

FDA CONSUMER

THE MAGAZINE OF THE U.S. FOOD AND DRUG ADMINISTRATION

• VOL. 29 NO. 9

NOVEMBER 1995 •

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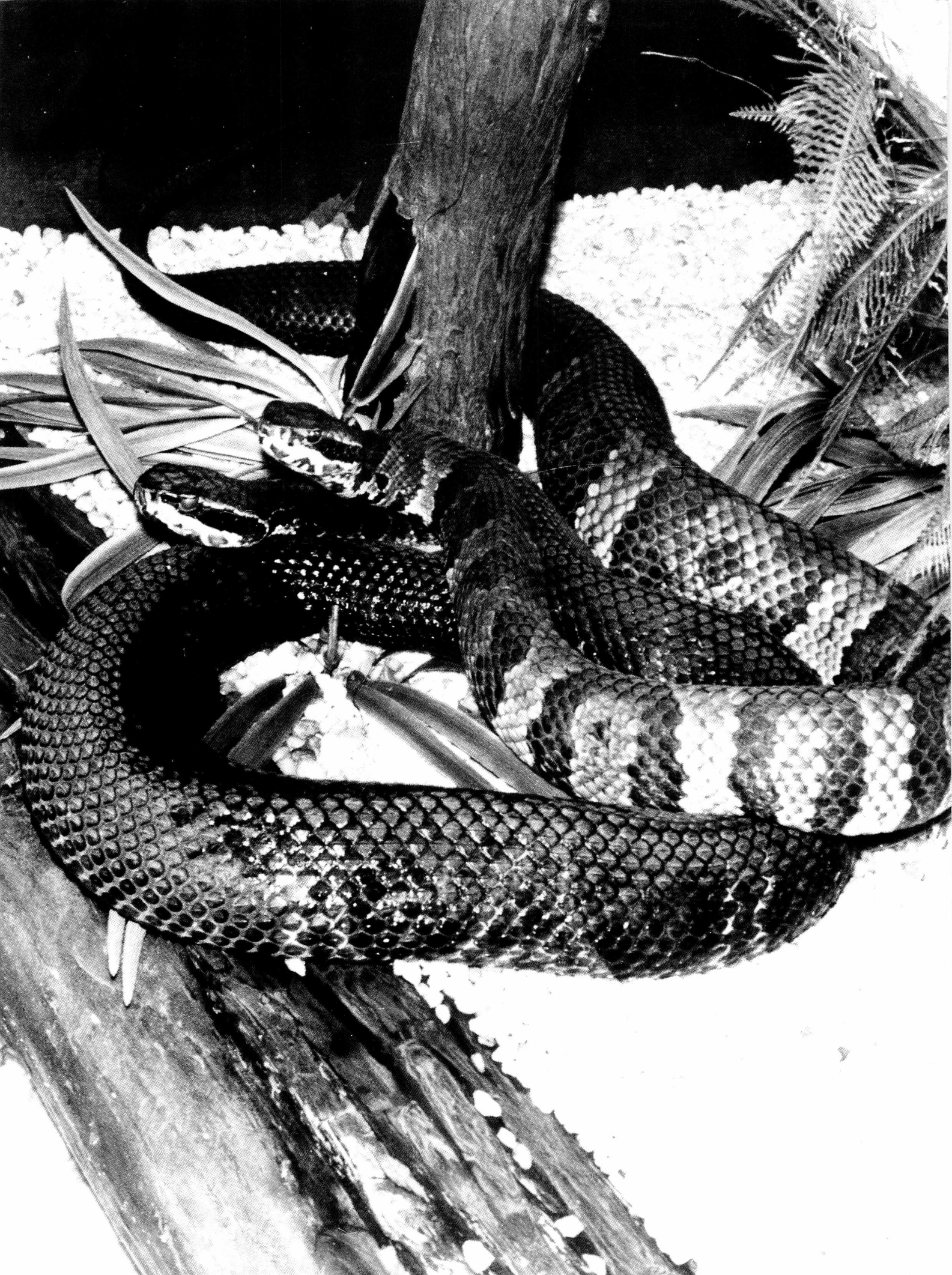
Adverse
reactions?

What's
it for?

With
food?

When
do I
take it?





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FDA's Rx for Better Medication Information 5

Under a newly proposed program, by the turn of the century at least 75 percent of patients getting new prescriptions would receive easily understandable written information. The public has until Nov. 22 to comment.

A Status Report on Breast Implant Safety 11

Though recent studies do not show a greatly increased risk of some well-defined autoimmune diseases among women with silicone gel-filled breast implants, other safety questions remain. FDA is also requiring manufacturers to collect safety data on saline-filled implants.

Guarding Against Glaucoma 17

Glaucoma is a group of eye diseases sharing certain features, but also differing from one another in their prevalence, ease of detection, and symptoms. Treatments include drugs and laser surgery.

For Goodness Snakes: Treating and Preventing Venomous Bites 22

Twenty kinds of poisonous snakes inhabit the United States (except for Maine, Alaska and Hawaii), and coping with a bite from any one of them is no picnic. There are ways to prevent getting bitten, however, and effective treatment if prevention fails.

Interstitial Cystitis: Progress Against Disabling Bladder Condition 28

Interstitial cystitis is a bladder condition far more common in women than in men. It can be devastating to quality of life. Treatments include drugs and special diets. Sometimes a diagnostic tool—cystoscopy—can temporarily improve the condition.

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Inside Front Cover Photo: *Cottonmouths (water moccasins), found chiefly in the deep South, are only one of many poisonous snakes slithering in many areas of the country. To find out how to avoid or treat their venomous bites, see page 22.*

(Photo by Jessie Cohen, National Zoological Park)



MSG Judged Safe For Most People

The food ingredient monosodium glutamate (MSG) is safe at normally consumed levels for the general population, according to results of a scientific review sponsored by FDA.

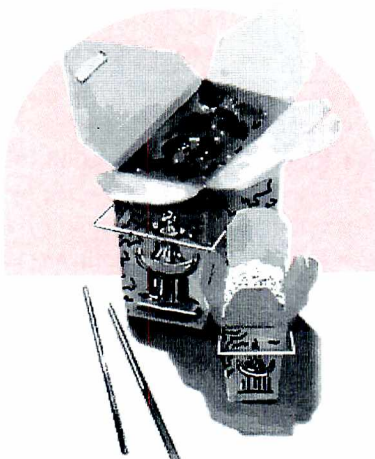
A panel of experts, convened by the Federation of American Societies for Experimental Biology under contract with FDA, found no evidence linking MSG to any serious, long-term medical problems in the general population.

But FASEB's report on the findings did state that evidence suggests certain people may develop short-term reactions when they consume large doses—approximately 3 grams or more per meal—of MSG or related “free glutamates.” These reactions, dubbed “MSG Symptom Complex” in the report, were not linked to low levels of glutamate consumption.

The report also expressed concern that glutamate may affect a small group of people with severe asthma. Limited clinical studies show some of these people experienced bronchospasm up to six to 12 hours after being exposed to MSG.

MSG is one of several types of glutamates—substances derived from glutamic acid, a major building block for proteins. When glutamate that has been bound within a protein is released during breakdown of the protein molecule, “free glutamate” is formed. These substances can be added to food to enhance its flavor and are the focus of much of the concern about glutamates. Some foods, such as ripe tomatoes and parmesan cheese, contain high levels of naturally occurring free glutamates.

Based on a preliminary review of the FASEB report, FDA plans to propose



that foods containing significant amounts of free glutamate declare glutamate as an ingredient on the label. This would allow consumers to distinguish between foods with insignificant free glutamate levels and those that might contribute to a reaction.

Currently, foods containing added MSG must declare it as an ingredient on their labels. Processed foods containing other ingredients with significant levels of free glutamate (such as autolyzed yeast, soy sauce, and some flavorings) must declare these ingredients, like any other ingredient, on their labels.

FDA sponsored extensive reviews of MSG and related substances in 1978 and 1980, both of which concluded MSG is safe for the general public at common-use levels. But the 1980 review noted that additional data were needed to judge whether a significant increase in glutamate consumption can cause adverse effects. FASEB's report, contracted by FDA in 1992, is the most comprehensive review of existing information on glutamate safety.

New Osteoporosis Therapy

Calcitonin salmon nasal spray was recently approved under the brand name Miacalcin Nasal Spray to treat osteoporosis in postmenopausal women, beginning five years after menopause. Previously, the only approved treatments for treating or preventing osteoporosis had been injectable calcitonin salmon and estrogen.

Two clinical trials demonstrated that daily use of calcitonin salmon nasal spray increases bone mass in the spine, although no bone-building effects were shown on bone mass of the forearm or hip. The manufacturer, Sandoz Pharmaceuticals Corp. of East Hanover, N.J., agreed to conduct additional studies to evaluate the product's long-term effectiveness in preventing fractures.

The most common side effects during the trials included inflammation of the membranes in the nose, nosebleeds, and sinusitis. Patients using the nasal spray should have periodic nasal examinations for ulceration or irritation.

Osteoporosis, the thinning of bones in postmenopausal women and elderly men, is a major cause of bone fractures that affect as many as 20 million Americans. Women over 45 commonly suffer fractures of the hip, wrist or spine due to loss of bone mass from osteoporosis.

Women on drug therapy for osteoporosis should take daily supplements of calcium and vitamin D. This, along with exercise, helps prevent loss of bone.

(For more information about osteoporosis, see “Osteoporosis Treatment Advances” in the April 1991 *FDA Consumer*.)

Information on Norplant Available

Women who choose Norplant—a contraceptive device surgically inserted into the upper arm—will now be given a form to sign, acknowledging that they received information on the risks and benefits of the device before insertion.

Norplant, which was approved in 1990, consists of six silicone rubber capsules containing the hormone levonorgestrel. The capsules are surgically inserted under the skin of a woman's upper arm and provide contraceptive protection for up to five years. The capsules are surgically removed at the end of that time or earlier if desired. Both procedures are done in the doctor's office.

To help ensure that women are appropriately informed of the product's risks and benefits before implantation, FDA and Norplant's manufacturer, Wyeth-Ayerst Laboratories of St. David's, Pa., developed new education materials for patients and providers. Included is the acknowledgment form and revisions of the product package insert for doctors and patients that include a discussion of reported adverse reactions.

Side effects commonly associated with Norplant include vaginal bleeding, headaches, nausea, dizziness, and nervousness.

FDA's postmarketing surveillance of Norplant and its ongoing analysis of adverse reaction reports have found no basis for questioning the product's safety and effectiveness when used as directed in the labeling.

For more information on Norplant and the names of providers experienced in inserting and removing the device, call Wyeth-Ayerst's toll-free telephone number (1-800) 934-5556.

(See also "Norplant, Birth Control at Arm's Length," in the May 1991 *FDA Consumer*.)

Experimental Drug Allowed For AIDS-Related Eye Infections

Under a treatment IND recently authorized by FDA, doctors may use the investigational drug intravenous Vistide (cidofovir) to treat HIV-infected patients with relapsing cytomegalovirus (CMV) retinitis that has progressed despite treatment.

CMV retinitis is an eye infection that can lead to blindness in people with impaired immune systems, such as AIDS patients.

FDA established the Treatment IND (investigational new drug) process for patients suffering from serious or life-threatening conditions who have exhausted existing treatments or have no satisfactory treatments. Under the process, patients can obtain promising experimental drugs that have undergone sufficient clinical testing to show they may be safe and effective. The agency based its decision to expand access to intravenous Vistide on a controlled clinical study that showed the drug may slow CMV retinitis progression.

Drugs already approved to treat CMV retinitis are Foscavir (foscarnet sodium) and Cytovene (ganciclovir sodium). Neither can cure CMV retinitis, but both can significantly delay disease progression.

Vistide is made by Gilead Sciences Inc., Foster City, Calif. The company started offering the drug free under this Treatment IND program on Sept. 5. For more information, call (1-800) GILEAD-5. For more about other AIDS clinical trials, call (1-800) TRIALS-A.

Pertussis Vaccine Trials

Recent results of pertussis vaccine clinical trials show that three experimental vaccines are highly effective in infants, according to the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health. Pertussis is also called "whooping cough."

The trials, sponsored by NIAID and conducted in Italy and Sweden, also reported that the experimental vaccines caused fewer side effects than a vaccine currently used in the United States.

FDA's scientists in its Center for Biologics Evaluation and Research have been instrumental in developing and evaluating acellular vaccines and have collaborated with NIAID and the vaccine manufacturers to design the European trials.

The experimental vaccines are called acellular vaccines because they contain only the parts of the pertussis bacterium thought to be important for immunity. U.S. vaccines licensed for use in infants are called whole-cell vaccines, because they contain the whole, inactivated pertussis organism.

The trials, which began in 1992, involved about 25,000 infants. Groups of infants received either an acellular



pertussis vaccine combined with diphtheria and tetanus toxoids (DTaP), a whole-cell (DTP) vaccine, or, in the control group, a diphtheria-tetanus vaccine.

Three DTaP vaccines were found to be approximately 85 percent effective, while the DTP vaccine was 36 percent effective in the Italian trial and 48 percent effective in the Swedish trial. A fourth DTaP vaccine was 58 percent effective.

Whole-cell pertussis vaccines currently marketed in the United States are reported to be 70 to 90 percent effective.

Only three doses were given in the trials, compared to five doses normally given in the United States. It is not known whether this difference in dosage accounts for some of the disparity in the effectiveness of the whole-cell vaccine. In addition, the epidemic conditions in Sweden and Italy, where pertussis vaccines are not as widely used as in the United States, differed from the United States, where pertussis is much less common.

Seizures were reported rarely in the trials, but occurred no more frequently in any of the pertussis vaccine groups than in the control group. Side effects, such as redness, pain and swelling at the site of the injection, fever, and protracted crying, were reported to be less common with the acellular vaccines than with the whole-cell one.

FDA has made special efforts to encourage submission of applications for the use of acellular pertussis vaccines in infants. The agency will target such applications for complete review within six months of receiving them. However, actual times to any licensing can vary, depending on the quality and completeness of the data submitted.

FDA recommends that parents continue to get their children vaccinated against pertussis with available vaccines. The agency has licensed four

whole-cell pertussis vaccines and, for the fourth and fifth doses, two acellular vaccines.

All vaccines pose risks of side effects, but for both whole-cell and acellular pertussis vaccines, serious, long-lasting problems are extremely rare. The disease itself can be fatal. In 1993, 11 pertussis deaths were reported to the national Centers for Disease Control and Prevention.

(For more information about pertussis vaccination, see "New Pertussis Vaccine Offers Prevention Alternative," in the September 1992 *FDA Consumer*.)

Saraflox Approved to Control Poultry Illnesses

Saraflox (sarafloxacin), the first fluoroquinolone antibiotic to be approved for food animals, was recently approved by FDA for use in poultry drinking water to control illnesses caused by *Escherichia coli* bacteria.

Fluoroquinolones are the newest class of antibiotics developed for treating infections in people and animals. Another fluoroquinolone drug, enrofloxacin, was approved in 1989 to treat certain pet infections.

"Sarafloxacin provides veterinarians a way of preventing disease in poultry flocks as long as it is used appropriately," said FDA Commissioner David A. Kessler, M.D.

During a public hearing in May 1994, FDA's veterinary medicine and anti-infective drugs advisory committees recommended approval of fluoroquinolones found to be safe and effective for animal use, but also recommended that the agency establish conditions for approval to minimize any potential for development of resistant bacteria.

To control unnecessary use of fluoroquinolones or unapproved uses, FDA's Center for Veterinary Medicine is edu-

cating veterinarians and producers on the drugs' appropriate use, and is including regulatory guidance for these drugs in its Compliance Policy Guide 7125.06, Extra-Label Use of Animal Drugs in Food-Producing Animals.

FDA is cooperating with the U.S. Department of Agriculture and the national Centers for Disease Control and Prevention in a program to detect and prevent drug-resistant microbes. In addition, the manufacturer will test samples of animal *E. coli* to measure emergence of any drug resistance.

Saraflox, available only by prescription, is manufactured by Abbott Laboratories, North Chicago, Ill. It was approved last Aug. 18.

Free Info from FDA

A free brochure warning people with certain medical conditions never to eat raw oysters is available from FDA.

Also available are three free *FDA Consumer* reprints. The titles and publication numbers are:

- If You Eat Raw Oysters, You Need to Know ... (FDA) 95-2293
- Public Affairs Specialists: FDA's Walking Encyclopedias (FDA) 95-1222
- An FDA Guide to Choosing Medical Treatments (FDA) 95-1223
- Keeping Medical Devices Safe from Electromagnetic Interference (FDA) 95-4261.

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 number.

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

FDA's Rx FOR BETTER MEDICATION INFORMATION

by Dixie Farley

More patients would receive more and better medication information with their prescriptions under a patient education program recently proposed by the Food and Drug Administration.

"This program will increase patient participation in decisions about their health, and encourage adherence to medical regimens," says FDA Commissioner David A. Kessler, M.D.

Under the new program, by the turn of the century, at least 75 percent of patients getting new prescriptions filled would receive adequate, useful, and easily understood written information



that meets quality standards. After reaching this goal, the agency would seek to ensure that by 2006, such information is provided to at least 95 percent of patients receiving new prescriptions.

