of the type typically seen with HBV treatments. They include headache, abdominal pain, diarrhea, fatigue, dizziness, and a severe, brief worsening of hepatitis B after discontinuation of Baraclude.

Baraclude's sponsor, Bristol-Myers Squibb Co. of Wallingford, Conn., has committed to conducting a large post-marketing study of the drug to evaluate the risks of cancers and liver-related complications.

First DNA-Based Test to Detect Cystic Fibrosis

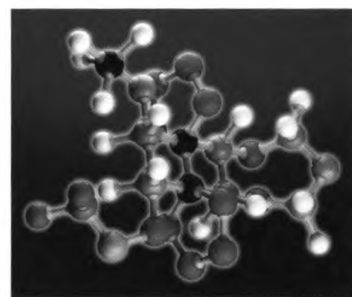
The FDA has approved the first DNA-based blood test to help detect cystic fibrosis. The Tag-It Cystic Fibrosis Kit analyzes human DNA to find genetic variations that may indicate the disease. The test will be used to help diagnose cystic fibrosis in children and to identify adults who are carriers of the gene variations.

Cystic fibrosis is a serious genetic disorder affecting the lungs and other organs. It is the number one cause of chronic lung disease in children and young adults. It is also the most common fatal hereditary disorder affecting Caucasians in the United States; it affects about 1 in 2,500 to 3,300 Cau-

casian babies. Half of the people with cystic fibrosis die by age 30.

The Tag-It test identifies a group of variations in a gene called the cystic fibrosis transmembrane conductance regulator, or CFTR gene, which causes cystic fibrosis. The FDA approved Tag-It based on a manufacturer study of hundreds of DNA samples showing that the test identifies the CFTR gene variations with a high degree of certainty.

Since Tag-It detects a limited number of the more than 1,300 genetic variations identified in the CFTR gene, the test should not be used alone to diagnose cystic fibrosis. Physicians should interpret test results in the context of a patient's clinical condition, ethnicity,



Artville

and family history. Also, patients may need genetic counseling to help them understand their test results.

The Tag-It Cystic Fibrosis Kit is manufactured by Tm Bioscience Corp. in Toronto.

Personalized Medicine

As part of an initiative to speed the development of new products through the science of pharmacogenomics, the FDA has issued a final guidance for industry titled *Pharmacogenomic Data Submissions*.

Through pharmacogenomics, health care providers can evaluate an individual's genetic profile and predict the best possible drug therapy and dose. For example, genomic tests are helping to identify cancers that have a good chance of responding to a particular medication or regimen. This technology has enabled the development of targeted therapies like Herceptin for metastatic breast cancer, Gleevec for chronic myeloid leukemia, and Erbitux for metastatic colorectal cancer.

"FDA's efforts will bring us one step closer to 'personalizing' medical treatment," says Janet Woodcock, M.D., acting deputy commissioner for operations at the FDA. "This new technology will allow medicines to be uniquely crafted to maximize their therapeutic benefits and minimize their potential risks for each patient."

The FDA also recently approved the AmpliChip Cytochrome P450 Genotyping Test. It's the first laboratory test that allows physicians to use genetic information to select the right doses of certain medications for cardiac treatment, psychiatric diseases, and cancer.

Visit www.fda.gov/cder/genomics/default.htm for more information on pharmacogenomics.



PhotoDisc

HHS Buys Children's Version of Radiation Emergency Drug

The Department of Health and Human Services (HHS) is purchasing liquid potassium iodide (KI) for children to be used in the event of a release of radioactive iodine, a commonly produced material in commercial nuclear power facilities. The department has awarded a \$5.7 million contract to Fleming & Company Pharmaceuticals of Fenton, Mo., to manufacture and deliver 1.7 million children's doses of liquid KI. The supply is being purchased under the BioShield program.

The liquid KI formulation is the first to be developed specifically for children. Its black raspberry taste is designed to make it more palatable. Current adult dose tablets must be broken into pieces to get a child's dose.

The FDA has approved KI in tablet form as a nonprescription drug to block the thyroid gland from absorbing radioactive iodine. In January 2005, the FDA approved Fleming's product ThyroShield Potassium Iodide Oral Solution for children.

Because the thyroid gland rapidly absorbs any iodine in the body, people need to take KI soon after an incident that involves the release of radioactive

iodine. The KI saturates the thyroid gland with iodine, preventing the thyroid from absorbing more radioactive iodine. Children are the most susceptible to the dangerous effects of radioactive iodine.

Children's KI will be available to states that receive approval from the department for plans they develop to distribute the product in communities around commercial nuclear power plants.

Sealant After Brain Surgery

In April 2005, the FDA approved a new sealant to protect against leakage of cerebrospinal fluid (CSF) after brain surgery. Leakage of CSF can lead to serious complications such as severe headaches, infection, and meningitis.

The DuraSeal Dural Sealant System is used in surgery involving the dura mater, the tough, outermost, fibrous membrane that covers the brain and spinal cord and lines the inner surface of the skull. The sealant is applied over stitches to prevent CSF fluid from leaking out of the incision site.

Surgeons currently use other approaches to make sure the incision site doesn't leak. One approach involves sewing the stitches closer together in the tissues immediately overlying the surgical site. Some surgeons pack the area with other tissues from the patient, such as fat, muscle, or connective tissue.

DuraSeal, which was evaluated in 111 patients, consists of synthetic, absorbable sealant materials. "This product is unique because it is the first device specifically designed and studied to seal sutured dura mater incisions," says Daniel Schultz, director of the FDA's Center for Devices and Radiological Health.

The DuraSeal system is manufactured by Confluent Surgical Inc. in Waltham, Mass.

Counterfeit Drug Warning

The FDA warns that counterfeit versions of Lipitor, Viagra, and an unap-

proved product promoted as "generic Evista" are being sold to U.S. consumers at pharmacies in Mexican border towns. Consumers who have any of these counterfeit products should not use them and should contact their health care provider immediately.

Counterfeit versions of the cholesterol-lowering drug Lipitor; Viagra, a treatment for erectile dysfunction; and Evista, a treatment and prevention medication for osteoporosis in post-menopausal women, can pose significant risks. The counterfeit products were analyzed and found to contain no active ingredient.

Counterfeit Lipitor that contains no active ingredient could present a long-term risk for the various complications of high cholesterol, such as heart disease. Counterfeit Viagra that contains little or no active ingredient would be less effective, or altogether ineffective, compared with the legitimate product. Women who take the substandard "generic Evista" product that contains no active ingredient may be at risk for developing osteoporosis or for having their osteoporosis progress.

The "generic Evista" was purchased from Agua Prieta, Sonora, Mexico. It is labeled as "Raloxifeno, fenilox, 50 tabletas, 60 mg.," made or distributed by Litio and labeled as manufactured in Monterrey, Nuevo Leon, Mexico. The label has red triangles across the top and bottom. The counterfeit Lipitor and Viagra were purchased in Juarez, Los Algodones, Nogales, and Tijuana. The products were labeled only in English, whereas legitimate Mexican pharmaceuticals are usually labeled in Spanish. The counterfeit Lipitor was provided in round, white plastic bottles, but authentic Lipitor in Mexico is sold in boxes of blister packs.

The FDA warns consumers that prescription drugs purchased in foreign countries are not regulated by the FDA and do not carry the same FDA assurances of safety, effectiveness, and manufacturing quality as drugs purchased within the United States.

For more consumer information about counterfeit drugs, visit the following Web sites:

Counterfeit drug photographs: www.fda.gov/bbs/topics/news/photos/border.html

FDA consumer education for counterfeit medicine: www.fda.gov/cder/consumerinfo/counterfeit_text.htm

To report suspected counterfeit drugs: www.fda.gov/medwatch

New Oral Rinse Helps Treat Gingivitis

Decapinol Oral Rinse has been approved as a treatment for gingivitis, a common gum disease that affects most adults at some point in their lives. The prescription rinse treats gingivitis by reducing the number of bacteria that attach to tooth surfaces and cause dental plaque.

Gingivitis is an inflammation of the gums that often makes them swell, become red, or bleed. Scientists believe that gingivitis is caused by substances released by plaque-forming bacteria that live in the mouth and on tooth surfaces. Reduction of plaque bacteria can decrease the inflammatory substances and can reduce gingivitis.

In clinical studies in adults with mild to severe gingivitis, Decapinol was compared either to "no treatment" or to an antimicrobial rinse. The studies showed that Decapinol decreases gingivitis up to 60 percent compared to no treatment and when used as instructed with recommended brushing and flossing.

The FDA approved Decapinol for use in people ages 12 and older when routine tooth brushing and flossing are not enough to prevent gingivitis. It is not recommended for use by pregnant women.

The FDA is regulating Decapinol as a medical device and not as a drug



PhotoDisc

because its primary mode of action is to create a physical barrier, rather than to act chemically. Decapinol contains a substance called a surfactant that acts as a physical barrier, making it harder for bacteria to stick to tooth surfaces. The FDA has approved a number of other anti-gingivitis oral rinses, but since these products act chemically to kill bacteria that live in the mouth, they are regulated as drugs rather than as devices.

Decapinol Oral Rinse is manufactured by Sinclair Pharmaceuticals Ltd., based in the United Kingdom.

First-of-a-Kind Device Treats Aneurysms

The FDA has approved a new device to treat aneurysms of the thoracic aorta, the main artery that carries blood in the body. The GORE TAG Endoprosthesis System is the first endovascular grafting system intended to prevent ruptures of descending thoracic aneurysms by making a new path for blood flow.

A thoracic aortic aneurysm is a diseased, weakened, and bulging section of the aorta in the chest. If not treated, the condition could result in a rupture of the aorta, leading to potentially life-threatening internal bleeding. The

aneurysm may be caused by vascular disease, injury, or an inherited defect of the tissue.

Typically, descending thoracic aneurysms are managed either medically with blood pressure-lowering drugs to reduce the risk of rupture, or by surgical repair. Large aneurysms are at significant risk of rupture, which can be fatal. Conventional surgical repair requires a major chest operation in which the aneurysm is replaced by a graft. Such surgery is associated with prolonged hospitalization, post-operative monitoring in an intensive care unit, and a recuperation period of three to six months.

Approved in March 2005, the GORE TAG system consists of an endovascular graft made of an expanded form of PTFE (polytetrafluoroethylene), a metallic support structure, and a delivery system used to implant the graft. The endovascular graft is delivered by a catheter inserted into the femoral artery in the groin. The graft relines the inside of the weakened aortic wall, thus strengthening the vessel and relieving pressure that could cause a rupture.

The procedure, while less invasive than conventional surgery, does require regular follow-up medical visits and tests to monitor the success of the

treatment over time.

The FDA is requiring that the manufacturer, W.L. Gore and Associates Inc., Flagstaff, Ariz., conduct post-approval studies to assure that when the endovascular grafting system is used in the general population, its safety and effectiveness will be comparable to the clinical trials, and to evaluate the long-term clinical performance of the device. ■

An article titled "Dealing with Dry Eye" in the May-June 2005 issue of *FDA Consumer* incorrectly stated that Restasis (cyclosporine ophthalmic emulsion) is the only prescription product available for chronic dryness. Restasis is not the only prescription product for chronic dry eye. The prescription product Lacrisert (hydroxypropyl cellulose ophthalmic insert) also is approved by the FDA to treat symptoms of dry eye. The inserts are typically placed in each eye once daily. Possible side effects of Lacrisert include transient blurring of vision, eye irritation, and matting or stickiness of eyelashes. ■

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

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General FDA questions: E-mail webmail@oc.fda.gov.

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

Experimental Shingles Vaccine Proves Effective in Nationwide Study

In one of the largest adult vaccine clinical trials ever, researchers have found that an experimental vaccine against shingles (zoster vaccine) prevented about half of cases of shingles—a painful nerve and skin infection—and dramatically reduced its severity and complications in vaccinated persons who got the disease.

"This is very promising news for older persons," says Stephen E. Straus, M.D., director of the National Center for Complementary and Alternative Medicine (NICAM), who participated in the design, oversight and conduct of the trial. "These striking results indicate for the first time that we can use a vaccine to prevent shingles, one of the most common and debilitating illnesses of aging. And among vaccine recipients who did get shingles, the episodes generally were far milder than they otherwise would have been."

The Shingles Prevention Study, conducted over more than five years, was led by the Department of Veterans Affairs (VA) and carried out in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), and Merck & Co. Inc., based in Whitehouse Station, N.J. The findings appear in the June 2, 2005, issue of *The New England Journal of Medicine*.

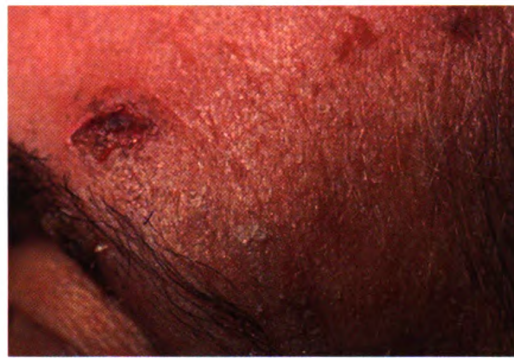
Shingles, also known as herpes zoster, is caused by reactivation of the virus that causes chickenpox. Once chickenpox infection has run its course, the virus is not eliminated; rather, it retreats to clusters of sensory nerve cells usually located near the spinal cord, where the virus persists in a dormant state. As immunity weakens with advancing age, the virus can reactivate, multiply in and damage sensory nerve cells to cause pain. It then migrates to the skin, causing the blistering rash of shingles.

Anyone who has had chickenpox, which includes most adults in the United States, could develop shingles, although not all will. The two major risk factors are increasing age and declining immunity. Half of all people who live to age 85 will get the disease. Experts estimate more than 1 million new cases of shingles occur in the United States each year.

Funded by Merck and the VA, the trial was conducted at 22 study sites nationwide, including 16 VA medical centers and six clinical research sites outside the VA system coordinated through NIAID. Between November 1998 and September 2001, the multicenter research team enrolled more

than 38,500 men and women ages 60 or older. Half of the participants received a single injection of the zoster vaccine—a live, weakened form of varicella-zoster virus, the virus responsible for chickenpox; the other half received a placebo vaccine. Neither the researchers nor the participants knew who received the vaccine and who received the placebo until after the study.

The zoster vaccine used in the study, manufactured by Merck, is a new, more potent version of the chickenpox vaccine, that has been used to prevent chickenpox in millions of American children every year since 1995. The zoster vaccine was developed specifically for study in older adults.



CDC

These skin lesions on the forehead of a woman are due to the herpes zoster virus. Shingles, or herpes zoster, is caused by the chickenpox virus that remains in the nerve roots of all people who had chickenpox.

During an average of more than three years of follow-up, the vaccine reduced the incidence of shingles by 51 percent: 642 cases of shingles occurred among those in the placebo group compared with only 315 in the vaccinated group. Among all vaccine recipients, the total burden of pain and discomfort due to shingles was 61 percent lower than in placebo recipients. Moreover, the zoster vaccine reduced the incidence of postherpetic neuralgia (PHN)—a form of chronic nerve pain that is the most common serious complication of shingles—by two-thirds, compared with the placebo.

Patients with PHN often describe the pain as burning,

throbbing, aching, stabbing, or shooting, and it can cause both physical and emotional suffering. PHN is difficult to treat. Antiviral medications can speed the healing of shingles and reduce the severity of nerve damage caused by the disease, but only if these medications are used within 72 hours of the first sign of a shingles rash. Antiviral medications do not help relieve PHN once it has begun.

The researchers emphasize that the zoster vaccine was tested only as a preventive therapy and is not intended as a treatment for those who already have shingles or PHN. On April 25, 2005, Merck announced that it had submitted a license application to the Food and Drug Administration for the zoster vaccine. With FDA approval, the research team estimates the vaccine could prevent 250,000 cases of shingles that occur in the United States each year and significantly reduce the severity of the disease in another 250,000 cases annually. ■

Study Shows Programs Can Teach Children to Eat Healthier

A study of preadolescent children found that those who attended a behaviorally oriented nutrition education program and were taught to follow a diet low in saturated fat and dietary cholesterol adopted significantly better dietary habits over several years, compared with their peers who received only general nutritional information.

