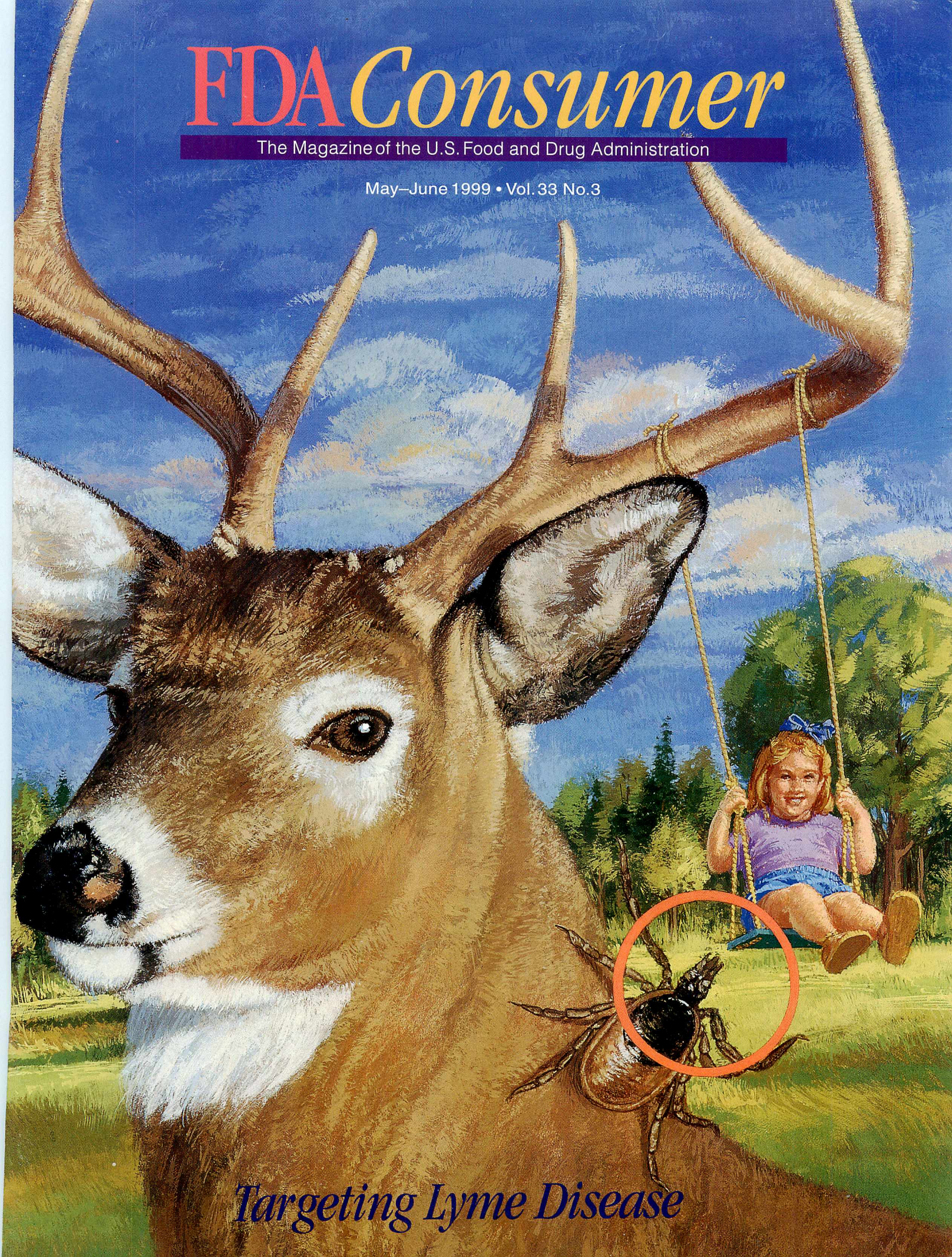


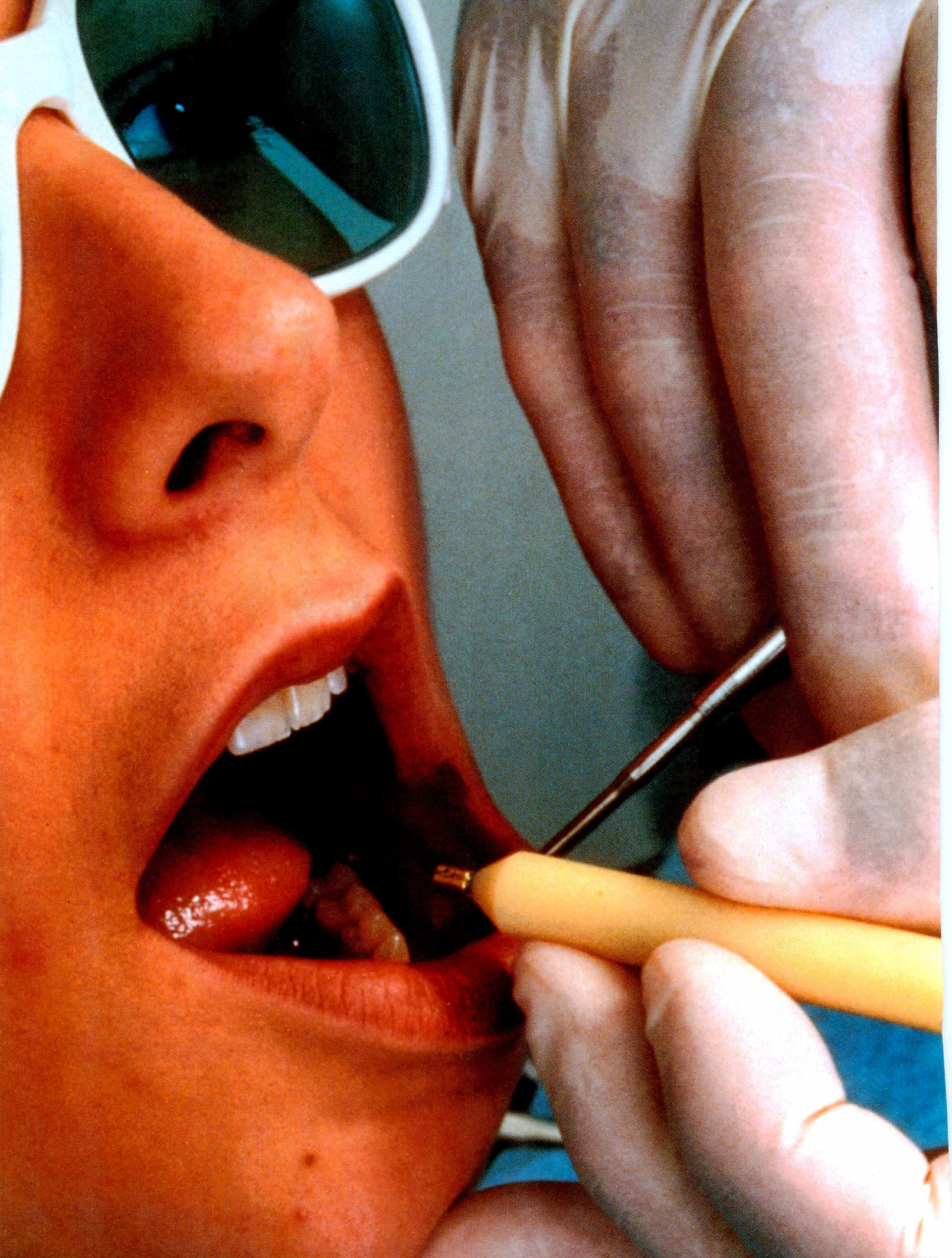
FDA Consumer

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

May-June 1999 • Vol. 33 No. 3



Targeting Lyme Disease



Donna E. Shalala, Ph.D.

Secretary of Health and
Human Services

Jane E. Henney, M.D.

Commissioner of Food and Drugs

Lorrie McHugh-Wytkind

Associate Commissioner for Public Affairs

Isadora Stehlin /Editor

Patricia N. Edwards / Art Director

Michael L. Herndon / Production Manager

Carol L. Ballentine / Copy Editor

Cover Design: Jack Pardue

FDA on the Internet: www.fda.gov

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

Editorial Matters

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

Subscriptions

Send inquiries concerning subscription problems or address changes to Superintendent of Documents, Government Printing Office, Washington, DC 20402. Include mailing label from the back cover for address changes.

To keep subscription prices down, the Government Printing Office mails each subscriber only one renewal notice. To determine when you will get your renewal notice, check the number that follows ISSDUE on the top line of your mailing label. When the label reads ISSDUE003, a renewal notice will be sent. When the label reads ISSDUE000, you have received your last issue unless you renew.

To continue to receive *FDA Consumer* without interruption, please return your renewal notice promptly. If your subscription has expired, send your mailing label with \$9 (\$11.25 foreign), using the form on the back cover, to Superintendent of Documents, Government Printing Office, Washington, DC 20402, and your service will be reinstated. Periodicals postage paid at Rockville, MD, and additional mailing offices. POSTMASTER: Send address changes to *FDA Consumer*, 5600 Fishers Lane, Room 15A-19, Rockville, MD 20857.

FDA Consumer

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

May-June 1999 • Vol. 33 No.3

Waging War on Lung Cancer

7

Though lung tumors kill more people than any other cancer, survival rates have improved, and new tools are helping doctors find the disease when treatment has the best chance for success.

New Vaccine Targets Lyme Disease

12

A new vaccine and improved screening tests may curb the rising numbers of Lyme infections. But simple precautions are still necessary.

Dental More Gentle with Painless 'Drillings' and Matching Fillings

18

"Ouchless" lasers and color-coordinated ceramics are helping lighten up a visit to the dentist.

Pediatric Drug Studies: Protecting Pint-Sized Patients

23

More than half of the prescription drugs that children are likely to use have not been adequately tested or labeled for youngsters. But an FDA rule now requires makers of many drugs to provide information on safe pediatric use.

Orphan Drug Law Matures into Medical Mainstay

29

In 1983, Congress passed a law to help bring treatments to people suffering from rare, or "orphan," disorders. The result is a growing list that currently includes nearly 200 drugs and other products.

Updates

2

fda.gov

33

Investigators' Reports

34



◀ Inside Front Cover Photo:

Those sunglasses aren't a fashion statement. This California woman is wearing them to protect her eyes while she receives laser treatment for a cavity. For the latest on cavity treatment and prevention, see page 18.



Biologic Treatment Ok'd for Rare Type of Non-Hodgkins Lymphoma

A new biologic treatment has received accelerated approval for treating a rare, slowly progressive form of non-Hodgkins lymphoma.

FDA approved Ontak (denileukin diftitox) Feb. 5 for certain patients with advanced or recurrent cutaneous t-cell lymphoma (CTCL) who have failed to respond to other treatments, such as interferon, chemotherapy or radiation. CTCL causes itchy, dry skin patches that can develop into tumors in the skin and other organs.

Known as "fusion protein," Ontak is made by genetically fusing protein from the diphtheria toxin to interleukin-2 (IL-2), a naturally occurring immune system protein. This stable fusion protein targets and kills cells with receptors for IL-2 on their surfaces, including cancer cells.

Of the 1,000 Americans diagnosed yearly with CTCL, the treatment ben-

efits only the 60 percent or so who have tumors with the IL-2 receptors.

A study of 71 patients with advanced CTCL who had failed at least one other treatment found that in patients receiving Ontak, 30 percent of tumors were reduced 50 percent or more for an average period of four months. Ten percent of patients achieved complete clinical remission for an average period of nine months. Such complete remissions would not be expected in an untreated group.

However, CTCL patients on Ontak need to be monitored carefully during treatment because of the increased risk of severe infection. Their disease makes them prone to infection, as does the treatment because it kills normal lymphocytes along with the cancer cells. Almost one-fourth of the patients in the study developed severe infections, although it was unclear whether Ontak

was the cause.

Other side effects related to the intravenous infusion of Ontak included allergic reactions, flu-like symptoms, and fluid retention, which could lead to other complications.

Ligand Pharmaceuticals Inc. of San Diego will market Ontak, which is manufactured by Ligand's subsidiary, Seragen Inc. of Hopkinton, Mass.

FDA granted Ontak "orphan" status in 1996, enabling the companies to receive the incentives for developing products for small patient populations. With accelerated approval came a commitment from Seragen to conduct further studies of the drug's long-term safety and efficacy.

(For more on orphan products, see "Orphan Drug Law Matures into Medical Mainstay" on page 29.)

New Test Can Detect Hepatitis C Infection More Accurately

An improved blood test to confirm the results of other hepatitis C screening tests has received licensing from FDA.

Approved in February, the RIBA HCV 3.0 Strip Immunoblot Assay (SIA) can detect one more type of antibody to the HCV virus than the other licensed supplemental test and is better at distinguishing true positive from false posi-

tive results. The older test, while rarely missing a true infection, sometimes falsely signaled the existence of infection. The new test is used when blood specimens test repeatedly positive on other licensed screening tests.

In one clinical trial using healthy blood donors, about 7 percent of repeatedly reactive test results were interpreted as inconclusive using the RIBA 3.0 test, versus about 30 percent when using the previous supplemental test, RIBA HCV 2.0 SIA.

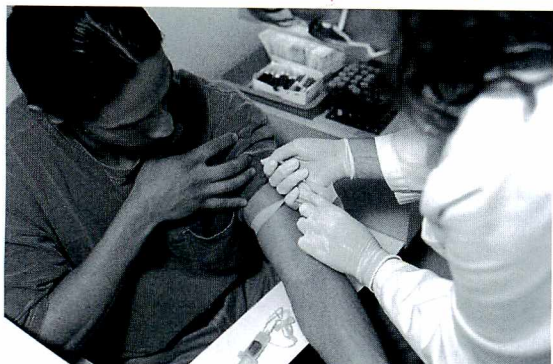
The RIBA 3.0 test has an important role in a recent recommendation by the Department of Health and Human Services that blood banks and medical facilities notify patients who received blood from donors found to be possibly infected with hepatitis C. The new test should prevent thousands of unnecessary

notifications and subsequent testing and counseling of blood recipients based on inconclusive tests.

While about 4 million Americans are infected with the hepatitis C virus, making it a major cause of serious injury and death, only 7 percent of cases were acquired from blood transfusions, and most of these infections occurred before 1990, when blood donor screening for hepatitis C became possible. Currently, the risk of contracting the virus from a unit of blood is about 1 in 100,000 units.

The RIBA 3.0 Strip SIA is made by Chiron Corp., Emeryville, Calif., and will be distributed by Ortho Diagnostic Systems Inc., Raritan, N.J.

(For more on hepatitis C, see "Hepatitis C: New Treatment Helps Some, But Cure Remains Elusive" in the March-April 1999 *FDA Consumer*.)



For Some, New Drug May Reduce Walking Pain

For those who experience severe pain, aches, or cramping in their legs when they walk due to atherosclerosis, or hardening of the arteries, a new drug treatment is available for the first time in more than 15 years.

FDA approved Pletal (cilostazol) in January to treat pain from intermittent claudication. This condition, affecting several million mostly elderly Americans, results from "peripheral arteriosclerotic vascular disease," when fatty deposits build up in the legs and interfere with the blood supply to leg muscles. It can cause considerable discomfort when walking and seriously interfere with people's ability to exercise and even participate in ordinary daily activities.

Clinical studies of Pletal did not identify serious toxicity. However, because the drug is related to phosphodiesterase III inhibitor drugs, which have been shown in several studies to increase death rates in patients with severe heart failure, Pletal's labeling states that it should not be used in patients with heart failure. The labeling also states that there is not enough information to determine whether Pletal may negatively affect survival in patients without heart failure.

Additionally, Pletal's labeling informs doctors that information is lacking on combining Pletal with the drug Plavix (clopidogril), recently approved for reducing serious adverse reactions in some patients with peripheral vascular disease. Both Pletal and Plavix inhibit platelet function, raising concerns that their combined use could lead to excessive bleeding. There was no apparent increase in bleeding, though, when Pletal was used with aspirin, which also inhibits platelet function. Further study of the Pletal/Plavix combination will be done after Pletal is marketed.

Pletal has not been evaluated for safety or effectiveness in patients with more severe peripheral vascular disease, who have claudication pain when they are resting, or who have leg ulcers or gangrene. Such studies are planned.

In clinical trials, patients treated with Pletal were able to walk farther than those treated with a placebo before claudication began and before their pain became intolerable and forced them to stop. Patients treated with Pletal also reported a greater increase than those on a placebo in walking distance and speed during daily routines.

Pletal is marketed by Otsuka American Pharmaceutical Inc., Rockville, Md.

Genetic link to Parkinson's questioned ... Genetic factors do not appear to play a major role in causing Parkinson's disease in patients over 50 years old, says a study by the Parkinson's Institute in Sunnyvale, Calif. However, a genetic cause is most common in about 10 percent of people diagnosed with the disease before age 50. Of more than 19,000 male twins over 50 tested, Parkinson's disease was most commonly caused by environmental factors, possibly including exposure to

chemicals, diet, and smoking. At least 1 million Americans have Parkinson's disease, making it second only to Alzheimer's disease as a degenerative condition of the brain and nerves (*Journal of the American Medical Association*, January 1999). For more information about Parkinson's disease, see "Parkinson's Disease: New Treatments Slow Onslaught of Symptoms" in the July-August 1998 issue of *FDA Consumer*.