If these goals are not met, FDA would either institute a mandatory comprehensive program of patient information or seek public comment on the issue.

FDA welcomes comments from the public on the proposed program. (See accompanying article, "You Can Comment.")

With each new prescription, a patient's first step to safe and effective treatment is to ask the doctor questions.

Lack of information is one of the main reasons why 30 to 50 percent of patients do not use medicines as prescribed. And that's a lot of medicine misuse, considering that U.S. pharmacists dispensed more than 2 billion prescriptions in 1994, according to the annual National Prescription Audit by IMS America Ltd., of Plymouth Meeting, Pa.

The Costs

Medical costs due to prescription medicine misuse and adverse reactions total more than \$20 billion a year. When consequences such as lost productivity are included, annual costs are as high as \$100 billion, reports the National Pharmaceutical Council, Inc. (NPC), of Reston, Va.

Most common misuses are:

- taking incorrect doses
- taking doses at wrong times
- forgetting to take doses
- stopping medicine too soon.

Treatment failure can be directly traced to medicine misuse. For example,

missed doses of glaucoma medicine can lead to optic nerve damage and blindness. And in patients taking certain medicines for high blood pressure, missing doses or stopping the medicine suddenly can cause a rebound rise in blood pressure higher than it was before the medicine was begun.

A factor increasing the risk for misuse is chronic illness causing no symptoms or erratic ones, according to NPC. Such illnesses include mental disorders, heart and blood vessel diseases, asthma,

glaucoma, and osteoporosis.

Another factor is old age. Older people tend to have serious illnesses and take several medicines. They often have vision so poor it interferes with reading labels. One in four prescriptions is for a person 65 or older, NPC states.

The American Association of Retired Persons says people have an in-

creased risk of medicine misuse if they:

- are depressed
- are going through a life change such as death of a loved one, retirement, moving, divorce, or remarriage
- frequently drink alcohol
- live alone and don't get out much
- suffer from pain
- can't easily talk to the doctor because they have language or hearing difficulty or feel uncomfortable asking questions.

What Can Patients Do?

With each new prescription, a patient's first step to safe and effective treatment is to ask the doctor questions.

Some patients need to overcome a certain barrier, says FDA's Ellen Tabak, Ph.D., of the agency's division of drug marketing, advertising and communications. "There is a feeling among some patients that it will be a bother if they ask a question." In Tabak's research before coming to FDA, patients who asked questions were more satisfied with their medical visits.

Pharmacist Michael Cohen, president

of the Institute for Safe Medication Practices, Warminster, Pa., adds, "If you can't ask questions comfortably, get someone to do it for you. There are patient advocates in the hospital, and relatives or friends on the outside."

It's vital to ask for written information about side effects and interactions with other prescription or over-the-counter (OTC) medicines, tobacco, alcohol, or food, including dietary supplements, and ways to prevent or counteract them.

Patients should ask if a medicine will affect sleep or activity level, Cohen says, and how to handle a missed dose. "To prevent mix-ups, patients ought to insist that the medicine's purpose be put on the label."

Following Regimens

For whatever reasons, intentional or not, some people may never fully comply with their prescribed medicine regimens. Others manage this responsibility easily. Still others want to comply, but have difficulty.

When help is needed, there's a medicine expert nearby—the pharmacist.

Also, various compliance aids are available. Women taking birth control tablets already know one: the calendar blister pack. Each tablet is encased on a card in a plastic "blister" marked for each day of the month. There's no mistaking whether a day's dose is taken.

Aids listed in the catalog of the National Council on Patient Information and Education, Washington, D.C., from which pharmacists can order, include a container that beeps when it's time for a dose, a computerized organizer-dispenser, and a cap fitting over the prescription vial cap that counts openings, indicating whether the day's doses were taken.

Pharmacies commonly carry simple compliance aids such as convenience containers (some with compartments labeled for meals and bedtime, some with braille markings) and spoons and syringes clearly marked with dosages for liquids.

While convenience containers aid compliance by helping to organize medicines in advance, it's a good idea to ask the pharmacist whether the container you're planning to use will affect your medicines' stability.

You Can Comment

The public has until Nov. 22 to send comments to FDA on a proposed agency program to provide adequate and useful written information to patients about their prescription medicines.

Comments on the proposal, published in the Aug. 24, 1995, *Federal Register* (carried in some libraries), may be sent to: FDA Dockets Management Branch (HFA-305), Rockville, MD 20857.

Working closely with health professional and consumer groups, FDA would establish broad standards for the information's content and format and its distribution. Pharmacists and other health professionals would select and distribute the information.

Medicines posing serious and significant health concerns would have to be accompanied by a *Medication Guide* leaflet (see illustration) providing information reviewed and approved by FDA.

Among other proposed standards, the information would:

- give the medicine's approved uses, circumstances when it should not be used, possible serious adverse reactions, and proper use, including related cautions

- be scientifically accurate, consistent in format, nonpromotional, specific, comprehensive, understandable, and legible
- be in a form that is permanent, easily accessed, and convenient to carry—most likely, in leaflets, brochures, or computer-generated printouts, but possibly in audiotapes, computer disks, or videotapes if they meet the proposed standards.

The agency intends to hold a public meeting after the comment period to further discuss the proposed program. ■

—D.F.

Medication Guide

Questions and Answers About
Ceclor
(generic name = cefaclor for oral suspension)

What is the most important information I should know about Ceclor?

Ceclor (pronounced SEE-klor) is used to treat infections caused by certain bacteria. You should not take Ceclor if you are allergic to penicillin or other similar antibiotics. Allergic reactions to Ceclor, as with other drugs, can be fatal. If you experience difficulty breathing, swelling of the throat, rash, or severe diarrhea or abdominal pain, call your doctor immediately or seek medical help.

Take Ceclor for the full amount of time prescribed by your doctor, even if you feel better.

Shake your bottle well every time before taking Ceclor.

What is Ceclor?

Ceclor is used to treat infections caused by certain bacteria. The infections include middle ear, bladder, and skin infections, as well as strep throat, pneumonia and chronic bronchitis. Ceclor works by killing certain bacteria or preventing them from growing. It works only for certain bacteria and not for others. Your doctor may need to get results from laboratory tests or cultures to make sure you are taking the correct antibiotic. Ceclor will not work for colds, flu, or any viral infection. Ceclor is in a class of drugs known as cephalosporin antibiotics.

Who should not take Ceclor?

Do not take this drug if you are allergic to penicillin or any other cephalosporin-class antibiotic because it is likely that you may also be allergic to Ceclor.

Check with your doctor if you:

- have abdominal problems such as colitis
- are pregnant
- are breast-feeding
- are a diabetic and are checking your urine for sugar.

(Ceclor can interfere with the urine test you may be using.)

How should I take Ceclor?

- Follow your doctor's advice about how to take Ceclor. Continue taking Ceclor even if you feel better. Be sure to take all of the medication for the length of time prescribed for you. If you stop taking your medication too soon, the bacteria can grow back and you may get sick again with the same infection.
- Shake your bottle well every time before taking this medicine.
- If you miss taking a dose of Ceclor, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and take your medicine as scheduled. Do not take double your prescribed dose.

What are the possible side effects of Ceclor?

The most common side effects are mild upset stomach, diarrhea, and rash. Call your doctor if these side effects persist or are bothersome.

Call your doctor immediately if the following side effects occur:

- Swelling of the throat or difficulty breathing
- Itching, and rash
- Stomach or bloody diarrhea
- Abdominal pain
- Tiredness or faintness (that lasts after taking this medication for 24 hours)
- Fever (that lasts after taking this medication for 24 hours)
- Joint aches or stiffness (that lasts after taking this medication for 24 hours)

How should I store Ceclor?

- Keep Ceclor in the refrigerator.
- Throw away any unused portion after the expiration date.

If you suspect that someone may have taken more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately. This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others.

This leaflet provides a summary of information about Ceclor. Medicines are sometimes prescribed for uses other than those listed in a Medication Guide. If you have any questions or concerns, or want more information about Ceclor, contact your doctor or pharmacist. Your pharmacist also has a longer leaflet about Ceclor that is written for health professionals that you can ask to read.

(name of company)
(revision date)

This Medication Guide has been approved by the U.S. Food and Drug Administration.

This prototype Medication Guide follows FDA's format for leaflets that, under the patient information proposed rule, would accompany medicines posing significant health concerns.

Even with one day's poor storage, tablets containing certain medicines could break down, says FDA chemistry reviewer Jeanne Taborsky. "It depends on where the medicine is stored and how sensitive it is to moisture, light or oxygen. Pharmacists consider a medicine's particular sensitivities when selecting its prescription container."

States and the U.S. Pharmacopoeia (USP) have set standards for testing prescription medicine containers, and drug firms use these standards to meet FDA's good manufacturing practices (GMPs) for proper packaging. GMPs do not gen-

know it could happen, but there's no immediate data."

USP plans to identify drugs whose deterioration could be critical, Grady says, and then advise pharmacists to attach time-temperature strips to the vials. The strips would alert patients by a color change if the environment will likely cause deterioration.

Informing Patients of Proper Use

Federal law requires labeling on OTC medicines to include adequate directions for proper use and warnings against misuse, because consumers take these medicines pretty much on their own. FDA

and others have long worked to better inform patients about prescription medicines, too.

A Health Care Financing Administration (HCFA) rule, effective January 1993, requires pharmacists or assistants to offer medicine counseling to Medicaid patients. Mail-order pharmacies must provide toll-free telephone service.

"States must set counseling standards," says HCFA health insurance specialist Christina Lyon, "on such issues as whether to extend the offer to counsel to refills."

Lyon says the offer to counsel (patients may refuse) must include all important aspects of the medicine, such as its description, dosage form, length of treatment, special directions, common severe side effects, interactions and their avoidance or remedy, storage, the way to handle a missed dose, and techniques for self-monitoring treatment, such as blood testing by diabetics.

The vast majority of states require a face-to-face offer for counseling for all patients, according to the National Association of Boards of Pharmacy, Park Ridge, Ill.

However, a July 1994 survey sponsored by the association found only 38 percent of patients receiving a verbal offer for counseling. And preliminary re-

Tips for Taking Your Medicine

Whether prescription or over-the-counter (OTC), no medicine is without risk. Besides benefits, medicines may cause side effects, allergic reactions, and interactions with other medicines, alcohol, tobacco, and even foods, including dietary supplements.

The National Council on Patient Information and Education, Washington, D.C., recommends asking the doctor these questions:

- What is the medicine's name, and what is it supposed to do?
- How and when do I take it, and for how long?
- What foods, drinks, other medicines, or activities should I avoid while taking this medicine?
- Are there side effects, and what do I do if they occur?
- Will this new prescription work safely with other prescription and OTC medicines I'm taking?
- Is there written information available about the medicine?

It's wise to write down the answers to these questions immediately, to make sure you'll remember all the details.

Here are more tips for helping your medicines work as safely and effectively as possible.

General Advice

- Keep a record of names, doses and regimens of current medicines; record medicine problems and the reasons for the problems.
- Ask the doctor or pharmacist to write out complicated directions and medicine names.
- Using adequate light, read labels carefully before taking doses.
- Ask the doctor's or pharmacist's advice before crushing or splitting tablets; some should be swallowed whole.
- Contact the doctor or pharmacist if new or unexpected symptoms appear.

Lack of information is one of the main reasons why 30 to 50 percent of patients do not use medicines as prescribed.

erally apply to OTC convenience containers, Taborsky says, but manufacturers may use the same procedures to test them. Whether any OTC convenience containers in fact meet the standards is unknown at this time, she says.

At its convention last March, USP voted to look into the problem of medicine storage.

"It can be a significant problem," says L. Timothy Grady, Ph.D., USP vice president and director of standard development, "when you carry medicine around in a poorly sealed container under high humidity, as occurs along the Gulf Coast. Carrying medicine in a pocket next to the body can raise the temperature." As some medicines break down, Grady says, they may no longer dissolve properly, and the body therefore can't use them. But this is hard to document, he says. "Someone who doesn't get blood pressure control for a few days may not notice it. Scientifically, you

Check-Off Chart

- Never stop medicine the doctor has told you to finish just because symptoms disappear.
- Ask the doctor periodically to reevaluate long-term treatments.
- If you have questions, talk to your pharmacist or doctor before using an OTC medicine the first time, especially if you use other medicine.
- Carefully read OTC medicine labels for ingredients, proper uses, directions, warnings, precautions, and expiration dates.
- Discard outdated medicine.

- Store medicine in the original container, where the label identifies it and gives directions. If, however, you choose to use an OTC convenience container, ask the pharmacist whether the container will affect your medicines' stability.
- Never store medicine in the bathroom. Unless instructed otherwise, keep it away from heat, light and moisture.
- Never store medicine near a dangerous substance, which could be taken by mistake.
- Never take someone else's medicine.
- Tell your health professional if you:
 - are breast-feeding or are, or may be, pregnant
 - are allergic to drugs or foods
 - have diabetes or kidney or liver disease
 - take other prescription or OTC medicines regularly
 - follow a special diet or take dietary supplements
 - use alcohol or tobacco.

Children and Medicine

- Keep all medicine out of children's reach. Some medicines, such as iron supplements, are very toxic to children.
- Use child-resistant caps, and never leave containers uncapped.
- Examine dose cups carefully. Cups may be marked with various measurement units and may not use standard ab-

NAME OF DRUG/ DIRECTIONS	SUN	MON	TUE	WED	THU	FRI	SAT

NAME OF DRUG/ DIRECTIONS	SUN	MON	TUE	WED	THU	FRI	SAT
DRUG A - 3 Times a day	8 12 5	8 12 5	8 12 5	8 12 5	8 12 5	8 12 5	8 12 5
DRUG B - once a day in A.M.	8	8	8	8	8	8	8
DRUG C - 3 Times a day	8 12 5	8 12 5	8 12 5	8 12 5	8 12 5	8 12 5	8 12 5

You can make photocopies of the top chart for your use. Write down the times to take your medicines and check them off after you've taken them. You can take it along if you're away from home a lot, or post it at home. The bottom chart example shows the user has taken all doses up to 5 p.m. on Tuesday of that week. (Source: "Using Your Medicines Wisely: A Guide for the Elderly," National Institute on Drug Abuse)

Abbreviations. Follow label directions. Never substitute a cup from another product.

- When using a dosing syringe with a cap, discard the cap before use.
- Never guess when converting measuring units—from teaspoons or tablespoons to ounces, for example. Consult a reliable source, such as the pharmacist.
- Never try to remember the dose used during previous illnesses; read the label each time.
- Check with the doctor or pharmacist before giving a child more than one medicine at a time.
- Never give medicine to children unless it is recommended for them on the label or by a doctor.
- Never use medicine for purposes not mentioned on the label, unless so directed by a doctor.
- Check with the doctor before giving a child aspirin products. Never give aspirin to a child or teenager who has or is

recovering from chickenpox, flu symptoms (nausea, vomiting or fever), or flu. Aspirin may be associated in such patients with an increased risk of Reye syndrome, a rare but serious illness.

Protect Against Tampering

- Read the label about the product's tamper-evident features.
- Look at the package for tampering signs such as broken seals, puncture holes, or open or damaged wrappings.
- Look at the medicine. Never take medicine that is discolored, has an unusual odor, or seems suspicious in some other way.
- Return suspicious medicine to the store manager or pharmacist.
- Look again when you take a dose. Never take medicine if you're not alert or can't see clearly. ■

—D.F.

sults of an FDA survey last winter show only 55 percent receiving written information beyond the label and warning stickers on the container.

In proposing its new program to provide useful, written patient information on prescription medicines, FDA urges patients to ask their health-care professionals questions about their medicines and urges professionals to counsel patients verbally and reinforce the verbal counseling with written information, says Thomas McGinnis, R.Ph., FDA associate director for pharmacy affairs.

Practically every pharmacy has a computer and printer, and patient information software is widely available, McGinnis says. "Yet only just over half the pharmacies generate computer information for patients. We would like that number to increase substantially."

FDA also would like better quality information.

"Too many brochures and leaflets give too much information about benefits and not enough about risks, such as adverse reactions and warnings," McGinnis says. "Some people think risk information will scare patients, and they won't take their medicines properly. That isn't true. Studies show patients

Facing a Hospital Stay?

For people in the hospital, the Institute for Safe Medication Practices, Warminster, Pa., offers this advice:

- Before taking medicine, to prevent mix-ups, make sure the medicine is the same size, shape, color, and dosage form as before. If not, ask why; the reason may be proper replacement with a generic.
- Before taking a new medicine, ask the name, dose, possible side effects, and reason for use.
- Have whoever gives you medicine check your ID bracelet or armband.
- Ask whether scheduled tests require drugs or dyes. If you've had a bad reaction to such substances before, tell the staff. ■

right side of the sheet. And if you wanted dosing information, you'd always look at the lower left."

Profiles and Reviews

In addition to generating patient information, pharmacists can use computers to maintain profiles on their patients.