The government-sponsored study showed that after three years, children in the intervention group consumed more than 67 percent of their total calories on average from heart-healthy foods, compared with less than 57 percent for children in the usual care group.

"We need to act now to prevent obesity in our children," says Elias Zerhouni, M.D., director of the National Institutes of Health. "Obesity is a high priority at NIH. This year, we will spend about \$440 million on a range of research on this important problem."

The results, published in the June 2005 issue of *Pediatrics*, are from a new ancillary study of the Dietary Intervention Study in Children (DISC). Scientists reviewed dietary recalls from 595 children who were ages 8 to 10 and who had high blood cholesterol levels at the start of the study. The researchers analyzed dietary information by food groups and measured adherence to recommended food patterns and changes over time.

"These new findings offer valuable lessons for finding effective ways to help children develop healthier eating habits—a critical need in light of the rising rates of obesity and related conditions among children," says Elizabeth G. Nabel, M.D., director of the National Heart, Lung, and Blood Institute (NHLBI), which sponsored the study.



Photo: FDA/Michael Ermarth

The study provides glimpses of real-world eating behavior and reveals the challenges of trying to eat a healthy diet in a fast-paced world. For example, the study documents a long-suspected phenomenon of modern society: About one-third of the total daily calories consumed by the children in both groups came from snack foods, desserts, and pizza.

The main DISC trial is the first long-term clinical trial of the effects of a fat-reduced dietary intervention on growing children. Over the seven years of the original study, children who adopted a low-fat, low-cholesterol diet decreased their intake of total fat, saturated fat, and cholesterol within the first year of the study and maintained lower levels for several more years. Those selected for the intervention group participated in a nutrition education program that included a behavioral component to promote healthier eating. Parents of the children in the intervention group participated in a similar program.

Researchers previously reported that the dietary changes made by children in the intervention group did not adversely affect the children's nutritional status, growth, or development.

For the new findings, researchers analyzed the dietary recalls collected over three days at the beginning of the study and again after three years. They found that the dairy food group and the desserts/snacks/pizza group had the greatest impact on the children's body mass index (BMI) and their levels of LDL, or "bad," cholesterol. Girls and boys who consumed more dairy products were more likely to have a lower BMI. Boys who consumed more desserts, snacks, and pizza were more likely to have higher BMI and LDL levels.

Specific foods within each food group were also classified based on the ingredients or preparation methods as either "Whoa" foods—those that were high in saturated fat and dietary

cholesterol—or heart-healthy "Go" foods—those that were low in saturated fat and dietary cholesterol.

Compared to baseline, after three years, children in the intervention group consumed more of the "Go" food choices in all the food groups except fruit, and they consumed fewer of the "Whoa" food choices with one exception: pizza. They also consumed on average slightly fewer snacks and desserts after three years compared with the usual care group. In addition, children in the intervention group chose more "Go" versions of desserts, such as low-fat frozen yogurt, gelatin, or angel food cake, and more "Go" versions of pizza, such as those made with low-fat cheese, compared with those in the usual care group. The authors note, however, that children in both groups ate fewer than recommended servings of fruits and vegetables.

The intervention group's greater consumption of total daily calories from "Go" foods shows that children and their families can be taught to improve children's diets, according to Linda Van Horn, Ph.D., R.D., professor of preventive medicine at Northwestern University and lead author of the study.

"You can raise a child to enjoy healthy eating and to be selective about food choices. Habits developed in childhood will hopefully last throughout their lives," says Van Horn. "With the right guidance and nutrition education, children learn to prefer healthy foods such as carrots and raisins or cereal as snacks, for example."

Eva Obarzanek, Ph.D., R.D., NHLBI nutritionist and DISC project officer, agrees that most children could benefit from healthier eating patterns like those followed by DISC participants. "DISC has shown that following a diet low in saturated fat and cholesterol is safe for children in this age group—and a heart-healthy diet can lower blood

The science-based We Can! Program helps parents teach their children to

- Eat a sufficient amount of a variety of fruits and vegetables each day
- Choose small portions at home and at restaurants
- Eat fewer high-fat foods and energy-dense foods that are low in nutrient value such as french fries, bacon, and doughnuts
- Substitute water or fat-free or lowfat milk for sweetened beverages such as sodas
- Engage in at least 60 minutes of moderate physical activity on most, preferably all, days of the week
- Reduce recreational screen time (such as television, computers, and games) to no more than two hours daily.

cholesterol levels," she says.

Other studies have shown that atherosclerosis, or hardening of the arteries, begins in childhood. The National Cholesterol Education Program recommends that children over the age of about 2 years, as well as all adults, adopt a heart-healthy eating pattern to reduce their risk of developing heart disease as adults. Children and adults can also lower their risk by maintaining a healthy weight and by being physically active.

To help families adopt healthier lifestyles, the NIH has launched a national public education program targeting parents and caregivers of children ages 8 to 13. Developed by the NHLBI and promoted in collaboration with several other NIH institutes, national health and youth organizations, and community-based groups, *We Can! Ways to Enhance Children's Activity & Nutrition* provides resources to encourage healthy eating, increase physical activity, and reduce sedentary time.

For More Information

<http://wecan.nhlbi.nih.gov>

Or call (866) 35-WE CAN (359-3226)

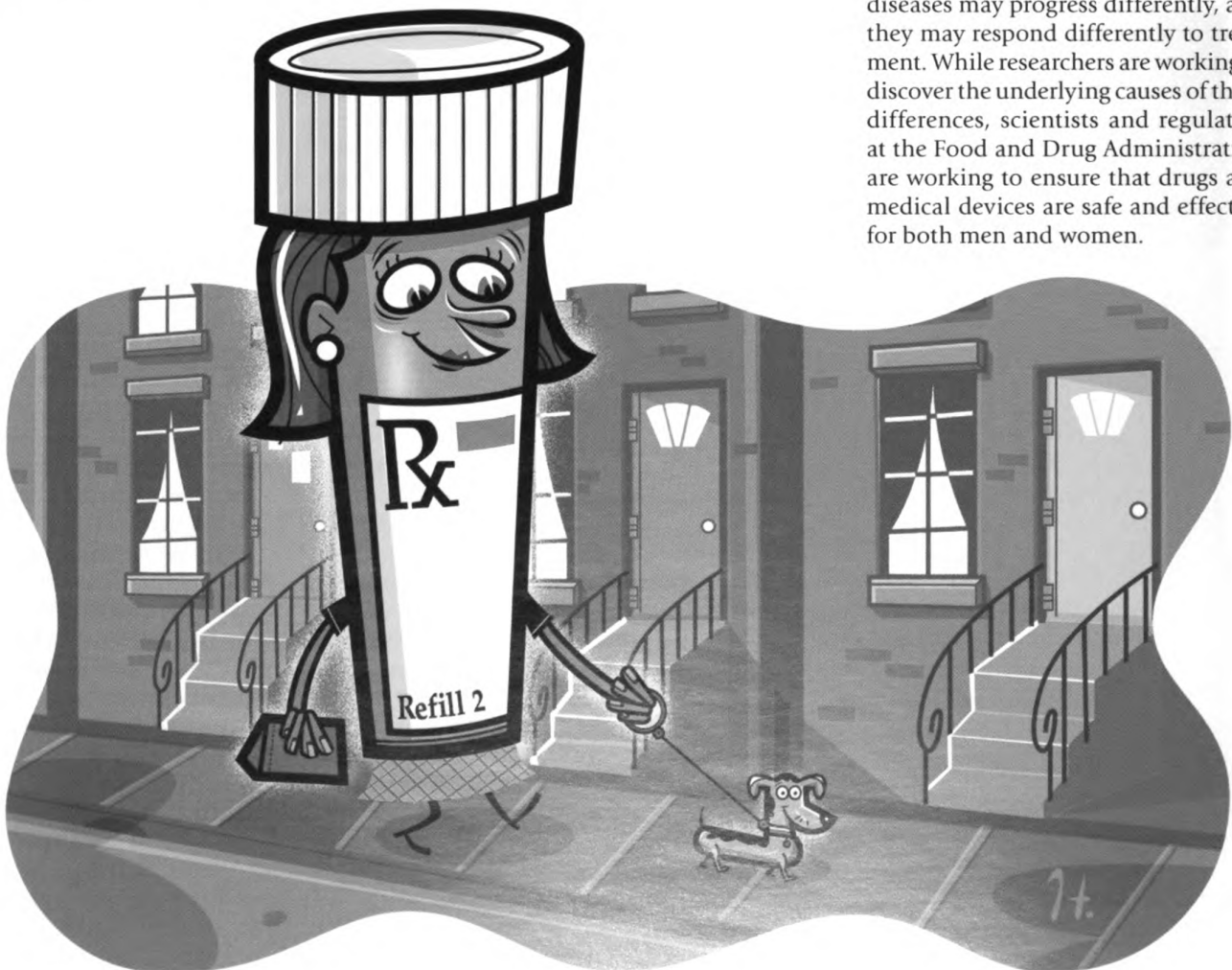
Does Sex Make a Difference?

By Linda Bren

When it comes to health risks, sex does matter. Women are twice as likely as men to get multiple sclerosis, rheumatoid arthritis, and migraines. They're also more likely to get cataracts, hepatitis, and thyroid disease. Women experience depression about twice as often as men. And irritable bowel syndrome (IBS) is thought to affect twice as many women as men. Although men have more heart attacks than women, more women die within a year after having a heart attack.

"Despite this increased susceptibility to so many diseases, females across the world have a longer lifespan," says Joseph Verbalis, M.D., clinical director of Georgetown University's Center for the Study of Sex Differences, in Washington, D.C. "We don't know why," says Verbalis, "but that's one of the things we're trying to find out."

Researchers are finding that men and women are different in ways that go beyond their reproductive systems, hormones, and bone structure. They get many of the same diseases, but they may have different symptoms, their diseases may progress differently, and they may respond differently to treatment. While researchers are working to discover the underlying causes of these differences, scientists and regulators at the Food and Drug Administration are working to ensure that drugs and medical devices are safe and effective for both men and women.





Jack Hornady

Just as one size doesn't fit all, one treatment or test doesn't fit all men or all women. It's important to test drugs and devices in both women and men of different races and ethnicities in clinical trials, says Margaret Miller, Ph.D., manager of scientific programs in the FDA's Office of Women's Health (OWH).

The FDA has regulations and guidance in place to ensure that both sexes are represented in clinical trials, that study results are analyzed by gender, and that medical products are labeled to alert physicians and patients to any difference in the way men and women respond to a product. In addition, the agency is supporting research to identify gender differences that may affect the use of FDA-regulated products.

Gender as a Starting Point

Men and women are different in every organ of the body—even their skin, says Marianne J. Legato, M.D., a cardiologist and founder and director of Columbia University's Partnership for Gender-Specific Medicine. They are different at the cellular level, and these

differences may influence the amount and type of medicine they need to treat a disease. "Dosage is not adjustable simply on the basis of body size anymore," says Legato. "I think we have to look at a whole variety of factors in prescribing dosages that are safe on the basis of gender."

"We know that different people, as individuals, respond to drugs differently," says Miller. "People routinely tell me, 'Oh, that drug doesn't do a thing for me.'" Some researchers place priority on studying differences in genetic makeup by individual, not gender, says Miller. They want to determine the exact sequence of DNA in a person's body in order to tailor treatments for that individual. "But even if the DNA is the same, men and women will express it differently," says Miller.

Researchers looking at DNA sequence may think that's a shortcut, says Legato, "which it obviously would be if we can take a slice of people's DNA and decide whether or not they would react appropriately to any medication to which they've not been previously exposed.

That would be the ultimate, but I fear that that's years away. I think it would be nice to know the difference between men and women as a starting point."

In 2001, the Institute of Medicine (IOM), part of the National Academy of Sciences, published a report that supported studying potential gender differences during drug development. The IOM concluded that "sex matters"; that is, "being male or female is an important basic human variable that should be considered when designing and analyzing studies in all areas and at all levels of ... health-related research." The IOM defined sex-based differences as biologically based differences in men and women, and described gender-based differences as distinctions shaped by the cultural and social environment. Generally, the FDA does not attempt to determine why men are different from women and refers to any identified difference as a "gender difference."

Drugs and Gender Differences

In 1998, the allergy drug Seldane (terfenadine) was removed from the

market, when a safer alternative was approved. It had been discovered that Seldane could cause a life-threatening heart rhythm irregularity when used with certain other drugs. More women took Seldane, and more were reported to have had this heart arrhythmia, called torsades de pointes.

Researchers at the Georgetown Center for the Study of Sex Differences believe that the male hormone testosterone may protect the heart from some types of arrhythmia, says Verbalis. In addition, he says, research has shown that women are at greater risk for tor-

symptoms. "The challenge in the evaluation of a drug for this disease is to determine if there is a gender difference in the patient's perception of symptoms and evaluation of relief of symptoms," says Joyce Korvick, M.D., acting director of the FDA's Division of Gastrointestinal and Coagulation Drug Products. "The perception of 'relief' of symptoms in men and women may be very different."

Because IBS is found more often in women, more women than men were enrolled in the clinical trials for Zelnorm. But for the nearly 300 men with

drug products group. "However, it should also be noted that the types of PTSD differed in the two groups," he says. Many of the men in these trials had a long-lasting and treatment-resistant PTSD, based on military combat experience, compared to many of the women who tended to have a more acute form of PTSD, based on recent physical abuse.

Scientists aren't sure why some drugs work better in one gender than in the other. But they do know that differences may occur in the way men and women absorb certain drugs into the bloodstream, distribute them to the body's tissues, break them down, and rid them from the body. The way the body handles a drug is known as pharmacokinetics (PK), and was the subject of an FDA study.

FDA researchers examined 300 drug applications submitted to the agency between 1994 and 2000. More than half of these applications contained information on the effect of gender on PK. The PK was the same for 80 percent of the drugs in which PK was studied. But for the other 20 percent of the drugs, the PK was different.

"There must be some reason for this difference," says Miller. "That's where research comes in. We want to understand the biology and the mechanism enough to predict what's going to be in the 80 percent group and the 20 percent group. Then we can predict how a product's safety or effectiveness will be influenced in each gender."

Shiew-Mei Huang, Ph.D., deputy director for science in the FDA's Office of Clinical Pharmacology and Biopharmaceutics, says that drug metabolism plays an important role in the way men and women respond to drugs. An enzyme known as cytochrome CYP3A helps metabolize many drugs, and studies have shown that women have more cytochrome CYP3A in the liver, says Huang. Some drugs or dietary supplements, for example, St. John's wort, increase the activity of this enzyme, which makes the drugs break down faster. This rapid breakdown reduces the amount of the drug in the body, decreasing its effectiveness in women.

The reverse scenario may also occur:

Men, Women, and Heart Disease

Heart disease is the leading cause of death in the United States for both men and women, according to the American Heart Association. "But the normal heart is different in men and women," says Marianne J. Legato, M.D., a cardiologist and founder and director of Columbia University's Partnership for Gender-Specific Medicine. "Women's hearts beat faster, even during sleep," she says. And women have different proteins in the heart cells.

"Some data suggest that the whole physiology of the coronary arteries and what keeps them open and what causes them to go into spasm might be significantly different in men and women," says Legato, adding that some women have had heart attacks without any of the fatty buildup of plaque seen in the coronary arteries in most people with heart attacks.

And the symptoms of a heart attack may be different. "Twenty percent of women will not have the 'typical symptoms' of chest pain radiating down the left arm," says Legato, "but will instead describe nausea, profound sweating, and shortness of breath and pain in the upper abdomen." ■

sades de pointes because of their QT interval—the time it takes for the heart to relax after it contracts to pump out blood. Women often have a longer QT interval than men, and taking certain drugs can further lengthen this interval, thereby increasing the risk of the fatal arrhythmia more in women than in men.

Some drugs are approved to treat a disease based, in part, on patients' reporting of the relief of their symptoms. For example, Zelnorm (tegaserod maleate) is approved only for women to relieve the symptoms of IBS. In clinical trials, more women taking Zelnorm reported relief of their symptoms than those taking an inactive pill (placebo).