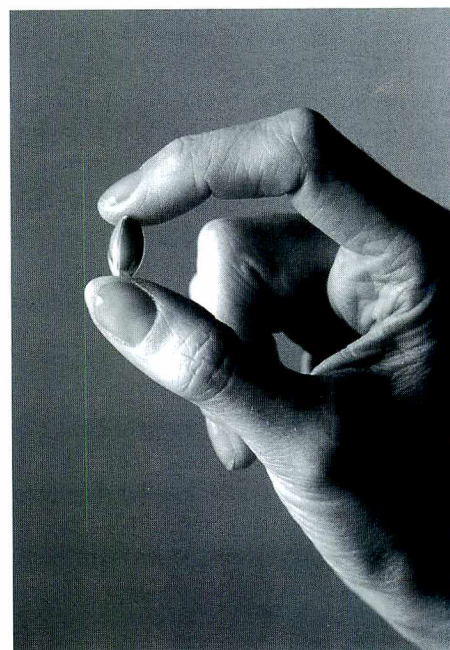
Coming Soon: Clearer OTC Drug Labels

To help consumers use nonprescription, or over-the-counter, drugs properly and understand the benefits and risks of these medicines, FDA is requiring that all OTC drugs have a new, easy-to-read label.

Patterned after the Nutrition Facts label for food, the new "Drug Facts" label must be written in plain language and identify active ingredients first, followed by uses, warnings and directions. It also must include inactive ingredients to help consumers avoid potential allergic reactions.

FDA also recommends that drug manufacturers include a phone number for consumers to call for more information.

The agency developed the new label format in cooperation with consumer and industry groups and after considering almost 2,000 comments on its February 1997 proposed rule. The new drug labels should appear on shelves in the next two to six years.



Don't Use Dangerous GHB-Related Product, Agency Warns

FDA has received reports of at least 55 adverse reactions, including 19 cases of unconsciousness or coma and one death, associated with dietary supplements containing the chemical GBL (gamma butyrolactone). The agency warns that consumers should not buy or consume GBL products and should throw out any such substances they have on hand.

Other reported reactions include seizures, vomiting, slow breathing, and slow heart rate. At least five children have experienced these kinds of effects.

The agency has asked the manufacturers of the products to recall them voluntarily. If they do not, FDA said it would consider all potential regulatory actions. Though the products are labeled as dietary supplements, FDA considers them illegally marketed unapproved drugs.

In the body, GBL converts to GHB (gamma hydroxybutyrate), a potent experimental drug that is being studied for the sleeping disorder narcolepsy. GHB is legally available only as part of these FDA-approved studies.

The GBL products are being sold on the Internet, in some health food stores, and in some gymnasiums and fitness centers for building muscle, improving physical performance, enhancing sex, reducing stress, and inducing sleep. They are sold in liquid or powder form under a variety of brand names, including Renewtrient, Revivarent or Revivarent G, Blue Nitro or Blue Nitro Vitality, GH Revitalizer, Gamma G, and Remforce. The chemical itself goes by several names, such as 2(3H)-furanone, 2(3H)-furanone dihydro, dihydro-2(3H)-furanone, dihydro, tetrahydro-2-furanone, gamma-butyrolactone, butyrolactone gamma, 4-butyrolactone, butyrolactone, and 4-butanolide.

FDA advises consumers who use these products and develop adverse reactions to contact a doctor immediately. Also, doctors and consumers are encouraged to report adverse reactions to FDA's MedWatch program at 1-800-332-1088 or on the Internet at www.fda.gov/medwatch/.

Growing strains ... Giving growth hormones to short but otherwise healthy children adds only an average of 2 inches to their adult height, a Stanford University study found. Experts now question whether long-term hormone therapy in these children is worthwhile. The study was based on the height patients were predicted to attain before treatment, and it compared their subsequent growth to children who weren't treated. (*New England Journal of Medicine*, February 1999)

Correction

The January-February issue of *FDA Consumer* contained an incorrect statement about the drug Arava (leflunomide) for rheumatoid arthritis. While other oral treatments are available for the disease, Arava is the first oral treatment approved for slowing its progression.



Risky raw shellfish ... Seafood lovers may find raw shellfish irresistible, but a recent report by the national Centers for Disease Control and Prevention says that *Vibrio parahaemolyticus*, a natural marine inhabitant found in shellfish harvested in New York waters, can inflict nausea and diarrhea on unwary diners. CDC says the bacteria isn't as dangerous as its counterpart, *Vibrio vulnificus*, which is linked to Gulf shellfish and can kill people with liver disease or weakened immune systems. CDC urges consumers not to eat raw or undercooked oysters or clams and to see a doctor and get a lab culture if they become ill within four days of eating raw shellfish.

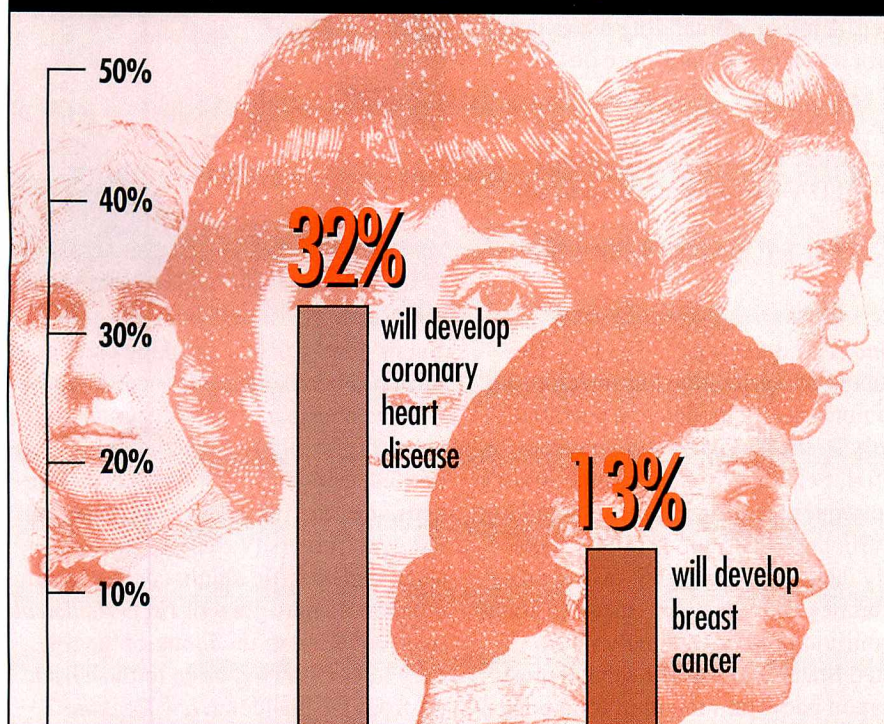
Safety of rbST Milk Affirmed

Milk from cows treated with recombinant bovine somatotropin (rbST) is safe to drink, FDA said in February, affirming the agency's original 1993 conclusions about the growth hormone.

Canadian health officials raised concerns about the safety of rbST, which is used to increase milk production in dairy cattle, while considering whether to approve the product in that country. In response to those concerns and questions raised by several groups and individuals in the United States, FDA's Center for Veterinary Medicine reexamined the human food safety sections of the original approval.

The "Report on the Food and Drug Administration's Review of the Safety of Recombinant Bovine Somatotropin" is available at www.fda.gov/cvm/fda/infores/other/RBRPTFNL.htm on FDA's Website.

Heart Disease and Breast Cancer Women's Lifetime Risk



Source: The National Heart, Lung, and Blood Institute, National Institutes of Health

Women in particular have been unaware of the extent of their heart disease risk. A woman's lifetime risk of heart disease (1 in 3) is far greater even than her risk of breast cancer (1 in 8). Women, like men, should check their blood pressure and cholesterol levels, eat heart-healthy food, and be physically active.

Researchers Pinning Down Risk of Heart Disease, Stroke

One out of every two men and one out of every three women aged 40 and under will develop coronary heart disease (CHD) in their lifetime, according to National Institutes of Health researchers involved in the Framingham Heart Study. In their first estimate of this risk, published in the Jan. 9 issue of the journal *The Lancet*, researchers found the risk of CHD still high at age 70: One out of three men and one out of four women will develop it in their remaining years.

Coronary heart disease is the most common form of heart disease, affecting 12 million to 13 million Americans. It occurs when the coronary arteries be-

come narrowed or clogged and cannot supply enough oxygen-rich blood to the heart. CHD can lead to angina (chest pain) and heart attacks.

NIH scientists also reported, in the Jan. 7 issue of the *New England Journal of Medicine*, that an ultrasound test can predict heart attack or stroke risk in older people who have no symptoms of cardiovascular disease. The noninvasive test uses sound waves to measure the thickness of the walls of two neck arteries, providing information beyond what is available from standard risk factors such as high blood pressure and elevated cholesterol levels.

Stroke "window" widened ... Researchers have shown that for the first time they can reverse massive strokes up to six hours after the onset of symptoms by squirting a new clot-dissolving medicine directly into the brain. In a study by the Cleveland Clinic Foundation, the new approach showed that the previous three-hour deadline for stroke victims to get help before permanent brain damage can set in has doubled. About 600,000 strokes are treated yearly in the United States. (For more information about strokes, see "New Success Against Stroke" in the March-April 1998 *FDA Consumer*.)

Hope for arthritis sufferers ... Researchers at Brigham and Women's Hospital in Boston report significant improvements in patients with rheumatoid arthritis when the standard treatment medication, methotrexate, was combined with Enbrel, a new genetically engineered drug. The study showed that pain and swelling decreased noticeably in 71 percent of patients who took both drugs for six weeks. Rheumatoid arthritis affects 2 million Americans, mostly women, and usually develops between ages 25 and 50. (*New England Journal of Medicine*, January 1999)





Guidance Finalized for Animal Drug Approval

A guideline on animal drug approval for minor uses and minor species was finalized by FDA in February.

Minor species are defined as any animals other than cattle, swine, chickens, turkeys, horses, dogs, and cats, and sometimes sheep. A minor animal drug use is use in a minor species or use in any animal species for a condition that is rare or that occurs in limited geographic areas.

The document, "Guidance for Industry—FDA Approval of Animal Drugs for Minor Uses and Minor Species," is intended to alleviate the scarcity of safe and effective drugs for these animals. It is available on FDA's Website at www.fda.gov/cvm/fda/infores/updates/NEWMUM.html.

(For more on minor uses and minor species, see "Sick Call of the Wild" in the July-August 1998 *FDA Consumer*.)



Free Publications

Full-Length Feature Articles:

- Safer Eggs: Laying the Groundwork (FDA) 99-2322
- An FDA Guide to Dietary Supplements (FDA) 99-2323
- FDA Sets Higher Standards for Mammography (FDA) 99-4271

Large-Type Article:

- Using the Food Label to Choose Healthier Foods (FDA) 99-2276

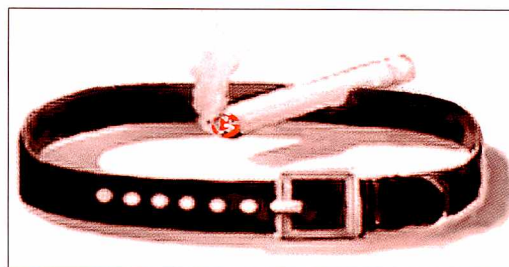
To order single copies, write to FDA, HFE-88, Rockville, MD 20857. To order 2 to 50 copies, write to FDA, HFI-40, at the same address, or fax your order to 301-443-9057. Include the publication number.

Salmonella detection ... The U.S. Department of Agriculture has developed a technique to rapidly detect a potentially deadly strain of *Salmonella* known as DT104. Scientists discovered the strain's gene sequence, allowing them to quickly identify the bacterium. DT104 is especially dangerous because it resists many antibiotics. *Salmonella* is linked to about 3.8 million illnesses annually in the United States and was the second most-common bacterium found in food poisoning cases in 1997.

Berry good juice ... Drinking cranberry juice has been touted for years as a way to prevent urinary tract infections. Because of the highly acidic nature of cranberries, many have felt that this discourages or even kills bacteria. But a recent Rutgers University study suggests instead that specific tannin compounds in cranberries may prevent *Escherichia coli* from adhering to the lining of the urinary tract, allowing urine to flush bacteria from the bladder. (*New England Journal of Medicine*, October 1998)

Smoking and weight loss ...

Contrary to popular belief, smoking does not keep people from gaining weight, says a seven-year study by the University of Memphis. In fact, the research showed that weight gain of more than a pound a year was common whether subjects smoked or not. (*Journal of Consulting and Clinical Psychology*, December 1998)



Staph increases resistance ... A major cause of sometimes fatal hospital infections, *Staphylococcus aureus*, is developing resistance to the last antibiotic now used to kill it completely, says a study by the national Centers for Disease Control and Prevention. The virulent bacterium is already shrugging off other antibiotics and is one step closer to resisting the antibiotic vancomycin. The findings suggest that hospitals should aggressively contain the bacterium with a combination of antibiotics. (*New England Journal of Medicine*, February 1999)

Waging War On

Lung Cancer

by Ellen Brown

Five years ago, when Ken Giddes was vacationing with his wife in Vancouver, British Columbia, the 61-year-old resident of Atlanta began feeling short of breath. But since he was "running around quite a bit," Giddes chalked up his problem to being an overachieving tourist. When he returned home, though, his shortness of breath persisted. The cause—uncovered by an x-ray—was a collapsed lung.

But it wasn't until he underwent surgery to repair his lung, that the cause of the collapse was clear: lung cancer had eaten a hole in the air sack of his lung. After surgeons removed his lung in an effort to contain the cancer, they checked Giddes for any traces of cancer every three months. Within a year there was more bad news: a CT scan revealed 13 spots on his remaining lung.

Surgery revealed the cancer had spread throughout his remaining lung. Giddes recalled that he was given less than a 30 percent chance of living another two years. But he decided to battle the cancer "with all the energy, hope and positive attitude I could muster." After 30 weeks of chemotherapy, he was told his cancer was in remission.

Today, he's glad he didn't give up because he's beaten the odds, surviving five years since his cancer was diagnosed. And as the head of the Caring Ambassador Program, sponsored by Republic Financial Corporation, he's helping other cancer survivors wage war on lung cancer, too.

Survival and Detection

Lung cancer is the leading cause of cancer deaths among both men and women, according to the American Cancer Society. Since 1987, more women have died each year of lung cancer than of breast cancer.

Detecting lung cancer in its early stages is difficult in some cases because the disease spreads very quickly and symptoms often don't appear until the disease is advanced. Only about 15 percent of lung cancers are found before the cells have spread to lymph nodes or distant organs.

Lung cancer patient Janet Dunkel gets advice and support from Ken Giddes, who has survived for five years since his lung cancer was diagnosed. Dunkel, who lives in Dunwoody, Ga., is currently undergoing treatment for her cancer.



Lung Cancer Warning Signs

Still, the survival rate for the disease has improved over the years. The one-year survival rate for patients is about 40 percent today compared with 32 percent in 1973. And five-year survival is up from 8 percent in the 1960s to 14 percent today. Improvement in survival rates can be attributed, at least partially, to diagnostics and new drugs that the Food and Drug Administration has approved.

Lung cancer can be diagnosed by:

- a chest x-ray or CT scan to check for spots on the lungs
- a microscopic analysis of phlegm cells

tissue changes than can be seen with the white light alone.

The approval of this device is significant, says Harry Sauberman, chief of the ear, nose and throat devices branch in FDA's Center for Devices and Radiological Health. It can spot moderate to severe dysplasia (irregular tissue), "some of which may turn out to be malignant and you'll have a case of lung cancer," he explains. Patients with dysplasia can then be closely monitored, and if cancer appears, it can be treated in its earliest stages.

The second diagnostic tool is an imag-

Detecting lung cancer in its early stages can lead to a cure for some people and extend the life of others, according to the American Cancer Society. So, if you are experiencing any of the following problems or symptoms, seek medical attention at once:

- a persistent cough
- chest pain
- weight loss and/or decreased appetite
- bloody phlegm
- shortness of breath
- hoarseness
- a fever for an unknown reason
- recurring infections, such as bronchitis and pneumonia.

Some of these symptoms may be related to another disease or condition. The only way to know if you have lung cancer is for a doctor to perform the necessary tests. ■

Detecting lung cancer in its early stages is difficult. The disease spreads quickly, and symptoms often don't appear until the cancer is advanced.

- a bronchoscopy, which involves passing a lighted tube through the tubes that carry air to the lungs to see if tumors or blockages exist.

If suspicious tissue or spots are detected, a needle biopsy is typically performed, so that a sample of the tumor can be obtained to confirm the diagnosis of lung cancer.

There also are two other diagnostic tools that may be used in place of a biopsy.

The Xillix LIFE-Lung Fluorescence Endoscopy System is a medical device FDA approved in 1996 for detecting bronchial tissue abnormalities in patients with previous, current or suspected lung cancer. A tube inserted through a patient's mouth into the bronchi (tubes leading from the trachea to the lungs) delivers a blue laser light to the bronchial tissue. The image the laser reveals is projected onto a video monitor. While normal tissue appears green, abnormal tissue will appear reddish brown. Suspicious areas can then be biopsied. The system was approved for use in conjunction with conventional white light bronchoscopy. While the illumination provided by the white light helps doctors identify tissue that looks abnormal, the new blue laser system detects more

ing agent called Nofetumomab (verluma). Approved by FDA in 1996, it can determine the extent of disease in patients already diagnosed with small cell lung cancer through a biopsy but who have not yet been treated.