Profiles are required by all states except Alaska, Arizona, Colorado, Maryland, and Missouri; neither are they required by the District of Columbia or Puerto Rico, says Carmen Catizone, executive director of the National Association of Boards of Pharmacy. Profiles may include patient information

Texas State Board of Pharmacy, in Austin. (An exception exists if the prescriber decides that providing the intended use isn't in the patient's best interest. Texas also strengthened its confidentiality requirements.)

"Having some idea of what the physician intends the drug to do," Morse says, "is a key ingredient to finding and identifying problems, working with the doctor to resolve those problems before they harm the patient, and then counseling the patient to get maximum benefit from the medication."

An additional benefit from a container label's stating the intended use, Morse says, is "patients are less confused about which of their medications treats which health condition."

Texas requires that patient counseling be reinforced with written information.

Except for Colorado, Connecticut, Hawaii, Maryland, Minnesota, South Carolina, Wyoming, the District of Columbia, and Puerto Rico, state laws have extended HCFA's rules to give all patients a *legal right* to counseling on their medicines, says Catizone.

"Patients should exercise that right," he says, "to make sure they've received the correct medicine and that they completely understand how to take that medicine and what side effects there may be." ■

Dixie Farley is a staff writer for FDA Consumer.

Treatment failure can be directly traced to medicine misuse.

can handle it and, in fact, want the information."

McGinnis says FDA wants pharmacists to dispense more comprehensive information about the medicine. Many handouts he and colleagues studied had only a few bullets of information or a simple paragraph.

The agency also wants to explore a standard format, he says, "as we did with food labeling, so that, for instance, if you wanted adverse reaction information, you'd always look at the lower

such as chronic conditions, medicines dispensed, allergies, and adverse reactions.

Pharmacists use profiles to meet another HCFA requirement: to review their Medicaid patients' medicine usage.

A recent Texas law requires doctors to include in all prescriptions the medicine's intended use. This law helps pharmacists better perform drug regimen reviews, says Steve Morse, R.Ph., assistant director of compliance with the

A Status Report On *Breast Implant Safety*

by Marian Segal



Signing a consent form is now part of the procedure for all women undergoing breast implant surgery. They also must be given information about the devices' known and possible risks.

Recently published studies have shown that women with silicone gel-filled breast implants do not have a greatly increased risk of some well-defined autoimmune diseases, which were among the serious health concerns surrounding the devices. These include potentially fatal connective tissue diseases such as scleroderma and lupus erythematosus.

Widespread reports of adverse reactions to silicone gel-filled implants and a lack of evidence supporting their safety led the Food and Drug Administration to order the devices off the market in April 1992. They remained available only to women in clinical studies, mostly women seeking breast reconstruction after breast cancer surgery. (See "Silicone Breast Implants: Available Under Tight Controls" in the June 1992 *FDA Consumer*.) Saline-filled implants were allowed to remain on the market for all uses.

Between Jan. 1, 1985, and March 16, 1995, FDA received 91,322 adverse reaction reports associated with silicone breast implants and 19,296 reports involving the saline implants.

The new studies do not, however, rule out the possibility that a subset of women with implants may have a small increased risk of these conditions, or that some women might develop other immune-related symptoms that don't conform to "classic" disease descriptions.

Nor did the studies address other important safety questions, including implant rupture rates and the incidence of capsular contracture (shrinking of scar tissue around the implant, which can cause painful hardening of the breast or distort its appearance). Answers to these and other questions await the results of new or ongoing studies.

Reasons for New Studies

Breast implants had been marketed since the early 1960s—several years be-

fore the first medical device law was enacted in 1976, charging FDA with regulation of medical devices. Every year, thousands of American women had had implant surgery for augmentation (to enlarge or reshape their breasts) or for reconstruction following mastectomy (removal of the breast) to treat breast cancer. Most of the implants consisted of a rubber silicone envelope filled with silicone gel; about 10 percent were filled with saline (salt water).

Under the 1976 law, implants and many other devices already in use were allowed to remain on the market, with the understanding that the agency would at some time ask manufacturers to submit scientific data showing these "grandfathered" products were safe and effective.

FDA requested this information for

silicone gel-filled implants in April 1991 in response to a growing number of adverse reaction reports that raised safety concerns about the devices. The data submitted did not prove the devices safe, as required by law, so the agency restricted their use to clinical trials designed to resolve the safety questions.

Between Jan. 1, 1985, and March 16, 1995, FDA received 91,322 adverse reaction reports associated with silicone breast implants and 19,296 reports involving the saline implants. These reports included risks clearly associated with the devices, as well as adverse effects attributed to the implants, but not proved to be linked to them. (See accompanying articles, "Known Risks of Breast Implants" and "Possible Risks of Breast Implants.")

Silicone Implant Studies

Some recent studies comparing the rates of immune-related diseases in women with implants versus those without implants have provided reassurance that women with implants are not at a greatly increased risk of these disorders.

The largest of these retrospective, or "look-back," studies is the Harvard Nurses' Health Study. The study used data from 87,501 nurses followed for other research purposes from 1976 through May 31, 1990, before there was widespread media coverage of the possible association between breast implants and connective tissue disease. None of the women had connective tissue disease at the start of the study.

In an article published in the June 22, 1995, *New England Journal of Medicine*, the researchers reported that 516 of the nurses had developed definite connective tissue diseases. Women with breast implants numbered 1,183. The types of implants included 876 silicone gel-filled, 170 saline-filled, 67 double lumen (silicone gel-filled implants with a saline-filled outer envelope), 14 polyurethane-coated, and 56 of unknown type. Only three of the 516 women with definite connective tissue disease had implants (one silicone-gel filled, one saline, and one double lumen).

The authors reported they "did not find an association between silicone breast implants and connective tissue disease, defined according to a variety

Polyurethane-Coated Implants

About 110,000 women have silicone gel-filled implants with a polyurethane coating, intended to reduce the risk of capsular contracture. In April 1991, an FDA analysis showed that polyurethane foam could break down under human body conditions to form a chemical called TDA, which can cause cancer in animals. As a result, the manufacturer immediately stopped selling the product.

Recently, however, a study to measure TDA in women with polyurethane implants found that a woman's risk of cancer from exposure to TDA released by the implant is negligible—about one in a million over a lifetime. FDA considers it unlikely that even one woman would develop cancer from these implants. The study supports the agency's original recommendation that women who are not having problems should not have the implants removed solely because of concern about cancer from TDA exposure. ■

—M.S.

of standardized criteria, or signs and symptoms of these diseases.”

Similarly, a 1994 study conducted at the Mayo Clinic found no increased risk of connective tissue diseases among implant recipients. The investigators based their conclusion on comparison of the medical histories of 749 women with breast implants in Olmsted County, Minn., with a similar group of women who did not have implants.

“Because of the limitations in the size and type of the studies, however, the true risk of these diseases is not known,” says S. Lori Brown, Ph.D., a research scientist officer in the epidemiology branch of the agency’s Center for Devices and Radiological Health. “Although the criteria others may be using to assess those studies show that some concerns are eliminated,” Brown says, “unfortunately, they don’t rule out a small, but significant, increased risk.”

An immunology and epidemiology expert, Brown explains that an inherent problem in the studies is that some connective tissue diseases are extremely rare. “If you have a disease that has an incidence of 1 in 100,000 in the general population, for example, and you do a study of 750 women with implants, like the Mayo Clinic Study, then you wouldn’t really expect to see even a single case of that disease,” she says, “unless there’s an exceedingly high—more than a hundredfold—increase in risk.”

Small studies like these can rule out huge risks, but not smaller, yet significant risk increases that would only show up in studies that include several thousand women with implants, Brown says. Nor do the studies fully examine or answer whether the implants might in some women lead to symptoms not typical of classical disease manifestations.

Other Concerns

Brown also stresses that connective tissue diseases are not the only issue of concern, especially since they may affect a much smaller proportion of women with implants. The larger issue, she says, is the local complications that are clearly related to breast implants, such as rupture and migration of the silicone gel, capsular contracture, and infection.

Some recent retrospective studies comparing the rates of immune-related diseases in women with implants versus those without implants have provided reassurance that women with implants are not at a greatly increased risk of these disorders.

Immunology Tests

Several laboratories are offering tests that claim to detect levels of antibodies to silicone that presumably indicate a leaking or ruptured implant.

FDA has not cleared or approved these tests for such purposes, and the agency has sent letters to several companies, warning of future regulatory action if they continue to promote the devices without a premarket approval application.

“There are important unresolved issues with these tests,” says Peter Maxim, Ph.D., chief of the Center for Devices and Radiological Health’s immunology branch of the division of clinical laboratory devices. “For one thing, the very existence of silicone antibodies has not been proven to the satisfaction of all scientists,” he says. “Secondly, if antibodies are detected, is there in fact a correlation with the presence or the status of implants, or do they reflect prior environmental exposure? Silicone is in a myriad of products, including foods, medicines, and antiperspirants absorbed by the skin, to name a few.”

The next problem, Maxim says, is that there are claims that extremely high antibody levels may indicate a leaking or ruptured implant. This, then, raises the question of what medical intervention, if any, should be taken.

Sahar M. Dawisha, M.D., a rheumatologist in FDA’s division of general and restorative devices, adds that no one really knows what the clinical significance of an antibody to silicone means or at what level it is harmful.

“Furthermore,” she says, “in autoimmune or connective tissue disease—where antibody tests are generally used—the presence of antibodies doesn’t define the disease. A disease is defined by clinical signs and symptoms, and antibodies are used as supporting evidence.”

Finally, John Nagle, consumer safety officer in the Center for Devices and Radiological Health’s diagnostic devices branch, says, “The tests themselves may be harmless, but they sure are expensive, somewhere between \$500 and \$1,000,” adding that “a lot of them are being done for litigation purposes rather than to help the patient medically.” ■

—M.S.

Known Risks of Breast Implants

Surgical Risks

- possible complications of general anesthesia, as well as nausea, vomiting and fever
- infection
- hematoma (collection of blood that may cause swelling, pain and bruising, perhaps requiring surgical draining)
- hemorrhage (abnormal bleeding)
- thrombosis (abnormal clotting)
- skin necrosis—skin tissue death resulting from insufficient blood flow to the skin. The chance of skin necrosis may be increased by radiation treatments, cortisone-like drugs, an implant too large for the available space, or smoking.

Implant Risks

- capsular contracture (hardening of the breast due to scar tissue)
- leak or rupture—silicone implants may leak or rupture slowly, releasing silicone gel into surrounding tissue; saline implants may rupture suddenly and deflate, usually requiring immediate removal or replacement
- temporary or permanent change or loss of sensation in the nipple or breast tissue
- formation of calcium deposits in surrounding tissue, possibly causing pain and hardening
- shifting from the original placement, giving the breast an unnatural look
- interference with mammography readings, possibly delaying breast cancer detection by “hiding” a suspicious lesion.

Also, it may be difficult to distinguish calcium deposits formed in the scar tissue from a tumor when interpreting the mammogram. *When making an appointment for a mammogram, the woman should tell the scheduler she has implants to make sure qualified personnel are on-site. At the time of the mammogram she should also remind the technician she has implants before the procedure is done, so the technician can use special techniques to obtain the best mammogram and to avoid rupturing the implant.* ■

—M.S.

Possible Risks of Breast Implants

- Autoimmune-like disorders—signs include joint pain and swelling; skin tightness, redness or swelling; swelling of hands and feet; rash; swollen glands or lymph nodes; unusual fatigue; general aching; greater chance of getting colds,

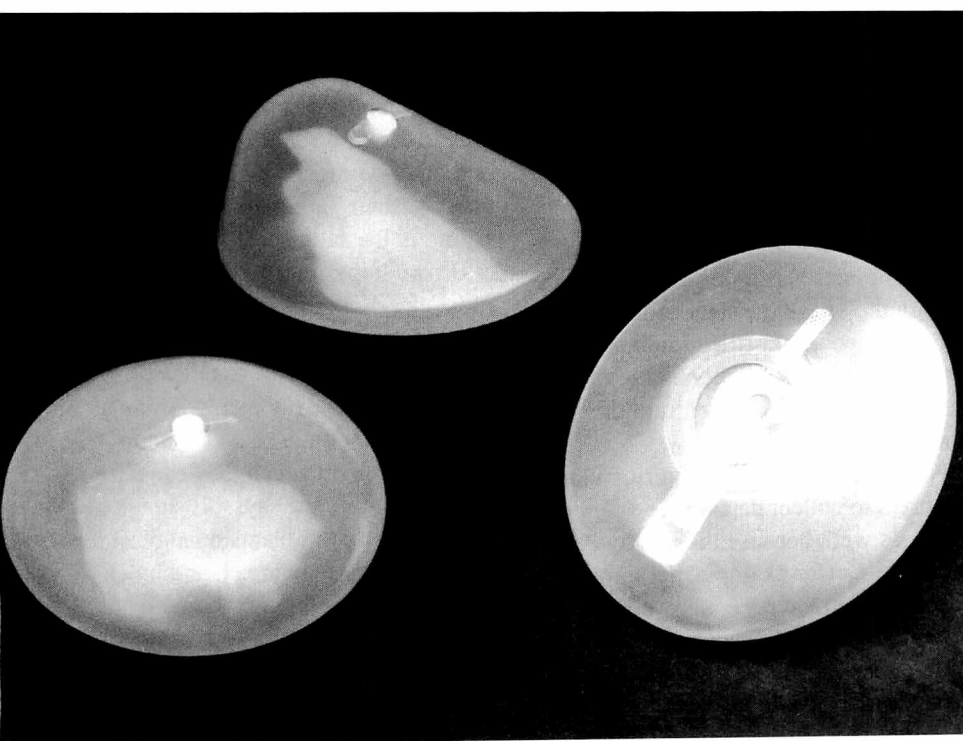
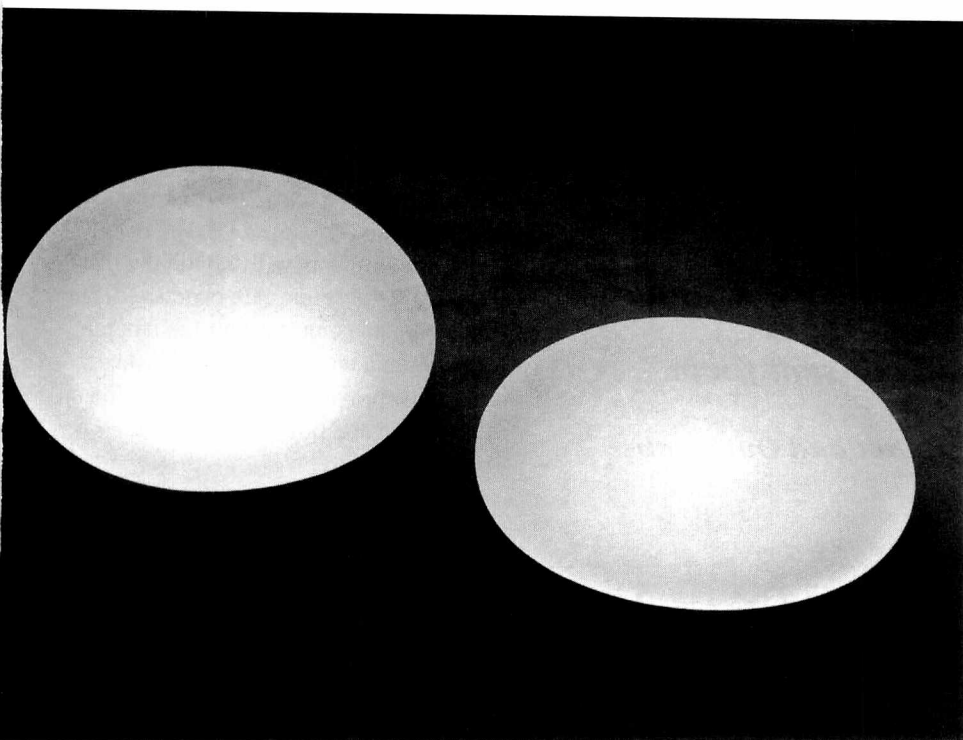
viruses and flu; unusual hair loss; memory problems; headaches; muscle weakness or burning; nausea or vomiting; and irritable bowel syndrome.

Recent studies have shown, however, that there is not a large increased risk of traditional autoimmune, or connective

tissue disease, from silicone gel implants.

- Fibrositis/fibromyalgia-like disorders (pain, tenderness and stiffness of muscles, tendons and ligaments). ■

—M.S.



Top: Silicone gel-filled breast implants.

Bottom: Saline-filled breast implants.

(Photos courtesy of Mentor H/S, Santa Barbara, Calif.)

"Of the two groups of women who consider getting implants—for breast reconstruction or for augmentation," Brown says, "the larger group wants them for cosmetic purposes. These are healthy women who may go out and get implants without a clear picture of what the possible risks are. They may end up going back in for surgery time and again and never be happy with the cosmetic effect."

In testimony before a congressional subcommittee in August 1995, FDA Commissioner David A. Kessler, M.D., stated that "Published studies to date suggest a rupture rate between 5 and 51 percent—an enormous range—and unfortunately, we do not know with any confidence where within that range the real rupture rate lies." He also cited two studies that indicate the risk of rupture increases as the implants age.

