Rabies On The Rise
Now Available Without a Prescription

Consumers can now buy a variety of drugs over the counter that used to be available by prescription only. These include nicotine patches and gum to help people stop smoking, and a variety of medications for vaginal yeast infections and heartburn.

Decreasing the Chance of Birth Defects

Though many birth defects may not be preventable, there are ways expectant mothers can reduce the risk. Important steps include seeing a doctor even before becoming pregnant, and knowing the relevance of nutrition, medications, and alcohol consumption.

Controlling Asthma

Asthma can be a mild condition or a deadly disease, with much depending on the care a person with asthma gets. Though there is no known cure, most asthma can be controlled and new information is changing the way health experts view the role of drugs.

Rabies on the Rise

Rabies is on the rise again in America, after years of decline. Vaccines are the only line of defense for humans exposed to the disease. The biggest challenge in this country is controlling the disease in wild animals.

Inside FDA: Agency Changes Include Medical Device Review

Quicker availability of medical devices is one of the aims of a pilot program in which private organizations may be allowed to participate in evaluating the products.

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Every expectant parent hopes for a perfect baby. To find out what can be done to decrease the chance of birth defects, see page 12.
First Drug to Protect Against Poison Ivy

The first drug to protect against poison ivy, oak or sumac covers the skin with a clay-like coating as it dries. Available without a prescription, Ivy Block (bentoquatam 5 percent), a lotion approved by FDA last Aug. 26, protects against or reduces the severity of the rash caused by poison ivy, oak or sumac if applied to the skin at least 15 minutes before exposure. After it dries, the clay-like coating indicates where the skin is protected.

The drug may be especially useful to park rangers, emergency workers, hikers, and others who find it difficult to avoid poison ivy. As long as the possibility of exposure to the poisonous plants exists, Ivy Block should be reapplied every four hours for continued protection. It can be washed off with soap and water.

Ivy Block should not be used by anyone who already has a rash from these plants. It is not recommended for children under 6.

Enviroderm of Louisville, Ky., manufactures Ivy Block.

(See also “Outsmarting Poison Ivy and Its Cousins” in the September 1996 FDA Consumer.)

Women’s Incontinence Product

A new device to prevent urine leakage is available for the millions of American women with stress urinary incontinence—a condition in which urine leaks from physical stress like coughing, laughing, or lifting heavy objects.

The Reliance Urinary Control Insert Device was approved by FDA Aug. 16, after an expedited review based on its potential usefulness.

Trained in the use of the device by her doctor, a woman places the insert in her urethra (tube that carries urine from the bladder) with the aid of a reusable syringe. Because the length of the urethra varies, doctors prescribing the device fit their patients for the insert using the Reliance Sizing Device, also approved in August.

After insertion, a balloon at the tip inflates in the bladder to block urine leakage. To urinate, the woman pulls an attached string to deflate the balloon and removes and discards the insert, replacing it with a new one after urination.

Women shouldn’t wear the insert for more than six hours and shouldn’t use it during sexual intercourse. The device’s safety and effectiveness in pregnant women has not been studied, and FDA does not recommend its use during pregnancy.

In approving the insert, FDA followed a July 25 recommendation of the Gastroenterology and Urology Devices Advisory Panel.

In a study of 215 women with incontinence, an evaluation of data from 50 women who used the device for one year showed it reduced urine leakage in those women.

Based on study results, about 44 percent of users will likely develop urinary tract infections within the first year of use. About 78 percent will likely have urethral discomfort and irritation—a problem that caused many women to drop out of the study. Other side effects were bleeding (20 percent) and undesirable movement of the device into or out of the bladder (6 percent).

FDA is requiring the product’s manufacturer, UroMed Corp. of Needham, Mass., to conduct a postmarketing study to determine the long-term rate of urinary tract infections and the effect of long-term use on urethral tissue.

Drug for Testing HIV Wasting Gets Early Approval

An injectable drug to treat wasting in people with HIV infection received accelerated approval by FDA after studies showed it provided meaningful therapeutic benefit.

Serostim (somatotropin), a human growth hormone, was approved last Aug. 23 for HIV wasting syndrome, a condition characterized by severe weight loss, leading to muscle weakness and organ failure and contributing to death. In one clinical study, patients receiving the
drug increased lean body mass by an average of 1.6 kilograms (3.5 pounds), compared with no increase for patients receiving a placebo.

As part of the approval, the drug’s manufacturer agreed to conduct additional studies both to confirm the finding of increased lean body mass and to evaluate whether Serostim helps improve the patients’ physical performance.

Under the accelerated drug approval process, FDA grants early approval of drugs found to provide meaningful benefit over existing therapies for serious or life-threatening diseases.

FDA granted Serostim treatment investigational new drug status in December 1994, allowing AIDS patients access to the drug before approval. Since then, more than 300 patients have been treated with it. The most common side effects are tissue swelling and muscle and joint pain.

Serostim is distributed by Serono Laboratories Inc. of Randolph, Mass. (See also “Warding Off HIV Wasting Syndrome” in the April 1995 FDA Consumer.)

**HIV-Related Use for Antibiotic**

Previously approved to treat other bacterial infections, the antibiotic Zithromax (azithromycin) has been approved by FDA to prevent or delay infection with mycobacterium avium complex, or MAC, which can be fatal in AIDS patients.

MAC causes chronic, weakening symptoms such as fever, weight loss, fatigue, and gastrointestinal problems.

To prevent or delay MAC symptoms, the new use approved last June, Zithromax is given in one weekly dose of 1,200 milligrams. Alternatively, the single weekly dose may be given in combination with daily doses of Mycobutin (rifabutin), the first drug approved to prevent MAC in patients with advanced HIV infection. (See “Mycobutin Approved to Prevent MAC,” in the Updates section of the April 1993 FDA Consumer.) Biaxin (clarithromycin) also is approved to treat MAC.

Zithromax is not for use in patients highly sensitive to other macrolide antibiotics, such as erythromycin and clarithromycin.

In clinical trials, Zithromax caused mild to moderately severe side effects, mainly nausea, vomiting, diarrhea, and abdominal pain. Rare but potentially serious side effects were localized swelling and jaundice. Studied both alone and in combination with other AIDS treatments, the drug showed very little interaction with the other therapies. It was not studied with the newest class of AIDS drugs, protease inhibitors. (See “Free Backgrounder on Protease Inhibitors” in the Updates section of the October 1996 FDA Consumer.)

**FDA Warning Concerning Certain Italian Cheese**

Consumers are warned not to eat certain brands of imported Italian mascarpone cream cheese because the cheese may be contaminated with the bacterium that causes botulism, a very serious, sometimes fatal, illness.

Giglio, Parmalet, or Sol di Valle mascarpone cream cheese should not be used for any reason, even if it does not look or smell spoiled. The products come in 500-gram (about 17.5-ounce) containers.

FDA warned the public about the cheese Sept. 9, after being notified by the Italian Ministry of Health that these brands of mascarpone have been linked to one death and at least three other cases of botulism in that country. These products, all made by the Giglio factory in Reggio Emilia, Italy, were recalled in Italy.

According to Italian authorities, some of the cheese may have been exported to the United States. At press time in October, FDA was working with the Giglio company and importers to track the volume and location of any suspect product that may have entered this country.

Botulism is caused by the bacterium *Clostridium botulinum*. Symptoms of this illness are general weakness, dizzi-
ness, double vision, speaking and swallowing difficulties, breathing problems, muscle weakness, abdominal distention, and constipation. Consumers with these symptoms should seek immediate medical attention.

Redux Relabeling Notes Higher Risk

At FDA's request, the manufacturer and distributor of Redux (dexfenfluramine) have updated the weight-loss drug's labeling to inform doctors and patients about the increased risk of a rare, but serious and life-threatening, lung disorder—primary pulmonary hypertension, or PPH.

FDA made the request last August after evaluating the final report on the International Primary Pulmonary Hypertension Study. Preliminary evaluation of the study, before approval of Redux, found the PPH risk in users of appetite-suppressant drugs for three months or longer to be about nine times higher than in nonusers. The final report estimates the risk to be about 23 times higher.

Previous labeling reported PPH occurrence to be about 18 cases per million for adults using Redux three months or longer, compared to about 1 or 2 per million adults in the general population. Occurrence is now estimated at 23 to 46 cases per million patients per year.

Although the risk of PPH in patients taking appetite-suppressant drugs remains small, this is a serious disorder with a four-year death rate of 45 percent.

Redux treatment should be stopped if the patient develops unexplained symptoms, including breathing difficulty, chest pain, faintness, or swelling in the lower legs or ankles. Those taking Redux should call a doctor if they have any PPH symptoms or problems exercising. Any appetite-suppressant drug should be taken only under careful medical supervision.

Questions have been raised about studies showing long-term changes in the brains of animals. The relevance of these findings to humans is unknown.

The manufacturer of Redux, Interneuron Pharmaceuticals Inc. of Lexington, Mass., and the distributor, Wyeth-Ayerst of Philadelphia, sent letters to more than 300,000 health-care providers advising that the new findings reinforce the conclusion that Redux should not be used for "cosmetic" weight loss—that is, when the person's height-to-weight ratio does not provide a medical reason for weight loss. (See "New Weight-Loss Drug" in the Updates section of the July-August 1996 FDA Consumer.)

Wyeth-Ayerst has agreed to report cases of PPH to FDA within 15 days.

Health-care professionals should report adverse events to Wyeth-Ayerst by calling (1-800) 934-5556, or to the FDA MEDWATCH Program by calling (1-800) FDA-1088, or by mailing the report to MEDWATCH, HF-2, FDA, Rockville, MD 20857.

(For more about weight loss, see "Losing Weight Safely" in the January-February 1996 FDA Consumer.)

Adrenal Cortex Extract Alert

Consumers or doctors who have adrenal cortex extract products bearing "Hallmark Labs" on the label should immediately stop using the product and contact FDA at (714) 667-7416.

Patients who have swelling, tenderness, other signs of infection at the site of injection, or other adverse reactions should contact their doctors immediately.

FDA announced a nationwide alert last Aug. 30 about the unapproved adrenal cortex extract, in 30-milliter vials, due to the product's potential for causing serious and life-threatening injuries. It is distributed by Phyne Pharmaceuticals of Scottsdale, Ariz.

FDA, the national Centers for Disease Control and Prevention, and numerous state agencies have received reports since April 1996 of abscesses—serious bacterial infections—forming at sites where patients had been injected with the product. By early September, there were at least 54 reports.

