

# FDA CONSUMER

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

• VOL. 28 NO. 1

JANUARY-FEBRUARY 1994 •

Aspirin!

a  
new  
look  
at  
an  
old  
drug

(PROPOSED STATEMENT)

IMPORTANT: See your doctor before taking this product for your heart or for other new uses of aspirin because serious side effects could occur with self treatment.







Donna E. Shalala, Ph.D.  
Secretary of Health and  
Human Services

David A. Kessler, M.D.  
Commissioner of Food and Drugs

James A. O'Hara III  
Associate Commissioner for  
Public Affairs

Judith Levine Willis / Editor

Patricia N. Edwards / Art Director

Michael L. Herndon / Production Manager

Carol L. Ballentine / Copy Editor

Cover Design: Jack Lefkowitz

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# FDA CONSUMER

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

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**How to Outsmart Dangerous *E. Coli* Strain** 7  
*The bacterium E. coli was once thought harmless when it stayed in the intestinal tract. But now a dangerous strain has emerged. Here's how you can avoid its ill effects.*

**Shiley Saga Leads to Improved Communication** 12  
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**Inside Front Cover Photo:** Many people were surprised when a harmful strain of *E. coli* was found in apple cider. For ways to avoid this bacterium's harmful effects in cider and other foods, see page 7.





## Unshielded Fluorescent Lamps And Skin Cancer Risk

While ultraviolet radiation exposure from unshielded fluorescent lamps is small compared to that from sunlight, a recent FDA study estimates that exposure from unshielded lamps could cause 1,500 new U.S. cases of squamous cell skin cancer a year. For comparison, sun exposure annually causes 110,000 U.S. cases of squamous cell skin cancer.

Lamp exposure in an eight-hour workday is equivalent, for example, to 1.2 minutes of sun exposure on a clear day in July in Washington, D.C., according to researchers at FDA's Center for Devices and Radiological Health, who conducted the study using a mathematical model based on human population-disease data.

The study estimated that for indoor workers exposed to unshielded lamps over their work lifetime (equivalent to exposure

eight hours a day for 50 years), the cumulative UV dose may increase their lifetime risk of squamous cell cancer by 4 percent. (Because recent data indicate that long-term UV exposure may apply only to squamous cell cancer, the study didn't include other types of skin cancer.)

Use of acrylic diffusers on lamp fixtures can prevent this unnecessary risk for individuals who want to avoid UV exposure. Diffusers remove most UV radiation without reducing visible light. Some diffusers actually improve illumination by directing the light where it's needed.

## FDA Approves bST for Cows

An animal drug has been approved to increase milk production in dairy cows, FDA announced last Nov. 5. The new drug is Posilac (somatotrope), a recombinant bovine somatotropin (bST) product.

Posilac increases milk output by supplementing a cow's natural bST, a hormone produced in the pituitary gland. Milk from treated cows has the same nutritional value and composition as milk from untreated cows.

"This has been one of the most extensively studied animal drug products to be reviewed by the agency," said FDA Commissioner David A. Kessler, M.D. "The public can be confident that milk and meat from bST-treated cows is safe to consume."

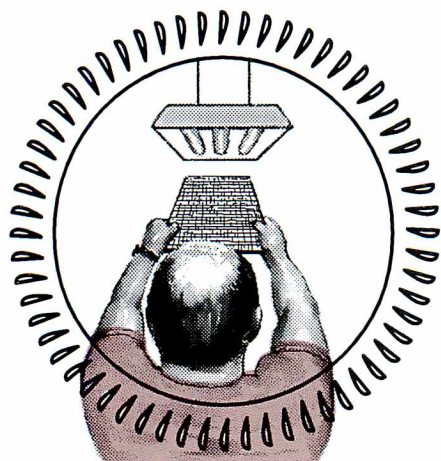
As reported by the General Accounting Office in September 1992, FDA found evidence in submitted clinical trials that bST-treated cows have a slightly increased incidence of mastitis, a common infection of a cow's udder.



In March 1993, an FDA advisory committee discussed GAO concerns that antibiotic treatments for mastitis could lead to increased drug residues in milk. The committee concluded that adequate safeguards prevent unsafe residue levels from entering the milk supply. States require that milk be tested for drug residues. Milk found with unsafe levels must be discarded, and producers responsible for violative residues are subject to regulatory sanctions.

Nevertheless, additional steps ensure detection of unsafe residues in the milk of bST-treated cows well before the milk or its products reach grocery shelves. Monsanto Co. of St. Louis, Mo., the manufacturer, will conduct a post-approval monitoring program that includes:

- tracking for two years in 21 top dairy





states to periodically compare the amount of milk discarded after bST is marketed with the amount discarded before approval

- comparing for 12 months the proportion of milk discarded due to positive drug tests between bST-treated and untreated herds

- monitoring of all bST use and follow-up on all complaints

- monitoring of 24 commercial dairy herds using Posilac for mastitis, animal drug use, and the resulting loss of milk.