Another concern—increased risk of breast cancer—has not been borne out by studies. "Several studies have indicated there is no increased risk of breast cancer in women with implants," Brown says. However, she adds, these women are not yet in the age group that is more prone to breast cancer, and it remains to be seen whether they will eventually have a higher incidence of breast cancer than women without implants. Long-term studies to look at this are under way.

Manufacturers' Studies

The events that led to removal of silicone implants from the market made it clear that prospective, or forward-looking, studies were also needed to answer important safety questions. Implant manufacturers agreed to conduct human trials in three phases: urgent need, adjunct, and core studies.

"The purpose of the first phase [urgent need] actually was simply to quickly provide implants to women who were already in the process of getting them for breast reconstruction or for another medical reason, and to bridge the time until the adjunct studies were begun," says Sahar M. Dawisha, M.D., a rheumatologist and medical officer who joined FDA's division of general and restorative devices in April 1993.

The women did, however, have to sign an informed consent form that summa-

“Women considering saline implants should ask their doctor for a copy of the manufacturer’s information sheet, a copy of the product insert sheet for the specific implant to be used, and a copy of the hospital informed consent form.”

—Barbara Stellar, FDA Breast Implant and Outreach

Coordinator

alized the risks and benefits of the implants. This form had not previously been required.

“The second phase, or adjunct, studies were intended to follow reconstruction patients for five years to assess short-term safety data, including rates of capsular contracture, rupture, and complications such as infection and hematoma [collection of blood that may cause swelling, pain and bruising],” Dawisha says. “These studies are open to all women wanting breast reconstruction with implants because of mastectomy, traumatic injury to the breast, or a disease or congenital disorder causing a severe breast abnormality. They do not include augmentation patients.”

Mentor Corporation of Santa Barbara, Calif., began adjunct studies in 1992. According to Pamela Powell of the company’s Clinical Programs Department, as of July 5, 1995, 12,125 patients were enrolled in the studies.

The third phase, or core studies, Dawisha says, were intended to determine the full safety and effectiveness profile of the device, including rupture rates, quality-of-life benefits, extent of interference with mammography, and

many more safety concerns—including rheumatologic assessments—that would need a large number of women. They were also to include augmentation patients. The sponsors, however, have not initiated these studies.

Saline Implants

Although many of the local complications of gel-filled implants are also associated with saline implants, the latter were permitted to remain on the market unrestricted for both reconstruction and augmentation. FDA considers saline-filled implants less risky, because although they have the same silicone rubber envelope as gel-filled implants, leakage or rupture would release only salt water, not silicone gel, into the body.

Nevertheless, FDA is requiring manufacturers to collect data on the saline implants as well, because the incidence of known risks (for example, deflation and capsular contracture) is not well defined. When the Medical Device Amendments were passed, it was determined that these devices would also eventually require premarket approval. In January 1993, FDA notified saline implant

manufacturers that they would have to submit safety and effectiveness data for their products. In December 1994, the agency told them what type of safety and effectiveness data were needed, and delineated objectives and time frames for the trials.

Saline implants will stay on the market while the studies are conducted, but the companies must report the laboratory, animal and clinical data in stages, and must provide written information on the known and possible risks of their products.

“Women considering saline implants should ask their doctor for a copy of the manufacturer’s information sheet, a copy of the product insert sheet for the specific implant to be used, and a copy of the hospital informed consent form,” says Barbara Stellar, FDA’s breast implant information and outreach coordinator.

Stellar recommends women be given these documents at least a month before surgery is planned, if possible, so they can thoroughly discuss benefits and possible risks with surgeons, radiologists, and other women. These women should also ask their physicians about participating in the saline breast implant trials.

Brown hopes that further studies will more clearly define risks associated with all types of implants.

“We need to be able to tell women considering breast implants—whether for augmentation or reconstruction—the specific risks on which they can base their decision,” she says. “It should be made clear that implants do not last forever, that they may break, and in what time period it is thought they might break. Most women have no idea implants break and there’s very little information about rupture rates.

“The same is true for other complications, some of which may require further surgery or may cause the woman to be displeased with the cosmetic effect, which, of course, is the reason she got them,” Brown says. “For a product that a person is putting in her body presumably for 20 years or more, we should have this information.” ■

Marian Segal is a member of FDA’s public affairs staff.

Information Packet

To obtain a comprehensive packet of information on breast implant issues, request FDA’s publication, “Breast Implants, An Information Update,” by calling the agency’s breast implant information line at (1-800) 532-4440. ■

Guarding Against GLAUCOMA



by S.J. Ackerman

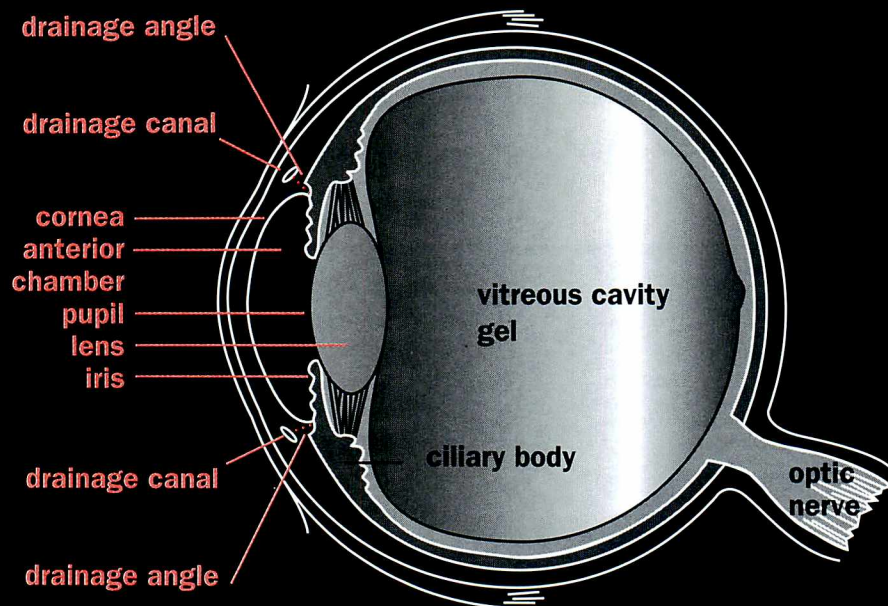
An outstanding scholar still in his 30s, John felt his "sight getting weak and dull"—occupational eyestrain, he supposed. Soon his left eye dimmed, starting from the left side. Then his right eye failed, "perceptibly and gradually over three years." By age 43, he was totally blind.

That was in 1652. John Milton triumphed over blindness, still serving the British foreign office and writing literary classics like "Paradise Lost." Yet he

never ceased lamenting "how my light is spent/Ere half my days, in this dark world and wide."

What relegated him to seeing "a universal blank" was probably open-angle glaucoma, which today needlessly blinds 80,000 Americans each year. It causes another 900,000 to lose some vision. Yet now we have means Milton lacked to thwart "the sneak thief of sight" with a number of treatments approved by the Food and Drug Administration.

Eye Drainage



Aqueous humor, an eye fluid unrelated to tears, originates in the ciliary body just behind the iris (the colored part of the eye). This fluid fills and inflates the anterior chamber, located between the iris and the cornea (clear outer eye covering). The aqueous humor nourishes eye tissue and keeps it from collapsing. The fluid normally maintains a pressure of 10 to 20 millimeters of mercury by draining through drainage canals and angles. In glaucoma, the aqueous humor does not drain properly, backs up, and exerts pressure on the gel in the vitreous cavity, eventually affecting the optic nerve and impairing vision.

Glaucomas are a group of diseases sharing certain features, commonly including high intraocular pressure (IOP), damaged optic nerves, and loss of peripheral vision. Early detection can contain two glaucomas: chronic (sometimes called common) and acute.

Primary open-angle glaucoma (chronic glaucoma) affects mostly adults over age 35. This most prevalent glaucoma is the sneak-thief disease without noticeable symptoms. By the time it's detected, it has started doing damage.

The uncommon primary angle-closure glaucoma (acute glaucoma) may seem the opposite of common glaucoma, erupting in a sudden, violent attack. It's also possible to get both common and acute ("combined-mechanism") glaucoma together. The unusual low-pressure glaucoma is another variant. Regular eye examinations can help protect

against the onset of open-angle and closed-angle glaucomas.

The cornea is the clear outer covering of the eye. Separating it from the iris (the colored part) is the anterior chamber, a space filled and inflated by aqueous humor. This fluid (unrelated to the tears which bathe the outside surface of the cornea) originates in the ciliary body just behind the iris. It circulates in the anterior chamber, nourishing the eye's delicate tissue and keeping it from collapsing, at a pressure usually measuring between 10 and 20 millimeters of mercury. To maintain equilibrium, the aqueous humor drains through a porous tissue in the angle in front of the iris, where it meets the cornea, called the trabecular meshwork.

If the aqueous humor cannot drain properly, either because the drainage canals become clogged (as in chronic glau-

coma) or because the iris is pushing against the cornea (as in angle-closure glaucoma), it backs up, exerting pressure on the gel in the vitreous cavity at the center of the eye. Eventually the building pressure affects the delicate optic nerve at the rear. Since the optic nerve transmits visual images to the brain, damage to parts of it correspondingly reduces vision.

Pressure over 21 millimeters may prompt concern, while pressure over 24 mm can indicate glaucoma level—but not always. These measures are not absolute. Some individuals tolerate higher pressures than others. Half the people with undiagnosed glaucoma have pressures below 22 mm, while others with higher pressures never develop glaucoma, with optic nerve damage causing loss of vision. Low-pressure glaucoma can be especially elusive. Moreover, tonometry (the measurement of eye pressure) can be affected by many factors, even by the time of day (IOP measuring highest in the morning).

Tonometry measures the force necessary to indent the eye. One method is to anesthetize the eye, then press a tonometer onto it. Another is to measure the force needed for a puff of air to indent the cornea.

While widespread eye-puff testing at health fairs detects pressure levels, a more thorough examination calls for an ophthalmoscopic test enabling doctors to see into your eye to examine the optic nerve for damage or a high ratio of its central cup to the surrounding disc. (See accompanying article.) They must also take personal characteristics into account in evaluating an individual's risk of glaucoma.

Chronic Glaucoma

Physicians do not like to begin therapy prematurely in individuals identified as at risk for chronic glaucoma. Patients who are considered "pre-glaucoma" should have their eyes examined as often as their doctors think necessary.

Increasingly frequent dosages of medications may be needed as the eye develops tolerance to the medicine. Drug therapy can effectively thwart the progress of glaucoma, but it can mean taking an escalating variety of eye drops

and pills, with various side effects, for life.

Topical medications for glaucoma are serious medicine, not to be confused with over-the-counter eye drops for easing common eye irritations. The most popular maintenance eye drop, Timoptic (timolol maleate), may have side effects on the nerves, digestion, vision, skin, respiration, and heart of some individuals. Timoptic is a beta-blocker eye drop. Taken usually twice daily, beta blockers decrease production of aqueous humor. Side effects may include lowered pulse rate and blood pressure, exacerbated asthma, and fatigue. In June 1995, British researchers reported that drops in this class may be related to breathing impairment in elderly people with previously unrecognized respiratory problems.

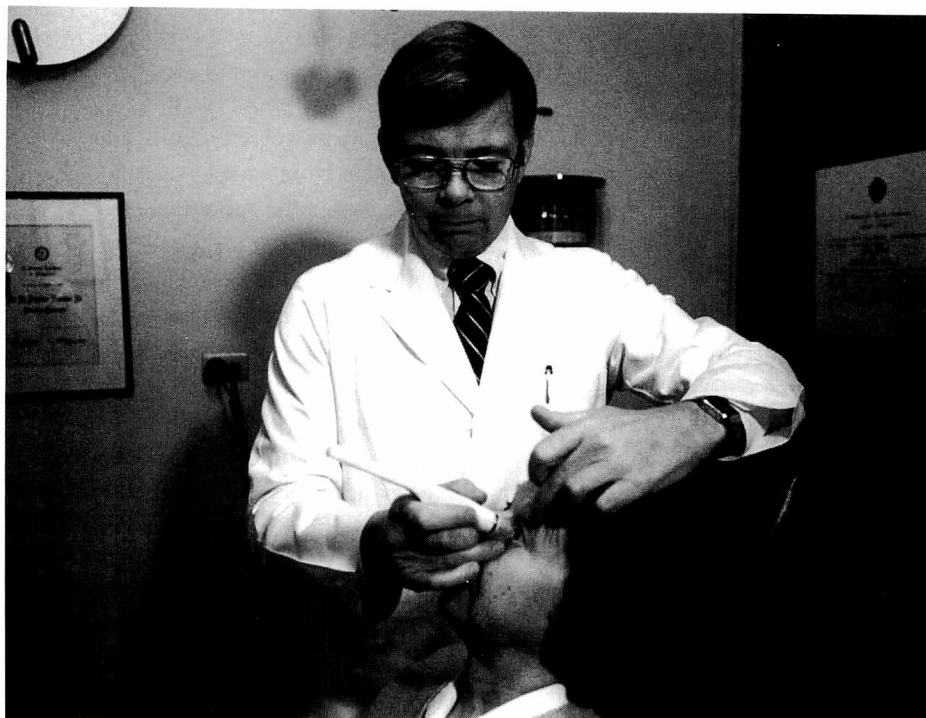
Timoptic's century-old predecessor, pilocarpine, requires more frequent use to do its job, increasing drainage of aqueous fluid in both open- and closed-angle glaucomas. Pilocarpine is a miotic, designed to increase aqueous fluid drainage. Because miotics work by making the pupil smaller, they can result in dim vision and may increase the risk of cataracts.

Another class of medications, adrenergic agonists, such as epinephrine, also increases aqueous humor drainage, with possible side effects of allergic reactions, blurred vision, headache, and increased heart rate. Alpha adrenergic agonists decrease aqueous humor production after surgery or aid patients taking maximum dosages of other medications. Side effects include red eyes, allergic reactions, and dry mouth.

Diamox carbonic anhydrase inhibitor tablets, like beta blockers, decrease production of aqueous fluid, but these drugs seem to provoke more prominent side effects in some people, including mental depression, kidney stones, tingling in the hands and feet, and sometimes anemia.

FDA's May 1995 approval of a Carbonic Anhydrase Inhibitor in eye drop form as Trusopt (dorzolamide) provides a medication that may have fewer and reduced incidence of these severe side effects.

Since reactions to medications vary so much from person to person, a drug



An ophthalmologist measures a patient's eye pressure with a tonopen, one of several devices for measuring intraocular pressure to determine if a person may be developing glaucoma.

(Photo courtesy of the Glaucoma Research Foundation)

that causes one individual problems may be easily tolerated by another. An appropriate drug regimen, therefore, needs to be worked out carefully between patient and health professional.

Glaucoma medications are potent drugs. Those who take them should consult a pharmacist to be certain that they won't interact adversely with any other prescriptions or over-the-counter drugs being taken. For example, some over-the-counter products, including decongestants, may not be suited for people at risk of glaucoma.

Acute Glaucoma

A century after Milton gradually lost his sight, composer Johann Sebastian Bach went blind in a violent flash, probably from acute (closed-angle) glaucoma. Bach thought he aggravated his weak vision by a lifetime of copying music in the dim light of church organ lofts; his portrait shows a characteristic squint. Though a surgeon claimed to have operated successfully on Bach's eyes, the composer's vision failed again in a few days. He died a few months

later, after a futile—and possibly harmful—second operation.

Acute glaucoma may seem the opposite of open-angle because it erupts in violent attacks and intense pain, rather than emerging subtly. Yet patients may not notice minor preliminary episodes, which pave the way for serious seizures. People beset by a major seizure must get to an ophthalmologist, or at least a hospital emergency room, promptly to save their vision.

Monitoring can protect people prone to acute glaucoma from major attacks.

Acute glaucoma attacks are emergencies because aqueous fluid gets trapped in the angle of the eye suddenly. Having nowhere to go, its abrupt backup can damage the optic nerves, eventually squashing them irreparably.

Regular, thorough eye checkups can detect the risk of acute glaucoma. High IOP, family history, and other indicators resemble those for common glaucoma, but very farsighted people and those of Asian descent are most vulnerable to angle-closure glaucoma. Once a major angle-closure attack seems imminent,

Risks and Responses

Elevated eye pressure and detectable damage to the optic nerves are significant risk indicators for glaucoma. To prevent needless blindness from undetected, untreated glaucoma, the American Academy of Ophthalmology offers additional guidelines for assessing risk.

The academy's guidelines include comparing the diameter of the eye's cup to that of its disc to obtain a physical gauge of the likelihood of glaucoma. Estimates are made vertically along an imaginary line drawn through the center of the disc from the 12 o'clock to the 6 o'clock position. The normal optic nerve illustrated with a small cup has a cup-to-disc ratio of less than 0.5, indicating a low probability of glaucoma. Moderately advanced cupping, with a cup-to-disc ratio of 0.6 to 0.8 and a neural rim starting to thin, increases the suspicion of glaucoma. Almost total cup-to-disc ratio of 0.9, exhibiting a very thin neural rim, creates a high level of glaucoma suspicion.

Personal history factors also enter the assessment, as shown in the chart below. The greater the number in the third column, the greater the risk.