Adrenal cortex extract is not approved by FDA for any use. It is usually derived...
from the adrenal glands of cattle, sheep or swine. Although it has never been shown to be effective for treating any medical condition, it has been promoted over the years for a wide variety of uses, including weight loss, burn treatment, and combating substance abuse addictions.

Other possible problems with the Hallmark Labs adrenal cortex extract include preparation under conditions that could lead to its contamination and labeled indications for use that might expose patients with low immunity to particular risk.

FDA has worked with other government agencies to investigate how this potentially contaminated product was manufactured and distributed. The agency has taken regulatory steps to identify the responsible parties and to ensure prompt removal of the products from the market.

**Lung Cancer Imaging Agent**

A kit using a new diagnostic imaging agent that can determine the extent of disease in patients diagnosed with small cell lung cancer (SCLC) has been licensed by FDA.

The agent, Nofetumomab, is a fragment of a monoclonal antibody that, when “tagged” with the radioisotope technetium, can detect a protein found on the surface of most SCLCs. By detecting tumors in different parts of the body at one time, the product can help doctors advise certain patients with extensive disease about treatment options without requiring further diagnostic tests.

FDA licensed the new agent last Aug. 20 for patients diagnosed with SCLC through a confirmed biopsy but not yet treated. Nofetumomab should be used only once. The product should not be used to rule out suspected lung cancer or its spread in patients without confirmed SCLC. It also should not be used to evaluate subsequent treatment.

In a clinical trial of 89 patients with confirmed SCLC, Nofetumomab accurately determined 82 percent of the time whether the disease was extensive or limited. If the agent indicated extensive disease, the result was true in 94 percent of patients. But if the agent indicated limited disease, it was less valuable as a diagnostic aid, failing to image some tumors in about 23 percent of patients. Because of this potential for false negatives, additional standard diagnostic tests should be performed when Nofetumomab indicates limited disease.

Each year in the United States, about 30,000 new cases of SCLC are diagnosed. For those with extensive disease, the median survival is 33 weeks, and only 1 to 3 percent of these patients survive more than three years. In contrast, up to 20 percent of patients with limited disease may survive more than three years.

The Nofetumomab kit will be distributed under the trade name Verluma by the DuPont Merck Pharmaceutical Co., Billerica, Mass.

**Free Food Pubs**

A new low-literacy brochure on choosing heart-healthy foods and an updated version of an *FDA Consumer* reprint on genetically engineered foods are available free from FDA.

Their titles and publication numbers are:
- Eating for a Healthy Heart (FDA) 96-2302
- Genetic Engineering: Fast Forwarding to Future Foods (FDA) 96-2295

To order single copies, write to FDA, HFE-88, Rockville, MD 20857. To order 2 to 100 copies, write to FDA, HFI-40, at the same address, or fax your order to (301) 443-9057. Include the publication numbers.

*FDA Consumer* welcomes comments from readers. Send letters to: Editor, *FDA Consumer*, HFI-40, 5600 Fishers Lane, Rockville, MD 20857.
Now Available

Without

A Prescription

by Tamar Nordenberg

For those who yearn to break their cigarette addiction but don’t fancy a trip to the doctor’s office, the ability to get the nicotine patch without a physician’s prescription may be just what the doctor ordered.

Until less than a year ago, the nicotine patch was available by prescription (Rx) only. In July 1996, the Food and Drug Administration approved the “switch” of the Nicotrol patch to over-the-counter (OTC) status, following on the heels of a February 1996 switch of another stop-smoking aid containing nicotine, Nicorette gum. Then, on Aug. 2, FDA approved the switch of a second nicotine patch, Nicoderm CQ.

The patch and gum join more than 600 other OTC drugs that, according to the Nonprescription Drug Manufacturers Association, would have required a prescription only 20 years ago. The 600-plus products are now available without a prescription because FDA, in cooperation with panels of outside experts, determined they could be used safely and effectively without a doctor’s supervision.

In the last year and a half alone, FDA has given OTC approval to drugs with such household names as Children’s Advil and Children’s Motrin (ibuprofen), Orudis KT (ketoprofen) and Actron (naproxen sodium), for pain relief and fever reduction; Femstat 3 (butoconazole nitrate) for vaginal yeast infection; Pepcid AC (famotidine), Tagamet HB (cimetidine), Zantac 75 (ranitidine hydrochloride), and Axid AR (nizatidine), for heartburn; and Rogaine (minoxidil) for hair growth.

Over-the-counter switches provide increased access to effective drugs. Eighty-five percent of Americans feel it is important to have OTC medications available to relieve minor medical problems, according to a 1992 Heller Research Group study of “Self Medication in the ’90s: Practices and Perceptions.”

“There is an important trend toward consumer participation in their own health care,” says Debra Bowen, M.D., director of FDA’s division of over-the-counter drug products. “It’s part of our mission to keep up with the consumers’ wish to be more involved.”

Switches have a huge impact on the health-care economy. The greater availability of medicines over the counter saves approximately $20 billion each year, according to the 1995 Physicians’ Desk Reference for Nonprescription Drugs, a book of drug information published annually by Medical Economics.
More than 600 products are now available without a prescription because FDA, in cooperation with panels of outside experts, determined they could be used safely and effectively without a doctor's supervision.

in cooperation with drug manufacturers. The $20 billion takes into account prescription costs, doctor visits, lost time from work, insurance costs, and travel.

The Switch Process

The original Federal Food, Drug, and Cosmetic Act of 1938 made no clear-cut distinction between Rx and OTC drugs. The 1951 Durham-Humphrey amendments to the act set up specific standards for classification.

The amendment requires that drugs that cannot be used safely without professional supervision be dispensed only by prescription. Such drugs may be deemed unsafe for nonprescription use because they are habit-forming or toxic, have too great a potential for harmful effects, or are for medical conditions that can’t be readily self-diagnosed.

All other drugs can be sold OTC. A drug must be made available without a prescription if, by following the labeling, consumers can use it safely and effectively without professional guidance.

Some drugs are approved initially as OTC drugs. More often, though, medications are first approved Rx and later switched. "While a product is available by prescription, we can learn about the drug's safety profile in a much more

On the right is the prescription-strength Axid and on the left the OTC product. Axid and three other heartburn medications—Pepcid, Tagamet and Zantac—were recently switched to OTC status. To enable consumers to treat their own heartburn safely, FDA approved the over-the-counter drugs with easy-to-understand labeling and at a lower dosage than the prescription versions.

PHOTOS BY NORMAN WATKINS
Medicines that can be used safely and effectively on the basis of product labeling alone must, by law, be made available to Americans without a doctor’s prescription. This chart illustrates the cumulative number of drugs switched from prescription-only to OTC availability by FDA on a yearly basis. The number of switches for 1996 is the total as of Sept. 15, 1996.

(Source: Nonprescription Drug Manufacturers Association)

controlled environment,” Bowen says.

Drugs are commonly switched one of two ways: under the “OTC drug review,” or by a manufacturer’s submission of additional information to the original drug application.

The OTC drug review is an ongoing assessment by panels of nongovernment experts of the effectiveness of all drugs approved before 1962, before proof of efficacy was a requirement. The panels also review prescription ingredients to determine if some are appropriate for OTC marketing. About 40 former prescription-only drug ingredients have been switched by this process.

The second common path to OTC approval is submission of data to FDA (almost always by a manufacturer) showing the drug is appropriate for self-administration. Often the submission includes studies showing that the product’s labeling can be read, understood and followed by the consumer without the guidance of a health-care provider. FDA reviews the new data, along with any information known about the drug from its prescription use.

In almost every case, the agency has sought the recommendation of a joint advisory committee made up of members of the agency’s Nonprescription Drugs Advisory Committee and another advisory committee with expertise in the type of drug being considered. For example, because Rogaine is for conditions of the hair and scalp, representatives of the Dermatologic and Ophthalmic Drugs Advisory Committee participated.

While not bound by the advisory committee’s counsel, FDA almost always follows its recommendation.

**Benefit-Risk Comparison**

When considering an Rx-to-OTC switch, the key question for FDA is whether patients alone can achieve the desired medical result without endangering their safety.

No drug is absolutely safe. There are risks associated with every medication,
An FDA advisory committee voted “yes” on Nov. 17, 1995, to a prescription-to-OTC switch for Rogaine for treatment of common hereditary hair loss.

This wasn’t the first time an FDA advisory committee had considered the switch. A July 1994 meeting ended in a 10-to-4 vote against OTC availability. Ten of fourteen advisory committee members weren’t convinced that the benefit of Rogaine outweighed the drug’s risks. Mainly, the committee was concerned that consumers would misdiagnose their hair-loss problem, and in some cases dangerously delay needed treatment.

To address this issue, Rogaine’s manufacturer, Pharmacia & Upjohn, conducted six studies to see whether consumers could understand the labeling and determine if they had the common hereditary hair loss for which the product is intended. The studies showed, to the second committee’s satisfaction, that consumers could self-diagnose their condition and comprehend the directions and other labeling information.

Upjohn also previewed the marketing campaign for the committee. The television ads, the company said, would be designed to educate consumers about whether the product is right for them. A toll-free number for consumers and an educational brochure at the place of purchase would be available, too.

The brochure graphically depicts the hair loss at the top of the head for which the drug is most effective. It states, in bold lettering, “If you have no family history of gradual thinning hair or hair loss, or if you are unsure of the cause of your hair loss, talk to your doctor.”

The second time, members voted 12-to-4 in favor of the switch. Following the committee’s recommendation, FDA approved OTC Rogaine on Feb. 9, 1996.

The product, which has been marketed since 1988 and used by over 3 million people, is now available over the counter.

—T.N.
Nicotrol was the first nicotine patch for smoking cessation approved by FDA.

It received an advisory committee’s unanimous recommendation for a prescription-to-OTC switch on April 19, 1996. Worn for 16 hours a day, the patch reduces nicotine cravings by providing a constant, controlled flow of nicotine into the bloodstream.

The committee concluded that the benefits of the stop-smoking aid outweigh its risks, but only after considering manufacturer McNeil Consumer Products’ proposed labeling and marketing plans, and the company’s studies comparing quit rates for OTC and prescription patches.

The company presented data showing that prescription and OTC patch users achieved similar quit rates (19 percent of OTC users abstained in weeks 2 through 6, versus 16.6 percent of Rx users) and experienced no serious adverse reactions.

McNeil demonstrated that smokers understood the proposed labeling, including the warning not to smoke while using the patch and directions on how to apply and remove the patch. According to the company, more than 80 percent of consumers used the behavioral modification materials, including handbooks, an audiotape, and toll-free help-line.

The committee was told that abuse was not expected to be a problem, especially for adults. The patches are not to be sold to minors and will not be distributed through vending machines. Advertising will be targeted to adults.