In the Aug. 24, 1990, issue of *Science* magazine, FDA scientists summarized more than 120 studies examining the human safety of recombinant bST. The agency's conclusion that bST poses no risk to human health has been affirmed in scientific reviews by the National Institutes of Health, the Congressional Office of Technology Assessment, and drug regulatory agencies of Canada, the United Kingdom, and the European Economic community, and by an audit by the HHS Office of Inspector General.

Special labeling is not required for food products derived from bST-treated cows. However, food companies may voluntarily label their products, provided the information is truthful and not misleading.

### **Three Agencies Propose Pesticide Reforms**

Reforms that would update and improve U.S. food safety and pesticide laws to reduce pesticide risks, especially to infants

and children, were proposed last September by FDA, the U.S. Department of Agriculture, and the Environmental Protection Agency. The reform package was presented to a joint House and Senate committee hearing.

The reforms would extend the strict FDA health-based food additives standard of a "reasonable certainty of no harm" to all pesticide-treated foods, including raw fruits and vegetables. Proposals contain specific provisions to protect infants and children from pesticide risks. EPA and USDA would identify the foods children eat in large quantities and focus on child safety when setting tolerances for these foods.

Other proposals of the reform package would:

- require that most high-risk pesticides meet the safety standard within three years and all other pesticides meet the standard within seven years

- initiate a USDA-EPA one-year project to establish goals for reducing pesticides in individual commodities; the goals would be met by the year 2000

- eliminate the consideration of economic benefits when reviewing and approving pesticides except in cases involving significant disruption of the food supply; in these cases the benefit consideration would be limited to five years

- require EPA to issue specific findings that a tolerance is safe for infants and children

- make it easier to remove from the market pesticides suspected of posing a risk to health and the environment and make lower-risk pesticides a top priority in the approval process

- strengthen enforcement provisions for violations of statutes and regulations governing the use of pesticides

- establish national goals for better pest-control methods, including crop rotation, cultivation of predator insects, and the use of biological pesticides together with limited chemical pesticides; 75 percent of farms would be using these methods by 2000

- prohibit the export of pesticides that have been banned or voluntarily withdrawn in the United States because of health concerns

- protect farm workers from the hazards of working with pesticides.

The proposals are the first reforms of pesticide laws since the 1970s.

### **Incontinence Treatment Approved for Certain Patients**

The first injectable treatment for urinary stress incontinence, a bladder control disorder, received FDA approval last Sept. 30.

Called the Contigen Bard Collagen Implant, the new product is expected to help most patients recover partial bladder control, while many may regain complete control. It is intended for use only in patients who have been incontinent without improvement for at least 12 months.

Urinary stress incontinence affects 1 million to 2 million people in the United States. It is characterized by involuntary loss of urine when abdominal pressure is



exerted on the bladder. Simple actions such as sneezing, laughing, walking, coughing, and exercising may cause the bladder to lose urine.

The new product, a purified form of bovine collagen, is injected into the tissue surrounding the urethra (bladder neck). It adds bulk to the tissue and boosts urethral resistance to leakage.

Physicians can perform the injection as an outpatient procedure using local anesthetic. Repeated injections are usually required. Patients must be tested before treatment for hypersensitivity to bovine collagen.

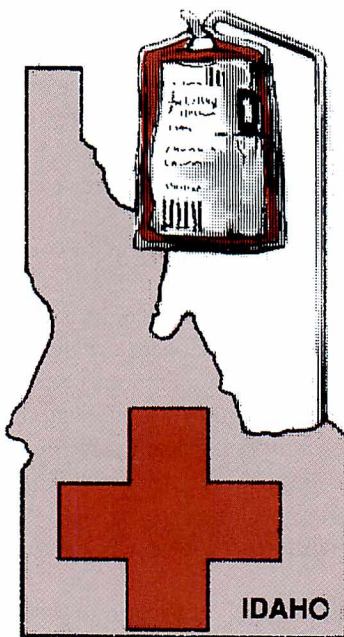
Only incontinence specialists with urology training in the procedure should perform the injection treatments.

FDA approved the product based on a clinical study of 271 men and women, of whom 90 to 96 percent experienced bladder control improvement. After one year, 69 to 80 percent remained improved.

The Contigen Bard Collagen Implant is made by Collagen Corporation of Palo Alto, Calif.

### Blood Products Recalled in Idaho

The American Red Cross in Boise, Idaho, recalled more than 2,000 units of blood products last October after Red Cross audits revealed the units had been collected from donors who had repeatedly tested reactive in previous HIV screening tests in 1985 and 1986. All recalled units tested negative for HIV antibody.



The American Red Cross in Idaho phoned and wrote letters to the 21 blood centers, 47 hospitals, and seven manufacturers in the 20 states that had received the blood products. It also notified FDA of the audit results.

The 2,291 units included whole blood, red blood cells, platelets, plasma, and cryoprecipitate blood component used to aid clotting. Of these units, 1,169 were collected from donors whose original test results were later determined to be false positives. The remaining 1,122 units were collected from donors ineligible to donate due to previous test results.