IBS, which is found more commonly in women, produces a variety of

IBS enrolled in the trials, Zelnorm was not shown to be effective. "More research regarding men and women's perceptions of specific disease symptoms is needed to ensure that differences seen in clinical trials are meaningful to the gender being studied," says Korvick.

Another drug, Zoloft (sertraline hydrochloride), is approved for both men and women to treat several conditions, including post-traumatic stress disorder (PTSD). This approval was based on clinical trials in which Zoloft showed little effect in men with PTSD, while the drug's benefit over a placebo was clear in the women studied.

"True gender differences in responsiveness may have been one explanation," says Thomas Laughren, M.D., team leader for the FDA's psychiatric

Men, Women, and Disease Risk

Heart attack	Men have more, but women are more likely to die within a year after a heart attack; women tend to get heart disease seven to 10 years later than men
Stroke	Women have fewer strokes, but are more likely to die from them than men; women are generally older than men when they have a stroke
Depression	Twice as common in women
Migraine	Three times more common in women
Hearing loss	More common in men
Nearsightedness (myopia)	More common in women through age 60
Irritable bowel syndrome	More common in women
Cancer	Cancer of the lungs, kidneys, bladder, and pancreas are more common in men; thyroid cancer is more common in women
Osteoporosis	More common in women
Rheumatoid arthritis	Two to three times more common in women
Gout	More common in men
Lupus	Nine times more common in women
Fibromyalgia	Nine times more common in women

National Institutes of Health

A drug could slow down enzyme activity, causing too much of the drug to build up in the body and resulting in more side effects.

But biology can't explain all the differences in the way men and women respond to drugs, cautions Huang. Other factors, such as medication use, must be considered. "A recent survey showed that women, in all age groups, tend to take more medications, including dietary supplements, than men," says Huang. This difference may put women at more risk for certain drug interactions than men.

Medical Devices and Gender Differences

Men and women may also respond differently to certain medical devices and the procedures in which they are

used. Several FDA studies have focused on identifying some of these differences.

In 2003 and 2004, FDA researchers studied more than 150,000 people with suspected heart disease and found that women had about twice the risk of men for local complications after cardiac catheterization. In the catheterization procedure, a slender tube is inserted into a large artery in the leg (femoral artery) and is threaded up through the body to the heart to diagnose or treat narrowed heart arteries that block blood flow.

"The study was done to look at risks associated with hemostasis devices," says Dale Tavis, M.D., M.P.H., an FDA epidemiologist specializing in preventive medicine. These devices are used after cardiac catheterization to prevent

continued bleeding of the femoral artery where the catheter is inserted.

We don't know why complications, such as hemorrhaging, occurred more in women, says Tavis. "There's speculation that it may be due to blood vessel size or hormonal differences. And the risk applies whether or not the hemostasis devices are used." Further information is needed to understand these occurrences, says Tavis, before we can determine whether any changes to the catheterization procedure or to hemostasis devices or their labeling are appropriate.

An FDA-sponsored study at Boston University involves men and women with diabetes who are using blood glucose monitors at home to test their blood several times a day. Researchers are looking for any differences in

Zelnorm®

Brand Name:	Zelnorm®
Active Ingredient:	tegaserod maleate
Strength(s):	2 mg and 6 mg
Dosage Form(s):	Tablet
Company Name:	Novartis Pharmaceuticals
Availability:	Prescription only
*Dated Approved by FDA:	July 24, 2002

*Approval by FDA does not mean that the drug is available for consumers at this time.

What is Zelnorm used for?

Zelnorm is a medicine for the short-term treatment of women who have irritable bowel syndrome (IBS) with constipation (not enough or hard bowel movements) as their main bowel problem.

Zelnorm has not been shown to work in men with IBS.

Who should not take Zelnorm?

You should not start taking Zelnorm if you:

- have diarrhea or have diarrhea often
- have bad kidney or liver disease
- have ever had bowel obstruction (intestinal blockage), symptomatic gallbladder disease, or abdominal adhesions causing pain and/or intestinal blockage

Zelnorm has not been shown to work in men with IBS.

Some drugs appear to work better in one gender than in the other.

testing blood drawn from the fingertip or from another part of the body, since newer glucose monitors use blood samples from alternate body areas. "We found that the fingertip can have a different glucose value from an arm or leg, especially when sugar levels are changing rapidly, for example, after a meal or after exercise," says Jean Cooper, D.V.M., director of the Division of Chemistry and Toxicology in the FDA's Center for Devices and Radiological Health. The study is continuing to determine whether gender might be a factor in this difference in glucose values.

The FDA now requires glucose monitors to carry a warning label cautioning against using alternate sites when glucose levels are changing rapidly. If a manufacturer can show in clinical trials that its device doesn't demonstrate this variance, the warning is not required.

Studies of Both Sexes

In 1977, an FDA guidance said that women able to become pregnant should

not participate in the early phases of drug studies, with an exception for studies of potentially life-saving drugs. The exclusion reflected the concern that if a woman became pregnant, the baby might have birth defects.

Over more than two decades, the FDA has worked to ensure that both women and men are represented fairly in clinical trials involving drugs, biologics such as vaccines and blood products, and medical devices.

In 1988, the agency issued guidance to drug makers asking that the safety and effectiveness data in drug applications be analyzed according to gender, age, and race. And, in 1993, the agency issued its Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, known as the gender guideline.

When the gender guideline was published, the FDA also revoked the 1977 restriction on women of childbearing age in early drug studies and reiterated the need to include patients of both sexes in the development of drugs, biologics, and medical devices. The

guideline also recommended that drug companies analyze separately men's and women's responses to drugs.

Attention to potential gender differences became part of a larger agency effort to ensure that the safety and effectiveness of drugs are adequately studied in people who represent the full range of patients who could use the drugs when approved. In a 1998 regulation known as the Demographic Rule, the FDA again addressed the importance of collecting data on clinical trial volunteers by gender, race, and age. The regulation required companies to analyze the data to look for possible differences in effectiveness, safety, and

dose-response and to submit this information in applications for new drugs. It also required reporting demographic data in annual reports during a drug's investigation phase.

A regulation in 1999 gave the agency the authority to halt studies of new drugs to treat life-threatening diseases if clinical trials excluded women solely because they could become pregnant. "The Demographic Rule and gender guideline represent our commitment to looking at possible differences in various subgroups' response to drugs, whether men and women, black and white, old and young," says Robert Temple, M.D., director of the FDA's Office of Medical Policy. "The guidance tells drug sponsors what our expectation is and what we're looking for."

So far, a small number of differences have been found in the way men and women respond to drugs, says Temple. An FDA study reviewed gender-related labeling for 171 new drugs that were approved for both males and females from 1995 through 1999. Labeling for two-thirds of the drugs contained some statement about gender, although only 22 percent described actual gender differences and none of these differences were considered significant enough to recommend any change in

dosage for one gender.

"But just knowing that is useful information," says Miller. "You know you can take these drugs without a higher risk because of your gender."

The FDA is also working to revise drug labeling so that both consumers and health care providers can better understand important information about a drug. A proposed FDA rule will require prescription drug labels to contain "highlights" in a prominent place. The highlights will discuss the more serious and common side effects and significant gender differences found in clinical trials.

Continuing Efforts

The FDA's Office of Women's Health is funding research within the agency to examine gender differences—particularly in the areas of heart disease, obesity, and HIV—that are important for the agency to consider in regulating medical products.

In one project funded by the OWH, scientists within the FDA's Center for Biologics Evaluation and Research are studying the replication of HIV, the virus that causes AIDS, in human blood cells from male and female blood donors. By infecting the blood cells with HIV in a culture medium and then adding various sex hormones, scientists are learning more about the influence of gender on the concentration of the virus. They are also studying the effect of sex hormones on certain antiviral drugs used to treat HIV.

"Some of the things we're looking at may affect when treatment should be started in men and women," says Andrew Dayton, M.D., Ph.D., an FDA research medical officer. And it may give us preliminary insight into how gender might affect response to HIV treatments, he adds. This information may help in designing clinical trials to test the effectiveness of HIV treatments in men and women.

In another initiative, the OWH is developing an innovative knowledge management approach to make better assessments in groups of people (subpopulations) to protect patient safety. The Demographic Information and Data Repository (DIDR) was mandated by Congress in 2002 to moni-



Black Star/Dennis Brack

FDA researcher Andrew Dayton, M.D., Ph.D., adds sex hormones to blood cells infected with HIV to learn about the influence of gender on the virus. This knowledge may help determine which HIV treatments are the most effective in men and women.

tor the inclusion of women in clinical trials and to study gender differences and variability in response to medical products.

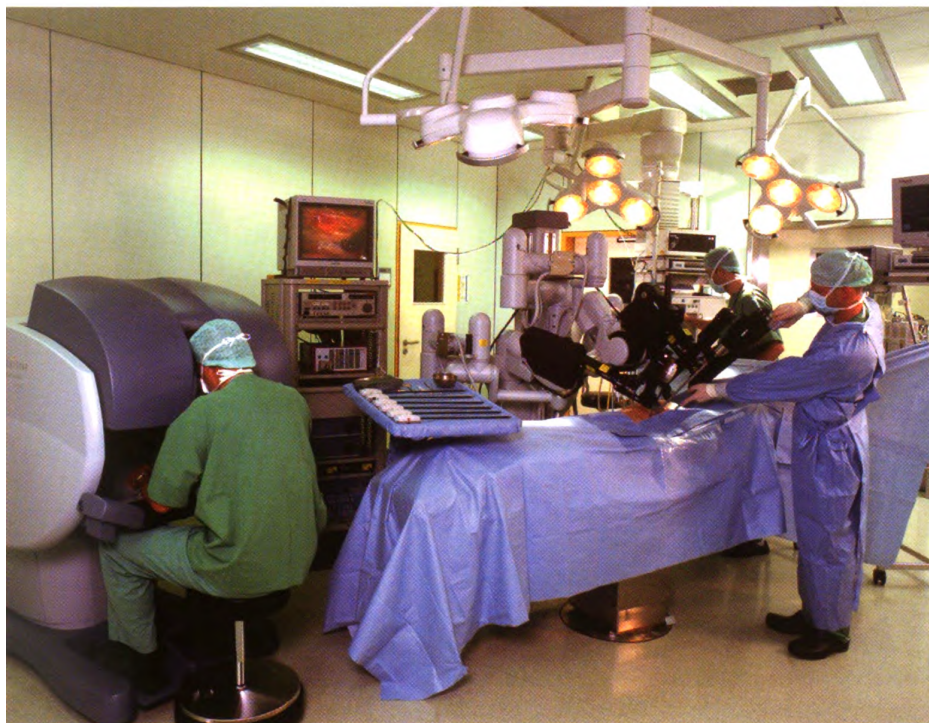
Katherine Hollinger, D.V.M., M.P.H., a senior health promotions officer in the OWH, says the DIDR will help the agency to look at groups of people—including groups characterized by gender, race and ethnicity, older people, and children—in a more informed way. "It will allow us to better look at subpopulation issues and differences in drug response that may affect safety and effectiveness," says Hollinger. "And it will allow us to not only track inclusion of women and other populations in clinical trials, but to monitor the types of trials women, children, or the elderly are participating in and identify patterns that are observed."

Other benefits of the agency-wide

DIDR include helping the agency to design better studies for new products, enabling more efficient and informed reviews and approval decisions, and allowing better assessments of product labeling.

Part of the problem in looking at study data to determine subpopulation differences in response to medical products is the lack of standard approaches and terminology used in individual studies. The agency is working with the pharmaceutical industry and standards organizations to establish standardized approaches to labeling, study data, and study protocols that will be used in the DIDR to protect the safety of women, men, children, and older people of every race and ethnicity. ■

Computer-Assisted



Intuitive Surgical

By Michelle Meadows

The Food and Drug Administration first cleared the da Vinci Surgical System in 2000 for general laparoscopic surgeries such as gall bladder removal and for treatment of severe heartburn. Since then, use of the system has increased and expanded into several other surgical areas. These include removal of the prostate (radical prostatectomy); non-cardiac chest procedures involving the lungs, esophagus, and a blood vessel inside the chest cavity (internal thoracic artery); and certain procedures involving surgical incisions into the heart, such as mitral valve repair.

In April 2005, the FDA cleared the da Vinci system for gynecological laparoscopic procedures. Surgeons are now able to remove the uterus (hysterectomy) and to remove uterine fibroids (myomectomy) using the device. The system has also been cleared for use in all urologic procedures. And, in 2004, the FDA broadened the application of the da Vinci system for assisting in coronary artery bypass surgery.

"The development of this system for use in the heart is a step forward in new technology that eventually could change the practice of surgery," Acting FDA Commissioner Dr. Lester M. Crawford says.

A Minimally Invasive Approach

Experts say the key benefit of computer-assisted surgery is being able to perform surgery through smaller incisions. W. Randolph Chitwood Jr., M.D., chairman of the department of cardiothoracic surgery at East Carolina University, in Greenville, N.C., says he's experienced the long healing time that comes with big incisions firsthand. For his own heart surgery in 1994, he underwent the traditional procedure for open heart surgery called a sternotomy. It involves a foot-long incision through the breast bone. "It was around that time that I became interested in minimally invasive heart surgery," says Chitwood, who has performed close to 200 mitral valve repairs using the da Vinci system.

"Making smaller incisions means the potential for less pain, less blood loss, and faster recovery for patients," Chitwood says. He is able to repair narrowing or leaking heart valves by making a few small incisions between the ribs. In 2004, the da Vinci system was used in more than 2,400 surgeries related to the heart and chest in the United States. These include mitral valve repair and coronary revascularization, a procedure that bypasses blockages in the coronary arteries so that blood flow to

Surgery: An Update

the heart can be restored.

While sitting at a console several feet away from the operating table, the surgeon views the inside of the patient's body by looking through lenses. A magnified 3-D vision system gives an enhanced view of the surgical field. The surgeon moves controls to manipulate the device at the operating table. The da Vinci system has up to four arms that are inserted into the patient through small incisions. One arm holds a miniature camera, and the other arms hold a variety of instruments. Chitwood says the camera serves as his "eyes."

work in 10 to 14 days, about half the recovery time required for conventional, open surgery, he says. Conventional surgery for removal of the prostate typically requires about a seven-inch incision in the lower abdomen.

"With the da Vinci system, the blood loss for patients is about one-fifth to one-tenth of what it would be for open surgery," Ahlering says. "Also, the urinary catheter remains in for about half as long, and patients tend to get urinary control and sexual function back more quickly." Research has shown that

Surgical Inc., of Sunnyvale, Calif. The FDA tracks adverse events related to medical devices. Chitwood says he has had one patient die during a computer-assisted procedure. "This was due to a medication reaction, not a device failure," he says.

In 2002, a Florida man died two days after blood vessels were accidentally cut during a surgery for kidney removal with da Vinci. Shortly after the death, officials at St. Joseph's Hospital in Tampa, Fla., called the incident "a tragic, isolated event."

Patients considering robotic surgery

'Making smaller incisions means the potential for less pain, less blood loss, and faster recovery ...'

The arms have flexible wrists that give surgeons access to hard-to-reach areas. The device doesn't move on its own, but rather cuts and sews at the surgeon's direction.

"The improved vision and flexibility of the instruments allow for increased precision," says Thomas Ahlering, M.D., chief of the division of urologic oncology at the University of California, Irvine, Medical Center. Since 2002, Ahlering has used the da Vinci system to remove the prostate (prostatectomy) in men with prostate cancer. He performed about 100 radical prostatectomies with da Vinci in 2004.

"Even though it's a walnut-sized gland, the prostate is highly functional," Ahlering says. Located below a man's bladder, the prostate is surrounded by nerves and muscles that affect urinary, rectal, and sexual function. Great care and precision are required to remove the prostate without damaging these structures.

With computer-assisted surgery, Ahlering's patients have returned to

there is also less use of narcotic medication during the recovery period. In 2004, there were more than 8,000 radical prostatectomies performed with the da Vinci system in the United States.

Patient Safety

Ahlering says that based on his experience so far, the risks with computer-assisted surgery appear to be less than with other forms of surgery. "Risks such as bleeding and needing a transfusion or cutting into the rectum are lower with this procedure," he says.