FDA agreed that the benefits of the patch—an increased chance for people to quit smoking—outweighed any slight risks, and approved the product for OTC sale last July 3. The OTC patches became available in retail stores July 18.

—T.N.
OTC switch applications for two very different drugs—Rogaine for hair growth and the nicotine patch for smoking cessation. Each raised unique issues, yet the risk-benefit comparison led FDA to the same conclusions in the two assessments—over-the-counter status is appropriate. (See accompanying articles.)

Concerns about side effects can sometimes be managed by approving OTC drugs at lower doses than their prescription counterparts. The drugs must still be effective for the short-term symptoms for which they’re intended.

The issue of whether a condition can be self-diagnosed was a central one for the Rogaine advisory committee. Most OTC drugs are intended for treatment of symptoms that can be easily recognized, like headache or upset stomach. Others, though, are intended to treat diseases like asthma or vaginal fungal infections, which cannot be consumer-diagnosed.

Consumer-Friendly Labeling

Labeling is an influential element in the OTC risk-benefit comparison. The decision about a drug’s safety for OTC use can’t be made in a vacuum, by looking only at the drug ingredients. Every drug, used improperly, can cause adverse reactions. Even appropriate use can lead to side effects (antihistamine use may cause drowsiness, for example). And some drugs can be dangerously unsafe or ineffective if taken while using certain other drugs.

Labeling can alert consumers to such potential problems. Labeling of all drugs must be clear and truthful. For OTC drugs, the intended uses, directions and warnings have to be written so consumers, including individuals with low reading comprehension, can understand them.

FDA is working with the pharmaceutical industry to increase the readability of OTC labels by making the language more consumer-friendly and standardizing the format, including where important information is placed.

In some cases, Bowen says, consumers can get more information in the OTC labeling than they would get from their doctors. “For the nicotine patch, we developed a package—a package containing not only a drug that relieves withdrawal symptoms, but also behavioral modification information. The package provides an element of support that studies showed some people weren’t getting from their doctors, by telling them when they’ll most likely feel the urge to smoke, what they can do in place of smoking, and where they can go for support.”

A Popular Alternative

Under the law, OTC drugs may be advertised directly to consumers without the many restrictions placed on Rx products. OTC status provides a greater opportunity for direct communication with the consumer, not only by advertising in magazines and on television, but also with packaging, brochures, and retail displays.

Nicorette gum magazine ads announce, “Nicorette Gum Is Now Available Full Strength Without A Prescription. Hallelujah!” “Hallelujah” may be the victory cry for those who, with the aid of OTC nicotine gum, were able to beat the cravings. But consumers aren’t the only ones with something to gain from Rx-to-OTC switches.

Some manufacturers are exclaiming “Hallelujah” as well, over profits gained from direct access to millions of consumers. Pepcid AC for heartburn, for example, had sales topping $200 million in the first year after the product’s April 1995 switch approval, making it the most profitable switch to date.

Today’s emphasis on self-care fuels the popularity of nonprescription drugs. But OTC products are intended to supplement the medical options of the consumer, not substitute for a prescriber’s medical knowledge. If a health problem persists or worsens while using an OTC drug, consult a healthcare provider.

“People must be in a partnership with their health-care providers for optimal health,” Bowen says. “Many situations aren’t appropriate for self-treatment, and others may require professional guidance for self-treatment.”

If you do choose OTC treatment, heed Bowen’s warning: “Drugs aren’t candy; they aren’t risk-free. You have to follow the label and take appropriate responsibility for your own self-care.”

Tamar Nordenberg is a staff writer for FDA Consumer.
Decreasing The Chance Of Birth Defects

by Rebecca Williams

Tammy Troutman, born with spina bifida, sits on the porch of her Knoxville home with her son, Evan, 3. Troutman took prenatal precautions, and Evan was born with a normal spine.
When Tammy Troutman of Knoxville, Tenn., was planning her first pregnancy, she had a good reason to be concerned about birth defects.

Born with a mild form of spina bifida, Troutman worried her child would also have the condition. So she did what health-care experts say is the best first step toward preventing birth defects: She visited her physician for an exam well before she and her husband tried to conceive.

"Before I decided to have children, I went to the doctor to make sure everything would be OK," Troutman remembers.

He advised her to take a daily multivitamin supplement containing folic acid, a B vitamin that would decrease her chances of having a baby with spina bifida. Troutman took the vitamins for five months before conceiving her son, Evan, who was born in August 1993 with a normal, healthy spine.

"Even if he had been born with spina bifida," Troutman says, "I felt secure knowing that I had done everything I could to prevent it."

Of the 4 million infants born annually in the United States, about 3 to 5 percent are born with birth defects, according to the March of Dimes. Birth defects account for 20 percent of all infant deaths in the United States, more than from any other single cause.

"For the majority of birth defects, the cause is unknown," says Franz Rosa, M.D., a pediatrician with the Food and Drug Administration who monitors reports of prescription drugs causing birth defects. Rosa cites a list of drugs that are known to be birth-defect causing, but he says they only account for a small percentage of all malformations.

"There's a lot we just don't know," Rosa says. "Most birth defects are not preventable and mothers should not feel guilty about causing defects that they really didn't. Worrying too much is not good for pregnancies."

What experts do know is that most birth defects occur in the first three months of pregnancy, when the organs are forming. It is in these crucial first few weeks—often before a woman even knows she’s pregnant—that an embryo is most susceptible to teratogens, substances that can cause defects. However, some birth defects do occur later in pregnancy as well.

"The key is what your life is like at the time you become pregnant," says Deborah Smith, M.D., an obstetrician and gynecologist in FDA's Office of Women's Health. "Are you getting enough folic acid, are you immune to..."
rubella, are you avoiding alcohol and smoking? These are some of the things we know are important.”

Despite the benefits of seeing a doctor before conceiving, only 26 percent of women planning a pregnancy do so, according to the March of Dimes. Furthermore, health experts estimate more than 50 percent of pregnancies are unplanned. That’s why a healthy lifestyle for all women who could become pregnant—even if they don’t intend to—is the best way to minimize the risk of birth defects.

Healthy Diet

The maxim “You are what you eat” is sterling advice during the first three months of pregnancy.

Studies of women who had endured starvation during World War II illustrate the importance of diet early in pregnancy. Contrary to what researchers expected, it was not the babies born during food deprivation that had the most malformations, but those conceived during food deprivation.

One nutrient known to prevent birth defects is folic acid, the B vitamin Tammy Troutman took before her pregnancy. Folic acid is the chemical form of folate, which is found in green leafy vegetables, citrus fruits, and legumes. Folate aids in cell division, and taking extra folic acid reduces a woman’s chance of having a child with spina bifida and other abnormalities of the spine and brain.

Spina bifida occurs when the vertebrae do not close completely. It is one of several conditions known as neural tube defects, because the neural tube is the portion of the embryo that develops into the brain and spinal column. In very mild cases, spina bifida causes few or minor problems, but in more severe cases, the spinal cord protrudes through the vertebrae into a sac outside the child’s body. This impairs the child’s mobility and other neurological functions and requires surgery to repair the opening.

To help prevent neural tube defects, the U.S. Public Health Service has recommended that all women of childbearing age who are capable of becoming pregnant consume 0.4 milligrams (mg) of folic acid per day. (For pregnant or lactating women, the daily value increases to 0.8 mg per day.) It is especially important that women take in sufficient folate before they become pregnant.

FDA recently published regulations requiring manufacturers to add folic acid to enriched grain products such as flour, noodles, bread, rolls, buns, farina, cornmeal, grits, and rice by January 1998. (See “How Folate Can Help Prevent Birth Defects” in the September 1996 FDA Consumer.)

Although the main challenge in pregnancy is getting enough nutrients, too much of a good thing is not good for a developing baby, either. Vitamins A and D are the most notable examples. Both can be toxic at levels higher than the recommended daily allowance. Such levels are rarely reached through food intake; however, women taking dietary supplements need to be aware of this risk and the amount of these vitamins they are taking. Women who take vitamin and mineral supplements should discuss with a health-care professional what vitamins are safe to continue taking during pregnancy.

Only a few foods are completely off-limits during pregnancy. These include raw or undercooked meat, such as “pink-in-the-middle” burgers, and raw or undercooked seafood. Bacteria from these can cause severe food poisoning, which is dangerous to a fetus and very unpleasant for the mother.

Soft drinks, coffee, tea, and other caffeinated drinks can be used in moderation. Although large doses of caffeine have caused skeletal defects in rats, one or two cups of coffee daily are not considered dangerous for developing fetuses.

Alcohol should be avoided at all times during pregnancy because it leads to low birth weight and can cause deformities as well.

According to the March of Dimes, alcohol is the most common known cause of fetal damage in the country and the leading cause of preventable mental retardation. Pregnant women who drink
Accutane (isotretinoin), a relative of vitamin A, is approved to treat severe cystic acne that doesn’t respond to other drugs. It has some serious side effects, though, especially if a woman taking it becomes pregnant.

Pregnant women who take Accutane even for a short time are at great risk of having a baby with severe facial birth defects, malformed thymus glands, and mental retardation.

The risk is so great that any woman of childbearing age who is taking Accutane—even if she’s not sexually active—must also use contraception, such as the birth control pill.

The drug’s manufacturer has included strong warnings in the package labeling to inform doctors and patients about the birth defects this drug can cause.

Accutane does not appear to cause any birth defects in women who get pregnant after they have stopped taking the drug.

—R.D.W.

alcohol, especially in large amounts, put their babies at risk for fetal alcohol syndrome, which causes growth retardation, facial deformities such as a small head, thin upper lip, and small jaw bone, an underdeveloped thymus gland, and mental deficiencies or developmental delays.

If a woman has had a glass or two of wine before finding out she was pregnant, she probably has not harmed her child. But since no one knows the exact amount of alcohol that is dangerous, it’s best to avoid alcohol when pregnancy is possible.

Healthy Mothers, Healthy Babies
A pregnant woman who has a serious medical condition may face a greater than normal risk that her child will have a birth defect.

Diabetes, for example, can complicate a pregnancy in many ways. Women who must take insulin daily to control their blood sugar are three or four times more likely to have a baby with major birth defects than are other mothers. That’s not to say they should abandon insulin, however. Without it, many diabetic women and their babies wouldn’t survive pregnancy at all.

Birth defects among diabetics can be greatly reduced if women get their blood sugar levels under control before becoming pregnant and strictly manage their diets throughout pregnancy. Gestational diabetes, which develops during pregnancy, can also be harmful to mother and child, but it can be controlled through diet or medication.