The audits indicated that due to a data entry error, these ineligible donors were not properly classified as "deferred donors." Deferred donors are excluded from giving blood because of questionable

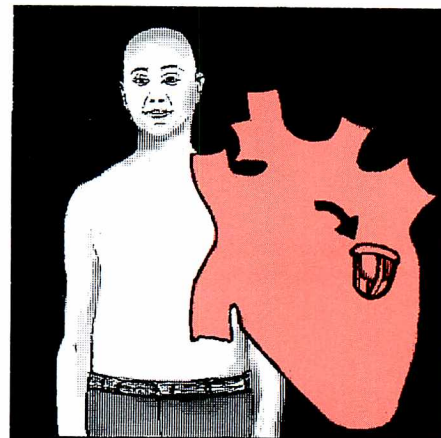
health history or disqualifying blood tests.

During a routine inspection following the audits, FDA determined that proper procedures were currently being followed.

### Distributors Must Make Device Reports

Medical device distributors must submit to FDA and to manufacturers reports of deaths and serious illnesses and injuries related to medical devices, according to a final rule published in the *Federal Register* Sept. 1, 1993.

Distributors must also report to manufacturers certain malfunctions that may cause death or serious illness or injury. Reports must be submitted within 10 working days after the distributor learns of the problem. Distributors must also certify to FDA each year the number of medical device reports from the previous year, and must establish files of information related to these reports.





The rule became effective May 28, 1992, following a tentative final rule published in the Nov. 26, 1991, *Federal Register*. The May effective date was mandated by the 1992 Medical Device Amendments to the Safe Medical Devices Act of 1990.

### **Volunteers Sought for Prostate Cancer Study**

The National Cancer Institute (NCI) and Southwest Oncology Group, San Antonio, Texas, are seeking 18,000 healthy men over 55 to participate in the first large-scale prevention trial for prostate cancer.

The Prostate Cancer Prevention Trial, to be conducted at 222 sites across the United States, will test whether taking the drug Proscar (finasteride) reduces the incidence of prostate cancer.

About 165,000 new cases of prostate cancer, and about 35,000 deaths, were expected in 1993, according to NCI director Samuel Broder, M.D. About 98 percent of prostate cancers are diagnosed in men 55 or older.

FDA approved Proscar in 1992 for treating benign prostatic hyperplasia (BPH), a noncancerous enlargement of the prostate gland. Because BPH and prostate cancer are influenced by similar hormonal factors, researchers believe that Proscar may prevent prostate cancer.

Half the men in the trial will take one 5-milligram tablet of Proscar per day for seven years, and half will take a placebo. The two groups will then be compared to

determine whether their prostate cancer rates differ. Researchers will also compare the stage and grade of prostate cancer, incidence and severity of BPH, deaths from prostate cancer, and overall deaths in the two groups.

Merck and Co., Inc., Whitehouse Station, N.J., manufacturer of Proscar, will provide both the drug and the placebo for the study.

"Ideally, we'd like to recruit men from all racial and ethnic groups—African-Americans, whites, Native Americans, Hispanics, Asian-Americans—roughly in proportion to their risk of developing the disease," said Otis Brawley, M.D., of NCI's Community Oncology and Rehabilitation Branch.

Healthy men aged 55 or older who are interested in participating in the trial should call NCI's Cancer Information Service at (1-800) 4-CANCER to locate the center nearest them. The center will provide more information on eligibility.

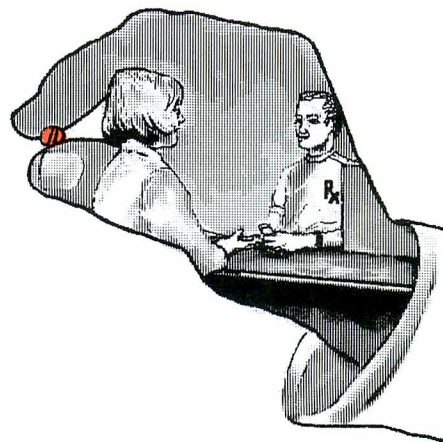
### **Correct Use of Medicine**

Americans have made significant progress over the past 10 years in using medicines correctly, according to a report by the National Council on Patient Information and Education (NCPIE). People have learned to ask more questions about their medicines, senior citizens are getting their medicines reviewed, and health-care professionals are counseling patients better, the report says.

The report, "Making Proper Medicine Use a National Priority," credits this progress to education efforts of consumer

groups, physicians, pharmacists, nurses, drug manufacturers, voluntary health organizations, and FDA. Through the efforts of these groups:

- Eighty-eight percent of patients were told by their doctors how much medicine to take and how often to take it.



- Eighty-one percent of patients received instructions on how long to continue use.
- Eighty-one percent of persons 45 and older were "very likely or somewhat likely" to ask the doctor questions about a new prescription.
- Eighty-four percent of persons 45 or older were told by or asked their doctor about how and when to take their prescription medicine.
- Fifty-nine percent were told or asked about precautions.
- Fifty-five percent were told or asked about side effects.



## UPDATES (continued)

The NCPIE report identifies current goals and ways to accomplish them, including research into consequences of poor compliance, working groups to establish guidelines for medicine counseling, and a national clearinghouse of medicine information and resources.

For more information on the report write to NCPIE, 666 11th St., Suite 810, Washington, DC 20001; telephone (202) 347-6711.