Rarely, doctors may have to switch from the device to a traditional method of surgery. "Once a camera went out, but we had another system and were able to use that," Ahlering says. "If I didn't have another one, I would have either had to switch to open surgery or reschedule it for another day if it was early enough in the procedure."

To date, there have been no patient injuries or deaths attributed to system failures with the device, according to the da Vinci manufacturer, Intuitive

should talk with their doctors about the benefits, risks, and any factors that would exclude them as candidates. For example, previous abdominal surgery, obesity, or a prostate that's too large are among the factors that might exclude a patient from having a radical prostatectomy with da Vinci, Ahlering says. He suggests that consumers consider the experience of the surgeon and seek out medical centers that focus on computer-assisted procedures.

The da Vinci Surgical System is the only operative surgical device of its kind on the market in the United States. In 2003, Intuitive Surgical bought Computer Motion of Goleta, Calif. Computer Motion was the manufacturer of the Zeus Robotic Surgical System, which is no longer actively being marketed.

According to Intuitive Surgical, there are 286 da Vinci systems installed worldwide, including 204 in the United States, 56 in Europe, and 26 in Asia and other parts of the world. ■

Antiperspirant Awareness: It's Mostly **NO SWEAT**

By Carol Rados

OFFENSIVE BODY ODOR is against the law in libraries in San Luis Obispo County, Calif. A code of conduct, officials say, is necessary to ensure that one person's right to use a public library doesn't infringe on the rights of another and law enforcement officers have the authority to remove library patrons who smell bad.

An extreme measure? Perhaps. But social awareness, coupled with the availability of dependable personal care products, may be a more practical way to hold body odor at bay.

The agency defines antiperspirant as a drug product applied topically that reduces the production of sweat (perspiration) at the site where it is applied. Antiperspirants, according to the Food and Drug Administration, can safely and effectively reduce sweat for up to 24 hours, if formulated and tested properly. And for most, this means protection against both wetness and odor.



Chicago Tribune

After emerging from a specially heated room at Unilever's Global Technology Center in Rolling Meadows, Ill., women serving as antiperspirant test subjects wash their armpits.

The FDA issued a final rule in June 2003 establishing conditions under which over-the-counter (OTC) antiperspirants are generally recognized as safe and effective (GRASE), and are not misbranded. The final rule establishes allowable ingredients and labeling for the products.

In October 2004, the agency reopened the record on this final rule to consider one manufacturer's request to double the length of time—from 24 hours to 48 hours—during which an OTC antiperspirant is considered to be effective. The request in this case, called an enhanced duration claim, applies to the testing and labeling of this particular claim.

Matthew R. Holman, Ph.D., an FDA scientist in the Division of Over-the-

Counter Drug Products, says that the agency needs scientific evidence that extended duration products work. "Manufacturers have to back up such claims with studies," he says. The FDA must be satisfied that the testing is valid for 48 hours.

Under the Federal Food, Drug, and Cosmetic Act, the FDA legally defines products by their intended uses. Therefore, drugs are defined as products intended for treating or preventing disease or for affecting the structure or any function of the body. Antiperspirants are considered drugs because they affect the function of the body by reducing the amount of sweat that reaches the skin.

But different laws and regulations apply to each type of product. Some

products, for example, must comply with the requirements for both drugs and cosmetics. This happens when a product has two intended uses, for example, when an antiperspirant is also a deodorant. Cosmetics are defined as substances that cleanse, beautify, promote attractiveness, or alter the appearance, without affecting the body's structure or function. Deodorants are regulated as cosmetics because they promote attractiveness only by masking odor, not by reducing sweat.

Unlike drugs, neither cosmetic products nor cosmetic ingredients are reviewed or approved by the FDA before they are marketed. But the agency urges manufacturers to do any necessary testing to prove that their products are safe. And cosmetic makers



Chicago Tribune

Antiperspirant testing in Unilever's "hot room."

must put a warning statement on the front labels of those products that have not been safely tested. The agency can take action against cosmetic products found to cause harm after they are on the market.

Why People Sweat

Whether the extra heat comes from hardworking muscles in the gym, from over-stimulated nerves due to stress, or from high air temperatures and humidity, sweating is the body's way of naturally regulating its temperature.

During extended, vigorous activity, a person can lose several quarts of fluid through the evaporation of perspiration. A pea-sized bead of sweat can cool about one quart of blood 1 degree Fahrenheit, according to the Mayo Clinic, and only about 1 percent of the body's sweat is produced under the arms.

Sweat itself is odorless. It's the bac-

teria that live on the skin and break down the sweat that cause the unpleasant odor. Keeping underarms dry and smelling good are big business. According to the Mintel Group, a marketing and research organization in Chicago, Americans spent an estimated \$1.7 billion in 2004 on antiperspirants and deodorants. These products, designed for both men and women, include aerosols, sprays, pumps, roll-ons, solid sticks, gels, and creams. The FDA refers to these various forms of application as "dosage forms."

Given the amount of money people spend on personal hygiene products, it would seem that an offensive body odor shouldn't be much of a problem. However, according to *Gray's Anatomy*, most people have several million sweat glands distributed over their bodies, providing plenty of opportunity for odors to develop.

There are two types of sweat glands. The eccrine glands, which we are born with and which are the most numerous, produce most of the sweat in the underarms. These glands open directly onto the surface of the skin. Apocrine glands, which are triggered by emotions, develop in areas abundant in hair follicles, such as the scalp, underarms, and genitals. These glands only begin to secrete sweat after puberty, and have little, if anything, to do with temperature regulation.

The sweat glands are located in the middle layer of skin called the dermis, which is also made up of nerve endings, hair follicles, and blood vessels. A sweat gland is a long, coiled, hollow tube of cells. Sweat is produced in the coiled part in the dermis, and the long part is a duct that connects the gland to the opening, or pore, on the skin's outer surface. When the sweat gland is

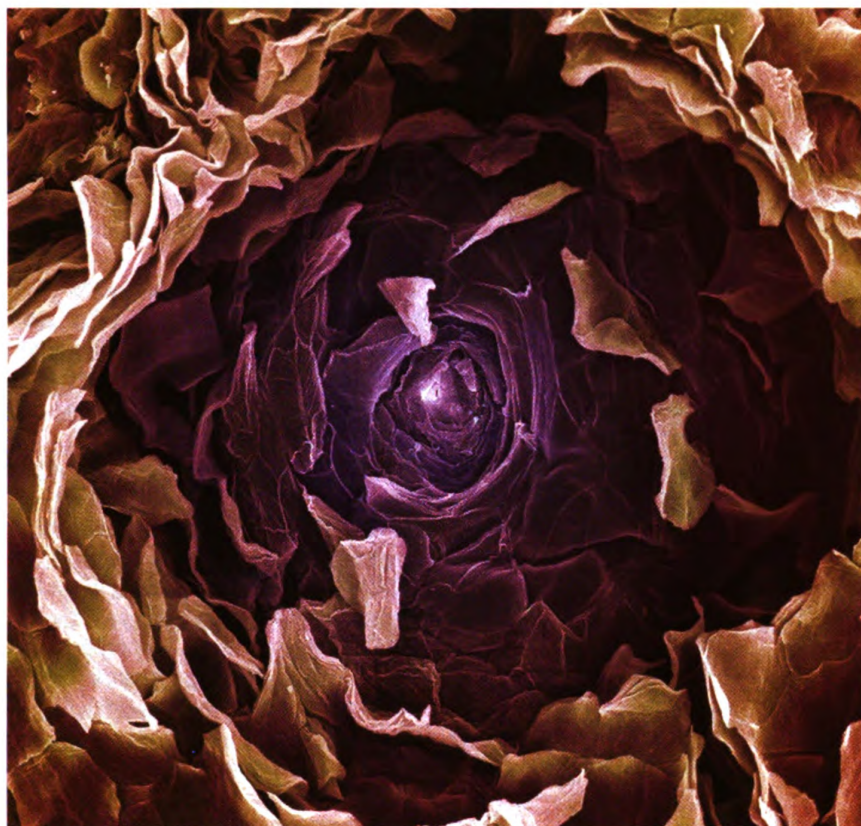


Photo Researchers Inc.

Enhanced photo taken through a microscope of a sweat gland pore (purple) opening onto the surface of human skin. This pore brings sweat from a sweat gland to the skin surface. The sweat evaporates, removing heat and playing a vital role in cooling the body. Skin cells can be seen flaking off the skin around the pore opening.

stimulated, the cells secrete perspiration that travels from the coiled part of the gland up through the straight tube and out onto the skin's surface.

The American Academy of Dermatology (AAD) says that perspiration is 55 percent to 60 percent fluid, mainly water. Perspiration also contains salt (sodium chloride), as well as trace amounts of other substances, such as ammonia, calcium, chloride, copper, lactic acid, phosphorous, and potassium. These substances, called electrolytes, help to regulate the balance of fluids in the body. The most abundant electrolytes are phosphorous and sodium, which cause sweat to sting the eyes and give sweat its salty taste.

The loss of excessive amounts of salt and water from the body can quickly dehydrate a person and can lead to circulatory problems, kidney failure, and heat stroke. So, although it's literally

cool to sweat, it's also important that people drink fluids when exercising or when outside in high temperatures.

Antiperspirants 101

People tend to interchange the words "antiperspirant" and "deodorant," but as regulated by the FDA, they are not the same. Antiperspirants have an aluminum-based compound as their main, "active" ingredient, which can be any number of compounds within an established concentration and dosage form. The active ingredient gives antiperspirants their sweat-blocking ability by forming a temporary plug within the sweat duct that stops the flow of sweat to the skin's surface.

The aluminum-based compound is always the first ingredient listed on the back of an antiperspirant container. A few common active ingredients are aluminum chloride, aluminum chlo-

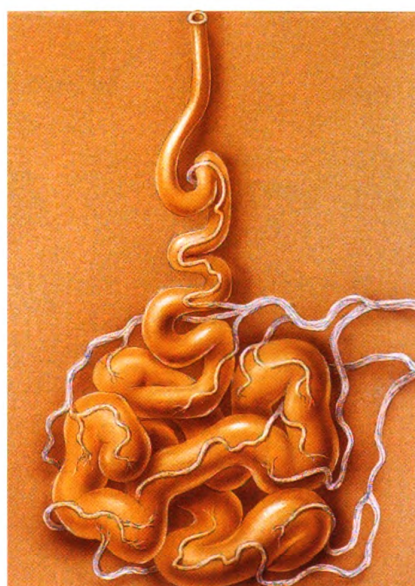


Photo Researchers Inc.

Sweat gland consists of a coiled tube (yellow), which secretes sweat, and a duct that travels through the hypodermis (pink) and the dermis (beige and violet), before opening onto the surface of the skin.

rohydrate, and aluminum zirconium. An "inactive" is any ingredient besides the active ingredient. Some of the inactive ingredients in an antiperspirant include talc, fragrance, and butane, used as an aerosol propellant.

With so many choices available, how do people choose a product that's right for them?

"Looking for a favorite scent is a great



Black Star/Dennis Brack

Matthew R. Holman, Ph.D., is an FDA scientist who handles all antiperspirant issues within the Division of Over-the-Counter Drug Products.

way for a consumer to narrow down the search," says Michelle Vaeth, a spokeswoman at Cincinnati-based Procter & Gamble Co. Product development, she says, is constantly driven by what consumers want, and the consumer products company regularly conducts detailed home interviews, quantitative questionnaires, and surveys to get this information.

Another factor is aesthetics, or how a product feels when applied to the skin. "Maybe a woman enjoys the cooling sensation of a clear gel and loves the fact that there's no residue," Vaeth says. Roll-ons tend to have a wet, cool, refreshing feeling upon application, and Vaeth says that many people like how this product feels on their skin after it dries—"they can tell it's still there and working."

Jonathan Hague and Cindy Dumlao, who both work in product development with Unilever, an Anglo-Dutch consumer products company, agree that people tend to go with products they trust. "They want good, high-performance products," says Hague, "and what our consumers think is important to us."

So important, Dumlao adds, that Unilever keeps a database of 18,000 consumers who come to participate in the effectiveness of antiperspirant formulas at the company's clinical and consumer testing facility.

"Basically," she says, "we put people in a hot room, about 100 degrees Fahrenheit, with a relative humidity of 35 percent, and collect their sweat."

The facility is also where "new formulations and fragrances are discovered," says Hague. In his experience, "stick antiperspirants appear to be the preferred dosage form in North America."

Many factors control how effective an antiperspirant is, such as the type and size of the active ingredient used in the formulation.

"Different actives have different levels of effectiveness at stopping sweating," says Timothy J. Long, Ph.D., a scientist with P&G Beauty. The active ingredient also must be pH balanced—basic enough, Long says, not to cause irritation to the skin, but acidic enough to form the solid plugs in the sweat ducts.

The antiperspirant effectiveness test required by the FDA determines that a product is effective or ineffective in its final formulation. But, says Holman, "we do not have any data that suggest any dosage form is better than another." He also says there's a lot of variability between dosage forms. An antiperspirant in finished form may vary in degree of effectiveness because of minor variations in formulation, or in individual interpretation of the directions for its use.

For example, while a product label may instruct the user to hold a can of aerosol six inches from the underarm and then spray, Holman says, how long each person sprays, swipes, glides, wipes, or rolls will vary. Therefore, the directions don't directly reflect the con-

Many factors control how effective an antiperspirant is, such as the type and size of the active ingredient used in the formulation.

ditions of effectiveness. But Holman adds that consumers can be assured that products are effective whether they are gels, sticks, aerosols, or others, if they pass the FDA's test.

Antiperspirants and the FDA

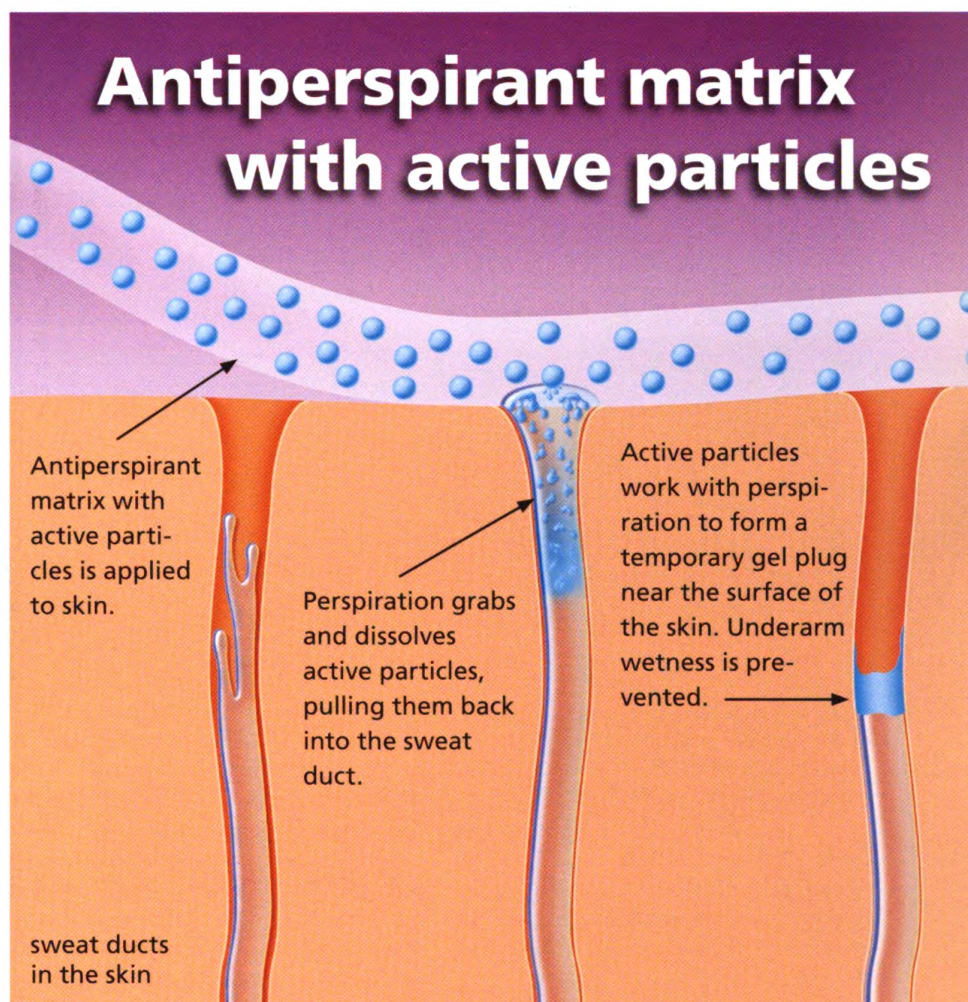
"People feel that those products on the shelf are a direct reflection of what we regulate," says Holman. "But mostly, it's based on what's selling."