Nofetumomab is a fragment of a monoclonal (synthetic) antibody that, when tagged with a radioisotope, can detect a protein found on the surface of most small cell lung cancers. The antibody collects in tumor sites and other areas of the body where protein is detected and, using special cameras, doctors can see the areas as "hotspots." This information helps physicians see how far the cancer has spread without exploratory surgery or other diagnostic tests and allows them to develop a more effective treatment plan.

According to Patricia Keegan, M.D., deputy director for the division of clinical trials design and analysis in FDA's Center for Biologics Evaluation and Research, the major advantage of using the imaging agent is that it allows doctors to do a full body scan of a patient. "The disadvantage is that it isn't as sensitive in any one area as other scans," she says. "It's not as good as a CT scan for picking up every liver metastasis. And it isn't as good as an MRI or CT scan of the head to pick up brain metastasis. But

if all you want is a quick and dirty answer about whether the cancer is widely disseminated or not, it's a relatively simple test to do."

Treatment

About 75 percent of lung cancer cases are categorized as non-small cell lung cancer, and the other 25 percent are small cell lung cancer. Lung cancer can multiply quickly and form large tumors, which sometimes spread to lymph nodes and other organs.

Once lung cancer is detected, a treatment plan is developed based on the patient's physical health, whether the lung cancer is small cell or non-small cell and how extensively the cancer has spread. (See "Stages of Lung Cancer.") Treatment may include surgery, chemotherapy, radiation, or a combination of two or more of these therapies.

FDA recently approved three therapies to treat non-small cell lung cancer: Photofrin (porfimer sodium), Taxol (paclitaxel) in combination with the commonly used cancer drug cisplatin, and Gemzar (gemcitabine hydrochloride) in combination with cisplatin.

Photofrin, a light-activated drug, was approved in January 1998 for patients
(Continued on page 10)

The Risks Of SMOKING

You have undoubtedly heard the warnings: if you smoke cigarettes, stop now, and if you don't smoke, don't start. Why? Because cigarette smoke is made up of over 4,000 chemicals, including 43 known to cause cancer. According to the American Cancer Society, tobacco use accounts for 30 percent of all cancer deaths in the United States, and smoking is responsible for 90 percent of lung cancers in men and more than 70 percent in women. The ACS estimates that 28 percent of men, 23 percent of women, and about 30 percent of adolescents smoke.

According to the American Lung Association, the more you smoke and the longer you smoke, the more likely you are to develop lung cancer. But the ACS contends that if you quit smoking when pre-cancerous signs are found, the damaged lung tissue often may return to normal, oftentimes within five years.

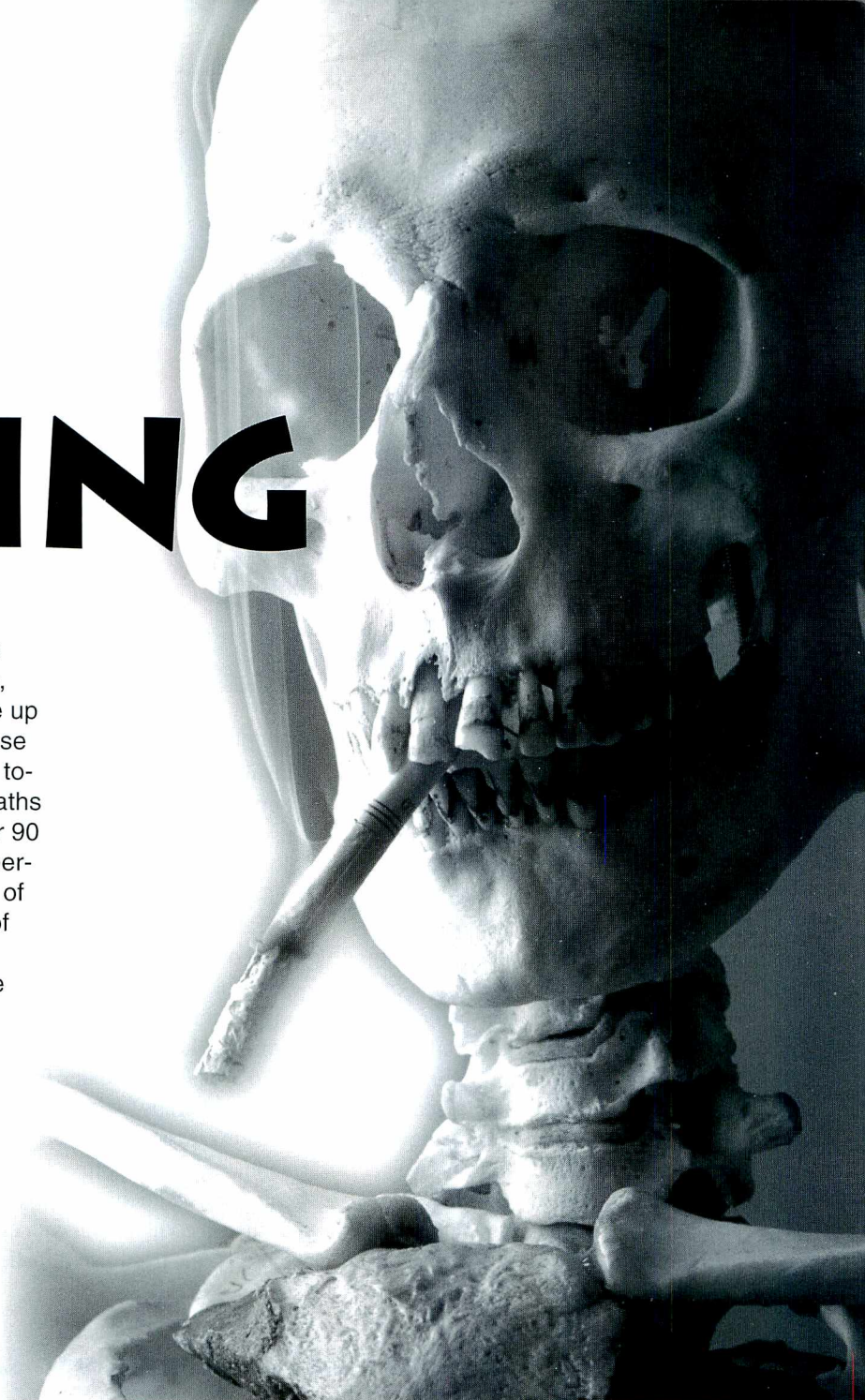
There has been some debate, however, on this subject. In 1997, researchers at the University of Pittsburgh Cancer Institute concluded after a preliminary study, that just because people quit smoking doesn't mean they won't develop lung cancer at some point in their lives. The study, which was published in the *American Journal of Respiratory and Critical Care Medicine*, determined that 77 percent of the people who smoked at least a pack of cigarettes a day for 25 years had irregularities in their lung cells even if they weren't smoking at the time the lung tissue was examined. While those who smoked fewer cigarettes weren't home free, they were less likely to develop abnormal lung cells. Only about 15 percent of the people who smoked for less than 25 years showed similar cellular changes.

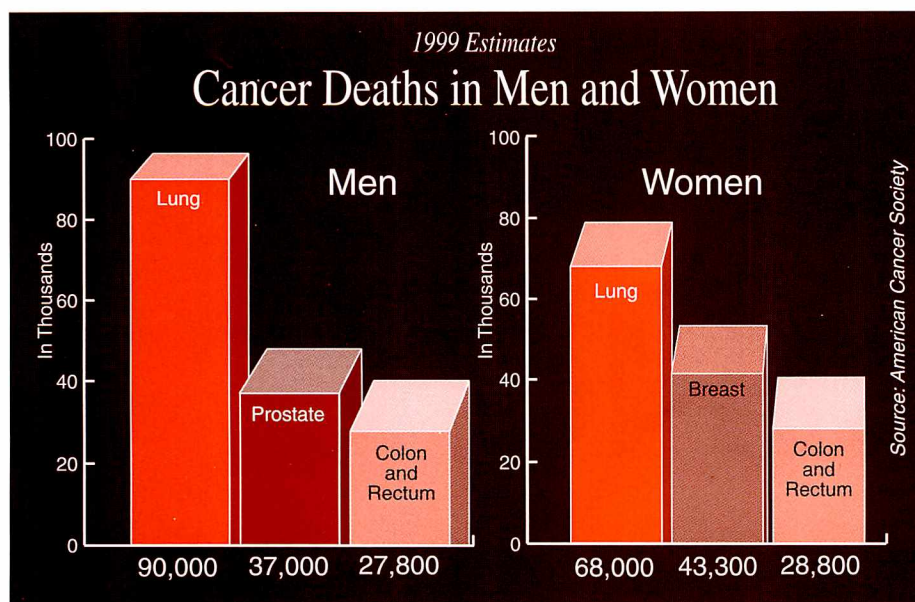
More research still needs to be conducted on this topic, and most doctors still recommend that people stop smoking, no matter how long they've been keeping up the habit. This is especially true for people who have been diagnosed with lung cancer. "People with lung cancer who stop smoking live longer and have higher cure rates and lower rates of second cancers, which is

a major problem for these patients," says Paul Bunn Jr., M.D., director of the University of Colorado Cancer Center and past president of the International Association for the Study of Lung Cancer. "They also have lowered risk of death from other problems such as heart disease." Bunn says it's a myth that most lung cancer patients don't quit smoking; in fact, they have a much higher quit rate, he says.

For more information on how to quit smoking, see "It's Quittin' Time" in the November-December 1997 *FDA Consumer* (available on FDA's Website at www.fda.gov/fdac/features/1997/797_smoke.html). ■

—E.B.





(Continued from page 8)

with early stage, non-small cell lung cancer who cannot undergo surgery or radiotherapy due to other medical conditions. Administered intravenously, Photofrin accumulates in the tumor cells. A laser, directed toward the cancerous tissue, then activates the drug. A significant side effect is extreme photosensitivity, making it necessary for patients to stay out of the sun "almost completely for about a month," says Grant Williams, M.D., a medical team leader in the division of oncology drug products in FDA's Center for Drug Evaluation and Research.

Williams admits that the number of patients with early stage lung cancer

ing difficulties caused by tumors that are obstructing the flow of air through patients' bronchial tubes. Approval for this use was recommended by an FDA advisory committee in September 1998. Final FDA action is pending.

Taxol (paclitaxel), already approved to treat other cancers, was approved last year for use in combination with cisplatin for the first-line treatment of non-small cell lung cancer in patients who are not candidates for surgery or radiation therapy.

Gemzar (gemcitabine hydrochloride), another already approved cancer drug, received an additional approval in August for use in combination with cisplatin for the first-line treatment of patients with in-

tested, it generally cannot be cured by surgery. Treatment usually begins with a combination of two or more drugs to kill cancer cells throughout the body. Later, treatment with more drugs combined with radiation therapy or radiation alone, is often prescribed. Chemotherapy (drugs) and radiation therapy shrink tumors in most patients, and sometimes the disease goes into remission. But in many cases the cancer begins to grow again when it becomes resistant to treatment.

The Road Ahead

The future and course of lung cancer research seems to vary tremendously depending on who you talk to. Some experts believe prevention and early detection are the best bet. Others insist that improved treatments and gene therapy will be the answer. Paul Bunn Jr., M.D., believes that more research needs to be conducted to see if it's feasible to use x-rays to screen cigarette smokers and people exposed to asbestos, who are at highest risk of developing the disease. Bunn, the director of the University of Colorado Cancer Center and past chairman of FDA's Oncologic Drugs Advisory Committee, believes that the increased use of tobacco among teenagers and adults must be curtailed and that one of the best weapons against lung cancer is prevention.

As for lung cancer patient Ron Norgord, he's banking on a drug that's intended to cut off the blood supply to tumors using molecular technology. The 63-year-old resident of Pasadena, Calif., who has been on a variety of chemotherapy and radiotherapy treatments since he was diagnosed about a year and a half ago, was accepted in September into a clinical trial of a drug that inhibits the growth of tumor blood vessels at UCLA's Cancer Center. "I'm quite encouraged by the results so far," Norgord says. "It's too early to see yet, but I see some positive things coming out of the treatment." One positive sign came after his first treatment, when his chances for fighting infections improved because his white blood cell count finally came up into the normal range.

Researchers are currently studying a variety of drugs and drug combinations designed to extend patients' lives and improve their quality of life. They are

The more you smoke and the longer you smoke, the more likely you are to develop lung cancer.

who will be helped by Photofrin will be quite limited. "We're talking about a very small number of patients compared to the number of lung cancer patients who have extensive cancers that can't be operated on," he says.

Williams notes, however, that Photofrin may also be able to relieve symptoms in some patients with advanced non-small cell lung cancer. He explains that Photofrin has been demonstrated to be helpful in relieving breath-

operable, locally advanced or metastatic non-small cell lung cancer.

Although results of some studies have shown that new treatments may only give patients an additional month or two to live, "there are not a lot of effective treatments for advanced stage non-small cell lung cancer," says Isagani Chico, M.D., a medical officer in FDA's division of oncology drug products.

Because small cell lung cancer has typically spread by the time it's de-

Stages of Lung Cancer

Lung cancer treatment depends on tumor size and on how far the cancer has spread. To help doctors decide on the best treatment plan for their patients, a system of stages that describes the growth and spread of the cancer has been developed.

There are two stages for small cell lung cancer. In the limited stage, the tumor is usually confined to one lung and lymph nodes on the same side of the chest. In the extensive stage, the cancer has spread to the other lung and to lymph nodes on the other side of the chest, or to distant organs.

The stages of non-small cell lung cancer are:

Occult Stage:

Cancer can be detected in patient's saliva, but tumors cannot be found in the lungs.

Stage 0:

Cancer is localized in a few layers of cells and has not grown through the lung's top lining.

Stage I:

The tumor is only in the lung and surrounded by normal tissue.

Stage II:

Cancer has spread to nearby lymph nodes.

Stage III:

Cancer has spread to the chest wall or diaphragm near the lung, or to the lymph nodes in the mediastinum (the area that separates the two lungs), or to the lymph nodes on the other side of the chest or in the neck. This stage is divided into IIIA, which can usually be operated on, and stage IIIB, which usually cannot withstand surgery.

Stage IV:

The cancer has spread to other parts of the body.

Recurrent:

Cancer has returned after treatment.

also studying various aspects of the disease in the hope of someday developing more effective treatments. Here are just a few of the recent findings, studies and developments related to lung cancer:

- Researchers at the Dana-Farber Cancer Institute and the Brigham and Women's Hospital in Boston have identified six factors that place patients with early-stage lung cancer at risk for recurrence. These factors include: large tumor size, a specific tumor subtype of adenocarcinoma (a type of lung cancer), evidence that the cancer has entered the channels of the lymph system, and the presence of certain proteins commonly associated with cancers. Patients with two or more of these risk factors have an increased chance of their cancers recurring. This knowledge may help doctors decide which patients would benefit most from chemotherapy after surgery.

- The Radiation Therapy Oncology Group, a federally funded cancer clinical trials cooperative group, which carries out multi-disciplinary research nationwide, recently began a randomized clinical trial that will evaluate whether amifostine, a radio-protective agent, can effectively reduce some side effects in certain lung cancer patients treated with combined radiation therapy and chemotherapy. The trial, which will study patients with inoperable non-small cell lung cancer, is important because lung cancer patients who are treated with radiation and chemotherapy sometimes develop inflammation of the esophagus, making it difficult for them to swallow.

- At an American Association for Cancer research meeting in March, E. Premkumar Reddy, Ph.D., director of the Fels Institute for Cancer Research at Temple University School of Medicine in Philadelphia, reported that discovery of a new pathway for tumor growth may help researchers develop new types of diagnostic tests and anti-cancer agents. The new pathway, Src-Stat-3, is believed to play a critical role in the proliferation of cancer cells in the lung, breast, prostate, and ovary.