### Free Reprints

New *FDA Consumer* reprints are available free. The publications are:

- Lead Threat Lessens, but Mugs Pose Problem (FDA 93-1209)
- Protecting Patients and Professionals from Blood-Borne Disease (FDA 93-9010)

- On the Teen Scene: Preventing STDs (FDA 94-1210)

- Hair Dye Dilemmas (FDA 94-5014)

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## CONSUMER FORUM



### NFP Explained

"Choosing a Contraceptive," *FDA Consumer*, September 1993, gives such an inadequate description of the Natural Family Planning methods, otherwise known as periodic abstinence, that the piece invites misinterpretation. Calendar rhythm, while still widely used, is the least reliable of the natural methods because it only averages the last six cycles' lengths to estimate the occurrence and length of the fertile phase.

Modern scientific natural family planning is based on self detection of cervical mucus at the vulva which accurately reflects the rising estrogen of the developing follicle. It is also known that mucus will keep sperm alive in the woman's reproductive tract until ovulation. The mucus goes through a changing pattern called build-up, then changes abruptly when progesterone rises from the now-developing corpus luteum. The fertile phase of the couple is from the beginning of mucus until the fourth day after peak. When double index methods are used, the beginning of post-ovulatory infertility is confirmed by the thermal shift caused by the rising progesterone. Because mucus marks the beginning of fertility, NFP can be used by women with irregular cycles or no cycles, as during lactation.

The use effectiveness figures cited are very old and apply to calendar rhythm. When the method is properly taught and practiced, unplanned pregnancies are less than three percent. Total use effectiveness studies from 1980-1991 reported 2.0-27.9 cumulative life table net pregnancy rates. The 1980 and 1981 reports were above 20% while the more recent studies reported far lower rates. (Kambic, RT. "Natural Family Planning Use-Effectiveness and Continuation." *Am J Obstet Gynecol* 1991; 165:2046-8). Similarly, Ryder, writing in the *British Journal of Medicine* (1993; 307:723-6, 18 September 1993), writes "increasingly studies show that [effectiveness] rates [of natural family planning are] equivalent to those with other contraceptive methods [and] are readily achieved in the developed and developing worlds. Indeed a study of 19,843 poor women in India had a pregnancy rate approaching zero. Natural family planning is cheap, effective, without side effects, and may be particularly acceptable to and efficacious among people in areas of poverty."

Hanna Klaus, M.D.  
Executive Director  
Natural Family Planning Center of Washington, D.C., Inc.  
Bethesda, Md.

*Ed. replies: The description of periodic abstinence in "Choosing a Contraceptive" did include a short discussion of self-detection of cervical mucus and thermal shifts. We thank Dr. Klaus for this additional information. Effectiveness rates in the article for all contraceptive methods were based on scientific studies of actual use (not perfect use). As the article's chart points out, the rates were based on a number of different studies; methods dependent on conscientious use are subject to a greater chance of human error and, thus, reduced effectiveness. We thank Dr. Klaus for bringing specific NFP studies to our readers' attention.*

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



# HOW TO OUTSMART DANGEROUS E. COLI STRAIN

BY JUDITH E. FOULKE

**S**cientists have recently identified a rare but dangerous type of the *Escherichia coli* bacterium. Most *E. coli* are harmless inhabitants of the intestinal tract, but this variant, called *E. coli* O157:H7, produces toxins in the human gut that are capable of deadly damage.





On Jan. 13, 1993, a physician in Washington state reported a cluster of children with hemolytic uremic syndrome (HUS), the major cause of acute kidney failure in children in this country. There was also an increase in emergency room visits for bloody diarrhea in people of all ages.

Laboratory tests from the stools of infected patients showed *E. coli* O157:H7. Most infected people had eaten hamburgers from local restaurants of Jack-in-the-Box, a nationwide fast food chain.

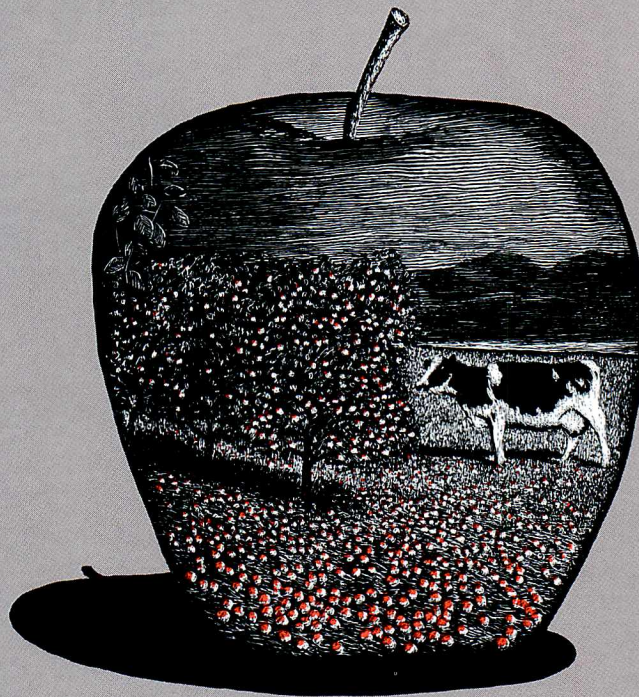
Health officials investigated the illness reports and traced the meat in the hamburger patties to one processing plant but were not able to determine the source of the meat. Investigators also discovered that the patties had been undercooked at the restaurant. Thorough cooking would have killed the bacteria, but live, they were free to do their damage.