Epilepsy also increases a woman’s chance of having a baby with a birth defect. It’s not clear whether the disease itself or the drugs used to control it cause malformations, but in either case, the woman’s neurologist and obstetrician should work together to find the safest course of treatment for the epilepsy and pregnancy.

Rubella, toxoplasmosis, cytomegalovirus, and syphilis can cause birth defects in the infants of women who have these infectious diseases. Rubella infection during early pregnancy can cause abnormalities of the heart, eyes and ears. Any woman planning a pregnancy should be tested for rubella immunity and vaccinated if necessary. She must wait three months after vaccination before becoming pregnant, however, because the vaccine itself can endanger a developing fetus.

Toxoplasmosis is transmitted only through raw meat and cat feces, both of which pregnant women should try to avoid. The disease causes malformations of the brain, liver and spleen if a fetus becomes infected in the first trimester.

If a woman has syphilis, she should be treated with antibiotics before pregnancy. If not treated by at least the fourth month, syphilis can cause bone and tooth deformities in the baby, as well as nervous system and brain damage.

Cytomegalovirus (CMV) is a herpes
Alcohol should be avoided at all times during pregnancy because it leads to low birth weight and can cause deformities as well.

A virus that causes no real problem—and sometimes not even symptoms—for adults and children. In pregnancy, however, it can damage the fetus’ brain, eyes or ears. Because most people contract the infection, whose symptoms are much like a cold, when they are children, most adults are immune to it. Pregnant women who do not know if they’ve had CMV and who work with large groups of young children should discuss the situation with their health-care provider.

Sometimes it is not a disease that causes birth defects, but the medication used to treat it. Unfortunately, no one knows for certain how most drugs will affect a developing fetus. Historically, most women of childbearing age have been excluded from clinical trials of new drugs, and, although that is changing, drug manufacturers are understandably reluctant to involve pregnant women in clinical trials for new drugs. Therefore, the effects of many drugs are not known until they are in wider use after market approval.

To be on the safe side, a pregnant woman shouldn’t take any drug unless it is absolutely necessary and not until she’s checked with her health-care provider. However, even physicians have little information when prescribing medication for pregnant women. What is known about most drugs in pregnancy is based either on animal studies or on reports of problems after the drug is on the market. To give guidance about pregnancy safety, FDA requires that manufacturers include in the professional labeling for each drug which one of several categories, reflecting known or unknown danger to the fetus, the drug is in. The categories also provide guidance on weighing the benefits and risks of use in pregnancy.

Two examples: Taxol (paclitaxel), used to treat ovarian and breast cancer, may in some instances be appropriate in pregnancy even though it causes birth defects in animals and is therefore believed to cause fetal harm in humans. The benefits of its use to fight life-threatening cancers may outweigh the potential harm to a fetus.

Accutane (isotretinoin) should never be used in pregnancy. It is highly effective for treating severe cystic acne, but it causes serious birth defects. There are other drugs available to treat acne, and the disease is not life-threatening to the mother (see accompanying article).

Who Should Paint the Nursery?

Chemicals—whether it’s paint in the nursery or exhaust fumes in a parking garage—have long been suspected of causing birth defects. It’s important for pregnant women to realize that most birth defects are not caused by a single factor, nor are they usually caused by faint traces of toxins. Scientists believe it takes a combination of factors to trigger a congenital malformation.

“Most birth defects have one or more genetic factors and one or more environmental factors,” explains Richard Leavitt, director of science information at the March of Dimes.

Most of the chemicals a pregnant woman encounters pose little threat compared with the harm in smoking, drinking alcohol, or eating a poor diet.

“Most environmental exposure is at a low level compared to things you put in your mouth or inhale purposefully into your lungs,” Leavitt says. “Public health warnings are aimed at the many to help the relatively few avoid a problem.”

Daily, heavy exposure to chemicals may be dangerous, however. If a pregnant woman must work around fumes or chemicals, such as in a dry-cleaning business, art studio, or factory, she should use gloves, masks and adequate ventilation. But if she just gets a whiff of dry-cleaning fluid while picking up her laundry from the cleaners, there’s little need to worry, Leavitt says.

Some environmental toxins such as lead are best avoided at any time, but especially during pregnancy. Scraping leaded paint off an old house window, drinking water from a pipe soldered with lead, or drinking out of decorative pot-
tery containing lead can all potentially cause lead poisoning—and mental retardation—in a fetus.

Radiation is also dangerous to developing babies. A pregnant woman who works in an x-ray department of a hospital must take precautions to avoid exposure. Elective dental x-rays should be postponed until delivery, and any non-pregnant woman who has an x-ray should have her reproductive organs shielded with a lead apron.

Taking hot baths, using saunas, or exercising in hot, humid weather can raise a woman’s core temperature and have the potential to cause birth defects, especially in the first trimester. Lukewarm baths and moderate exercise are fine, however.

And what about computers or video display terminals? Although they have at times been accused of causing harm, there’s probably no need to worry. Recent studies have not found any relationship between computer terminals and miscarriages.

And as for who should paint the nursery—today’s paints don’t contain lead and therefore probably aren’t dangerous. But there are other reasons to find someone else to do this task. The repetitive motion of painting can be a strain on back muscles already under pressure from the extra weight of pregnancy, and standing on your feet for hours can make advanced pregnancy miserable. If someone else can do it, pass this chore along.

Of all the environmental harms, undoubtedly the most harmful is one women can control—smoking. Although there is no evidence smoking causes birth defects, it deprives the fetus of oxygen and leads to a number of problems. If all pregnant women avoided smoking, the United States would see a 5 percent reduction in miscarriages, a 20 percent reduction in low-birth-weight births, and an 8 percent reduction in premature deliveries in this country, according to the March of Dimes.

In the Family

Finally, a number of birth defects are inherited. They are usually triggered when the child inherits a matching pair of disease-causing genes, one from each parent. This is most often an issue for couples of similar ethnic or geographic origins.

For example, African-American couples are most at risk for having a child with sickle cell anemia. According to the March of Dimes, couples of Ashkenazic Jewish or French Canadian descent may be carriers of Tay-Sachs disease. People who know of genetic disorders in their families, or those who have already had one child with a disorder are also at a greater risk, as are couples who are closely related, such as first cousins. Genetic testing is available to determine the risk of passing some genetic disorders to an unborn child. Once a pregnancy begins, prenatal testing is available to detect a number of disorders, as well.

Some genetic abnormalities, such as Down syndrome (a genetic abnormality that causes mental retardation, short stature, and flattened features), increase with the parents’ ages. Women over 35 are at higher risk of having a child with Down syndrome—about 1 in 100 for a 40-year-old, compared to 1 in 10,000 for a 20-year-old mother or 3 in 1,000 for a 35-year-old mother. And it’s not always just the mother’s age that matters. An estimated 25 percent of Down syndrome cases can be attributed to increased age of the father.

Finally, it’s important to remember that for most healthy women, the incidence of birth defects is very low—less than 3 percent. And of malformations that do occur, the most common are also the most treatable. Cleft palate and club foot, two of the more common birth defects, can be surgically repaired. Many heart malformations can be repaired with surgery so that children live normal lives.

For the most part, health experts say, a woman can do a lot to ensure the health of her child by maintaining a healthy lifestyle.

Rebecca D. Williams is a writer in Oak Ridge, Tenn.
CONTROLLING ASTHMA

by Ken Flieger

Think of someone—a child or an adult—racked by uncontrolled coughing. With a heaving, distended chest, neck muscles straining, and eyes showing alarm verging on panic, the person can utter only a few brief words between rasping, wheezing, frantic efforts to breathe.

The person puts a tubelike device in his or her mouth and inhales twice. Within minutes, remarkably it seems, the crisis is over. Breathing returns to normal. The per-
For reasons that are not well understood, the number of newly diagnosed cases of asthma in the United States is rising sharply.

Asthma attacks are often milder than this description—just a shortness of breath that soon passes without treatment. But they can also be much, much worse, requiring a hurried trip to the hospital for emergency—sometimes lifesaving—care. Even in severe cases, hospital treatment usually enables asthma patients to regain near-normal breathing. But not always. Almost 5,000 asthma deaths were reported in the United States in 1992, according to the American Lung Association (1992 is the most recent year for which statistics are available). Most of the deaths occurred in patients who misjudged the severity of symptoms or failed to reach a hospital or clinic in time to prevent respiratory failure.

Although African-Americans make up approximately 12 percent of the U.S. population, they account for 21 percent of deaths due to asthma, according to the American Lung Association.

For reasons that are not well understood, the number of newly diagnosed cases of asthma in the United States is rising sharply, up 56.7 percent between 1982 and 1992. Asthma deaths, too, are climbing—4,964 in 1992 compared with 2,598 in 1979. Lack of necessary health care, especially among the urban poor, is thought to play an important role in the rising asthma death rate.

Ironically, these increases are taking place at a time when some things believed to be associated with asthma—such as air pollution, dust, molds, and tobacco smoke—are better understood and often under better control than they once were. The reason for the increases remains a mystery, but some investigators think one contributing factor is modern, tightly sealed homes and workplaces that trap and recirculate contaminants, increasing exposure to them in the air we breathe.

Inflamed Airways

Most of America’s 12 million to 14 million people with asthma, of whom more than 4 million are under age 18, have a relatively mild illness. About a quarter of asthmatic children seem to “outgrow” their disease in their teen years or as young adults. It’s not certain, however, that they are completely free of asthma. Studies of people with late-onset asthma—asthma that first shows up in the fifth or sixth decade of life or even later—have found that many of them experienced asthma-like breathing difficulties as children.

There is no known cure, but most asthma can be controlled by a strategy aimed at preventing acute episodes and halting those that do occur.

This two-pronged attack is increasingly effective because scientists are piecing together a more comprehensive picture of the nature of asthma and gaining new insights into the cause, prevention and management of acute asthma attacks. New information is changing the way practicing physicians and the Food and Drug Administration view the role of drugs in asthma treatment and prevention.

Changing Theories

Until the 1970s and early 1980s, asthma was understood to result from over-responsiveness of the tubes (bronchi and bronchioles) that carry air to and from the lungs. People with hypersensitive airways, when exposed to certain irritants called “triggers”—such as household dust, tobacco smoke, cat fur (dander), cockroach droppings, air pollutants, even vigorous exercise or cold air—would experience “bronchospasm,” a narrowing of the airways caused by contraction of the muscles that encircle the bronchial tubes.

Asthmatics also tend to produce thick, sticky mucus and have inflamed, damaged airways, both of which worsen the breathing restriction caused by bronchospasm. During an acute attack, asthmatics seem to have a hard time getting their breath. Actually they are struggling to push air out of over-inflated lungs through constricted airways.