Meanwhile, lung cancer survivor Ken Giddes, who is also a voting patient representative on FDA's Oncology Drug Advisory Committee, continues to spread a message of hope to people throughout the country. "I want people

To Find Out More

For more information about lung cancer, contact the following organizations:

The American Cancer Society
1599 Clifton Road, N.E.
Atlanta, GA 30329-4251
1-800-ACS-2345
www.cancer.org

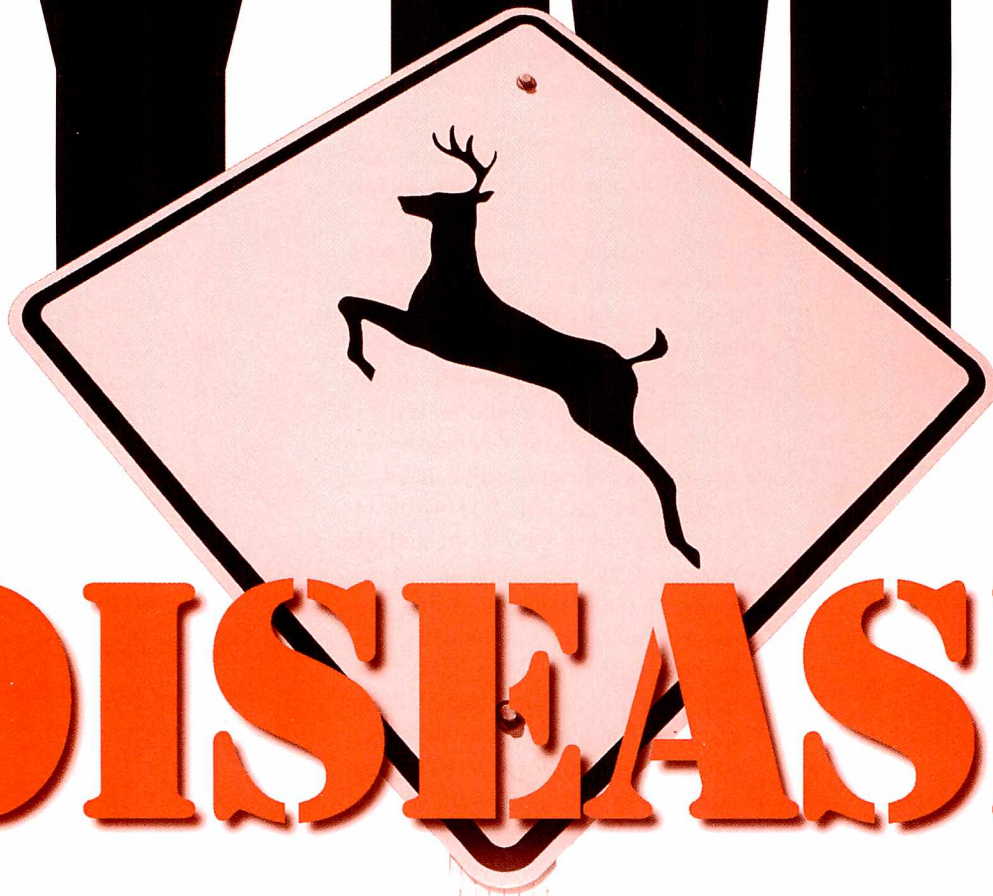
American Lung Association
1740 Broadway
New York, NY 10019
1-800-LUNG-USA (1-800-586-4872)
www.lungusa.org

National Cancer Institute
31 Center Drive, NSC 2580
Building 31, Room 10A07
Bethesda, MD 20892-2580
1-800-4-CANCER (1-800-422-6237)
http://cancernet.nci.nih.gov/wyntk_pubs/lung.htm

to know that the diagnosis of cancer is not an automatic death sentence and to inform people of the many options available to them," he says. "I also want people to know that just because they have lung cancer they shouldn't be written off or forgotten. People try to make you feel bad, especially if you smoked, like it's your own fault. But I see plenty of people who have lung cancer and haven't smoked. And even if they did smoke, they didn't plan to get lung cancer." ■

Ellen Brown is a writer in Lakewood, Ohio.

NEW VACCINE TARGETS



DISEASE

New Hope For Diminishing The 'Great Masquerader'



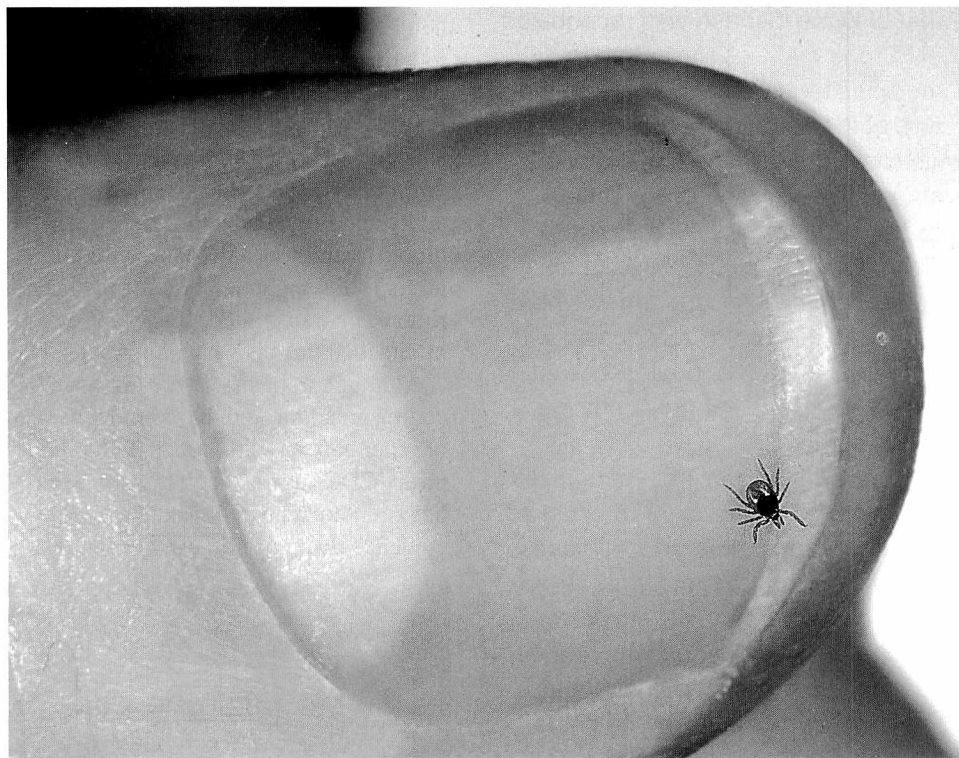
Don Chinnici's hands hurt for months. He kept getting sore throats. When he turned his head to either side, it was painful to move it back. He suffered from a lack of concentration, memory loss, aching joints, and depression. Yet, the then 41-year-old New Jersey native just assumed it was all part of getting older.

But as symptoms worsened, Chinnici became concerned that he was suffering from far more than the effects of middle age. A diagnostic questionnaire and extensive testing eventually confirmed that Chinnici had Lyme disease.

Last December, the Food and Drug Administration licensed the first vaccine to help prevent Lyme disease, a bacterial infection transmitted by tick bites. LYMERix, distributed by SmithKline Beecham Pharmaceuticals, Philadelphia, is an unusual vaccine. Like most vaccines, it stimulates the human immune system to produce antibodies, in this case directed against *Borrelia burgdorferi* (*B. burgdorferi*), the bacteria that cause Lyme disease. But unlike typical antibodies that fight the bacteria in a person's body, animal experiments suggest that when a tick bites a vaccinated person, the vaccine-induced antibodies enter the tick and kill the bacteria there.

FDA emphasizes that the vaccine, however, is not 100 percent effective, and should not be considered a substitute for other standard preventive measures against infection, including wearing protective clothing, using tick repellent, and removing attached ticks (see accompanying articles).

"The vaccine's effectiveness depends on people receiving three doses over a one-year period," says Karen Elkins, Ph.D., an immunologist with FDA's Office of Vaccines, Research and Review. The initial dose is followed by a second dose one month later, and a third dose 12 months after the first.



Is it the thumb of a giant? No, it's just how big a normal human thumb looks compared with a deer tick nymph.

The time of year the vaccination is given is important as well, Elkins stresses. Vaccine administration should be timed so that the second dose and the third dose are given several weeks before the beginning of the *B. burgdorferi* transmission season, usually April in the Northeastern United States.

FDA has approved the vaccine for people 15 to 70 years old who live or work in grassy or wooded areas, where infected ticks tend to thrive. But, although LYMERix may provide protection for most people, the vaccine does not prevent all cases of Lyme disease. It is also not known how long protection against Lyme disease lasts after vaccination.

The national Centers for Disease Control and Prevention says that people of all ages are susceptible to the infection,

but that the highest reported rates of Lyme disease are in children 2 to 15 years old, and adults aged 30 to 55.

The Bite of a Tiny Tick

The most common carrier of Lyme disease in the United States is the deer tick (so named for its dependency on deer to reach the adult stage of its complex, two-year life cycle), or black-legged tick. The Western black-legged deer tick also transmits Lyme disease along the coasts of northern California, Oregon and Washington.

Ticks become infected with the Lyme disease bacteria when they feed on the blood of an infected animal—most notably, the white-footed mouse, white-tailed deer, other mammals, and birds—a method necessary for them to progress to each of three life-cycle stages.

Lyme History 101

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, says a skin rash similar to that of Lyme disease was recognized in Europe and was described in medical literature dating back to the turn of the century. Researchers believe that the disease may have spread from Europe to the United States in the early 1900s. But it wasn't until the influx of suburban developments into rural areas where deer ticks are common, coupled with the exploding deer population, that the disease became prevalent, according to NIAID.

Lyme disease was first recognized in the United States in 1975 when a cluster of rheumatoid arthritis cases occurred in the town of Lyme, Conn. The victims were mostly children, and the outbreak began with rashes, headaches, and joint pains during the summer months—the height of tick season.

By 1994, 48 states and the District of Columbia had reported Lyme disease cases, although most were concentrated mainly in the coastal Northeast, the Mid-Atlantic states, Wisconsin and Minnesota, and northern California. Three years later, the national Centers for Disease Control and Prevention says, more cases of Lyme disease were reported than the combined total of cases reported for measles, mumps, rubella, whooping cough, cholera, tetanus, diphtheria, meningitis, and a host of other lesser known conditions.

But CDC also estimates that thousands of Lyme disease cases go undiagnosed, untreated and unreported, due in large part to the disease's uncanny ability to mimic other illnesses. ■

—C.L.

The vaccine is not 100 percent effective, and should not be considered a substitute for other standard preventive measures against Lyme disease.

According to CDC, ticks are usually in the nymph stage (between larva and adult) when they transmit Lyme disease to humans. Approximately the size of a poppy seed, the nymphs are most active between May and July. The spiral-shaped Lyme-causing bacterium, *B. burgdorferi*, enters the skin at the site of a bite and migrates until it penetrates the bloodstream. It usually takes at least 36 hours following a tick bite for the bacterium to be transmitted, so early removal of attached ticks is very important.

Although in theory Lyme disease could spread through blood transfusions or other contact with infected blood or urine, CDC says no such transmission has been documented. And there is no evidence that a person can get Lyme

disease from the air, food or water, through sexual contact, or directly from wild or domestic animals.

While at least one definitive case of Lyme disease acquired by either a deerfly or horsefly was documented in *The New England Journal of Medicine* in 1990, CDC says that no convincing evidence exists that the disease can be transmitted by insects such as mosquitoes, flies or fleas. In rare cases, CDC also says, Lyme disease acquired during pregnancy may lead to infection of the fetus, but the effects of such transmission on the fetus remain unclear.

Telltale Rash Not the Whole Story

Early-stage Lyme disease is usually marked by a telltale skin rash called



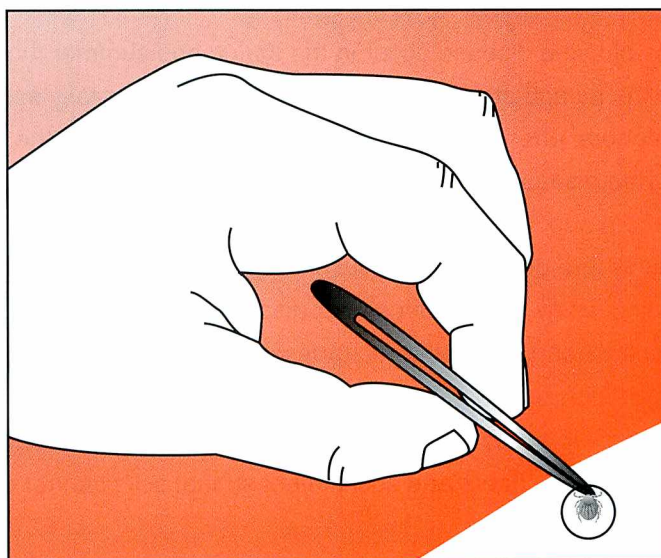
The erythema migrans rash (above) is characterized by a red circular patch that usually appears three days to one month after the bite of an infected tick. The center of the rash may clear as it enlarges, resulting in a bull's-eye appearance.

(Photo by N.Y. Medical College)

Proper Removal of a Tick

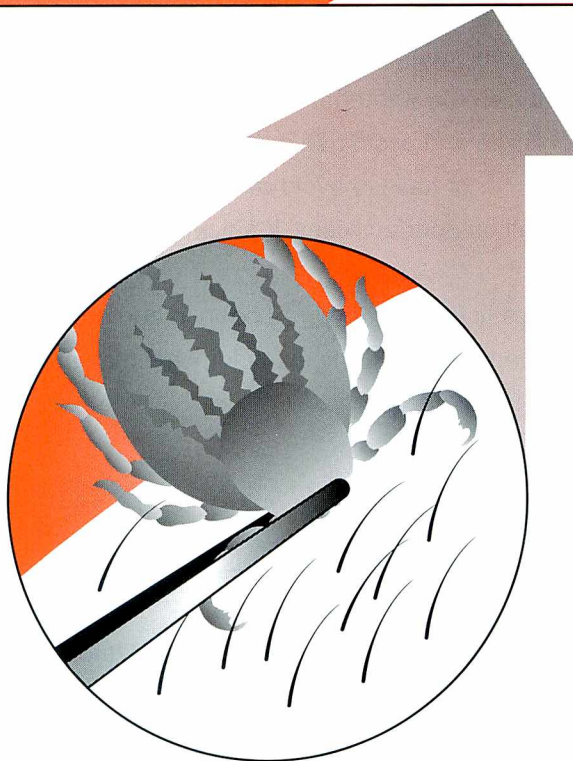
The best way to remove a tick is with fine-pointed tweezers. Grab as closely to the skin as possible and pull straight back, using steady but gentle force. In addition:

- Do not use your fingers to remove the tick.
- Do not twist the tick, which can cause breakage, leaving part of its body in your skin.
- Do not crush, prick, or burn the tick, which may cause it to salivate or regurgitate infected fluids.
- Do not try to smother the tick with products such as petroleum jelly or mineral oil. Ticks can store enough oxygen to complete feeding.



Proper Disposal of a Tick

Place the tick in a sealed container or small plastic bag and deposit in the trash. James Herrington, MPH, Public Health Education Specialist at the Centers for Disease Control and Prevention, says that the humidity ticks need to survive is lacking inside a plastic bag. Do not flush ticks down the toilet because they can easily survive in the water. ■



—C.L.

erythema migrans, which appears three days to one month after the tick bites. It starts as a small red spot at the site of the bite. As it enlarges, the center of the rash may clear, resulting in a bull's-eye appearance. Common sites for the rash are the thigh, groin, trunk, and armpits. CDC estimates that 85 percent of people with Lyme disease get the characteristic rash.

The rash is often accompanied by flu-like symptoms, including fever, fatigue and muscular pain. Other early signs can include secondary skin lesions and facial paralysis.

Although early Lyme disease almost always responds to appropriate antibiotic therapy, if untreated or inadequately treated, the condition can progress weeks, months or years after the tick

bite to late Lyme disease, which is characterized by distinctive arthritic, neurologic and cardiac problems.

Although a tick bite is an important clue for diagnosis, many people cannot recall having been bitten because the tick is so tiny and its bite is relatively painless. "I don't recall ever being bitten by a tick," says Chinnici. Therefore, NIH advises physicians to base their

Preventing Infection

Most cases of Lyme disease occur in the spring and summer months when ticks in the nymph stage are feeding and people generally spend more time outdoors, often with more skin exposed. To minimize the risk of contracting Lyme disease, the national Centers for Disease Control and Prevention recommends the following precautions:

- Avoid areas where deer ticks live, such as wooded, brushy, and grassy places (including lawns and gardens), especially from May through August.
- Wear long pants and long-sleeved shirts when frequenting these areas to minimize skin exposure.
- Tuck pant legs into socks or boots to form a barrier to tick attachment.
- Tape the area where pants and socks meet so that ticks cannot crawl underneath.
- Wear light-colored clothing so that ticks can be spotted more easily.
- Spray insect repellent that contains DEET on exposed skin, other than the face, or treat clothing with permethrin, which kills ticks on contact. Use sparingly on children and avoid use on their faces and hands.
- Walk in the center of trails to avoid overhanging grass or brush.
- Shower after all outdoor activities. If a tick is still wandering, it may wash off.
- Check periodically for ticks if you've been in and around brushy areas or working in a garden, looking particularly for what may appear to be a speck of dirt. ■

—C.L.

For More Information

For more information on Lyme disease, contact any of the following organizations:

National Centers for Disease Control and Prevention
Division of Vector-Borne Infectious Diseases
Box 2087
Fort Collins, CO 80522
(970) 221-6400
www.cdc.gov/ncidod/dvbid/lymeinfo.htm

National Institutes of Health
Lyme Lines
National Institute of Allergy and Infectious Diseases
Box AMS
9000 Rockville Pike
Bethesda, MD 20891
medlineplus.nlm.nih.gov/medlineplus/lymedisease.html

American Lyme Disease Foundation, Inc.
Mill Pond Offices
293 Route 100
Somers, NY 10589
(914) 277-6970
www.aldf.com

CDC estimates
that thousands of Lyme
disease cases go
undiagnosed, untreated
and unreported, due in
large part to the
disease's uncanny
ability to mimic other
illnesses.

diagnosis not only on the history of a tick bite, but also the patient's symptoms and a thorough ruling out of other diseases that may have triggered those symptoms.

The Importance of Proper Diagnosis

FDA's concern about the potential for misdiagnosing Lyme disease is based on results from commonly marketed blood tests used for detecting antibodies to the organism that causes infection. Antibodies in the patient's blood indicate that the body's immune system has detected invaders, but some tests cannot tell if those invaders are the Lyme disease bacteria. The test most often used to detect antibodies is called an enzyme-linked immunosorbent assay (ELISA) technique.