Like prescription drugs, the FDA oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks. OTC drugs account for more than 100,000 products on the market that involve about 800 active ingredients. The FDA classifies these nonprescription drugs by treatment category, such as laxatives, antacids, and antiperspirants, and evaluates their ingredients. So, rather than review thousands of individual antiperspirant products, the FDA evaluates the far fewer active ingredients found in them.

Most OTC drugs are subject to rules called monographs, which state requirements for categories of nonprescription drugs, such as what ingredients may be used and for what intended use. If the standards of the OTC monograph are met, premarket approval of a potentially new OTC product is not necessary.

The FDA is mainly concerned about claims being made for a product, Holman says. For example, in the familiar slogan, "strong enough for a man but made for a woman," the company had to prove that the product was tested in both men and women because there are physiological differences between them. Similarly, testing must confirm marketing statements such as "so effective you could skip a day."

By contrast, Holman says that if a company claimed that a new antiperspirant ingredient is effective, "it would



P&G Beauty

require a new drug application because the ingredient is not already included in the antiperspirant monograph as generally recognized as safe and effective."

Holman also says that manufacturers tend to test antiperspirant products on more women than men. One reason seems to be underarm hair. Women are required to shave two days before testing to keep hair to a minimum and to minimize skin irritation. "With that said, skin irritation related to shaving is not a major safety concern because it is not serious or life threatening," Hol-

man says. "And common sense dictates women will not keep using a particular product if it causes irritation."

The important thing to remember, says Holman, "is that antiperspirants don't completely eliminate sweat." According to the FDA's testing standards, the most effective products, those that claim "extra strength" or "maximum strength," are based on at least a 30 percent sweat reduction rate in most people. Regular strength products test at a 20 percent sweat reduction rate in most people.

Sweating Too Much, or Not Enough

If the complex biological mechanism of perspiration goes awry, it can result in either excessive perspiration (hyperhidrosis) or little or no perspiration (anhidrosis), a potentially life-threatening condition.

Dermatologists at the AAD say that excessive sweating is normal when a person is anxious or has a fever. However, excessive sweating can be a chronic condition and may signal other medical conditions such as thyroid problems, low blood sugar levels, a nervous system disorder, or the onset of menopause.

Excessive sweating is more than a mild nuisance that some people experience. According to the AAD, hyperhidrosis affects about 8 million Ameri-

Administered into the armpit, small doses of an injectable form of the sterile purified botulinum toxin stop release of the chemical messenger acetylcholine that supplies nerves to the eccrine glands, thereby temporarily paralyzing the nerves in the underarm that stimulate sweat production.

To avoid the possibility that Botox treatments can mask a potentially serious disease, the FDA advises patients to be evaluated by a doctor for other possible causes of excessive sweating. Botox is approved for treatment of the underarms, but not for excessive sweating of other sites such as the feet and palms.

The Cancer Myth

The rise of the Internet has made it easy for false health claims, scary sto-

Mayo Clinic, the American Cancer Society (ACS), and the Cosmetic, Toiletry and Fragrance Association agree. Razor nicks may increase the risk of skin infection, but not cancer.

According to the ACS, sweat glands are not connected to the lymph nodes. Most cancer-causing substances are removed by the kidneys, are released through urine or by the liver, and are eliminated with feces. The ACS says that lymph nodes may help to clear some toxins from the body, but they do not release these toxins through sweating. Sweat is not a significant route for eliminating toxins from the body.

And a study of 813 women with breast cancer and 703 women with no history of breast cancer, published in the October 2002 issue of the *Journal of the National Cancer Institute*, found

The NCI says that no existing scientific or medical evidence links the use of underarm antiperspirants or deodorants to the subsequent development of breast cancer.

cans. Depending on where it occurs on the body, hyperhidrosis has several treatment options, including topical agents such as prescription antiperspirants, oral medications, and surgery. Prescription antiperspirants contain higher doses of the active ingredient aluminum chloride. Skin irritation is the main side effect with prescription antiperspirants such as Drysol (aluminum chloride hexahydrate).

In July 2004, the FDA approved Botox (botulinum toxin type A), a drug that is used to temporarily erase wrinkles for cosmetic purposes, to treat severe underarm sweating (primary axillary hyperhidrosis) that cannot be managed by topical agents. Available by prescription only, botulinum toxin type A is a protein produced by the bacterium *Clostridium botulinum*. This protein works by interrupting the chemical messages released by nerve endings that tell the sweat gland when to sweat.

ries, and rumors to reach millions of people in a matter of minutes. One such myth says that antiperspirants may cause breast cancer.

According to the National Cancer Institute (NCI), the breast cancer-antiperspirant myth first appeared in the form of an e-mail in the 1990s, and continues to resurface and recirculate about every year or so. The false information suggests that antiperspirants contain harmful substances, which can be absorbed through the skin or can enter the body near the breasts through nicks in the skin caused by shaving. The e-mails also suggested that antiperspirants keep a person from "sweating out toxins," resulting in the spread of cancer-causing toxins via the lymph nodes.

But the NCI says that no existing scientific or medical evidence links the use of underarm antiperspirants or deodorants to the subsequent development of breast cancer. The FDA, the

that antiperspirants do not cause breast cancer.

Some speculate that the myth could have been started by women being told not to wear antiperspirants or deodorants before a mammogram. They were told this, not for safety reasons, but because residue from these products appearing in the X-ray is often mistaken for an abnormality in the breast. ■

For More Information

Food and Drug Administration
www.fda.gov

American Academy of Dermatology
www.aad.org

International Hyperhidrosis Society
www.SweatHelp.org

National Cancer Institute
www.cancer.gov

Reducing the Risk of Rabies



Most of the recent human rabies cases in the United States have been caused by a rabies virus from bats, says the Centers for Disease Control and Prevention. If you are bitten by a bat, wash the affected area thoroughly and get medical advice immediately.

CDC

By Linda Bren

A Suffolk, Va., couple didn't know they were being followed when they drove into their garage one evening in April 2005. When the man and woman got out of the car, they saw their stalker: a gray fox. The animal sprang at the woman, wrapped itself around her legs, and then tangled with the cat that came out of the house to greet its owners.

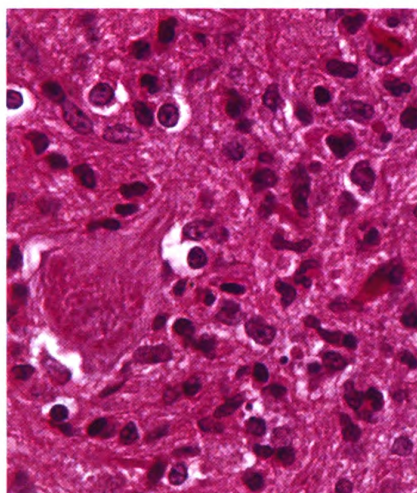
The fox was killed and found to have rabies. The woman, who had been scratched, received a series of rabies vaccinations and was fine. But sadly, the family cat was euthanized because it had not received its preventive rabies shot, says Calvin Jones, the environmental health manager for the Western Tidewater Health District in Virginia's Department of Health (VDH).

"The way we handled the case would have been different if the cat had a current rabies vaccination," says Jones, adding that the pet would have been revaccinated and confined for 45 days for observation. But to protect the public health, an unvaccinated pet exposed to rabies must be euthanized immediately or placed in strict isolation for six months with no direct human contact, says Jones.

Thanks to increased vaccination of pets and advances in human vaccines, the number of human deaths from rabies in the United States in the last century has decreased from 100 or more per year to an average of one to two per year, according to the Centers for Disease Control and Prevention (CDC). Yet rabid animals are found each year in every state except Hawaii.

In 2003, the CDC received reports of more than 7,000 cases of rabies in animals in the United States and Puerto Rico. More than 90 percent of the cases occurred in wild animals, mostly raccoons, skunks, bats, and foxes. Reports of domestic animals with rabies that year included 321 cats and 117 dogs.

Just three cases of rabies in humans were reported to the CDC in 2003, but more than 40,000 people may have been spared from the deadly disease by getting vaccinated after they were potentially exposed. The Food and Drug Administration has approved vaccines to prevent rabies in humans, and the U.S. Department of Agriculture (USDA) has licensed vaccines to prevent rabies in many animals.



CDC

This photograph taken through a microscope shows the brain tissue of a person infected with the rabies virus.

"It's critical to keep current on rabies vaccinations to protect pets," says Suzanne Jenkins, V.M.D., M.P.H., epidemiologist and state public health veterinarian for Virginia, "and, more importantly, so they cannot transmit rabies to people."

If a person is exposed to rabies, "the sooner treatment is begun after exposure, the better," says Robin Levis, Ph.D., regulatory coordinator in the FDA's Office of Vaccines Research and Review.

Deadly Virus

Rabies is caused by a virus that attacks the brain. The virus enters the

body through the saliva of an infected animal, usually by a bite, but it can also be transmitted if infected saliva gets into an open wound or splashes into mucous membranes such as those in the eyes, nose, or mouth. From the saliva's point of entry, the virus travels along nerve cells to the brain. It replicates there and moves to the salivary glands. In a rabid animal, the cycle is repeated when the animal bites a person or another animal.

Rabid animals may be aggressive and vicious, or lethargic and weak. In people, early rabies symptoms of fever, headache, and fatigue are followed by confusion, agitation, hallucination, and paralysis. Once symptoms begin, the disease is almost always fatal, says the CDC.

Only mammals get rabies—birds, reptiles, amphibians, and fish do not get the disease.

Human Rabies Vaccines

The FDA has approved several injectable products that are effective in preventing rabies in people who have been exposed to the virus. This post-exposure treatment consists of one injection of proteins that fight the infection (rabies immune globulin) and five injections of rabies vaccine over a 28-day period. The vaccine works by stimulating a person's immune system to produce antibodies that neutralize the virus. "The person develops a protective immune response before the virus reaches the brain and begins to actively replicate," says Levis.

Rabies immune globulin contains antibodies from blood donors who were given rabies vaccine. The antibodies provide interim protection until an exposed person's own antibodies develop in response to the vaccine. "In addition, injecting rabies immune globulin at the site of injury reduces the amount of virus that is able to enter the nerve cells and potentially initiate an active infec-

Rare Recovery From Rabies

Only one person in the United States is known to have recovered from rabies without receiving a rabies vaccination, according to the Centers for Disease Control and Prevention. While attending a church service in September 2004, 15-year-old Jeanna Giese of Fond du Lac, Wis., picked up a bat she saw fall to the floor and released it outside the building. The bat bit her on the left index finger, but she did not get medical treatment at the time. A month later, the teen complained of tiredness and a feeling of numbness in her left hand. Walking became difficult, and she experienced double vision, nausea, vomiting, slurred speech, twitching, and fever. Giese was diagnosed with rabies and after intensive care in a Milwaukee hospital, which included a drug-induced coma for seven days, she gradually improved. Doctors are unsure whether she will fully recover. ■

tion," says Levis.

No test can detect rabies in humans at the time of a bite. People who may have been exposed should immediately wash all bite wounds and scratches with soap and water to decrease the chance of infection. If the suspect animal cannot be captured and tested or observed for symptoms, the vaccine regimen should be started promptly. According to the CDC, no one in the United States has developed rabies when the currently recommended post-exposure treatment regimen was followed.

Rabies vaccine may also be given to people before they are exposed to the virus if they are considered at high risk for exposure, such as veterinarians, wildlife officers, animal handlers, and some laboratory workers. This pre-exposure regimen consists of three injections of vaccine instead of five. Being bitten by a rabid animal, though, requires two more vaccine injections. Pre-exposure vaccination simplifies therapy by eliminating the need for immune globulin and by decreasing the number of doses of vaccine needed after exposure, says Levis. It may protect people who unknowingly were exposed to rabies, as well as those who may be delayed in getting post-exposure vaccine, she says.

Before travel abroad, the CDC recommends consulting a health care provider, travel clinic, or health department about the risk of exposure to rabies and about ways to handle an exposure should it arise. A pre-exposure vaccine may be suggested when traveling to some developing countries or remote areas.

Older rabies vaccines required painful, daily injections in the abdomen for up to three weeks, and they could produce severe side effects, says Levis. Today's rabies vaccines require fewer injections, are given in the arm, and have few serious side effects.

Animal Rabies Vaccines

Rabies vaccines are available for dogs, cats, ferrets, horses, sheep, and cattle. To be effective, these vaccines must be injected before an animal is exposed to rabies. If exposed, the animal should get a booster shot.

"One of the most important ways to prevent rabies is to keep up to date on vaccinations for cats, dogs, and ferrets," says Jenkins. Depending on the type of vaccine used, it should be given yearly or every three years. Even indoor pets should have rabies vaccinations, Jenkins says, recalling a case in which a woman found her unvaccinated indoor cat with a bat in its mouth. The bat, which escaped, was assumed to have rabies, making for the tough decision of either euthanizing the cat or isolating it for six months.

Not only is it good preventive health care to vaccinate pets, but it's the law in most states for dogs and cats to be vaccinated against rabies, according to The Humane Society of the United States. Some states also require rabies vaccinations for ferrets.

In a cooperative program between the USDA, the CDC, and state governments, animals such as raccoons, coyotes, foxes, and skunks are being vaccinated orally in certain areas where rabid wildlife are frequently found. The oral vaccine is hidden in a bait of fishmeal or other food. The baits are dropped by airplanes into rural areas and spread by hand in urban and suburban areas.

Keep Your Distance

Many more wild animals than pets are reported to have rabies, Jenkins says. But the most common reason people get post-exposure vaccines is that they're bitten by a domestic animal that isn't available for testing. "They may see a cute dog or cat on the street that they try to pet, and it bites them and runs off," she says.

"Avoid wildlife and domestic animals that you don't know," advises Jenkins. Most healthy wild animals will generally try to avoid humans, she says, but wild animals at parks and camp sites may be more brazen if they're used to getting handouts.

If you're hiking in a remote area "and a raccoon is sitting in the middle of a path and doesn't want to move, I'd take a very wide path around it," says Jenkins.