Reports of illness continued to mount and by the end of February, three children in Washington state and one other in California had died of HUS complications. More than 500 people from Washington, Idaho, California, and Nevada had laboratory-confirmed *E. coli* O157:H7 infections. Of those, more than 50 people had been infected by person-to-person contact with someone who had eaten the contaminated hamburgers.

As news of the outbreak spread, reports of previous food-borne illnesses involving *E. coli* O157:H7 were collected and reviewed. One outbreak in 1991, caused by contaminated fresh-pressed, unpreserved apple cider from a southeastern Massachusetts mill, had resulted in the hospitalization of four children with HUS. Another 17 children required medical treatment (see "How Did It Get in Apple Cider?").

Before the Massachusetts mill incident, it was not common knowledge that this strain of *E. coli* could survive the acid environment of apple cider. Scientists from the national Centers for Disease Control and Prevention and from the University of Georgia continued to study the cider mill

## How Did It Get in Apple Cider?



Cider is often made with apples that have dropped from orchard trees and are not aesthetically pleasing enough to be sold for eating raw. On the ground, the apples may become contaminated with farm animal feces or manure fertilizer. If not washed and brushed before pressing, harmful bacteria could contaminate the cider. This is what scientists speculate happened in the 1991 Massachusetts cider mill outbreak, in which at least 21 people became ill. (Other apple products, such as applesauce and apple juice, are heated during processing or pasteurizing, thus killing the harmful bacteria.)

In a May 5, 1993, article in the *Journal of the American Medical Association*, Richard E. Besser, M.D., and colleagues from CDC concluded that fresh-pressed apple cider can transmit *E. coli* O157:H7 and cause illness. "Risk of transmission can be reduced by washing and brushing apples before pressing, and preserving cider with sodium benzoate," they said. They advise consumers to reduce their risk by only drinking cider made from apples that have been washed and brushed.

USDA advises that while most fresh cider on the market today is probably safe, you may want to take extra precautions if your family includes at-risk persons such as the very young, the elderly, or people with immune system problems. In that case, buy pasteurized cider or heat the cider to 160 degrees Fahrenheit (a slow simmer, with steam starting to rise from the pan) before serving or refrigerating. Hard cider, the kind sold in liquor stores, is pasteurized. ■

—J. E. F.



outbreak, and published a number of reports in professional journals.

Then, last July and August, several months after the ground beef outbreak in the northwestern states, people who had eaten at two Oregon restaurants of another nationwide chain became ill with confirmed *E. coli* O157:H7 infections. At press time, public health officials, including Food and Drug Administration scientists, were trying to identify the food source of the contamination.

### Bug Not Always Bad

Not all *E. coli* are harmful. *E. coli* is one of several bacterial types that are normal to the human gut and pass through the intestinal tract with feces. It has been known for many years that in healthy people, this group of bacteria and other normal microbial flora reduce the chance of pathogens—harmful bacteria that enter the body through food and water—from colonizing in the intestines and possibly causing illness.

*E. coli* is also helpful outside the body. In food laboratories, scientists use *E. coli* as an indicator of contamination, explains microbiologist Peter Feng, Ph.D., of FDA's Center for Food Safety and Applied Nutrition (CFSAN). If *E. coli* can be isolated from the suspect food, it implies that the food is contaminated by fecal matter, he says.

Research scientists also put the bug to good use in DNA studies (see "When *E. coli* Is Helpful").

"It's because of the knowledge that *E. coli* is a normal intestinal inhabitant that studies of potentially harmful strains were delayed," says CFSAN microbiologist Joseph Madden, Ph.D. "We now know of at least six types of *E. coli*, including O157:H7, that are particularly virulent and can cause serious illness."

CDC first isolated *E. coli* O157:H7 in 1975, and in 1982 identified it as the cause of severe bloody diarrhea traced to contaminated ground beef patties during two

illness outbreaks in Oregon and Michigan. Since then, CDC has reported about 16 major outbreaks in the United States, with 22 deaths. Most of the fatalities have been young children or elderly people, the two age groups most vulnerable to HUS from *E. coli* O157:H7.

Reports of outbreaks are increasing, according to CDC, mostly because of public awareness. Physicians have been alerted through professional publications and public announcements to report cases of bloody diarrhea, the most common symptom, to public health officials. Such reporting helps identify clusters of cases.

It is the toxin produced by *E. coli* O157:H7 in the intestines of humans that damages cells of the intestinal lining. This damage allows blood to pass into the patient's stool. Other symptoms include stomachache, nausea and vomiting.

HUS develops in 2 to 7 percent of *E. coli* O157:H7 illnesses. In these cases, the toxin enters the patient's bloodstream through the damaged intestinal wall, travels to the smaller arteries that supply the kidneys, and damages the vessels. HUS is fatal in about 3 to 5 percent of the cases.