That understanding of asthma led to treatments aimed primarily at opening up the bronchial tubes by using drugs that cause the bronchial muscles to relax their grip on air passages. Bronchodilators are still a mainstay of asthma therapy. But Robert Meyer, M.D., of FDA’s Center for Drug Evaluation and Research, notes that scientists’ understanding of asthma has changed significantly over the last decade or so.

He points out that since the early 1980s, increasing scientific evidence shows that inflammation is as much responsible for bronchospasm as anything else. Today, Meyer says, “putting primary emphasis on controlling bronchospasm rather than chronic airway inflammation “looks like putting the cart before the horse.”

The evidence Meyer refers to strongly indicates that asthma is a chronic inflammatory disease that usually develops within the first few years of life. Much of this evidence is discussed by H.W. Kelly of the University of New Mexico College of Pharmacy in the October 1992 issue of the Journal of Clinical Pharmacology and Therapeutics.

In people with asthma, whether mild or severe—even in asthmatics whose first acute attack occurs long after childhood—the air passages are continuously inflamed, causing them to be swollen and to react strongly to inhaled irritants. But because patients may not be aware of any symptoms, this inflammation is sometimes
Changes in Lung Airways

Before an asthma episode

After an asthma episode
People with asthma react to external irritants in a way that non-asthmatics don’t.

Asthma didn’t keep Tom Dolan of Arlington, Va., from winning the 1996 Olympic gold medal in the men’s 400-meter individual swimming medley. called “the quiet part” of asthma.

People with chronically inflamed airways may show no outward signs of asthma until the first acute attack requires urgent medical attention, often at a hospital emergency department. Emergency care physicians and nurses—who are all too familiar with acute asthma—are able to administer powerful drugs to open the patient’s air passages and restore virtually normal breathing. They are likely to recommend the patient be seen by an asthma specialist, who can devise a combination of treatment and prevention measures aimed at avoiding or minimizing further acute asthma attacks. The first step in that process is an accurate diagnosis.

Diagnosing Asthma

The diagnosis of asthma is based on repeated, careful measurements of how efficiently the patient can force air out of the lungs and on a thorough medical history and laboratory tests to find out what “triggers” the patient’s acute attacks.

People with asthma react to external irritants in a way that non-asthmatics don’t. Many but not all asthmatics have allergies that cause their bodies to produce an abnormal array of chemicals in response to environmental allergens. In that sense, asthma is akin to pollen allergies, hives, and eczema. But in asthma, the allergic reaction contributes to inflammation of the airways rather than of skin, eyes, or nose and throat. An acute asthma attack may come on rapidly after exposure to an irritant or develop slowly over several days or weeks, which can complicate the job of identifying a patient’s asthma “triggers.”

Which drugs asthma patients need, when to use them, and how much to use depend largely on the character of their illness, as shown by the degree of breathing impairment, and the frequency and severity of acute attacks. Asthma experts agree, however, that the first line
of defense is avoidance of whatever brings on an acute asthma episode. Though for most patients “triggers”—there are often more than one—are likely to be common allergens or air pollutants. In some asthmatics, attacks can be brought on by strenuous exercise, exposure to cold outdoor air, industrial or household chemicals (cleaning fluids, for example), and food additives such as sulfites. In other cases, the triggers cannot be identified, even after a thorough investigation.

Asthma Drugs

Knowing what provokes an asthma attack is critically important in prevention, but it’s often difficult or impractical to avoid contact with triggering irritants. Today, however, physicians can prescribe drugs to lessen the risk of acute attacks after exposure to an offending irritant, as well as halt attacks that can’t be prevented.

The drugs used to treat asthma fall into two broad categories: controllers to prevent acute attacks and relievers that check acute symptoms when they occur. Some drugs do both.

In light of mounting evidence that asthma is fundamentally an inflammatory disease, asthma authorities today regard inhaled corticosteroids—marketed under numerous brand names, including Aerobid, Azmacort, Beclovent, and Vanceril—as the most effective agents for controlling airway inflammation and thus preventing acute asthma attacks. Corticosteroids in pill or tablet form (such as Medrol) and in liquid form for children (such as Pediapred and Prelone) are prescribed for some patients with severe asthma.

Other inhaled anti-inflammatory controller drugs include Intal (cromolyn sodium), which is useful in preventing asthma brought on by exercise, and Tilade (nedocromil sodium). Long-acting inhaled bronchodilators, such as Serevent (salmeterol), and long-acting oral bronchodilators, such as Alupent (metaproterenol), Proventil (albuterol sulfate), Theo-24 (theophylline anhydrous), and many others, are often used in conjunction with anti-inflammatory agents to control symptoms. They don’t provide immediate relief of symptoms, but their preventive action persists for many hours, which makes them useful in controlling attacks that might occur during hours of sleep.

Drugs to bring quick relief in acute asthma attacks are chiefly short-acting inhaled bronchodilators that act rapidly but for a relatively brief time to relax bronchial constriction. There are many short-acting bronchodilators to choose from, including Alupent or Metaprel (metaproterenol), Brethaire (terbutaline), and Ventolin or Proventil (albuterol). Although these drugs are effective in treating asthma, there is some controversy about their safety, especially when they are overused. Scientific debate makes it clear, however, that an increasing need for inhaled bronchodilators, or a decreasing response to each dose, is a signal that the patient’s asthma is not being adequately controlled. Patients who have an increasing need for short-acting inhaled bronchodilators should be reevaluated promptly by their physicians.

Nonprescription Products

Both prescription and over-the-counter (OTC) short-acting bronchodilators are available. The OTC drugs generally contain lesser amounts of the active agent than prescription forms and are effective for a shorter period. They may be useful, however, as temporary treatment for mild asthma attacks. Ready availability in drugstores makes the OTC products potentially helpful as a “stopgap” for patients who do not have their prescription medication at hand when an asthma attack occurs.

In July 1995, FDA removed from the market OTC bronchodilators such as Primatene tablets that contain theophylline. The agency determined that the amount of such products needed to improve breathing could be toxic or life-threatening for some people. In addition, the agency’s review of numerous studies found no evidence that the theophylline in these OTC drug products contributed to the treatment benefits claimed for them.

The key to effective, long-term treatment of asthma is finding the drugs and dosage plan most effective in dealing with or preventing acute episodes. But effective treatment depends as well on the patient and the care-giver knowing what the various anti-asthma drugs do, when and in what amount each drug should be used, when a change in symptoms or the response to a particular drug requires a call or visit to the physician, and when to get emergency help.

Physicians who specialize in treating asthmatics go over these points in detail with each individual patient. Physicians who specialize in treating asthmatics go over these points in detail as part of an overall treatment plan designed and, as necessary, adjusted to meet needs of each individual patient.

A cure for asthma is judged by experts to be still a far-off possibility. But the majority of asthma sufferers can lead essentially normal, symptom-free lives by understanding and sticking to a well-planned strategy to keep clear of asthma triggers and to use the right drugs in the right way.

It isn’t easy, but it works.

Ken Flieger is a writer in Washington, D.C.
The sharp rise in animal rabies, particularly among raccoons, led to a 1995 conditional license approval for an oral rabies vaccine for raccoons.

After years of decline in America, a form of viral encephalitis transmitted through infected animal saliva is on the rise.

The life-threatening disease is rabies. According to John Krebs, a public health scientist with the Centers for Disease Control and Prevention, rabies cases in animals increased dramatically between 1990 and 1993. In 1990 there were 4,880 reported animal deaths from rabies; that figure jumped to 9,495 three years later.

With treatment, human deaths from rabies are rare in the United States. One death in 1990, three deaths in 1991, one death in 1992, and three deaths in 1993 were recorded, with six people dying in 1994 and four in 1995 from the disease.

Charles Rupprecht, V.M.D., Ph.D., chief of CDC’s rabies section, says education is the key to preventing the disease. Rupprecht says only one inadequately treated person is known to have recovered completely from rabies and escaped death.

“In 1970 Matthew Winkler was exposed [to rabies], treated [with postexposure vaccine], and because vaccines were not as good then, experienced a vaccine failure. He recovered despite the vaccine failure, which is a far different thing than catching the disease, [not being treated,] and recovering,” he points out. “Some people question to this day whether that case meets all the criteria [of a human known to survive rabies without treatment].”

Over the years, scientists have improved both the effectiveness and safety of human rabies vaccines, regulated by the Food and Drug Administration as biologics. Today’s vaccines are highly effective and produce few side effects. They work by causing the immune system to produce antibodies that neutralize the rabies virus before it causes the disease. Unlike most vaccines, which are given before disease exposure occurs, rabies vaccine is usually administered after someone has been exposed to the disease. A preexposure vaccine series designed for people considered high-risk for exposure to rabies—such as veterinarians, researchers, forest rangers, animal control officers, cave explorers,
Today’s rabies vaccines are highly effective and produce few side effects. 

animal handlers, or those who spend time in countries where rabies is prevalent—is also available.

But whether pre- or postexposure, rabies vaccines and rabies immune globulin are the first—and only—line of defense for humans exposed to rabies. There are no tests that can detect rabies in humans at the time of a bite, and by the time symptoms appear, it’s too late for treatment. The disease is a swift, deadly killer, and there’s no cure.

Vaccines

Three human rabies vaccines are currently licensed by FDA for U.S. use:

• Human diploid cell vaccine (HDCV), or Imovax, is the most widely used vaccine. It is produced in cultures of normal human diploid cells by Pasteur Merieux, a French company. Pasteur Merieux’s pre- and postexposure intramuscular HDCV vaccines were approved in 1980, while an intradermal preexposure HDCV vaccine was approved for use in 1988.

• A vaccine made by a Michigan state agency, Michigan Biologic Products Institute, uses fetal rhesus monkey cell cultures. It was approved for use in 1988 and is distributed outside of Michigan by Smith Kline Beecham.

• Inactivated diploid cell origin (DCO), a dried vaccine made by Connaught Laboratories in Toronto, Canada, was approved for use in 1991.

“Virtually all vaccines are made from living systems, whether you are talking about the oral polio vaccine or DTP shots that your kids get or rabies [vaccines],” explains Edward A. Fitzgerald, Ph.D., director of the division of product quality control in FDA’s Center for Biologies Evaluation and Research.

“All three human rabies vaccines are made in a similar fashion: Cells are grown in a monolayer, or single-cell layer, in an artificial medium that bathes the cells much as blood bathes human cells. The virus is added, replicates, and is released into the cell medium as the cells die. The medium is then harvested to produce the vaccine. Since the harvested medium contains live virus, a chemical is used to kill the virus; the chemical is then removed via a purification process, resulting in a final vaccine.