Wildlife are not found only in remote or rural areas, says Mark Dembert, M.D., M.P.H., district director of the VDH's Western Tidewater Health Dis-

Help Prevent Rabies

- Keep rabies vaccinations for all cats, dogs, and ferrets up to date. Many communities sponsor low-cost rabies vaccination clinics for pets. Check with your local animal control agency.
- Do not let pets roam.
- Enjoy wildlife from a distance.
- Do not approach a stray animal; report it to your local animal control agency.
- Seal off holes that can be entryways for animals into your home.
- Keep lids on garbage cans and don't leave pet food outside overnight.
- If bitten by an animal, immediately wash the wound with soap and water for at least five minutes and get medical help at once. Report the bite to your local health department. ■

CDC

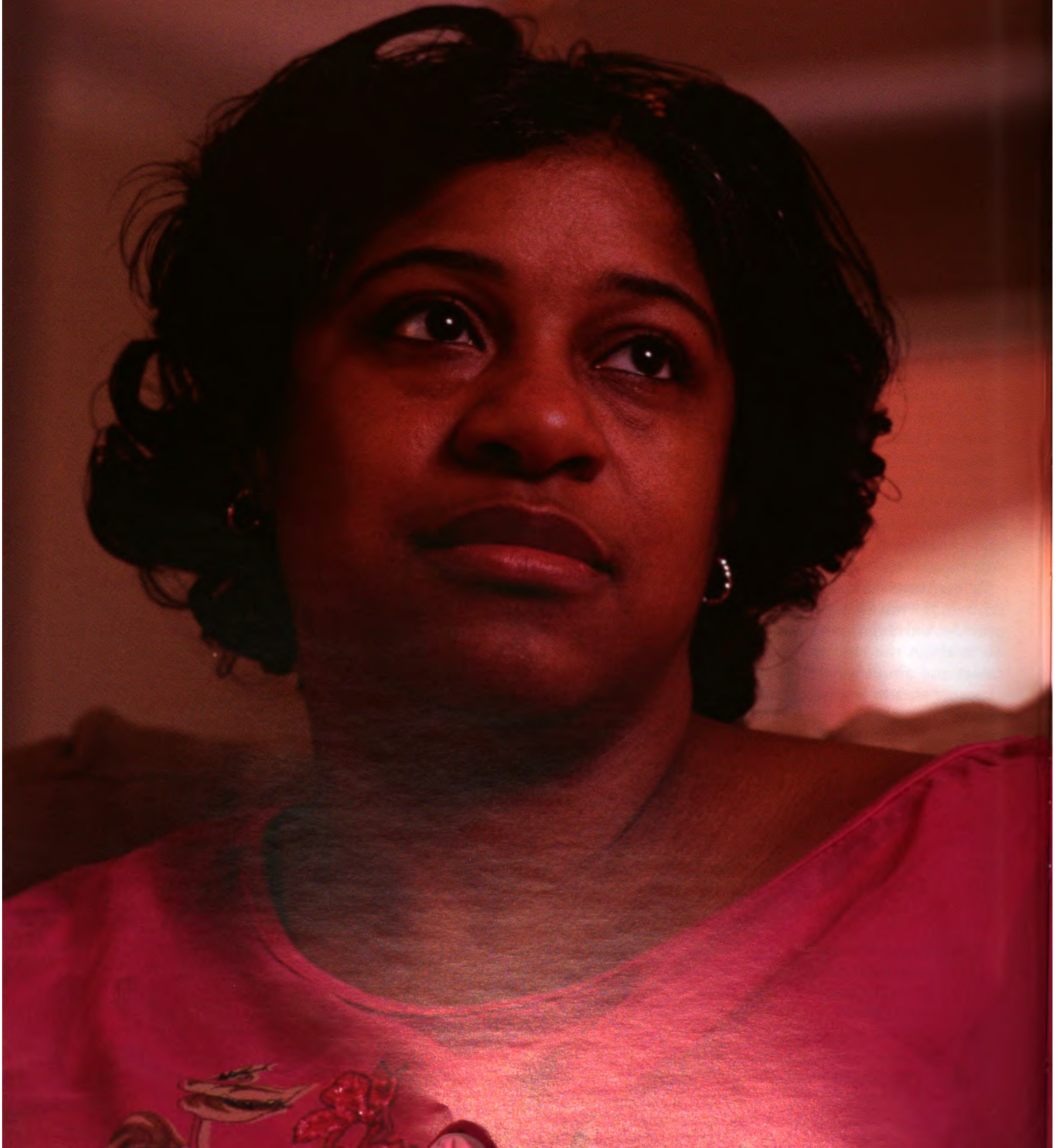
trict. Dembert says that new development disturbs wildlife habitats and wildlife become more visible. "People encroaching on nature is a factor in a lot of places," he says. "Rabies is becoming more of a suburban problem."

Dembert advises people who are planning a move or a vacation with their pets to call ahead and ask the health department whether rabies is a problem in the area. Vaccinate and be vigilant, he says. "It just makes good sense if you have pets. It can ruin a family's summer vacation if a skunk comes in and bites Fido at your vacation rental." ■

For More Information

www.cdc.gov/ncidod/dvrd/rabies/

Battling Lupus



By Michelle Meadows

Arlletha Manlove, 41, of Kansas City, Mo., first noticed feeling different after having her first child. She experienced unusual fatigue, but thought maybe it was the adjustment of taking care of a new baby.

Everything was a struggle, she says. "It was a chore to take a shower and a chore to get dressed." She also had unexplained fevers, recurrent upper respiratory infections, and swelling and aching in her hands. "I would wake up in the morning with swollen fingers, and by the time I got dressed, the swelling would go down."

She had six miscarriages in five years and repeated bouts of uterine pain. "I had been to gynecologists, psychiatrists, psychologists, and general practitioners," she says. "I started to think maybe they were right; maybe it was all in my head."

After a devastating miscarriage in the second trimester of pregnancy, Manlove's uterine pain became even worse and her other symptoms continued. At her mother's urging, she agreed to try one more doctor, a fertility specialist. He diagnosed her with both endometriosis and lupus in 1990 and referred her to a rheumatologist, a doctor who has additional training in diagnosing and treating arthritis and other diseases of the joints, muscles, and bones.

Manlove recalls feeling better right away after taking a combination of three medicines: prednisone, Imuran (azathioprine), and Plaquenil (hydroxychloroquine). "I remember thinking: 'I'm back! This is what it's like to feel good,'" she says. "But then the side effects kicked in. I had horrible mood swings, and within a very short time, I went from 121 pounds to 200 pounds."

Under close monitoring from her doctor, Manlove went on to have a successful pregnancy and had a second child 12 years ago. She says she's learned that good communication between patients and doctors is essential for coping with chronic illness. "I was very good about letting him know about side effects and asking questions, and we have been able to cut back on some of the medications over time," she says. She's also made important lifestyle changes. "You can't expect your doctor to give you a pill and then everything will be OK," she adds.

Lupus experts recommend that people with lupus have regular medical appointments and take their medication as prescribed. Other recommendations include sunscreen use and limiting sun exposure to prevent flares, regular exercise to improve joint flexibility and muscle strength, good eating habits, and plenty of rest.

"I've learned to stop when I need to, and sometimes I take three short naps in a day," says Manlove, who works full time and is active with the Lupus Foundation of America (LFA) as a support group facilitator. A chronic illness can take a toll on family and friends, too, so it's important to seek out support.

"My husband believes me when I say I feel bad," she says. "Without his support, the stress of this journey would have been much harder. Not everyone is so lucky."

Arlletha Manlove, 41, Kansas City, Mo., was diagnosed with lupus in 1990 after years of suffering from unusual fatigue, recurrent infections, and repeated miscarriages.

Black Star/Craig Sands

The body's natural defenses, called the immune system, protect us from viruses, bacteria, and other foreign invaders. But in people with systemic lupus erythematosus (SLE), the immune system can't tell the difference between foreign substances and the healthy cells and tissues.

"Instead of fighting infection, the immune system attacks 'self,' the person's normal tissues," says Michelle Petri, M.D., a professor of medicine and director of the Lupus Center at The Johns Hopkins University School of Medicine in Baltimore. Immune complexes then build up in the tissues, causing inflammation, tissue injury, and pain. "SLE can affect any organ system," Petri says, "but especially causes skin rashes after sun exposure, swollen joints, and kidney disease."

SLE, also commonly called lupus, is a chronic autoimmune disease that affects 1.5 million to 2 million Americans, according to the LFA. Nine out of 10 people who have it are women, and it mostly affects women of childbearing age, those between ages 15 and 44. But men, children younger than 15, and older people also get lupus. People of any race or ethnicity can develop lupus, but blacks, Hispanics, Asians, and American Indians are at increased risk.

There is no cure for lupus, but, in most cases, the disease can be managed. Because of better detection and early treatment, between 80 percent and 90 percent of people with lupus can look forward to a normal lifespan, according to the LFA.

"Although the overall outlook has improved, it is a disease that must be monitored very carefully," says David Isenberg, M.D., academic director of rheumatology at University College London. "It has a major effect on quality of lives, and a smaller, but significant, number of people still die from it."

Maribel Ramirez, 43, was diagnosed with lupus in 1989 and started a support group in the Houston area in 1995 for Spanish speakers who have the disease. "I see people dying, and it's very difficult," she says. "We are desperate for better treatments." Ramirez has suffered damage to her lungs, kid-

neys, and heart. In 1994, she had a stroke due to vasculitis, a condition in which blood vessels become inflamed. "I worry about the disease and all the medications that I've been taking for so long," she says.

There are effective drugs that decrease inflammation and suppress the immune system in people with lupus, but these drugs also can lead to damaging side effects. Doctors and patients have to weigh carefully the

there are no treatments for two common complaints of lupus patients—fatigue and memory loss. Ramirez says she once had to pull off the freeway and call a friend for help because she was lost, even though she was very close to home.

Researchers are looking for lupus treatments that are safer and more targeted, but the uniqueness of the disease poses challenges for drug development. The exact cause of

Lupus Symptoms

A list of the most common symptoms of lupus and the percentages of people with lupus who have a particular symptom:

Achy joints (arthralgia)	95
Fever more than 100 degrees F	90
Swollen joints (arthritis)	90
Prolonged or extreme fatigue	81
Skin rashes	74
Anemia	71
Kidney involvement	50
Pain in the chest on deep breathing (pleurisy)	45
Butterfly-shaped rash across the cheeks and nose	42
Sun or light sensitivity (photosensitivity)	30
Hair loss	27
Abnormal blood-clotting problems	20
Fingers turning white and/or blue in the cold	17
Seizures	15
Mouth or nose ulcers	12

Lupus Foundation of America

benefits and risks of treatment. Isenberg likens treating patients with lupus to putting them on a fence between two fields.

"One side represents the effects of the disease, and the other represents the side effects of treatment," he says. For example, people with lupus are at increased risk for developing hardening of the arteries that can cause a heart attack or stroke. The risk is due partly to having lupus and partly to taking corticosteroids, which decrease inflammation caused by the disease.

Another challenge, says Petri, is that

lupus is unknown. The disease varies in intensity. And the symptoms are wide-ranging, sometimes involving multiple organs. Symptoms also tend to come and go, with active periods, called flares, and quiet periods when the disease is in remission.

In March 2005, the Food and Drug Administration released a draft guidance for industry on testing drugs for lupus in clinical trials. The guidance includes a general discussion of outcomes and measurements of disease activity, as well as claims that the agency may be willing to approve if

'Because lupus can affect any organ, the disease can look different in different people.'

they are supported by substantial evidence. "This guidance is an important step in stimulating new drug development for lupus treatment," says Acting FDA Commissioner Dr. Lester M. Crawford. "We are intensely interested in this area."

Symptoms

The most common symptoms of lupus are skin rashes, extreme fatigue, arthritis, unexplained fevers, and kidney problems. According to the LFA, about 40 percent of people with lupus have a rash that spreads across the nose and over the cheeks in the shape of a butterfly, called the malar rash.

"Because lupus can affect any organ, the disease can look different in different people," says David Wofsy, M.D., chief of rheumatology at the San Francisco Veterans Affairs Medical Center and professor of medicine at the University of California, San Francisco. Inflammation in one person might lead to multiple organ damage, whereas another person might have just occasional joint pain. "There are many people who never encounter the life-threatening manifestations of the disease," Wofsy says.

When lupus is severe, such as with serious kidney damage, the symptoms are more obvious to a physician. But, in most cases, people experience mild symptoms, which can make the illness hard to diagnose. Lupus also may develop gradually. "In the hands of someone knowledgeable about lupus, it can be easy to diagnose," Wofsy says. "But it's not uncommon to hear that someone with lupus went to several doctors before being diagnosed or was misdiagnosed." Experts say that sometimes, it can take a couple of years to figure out what's going on.

"In mild forms of the disease, symptoms usually present in a confusing manner," Wofsy says. "Somebody comes in who is young with a variety of nonspecific symptoms, and a doctor

may not be thinking about lupus. The person might complain about feeling tired in the afternoons or about feeling achy. A doctor could think that these symptoms might be due to stress or depression, or a virus."

One of the most frustrating things for someone with lupus is being sick, but feeling like nobody believes you, Ramirez says. "People think you're lazy or crazy, or both," she says. "You can also look nice and healthy, even though you feel very bad."

Before she was diagnosed with lupus, Ramirez battled mysterious symptoms for 10 years. She had five miscarriages, and later found out that women with lupus have higher rates of pregnancy loss. She also had unexplained skin rashes, anemia, pain in her legs and arms, urinary tract infections, kidney infections, fevers, mouth sores, and overwhelming fatigue.

In an unpublished study done in 1999, Isenberg and his colleagues asked 100 lupus patients what they were most worried about regarding their illness. "Their biggest concern was fatigue," Isenberg says. "They were worried about sleeping all night and still being exhausted in the morning or about feeling too tired to pick their children up from school or to do other things that they want to do."

As a former police officer and member of the military, Tony Chisholm, 46, of Fall City, Wash., was used to being active. Feeling wiped out from lupus sent him into a deep depression. "I just couldn't get out of bed," he says. "But nothing would show up on a physical exam."

He also has had bouts of flu symptoms, swelling around the eyes, joint pain, and chest pain. "Sometimes, the



Photo Researchers Inc.

Skin lesions of lupus erythematosus. This autoimmune disorder affects the skin as well as many other organ systems.

symptoms last for four months, and then I might go four more months without any problems," he says.

It was a photograph that finally helped Chisholm get some answers. In 1997, he and his family went to Great Britain for vacation and met another couple. The couple mailed Chisholm a photo from the trip. "The red butterfly rash across my face was plain as day," he says. "My wife insisted that I go to the doctor." After looking at the photo, the doctor ran tests for lupus. "Before that, I hadn't been diagnosed with anything else, except maybe hypochondria."

Diagnosis

Early detection of lupus is important to lower the chance of organ damage and other complications. Doctors rely on a patient's report of symptoms, a



Photo Researchers Inc.

Close-up of a circular lesion on the leg of a 49-year-old woman due to discoid lupus erythematosus (DLE). About 10 percent of people with lupus have DLE, which is limited to the skin and usually less severe than systemic lupus, which can affect multiple organs.

medical history and exam, and blood and urine tests. "Lupus can lower blood counts and affect kidneys, causing protein and blood in the urine," Petri says. Doctors also may do skin or kidney biopsies, in which tissue is removed and examined for signs of autoimmune disease.

A commonly used test for lupus is the anti-nuclear antibody (ANA) test, which looks for autoantibodies that are reacting against the nucleus, also known as the command center, of the body's cells. "Most people with lupus have an elevated ANA, though a few rare patients have a negative ANA," Petri says. But a positive ANA isn't enough to confirm lupus. "Twenty percent of healthy women can have a positive ANA," she says. The ANA also detects other autoimmune diseases, including Sjögren's syndrome, scleroderma, and rheumatoid arthritis.

So if the ANA test is positive, more specific testing is used to confirm a lupus diagnosis. Doctors test for complement components, a group of pro-

teins in the blood that help destroy bacteria. Low complement levels can be associated with lupus. Doctors also do blood tests for antibodies to DNA and for other cell nuclear components. Two specific tests for lupus are the anti-double-stranded DNA (anti-dsDNA) antibody test and the Smith antibody (anti-Sm) test.

"Lupus is an unpredictable disease, but certain antibodies help to make some predictions," Petri says. For example, people with anti-dsDNA or low complement are more likely to develop kidney disease, she says. And some women with lupus have a syndrome in which antiphospholipid antibodies cause blood clots. This syndrome is associated with miscarriages, strokes, and deep vein thrombosis.

The American College of Rheumatology says that to be diagnosed as having lupus, a person should meet at least four of the following clinical and laboratory criteria:

- rash over the cheeks
- red, raised patches (discoid rash)

- photosensitivity
- ulcers in the nose or mouth
- arthritis (non-erosive arthritis in which the bones around the joints don't become destroyed)
- inflammation of the lining of the heart or lung (pleuritis or pericarditis)
- kidney disorder (excessive protein in the urine or cellular casts, or both)
- neurological disorders such as seizures, convulsions, or psychosis
- blood (hematologic) disorders such as repeated low blood cell counts
- positive ANA test
- immunologic disorder.

Multiple Factors

How and why lupus develops is not understood. Experts say the illness probably results from a complex mix of hormonal, genetic, and environmental factors. The hormone estrogen likely plays some role, which may explain why more women than men have the disease. And lupus involvement may worsen before menstruation and during pregnancy.