Variable	Category	Weight
Age	younger than 50 years	0
	50-64 years	1
	65-74 years	2
	older than 75 years	3
Race	Caucasian/other	0
	African American	2
Family History of Glaucoma	Negative or positive in non-first degree relatives	0
	Positive for parents	1
	Positive for siblings	2
Last Complete Eye Examination	Within last two years	0
	2-5 years ago	1
	more than 5 years ago	2

Level of Glaucoma Risk (Total Score)

High	4 or greater
Moderate	3
Low	2 or less

Other variables in risk assessment include extreme nearsightedness or farsightedness, high blood pressure, and steroid use.

People at risk of glaucoma should faithfully have eye checkups at the intervals their ophthalmologists recommend. Everyone over 40 should have a full eye examination every two years, regardless of risk factors; African Americans should be vigilant after age 30. Adult relatives of persons diagnosed with glaucoma should have regular eye checkups. Glaucoma seems to be hereditary, and even cousins may be at risk if you are.

Glaucoma treatment decisions are personalized. Even eye color may affect the rate at which a person absorbs eye medications. ■

preventive laser surgery is advisable, since an attack can damage the eye quickly.

Regular monitoring of people diagnosed with narrow-angle conditions looks for increased IOP or tissue damage. Telltale symptoms of an attack include blurred vision, halos around lights, and eye pain sharp enough to induce vomiting. The eye becomes reddened, feeling as if it could burst (though it can't). Persons experiencing such attacks should go immediately to an ophthalmologist or an emergency room, ideally calling in advance to ready staff to receive a case of closed-angle, acute glaucoma.

Emergency procedures use eye drops and clinical eye massage to reduce IOP and prevent the eye from hardening. Once stabilized, the patient may have laser surgery to create an artificial opening for aqueous fluid to drain. Acute glaucoma usually attacks one eye before the other, so laser surgery on the unaffected eye may be recommended at the time to forestall a second attack there.

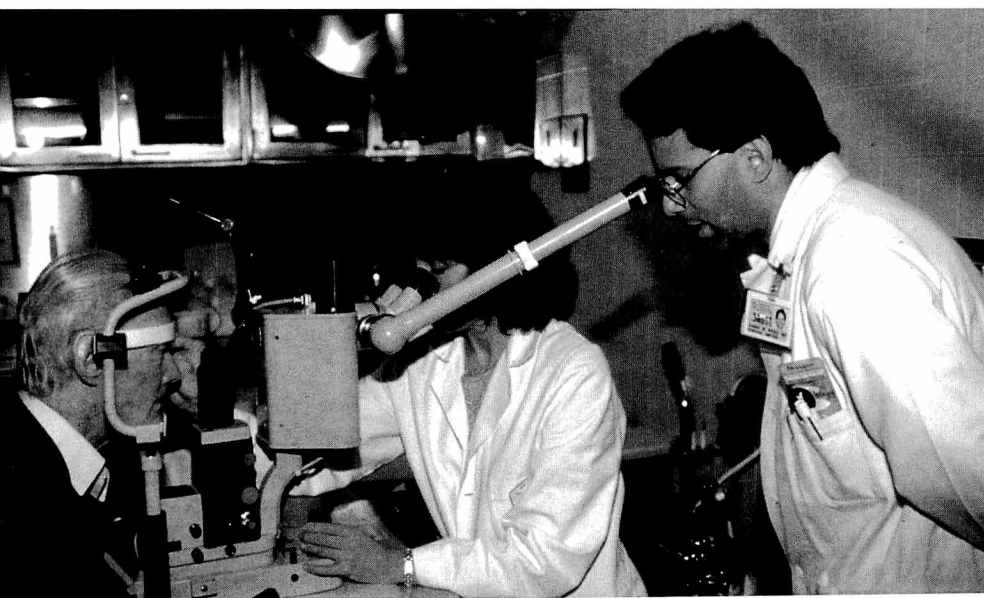
Laser Surgery

Some patients may require traditional scalpel surgery, but in recent years laser operations have come into favor. Laser surgery can't repair existing damage, but it usually stops glaucoma, both in acute emergencies and open-angle cases. It may involve minor side effects, includ-

For More Information

For more information about glaucoma, contact:

- your doctor
- American Academy of Ophthalmology's Glaucoma 2001 Campaign (for chronic open-angle glaucoma): (415) 561-8500
- Glaucoma Research Foundation: (1-800) 826-6693 or (415) 986-3162
- National Eye Institute: (301) 496-5248. ■



At top, the shadow of a penlight beam on the patient's nose can help doctors determine if a person predisposed to angle closure has narrowed angles. The penlight beam is directed at the patient's iris. If there is no shadow on the nose, then the angles are likely wide enough to dilate.

Below, clinicians use laser surgery to reduce a patient's intraocular pressure. Laser surgery succeeds in reducing intraocular pressure in about 75 percent of first treatments. Postoperative complications include inflammation and elevated pressure. Within two to five years, about half of patients will need additional medical or surgical treatment.

(Photos courtesy of the American Academy of Ophthalmology)

ing restrictions on wearing contact lenses, but its risks are quite low. Sometimes it must be repeated if its drainage openings begin to close.

Light amplification by stimulated emission of radiation—LASER—sends a uniform, focused beam of light to pinpoint applications. In glaucoma surgery for angle closure, the laser creates a minute hole in the iris, just large enough to allow aqueous fluid to flow freely.

Despite its high-tech wizardry, most laser surgery for glaucoma seems quite undramatic to the patient undergoing it. (See "Light for Sight," *FDA Consumer*, July-August 1990.) An acute glaucoma patient peers into the eyepiece on one side of a boxy device while a surgeon manipulating controls peers into an eyepiece opposite. There's little or no addi-

tional pain, often not even unpleasant sensation, as the surgeon beams an intense beam of light to "burn" an escape channel for aqueous fluid, usually in the upper edge of the iris.

The Nd:YAG (neodymium:yttrium aluminum garnet crystal) laser has emerged with several advantages over the earlier argon laser, including lower energy requirement, fewer pulses, reduced obstruction, and a lower rate of subsequent closure of incisions. Its portability allows the YAG laser to serve even remote Inuit villages in Alaska previously inaccessible for sophisticated optical surgery.

No wonder that laser surgery in just 25 years has largely displaced traditional scalpel surgery, which involves hospital stays and higher risks. Its low risk allows use earlier in the course of the disease, when its potential benefit is greater.

On the Horizon

Diligence in countering early the subtle onset of glaucoma is the best protection. Research is making such diligence easier.

Ongoing research aims to simplify dosage demands while reducing side effects. For instance, the nuisance of taking preventive eye medications several times a day discourages some people from protecting themselves fully. Work is under way to perfect a once-a-week eye preparation and one-a-day eye drops to ease the use of topical eye medications. Already, dispenser tips that measure more consistent doses of eye drops are improving their use.

Even the standard course of escalating treatment for common glaucoma is being reconsidered. The practice more common in Europe suggests that reversing this order by starting with surgery may be promising. In August 1993, the National Eye Institute announced the Collaborative Initial Glaucoma Treatment Study to compare the long-term effect of treating newly diagnosed primary open-angle glaucoma with standard treatment versus immediate laser surgery. ■

S.J. Ackerman is a writer in Washington, D.C.



SNAKES

Treating And Preventing Venomous Bites

by John Henkel

They fascinate. They repel.

Some pose a danger. Others are harmless.

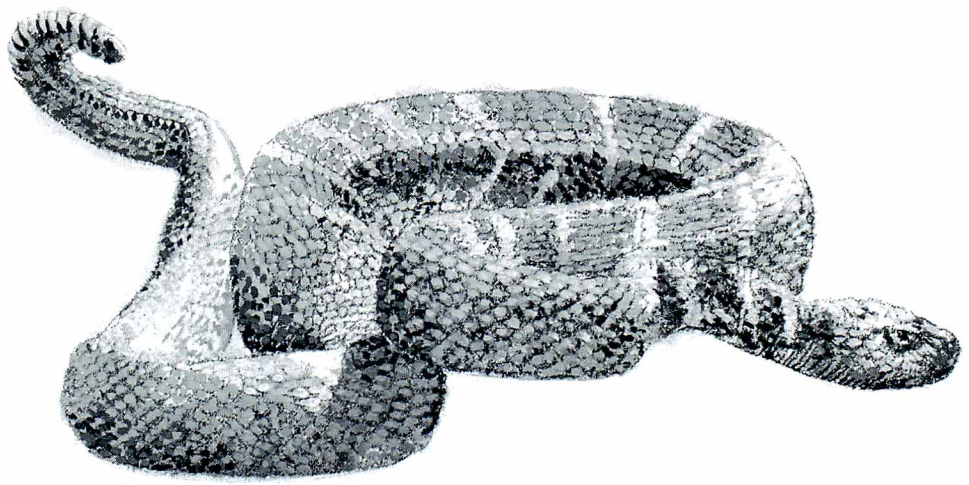
And whether they are seen as slimy creatures or colorful curiosities, snakes play important environmental roles in the fragile ecosystems of the nation's wildlife areas.

People who frequent these wilderness spots, as well as those who camp, hike, picnic, or live in snake-inhabited areas, should be aware of potential dangers posed by venomous snakes. Every state but Maine, Alaska and Hawaii is home to at least one of 20 domestic poisonous snake species. A bite from one of these, in which the snake may inject varying degrees of toxic venom, should always be considered a medical emergency, says the American Red Cross.

About 8,000 people a year receive venomous bites in the United States; nine to 15 victims die. Some experts say that because victims can't always positively identify a snake, they should seek prompt care for any bite, though they may think the snake is nonpoisonous. Even a bite from a so-called "harmless" snake can cause an infection or allergic reaction in some people.

Medical professionals sometimes disagree about the best way to manage poisonous snakebites. Some physicians hold off on immediate treatment, opting for observation of the patient to gauge a bite's seriousness. Procedures such as fasciotomy, a surgical treatment of tissue around the bite, have some supporters. But most often, doctors turn to the antidote to snake venom—antivenin—as a

rattlesnakes



copperheads

reliable treatment for serious snakebites.

Antivenin is derived from antibodies created in a horse's blood serum when the animal is injected with snake venom. In humans, antivenin is administered either through the veins or injected into muscle and works by neutralizing snake venom that has entered the body. Because antivenin is obtained from horses, snakebite victims sensitive to horse products must be carefully managed. The danger is that they could develop an adverse reaction or even a potentially fatal allergic condition called anaphylactic shock.

The Food and Drug Administration regulates antivenins as part of its oversight of biological products. The agency requires certain criteria to be met before these materials are sold, including standards for purification, packaging and po-

tency. FDA also regulates antivenin labeling, ensuring that data on potential side effects and other pertinent information are available. The agency also periodically inspects antivenin production facilities to ensure compliance with regulations.

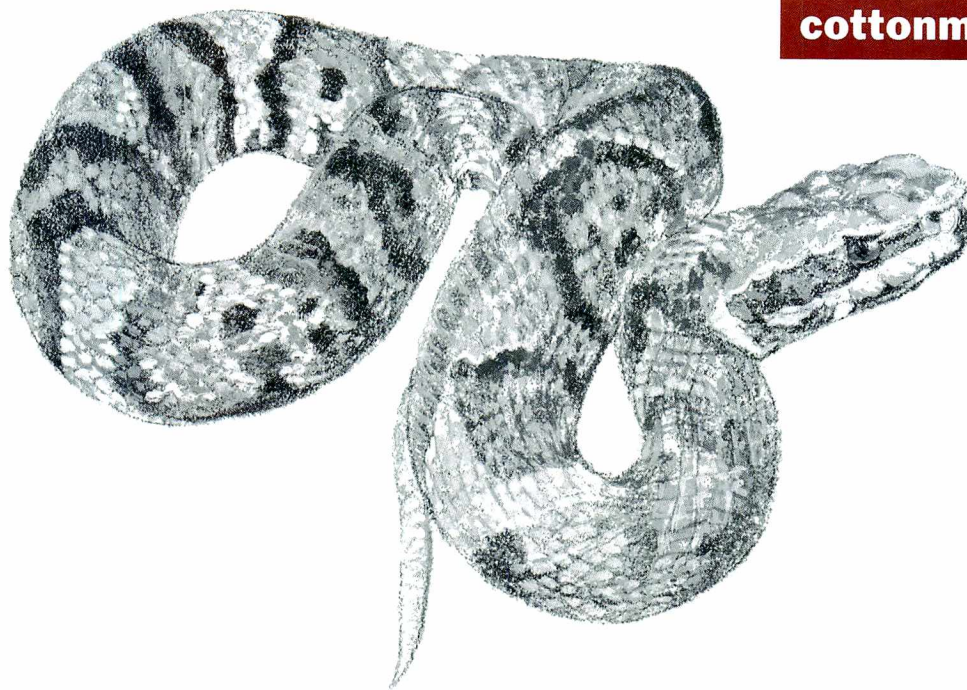
Types of Poisonous Snakes

Two families of venomous snakes are native to the United States. The vast majority are pit vipers, of the family Crotalidae, which include rattlesnakes, copperheads and cottonmouths (water moccasins). Pit vipers get their common name from a small "pit" between the eye and nostril that allows the snake to sense prey at night. They deliver venom through two fangs the snake can retract at rest but can spring into biting position rapidly. About 99 percent of the venom-

ous bites in this country are from pit vipers. Some—Mojave rattlesnakes or canebrake rattlesnakes, for example—carry a neurotoxic venom that can affect the brain or spinal cord. Copperheads, on the other hand, have a milder and less dangerous venom that sometimes may not require antivenin treatment.

The other family of domestic poisonous snakes is Elapidae, which includes two species of coral snakes found chiefly in the Southern states. Related to the much more dangerous Asian cobras and kraits, coral snakes have small mouths and short teeth, which give them a less efficient venom delivery than pit vipers. People bitten by coral snakes lack the characteristic fang marks of pit vipers, sometimes making the bite hard to detect.

Though coral snakebites are rare in



coral snakes

the United States—only about 25 a year by some estimates—the snake’s neurotoxic venom can be dangerous. A 1987 study in the *Journal of the American Medical Association* examined 39 victims of coral snakebites. There were no deaths, but several victims experienced respiratory paralysis, one of the hazards of neurotoxic venom.

Some nonpoisonous snakes, such as the scarlet king snake, mimic the bright red, yellow and black coloration of the coral snake. This potential for confusion underscores the importance of seeking care for any snakebite (unless positive identification of a nonpoisonous snake can be made).

The bites of both pit vipers and coral snakes can be effectively treated with antivenin. But other factors, such as time elapsed since being bitten and care

taken before arriving at the hospital, also are critical (see accompanying article).

First Aid for Snakebites

Over the years, snakebite victims have been exposed to all kinds of slicing, freezing and squeezing as stopgap measures before receiving medical care. Some of these approaches, like cutting into a bite and attempting to suck out the venom, have largely fallen out of favor.

“In the past five or 10 years, there’s been a backing off in first aid from really invasive things like making incisions,” says Arizona physician David Hardy, M.D., who studies snakebite epidemiology. “This is because we now know these things can do harm and we don’t know if they really change the outcome.”

Many health-care professionals em-

brace just a few basic first-aid techniques. According to the American Red Cross, these steps should be taken:

- Wash the bite with soap and water.
- Immobilize the bitten area and keep it lower than the heart.
- Get medical help.

“The main thing is to get to a hospital and don’t delay,” says Hardy. “Most bites don’t occur in real isolated situations, so it is feasible to get prompt [medical care].” He describes cases in Arizona where people have caught rattlesnakes for sport and gotten bitten. “They waited until they couldn’t stand the pain anymore and finally went to the hospital after the venom had been in there a few hours. But by then, they’d lost an opportunity for [effective treatment],” which increased the odds of long-term complications.

Some medical professionals, along with the American Red Cross, cautiously recommend two other measures:

- If a victim is unable to reach medical care within 30 minutes, a bandage, wrapped two to four inches above the bite, may help slow venom. The bandage should not cut off blood flow from a vein or artery. A good rule of thumb is to make the band loose enough that a finger can slip under it.
- A suction device may be placed over the bite to help draw venom out of the wound without making cuts. Suction instruments often are included in commercial snakebite kits.

Treatment Drawbacks

Antivenins have been in use for decades and are the only effective treatment for some bites. "Antivenins have a fairly good safety record," says Don Tankersley, deputy director of FDA's division of hematology. "There are sometimes reactions to them, even life-threatening reactions, but then you're treating a life-threatening situation. It's clearly a

case of weighing the risks versus the benefits."

People previously treated with antivenin for snakebites probably will develop a lifelong sensitivity to horse products. To identify these and other sensitive patients, hospitals typically obtain a record of the victim's experience with snakebites or horse products. But some people with no history of such exposures may have become sensitive through contact with horses, or possibly exposure to horse dander, and not know they are sensitive. Others may be sensitive without any known or remembered contact with horses. So hospitals also perform a skin test that quickly shows any sensitivity. Some hypersensitive patients may even react severely to the small amount of antivenin used in the skin test. Hospitals have procedures for reviving patients with serious reactions. Some victims with positive skin tests can be desensitized by gradually administering small amounts of antivenin.

Newer kinds of antivenins derived from sheep are under study now and

Ninety-nine percent of venomous snakebites in this country are from pit vipers, a group that includes rattlesnakes, copperheads, and water moccasins.