*E. coli* O157:H7 survive refrigerator and freezer temperatures. Once the bacteria get in food, they can multiply very slowly at temperatures as low as 44 degrees Fahrenheit. The actual infectious dose is unknown, but most scientists believe it takes only a small number of this particular strain of *E. coli* to cause serious illness.

*E. coli* O157:H7 bacteria can contaminate any food. Undercooked hamburger and roast beef, raw milk, improperly processed cider, contaminated water, and vegetables grown in cow manure have caused illness outbreaks in the United States. Undercooked ground beef has been the food source in most reported cases. Harmful bacteria that are

sometimes on the surface of raw meat get mixed through the meat in the grinding process.

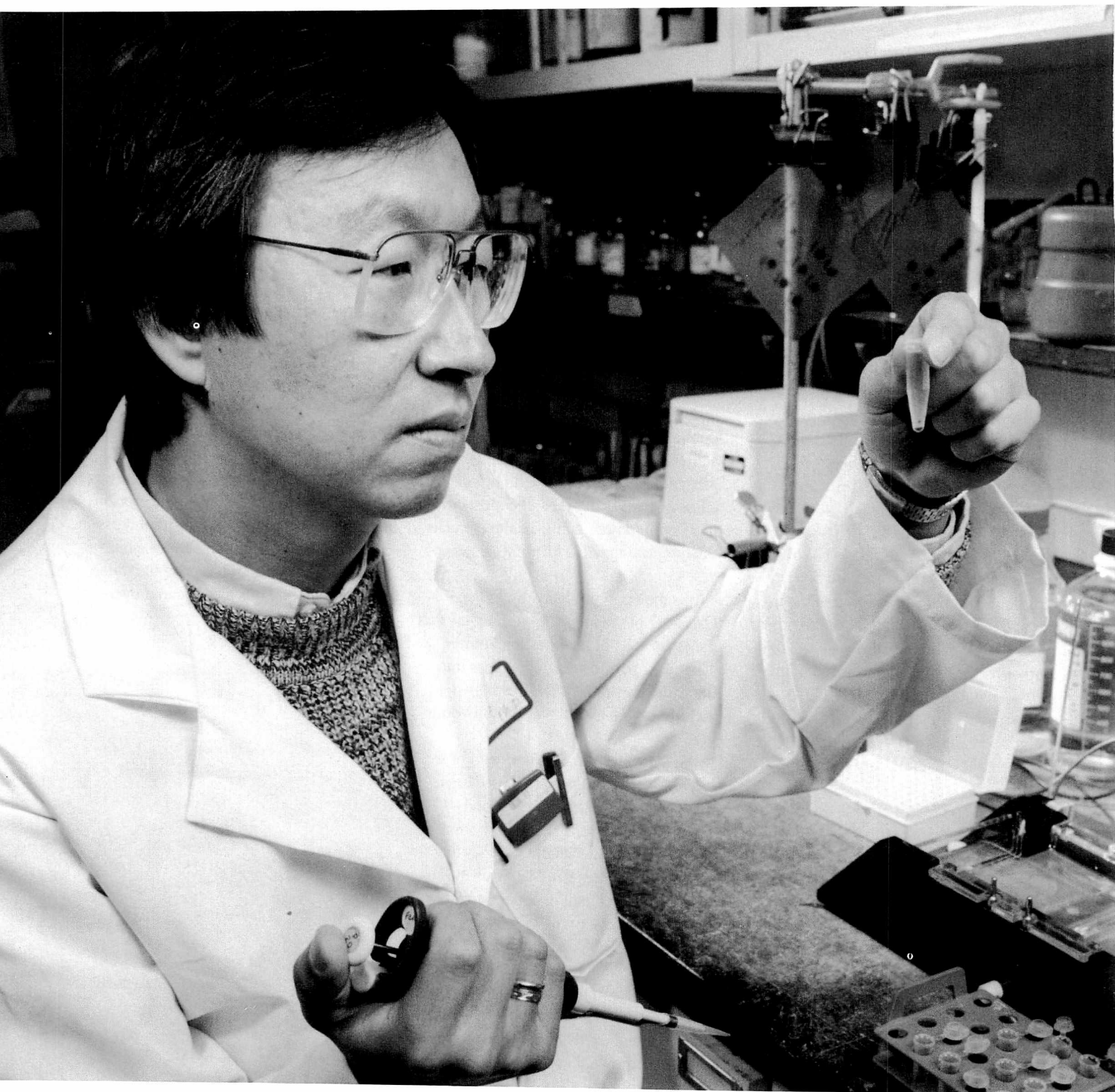
Thorough cooking kills *E. coli* O157:H7. A ground beef dish will be safely cooked when it reaches an internal temperature of at least 160 degrees Fahrenheit. The ground beef should not be pink in the center, and the juices should run clear. All leftovers should be reheated to 165 F.