In addition, in February, FDA cleared a new blood test for Lyme disease that can be used in a doctor's office. PreVue *B. burgdorferi* Antibody Detection Assay, made by Chembio Diagnostic Systems, Medford, N.Y., is intended, like the ELISA test, to be used as the first step in testing people suspected of having Lyme disease. The PreVue test searches for antigens made by the *B. burgdorferi* bacterium that is responsible for the infection.

Unlike ELISA, which must be performed in a lab, PreVue provides results in one hour at the doctor's office. Understanding the limits of such testing, however, is important in diagnosing and

Protecting Fido and Kitty

Household pets can get Lyme disease, too. Typical symptoms in animals include joint soreness and lameness, fever, and loss of appetite.

Currently three Lyme disease vaccines are available for dogs—LymeVax, Galaxy Lyme, and Canine Recombinant Lyme. Larry Elskin with the U.S. Department of Agriculture's Center for Biologics says that healthy dogs can be vaccinated when they are 9 weeks or older. (There is no vaccine available for cats.)

The American dog tick, which is more commonly found on pets, is much larger than the deer tick and, the national Centers for Disease Control and Prevention says, is not known to carry Lyme disease. Checking pets for all types of ticks before letting them enter the home reduces the risk of infection for both pet and owner. ■

—C.L.



treating the disease, says Sharon Hansen, Ph.D., a microbiologist with FDA's Center for Devices and Radiological Health. She advises that the tests be used only to support a clinical diagnosis of the disease, as in Chinnici's case, and not solely for making initial diagnostic or treatment decisions.

"In early diagnosis of Lyme disease these tests should not be used to rule in or rule out the infection," she advises, "especially in the absence of a rash." She explains that a positive test result does not conclusively indicate infection, and that people with active Lyme disease may get a negative result. She adds that when the ELISA test is positive, it must

be followed and confirmed by a supplemental, second-step test known as the Western blot. The ability of Western blot to detect antibodies specific for *B. burgdorferi*, she concludes, reduces the number of false positives obtained with ELISA.

Like ELISA, positive results from PreVue also must be confirmed with a Western blot test done by a laboratory.

Treatment and Prevention

Most Lyme disease patients can be successfully treated with standard antibiotics. FDA approved Ceftin (cefuroxime axetil) Dec. 19, 1996, for the treatment of early Lyme disease.

Physicians should base their diagnosis not only on the history of a tick bite, but also the patient's symptoms and a thorough ruling out of other diseases that may have triggered those symptoms.

Recommended regimens of oral antibiotics can speed the healing of the rash, and can help prevent subsequent symptoms such as arthritis or neurological problems.

Hansen says that patients treated in the early stages with antibiotics usually recover rapidly and completely. Patients treated in later stages of the disease also may respond well to antibiotics, but in some cases, symptoms of persisting infection or inflammation may continue or recur, causing permanent damage.

"Lyme disease is a great masquerader," she says. "The bacteria may lay dormant and the symptoms disappear, but as the bacteria becomes active again, the symptoms will reappear." Hanson adds, "Even when the bacteria is eradicated from the body, the damage that has already been done may persist."

FDA, CDC, and the National Institutes of Health all agree that education is the most important part of Lyme disease prevention. Research has indicated that early removal of a tick can ward off much of the danger, but diagnosing the disease and treating infection remain difficult.

"I can't emphasize strongly enough the importance of finding a doctor who is experienced in recognizing this infection," adds Chinnici. "As in my case, where Lyme disease is concerned, time is of the essence." ■

Carol Lewis is a staff writer for FDA Consumer.

Dental More Gentle with Painless 'Drillings' and Matching Fillings

by Paula Kurtzweil



**Today,
half of all
American
children
under 12
have never
had a
cavity.**

Kids today have it so good—computers in the classroom, Nickelodeon on cable TV, popcorn in the microwave. They also have it good because they rarely get dental cavities. And, for those who do develop tooth decay, newer dental devices the Food and Drug Administration has cleared in the past two to five years are less painful than the traditional dentist's drill.

Public health measures, such as fluoridation of drinking water and consumer education on proper dental hygiene, have helped bring about a decline in cavities in the past 50 years. Today, half of all American children

under 12 have never had a cavity. For adults, these preventive measures, along with new filling materials, are enabling many of them to keep their own teeth for the rest of their lives.

"There's really no reason in this country today that [people] can't maintain their own teeth for their entire life," says Kimberly Harms, D.D.S., a dentist in Farmington, Minn.

Digging Out the Decay

The only way to treat tooth decay, technically known as dental caries, is by cutting away the decaying portion of the tooth, a procedure that is done almost

170 million times a year. Until about five years ago, the only way to do that was with the standard handpiece, commonly known as the dental drill, a device that dates to the 1700s. Modern high-speed handpieces revolutionized dentistry when they were introduced in the 1960s.

Today, dentists have two other options—the erbium:YAG laser and the microair abrasion unit. FDA cleared the erbium:YAG laser for marketing for use on adults in May 1997 and for use on children in October 1998. Though the clearances were the first of their kind for treating "hard-tissue" in the mouth, the

laser actually was introduced into dentistry in 1995, when FDA cleared a laser device for gum surgery.

As of March 1999, two companies market the laser for dental decay: Premier Laser Systems Inc., of Irvine, Calif., and BioLase, of San Clemente, Calif.

The erbium:YAG laser essentially vaporizes decayed tooth tissue. A stream of laser light that passes through a fiber connected to a pencil-like handpiece is directed to the decay. The laser handpiece looks like the standard handpiece and, like the standard handpiece, must be used in a controlled manner so that it doesn't slip and damage healthy tissue.

"The laser is a cutting instrument," says Susan Runner, D.D.S., branch chief of dental devices in FDA's Center for Devices and Radiological Health. "And like any cutting instrument, dentists have to be careful any time they use it. The laser has many of the same risks as the drill."

Another similarity between the dental drill and the laser is that both use water and air to cool the tooth and clean the surface during removal of decay. While dentists and patients *may* wear eye protection during conventional treatment to protect against the spray of water and particles, they *must* wear goggles during the laser procedure to protect their eyes from straying laser light.

The laser has several benefits over the handpiece: Because laser treatment is usually painless, there is no need for anesthesia—or anesthetic injections—in many patients, and dentists do not have to wait until their patients' mouths are numb to begin treatment. Also, the laser eliminates the vibrating sensations of the high-speed handpiece.

Also, compared with the standard handpiece, the laser can work with better precision, saving more of the healthy tooth. And when the laser procedure is done, patients do not have to wait for the numbness and puffiness related to the use of anesthesia to fade.

For many patients, especially those particularly fearful of the dental drill, the laser has drawn rave reviews. "My patients love it," says Edward Romano, a dentist in Morristown, N.J., who has used the laser since 1997. "They say: 'I can't believe it's so comfortable, that dentistry has come this far.'"

However, the laser is not without its own shortcomings. For one, it can't be used on teeth with fillings already in place. According to Runner, there is the risk of damage to the tooth because the filling heats up. Romano says silver fillings also damage the laser tip. Also, studies show that the laser procedure takes longer than the conventional method.

"The laser is really ideal for virgin teeth—for new decay," Runner says. "Dental lasers is a growing field, but they can't do everything. There's still a need for the standard handpiece."

Another potential pitfall is expense. In December, Premier Laser Systems was citing a list price of about \$45,000 for its Centauri laser. That includes training for the dentist. The standard high-speed handpiece typically sells for around \$600.

Premier Laser estimates, however, that while the typical laser procedure costs about \$13 more on average than the same drill procedure, the cost reductions of not using anesthesia and having more time to spend with other patients could actually save dentists about \$70,000 over three years.

Still, some dentists say they are putting off buying a laser for treating cavities, at least for the near future. "Our position [in my dental practice] is that the laser looks promising," Harms says.

"But we're not using it yet. We're waiting for long-term studies and newer tools."

The other alternative to the traditional high-speed handpiece is the air abrasion handpiece. Air abrasion involves the use of a high-pressured instrument similar to a tiny sandblaster. A stream of tiny aluminum oxide particles cuts away the decay. There is no heat and no vibration, and often, it can be used without anesthesia. It also can be used to remove some fillings, although it is not yet cleared for removing amalgams (silver-colored fillings).

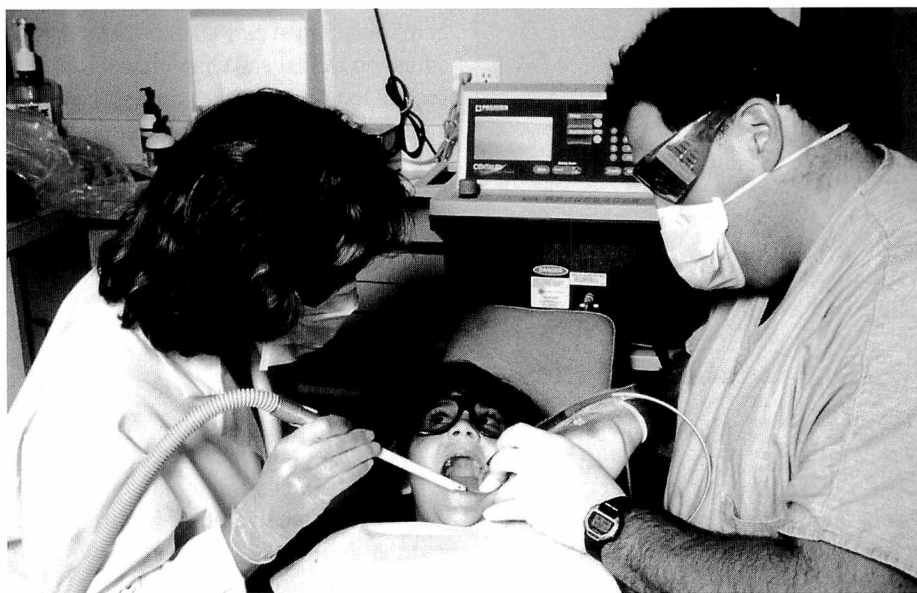
Harms, who uses air abrasion, says the technique is ideal for small cavities and fillings in children, but she notes, "It doesn't replace the drill."

Fillings

Once decay is removed, a filling is placed inside the cut-out area to retain the tooth's shape and function, including chewing. Today, a variety of filling materials is available.

One of the oldest and now most commonly used is amalgam, a metal alloy of silver, tin, copper, and sometimes indium, palladium and zinc that is mixed with about an equal amount of mercury. FDA regulates amalgam alloy as a medical device.

According to a November 1998 article (*Continued on page 20*)



With help from dental assistant Maria D'Andrea, Edward Romano, a dentist in Morristown, N.J., uses a laser to remove tooth decay in a 6-year-old boy. FDA approved the laser for treating cavities in kids in October 1998.

How Decay Occurs

For most people, the first sign of a cavity is pain, but the actual start of tooth decay begins much earlier, with the accumulation of minute amounts of a sticky film, called plaque, on the tooth's surface.

Plaque contains bacteria, which feed on carbohydrates in the mouth. As a result of their feeding frenzy, the bacteria produce acids, which can attack the tooth enamel—the outermost layer of the tooth. If the plaque isn't removed, it continues to build, creating more acid that continues to damage the tooth enamel. There usually is no pain until the acids eat through to the tooth's underlying dentin and pulp layers, where the nerves are located. This decay, technically known as dental caries, is the point at which treatment is needed to prevent further tooth damage and loss.

Dental decay usually occurs in the

back teeth, where it is more difficult to remove food debris and plaque. There are two notable exceptions: early childhood decay in bottle-fed babies and root decay in older adults.

Baby-bottle decay usually occurs in the upper front teeth as a result of continuous feeding on sweet liquids, including milk, formula and fruit juice. Nighttime use of a bottle is the most dangerous because the sugars sit on the baby's teeth for an extended time. Tooth loss can result, causing spacing and development problems when the permanent teeth erupt.

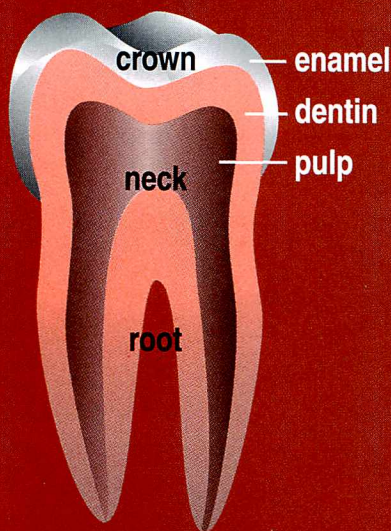
"It's very nasty," says Cleveland dentist Matthew Mecini, D.D.S. "You don't see it too often, but when you do, it's severe. The amount of damage that can be done to children's teeth in a short time is amazing."

Root decay occurs on the exposed root surfaces of older adults whose gums have receded as a result of gum disease. Many types of medicines older people typically use decrease saliva production, which can aggravate the problem. Saliva is important in preventing tooth decay because it can wash away food particles and bacteria and help neutralize acids formed by bacteria in the mouth.

The first sign of a cavity forming may be a white spot that in time may turn brown. Most patients, however, remain unaware of the decay until it is well advanced. Common signs that people notice include sensitivity of the tooth when exposed to hot or cold and brief pain after eating a sugar-containing food.

The dentist can diagnose decay with x-rays or by probing the tooth with a sharp instrument. Decayed enamel or dentin will feel soft. ■
—P.K.

Anatomy of a Tooth



(Continued from page 19)

in the *Journal of the American Dental Association*, dentists continue to use amalgam primarily because it is inexpensive and durable and withstands the tremendous forces of chewing. A 1993 U.S. Public Health Service report on dental amalgam said that amalgam typically lasts from 8 to 12 years. Only gold alloy and metal-ceramic crowns

last longer—up to 18 years.

Amalgam has drawn controversy in the past 10 years because its critics contend that the mercury emits minute amounts of vapor, causing a variety of health problems ranging from multiple sclerosis and arthritis to mental disorders. However, several investigations by the federal government and others have not borne this out, and the use of amalgam is supported by FDA, the National Institute on Dental and Craniofacial Research, the American Dental Association, and other professional organizations.

In a scientific literature review published in the November 1998 *Journal of the American Dental Association*, professors of dentistry in the United States and China found that research has not yet shown that mercury vapors escaping amalgams are "in concentrations high enough to produce any detectable effect on the body." The authors concluded that, contrary to some dentists' current practice, "dentists cannot ethically tell patients that amalgam is a health hazard and that removal of restorations will benefit their health."

While amalgam remains the most commonly used dental filling, its use does appear to be declining. According to the dental association's journal article,

the use of amalgam for filling back teeth has dropped from 85 percent in 1988 to 58 percent in 1997. "The use of amalgam will likely continue to diminish, and it will eventually disappear from the scene," the journal article said.

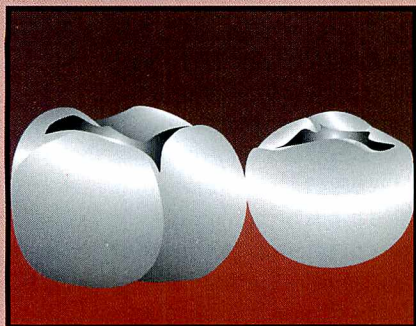
One reason for the decline is the introduction of new materials that afford similar durability and strength as amalgam and, unlike the silver-colored fillings, can be made to match the color of a patient's teeth. "The aesthetics' side of it is very important to many patients," Runner says. However, using these materials—composites, glass ionomers, and metal-ceramic crowns—can cost a patient from 1.5 times to 8 times the cost of an amalgam restoration.

Prevention of Decay

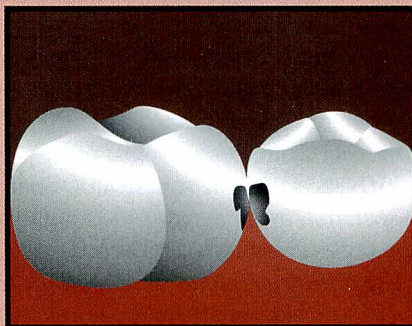
Of course, much of the pain and expense of treating cavities can be eliminated through preventive measures.

Many of these measures, says Dennis Mangan, Ph.D., chief of the Infectious Diseases Branch of the extramural division of the National Institute on Dental and Craniofacial Research, are aimed at interrupting the decay process—for example, eliminating the sugars that serve as a source of food for bacteria in the mouth, eliminating the bacteria that feed

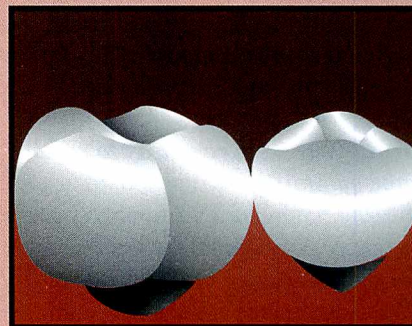
Where Cavities Usually Form



On Chewing Surfaces: Cavities often begin in the depressions and grooves of chewing surfaces of teeth, where it is difficult to remove plaque. This is the most common form of cavities in children.



Between Teeth: Cavities form between teeth when plaque is allowed to accumulate there.



On the Roots: Root cavities occur on exposed root surfaces of people whose gums have receded. The root is especially vulnerable because it is not protected by enamel like the rest of the tooth, making it easier for bacteria and acids in the mouth to attack the root surface.

on the sugars, strengthening the tooth's enamel to make it harder for acids to attack. Or, Mangan says, "It can be some combination of all of them."