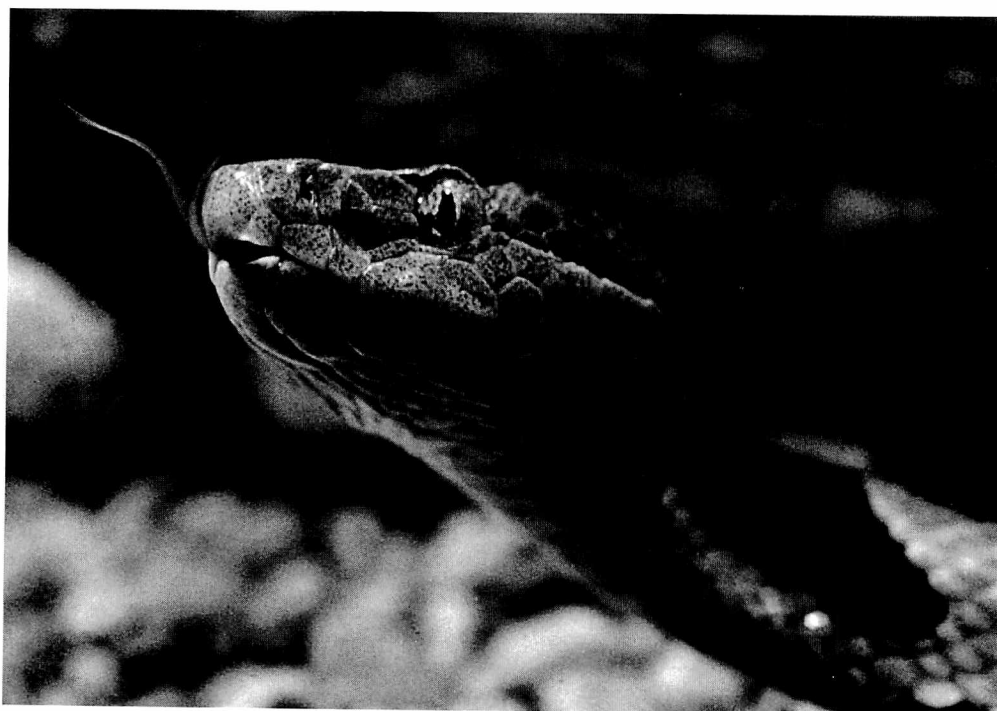
show some promise, according to FDA officials. But progress has been slow due to low demand and the small number of venomous bites a year.

Certain venomous snakebites may be treated without using antivenin. This is usually a judgment call the doctor makes based on the snake's size and other factors, which normally involves close monitoring of patients in a medical facility.

"In some areas, such as desert areas, most rattlesnakes are small and don't have as potent a venom," says Edward L. Hall, M.D., a Thomasville, Ga., trauma surgeon who treats snakebites. "You might get by with those patients in not using antivenin." But with other snakes, Hall says, antivenin can be a lifesaver. For example, the Eastern diamondback rattlesnake—found in large quantities in the region of Georgia where Hall practices medicine and in other Southern states from the Carolinas to Louisiana—can reach six feet in length and deliver a potent payload of venom. "It's an enormously dangerous bite that requires very aggressive treatment [with antivenin] or the patient will die," Hall says.

Treatment Dilemmas

Because not all snakebites, including those from the same species, are equally dangerous, doctors sometimes face a dilemma over whether or not to administer antivenin. Venomous snakes, even dangerous ones like the Eastern diamondback, don't always release venom when they bite. Other snakes



As ferocious as this copperhead snake looks, it is one of the least dangerous pit vipers found in the United States. Some victims of copperhead bites may get by with little or no antivenin treatment, but such decisions should be made only by a doctor, and all snakebites should be considered medical emergencies.

(Photo by Jessie Cohen, National Zoological Park)

How NOT to Treat a Snakebite

Though U.S. medical professionals may not agree on every aspect of what to do for snakebite first aid, they are nearly unanimous in their views of what *not* to do. Among their recommendations:

- *No ice or any other type of cooling on the bite.* Research has shown this to be potentially harmful.
- *No tourniquets.* This cuts blood flow completely and may result in loss of the affected limb.
- *No electric shock.* This method is under study and has yet to be proven effective. It could harm the victim.
- *No incisions in the wound.* Such measures have not been proven useful and may cause further injury.

Arizona physician David Hardy, M.D., says part of the problem when someone is bitten is the element of surprise. "People often aren't trained in what to do, and they are in a panic situation." He adds that preparation—which includes knowing in advance how to get to the nearest hospital—could greatly reduce anxiety and lead to more effective care. ■

—J.H.

may release too small an amount to pose a hazard.

Hall says his experience in Georgia bears this out. "Some 20 to 30 percent of patients we see who have been bitten by a snake, who actually have fang marks, have not received any venom at all." He says one reason for this may be poor timing by the snake. "Pit vipers have a very sophisticated mechanism that allows them to deliver venom at the exact instant the teeth are sunk into the flesh. So it has to be precise timing. But what we often see is that the [snake's timing is off and] venom is squirted on the pants leg or released prematurely."

Another complicating factor is the diverse potency of venom. "Venom can vary within species and even within litter mates—brothers and sisters," says Arizona physician Hardy. For example, he says, a common pit viper in the Southwest, the Mojave rattlesnake, may carry a powerful neurotoxic venom in some areas and a less toxic one in others.

Hall's work in Georgia and Florida shows that factors such as genetic differences among snakes, their age, nutri-

tional status, and the time of year also can affect venom potency. All these variables make it nearly impossible for doctors to characterize a "typical" venomous snakebite. That's why there exists what Hall calls "so much controversy" about snakebite treatment.

The solution, Hall says, lies with the patient. "Truly the only way to look at snakebites is on an individual basis and on the patient's actual reaction to the venom." Basic signs like pain, swelling and bleeding, along with more complicated reactions such as ecchymosis (purple discoloration), necrosis (tissue dies and turns black), low blood pressure, and tingling of lips and tongue give medical professionals clues to the seriousness of bites and what treatment route they should take.

Some experts emphasize that though antivenin can effectively reverse the effects of venom and save life and limb, there is no guarantee that it can reverse damage already done, such as necrosis. Some patients may later require skin grafts or other treatment. Arizona physician Hardy says the potential for limiting complications is one compelling rea-

Because antivenin is obtained from horses, snakebite victims sensitive to horse products must be carefully managed.

son to seek medical treatment as soon as possible after a snakebite.

Avoiding Snakebites

Some bites, such as those inflicted when snakes are accidentally stepped on or encountered in wilderness settings, are nearly impossible to prevent. But experts say a few precautions can lower the risk of being bitten:

- *Leave snakes alone.* Many people are bitten because they try to kill a snake or get a closer look at it.
- *Stay out of tall grass unless you wear thick leather boots, and remain on hiking paths as much as possible.*
- *Keep hands and feet out of areas you can't see.* Don't pick up rocks or firewood unless you are out of a snake's striking distance. (A snake can strike half its length, Hardy says.)
- *Be cautious and alert when climbing rocks.*

What do you do if you encounter a snake when hiking or picnicking? Says Hardy: "Just walk around the snake, giving it a little berth—six feet is plenty. But leave it alone and don't try to catch it."

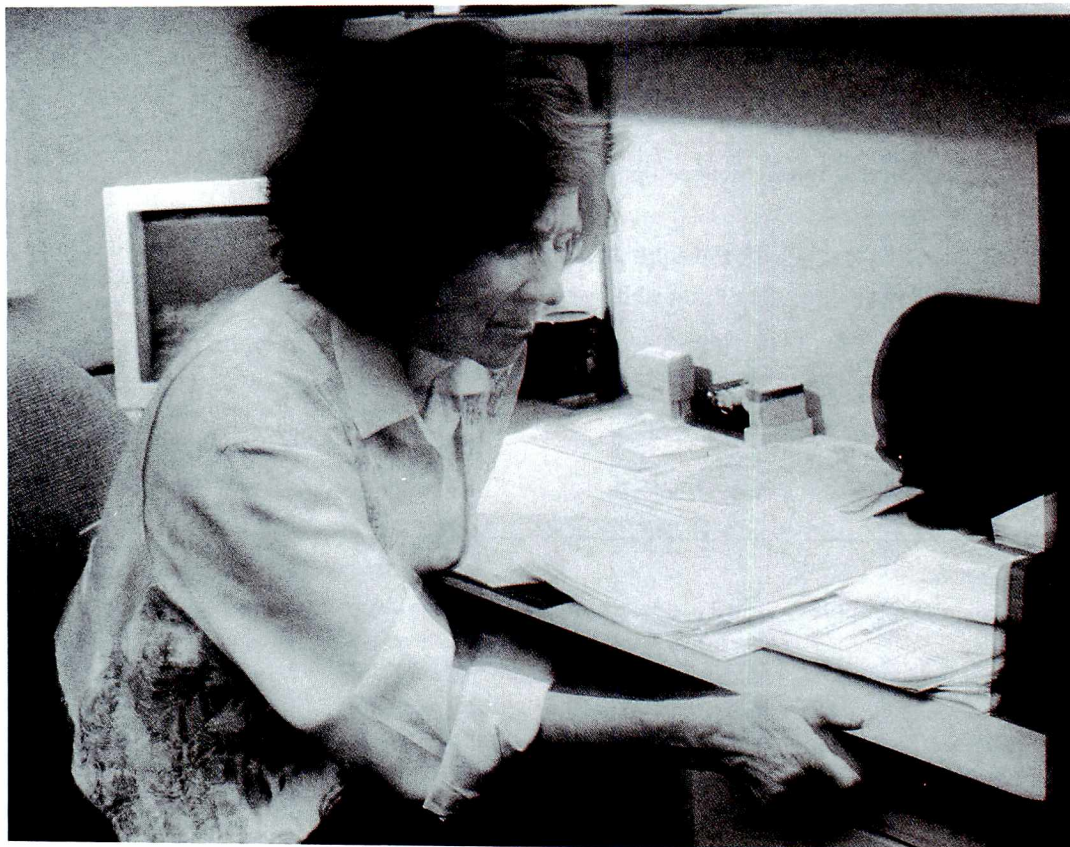
Though poisonous snakes can be dangerous, snake venom may have a positive side. Clinical trials are presently under way to test the therapeutic value of a venom-derived product called ancrod in treating stroke. Earlier proposals, using snake venom to treat neuromuscular disorders such as multiple sclerosis, never reached the clinical trial stage. ■

John Henkel is a staff writer for FDA Consumer.

INTERSTITIAL Cystitis

Progress Against Disabling Bladder Condition

by Evelyn Zamula



The woman knew she was going to be fired from her job. Since her 20s, this insurance firm middle manager has suffered from interstitial cystitis (IC), an inflammatory disease of the bladder wall.

The chief symptoms Marsha (not her real name) has are a smaller than normal bladder capacity, urgent and frequent urination, feelings of pressure and pain around the bladder and in the pelvic area, and painful sexual intercourse. Now 46 years old, she has coped with these symptoms fairly well until recently, when they have worsened. On some days, Marsha is in such agony that she can barely walk.

Though sympathetic at first, Marsha's supervisor became impatient with her frequent bouts of pain and trips to the bathroom, as well as time lost from sick

days and doctor's appointments, even though she's made up every minute. When she started to miss policy meetings, Marsha began to get indications that she would be fired. Her boss would comment that she couldn't know what was going on because, "You aren't always here."

Finally, when Marsha needed to urinate every 20 minutes at work and 10 times during the night, leaving her exhausted and depressed in the morning, she became so fearful of being asked to leave that she decided to retire on disability instead. She hopes to return to her job when she feels better, but so far it hasn't been possible.

Marsha counts herself among the more fortunate of IC sufferers because she receives long-term disability ben-

efits and has both Medicare and private medical insurance. Also, unlike many other women, whose marriages and relationships are put under severe stress by IC, Marsha is lucky to have a supportive husband.

Cause Elusive

No one knows what causes IC. It wasn't recognized as a disorder until about 20 years ago. In 1978, the Food and Drug Administration approved Rimso-50, a purified form of the industrial solvent dimethyl sulfoxide (DMSO), for symptomatic relief of IC. Before that, many patients were neither diagnosed nor treated.

Because physicians could find no organic cause, the prevailing medical opinion was that IC was a "hysterical female condition," even though at least 10 percent of cases are in men. Even Campbell's *Urology*, the definitive text of urologic diseases, stated as late as 1986 that IC was "daunting in its evasion of being understood. [It] may represent the end stage of a bladder that has been made irritable by emotional disturbance." The book further states that interstitial cystitis may be a pathway for the discharge of unconscious hatreds.

People with IC have had to put up with this type of disbelief for a long time. Kristene E. Whitmore, M.D., chairwoman of the Department of Urology, Philadelphia Graduate Hospital, Philadelphia, Pa., says, "The average number of doctors seen before diagnosis is five, and it takes three to five years to get that diagnosis."

When the columnist Ann Landers wrote about IC in 1987, she received 10,000 letters from patients or their families, relieved that the condition was finally being recognized. A 1987 study conducted by the Urban Institute in Washington, D.C., found that IC makes people so miserable that they contemplate suicide four times more often than the general population and that they rate their quality of life lower than those who undergo kidney dialysis. Nearly 30 percent of IC patients can't work full-time, according to the study.

Although no bacteria or fungi or viruses are found in patients' urine, many researchers believe it's possible that IC is caused by an infectious agent that

hasn't yet been identified.

Researchers have also suggested it may be an autoimmune disorder of the bladder's connective tissue, in which the body's defense mechanisms against invading bacteria turn suddenly against healthy tissue. In some patients, special white blood cells called mast cells, which are associated with inflammation, are found within the bladder's mucous lining. Or, some scientists theorize that the disorder may be an allergic reaction, because many patients have a history of allergies.

Some women go into remission during pregnancy, while others get worse, suggesting that in some patients hormones may be involved. Complicating the picture, many women with IC also suffer from a variety of other conditions, such as irritable bowel syndrome, migraine headaches, fibromyalgia (chronic aching of the muscles, joints, and connective tissues), low back pain, and similar disorders.

One theory in favor at present holds that the inner lining of the bladder (the glycosaminoglycan or GAG layer) that protects the bladder wall from toxic effects of urine may be "leaky," allowing substances in the urine to penetrate the bladder wall and trigger IC symptoms. A California study found that 70 percent of IC patients they examined had a "leaky" bladder lining.

More likely, any or all of these factors may exist, leading many researchers to conclude that IC is a syndrome, or a collection of signs and symptoms, rather than a specific disease. Others, such as Whitmore, believe it's more than one disease and is different in every person.

Making a Diagnosis

Although there is no test that identifies IC, urologists rely on several criteria to make a diagnosis:

- Frequent and urgent urination, and pelvic or bladder pain, especially as the bladder is filling.
- Pinpoint hemorrhages that can often be seen on the bladder wall during cystoscopy (an examination of the bladder's interior with a long, lighted tube, performed under anesthesia). This is called nonulcerative IC, seen in about 95 percent of patients.
- Cracks, scars, and star-shaped sores

called Hunner's ulcers that are found in the bladder wall in ulcerative IC. Bladder capacity is decreased because the usually elastic bladder walls become stiff and don't expand normally.

Because it's easier to define IC by what it isn't than by what it is, a diagnosis must rule out bacterial cystitis—the most common urinary tract infection—whose symptoms it most closely resembles. Bladder cancer, kidney stones, vaginitis, endometriosis, sexually transmitted diseases, and tuberculous and radiation cystitis, as well as prostate infections in men, are some other conditions that must be considered. Thus, interstitial cystitis becomes a diagnosis of exclusion.

Although about 10 times more women than men get IC, it's possible that men have been underdiagnosed. "We haven't been real sensitive in screening our prostatitis patients, so maybe more men have IC than we think," says Whitmore.

Symptoms usually begin between 20 and 50 years of age, but the average age of onset is 40. Some cases have been diagnosed in children. About 450,000 people in the United States are believed to have IC, but true numbers are hard to come by, because many cases are either undiagnosed or misdiagnosed. Although occasionally more than one member of a family has IC, the disorder is not believed to have a genetic component.

IC Symptoms

The symptoms of interstitial cystitis are similar to those of a urinary tract infection. Most people have some of the following symptoms:

- urgent need for frequent urination both day and night
- reduced bladder capacity
- feelings of pressure, pain and tenderness around the bladder, pelvis and genital area, which may increase as the bladder fills and decrease as it empties.
- painful sexual intercourse
- in men, discomfort or pain in the prostatic area. ■

—E.Z.

Treating the Condition

There is no cure for IC. All doctors can do is try to relieve the symptoms, a challenging task, because they vary from person to person. People may have flare-ups and remissions, and different patients respond to different treatments. A particular type of therapy may work for a while and then lose its effectiveness. Sometimes, stress or a change of diet triggers symptoms. Occasionally, IC goes into remission spontaneously.

Paradoxically, the cystoscopy used to diagnose IC also seems to make some people feel better. To enable the doctor to look inside the bladder with the cystoscope, the bladder is filled with water. This bladder distention helps about 30 percent of patients, at least for the short term, probably because the bladder is stretched and capacity is increased. It's also possible that the procedure may interfere with the transmission of pain signals by nerves in the bladder. The fact that IC can only be diagnosed by cystoscopy under anesthesia explains why many cases are overlooked even by urologists.