Human diploid cell vaccine is made by allowing the rabies virus to multiply in human diploid cells, normal cells that contain two complete sets of human chromosomes, grown in glass or plastic bottles. Like HDCV, DCO vaccines are made with human diploid cells, but use a different purification process. The Michigan-produced vaccine uses fetal rhesus monkey diploid cells. At first, live rhesus monkey fetuses were used to establish a cell line. But today, live monkey fetuses are no longer needed: only the cell line, frozen in liquid nitrogen, is used.

Shot Schedule

“The preexposure series for all human rabies vaccines is given in three shots: on day 0, day 7, and on day 21 or day 28 for the third shot. How often booster shots are taken depends on how good you are at producing antibody,” Fitzgerald says.

People who have received the preexposure series need only two booster shots if they are later exposed to rabies. People in high-risk jobs are encouraged to have their blood tested at regular intervals so boosters can be given if antibody levels fall below a baseline value. Fitzgerald says the average high-risk worker usually needs boosters only about once every two years.

“Postexposure rabies vaccine consists of five shots, given on day 0, day 3, day 7, day 14, and day 28 [after exposure]. On day zero rabies immune globulin is also given because the vaccine takes, depending on the individual, seven to fourteen days to provide an active antibody response,” Fitzgerald says.

Rabies immune globulin, which consists of antibodies from blood donors given rabies vaccine, acts as a kind of safety net, providing passive immunity, interim protection until active antibodies are produced from the vaccination.

Many people shudder at the mention of human rabies vaccines because they are recalling an older form of human
vaccine, made from duck embryos and requiring 21 shots, many of which were given in the abdomen. Today most shots are given intramuscularly, usually in the shoulder muscle. (It’s important that the vaccine be injected into muscle, since studies have shown that vaccine injected into fatty tissue may induce a lower response.) The preexposure intradermal vaccine normally is given in the forearm or shoulder, and rabies immune globulin is injected both at the bite site and in the buttocks.

Forms
There are two forms of rabies. “Furious” rabies largely affects the brain and causes an infected animal to be aggressive or excitable (the very picture of the foaming-at-the-mouth, “mad dog” image people have of rabies). “Paralytic” or “dumb” rabies, mainly affects the spinal cord, causing the animal to be weaklimbed, lethargic, and unable to raise its head or make sounds because neck and throat muscles are paralyzed. In the beginning phase of paralytic rabies, an animal may also appear to be choking.

A wild animal acting unusually tame can also be an early warning sign for rabies. Both types of rabies are the result of the virus multiplying as it moves to the central nervous system and, finally, to all body organs and tissues.

Because rabies may be contagious before any clinical signs appear, a healthy-looking animal can transmit the disease. Rabies’ incubation period, the time between infection and the appearance of symptoms, can range from a few weeks to a year or longer in humans, although 30 to 50 days is average. Animals usually develop symptoms between 20 and 60 days after exposure. The incubation period depends on bite location and the dose of virus received.

In humans, a string of worsening symptoms appears: itching or burning at the bite site, fever, headache, and appetite loss. The rabies sufferer grows restless, may experience hydrophobia (a fear of water, because of difficulty swallowing), have convulsions, or hallucinate. Signs of nervous system damage, such as paralysis or disorientation, follow; the only treatment is sedatives and
Rabies Prevention

Prevention is the best way to keep you and your pets safe from rabies:

- Keep pet shots up-to-date and observe leash laws. Don’t leave your dog chained alone in the yard; If attacked by a rabid animal, it can’t escape.
- Don’t make your house or yard attractive to wildlife; feed your pet indoors, and keep garbage cans closed tightly.
- Seal basement, porch, and attic openings, and cap chimneys with screens.
- No matter how cute, avoid contact with wild or unfamiliar animals.
- Don’t touch a wild animal even if it’s dead.
- Report strays or animals acting strangely or sick to local authorities.

If you are bitten, immediately wash the wound with soap and water. Clean the bite by allowing the wound to bleed, and get medical help at once. If possible, use a large box to trap and confine the animal, but only if it can be done safely. ■

—A.T.H.

painkillers. The person may slip into a coma, or die suddenly of respiratory or cardiac arrest.

Control in Animals

Experts agree that preventing rabies in people depends on controlling rabies in animals. Animal rabies vaccines are available for domesticated animals like dogs, cats, sheep, cattle, horses, and even ferrets. But controlling rabies in wildlife populations is a more challenging problem.

The sharp rise in animal rabies, particularly among raccoons, the most common animal carrier, led to a 1995 conditional license approval for an oral rabies vaccine for raccoons. The conditional license was issued by the Animal and Plant Health Inspection Service (APHIS), an arm of the U.S. Department of Agriculture, which regulates animal vaccines. The conditional license allows the vaccine to be dropped to wildlife habitats in vaccine-laced bait. Such conditional licenses are issued to meet emergency situations or “special circumstances,” limited markets, or local situations, in this case defined by APHIS as a raccoon rabies “epizootic,” or outbreak, stretching from Maine to Florida.

The oral raccoon vaccine is unique because it was created using genetic engineering.

“Scientists took a gene from the rabies virus and inserted it into a vaccinia virus using recombinant DNA technology, or technology where the genetic material in a cell is manipulated,” explains Robert B. Miller, D.V.M., chief of virology in Veterinary Biologies with APHIS. “When the modified vaccinia virus, a member of the pox virus family, infects a cell, it produces a protein normally produced by the rabies virus. The animal’s body recognizes the protein as foreign, and the animal develops an active immunity.”

Preliminary studies showed that if the vaccine went directly to the stomach, it would be killed by stomach acids, so the vaccine is placed inside a tube of fish meal and is absorbed by the animal’s tonsils, prompting the immune response. Although aimed at raccoons, Miller says the recombinant virus was tested for safety in over 50 different animal species before the conditional license was issued.

Because of how the vaccine is distributed, Miller says few humans are expected to be exposed. APHIS advised that local public health authorities in the areas where the vaccine is to be distributed be notified before bait distribution, and said authorizing state or federal agencies should be notified of any reports of human contact with vaccine-laden baits.

Nevertheless, Miller is concerned about the vaccine’s use.

“One of my concerns is that we license its use but we don’t control how it’s used. I think a lot of art will be required in the use of this vaccine, because not only does it have to be effective, but [bait] placement requires special knowledge,” he explains. “Baits are attractive to animals other than raccoons, so you need the proper timing of application and the appropriate number of baits so you get the most benefit.”
Rabies—its name comes from a Latin word meaning “to rage”—has struck fear in people for centuries. An Italian physician, Girolamo Fracastoro, discovered that rabies was a disease fatal to humans as well as animals in the 16th century, calling it “an incurable wound.” Louis Pasteur created the first rabies vaccine in 1885 using live rabies virus. Pasteur’s early vaccine could cause serious, even fatal, reactions, but it was a start on the road to today’s effective rabies vaccines.

The fear caused by rabies begins with its very transmission. A viral infection affecting the brain and spinal cord, rabies is transmitted through the saliva of an infected animal, usually by a bite. It can also be transmitted when infected saliva comes in contact with a cut or skin break. Infected bat droppings are suspected of transmitting the disease, and at least two people are believed to have been exposed to rabies by breathing the air in caves where rabid bats live. Other rare deaths have occurred in people who have received corneal eye transplants from donors with undiagnosed rabies.

Bite transmissions can be difficult to detect, as illustrated by the death of a 4-year-old girl last year who was exposed to rabies from a bat that flew in her room while she was sleeping. The bat was killed and buried, and no signs of a bite were found on the girl. When she died a month later of rabies, health authorities recovered the bat carcass, tested it, and found the bat and the child both had the same variant of rabies. —A.T.H.

CDC’s Ruprecht says he is “encouraged” so far by the vaccine’s use.

“We are encouraged with the use of the vaccine and the results we have seen in the Northeast to date. It took from 1983 to 1995 to get a conditional license because we don’t have all the bugs worked out yet, but by the next decade we should be generating enough data to come to grips with that,” he notes. “The United States has the most complex rabies problem in the world because of the size of the country, the affected area, the diversities of reservoirs [host animals], and the viruses adapted to them. Socio-economic philosophies here have also not [traditionally] supported the concept of oral vaccination.”

The four human deaths that occurred in 1995 in the United States were due to bites from bats or from animals bitten by rabid bats. In that sense, the four human fatalities were not related to the current raccoon epizootic. (Rabid bats have been associated with at least 21 human deaths since 1951 in the United States.) Although most animal cases involve raccoons, there has never been a reported human rabies death directly or indirectly connected to a raccoon.

CDC has provided the 1995 compendium of animal rabies control recommendations to veterinarians, public health officials, and others concerned with rabies control. The recommendations included immunization procedures with detailed vaccine information; information on human rabies prevention and rabies in domestic animals and wildlife; preexposure animal vaccination and management; and postexposure management directives.

CDC’s Ruprecht emphasizes that despite the advent of oral vaccines for wildlife and advances in human rabies vaccines, the key to rabies control remains education.

“We need to keep nature in perspective; the world is not all bright and beautiful. That’s the reason why we perceive wildlife as wild,” he says. “The same old things that worked 50 years ago still work: Vaccinate your pets, and have a healthy attitude toward wildlife. To paraphrase a common rabies control idiom: Love your own, leave others alone.”

He adds, “But the dynamics of rabies have changed, and will continue to change. The dynamics have changed both in shifts of rabies from domestic to wild animals, within domestic animals from dogs to cats, and shifts in the number of important wildlife species annually and geographically that are affected by rabies. This will continue to press us to come up with novel ways to control the disease in wildlife.”

FDA’s Fitzgerald agrees with the concept of change in terms of human rabies vaccine.

“I’ve seen an awful lot change over the years. Rabies vaccines were much cruder, such as those made from duck embryos. We are now into a whole new level of purification and potency,” Fitzgerald says. “We have good vaccines for humans with few side effects. You only have to look at other countries where people by the thousands die of rabies to know how lucky we are here.”

Audrey T. Hingley is a writer in Mechanicsville, Va.
Agency Changes Include

by Dixie Farley

This article is part of a series on FDA activities and concerns.

Private organizations may be allowed to participate in evaluating medical devices under a pilot program that began Aug. 1.

The program is one of several FDA initiatives in what Vice President Al Gore termed “a common sense approach” to streamlining, simplifying and reducing the regulatory costs of the medical device industry while maintaining public health and consumer safety. “The result is safe, new medical devices that will be available to the American people in record time,” Gore said when FDA announced the initiatives in April.