Besides food-borne transmission, *E. coli* O157:H7 can be passed from one person to another or through food-to-food cross-contamination. Thorough hand washing with soap and water after using the toilet or changing a baby's diaper can prevent

## Quick Information

Information about safe handling of ground meat and ground poultry is available from USDA's toll-free Meat and Poultry Hotline, (1-800) 535-4555, 10 a.m. to 4 p.m. Eastern time, Monday through Friday. Seafood safety information is available through FDA's Seafood Hotline, (1-800) FDA-4010—in the Washington, D.C., area, call (202) 205-4314—24 hours a day. FDA public affairs specialists can be reached from noon to 4 p.m. Eastern time, Monday through Friday. ■





*FDA microbiologist Peter Feng, Ph.D., examines a test tube holding E. coli O157:H7 DNA. Feng developed the DNA probe to specifically identify this organism.*



# When *E. coli* Is Helpful

Some types of *E. coli* bacteria coexist peacefully in the human mouth and gut, and even contribute to our well-being. For example, bacteria in our intestines produce bacteriocins, bactericidal proteins that kill only the few organisms closely related to the one that produced it. (Bacteriocins from *E. coli* are known as colicins.) Bacteriocins, normal intestinal bacteria and their waste products, and the lack of available oxygen prevent other, perhaps dangerous, types of bacteria from competing for space. Antibiotics, taken indiscriminately, reduce the normal bacteria in the intes-

tines, sometimes allowing illness-producing types to get the upper hand.

*E. coli* in the gut also produce vitamins B<sub>12</sub> and K in amounts large enough to be valuable should the diet become deficient.

Starting in the 1940s, scientists began working on the genetics and biochemistry of *E. coli*. That work and subsequent research has made *E. coli* a very well-understood organism. Since the 1970s, when scientists discovered that genetic material could be spliced into the bacteria and replicated, *E. coli* has become the "bug of choice" for cloning genes, says FDA geneticist Thomas Cebula, Ph.D.

In 1974, scientists spliced frog DNA into *E. coli*, and the bacteria replicated the gene. In 1977, the first human gene was spliced into *E. coli* for cloning the hormone somatostatin. In 1978, human insulin was synthesized, and in 1982, using the cloning technique, bioengineered insulin became commercially available. Also in 1982, a cancer gene from human bladder cancer cells was isolated and cloned in *E. coli*, beginning a new technique for cancer research. ■

—J. E. F.

person-to-person transmission. Proper food handling, such as not allowing raw meat juices to mix with cooked food, will help avoid cross-contamination.

## Solving the Problem

Food scientists from CFSAN, USDA's Food Safety and Inspection Service, CDC, and state health departments have been working together to track down possible sources of transmission of *E. coli* O157:H7. Public health officials first needed a laboratory test that would specifically identify O157:H7. Available laboratory tests identified toxins or toxin genes from *E. coli* O157:H7 that are similar to *Shigella* bacteria, but were not specific for O157:H7.

This year, FDA's Feng developed a DNA probe that reacts only with *E. coli* O157:H7 and can specifically identify the organism in about 36 hours. Though this is an improvement, scientists hope for even better tests.

"Faster tests are needed, but we need technology that is more sensitive than what we have today to create a more rapid test," says Feng. "The problem is that sometimes it doesn't take large num-

bers of the bacteria to make people sick—it can be dangerous in low numbers. In order to find the few cells that might be there, we have to put the suspected contaminated food in a growth medium for hours or days to allow the bacteria to grow. The O157:H7 bacteria have to multiply to at least 10,000 for current tests to 'see' them. The need for an enrichment process will continue to slow us down until more sensitive technology is available."

(For information about DNA laboratory techniques, see "High-Tech Tools for Food Safety Sleuths" in the November 1992 *FDA Consumer*.)

USDA recently developed a Pathogen Reduction Program to strengthen efforts to keep harmful pathogens out of the food supply. As part of this food safety initiative, USDA is working with CDC to identify critical control points in meat processing at which contamination might occur. The agencies are preparing recommendations that will help processing plants avoid contamination at these points.

USDA also recently published two new regulations aimed at food safety: One requires labeling on all raw meat and poultry products to give consumers safe handling

instructions, and the other specifies the heat-processing, cooling, handling, and storage requirements to be followed by processors of partially and fully cooked uncured meat patties, including veal and pork sausage. (At press time, enforcement of the safe handling labeling for consumers had been delayed.)

In addition, USDA has asked researchers at the University of Georgia to study the possibility of immunizing cattle against *E. coli* O157:H7. Preliminary research has identified an antigen specific to enterohemorrhagic *E. coli* that may be useful in developing a vaccine.

Although food scientists and public health officials are constantly improving techniques to ensure food safety, Feng reminds consumers that raw foods will never be bacteria-free and even cooked foods can easily be recontaminated. But proper cooking will kill most harmful bacteria. Consumers can help guard against food-borne illness by applying some commonsense food safety rules for storing, cooking and serving foods. ■

Judith E. Foulke is a staff writer for *FDA Consumer*.







# Shiley SAGA LEADS TO IMPROVED COMMUNICATION

by Dixie Farley

**C**arol Barbee's mechanical heart valve fractured. But because she and her husband, Fred, didn't recognize the symptoms or her need for immediate valve replacement, he rushed her to the nearest clinic rather than a hospital equipped for open-heart surgery. After she received treatment inappropriate for a patient with a fractured heart valve, she was finally taken to a hospital and had the operation. It was too late. Carol Barbee died.