In a similar procedure, Rimso-50 is instilled directly into the bladder by a catheter. The solution is retained in the bladder for about 15 minutes before being expelled by spontaneous voiding. This treatment is given every two weeks until maximum symptomatic relief is obtained, then repeated as needed.

For some patients, Rimso-50 treatments become less effective over time. About 50 percent of patients experience significant pain relief for an average of about 10 months. The drug works by penetrating the bladder wall to reduce inflammation and acts as a muscle relaxant by preventing muscle contractions that cause pain, frequency and urgency.

Disadvantages of Rimso-50 include a garlic-like odor on the skin and breath that may last up to 72 hours. Some patients may develop a chemical cystitis after use of the drug that goes away within one or two days. Patients taking Rimso-50 also require a blood test every six months to make sure the blood count and liver and kidney function are normal. Periodic ophthalmologic examinations are also recommended.

"You have to customize therapy for the person," says Whitmore, who advo-

For More Info

More information about interstitial cystitis is available from:

Interstitial Cystitis Association
P.O. Box 1553
Madison Square Station
New York, NY 10159
(1-800) 422-1626

American Foundation for Urologic
Disease, Inc.
300 West Pratt St.
Suite 401
Baltimore, MD 21201
(1-800) 242-2383

cates a number of untraditional therapies, many of which have not been reviewed by FDA for this purpose. They include acid-restricted diets, alkalization of urine, bladder holding and retraining (delaying voiding for increasingly longer intervals), biofeedback and electric stimulation, acupuncture, muscle relaxants, antidepressants, anti-inflammatories, antihistamines and analgesics, and an experimental bladder "wash" consisting of an anesthetic, an antibiotic, an anticoagulant, and hydrocortisone.

From 40 to 60 percent of IC patients may benefit from low doses of the tricyclic antidepressant amitriptyline (Elavil and others), according to Vicki Ratner, M.D., and colleagues in the *Journal of Women's Health*, Vol. 1, No. 1, 1992. Physicians prescribe it not only to treat the depression that is common in IC patients, but to take advantage of its bladder-relaxing, allergy-fighting, pain-blocking, and sedating properties.

When pain is severe, some people may benefit from transcutaneous electrical nerve stimulation (TENS). Mild electrical impulses delivered to the body through wires placed on the lower back or abdomen or through devices implanted in the body may alter nerve transmissions to the bladder and help trigger release of pain-blocking hormones.

A bland diet helps some IC people.

Doctors recommend avoiding high-acid foods, such as citrus fruits, that may irritate the bladder, or spicy foods that may cause the release of histamine. Restricting alcoholic beverages, carbonated sodas, coffee and other caffeinated products, and beverages and foods with artificial sweeteners appears to reduce symptoms in some people.

Surgery is an option when all else fails. Some urologists may remove the diseased portion of the bladder and attach a piece of the patient's bowel to the remaining healthy tissue to make a larger bladder. In other cases, the bladder is completely removed and urine is rerouted to a bag outside the body or a pouch inside the abdomen. However, about half of patients don't get pain relief from this procedure.

"I don't take the bladder out unless I've used all the tricks up my sleeve," says Whitmore. "When patients have bladders the size of a walnut or smaller, or when they have intractable pain, then they're candidates for cystectomy [bladder removal]. The operation has allowed some people to get out of the house and have a life."

Whitmore tells her patients that, as with all disorders of chronic pain, there is going to be a certain amount of anger, anxiety and depression. "I say to them, 'I have an 85 percent chance or greater to make you better, but I can't teach you how to cope with your illness, so you've got to get some help.' I encourage them to go for self-hypnosis, self-relaxation, and other coping techniques, or to seek therapy with psychologists or psychiatrists. I tell them, 'if you can't cope, you're not going to get better.'"

Researchers funded by the federal government, drug companies, and the Interstitial Cystitis Association have stepped up their efforts to find out more about the disorder. Philip Hanno, M.D., chairman, Department of Urology, Temple University School of Medicine, Philadelphia, Pa., expects that in the next decade, treatment for IC will be more beneficial than the therapy available now. He believes that ultimately there will be a cure for most cases of this painful and disabling condition. ■

Evelyn Zamula is a freelance writer in Potomac, Md.



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.

■ **Cigarette and smokeless tobacco** and the reasoning behind FDA's proposed regulation of them are the subject of a report published by FDA last Aug. 11. "Nicotine in Cigarettes And Smokeless Tobacco Products Is A Drug And These Products Are Nicotine Delivery Devices Under the Federal Food, Drug, and Cosmetic Act" explains agency findings that nicotine in cigarettes and smokeless tobacco is a drug, and that these products are drug delivery devices and, therefore, fall under FDA jurisdiction. Single copies are available for \$21 from Superintendent of Documents, Government Printing Office, Washington, DC 20402; telephone (202) 512-1800. Request stock number 017-012-00373-7. The document is also available on FDA's Internet site at <http://www.fda.gov/opacom/campaigns/tobacco.html>. (FR Aug. 11)

■ **Condoms and condom-like products**, including those marketed as novelty items, are subject to all medical device regulatory requirements, according to a new FDA policy statement. The statement supersedes the agency's 1989 policy on condom labeling. For a free copy of the statement, send two self-addressed labels to Division of Small Business Manufacturers Assistance (HFZ-220), Rockville, MD 20857. Request Docket No. 95D-0162. (FR Aug. 3)

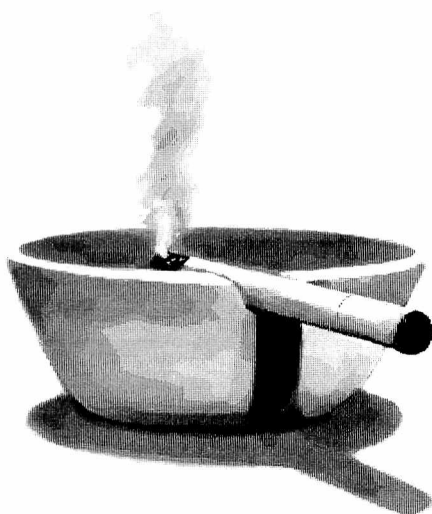
■ **Revised guidance** for certain frozen and canned fish, with decomposition and histamine information, is available from FDA. "Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species" provides lower histamine action levels. For a free copy, send two self-addressed labels to Office of Constituent Operations, Industry Activities Staff (HFS-565), Washington, DC 20204. Request Docket No. 95D-0157. (FR Aug. 3)

■ **Safety and effectiveness information** for 27 class III (high-risk) medical devices must soon be submitted to FDA. The agency is requesting the information to determine whether to revise its classification of the devices or issue new regulations requiring premarket approval. The 27 devices include such products as lung water monitors and implanted neuromuscular stimulators. (FR Aug. 14)

■ **Computer submission** of pharmacology and toxicology studies for new drugs is now an option for drug sponsors under a Center for Drug Evaluation and Research pilot program. Sponsors who want more information should contact Patricia A. Sylvia, CDER (HFD-72), Rockville, MD 20857; telephone (301) 443-3695. (FR Aug. 30)

■ **Pesticide residue** monitoring data for fiscal year 1994 is available from FDA on computer diskette. This is the third annual comprehensive compilation of monitoring data for pesticide residues in foods that FDA has offered. To order copies of the diskettes (at \$50 each), request order number PB95-503132 from the National Technical Information Service, Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161; telephone (703) 487-4650. In addition, shipping and handling costs are \$4 for one copy, \$6 for two, and \$8 for three or more copies. (FR Aug. 24)

■ **Lead information** is available in a new pamphlet, "Protect Your Family from Lead in Your Home," developed by the Environmental Protection Agency and Consumer Product Safety Commission. For one free copy, call the National Lead Information Clearinghouse at (1-800) 424-LEAD (TDD 1-800-526-5456). The document is also available through the Internet at [gopher://gopher.epa.gov:70/00/Offices/PestPreventToxic/Toxic/lead_pm/lead](http://gopher.epa.gov:70/00/Offices/PestPreventToxic/Toxic/lead_pm/lead). Multiple copies are available for \$26 per pack of 50 copies from the Superintendent of Documents, P.O. Box 371954, Pittsburgh, PA 15250-7954; telephone (202) 512-1800. Request the pamphlet by title and stock number 055-000-00507-9. (FR Aug. 1)





Device Firm Closes Pending Compliance with FDA Regulations

by Dixie Farley

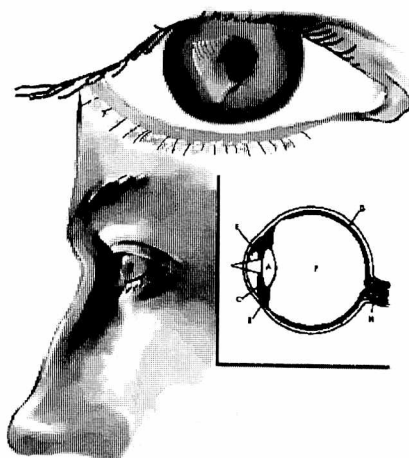
After FDA found manufacturing problems with sensitive eye treatment devices, a device firm and two of its officers agreed to stop operating until FDA requirements are met.

U.S. District Court Judge Robert E. Keeton of the District of Massachusetts in Boston last April 25 entered a consent decree of permanent injunction against Mira Inc., of Waltham, Mass., and Luc Schepens and Roger O'Brien. Schepens was Mira's president, and O'Brien its manager of quality assurance, quality control, and regulatory affairs.

The firm specializes in devices such as cryogenic probes used to freeze eye tissue for surgery and sterile implants used to reattach detached retinas. The government's complaint for injunction filed with the consent decree alleges that the devices violated FDA's good manufacturing practice (GMP) regulations since at least 1991.

FDA inspections of Mira since 1986 had revealed numerous GMP deficiencies. In a regulatory letter dated Feb. 20, 1991, the agency's Boston district office advised Mira of problems with implants, such as inadequate controls for specifications and quality assurance, uninvestigated complaints, inadequate record keeping, unclean conditions, and no written procedures for finished device inspection.

Further, FDA advised, Mira hadn't reported to the agency complaints about a laser and a glaucoma device. A health-care professional complained, for example, that filters didn't protect the operator from possible injury from reflected laser beams. If Mira did not act



promptly to make corrections, FDA warned, the agency might invoke legal actions such as seizure or injunction. Mira promised corrections.

Then, between November 1991 and December 1992, complainants told FDA's Boston office that the deficiencies with the agency's GMP regulations were continuing at the firm.

Following these complaints, FDA investigators inspected Mira and found additional evidence of continuing violations. A 1992 inspection revealed the firm was marketing a device without FDA clearance. Mira voluntarily recalled the device.

During a March and April 1993 inspection, FDA engineer Richard Wright observed practices relating to violations of GMP regulations in the manufacture of Mira's Imex silicone implants and

cryogenic freezing instruments.

Mira buys Imex strip and sponge implants ready-made and cuts them to size. But the firm itself molds a third Imex variety, silicone tire implants (so-named because of their tire shape), from purchased raw material—a medical grade elastomer.

Information included with the elastomer indicated a shelf life of only six months, Wright found, yet Mira was using elastomer produced in 1987 to make the tire implants.

Wright found Mira had lost the elastomer's original certificate and had the material tested only once, in September 1992. During that test, Wright learned, the material failed the firm's own specifications for tensile strength and elongation and wasn't tested for another specification.

Also, Wright found Mira made a design change in its cryogenic devices but never tested the new products to make sure they worked properly. "The change in fact caused them to fail," he says, "so Mira had to go back to the original design."

Wright informed Mira of his findings.

In a letter dated April 30, 1993, Mira told FDA it planned to take corrective action "as logistical and manpower limits allow."

In July and August 1994, Wright and investigator John McCann inspected Mira.

"Mira was not operating in a state of control," Wright says. "The GMP problems were systemic, and the corrective actions didn't address the root causes. Therefore, each time we'd go in, we'd

invariably find similar problems.”

As a result of this inspection, FDA requested a permanent injunction.

Under the consent decree, Mira and its officers Schepens and O'Brien agreed to:

- stop making and shipping medical devices until the company complies with FDA's GMP regulations

- undergo FDA reinspection to ensure practices comply with the law before resuming full operation
- destroy devices that can't be brought into compliance with the Federal Food, Drug, and Cosmetic Act
- maintain compliance with laws and regulations enforced by FDA
- hire an expert consultant to conduct

audits during the next two years to ensure operations continue to meet FDA's GMP regulations.

At press time, FDA was continuing to work with Mira to meet the terms of the decree.

Dixie Farley is a staff writer for FDA Consumer.

Bribery Attempt Lands Businessman in Jail

Bribery awareness training paid off for an FDA investigator when a San Francisco Chinatown importer tried to pay him off during a routine inspection.

The importer, Phillip Chew, 38, owner of Wha Shing Trading Co., was sentenced June 13, 1995, in U.S. District Court for the Northern District of California to four months in prison, followed by four months of electronic home monitoring and three years' probation for bribing FDA investigator Junes Valdemoro of FDA's San Francisco district office. He also was fined \$5,000.

Chew had hoped to sway Valdemoro into allowing possibly contaminated food from China into the country.

Acting on what he learned in a mandatory training course, Valdemoro enabled the Department of Health and Human Services' Inspector General's Office of Investigations to conduct a sting operation that led to Chew's conviction. Valdemoro assisted in the sting operation.

Chew initially offered Valdemoro money on May 4, 1994, at his Chinatown business, after Valdemoro rejected the entry of food whose packaging was covered with rodent droppings.

Chew told Valdemoro he would clean it up and then left the room. When he came back, Valdemoro recalled, Chew held out a wad of money to him.

"I told him, 'No, no, that's illegal,' but he was persistent," Valdemoro said. "He

told me that it was a Chinese New Year present and that I was his friend. Then I remembered what I learned in training: that I shouldn't close the door on this guy. So I said, 'I'll have to think about this.'"

Valdemoro then left the premises and called his supervisor and the Office of the Inspector General (OIG) in San Francisco. At the OIG's request, he participated in plans to secretly monitor his future dealings with Chew. Officials briefed Valdemoro on what he should do and say on subsequent visits and arranged for him to be wired for secret audiotaping.

As directed by the OIG, Valdemoro contacted Chew later that day. Chew offered him \$300 in return for a "clean report." Valdemoro accepted the money and turned it over to the OIG for use in its investigation.

Valdemoro returned to Chew's warehouse on May 19 for a routine examination of a Customs entry. While Valdemoro was there, Chew put a \$100 bill into Valdemoro's lab coat and said it was a gift. Again, Valdemoro accepted the money and turned it over to the OIG.

That same day, Chew offered to pay Valdemoro \$200 to \$500 to release seven food items detained by FDA because of contamination with insects, animal filth, feathers, rat or mouse hair, cat or dog hair, and rabbit hair. One item had to be relabeled to include sulfites as an ingredient. No money was exchanged.

On May 23, Chew gave Valdemoro

\$1,000 to have the seven food items released, and on Aug. 17 gave him \$900 to release another detained entry.

Valdemoro again gave the money to the OIG. The detained items were never released for sale in this country. Chew also offered to give Valdemoro a pager and cellular phone to simplify future illegal transactions.

Chew and a business partner, Ada Lee, were arrested Oct. 13 for bribing a government official. Chew pleaded guilty to one count of bribery. The U.S. Department of Justice did not seek prosecution of Lee.

For his exemplary work, Valdemoro received the DHHS Inspector General's annual Integrity Award last August.

—Paula Kurtzweil

Seafood Maker Fined For Misbranding

When customers bought Miss Sally's stuffed crabs from Sam's Club membership stores in southern and midwestern states through early 1994, they got a handsome window package revealing crab shells stuffed with what appeared to be huge chunks of crab meat. Labels listed crab meat as a major ingredient and bore a bright orange sticker claiming "more crabmeat than ever."

But little or no crab meat was in many of those products. Instead, the shells were stuffed with surimi, a whitefish sometimes used as an inexpensive crab substitute, which should have been listed on the label.

As a result of fraudulent use of the word "crabmeat," David R. Carrington and his company, Carrington Foods Inc., of Saraland, Ala., were ordered to pay \$78,000 in fines last May 15 after pleading guilty to one misdemeanor count and one felony count of food product misbranding.

Carrington, 50, also was sentenced to two years' probation, and his company received five years' probation. Initially, Carrington was indicted on a felony misbranding charge, but when he agreed to plead guilty, the court downgraded the charge to misdemeanor, while retaining the felony charge for his company.

FDA first became aware of Carrington's misdeeds in late 1993, when a seafood industry consultant told FDA investigators that Carrington Foods was not putting any crab meat in its stuffed crabs. (FDA considers stuffed crabs without crab meat to be "imitation stuffed crabs.") In response, FDA collected numerous samples of Carrington's products and confirmed that little or no crab meat was present.

In late November and early December 1993, investigators from FDA's Mobile, Ala., resident post inspected Carrington Foods and observed its manufacturing procedures. At the beginning of the inspection, investigators noticed more than 1,100 pounds of frozen surimi being thawed in the firm's production areas. Within three hours, plant employees placed the surimi in one of the company's large coolers, where it remained for the rest of the inspection.