Other initiatives change the way FDA inspects certain device firms and reduce the number of environmental assessments that industries, mainly the food and drug industries, have to prepare for FDA's review.

Third-Party Review

This initiative tests whether third-party review of medical devices will reduce review times and whether strong conflict-of-interest rules can be maintained in such a process.

The program applies only to low- and moderate-risk devices for which FDA does not require clinical data on safety and effectiveness—products such as electronic thermometers and surgical gloves. A manufacturer must show in a premarket notification application that such a product’s safety and effectiveness are comparable to a device already legally marketed. Each year, FDA receives about 1,500 applications for low- and moderate-risk devices that would qualify for third-party review.

Participation in the pilot program is voluntary. Firms may choose to have most of the review by a third party, or leave the entire procedure up to FDA.

If a firm does choose third-party review, this is how the program works:

- The firm selects an organization FDA has recognized for participation in the program.
- The firm submits its application to the organization.
- When the review is complete, the organization submits the application, the review results, and a recommendation to an FDA supervisor for final assessment. This bypasses the first phase of the agency’s routine review process.
- Within 30 days, FDA makes its decision.

“The test for any reform is whether it protects the public health,” said FDA Commissioner David A. Kessler, M.D. “Our proposal will test whether this speeds up the process and if the integrity of the review can be maintained.”

FDA will closely monitor the pilot program, which will run for two years, and make any necessary changes to protect the public health. The agency announced the program in the April 3, 1996, Federal Register.
New Inspection Procedures

Another initiative, also a pilot program, changes the way FDA inspects firms with a good history of compliance with agency requirements. The changes were jointly developed by FDA and a task force of industry officials following "grassroots" meetings FDA held with device manufacturers last year. If successful, it will be expanded to manufacturers of other products regulated by FDA.

Among other changes, FDA will:

- Notify firms of inspection in advance, instead of inspecting unannounced, as previously done. Advance notice would enable the firm to prepare for the visit and be better ready to answer questions.
- Give firms opportunity to note on the official inspection record violative findings that were corrected immediately. In the past, FDA records listed only the findings, without noting immediate corrections.
- Give firms found in compliance a letter informing them they successfully passed the inspection. In the past, FDA has not given such recognition.

Fewer Environmental Assessments

Although the third initiative affects mainly the food and drug industries, it also applies to the medical device industry and other FDA-regulated areas. The proposal would streamline and simplify FDA's procedures for complying with the National Environmental Policy Act. The proposal greatly reduces the number of environmental assessments the industries have to prepare for FDA's review.

FDA found that many actions for which it presently requires such assessments have no significant effect on the environment. By eliminating them, the agency can focus greater resources on areas that present real potential for environmental impact. The proposed reforms would add no environmental risks, FDA believes. They would save the industries as much as $15 million and the agency as much as $1 million each year. Some firms are already beginning to submit abbreviated assessments under informal guidance by FDA.

The initiatives are among more than 40 reforms identified by FDA and the Vice President's National Performance Review program to make the U.S. government work better and cost less.

Dixie Farley is a staff writer for FDA Consumer.
The Notebook: a potpourri of items of interest gathered from FDA news releases, other news sources, and the Federal Register (designated FR, with date of publication). The Federal Register is available in many public libraries.

- **High-fructose corn syrup**—used widely to sweeten foods such as sodas, juices, and canned goods—has been affirmed by FDA in a final rule to be generally recognized as safe (GRAS) in most formulations. An FDA rule published in 1988 proposed a comprehensive evaluation of the sweetener while allowing it to remain on the market. The new rule covers the commonly used formulations of 43 and 55 percent fructose, but not a 90 percent formulation, which the agency says has “minor uses” in low-calorie foods and will need further evaluation before GRAS status can be affirmed. *(FR Aug. 23)*

- **Food labels** can claim that various sugar alcohols such as sorbitol, mannitol and xylitol do not promote tooth decay, according to an FDA final rule effective Jan. 1, 1998. These sweeteners are used in some chewing gums. FDA announced the action in response to a petition by the National Association of Chewing Gum Manufacturers Inc. and several sugar alcohol manufacturers. *(FR Aug. 23)*

- **High-intensity pulsed light** may be used safely to control microorganisms on the surface of food, according to an FDA final rule. Foods may be exposed to wavelengths ranging from 200 to 1,100 nanometers, emitted as high-intensity flashes by xenon lamps. This range covers the entire spectrum of visible light, as well as small portions of ultraviolet and infrared light regions. FDA placed no restrictions on the types of foods that can be treated with pulsed light. *(FR Aug. 15)*

- **Cats** may spread multidrug-resistant bacteria, which can cause serious illness, say researchers at the UK Public Health Laboratory Service in London. They found that of 110 cases of infection by *Salmonella* bacteria in cats, 78 were the species *Salmonella typhimurium*. Of those, 40 were of a type resistant to six commonly used antibiotics in humans, which would make infection in humans difficult to treat. The researchers say cats may pick up the infection from their food, possibly from eating scraps of contaminated human food or from eating raw or undercooked meat. They also warn that cats should not be given free access to unprotected food and food preparation areas and that people who touch cats should wash their hands before eating or preparing food. *(The Lancet, Aug. 17)*

- **Men with early prostate cancer** who have the prostate surgically removed have a high 10-year survival rate, according to research at the University of Chicago. Doctors monitored outcomes of 2,758 men in the United States and Europe, all but 91 of whom had radical prostatectomies. Researchers found that tumor grade—a gauge of the tumor’s aggressiveness—was the most important factor in determining the outcome of those who underwent the surgery. Men with a grade 1 tumor (the least aggressive) had a 94 percent chance of 10-year survival. This dropped to 80 percent for grade 2 tumors and to 77 percent for grade 3. *(Journal of the American Medical Association, Aug. 27)*
Promoter of 714X Cure-All Faces Prison For Selling Unapproved Drug

by Paula Kurtzweil

A New York book publicist has been sentenced to prison for selling an unapproved new drug espoused in a book he was promoting. The book deals with a French-born biologist living in Canada who developed a camphor-derived drug he calls 714X, which he claims can cure cancer, AIDS, and other diseases. The drug has never been approved in Canada or the United States.

Charles Pixley, 48, president of Writers & Research Inc., of Rochester, N.Y., was sentenced last July to one year and one day in prison, plus three years of supervised release and 200 hours of community service for selling 714X to Americans, including undercover FDA investigators. He arranged for the product to be brought in from Canada. He is appealing his conviction.

According to FDA forensics chemistry analysis of a sample of 714X, the product was 94 percent water, about 5 percent nitrate, 1.4 percent ammonium, less than 1 percent each ethanol, sodium and chloride, and less than one one-hundredth of a percent of camphor. A Writers & Research sales report submitted as evidence during a two-day bench trial indicated patients paid between $300 and $400 for two 6-milliliter (about 1 teaspoon) vials of 714X. According to product literature, 714X could be injected into the groin, breathed in through a nebulizer, or placed under the tongue for absorption.

While FDA believes that 714X does not pose an immediate danger to patients, its use can prevent patients from receiving proper medical treatment. Two doctors who complained to FDA about 714X expressed concern about two of their cancer patients who refused conventional therapy in lieu of treatment with 714X. Both patients died.

The agency became aware of Pixley's activities in January 1992, when a consumer called the agency's Seattle district office to inquire about 714X. The consumer heard about the treatment on a radio show and had written for and received written information from Pixley's company.

On Jan. 24 and 30, 1992, Sherry Phillips, an investigator with FDA's Buffalo district office, inspected Pixley's business, located in the front porch area of his house. She interviewed Pixley, who admitted that he brokered the sale of 714X between the Canadian manufacturer in Rock Forest, Quebec, and U.S. patients. He promoted 714X in his book, Do No Harm, which summarized the theories of 714X's inventor on the causes of disease and advocated the use of 714X. Pixley's promotional activities also included distributing flyers and other literature, giving oral presentations, and participating in radio talk shows.

Literature available at Pixley's business showed the product was promoted for various diseases. One piece of literature stated that 714X was "effective in restoring to perfect health, 75% of cases treated against AIDS, cancer, Lupus, MS [multiple sclerosis], rheumatoid arthritis, and other viral, immunological or degenerative diseases."

Invoices supplied by Pixley indicated that during a three-month period in 1992, Writers & Research arranged for 960 vials of 714X from Canada. The vials had a wholesale value of $96,000 and a retail value of $168,000. They were brought into the country by a delivery service or as undeclared personal items at the U.S.-Canadian border in Buffalo.

Following the inspection, Phillips informed Pixley that his activities violated federal law because FDA had never approved a new drug or investigational new drug (IND) application for 714X. In July 1992, FDA issued an import alert, prohibiting 714X from entering the United States.

However, Pixley continued to sell...
714X; he sold some to undercover FDA investigators. In addition, the agency continued to receive inquiries and complaints about 714X from consumers and doctors. So, Phillips returned to Pixley's place of business in March 1993.

During the inspection, Pixley admitted to Phillips that he was selling 714X to U.S. patients and smuggling it in from Canada. Phillips observed an inventory of 714X on hand and collected records documenting the sale of 714X to patients across the country.

Pixley indicated to Phillips that, in partial fulfillment of the requirements for an IND application, he had formed an institutional review board, or IRB. These boards review clinical studies of investigational drugs to ensure that patients participating in the studies are not exposed to unnecessary risks. Pixley's IRB included himself and doctors who bought and prescribed 714X.

At the end of her inspection, Phillips told Pixley that his IRB did not comply with FDA's regulations. For example, she cited him for being a member of the group, even though he had a financial interest in the drug being studied. Also, the IRB did not provide adequate informed consent or disclose potential risks of the drug to study participants. She passed on her findings to FDA's Center for Drug Evaluation and Research.

In August 1993, center representatives held an informal hearing with Pixley and informed him that his IRB did not conform with FDA regulations, that he should stop referring to Writers & Research as an IRB, and that he should file an IND application for 714X. Later, the center informed Pixley that it was considering disqualifying his IRB.

In February 1994, Beverly Ritter, an investigator in FDA's San Francisco district office, called Writers & Research, posing as a patient. Using an alias, she ordered $22 worth of patient literature on 714X, a $15 physicians' handbook on 714X, and $400 worth of 714X. The literature and the first of what were considered two orders of 714X arrived at an undercover address within one month. Checks FDA sent as payment for the literature and 714X were returned to FDA's undercover location, stamped as paid. The stamped information indicated the checks had been deposited to an account with a Rochester, N.Y., bank. Under subpoena, the bank provided information about the account that showed it was held in the name of Writers & Research and that between April 1, 1993, and March 31, 1994, more than $472,000 had been deposited to the account. One check made out for more than $7,000 in cash was stamped to indicate it had been credited to the account of Pixley's 714X supplier in Canada.