Some of the most successful preventive measures involve fluoride, a mineral that occurs naturally in many foods and water. Fluoride helps prevent decay by making the tooth more resistant to acid attacks. It also has been found to reverse early decay where acid has broken through the enamel by remineralizing the affected area.

To function effectively as an anti-decay substance, fluoride should not only be applied to the teeth but ingested, as well. The most important way in which fluoride is ingested is through fluoridated public drinking water. Dental experts cite water fluoridation, which began 50 years ago, as the main reason for the decline in cavities in children since World War II.

In areas with inadequate or no water fluoridation, children between 6 months and 16 years may need fluoride supplements. A dentist can prescribe the correct dose.

Fluoride can be applied directly to teeth with the use of fluoridated toothpastes and mouth rinses. Less-concentrated rinses are available over-the-

counter, while stronger concentrations require a dentist's prescription.

Consumers need to be sure that children don't use fluoride products without supervision because excess ingestion of fluoride can cause defects in the tooth's enamel that range from barely noticeable white specks or streaks to cosmetically objectionable brown discoloration. The defects, known as fluorosis, occur while the teeth are forming, usually in children under 6 years. Although tooth staining from fluorosis cannot be removed with normal hygiene, a dentist may be able to lighten or remove these stains with professional-strength abrasives or bleaches.

Although excess fluoride intake can be toxic, most reported adverse reactions involve vomiting, diarrhea and eye irritation. Because fluoride is a drug, FDA requires toothpaste manufacturers to include on the labels of fluoride toothpastes a warning that the products should be kept out of the reach of children under 6. In addition, because FDA requires all over-the-counter oral drugs to bear an accidental-ingestion warning, toothpaste labels also must carry a warning that instructs consumers to contact a professional or a Poison Control Center if more than the normal amount used for

brushing is swallowed. This labeling requirement took effect April 1997.

Another highly effective way to prevent cavities is sealants. Plastic material that is usually applied to the chewing surfaces of the permanent back teeth, sealants bond into the depressions and grooves of the chewing surfaces, acting as a barrier to plaque and acid.

According to the American Dental Association (ADA), sealants are "virtually 100-percent effective at preventing tooth decay." They can be used on the permanent teeth of both children and adults.

Though sealants are considered to be most beneficial to children, a 1996 study published in ADA's journal found that only 20 percent of school-aged children have dental sealants on their permanent molars. Cost-wise, sealants average about half the cost of a filling, according to the American Academy of Pediatric Dentistry.

Another reason for the decline in dental caries can be attributed to public education aimed at encouraging consumers to follow good oral health practices at home and see a dentist regularly, beginning as early as age 1.

"Most patients now know [they should] see a dentist regularly," says Cleveland dentist Matthew Mecini,

Healthy Habits to Help Prevent Cavities

- **See your dentist regularly.** How often will depend on your particular needs. Your dentist can advise you.

- **Brush your teeth regularly to reduce plaque buildup.** Brushing should last for about 2 to 3 minutes each time to make sure you're reaching all teeth surfaces. Even though there are many kinds of toothbrushes on the market, including electric and sonic models, any will do, says Susan Runner, D.D.S., chief of



FDA's dental devices branch. "The most important thing about the brush is to use it and to have appropriate instruction from your dentist or hygienist on how to use it," she says. The American Dental Association recommends switching to a new brush every three to four months.

- **Use a fluoride-containing toothpaste.** Check to make sure there is fluoride in the product, says Fred Hyman, D.D.S., a dental officer in FDA's Center for Drug Evaluation and Research, because not all toothpastes contain it. Three kinds of fluoride ingredients are allowed, based on their effectiveness and safety, according to FDA's final monograph on over-the-counter anticaries drug products, which took effect in spring 1997. They are sodium fluoride, stannous fluoride, and sodium monofluorophosphate. Toothpaste manufacturers sometimes combine fluoride with other ingredients that are said to reduce plaque and gingivitis (inflammation of the gums). Although FDA has approved one such product, Colgate's Total toothpaste, for helping to prevent cavities, plaque and gingivitis, FDA has

not determined the effectiveness of many of the antiplaque and antigingivitis ingredients. Also, consumers should be wary of claims that a dental product can do more than simply reduce tooth decay because, based on current scientific knowledge, this is the only cavity-fighting labeling claim FDA allows.

- **Floss daily.** Like toothbrushes, any kind will do, as long as you use it daily. Flossing helps reduce plaque buildup in areas the toothbrush can't get to.

- **Eat a variety of foods,** but eat fewer foods containing sugars and starches between meals, according to the federal government's Dietary Guidelines for Americans. The guidelines say that the more often you eat foods with sugars and starches and the longer these foods stay in your mouth before you brush your teeth, the greater the risk for tooth decay. Consider sugarless candy and gum made with certain sugar alcohols because they may not promote tooth decay. FDA allows these kinds of foods to carry a health claim to this effect, if the foods meet certain criteria. (See "Staking a Claim to Good Health" in the November-December 1998 *FDA Consumer*.) ■

—P.K.

D.D.S., citing statistics that show that 50 to 55 percent of adults actually follow that advice. "We [the dental community] are doing a better job of educating the public on the need for regular dental care."

What's Ahead

Efforts to reduce cavities don't end there. One of the most promising preventives on the horizon is a vaccine-like product against decay. In April 1998, British scientists reported that they had developed a plant-based treatment, which, when applied to the teeth, effectively prevented *Streptococcus* bacteria, the main bacteria involved in tooth decay in humans, from growing in the mouth for up to four months.

In the United States, researchers

funded by the National Institute of Dental and Craniofacial Research are studying a similar preventive, known as "plantibodies." Using genetic engineering techniques, scientists transfer a gene for antibodies specific for streptococci to the tobacco plant, which produces large quantities of these antibodies. Antibodies purified from the tobacco plant are then applied to the teeth with a goal of preventing streptococci from adhering to the teeth.

"The concept is good," Mangan says, but notes that the high cost of genetic engineering and the bother of applying the substance on a routine schedule may make the product somewhat impractical.

Other research, he says, focuses on a vaccine that boosts children's immune

systems to prevent decay. The intent of this experimental product is to stimulate the body's own production of antibodies to prevent streptococci from adhering to the teeth.

While these experimental products promise an even brighter dental outlook for future generations, kids today can look forward to a life of dental care that even their parents never envisioned.

"If you can reduce the anxiety that often accompanies dental treatment," FDA's Runner says, "that's a very positive step, especially for children. That's where a lot of these devices have the most potential—in children." ■

Paula Kurtzweil is a member of FDA's public affairs staff.

Pediatric Drug Studies

PROTECTING PINT-SIZED PATIENTS

by Tamar Nordenberg



Despite seven days, “about 26 hours a day,” spent preparing to testify about the labeling of drugs for children’s use, Wendy Goldberg told Food and Drug Administration experts at a 1997 hearing, “I have become neither a scientist nor a doctor. Not even close.” But, she said, “I do know one thing—I use a lot of medicines on Abby that are not approved by the FDA for use on children her age.”

*Wendy Goldberg and
her daughter Abby.*

MORE THAN HALF OF THE DRUGS APPROVED EVERY YEAR THAT ARE LIKELY TO BE USED IN CHILDREN ARE NOT ADEQUATELY TESTED OR LABELED FOR TREATING YOUNGSTERS.



Of the nine-item laundry list of medicines Goldberg's 6-year-old daughter Abby was taking for her severe asthma, not a single one was tested or approved in the United States for children under 12. "I feel as though I am testing drugs on my own child, every day, and it isn't helping anyone," Goldberg said.

While some drugs do come with pediatric use information (notably, vaccines and antibiotics), asthma medications by no means stand alone in their lack of labeling for kids' treatment. Other types of drugs that often lack pediatric labeling include those for depression, epilepsy, severe pain, gastrointestinal problems, allergic reactions, and high blood pressure.

Overall, more than half of the drugs approved every year that are likely to be used in children are not adequately

tested or labeled for treating youngsters, according to FDA estimates. Safety and effectiveness information is especially sparse for the over 7 million children under age 2.

A recent survey by the agency identified the 10 drugs that were prescribed most often to children in 1994 that lacked pediatric labeling. Together, they were prescribed for kids more than 5 million times. (See "Top 10 Drugs Prescribed to Kids Without Pediatric Labeling.")

"At times, children have been harmed and maybe even killed because of a lack of knowledge of how drugs would affect them," says Robert M. Ward, M.D., chair of the American Academy of Pediatrics' Committee on Drugs. Among Ward's historical examples: the deaths of a number of newborn babies in the 1960s when their immature livers were unable to break down the antibiotic chloramphenicol. "Those types of therapeutic misadventures are certainly part of pediatric medicine, and we'd rather they didn't repeat," he says.

To help prevent future chloramphenicol-type disasters, FDA finalized a rule last December requiring manufacturers of many drugs to provide information about how their drugs can safely and effectively be used in children (from newborns to adolescents), including information on the proper doses for kids.

A Healthy Dose of Regulation

The pediatric studies rule, published in the Dec. 2, 1998, *Federal Register*, requires that new drugs (generally prescription drugs, including biologics, or drugs derived from living organisms) that are important in the medical treatment of children or will be commonly used in children include labeling information on safe pediatric use.

The information would usually be required when a drug is approved. For

drugs already on the market, FDA can require children's studies in certain compelling circumstances—when pediatric labeling could avoid significant risks to kids, for example.

The rule expands on a 1994 regulation that simplified the information needed for a manufacturer to label its drugs for children's use. That rule required drug makers to look at *existing* data and determine if they could support safe and effective use in children.

"That was the voluntary effort, and we weren't making much headway," says Rosemary Roberts, M.D., chair of the pediatric subcommittee in FDA's Center for Drug Evaluation and Research.

"Most manufacturers just went back to saying that safety and effectiveness had not been established for children."

Without pediatric data about a drug, Roberts says, doctors are sometimes reluctant to treat a child with it. "Some physicians won't even try a drug in a child if they don't have enough information," she says. It is legal, however, to prescribe a drug for use in children despite its approval only for adults (termed "off-label" use).

If doctors decide against using adult drugs in their young patients because the appropriate dose is unknown, children may be deprived of useful treatments, especially some AIDS drugs and other breakthrough therapies that carry considerable risks.

Doctors can be faced with quite a dilemma, says Timothy Westmoreland of the Elizabeth Glaser Pediatric AIDS Foundation. "Do you choose to withhold a potentially effective drug that is useful in adults or expose a child to a drug you don't know is safe?"

Because of their immature organs and different metabolic and immune systems, children react unlike adults to many drugs. Treating children with adult
(Continued on page 28)

Protecting Older Patients

To help ensure the safe and effective use of prescription drugs in *older* people (specifically, aged 65 and older), a rule finalized by FDA in August 1997 requires drug companies to include a separate "Geriatric use" section in their drugs' labeling. Drug companies do not have to perform additional studies like the pediatric rule requires, but must include available information in a specific format and location.

"If the information is dispersed throughout the whole label, it doesn't make for a user-friendly information source," says Robert Michocki, a clinical pharmacist and professor at the University of Maryland's school of pharmacy. "People are busy. Physicians don't sit down and read the whole drug label. They try to read the important sections that answer questions like 'what's the dose?' or 'what are the side effects?'"

While drugs for everything from heart problems and high blood pressure to pneumonia and the flu can be life-savers for older people, the dangers of medicine can be magnified in this population, too.

One reason for the increased risk is people's changing physiology as they get older, says Charles Ganley, M.D., FDA's medical team leader for cardiovascular drug products. For example, he says, certain drugs that are eliminated from the body by the kidneys could cause problems in the elderly because kidney function can decline with age.

mined. The cause of these deaths is not known. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when Paxil (paroxetine hydrochloride) is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In worldwide premarketing Paxil clinical trials, 17% of Paxil-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Twenty percent (1,199/6,145) of Paxil patients in worldwide clinical trials in depression and 11.8% (64/542) and 9.4% (44/469) of Paxil patients in worldwide trials in OCD and panic disorder, respectively, discontinued treatment due to an adverse event. The most common events ($\geq 1\%$) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for Paxil compared to placebo) included the following:

9

term (6-week) placebo-controlled trial patients were dosed in a range of 20 mg/day. Reported adverse events were using a standard COSTART-based terminology.

The prescriber should be aware that these effects cannot be used to predict the incidence of side effects in the course of usual practice where patient characteristics and clinical investigations involving different doses, uses and investigators. The cited frequencies, however, do provide the prescribing with some basis for estimating the relative contribution of drug and nondrug factors to the effect incidence rate in the population.

Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Depression

Body System	Preferred Term	Pax (n=42)
Body as a Whole	Headache	18%
	Asthenia	15%
Cardiovascular	Palpitation	3%
	Vasodilation	3%
Dermatologic	Sweating	11%
	Rash	2%
Gastrointestinal	Nausea	26%
	Dry Mouth	18%
	Constipation	14%
	Diarrhea	12%
	Decreased Appetite	6%
	Flatulence	4%
	Oropharynx Disorder ²	2%
Musculoskeletal	Dyspepsia	2%
	Myopathy	2%
	Myalgia	2%
	Myasthenia	1%
Nervous System	Somnolence	23%
	Dizziness	13%
	Insomnia	13%
	Tremor	8%

10

Also, the elderly take more medicines than any other age group—around 30 percent of the prescription drugs sold in the United States, according to FDA, although they make up only about 12 percent of the country's population. The use of multiple drugs can increase the risk of dangerous drug interactions.

Michocki says, "start low and go slow" is an adage that applies to giving older people medicines. "For the most part, with older people you're using medications to try and manage their chronic diseases like diabetes or arthritis. There's no reason to go in there and try to fix something overnight."

The rule will prove beneficial, Michocki thinks, because "after reading the special section on geriatrics, a physi-

cian who is not familiar with the drug may start out giving half the dose he was going to give in the first place."

New labels are appearing gradually, first on those drugs that FDA has determined are most likely to create problems for geriatric patients. These include psychotropic drugs such as antidepressants and antipsychotics, as well as some heart medications and nonsteroidal anti-inflammatory drugs (NSAIDs). ■

—T.N.

Top 10 Drugs Prescribed to Kids Without Pediatric Labeling

These 10 drugs were prescribed more than 5 million times in a single year to children in age groups for which the drugs were not adequately labeled.

Drug	Condition	Prescribed
1. Albuterol inhalation solution for nebulization	Asthma	1,626,000 times to children under 12
2. Phenergan	Allergic reactions	663,000 times to children under 2
3. Ampicillin injections	Infection	639,000 times to children under 12
4. Auralgan otic solution	Ear pain	600,000 times to children under 16
5. Lotrisone cream	Topical infections	325,000 times to children under 12
6. Prozac	Depression, obsessive-compulsive disorder	349,000 times to children under 16, including 3,000 times to infants under 1
7. Intal	Asthma	Solution prescribed 109,000 times to children under 2; aerosol prescribed 399,000 times to children under 5
8. Zoloft	Depression	248,000 times to children under 16
9. Ritalin	Attention deficit disorder, narcolepsy	226,000 times to children under 6
10. Alupent syrup	Asthma	184,000 times to children under 6

(Based on 1994 data from research firm IMS America, Ltd.)

Label Warnings Create A Pediatric Guessing Game

Rx Safety and effectiveness in pediatric patients have not been established.

Rx The effectiveness in pediatric patients with depression or panic disorder has not been systematically evaluated.

Rx This product should not be used in children under 2 years because safety for such use has not been established.

Rx Tablets are not recommended for use in children under 6 years at this time.

Rx Should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

"A CHILD IS NOT JUST HALF AN ADULT TO BE GIVEN HALF THE ADULT DOSE."

—Janis Stire, Elizabeth Glaser Pediatric AIDS Foundation



(Continued from page 24)

drugs, then, can carry the risk of unforeseen adverse reactions.

Besides the chloramphenicol tragedy, other serious adverse reactions in children have included:

- jaundice in newborns from sulfa drugs
- seizures and cardiac arrest from the local anesthetic bupivacaine
- withdrawal symptoms from prolonged use of the painkiller fentanyl
- staining of teeth from the antibiotic tetracycline.

"It can be a real guessing game as to whether we're treating a child effectively," Roberts says. "Sometimes a child's body will handle the drug very much like an adult's, she explains, 'while other times a child's body will react quite differently. There may be no way of knowing in advance.'"

While dosing information sometimes becomes available to physicians through references such as journal articles and pediatric handbooks, it may take years for this information to appear. Even then, the information may not be based on adequate testing and may contain

gaps, about its use in certain age groups, for example.

Even if the correct dose is known, the medicine will do no good, of course, if a child can't ingest it. So the 1998 rule in some cases requires manufacturers to make a special formulation of a drug product—liquid or chewable tablet instead of a tablet that must be swallowed whole, for example—to enable kids to take the drug.

Wendy Goldberg knows first-hand the frustrations of treating her child with drugs made in tablet form for adults. "I need to cut two of them in half," she told the panelists at the hearing preceding the rule. One, she said, is "like a little stone. I got a gadget from my pharmacist that is supposed to cut it in half, but it doesn't work exactly right. Do I give her the big 'half' or the small 'half'? I usually give her the big piece in the morning, on the theory that if something bad happens, at least she'll be awake."

Controlled Risk

To those who point out that bad things can happen during drug studies, too, the American Academy of Pediatrics has re-

sponded that treating children with untested drugs may place more kids at risk than including them in controlled studies of the drugs in the first place.