Genetics may partly explain racial and ethnic differences in the incidence and severity of lupus. Blacks not only have a higher incidence of lupus, but they tend to develop it earlier and experience more severe disease.

To look for patterns, researchers are studying families in which one or more members have lupus. Lupus sometimes runs in families. About 5 percent of children develop lupus if a parent had the disease, according to the LFA. Research shows that if an identical twin has lupus, the other twin is more likely to have or develop the disease than a non-identical twin would be.

Petri says the environmental factors that may trigger lupus in genetically susceptible people include ultraviolet light, infections such as the Epstein-Barr virus, some drugs such as antibiotics in the sulfa group (Bactrim, Gantrisin, and Septra), and echinacea. Some people experience drug-induced lupus caused by extensive use of medications. The symptoms are similar to SLE but usually go away when the medications are stopped. Drugs most commonly connected with drug-induced

'It's as if you shuffle a deck of cards and lupus patients get the bum deal.'

lupus are hydralazine for hypertension and procainamide for irregular heart rhythms.

"It's believed that somehow the wrong immune system meets the wrong insult," says Joan Merrill, M.D., medical director of the LFA and head of the Clinical Pharmacology Research Program at the Oklahoma Medical Research Foundation. "Healthy people may inherit protective genes," Merrill says. "It's as if you shuffle a deck of cards and lupus patients get the bum deal."

In 2003, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) announced that scientists had discovered a genetic "signature" in some people with SLE who develop life-threatening complications, such as blood disorders, central nervous system damage, and kidney failure. Fourteen of the thousands of genes studied were linked to a subset of SLE patients with severe disease. The 14 genes are known as the interferon (IFN) expression signature. The genes are turned on by IFN, a family of proteins that have a role in regulating immune responses.

The Alliance for Lupus Research created the International SLE Genetics Consortium, a group of researchers who are working to find the genes that put people at risk of lupus. Consortium members will contribute genetic material from all over the world in the hope of finding more targeted treatment.

Scientists have also recently discovered that people with lupus may have a genetic defect in a cellular process called apoptosis. Normally, special white blood cells work to clear dying cells from the body. But if there is an abnormality in this process, the lingering cell debris may trigger the production of autoantibodies that attack healthy tissue.

Researchers continue to investigate abnormalities in T cells and B cells of mice and humans with lupus. These

white blood cells control immune response.

Typical Treatment

Doctors take an individualized approach to treatment, depending on the nature and severity of the disease. Sometimes, a combination of drugs is needed. Through early treatment, doctors want to prevent flares, to treat them when they occur, and to lower the risk of organ damage. At the same time, a key goal is minimizing the side effects of medication.

Commonly Used Drugs for Lupus

.....
Acetaminophen

.....
**Non-steroidal
anti-inflammatory drugs**

.....
Corticosteroids

.....
Anti-malarials

.....
Immunosuppressives

Many people with lupus need only Tylenol (acetaminophen) or non-steroidal anti-inflammatory medications (NSAIDs), such as aspirin, Advil, and Aleve. These medications control pain, fever, and inflammation. Risks of NSAIDs include stomach or bowel irritation. And when prescription NSAIDs are used chronically, there appears to be a possibility of an increased risk of heart attacks and strokes.

For serious problems such as kidney inflammation, corticosteroids may be needed. Examples are prednisone, prednisolone, and cortisone. These are either applied to the skin or taken by pill or injection. Side effects include

weight gain, puffy cheeks, thinning hair, acne, mood swings, and trouble with concentration.

Taken over long periods, corticosteroids also can raise blood pressure and cholesterol levels, as well as increase the risk of infections, diabetes, cataracts, and osteoporosis. "As many as 90 percent of SLE patients require prednisone, which has side effects even at low doses," says Petri. These drugs shouldn't be stopped suddenly.

Another category of drugs that has worked in some lupus patients is called anti-malarials. They work to prevent flares, new kidney disease, and blood clots, Petri says. Experts say that Plaquenil (hydroxychloroquine sulfate) is the one most commonly used. The risk of side effects is low, but, in very rare cases, anti-malarials can cause changes in the retina. People who take anti-malarials are advised to get regular eye exams. More common side effects include nausea, diarrhea, and blurry vision.

Some people who experience severe flares also may need immunosuppressive or chemotherapy drugs, which are given by mouth or infusion. Examples are Imuran (azathioprine), Cytosan (cyclophosphamide), and Sandimmune and Neoral (both cyclosporines). These drugs suppress the immune system and help limit organ damage. But they also make it harder to fight off infection, and all raise the risk of anemia and cancer. Other side effects are nausea, vomiting, hair loss, osteoporosis, and ovarian failure.

"Our biggest challenge is the toxicity of the drugs—trying to control the pathological immune response without doing considerable harm," says Wofsy. "In some cases, the treatment is worse than the disease. We always have to ask: 'Are we making the person susceptible to infection? Are we causing osteoporosis? What other harm are we doing?'"

Progress has been made in prevent-

ing and treating some of the secondary problems related to lupus, Wofsy says. For example, people taking corticosteroids may also require other medications to help prevent bone loss.

"We do a much better job of controlling hypertension, preventing osteoporosis, and treating infections with antibiotics in patients with lupus than we used to do," Wofsy says. "But the advances with lupus have not yet come in the form of treatments that reverse the immunologic problems that are at the heart of the disease."

short- and long-term results.

Promising approaches under investigation for lupus include hormone modification drugs, immunosuppressive drugs that are more selective, and new biologics. Researchers are especially looking for lupus treatments that can minimize the use of corticosteroids.

In people with lupus who have severe kidney disease, CellCept (mycophenolate mofetil), a drug approved for organ transplants, has helped some of them. Of the biologics under study for lupus treatment, some block B cells and

of making an important contribution to medical research. The NIH recommends that people find out about the benefits and risks of any clinical trial they are considering, including information on why researchers believe that an experimental treatment holds promise. In order to achieve the most reliable results, clinical trials have inclusion and exclusion criteria to determine who can participate.

Wofsy calls this an exciting time for lupus research. "There are more active clinical trials for lupus than

'We do a much better job of controlling hypertension, preventing osteoporosis, and treating infections with antibiotics in patients with lupus than we used to do.'

Developing New Therapies

The FDA hasn't approved any drugs specifically for lupus in nearly 40 years. Lupus experts say that the disease has not attracted enough of an investment from drug companies. It also can be difficult to develop data that prove a drug's safety and effectiveness because lupus is such a highly variable disease. And the FDA can approve a drug only after determining that the benefits outweigh the risks in a comparative study.

One concern in drug development is that a drug may prove beneficial for one organ but may turn out to damage another. There are also challenges with assessing effectiveness in a disease in which symptoms come and go in cycles. And because lupus develops gradually, a patient may develop a new symptom that could be due to the disease. Or it could be a side effect of medication.

According to the FDA, creative trial design is needed to overcome these challenges. The agency's recently released guidance discusses the need for clear clinical endpoints to show what's being measured in trials and what the outcome means for both

other parts of the immune system to both increase effectiveness and lower side effects. Examples include Rituxan (rituximab), made by Genentech Inc. of South San Francisco, Calif., and Lymphostat-B (belimumab), made by Human Genome Sciences Inc. of Rockville, Md.

Researchers are also investigating stem cell transplantation. In this process, stem cells are selected from the person's blood or bone marrow through a procedure known as leukopheresis. The stem cells are stored outside of the body. The individual receives potent systemic drugs or biologics in an attempt to destroy the immune system cells that are attacking normal tissue, and is then reinfused with his or her stored stem cells. The goal is to destroy the cells that may be responsible for initiating inflammation, and to stimulate new cells that will no longer be programmed to attack normal tissues.

According to the National Institutes of Health (NIH), participating in clinical trials for new treatments can give people a more active role in their health care, access to new treatments before they are widely available, and a sense

ever before, and there are a number of promising ideas," he says. "They won't all work, but there is reason to hope that we will find treatments for lupus that are safer and more effective."

For more information about clinical trials studying lupus treatments, talk with your doctor or contact www.clinicaltrials.gov ■

For More Information

Lupus Foundation of America
2000 L St., N.W., Suite 710
Washington, DC 20036
(202) 349-1155
www.lupus.org

National Institute of Arthritis and Musculoskeletal and Skin Diseases
1 AMS Circle
Bethesda, MD 20892
(877) 226-4267
www.niams.nih.gov

American College of Rheumatology
1800 Century Place, Suite 250
Atlanta, GA 30345
(404) 633-3777
www.rheumatology.org

Drug Name Confusion: Preventing Medication Errors

By Carol Rados

An 8-year-old died, it was suspected, after receiving methadone instead of methylphenidate, a drug used to treat attention deficit disorders. A 19-year-old man showed signs of potentially fatal complications after he was given clozapine instead of olanzapine, two drugs used to treat schizophrenia. And a 50-year-old woman was hospitalized after taking Flomax, used to treat the symptoms of an enlarged prostate, instead of Volmax, used to relieve bronchospasm.

In each of these cases reported to the Food and Drug Administration, the names of the dispensed drugs looked or sounded like those that were prescribed. There have been others: Serzone, an antidepressant, for Seroquel, used to treat schizophrenia, and iodine for Lodine, a non-steroidal anti-inflammatory drug.

Adverse events that can occur when drugs are dispensed as the wrong medications underscore the need for clear interpretation and better communication between the doctors who write prescriptions and the pharmacists who fill them. The FDA says that about 10 percent of all medication errors reported result from drug name confusion.

"These errors are not usually due to incompetence," says Carol A. Holquist, R.Ph., director of the Division of Medication Errors and Technical Support in the FDA's Office of Drug Safety. "But they are so underreported because people are afraid of the blame." Errors occur at all levels of the medication-use system, from prescribing to dispensing, Holquist says, which is why those people who receive the prescriptions must take action, too. "Everybody has a role in minimizing medication errors," she says.

The Problems

Medication errors can occur between brand names, generic names, and

brand-to-generic names like Toradol and tramadol. But sometimes, medication errors involve more than just name similarities. Abbreviations, acronyms, dose designations, and other symbols used in medication prescribing also have the potential for causing problems.

For example, the abbreviation "D/C" means both "discharge" and "discontinue." The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) notes that patients' medications have been stopped prematurely when D/C—intended to mean discharge—was misinterpreted as discontinue because it was followed by a list of drugs.

Illegible handwriting, unfamiliarity with drug names, newly available products, similar packaging or labeling, and incorrect selection of a similar name from a computerized product list, all compound the problem. And, although some drug names and symbols may not necessarily sound alike or look alike, they could cause confusion in prescribing errors when handwritten or communicated verbally, according to the United States Pharmacopeia (USP).

For example, Holquist says that several errors have occurred involving mix-ups with the oral diabetes drug Avandia and the anticoagulant Coumadin. Although they don't look similar when typed or printed, the names have

been confused with each other when poorly written in cursive. The first "A" in Avandia, if not fully formed, can look like a "C," and the final "a" has appeared to be an "n."

The XYZs of Naming Drugs

Names are part of developing a new drug. And coming up with a catchy, snappy moniker that distinguishes one drug from another isn't easy. For the most part, drug companies want a name that will boost sales, while consumers long for some indication from the name of what the drug does. The FDA, however, won't allow names that imply medical claims, suggest a use for which a drug isn't approved, or promise more than they can deliver.

Naming a drug can be as complicated as creating a rhythmic cacophony of unpronounceable syllables and emphatic-sounding letters, such as C and P. Other naming strategies include letters that when strung together sound like something high-tech—think Zyprexa, Lexapro, and Xanax.

But whether it's the sound of certain letters that manufacturers like, or the vision that a name conjures up, the FDA says that selection must take into account concerns for reducing errors and for avoiding trademark infringement.

Because of today's tough trademark requirements, many drug companies are turning to a growing industry of "naming" consultants for the task. These consultants are charged with creating a unique name that will appeal to both doctors and patients, particularly given the recent surge in direct-to-consumer advertising.

"Global companies want a name to be a worldwide mark," says Doug Kapp, vice president of brand strategy at RTi-DFD, a market research company in Stamford, Conn. In helping pharma-

ceutical companies set their products apart from others, Kapp says his company recognizes that the name must resonate with the market target and also must pass worldwide trademark requirements.

That recognition, he says, drove his company to develop "relational asemantics," a name-generation process

that assists physicians in identifying the nature of a drug. Just as the erectile dysfunction drug Viagra might suggest vitality and vigor, two of RTi-DFD's successes include Advair, linked to "advantage air for asthma," and Amerge, named for "emerging from the pain of a migraine." Kapp says that regardless of how good a name seems,

it must be reviewed for potential confusion with other drugs so that "any other associations would not harm the patient in the event of an error."

Satisfying the FDA

Every drug usually has three names: chemical, generic (non-proprietary), and brand (proprietary), and each is

Examples of Error-Prone Drug Information

Abbreviations	Intended Meaning	Misinterpretation	Correction
AD, AS, AU	Right ear, left ear, each ear	OD, OS, OU (right eye, left eye, each eye)	Spell out "right ear," "left ear," "each ear"
IJ	Injection	"IV" or "intrajugular"	Spell out "injection"
TIW or tiw	3 times a week	"3 times a day" or "twice in a week"	Use "3 times weekly"
Dose Designations			
Trailing zero after decimal point (1.0 mg)	1 mg	10 mg if the decimal point is not seen	Do not use trailing zeros for doses expressed in whole numbers
Abbreviations with a period following (mg. or mL.)	mg, mL	The period is unnecessary and could be mistaken as the number 1 if poorly written	Omit period and use mg, mL
Drug name and dose run together (especially problematic for drug names ending in "L" such as Tegretol300 mg)	Tegretol 300 mg	Tegretol 1300 mg	Place adequate space between the drug name, dose, and unit of measure
Symbols			
x3d	For three days	"3 doses"	Use "for three days"
/ (slash mark)	Separates two doses or indicates "per"	Number 1 (e.g., "25 units/10 units" misread as "25 units and 110" units)	Use "per" rather than a slash mark to separate doses
&	And	"2"	Use "and"

subject to different rules and regulations. The chemical name specifies the chemical structure of the drug. It is not preapproved by any organization, nor is it recognized in any standard manuals, such as USP publications. Therefore, chemical names are primarily used by researchers, but not in medical practice.

The FDA requires that either the established, or official, name or in the absence of an official name, the common or usual name, appears on labels and labeling of a drug product. The common name, loosely referred to as the generic name, must accompany the brand name, if there is one. The established name for a drug substance is usually found in the originating country's pharmacopeia, an official book or list of drugs and medicines and the standards established for their production, dispensation, and use.

The generic name is usually created for drug substances when a new drug is ready for marketing. It is selected by the United States Adopted Names (USAN) Council, whose expertise is recognized by the FDA, according to principles developed to ensure safety, consistency, and logic. These names are typically used by health care professionals.

Generic names are coined using an established stem, or group of letters, that represents a specific drug class. For example, the USAN stems include suffixes like *-mab* for monoclonal antibodies, such as infliximab, or prefixes like *dopa-* for dopamine receptor agonists. The arthritis medications celecoxib, valdecoxib, and rofecoxib are generic names containing the *-coxib* stem. Each belongs to a class of drugs known as the COX-2 inhibitors.

Names that include such stems, chemistry roots, or any other coded information are easier to remember, and give clues about what a drug is used for. These names, however, typically sound or look so much alike that they contribute to medication errors, especially if the products share common dosage forms and other similarities.

The brand name, also called trademark, can be created as soon as a generic name has been established.

Reducing Drug-Name Medication Errors

Here's a list of steps you can take:

- ❑ Know the name and strength of prescribed drugs before leaving the doctor's office
- ❑ Insist that the doctor include the purpose of the medication on the prescription
- ❑ Ensure that a refill is what it should be
- ❑ Tell your doctor of any medical history changes.

Only brand names of products subject to a new drug application or an abbreviated new drug application must be approved by the FDA first. This requirement distinguishes them from generic names.

According to a report in the January–February 2004 issue of the *Journal of the American Pharmacists Association*, there are more than 9,000 generic drug names and 33,000 trademarked brand names in use in the United States.