In July 1994, special agents with FDA's Office of Criminal Investigations requested and obtained a search warrant for Pixley's place of business. They seized various documents related to 714X, including correspondence between doctors and other clinicians; records of telephone calls from customers; product order forms; customer sales receipts; patient and physician literature, cassettes and videotapes; and copies of FDA statutes and regulations.

On Oct. 25, 1995, a grand jury for the U.S. District Court for the Western District of New York returned a 19-count indictment against Pixley and Writers & Research. Count 1 charged both parties with conspiracy to defraud FDA by selling an unapproved new drug. Counts 2 through 19 charged Pixley with illegal interstate commerce of an unapproved new drug. Counts 2 through 19 each represented a date on which an individual had received 714X.

During the bench trial April 10 and 18, 1996, U.S. District Judge Michael Telesca heard testimony from various FDA employees, including Paul Goebel, in FDA's Center for Drug Evaluation and Research, who testified on the appropriateness of IRBs, and forensics chemist Rick Flurer, Ph.D. Also, David Feigal, M.D., director of FDA's division of anti-viral drug products, and Gerald Sokol, M.D., a medical reviewer in FDA's division of oncology and pulmonary products, testified in writing that they consider 714X a new drug because it is not generally recognized among scientific experts as safe and effective. Another FDA employee, Elaine Abraham, Ph.D., also testified in writing that she had searched FDA files and found that neither IND nor new drug applications for 714X had ever been filed.

Pixley's lawyer argued that 714X is a homeopathic drug and therefore not subject to FDA regulation. As a homeopathic drug, the defense argued, 714X is considered safe and effective based on the listing of its ingredients in the Homeopathic Pharmacopoeia. However, when questioned about the chemical name (trimethylbicyclohexane-phosphate-chloride) placed on the 714X vial, defense witness Harris Coulter, Ph.D., editor and chief of the eighth edition of the Homeopathic Pharmacopeia, said he did not understand that label and would not know the contents of the vial based on the label.

On April 19, 1996, Telesca found Pixley and Writers & Research guilty of count 1 and Pixley guilty of counts 2 through 19 of the indictment. In his decision and order, Telesca wrote that the "overwhelming proof at trial" established 714X as a drug and therefore subject to the regulations governing the marketing of new drugs in the United States.

"[T]here is absolutely no proof that 714X is a homeopathic drug," he wrote. "It was not listed as such in the Homeopathic Pharmacopoeia nor was it labelled as such on vials of the substance which were marketed to individuals."

Telesca sentenced Pixley and Writers & Research on July 9. In addition to a prison sentence, supervised release, and community service, he ordered Pixley to refrain from "possessing, distributing, or aiding in the distribution" of unapproved drugs and assessed him $500. He fined the company $1,000 and assessed it $200.

Pixley filed a notice of appeal in the U.S. Court of Appeals for the Second Circuit on July 9.

Paula Kurtzweil is a member of FDA's public affairs staff.
Lights Out on Illegal Laser Light Show

The same class of lasers used in a type of vision-correcting surgery, in the wrong hands, jeopardized the eyesight of partiers at an all-night bash in San Francisco.

As a result, on July 8, FDA sent a warning letter to Warren Zerra, operator of the party’s laser light show, telling him that the light display at the May 17 party was operated in a “grossly hazardous manner,” and that Zerra must stop his show until he takes steps to bring it into compliance with the agency’s safety standards.

The letter followed an FDA inspection in which Gary Zaharek, electro-optics specialist with FDA’s Pacific regional staff, identified serious problems, including the unsafe practice of striking people directly with laser beams. There were no known injuries.

FDA regulates laser light shows, along with all other laser equipment—from surgical instruments to compact disk players—under the Radiation Control for Health and Safety Act and the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act.

An informant alerted FDA to Zerra’s violations. FDA sent Zaharek to inspect the light show operation at the party, which was held on a dance floor at a San Francisco restaurant and club.

“We had to observe the person actually committing these illegal acts,” says Frank Mackison, a consumer safety officer in FDA’s Center for Devices and Radiological Health, “just like a policeman has to actually observe you speeding before he issues a ticket.”

Zaharek observed numerous violations by the light show operator. The most dangerous, according to the investigator, was the absence of a safe distance between the audience and the lasers. For light shows like Zerra’s, FDA requires beams to be at least 3 meters (3.3 yards) above the floor.

“People were being struck directly with the laser beams,” Zaharek says. “That’s the most dangerous aspect of illegal laser light shows. If a beam hits someone directly in the eye, it could cause serious eye burns.”

The setup was especially dangerous, according to Zaharek, because a stationary beam hit people as they walked up or down a staircase at the party. A moving beam is less hazardous, he says, because in the mere blink of an eye, the beam has passed.

Other serious violations included:
- lack of written permission (called a “variance”) for use of laser beams capable of achieving Zerra’s desired graphic effects
- lack of “protective housing” on equipment to shield the audience from excessive radiation
- inadequate warnings and descriptive labeling on equipment
- lack of documentation of the operator’s required training
- no notification to FDA of the pending show
- no documented quality control procedures.

FDA’s warning letter lists these violations.

FDA will monitor Zerra’s operations and is prepared to reinspect. If Zerra continues to operate illegal light shows, he may be subject to a fine of up to $1,000 per violation and a court-imposed injunction of the illegal shows.

The warning letter is one of at least nine FDA has sent to laser light show operators since January. “We want to get the message out to operators that are putting on shows in a haphazard manner,” Zaharek says. “Shape up before something serious happens.”

—Tamar Nordenberg

Calf Company Cleans Up Act

In more than 50 instances over a two-year period, livestock dealers Daniel Slenders and Stacey Absher were caught selling calves to be slaughtered for food containing illegal residues of antibiotics and other drugs. Those incidents—a “phenomenal number,” according to one FDA official—led to a consent decree of permanent injunction in which Slenders and Absher agreed to stop selling calves until they had implemented safeguards.
to prevent future violations.

Slenders and Absher, owners of D & S Calf Co., Chowchilla, Calif., signed the decree, which the U.S. District Court for the Eastern District of California entered on April 23, 1996, after an FDA investigation documented illegal residues of penicillin, tetracycline, gentamicin, neomycin, streptomycin, sulfamethazine, and sulfamethoxazole in D & S calves.

A calf that is treated with a drug or that has nursed from a drug-treated cow must be withheld from the market until the drug withdrawal time is complete. Drug residues in edible animal tissue may cause allergic reactions in some people consuming meat from these animals. The residues also may cause changes in the intestinal microflora, affecting such processes as vitamin synthesis, therapeutic drug metabolism, and development of antibiotic-resistant bacteria.

FDA investigator Robert J. Anderson first inspected D & S Calf in July 1989, after the U.S. Department of Agriculture found excessive drug residues in four calves sold for slaughter by Slenders. When calves are sent to slaughterhouses, USDA collects liver, kidney, and sometimes muscle tissue samples from a certain percent of the animals. If the samples indicate the presence of illegal drug residues, the carcass is condemned, and USDA notifies the producer and FDA.

FDA's inspection revealed that D & S Calf did not maintain adequate records showing where the calves were bought, the medications given to the calves, or the withdrawal periods for the medicated calves. On Sept. 18, FDA's San Francisco district office sent a regulatory letter to Slenders warning him that he must maintain the required records if he continues to sell calves in interstate commerce.

FDA's Anderson returned to D & S Calf in October 1990 after USDA again found illegal residues in several calves sold by D & S Calf. Slenders told Anderson he would record the source and medicated status of the calves he sold for slaughter as food.

The level of violations did diminish after that inspection. “He cleaned up his operation for awhile,” recalls John Reves, a compliance officer with FDA's San Francisco district. But in late 1994 USDA again detected illegal residues of antibiotics in a calf Slenders sold for slaughter.

When FDA returned to D & S Calf in January 1995, Slenders admitted to the investigator that he knew the calf was medicated but had forgotten to tell the slaughterhouse. On March 17, FDA's San Francisco office again warned the firm to stop delivering medicated calves for slaughter for food and advised it to maintain proper records. In response to that warning, Slenders told the agency he would not purchase or sell medicated calves for slaughter.

But his assurances were false. From September 1995 through March 1996, USDA detected illegal drug residues in more than 40 calves sold by Slenders and Absher. That brought the total since October 1994 to more than 50. “That's a phenomenal number of violations in such a short period of time,” says Reves.

Because the agency's warnings did not result in compliance, on March 15, 1996, FDA asked the U.S. Department of Justice to initiate injunction proceedings against D & S Calf. After the department contacted the defendants, they agreed to sign a consent decree to settle the case without admitting or denying any wrongdoing.

Under the decree, the defendants agreed not to sell animals for slaughter for human food until residue avoidance systems were in place.

FDA and the Department of Justice worked with the defendants to establish an acceptable residue avoidance plan. The resulting plan requires Slenders and Absher to:

- Obtain certification from the animal producer that the animal they are buying has not been medicated or, if it was medicated, information on how much drug was given and the remaining drug withdrawal time, if any.
- Keep records indicating where they bought the animals.
- Identify the animals they purchase with a permanent tag.

At press time, the residue avoidance plan was in place, and no new reports of illegal drug residues had been made.

—Isadora B. Stiehlin

Summaries of Court Actions will not appear in this issue of FDA Consumer, but will return in the December 1996 issue.
This Year You Get To Cook The Holiday Bird!

You stare blankly at this 15-pound, two-legged creature wondering, “Now what do I do?”

From turkey to shrimp, there is someone waiting to help you. The U.S. Food and Drug Administration, U.S. Department of Agriculture, and various private companies offer food safety tips to get you through the holidays in good health and taste. For tips on preparing, serving and storing food safely, here's a list of some available help:

FDA Seafood Hotline: (1-800) 332-4010
Recorded messages 24 hours a day. Consumer educators available to answer questions Monday to Friday, noon to 4 p.m. Eastern time.

USDA Meat and Poultry Hotline: (1-800) 535-4555
Recorded messages 24 hours a day. Home economists and registered dietitians available to answer questions 10 a.m. to 4 p.m. Eastern time. Special Thanksgiving Day hours 8 a.m. to 2 p.m. Eastern time.

Butterball Turkey Talk Line: (1-800) 323-4848

HoneyBaked Ham Consumer Hotline: (1-800) 641-8290

Ball Consumer Hotline: (1-800) 240-3340
For questions about home-canned food items. Monday to Friday, 8:30 a.m. to 4:30 p.m.