Children enrolled in drug studies "are sick children that stand to benefit from getting new drugs sooner," says AAP's Ward. "Yes, they will be at risk, just like adults are at risk, if the drug is later found to have problems. But because we're treating children with illnesses, that risk is justified."

Under the rule, the timing of studies in children will depend on the seriousness of the disease, the availability of other treatments, the amount of safety and effectiveness information already available, and the types of studies that are needed.

FDA will not delay the approval of a drug for adults to await completion of children's studies. Instead, the agency could approve the drug for adults on the condition that the company completes pediatric studies in a timely way.

The pediatric study requirement may be waived entirely if a drug is not medically important for children *and* will not be commonly used in children *or* if:

- there is strong evidence that the drug product would be ineffective or unsafe in all pediatric patients *or*
- children's studies are impossible or highly impractical because, for example, the number of patients is too small or geographically spread-out *or*
- attempts to develop a pediatric formulation have failed.

The Pediatric AIDS Foundation's Westmoreland is confident that "virtually all" drugs with significance to children will be studied because of the new FDA rule, as well as the complementary financial incentives under the FDA Modernization Act of 1997, which gives an extra six months of exclusive marketing or patent protection for studying certain drugs in children.

"We see the rule as a real victory," says Janis Stire, executive director of the foundation. "For too long, children have been seen as an afterthought, with so many drugs not available to them. A child is not just half an adult to be given half the adult dose." ■

Tamar Nordenberg is a staff writer for FDA Consumer.

Orphan Drug Law

Matures Into Medical Mainstay

by John Henkel

Deborah Kaback noticed the turnaround in her son, Matthew, right away. After spending his first five years of life fighting fatigue, crippling lung congestion, and other symptoms of cystic fibrosis, his condition improved quickly when he started taking a drug called Pulmozyme (dornase alpha) in 1994.

"His energy level soared and has stayed [high] ever since," says Kaback. "Although it hasn't prevented lung in-

fections entirely, I believe that it has helped reduce the frequency."

Infections also were a big concern for Kim Payne, whose son, Brian, was able to halt one menacing type of cystic fibrosis-related lung infection by using the antibiotic TOBI (tobramycin). He took the drug through two years of clinical trials starting in 1995, when he was 15, and continued the regimen after the drug's approval in 1997. "TOBI allowed

him to have a normal and very healthy high school experience," says Brian's mother.

Success stories like these are common among cystic fibrosis (CF) patients nowadays. But as recently as the early 1980s, tragic tales were the norm. CF patients faced a life that was miserable and short. Children with the disease rarely lived beyond their early teens. Now, CF patients often live into their



The medicine this young boy is taking for the lung disease cystic fibrosis (CF) might not have been available without the law that helps bring to market treatments for rare diseases like CF.

30s, some even into their 50s. What's made the difference? For countless sufferers of rare or "orphan" diseases such as CF, the improved outlook is due in part to the Orphan Drug Act of 1983, which has helped make treatments such as Pulmozyme and TOBI available.

What Is an Orphan?

The Orphan Drug Act defines an orphan disease as a condition that affects fewer than 200,000 persons in the United States. More than 5,000 of these rare conditions exist in about 20 million Americans, according to the National Organization for Rare Disorders (NORD). Because no one would "adopt" the products to treat these diseases in the days before the law, they became known as "orphans."

An orphan disease may affect only a few thousand people—some, such as infant botulism, have patient populations of less than a hundred—so the potential for a company to profit from developing an orphan treatment is small.

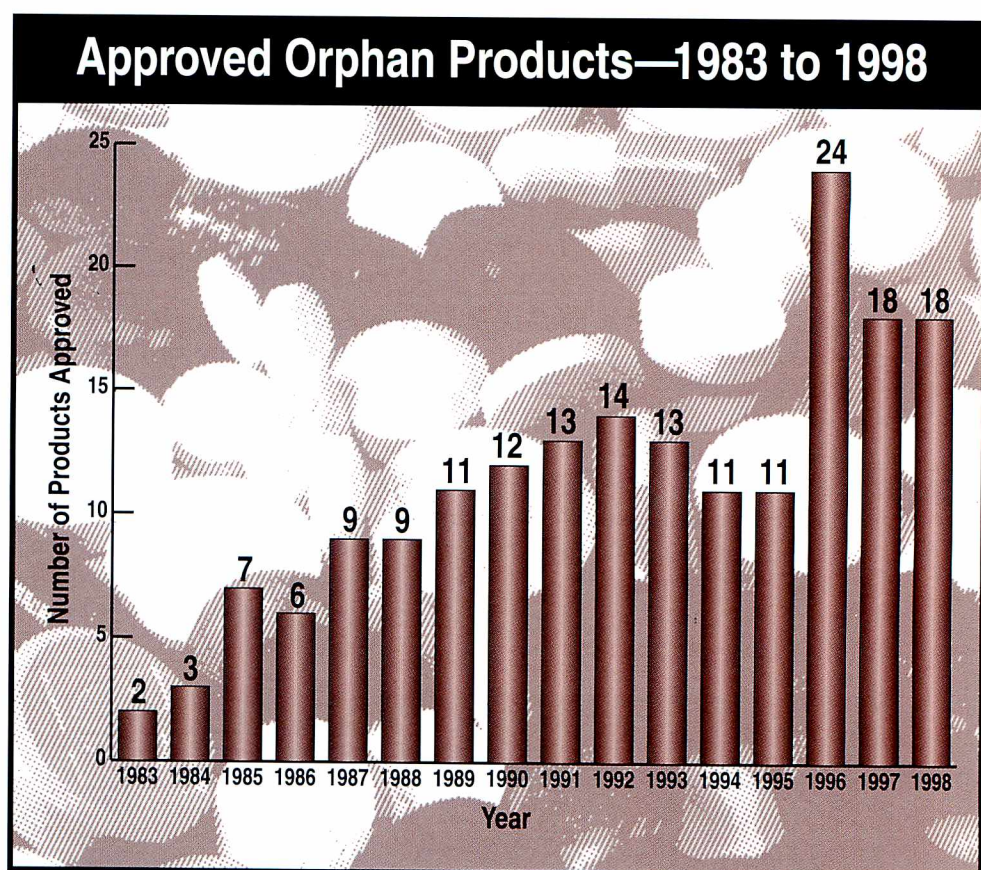
This means that few firms, including large pharmaceutical companies, have been interested in investing the time and money in orphan products, says NORD president Abbey Meyers.

So for years, patients suffering from orphan diseases such as Gaucher's disease, rare cancers, hemophilia, multiple sclerosis, and Parkinson's disease simply were out of luck. With no financial incentives available, companies couldn't risk the investment. Other possible development outlets, such as universities or research hospitals, often lacked the capital or business savvy to develop treatments for small patient groups.

Orphans on a Roll

Pharmaceutical companies did, however, develop a few drugs of limited commercial potential in the 1960s and 1970s and even provided some at little or no charge. For example, the industry marketed Mithracin (plicamycin) to treat testicular cancer before the Orphan Drug Act was passed.

But by the early 1980s, only a handful of orphan treatments existed. A series of events, however, thrust the orphan issue into the public eye (see "How TV



Launched the Orphan Drug Act," on page 31), and in 1982 Congress passed legislation giving generous incentives to companies willing to adopt orphans and bring treatments to market.

Since the act was signed, FDA has approved 182 orphan products—including drugs and biologics. Sponsors have submitted 1,252 applications for orphan designation, of which FDA has granted designation to 917. Orphan designation allows a company to proceed with development and take advantage of the law's financial incentives.

In 1998, FDA approved 18 new orphan products to treat conditions that include:

- **Crohn's disease**—Remicade (infliximab) is the first approved treatment for this chronic, incurable inflammatory bowel disease.
- **Hansen's disease (leprosy)**—FDA cleared thalidomide to treat a serious inflammatory symptom seen in Hansen's patients. Because of its well-known potential for causing birth defects, the drug

was approved with tight restrictions on its use. "How encouraging it is that a medical tragedy [thalidomide birth defects in the 1960s] led to a medical breakthrough that will likely help people with many diseases," says Meyers. "Nobody would have done research on this aspect of thalidomide without the Orphan Drug Act." Thalidomide also has received orphan designation, though not approval yet, for treating primary brain tumors and Kaposi's sarcoma, an AIDS-related cancer.

- **Sickle cell anemia**—Under the orphan program, a decades-old cancer drug, hydroxyurea (Droxia) was approved to treat adults who suffer from this inherited blood disorder that causes chronic anemia and periodic episodes of pain.
- **Cutaneous t-cell lymphoma**—Ontak (denileukin diftitox) treats this slow-growing form of non-Hodgkin's lymphoma when other therapies have not worked.

- **Pneumocystis carinii pneumonia**

(Continued on page 32)

HOW TV LAUNCHED

The Orphan Drug Act

Before the 1980s, victims of many rare disorders faced suffering and even death, with little hope for treatment. It simply was not cost effective for pharmaceutical companies to spend millions developing treatments that would only be used by a few hundred or a few thousand patients.

The landscape changed, however, when Congress passed a bill in 1983 that created incentives for developing products for these rare, or orphan, diseases. But the Orphan Drug Act navigated a long, bumpy road before becoming law, several times appearing to be doomed. While many in the rare disease community credit increased awareness of the orphan problem to an array of groups, including Congress, industry and the news media, others give thanks to a person who, in the early '80s, was riding high with a hit TV show: actor Jack Klugman.

"There just wouldn't be an Orphan Drug Act without Jack Klugman," says Abbey Meyers, president of the National Organization for Rare Disorders. "The issue simply wouldn't be known to the public without him."

Klugman used his weekly TV medical drama, "Quincy," on two occasions to spotlight the plight of rare-disease patients, prompting a huge outpouring of support that ultimately pushed the orphan drug bill through Congress.

Meyers recalls that the situation was bleak before Klugman's involvement. Rep. Henry Waxman (D.-Calif.) had received a call in 1980 from the mother of a boy, Adam Seligman, whose drug treatment for the rare disorder Tourette syndrome had been seized at the Canadian border. Because the drug was approved in Canada but not in the United States, Adam's doctor had arranged to bring the drug from Canada for his patient. Adam's mother was frantic that her son was about to run out of medication.

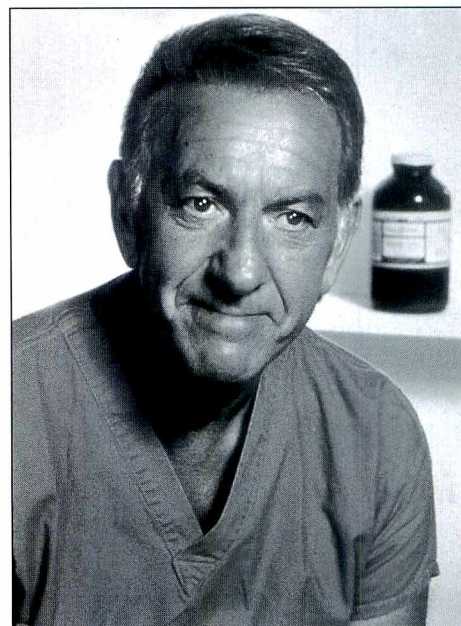
For his part, Waxman held hearings to gauge the extent of the rare disease problem. Witnesses, including Adam, gave emotional testimony, but the hearings were sparsely attended. However, one person present was a reporter from the *Los Angeles Times*, who wrote a story about the orphan issue.

The next day, Jack Klugman's brother, Maurice, saw the *Times* article. He told the story to Jack, who decided to create a "Quincy" episode devoted to Tourette syndrome and the orphan problem. After it aired in March 1981, viewers responded by sending thousands of letters to Jack Klugman voicing support and asking how they could help.

With the issue now more visible, Waxman introduced an orphan drug bill and held a second hearing—this time with Klugman as a witness. With Klugman's celebrity on board, the news media covered the issue extensively, and even greater popular support followed. But when the bill stalled in Congress, Klugman put together another "Quincy" episode, this time mirroring the real-life holdup of the bill taking place on Capitol Hill. He used 500 "extras," who were real victims of orphan disorders. By the time the show aired in 1982, the House had passed the bill, but it was on hold in the Senate. It later passed but faced veto by President Reagan, in part because the administration objected to the bill's tax credits.

Rare-disease activists then took out full-page ads in major newspapers urging the president to sign the bill. It worked. On Jan. 4, 1983, the Orphan Drug Act became law. ■

—J.H.



Jack Klugman, as "Quincy"
(Credit: fotos international/Archives Photos)

For More Information ...

Additional details on rare diseases and orphan products are available from:

FDA Office of Orphan Products
Development

HF-35

5600 Fishers Lane

Rockville, MD 20857

301-827-3666

www.fda.gov/orphan/

National Organization for Rare
Disorders Inc.

P.O. Box 8923

New Fairfield, CT 06812-8923

1-800-999-6673

www.rarediseases.org

(Continued from page 30)

(PCP)—Mepron (atovaquone) treats this infection that strikes high-risk, HIV-infected patients.

While only drugs and biological products are eligible for orphan designations, regulations finalized in 1996 as part of the Humanitarian Use Devices (HUD) provisions of the Safe Medical Devices Act of 1990 created an exemption that makes it easier and less costly for manufacturers to bring orphan-related medical devices to market.

Under the exemption, FDA allows these devices to be sold if sponsors can show they are safe and have a probable benefit for patients. Sponsors do not need to prove effectiveness to get a HUD designation. Since July 1996, FDA has allowed 17 devices to be marketed as HUDs. None of these has yet received full FDA approval as a medical device, which would require clinical trials to prove effectiveness.

Powerful Incentives

While orphan interest from the large pharmaceutical firms remains limited in the wake of orphan law—only about 15 percent of applications come from the giant drug makers—some small companies have sprung up just to develop and market orphan products. In fact, orphan law can be credited with helping establish the American biotechnology industry, says John McCormick, M.D., deputy director of FDA's Office of Orphan Products Development.

"In the early '80s, patent laws for biotechnology were vague, so biotech companies had little protection for their products," says McCormick. He says a provision of the law that grants seven years of exclusive marketing rights is tantamount to a patent and allows a small company to proceed without fear that a competitor might market a similar product for the same condition. "Because many orphan diseases lend themselves to treatment with biotech products," says McCormick, "the exclusivity incentives have worked beautifully to foster innovative treatments by sheltering them from competition."

Though marketing exclusivity is likely the law's most powerful industry incentive, McCormick says, other provisions

for orphan-designated products also are important motivators, including:

- **Research grants**—Managed by FDA, the Orphan Products Grant Program currently funds \$11.5 million worth of clinical studies yearly. Sponsors engaged in clinical trials on the safety and effectiveness of orphan products can receive up to \$200,000 a year for a maximum of three years. Since 1983, the program has awarded a total of \$115 million and has funded 384 grant studies. In 1998, 28 researchers received grant money. Twenty-four grant-supported products have gone on to win FDA approval, including the most recent, Busulfex (busulfan), a treatment for a rare form of leukemia. A few devices have been approved as a result of FDA's Orphan Products Grant Program, including "neurostimulator implantable electrodes," which can restore some hand movements in quadriplegic patients.

- **Protocol assistance**—FDA helps orphan sponsors design research that conforms to regulatory requirements and shows them how to use the agency's review system. Small firms especially can save time and money using this service. "These companies just may not be as adept at jumping through the hoops as someone more experienced," says Meyers.

- **Tax credits**—Sponsors may claim 50 percent of clinical trial costs as a credit against taxes owed.

Meyers says NORD, which is a grassroots coalition of 140 voluntary rare-disease groups, is pleased with the approval rate of orphan products. "The thing that is so encouraging," she says, "is that the rest of the world has seen how the American [orphan] law has been so effective, and now they feel they have to have similar programs." Indeed, the European Union, Japan and Australia all have begun orphan programs of their own based on the U.S. model.

But are the goals of the original act on track 16 years later? "Definitely," says FDA's McCormick. "I think the framers of the act are all pleased as punch." ■

John Henkel is a staff writer for FDA Consumer.



Hot Lines to Health

Getting information on hundreds of consumer health topics can be as easy as picking up the phone. But what numbers do you call? The National Library of Medicine has the answers at www.sis.nlm.nih.gov/hotlines/. A variety of health organizations sponsor the toll-free numbers listed on this site, which provide information on AIDS, cancer, maternal and child health, aging, substance abuse, disabilities, and mental health. The site also has information on services available in Spanish.

Pesticides And Food

How does the government regulate pesticides? What are pesticide residue limits for foods? Why may children be especially sensitive to pesticides, and how can consumers reduce their exposure? The Environmental Protection Agency can tell you at www.epa.gov/pesticides/food/. Here you can learn what "integrated pest management" and "organically grown" mean. You can review the types of pesticides used in this country and health problems they may pose, and pick up tips for food buying and preparation that will help minimize pesticide exposure.

Supplemental Information

It's easy for consumers to find and buy dietary supplements. But where can they find out the facts about those supplements? The National Institutes of Health's Office of Dietary Supplements has a database at odp.od.nih.gov/ods/databases/ibids.html filled with those facts. Designed for people with all levels of Web expertise and scientific knowledge, the site searches existing medical, botanical, agricultural, chemical, and pharmaceutical databases. It also offers links to other government, scientific and professional sites related to dietary supplements.