Fixing the Problems

To minimize confusion between drug names that look or sound alike, the FDA reviews about 400 brand names a year before they are marketed. About one-third are rejected. The last time the FDA changed a drug name after it was approved was in 2005, when the diabetes drug Amaryl was being confused with the Alzheimer's medication Reminyl, and one person died. Now the Alzheimer's medicine is called Razadyne.

Generic name confusion also has led to regulatory action, as well as to pharmacy practice recommendations. For example, the USP and the USAN changed the drug name "amrinone" to "inamrinone" after receiving reports of serious outcomes from medication errors involving the similar name pair "amrinone/amiodarone." The generic drug industry also has responded to requests from the FDA to use a mixture of uppercase and lowercase letters to highlight differences in similar generic names, such as vinBLAStine and vinCRISStine. This step also encouraged

manufacturers to supplement their new drug applications with revised labels and labeling that visually differentiated their generic names with the so-called "tall man" letters. And the NCCMERP recommendations encourage doctors to write both brand and generic names on prescriptions.

A number of other efforts are under way to reduce the incidence of medical errors stemming from similar-looking or similar-sounding names. The FDA, for example, is encouraging people to talk with their physicians to ensure that they have a complete understanding about their prescription before leaving the doctor's office, and to verify the information with the pharmacist before the medication is dispensed.

FDA health professionals also are requested to interpret both written prescriptions and verbal orders through weekly in-house studies, in an attempt to simulate the prescription-ordering process. Holquist says that these studies are a valuable tool used in every review of proposed brand names. It is important, she adds, to be able to detect any potential sound-alike, look-alike confusion with proprietary names before a new drug application is approved.

Other efforts strongly encouraged for physicians include writing prescriptions more clearly, printing in block letters rather than writing in cursive, avoiding the use of abbreviations, and indicating the reason for the drug.

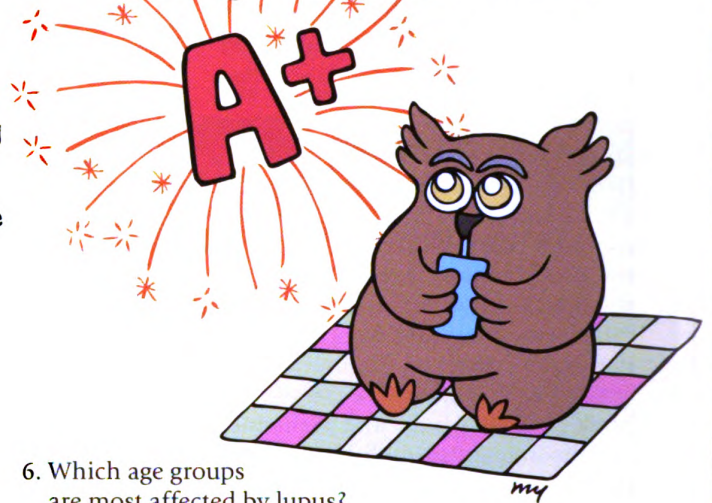
According to the FDA, pharmacists can help by keeping look-alike, sound-alike products separated from one another on pharmacy shelves, by avoiding stocking multiple product sizes together, and by verifying with the doctor information that is not clear before filling a prescription.

The FDA encourages pharmacists and other health professionals to report any actual or potential medication errors to the agency's MedWatch Adverse Event Reporting System online at www.fda.gov/medwatch/, by phone at (800) 332-1088, or by fax at (800) 332-0178. Caller identification is kept confidential and is protected from disclosure by the Freedom of Information Act. ■

Take the FDA Consumer QUIZ

How's your knowledge of antiperspirants, rabies, the autoimmune disease lupus, and medication errors? Test your knowledge of these and other health-related topics by taking our quiz.

Hint: The answers to all of these questions can be found in the July-August 2005 issue of FDA Consumer (and at the bottom of this page). Good Luck!



- What is the only U.S. state that does not have rabid animals?
 - North Dakota
 - Alaska
 - Hawaii
 - Rhode Island
 - Florida
- Which of the following animals does not get rabies?
 - skunk
 - bobcat
 - vulture
 - coyote
 - groundhog
- Which government agencies regulate rabies vaccine?
 - The FDA regulates human rabies vaccine and the U.S. Department of Agriculture regulates animal rabies vaccine
 - The Centers for Disease Control and Prevention regulates human rabies vaccine and the FDA regulates animal rabies vaccine
 - The National Institutes of Health regulates human rabies vaccine and the FDA regulates animal rabies vaccine
 - The FDA regulates both human and animal rabies vaccine
- Why did the FDA approve the drug Zelnorm for women—but not for men—with irritable bowel syndrome (IBS)?
 - Only women get IBS
 - There's never a line at men's restrooms, so they don't need drugs for IBS
 - The drugs were not found to be safe for men with IBS in clinical trials
 - The drugs were not found to be effective for men with IBS in clinical trials
 - Other drugs have already been approved for men with IBS
- How many Americans have lupus?
 - 250,000 to 300,000
 - 500,000 to 750,000
 - 1.5 million to 2 million
 - 3 million to 3.5 million
- Which age groups are most affected by lupus?
 - ages 4 to 12
 - ages 15 to 44
 - ages 45 to 65
 - over 70
- About how many people with lupus have the malar "butterfly" rash?
 - 10 percent
 - 40 percent
 - 85 percent
 - 100 percent
- About how much of the body's sweat is produced under the arms?
 - 1 percent
 - 20 percent
 - 30 percent
 - 40 percent
- According to the FDA's definition, an antiperspirant is regulated as:
 - a cosmetic
 - a drug
 - a medical device
 - a biologic
- Medication errors can occur between:
 - brand names
 - generic names
 - brand and generic names
 - all of the above

Answers

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

By John Henkel

A New Option to Enhance Distance Vision

People who are nearsighted have several options to correct their vision, including eyeglasses, contact lenses, or, if they are eligible, surgical techniques such as LASIK. Now there's a new type of device recently approved by the FDA that could offer yet another choice for nearsighted consumers who would like to improve their ability to see distant objects.

The devices are called phakic lenses. Made of plastic or silicone, they are implanted permanently into the eye without removal of the eye's natural lens as in cataract surgery. The phakic lens is inserted through a small incision and placed just in front of or just behind the iris.

Want to know more? The FDA has created a Web site containing the facts you need to make an informed choice about whether phakic lenses might be right for you. The site offers a helpful animated movie that shows how phakic lenses fit into the eye structure.

Once you've pictured how the lenses work, you can move on to individual pages that give detailed answers to questions you may have about the risks; what you can expect before, during, and after surgery; and what brands have been approved.

Though the site has loads of useful information, the FDA stresses that it is not meant to replace a discussion with your doctor. Also, phakic lenses are intended to be permanent, and though they can be surgically removed, a return to one's previous level of vision is not guaranteed.

Visit www.fda.gov/cdrh/phakic/ to find out more.

Be Aware and Beware of Identity Theft

You can hardly see or hear a news report these days that doesn't contain an item about identity theft. This disturbing problem is rampant across the United States, possibly affecting more than 19,000 people a day, according to two 2003 studies reported by the Identity Theft Resource Center.

Though it may be tempting to say, "It couldn't happen to me," the fact is, it could. Identity theft is a serious crime that can leave its victims in ruin. It can take months or years, and the spending of much personal money, to clean up the mess identity thieves can make of your good name and credit record.

To help you learn more about identity theft, and to give you tips about how to prevent it, the Federal Trade Commission, which investigates identity theft, has created a Web site called ID Theft. The site describes how thieves can—without your permission—use your name, Social Security number, credit card number, or other identifying information to commit fraud or other crimes. It explains that victims may

lose job opportunities; may be refused loans, education, housing, or cars; or may even be arrested for crimes they didn't commit.

The site tells you what to do if you suspect an identity thief has victimized you. It describes four important steps and urges you to take them immediately.

But how do you keep the crime from happening in the first place? The site offers a useful overview of preventive measures including how to protect sensitive information stored on your computer and when it is appropriate to give out your Social Security number.

The site also has a section called "Take Charge: Fighting Back Against Identity Theft," containing detailed information about how to recover from the crime.

See www.consumer.gov/idtheft/index.html to get facts on ID theft.

Keeping the Pressure Down

High blood pressure affects about 50 million—or about 1 in 4—adult Americans, according to the National Institutes of Health. It is especially common in blacks and older Americans. Uncontrolled, it can lead to heart attack, stroke, and kidney disease.

Elevated blood pressure can be controlled with drugs and other therapies. One of these is the subject of an online brochure created by the National Heart, Lung, and Blood Institute. It describes the Dietary Approaches to Stop Hypertension, or DASH, a program that has been clinically proven to reduce blood pressure significantly through changes in diet and lifestyle.

The brochure gives details on creating a diet that reduces sodium intake; is low in total fat, saturated fat, and cholesterol; and is rich in fruits, vegetables, and low-fat dairy products. It also has a form to track food habits before starting the plan and a chart to help with meal planning and food shopping.

Go to www.nhlbi.nih.gov/health/public/heart/hbp/dash/ to view "Facts About the DASH Eating Plan." ■

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

THE LAST WORD

A New Era of Hope for People With Lupus

By Sandra C. Raymond



Women, men, and children stricken by lupus, the prototypical autoimmune disease, often experience many setbacks as they struggle to overcome the disease. For far too long, those with the disease have been disappointed about how little was being done to find the causes and cure for lupus. However, we believe there are numerous signposts on the road to a cure that signal a new era of discovery and hope.

In this new era, federal funding for lupus research is steadily increasing, and additional biotechnology and pharmaceutical companies are investing money to develop safe, nontoxic, and effective therapies for lupus. And while a cure remains elusive, promising research studies to find a cure have begun.

The federal government is more engaged in lupus than ever before. For example, a new Federal Working Group on Lupus has been established through the National Institute of Arthritis and Musculoskeletal and Skin Diseases to coordinate federal efforts on lupus; the Centers for Disease Control and Prevention is supporting patient registries in Atlanta and in Detroit to ascertain the incidence and prevalence of lupus; the National Institutes of Health has created a program to validate lupus biomarkers; and the FDA has released a much anticipated draft guidance document to provide industry with guidelines on lupus drug development.

The availability of new safe, nontoxic, and effective therapies is a key priority for people with lupus and the health professionals who treat them. Many existing therapies for lupus, although often effective in controlling disease activity, are toxic and cause other potentially serious health effects from their use over time. There has not been a new, FDA-approved therapy for lupus in almost 40 years.

While the number of companies developing new treatments for lupus has increased, there is an urgent need to bring down barriers that in the past have obstructed the progress of clinical trials on lupus. As these scientific barriers are overcome, an increasing number of pharmaceutical and biotechnology companies will make substantive investments to find the causes and cure for lupus.

Industry, however, must be enabled to conduct successful

clinical trials of potential new treatments for lupus. Because of the heterogeneity of lupus patients, clinical trials of new lupus drugs require a large number of patients treated over a long period. There is an urgent need to validate biomarkers to efficiently measure the safety and efficacy of new drugs. Validated biomarkers will enable pharmaceutical and biotechnology companies to determine whether their drugs are working within a shorter period of time using a smaller group of patients. There are many candidate markers for lupus, and efforts are under way to validate them for use in clinical trials.

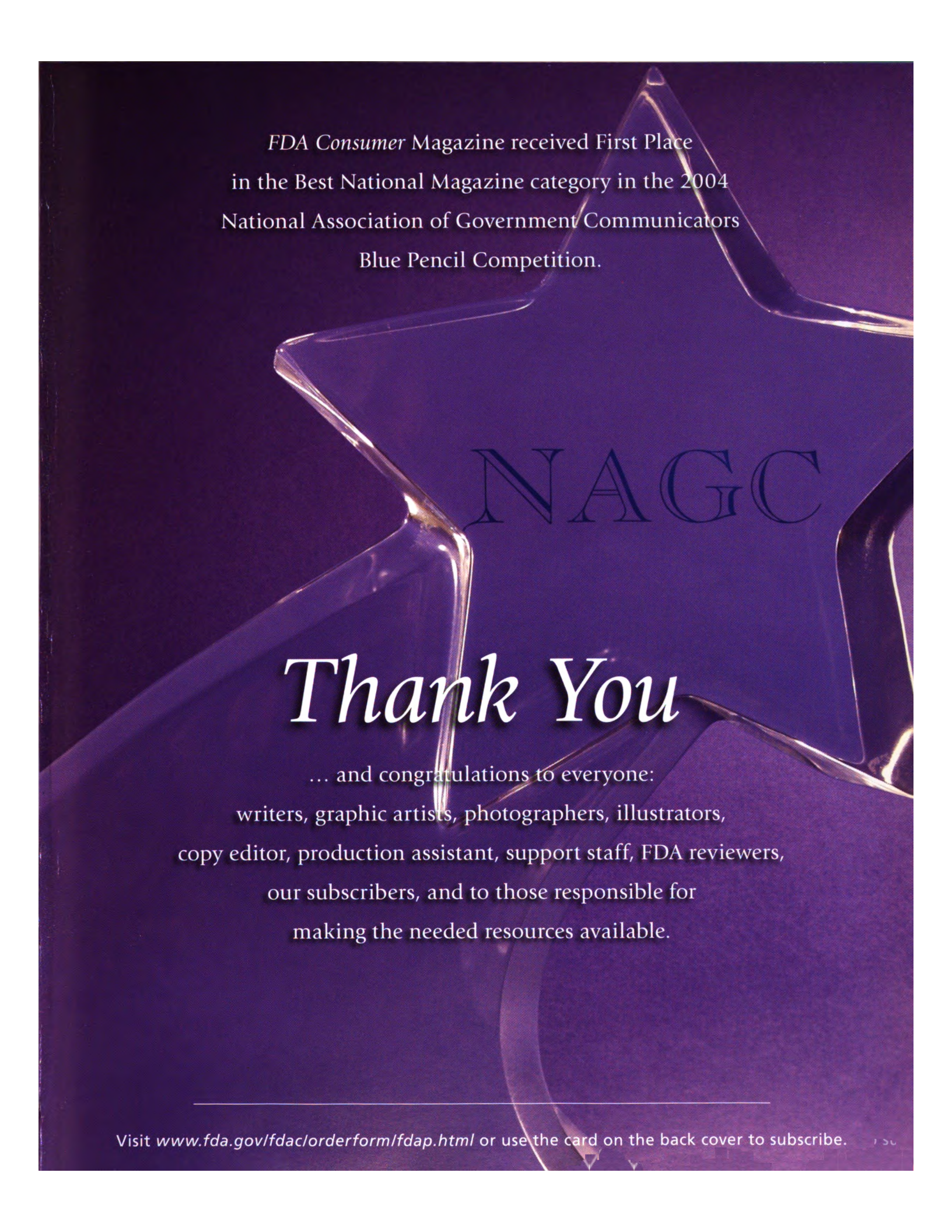
In addition, achieving better outcomes for individuals with lupus by improving early diagnosis of the disease is needed. More than one-half of the people with lupus report they visited three or more doctors over four or more years before being diagnosed. Through increased public awareness of lupus symptoms, better training of health professionals, and improved diagnostic tests, individuals with lupus can receive earlier treatment, impeding progression of the disease and improving their quality of life.

It is also important to have reliable, evidence-based epidemiological information on the incidence and prevalence of lupus among different populations.

Existing epidemiological studies on lupus have not included all the syndromes associated with lupus and all the subsets of the population believed to be disproportionately affected by lupus. The benefits of a national scale study will enable researchers to better study the disease, will encourage industry to identify the market potential of new therapies to treat manifestations of lupus, and will enhance efforts to plan effective educational strategies to reach those individuals at risk for the disease.

This is an exciting time for everyone affected by lupus: patients, family members, physicians, and researchers. The pace of discovery for lupus is escalating, and new scientific pathways have created opportunities to gain insight into the causes of the disease. In this new era of discovery, the Lupus Foundation of America will lead a nationwide crusade to ensure that people with lupus will have hope that this disease will be brought under control and that a cure will be found. ■

Sandra C. Raymond is president and CEO of the Lupus Foundation of America Inc.



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National Association of Government Communicators
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