Investigators observed Carrington's production of stuffed crabs for Sam's Club. The firm used minced crab meat, an inexpensive "mushy" product with little or no texture, unlike the chunky texture normally seen through package windows in Miss Sally's stuffed crabs. But because minced crab is a crab product, the plant appeared to be processing the food legally. Analysis of a stuffed-crab sample produced during the inspection re-

vealed some crab meat but no surimi.

After the inspection, FDA's Nashville district office requested more samples of Carrington Foods' stuffed crabs. Samples analyzed in FDA's Seattle laboratory showed Carrington had been substituting surimi for crab meat before the 1993 inspection, was using minced crab meat during the inspection, and then switched back to surimi after the inspection.

Because the samples clearly documented consumer fraud, in April 1994 the agency's Office of Criminal Investigations began working with the U.S. Attorney's Office to bring charges. In December 1994, a grand jury indicted Carrington and his firm on misbranding charges.

Carrington Foods has since lost its contract with Sam's Club.

—John Henkel

Defective Lenses Reconditioned

A manufacturer of implantable intraocular lenses (IOLs) was forced to reinspect and resterilize nearly 60,000 lenses under a consent decree the company entered into with FDA.

At press time in August, FDA expected Mentor ORC Inc., formerly Optical Radiation Corp. (ORC) of Azusa, Calif., and Cidra, Puerto Rico, to complete the reconditioning process in October. ORC agreed to recondition the lenses, worth as much as \$20 million, after numerous FDA inspections found that they were not made in compliance with good manufacturing practices (GMPs). The lenses were among 92,000 seized in 1993 because of possible defects.

The U.S. District Court for the Central District of California entered the consent decree on July 5, 1994, and ORC sold its IOL business to Mentor Corp. of Santa Barbara, Calif., a few months later. Mentor renamed the company.

Following surgery to remove cataracts, the IOLs are permanently placed in the eyes of patients, who are typically at least 60 years old. Defective IOLs pose an unreasonable risk to patients because damaged IOLs can impair sight and injure tissue, leading to the need for more surgery. Surgery may be especially risky in older people, who may have other health problems.

FDA first uncovered GMP violations during a routine inspection of the company's Puerto Rico facility in 1989. (The IOLs were made in San Juan and then shipped to California for sterilizing and packaging.) Violations continued to show up during inspections in 1991 and 1993, despite an FDA warning and notice of adverse findings. Most of the violations were at ORC's Puerto Rico facility, although an inspection of the company's California plant in 1993 also uncovered deficiencies.

The inspections found that, among other things, the company failed to:

- establish and carry out measures to ensure the devices were made according to design plans
- adequately investigate physicians' complaints about the IOLs
- validate certain manufacturing processes
- investigate the reasons for high defect rates.

On Nov. 23, 1993, at FDA's request, U.S. marshals seized nearly 92,000 IOLs at the company's California plant. FDA allowed the IOLs to remain at the plant until a decision was made on their fate.

Posting a \$1 million bond, the company agreed to recondition the lenses, dispose of those that failed reinspection, and pay the federal government up to \$56.50 an hour for FDA to supervise the process, which began early this year.

The company was reconditioning the lenses at its Puerto Rico facility and plans to move its entire IOL business to that site in the near future.

—Paula Kurtzweil

SUMMARIES OF COURT ACTIONS



SEIZURE ACTIONS

Food/Contamination, Spoilage, Insanitary Handling

PRODUCT: Pure Egg Noodles, imported, at Brooklyn, N.Y. (E.D.N.Y.); Civil No. CV-95-0270.

CHARGED 1-19-95: While held for sale after shipment in interstate commerce at Beluga Caviar International Foods, Inc., in Brooklyn, N.Y., the articles were adulterated in that they consisted of rodent excreta and rodent hair, and they were held under insanitary conditions whereby they might have been contaminated with filth—402(a)(3) and 402(a)(4).

DISPOSITION: A final order and judgment on default ordered the articles destroyed. (F.D.C. No. 67038; S. No. 94-726-191; S.J. No. 1)

PRODUCT: Mushrooms, stems and pieces, at St. Cloud, Minn. (D.Minn.); Civil No. 3-94-1629.

CHARGED 1-27-95: While held for sale after shipment in interstate commerce at Cobarn's Inc., in St. Cloud, Minn., the articles were adulterated in that they contained staphylococcal enterotoxin, and they were prepared and packed under conditions which might have rendered them injurious to health—402(a)(1) and 402(a)(4).

DISPOSITION: A default decree of condemnation, forfeiture and destruction ordered the articles destroyed. (F.D.C. No. 67041; S. No. 94-742-475; S.J. No. 2)

PRODUCT: Tuna Loins, yellow fin, at Seattle, Wash. (W.D.Wash.); Civil No. C94-1745.

CHARGED 11-23-94: While held for sale after shipment into interstate commerce at Cityice Cold Storage Co., in Seattle, Wash., the articles were adulterated in that they consisted of decomposed fish—402(a)(3).

DISPOSITION: A consent decree of condemnation, forfeiture and destruction ordered the articles destroyed. (F.D.C. No. 67033; S. No. 95-737-665; S.J. No. 3)

Drugs/Human Use

PRODUCT: Aidex Antimicrobial Liquid Soap, Aidex Antimicrobial Cream, Aidex Antimicrobial Aqueous Lotion, and Aidex Spray Cleaner, at Jessup, Md. (D.Md.); Civil No. WN94-685.

CHARGED 3-18-94: This was a drug and device seizure. While held after shipment in interstate commerce at Service Warehouse and Distribution Co., Inc., in Jessup, Md., the articles were adulterated in that the Aidex spray cleaner contained mold and an insect, and it was a class III device without

an approved application or investigational device exemption—501(a)(1) and 501(f)(1)(B). The Aidex antimicrobial liquid soap and aqueous lotion were non-compendial drugs whose strengths differed from what they were represented to possess, and their labeling falsely represented that they contained resorcinol—501(c) and 502(a). The drugs failed to bear labeling containing adequate directions for their intended purposes—502(f)(1). Information or notice regarding the device was not provided at least 90 days prior to their introduction into interstate commerce—502(o).

DISPOSITION: A stipulated order of condemnation and destruction ordered the articles destroyed. (F.D.C. No. 66791; S. No. 93-623-9229; S.J. No. 4)

PRODUCT: Oxycodone and Aspirin, tablets, at Brooklyn, N.Y. (E.D.N.Y.); Civil No. CV-93-2899.

CHARGED 6-30-93: While held for sale after shipment in interstate commerce at Halsey Drug Co., Inc., in Brooklyn, N.Y., the articles were adulterated in that the methods used in, and the facilities and controls used for, their manufacture, processing, packing, and holding did not conform to and were not operated and administered in conformity with current good manufacturing practice requirements—501(a)(2)(B).

DISPOSITION: A consent decree ordered the articles destroyed. (F.D.C. No. 66735; S. No. 93-726-092; S.J. No. 5)

CRIMINAL ACTIONS

DEFENDANTS: Quad Pharmaceuticals et al., at Indianapolis, Ind. (D.Md.); Criminal No. 93-HAR-0147.

CHARGED 9-30-93: Count 1: The defendants, willfully and knowingly, (a) made false statements and representations in matters within the jurisdiction of FDA; (b) concealed material facts from FDA; (c) failed, with intent to defraud, to establish and maintain required records; (d) manufactured and introduced adulterated and misbranded generic drug products into interstate commerce; and (e) corruptly influenced the administration of law—18 U.S.C. section 371.

Count 2: Defendant Dilip Shah knowingly and willfully made a material false statement and representation to FDA in that he submitted separate batch production records for a generic drug and stated that the batch records reflected the manufacture by Quad of "two separate 10-liter production batches" of the product, when only one 10-liter batch was manufactured and was reprocessed so that it would appear that multiple batches were manufactured—18 U.S.C. sections 2 and 1001.

Count 3: Defendants Dilip Shah and Raja Feroz, knowingly and willfully, made a material false statement and representation to the FDA in that they sent an annual report to FDA stat-

SUMMARIES OF COURT ACTIONS (continued)

ing that in Quad's production of a generic drug there were no changes to the manufacturing and control of the drug that had not been already submitted and approved as a supplemental application, when in fact Quad manufactured the product using more anti-oxidant than was specified in the FDA-approved master formula—18 U.S.C. sections 2 and 1001.

Count 4: Defendants Dilip Shah and Arun Kumar, knowingly and willfully, concealed from FDA inspectors the existence of certain drug product complaints, which are written records that must be maintained and made readily available for inspection by FDA—18 U.S.C. sections 2 and 1001.

Counts 5-6: Defendants Raja Feroz, Arun Kumar, and Asad Ullah, with the intent to defraud, introduced into interstate commerce quantities of a generic drug which were adulterated in that the batch production records were required to include complete information regarding the identity and quantity of all components and materials used in the manufacturing process and the results of all laboratory tests performed on the drugs; however, the batch production records failed to disclose either the addition of a residue into the batch of a previously manufactured batch of the same product or the results of laboratory tests performed on the residue prior to its addition—301(a), 303(a)(2), and 18 U.S.C. section 2.

DISPOSITION: Dilip Shah pleaded guilty to one count of making a false statement to FDA. He was sentenced to 46 months in prison and fined \$15,000. Dulal Chatterji pleaded guilty to two felony counts, one count of obstructing a federal agency proceeding, and one count of conspiring to defraud an agency of the United States. He was sentenced to 30 months in prison and fined \$100. Jan T. Strum pleaded guilty to concealing material facts from FDA. He was sentenced to six months of electronically monitored home confinement and fined \$2,500. Andrew Morris pleaded guilty to conspiring to defraud FDA and obstruction. He was sentenced to 10 months in prison and fined \$3,000. Arun Kumar pleaded guilty to aiding and abetting the introduction into interstate commerce of adulterated drug products with the intent to defraud. He was sentenced to four months in prison and four months home detention. (F.D.C. No. 65984; S.J. No. 6)

DEFENDANT: **Jesus Rodriguez, d/b/a Farmacia de Watto**, at Canovanas, Puerto Rico (D.Puerto Rico); Criminal No. 94-040(RLA).

CHARGED 2-4-94: The defendant knowingly sold and offered to sell a prescription drug that was clearly labeled "Sample—Not for Sale"—301(t) and 303(b).

DISPOSITION: Guilty plea; sentenced to one year's probation and ordered to pay a \$50 special assessment. (F.D.C. No. 66548; S. No. 91-633-596; S.J. No. 7)

DEFENDANT: **Symbion, Inc.**, at Salt Lake City, Utah (C.D.Utah); Criminal No. 94-CR-088G.

CHARGED 6-6-94: The defendant obtained investigational device exemptions ("IDEs") for its Total Artificial Heart and Acute Ventricular Assist Device. As the sponsor of the IDEs,

the defendant was required to monitor the investigations and submit annual reports to FDA. The defendant submitted an annual report which falsely represented that Symbion fulfilled its own procedure and performed on-site monitoring visits to the sites participating in the IDE studies—301(g) and 510j(g). **DISPOSITION:** Guilty plea; fined \$200,000 and ordered to pay a \$250 special assessment. (F.D.C. No. 65990; S. No. 90-486-276; S.J. No. 8)

INJUNCTION ACTIONS

DEFENDANTS: **Advance Medical Designs, Inc., Thomas E. Cottone Jr., Ronald D. Arken, and Joseph R. Cottone Sr.**, at Marietta, Ga. (N.D.Ga.); Civil No. 1-93-CV-2970.

CHARGED 12-27-93: While held for sale at Advance Medical Designs, Inc., in Marietta, Ga., sterile equipment covers and transfer/decanting devices were adulterated in that the methods used in, and facilities and controls used for, their manufacture, packing and storage were not in conformity with current good manufacturing practice regulations—501(h). The devices were also adulterated in that their purity and quality fell below that which they purported to possess because they were labeled "sterile" when they were not subjected to an adequate sterilization process—501(c). The devices were misbranded in that their labels were false and misleading because the devices were labeled as "sterile" when they were not subjected to an adequate sterilization process—502(a). The devices were also misbranded because they were dangerous when used in the manner recommended or suggested in their labeling because they were labeled as "sterile" when they were not subjected to an adequate sterilization process—502(j). The defendants introduced or caused to be introduced into interstate commerce the adulterated and misbranded devices—301(a).

DISPOSITION: A consent decree of permanent injunction was filed, and the defendants came into compliance with the decree. (Inj. No. 1330; S. No. 93-617-912; S.J. No. 9)

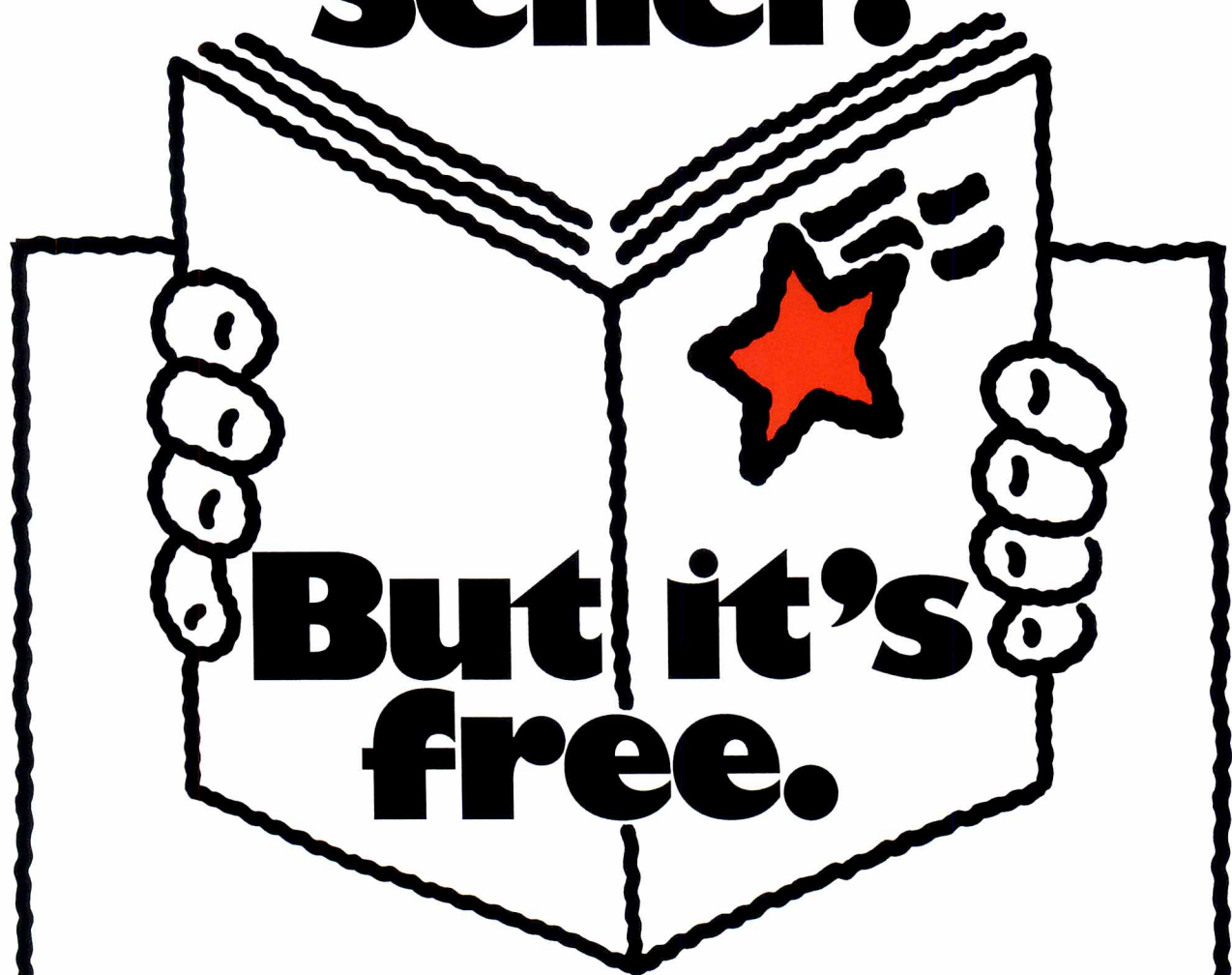
MISCELLANEOUS

ACTION: **Back Technologies, Inc. v. Donna Shalala et al.**, at Everett, Wash. (D.D.C); Civil No. 1:94CV02247.

CHARGED 10-19-94: Back Technologies, Inc., manufactured and marketed the BACKTECH Back Machine, which claimed to relieve back and neck pain. The device was not approved by FDA. FDA requested the company stop marketing the exercise machine and submit the necessary applications for approval. The firm failed to file a premarket approval application or a premarket notification, yet continued to market the product—510e(a) and 510(k).

DISPOSITION: A memorandum opinion denied the plaintiff's request for declaratory relief and granted the defendant's motion for summary judgment. The plaintiff decided not to appeal the decision and will see that future advertising and labeling for the product conforms with FDA's requirements. (Misc. No. 1069, S.J. No. 10)

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