A 'TRUSTED' WOMEN'S SITE

Calling it "one reliable place to go for information that can be trusted," Surgeon General David Satcher, M.D., launched the National Women's Health Information Center (NWHIC) last November. The new service, managed by the U.S. Public Health Service, combines a Website (www.4woman.gov) and a toll-free number (1-800-994-WOMAN). The Website links to more than 1,000 other women's health Websites, including more than 300 federal sites, hundreds of government-screened private organizations, and more than 2,700 federal documents on women's health. Included are frequently asked questions on dozens of top health issues of concern to women, such as breast cancer, endometriosis, hysterectomy, and pregnancy.



Prescription for Jail Pharmacists Caught in Illegal Rx Drug Scheme

by Paula Kurtzweil

He tried to compete with the big-name drugstore chains in his area, but what pharmacist Mohammad Hussain of Gaithersburg, Md., got was the big house in Morgantown, W.Va.

Hussain, 35, former owner of the Rock Creek Pharmacy in Silver Spring, Md., is serving three years in federal prison for buying and selling prescription drugs illegally, including many stolen from a local hospital. He violated federal law by removing the drugs from their original packaging and transferring them to drug containers bearing inaccurate labeling information, such as expiration dates and lot numbers, which are used to maintain drug safety and effectiveness.

A special agent with FDA's Office of Criminal Investigations (OCI) who helped investigate the case said Hussain bought many of the drugs at half their wholesale value from a pharmacist friend who stole the drugs from the hospital where he worked.

One of Hussain's cohorts, Robert Mark, 41, of Adelphi, Md., a pharmacist who owned Rajon Pharmacy in Washington, D.C., also is serving time—one year and three months at the Petersburg, Va., Federal Correction Institute. A jury in the U.S. District Court for the District of Maryland convicted both men March 25, 1998, of illegally buying and selling a variety of prescription drugs, including the anti-ulcer drug Pepcid and the antibiotic Cipro. Hussain also was found guilty of fraudulently billing an insurance company for drugs never prescribed by a doctor and never intended for a patient.

Both pharmacists were sentenced in summer 1998. The Maryland Board of Pharmacy has since suspended



Hussain's pharmacist license, though no action has been taken against Mark's license, according to a spokeswoman for the Washington, D.C., Board of Pharmacy.

Also, Rock Creek Pharmacy has closed down, and a call to Rajon Pharmacy was answered by a recording that the telephone number had been disconnected.

A third person, Patricia Brown, 58, of Silver Spring, Md., who served as an intermediary between both pharmacies, entered into a plea agreement March 9, 1998, before trial, agreeing to serve six months of home detention and five years' probation, as well as to undergo drug and alcohol treatment.

FDA's OCI entered the case in November 1996, after receiving a call from Montgomery County (Md.) Police. The police reported that they had arrested Jaspal Kochar, a pharmacist at Holy Cross Hospital in Silver Spring, Md., for stealing drugs from the hospital pharmacy. Secret videotaping had caught him in the act of removing controlled substances from the pharmacy's drug safe and putting them in his pocket.

Kochar, who awaits sentencing for his conviction, told police that one of his customers was Hussain, owner of a nearby neighborhood drugstore.

OCI agents executed a search warrant of Hussain's Rock Creek Pharmacy Feb. 10, 1997. During the search, Hussain confessed to OCI agents that he was buying drugs from Kochar and other sources, though he later refused to cooperate with government investigators.

Also during the search, Brown called to arrange a time for Hussain to pick up an order at Rajon Pharmacy that he had placed earlier. After taping the phone call, OCI agents sent an undercover agent posing as Hussain's driver to Mark's pharmacy to pick up the order. When the agent arrived at the pharmacy, he found an empty store and Mark behind a small glass partition.

Mark handed the agent a bag holding about five different prescription medicines in exchange for an envelope of cash. Some of the medicine bottles came with handwritten notes that listed only the name of the drug. Other bottles had no information.

OCI estimated that the drugs in the

bag were worth thousands of dollars on the legitimate market, although based on the cash in the envelope, Hussain paid a lot less.

At Rock Creek Pharmacy, special agents confiscated a variety of drugs as evidence, including expired drugs, blister packs marked "for institutional use only," and unmarked bottles and a bag of drugs with no lot numbers or expiration dates. OCI agents also found on Hussain's shelves several kinds of drugs of the same strength in multiple bottles, containing four times to five times the original contents.

"Every one of these bottles was stuffed," the special agent said. "Hussain was hiding the stolen drugs in the bottles."

Other evidence seized included prescription drug samples. Drug company representatives routinely give free drug samples to doctors so that they can hand the drugs out free to their patients in place of a prescription or to get them started on a drug. It is not illegal for pharmacists to have them in their pharmacies, but it raises questions about where the drugs came from. Under the 1988 Prescription Drug Marketing Act, diverting drug samples from their original intent is illegal because of the risk of counterfeit, adulterated, misbranded, subpotent, or expired drugs being sold to consumers. It also constitutes fraud against legitimate drug sellers.

OCI agents also seized computerized sales records Hussain had kept since assuming ownership of Rock Creek Pharmacy in 1995. OCI audited these records, as well as sales records kept by the wholesale drug company that sold legitimate prescription drugs to Hussain. This audit showed that over two years, Hussain had obtained \$333,000 worth of prescription drugs by unknown means, and five of the drugs audited had never been legitimately purchased.

The audit further showed that almost 80 percent of the audited drugs came from unaccountable sources. Hussain accounted for the drugs by claiming he had bought them from his brother, a pharmacist who went out of business after being convicted in another federal case.

OCI also learned from one of its sources during the investigation that Hussain had falsely billed an insurance company for drugs never prescribed by a doctor for a patient who never received the prescription medicines. When OCI checked with the people named in the claim, the doctor denied prescribing the medicines to the patient and the patient denied receiving them.

OCI agents contacted some of Hussain's customers to learn whether they had received any illegal prescription drugs. They found one patient who still possessed a prescription drug Hussain had dispensed. It was stamped "sample."

On Dec. 17, 1997, a federal grand jury handed down a six-count indictment against Hussain, Mark and Brown. Brown pleaded guilty one day before the trial was set to begin.

In addition to home detention, probation, and drug and alcohol treatment, Brown's sentencing June 15 called for her to perform 500 hours of community service. She waived her right to appeal her sentence.

Mark was sentenced July 8. In addition to prison, he also was sentenced to three years' probation and ordered to pay a \$200 special assessment fee.

Hussain, sentenced July 27, was ordered to pay a \$500 special assessment fee and, following his prison term, to spend three years under supervisory release. The court also ordered him to pay \$80,358 in restitution to the insurance companies he had fraudulently billed.

Though the court considered the insurance companies to be Hussain's victims, the OCI special agent noted that Hussain's customers lost out, too. "There's a matter of trust there," she said. "People rely on their pharmacists to provide safe and effective drugs."

According to FDA's OCI, the office continues to investigate illegal sales of prescription drugs in the Washington, D.C., area.

Paula Kurtzweil is a member of FDA's public affairs staff.

Physician Sentenced for Doctoring Drug Data

by Tamar Nordenberg

For falsifying test results used by FDA in deciding whether to approve new drugs, the physician owner of a California research company was sentenced to 15 months in prison. He also was ordered to repay \$800,000 to the seven or so drug companies that didn't get the reliable study data they had paid his laboratory to provide.

Robert Fiddes, M.D., was president and primary researcher, as well as owner, of Southern California Research Institute, or SCRI (now known as American Pharmaceutical Research Inc.), of Whittier, Calif. SCRI tested medicines for high blood pressure, migraine, asthma, diabetes, and other medical conditions.

While FDA does not believe that the drugs SCRI studied and the agency subsequently approved pose any threat to patients' health, the agency is reviewing data related to the drugs to confirm their safety and effectiveness.

FDA and the FBI collected evidence showing that SCRI, under Fiddes' direction, fabricated drug study information

over a several-year period ending in 1996, the year in which the government began investigating the company.

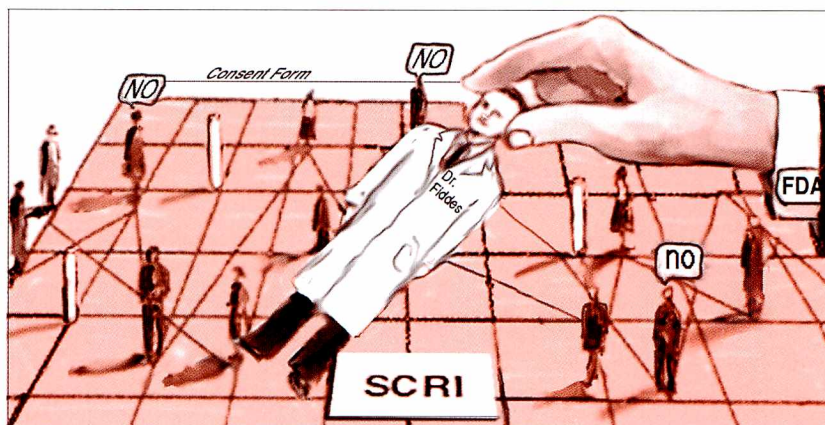
Investigators with FDA's Los Angeles district office first learned of the company's misdeeds from an SCRI employee during a routine inspection in June 1996. After interviews with current and past employees corroborated the first employee's complaints, the Los Angeles district in August 1996 turned the case over to FDA's Office of Criminal Investigations.

Over the next several months, mostly in February and March 1997, OCI special agents conducted more than 10 searches of the offices of SCRI and its employees, other offices controlled by Fiddes, and one SCRI employee's house. Agents followed up by speaking with more past and current SCRI employees and with patients supposedly enrolled in Fiddes' studies.

"We asked the drug manufacturers for Dr. Fiddes' list of study participants, found their addresses, and presented them with the consent forms they were said to have signed," says the OCI case agent. "We asked, 'Did you sign this?' 'No.' 'Were you ever in a study for vaginitis for SCRI?' 'No.' 'Were you ever seen by Dr. Fiddes?' 'No.'"

Evidence uncovered during FDA's searches and interviews showed that SCRI:

- Made up study patients entirely. For one vaginal yeast infection study, Fiddes falsified virtually all the results, using data from old patients' charts to make it appear that more than 25 patients had participated in the study when only one patient was actually enrolled. In a birth control study, employees made up information to continue medical records of patients who had actually dropped out of the study. In that study, too, patients who remained in the study were told to stay on the birth control they were already using. In a study of a drug for sinusitis (sinus inflammation), employees' family members were enrolled in a study but



didn't participate, and their records were fabricated.

- Failed to conduct required physical examinations on some patients and falsified the results of physical exams on others. Some physical exams were skipped altogether. In one study for an osteoarthritis drug, Fiddes documented normal x-rays as abnormal, saying they showed bone spurs or other signs of disease.
- Substituted medical information of an SCRI employee for a patient's true data. For example, an employee substituted her own high-protein urine for the urine of various patients who did not have protein levels high enough to qualify for a diabetes and high blood pressure study. Also, employees used their own blood samples for three fictitious patients in a birth control study.

In these and many other instances of falsification, Fiddes' motivation was "out-and-out greed," the case agent says. "His goal was high enrollment, to get the studies done no matter what. There was never anything that showed he had any care for the well-being of the patient or the public."

Despite the seriousness of Fiddes' illegal activities, FDA does not believe that his bogus studies cast doubts as to the safety and effectiveness of any drugs SCRI studied and FDA later approved, says Jim Kozick, director of domestic investigations at FDA's Los Angeles dis-

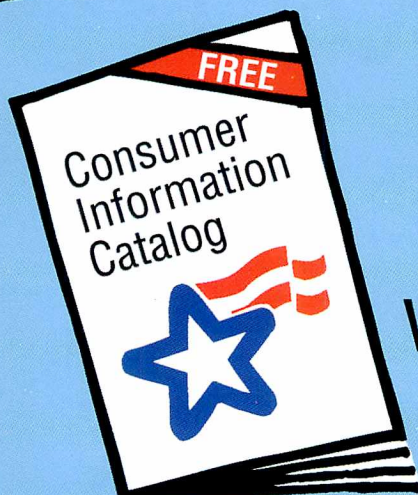
trict office. With few exceptions, FDA requires two large scientific trials, each at multiple research centers, to support approval of a drug. However, the agency is scrutinizing SCRI's studies to ensure that drugs approved based even in part on Fiddes' data will not jeopardize patients' health.

"Cases like this send a very strong message to all clinical investigators about the need to conduct valid scientific trials," Kozick says. "Any allegations of fraud in the conduct of clinical studies will be aggressively investigated."

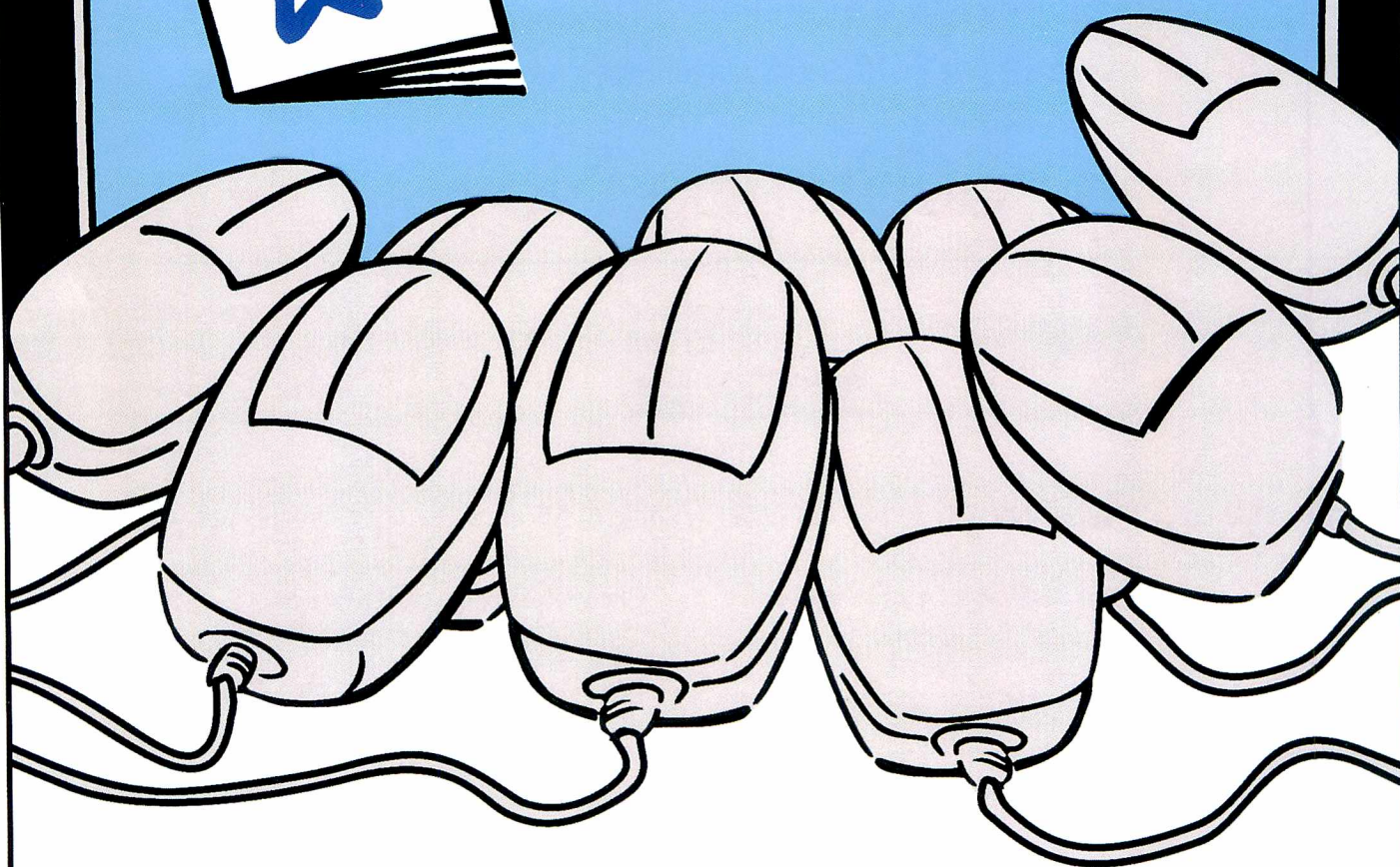
The U.S. District Court for the Central District of California sentenced Fiddes to prison in September 1998, about one year after he pleaded guilty to conspiring to make false statements to the agency. Two of SCRI's study coordinators, Delfina Hernandez and Laverne Charpentier, and its chief operating officer, Elaine Lai, were sentenced to probation after they, too, pleaded guilty to charges related to SCRI's bogus data.

Tamar Nordenberg is a writer for FDA Consumer.

Summaries of Court Actions will not appear in this issue of FDA Consumer, but will return in the July-August issue.



www.pueblo.gsa.gov



9 out of 10 mice prefer it.

If there's a mouse in your house, you can catch the free Consumer Information Catalog online. There you'll find a web site with the latest federal info from more than 40 government agencies.

Just point and click your way to www.pueblo.gsa.gov to nibble on hunks of useful information on saving money, getting federal benefits, staying healthy,

even educating your children. In fact, there are more than 250 free publications—complete for you to read or download.

Or you can order the Catalog the way you always have. Just mail your name and address to **Free Catalog, Pueblo, CO 81009**.

But for the fastest info running, mice everywhere are scurrying to the Consumer Information Catalog online.

www.pueblo.gsa.gov (It's the cat's meow.)

A public service of this publication and the Consumer Information Center of the U.S. General Services Administration