The tragedy was described in February 1990 at a congressional hearing on Bjork-Shiley Convexo-Concave (C-C) heart valves, which had earlier been taken off the market because of their increased fracture risk. (Current mechanical heart valves aren't subject to the extent of fractures affecting C-C valves.) "Convexo-Concave" refers to the shape of the disk portion of the valve.

In 1990, the fracture risk for the C-C valve was estimated at 2 to 30 per 10,000 patients per year, depending on valve size and other factors. It is now known that a small number of C-C valve patients face a much higher risk. Although the overall fracture risk is small, fracture is very serious. Only about 1 in 3 patients survive valve fracture. Prompt diagnosis and proper treatment can increase a patient's chance of survival.

Indeed, had the Barbees known her increased risk of fracture and the symptoms to watch for, and had she had her valve replaced promptly after it fractured, Carol Barbee might have been among those surviving patients.

It's estimated that, in 1990, some 23,000 Americans and Canadians were

living with implanted C-C heart valves. For these people, says the Food and Drug Administration's Carol Vetter, "Barbee's story brought forth an important message: Armed with information about their risk of valve fracture, symptoms of possible fracture, and steps to take if symptoms appear, patients can help save their lives." Vetter is director of the division of consumer affairs at FDA's Center for Devices and Radiological Health (CDRH).

Like Barbee, many patients hadn't received this information.

But in the spring of 1990, Vetter says, Shiley Incorporated, of Irvine, Calif., the manufacturer, discussed with CDRH plans to develop a program with Medic Alert to locate, register and inform C-C valve patients, with the assistance of their doctors, about the fracture risk.

## Many Changes

CDRH's concurrence led to a change in the way FDA expects manufacturers to communicate information about significant risks with critical devices (those permanently implanted or whose failure may be life-threatening). And it led to unprecedented efforts by a manufacturer, with FDA oversight, to directly notify patients so they can take part in making informed decisions about their health care.

The C-C valve episode prompted new legislation (see "Regulatory Changes") that strengthens FDA enforcement, thereby ensuring as much as possible that defective critical devices are off the marketplace.

"Today," says Ronald Johnson, director of CDRH's Office of Compliance, "our own sophistication and ability to judge critical device issues and our own statisti-



## FOR PEOPLE WITH C-C VALVES

Patients who have Bjork-Shiley C-C heart valves should:

- get medical help immediately if these symptoms *suddenly* appear: unconsciousness, shortness of breath, chest pain, irregular or rapid heartbeat, or change or absence of the usual sound or sensation of the valve opening or closing
- know the location of the nearest hospital equipped for open-heart surgery
- enroll free in Medic Alert's International Implant Registry by calling (1-800) 245-1492.
- discuss concerns with their doctors.

Replacing an intact valve is not recommended for most patients because the risk of death from the surgery may be greater than the risk of strut fracture. Both risks vary due to such factors as valve size, weld date, and position and may also depend on the patient's age, gender, and state of health. ■

—D.F.



PROMPT diagnosis AND PROPER TREATMENT CAN  
INCREASE A PATIENT'S CHANCE TO SURVIVE A FRACTURED  
HEART VALVE.

cal and epidemiological expertise help to safeguard our decisions."

FDA had approved the C-C valve in 1979, before the full extent of the fracture problem was known. In ensuing years, it became more and more apparent that fractures were continuing to occur with this valve, even though Shiley made various attempts to correct the problem—including, on several occasions, recalling some particular valves.

Throughout, Shiley maintained that the fracture risk was more than offset by the C-C valve's lower frequency of blood-clotting (thromboembolic) complications, which may cause stroke or kidney failure. This appeared to be a compelling argument, because such complications are a serious risk with all mechanical heart valves, occurring in 1 to 4 percent of heart valve patients each year. But in 1984, FDA performed its own study comparing the rate of clotting complications in the C-C valve with an older Shiley valve. Statistician Harry Bushar, Ph.D., of CDRH's division of biometric sciences, performed the analysis. "I found no significant difference in thromboembolic complications between the two types of valves," Bushar says.

Shiley decided to stop marketing C-C valves in 1986.

The firm sold its manufacturing facilities in February 1992 to Sorin Biomedica, a subsidiary of Fiat Company, Italy. Shiley no longer makes any products. Neither Sorin nor any firm currently makes C-C valves.

### Patients Need to Know

Under the Federal Food, Drug, and Cosmetic Act, FDA has authority to require that patients be directly notified about device problems posing an unreasonable risk of substantial harm to the public health.

However, if FDA determines a direct

notification would increase rather than decrease harm to the patient, the agency may look to doctors to inform their patients.

Traditionally, FDA relied on manufacturers to notify medical facilities and doctors about the risk of a particular implanted device failing or malfunctioning. Doctors could then use discretion, based on knowledge of a patient's medical or mental state and other factors, about whether and how to inform patients. A doctor might decide, for instance, that a letter about an increased risk sent directly to someone already sick would be so shocking the person would become even more ill.

However, Vetter, who coordinated CDRH's early efforts to examine the notification process, says, "We learned that not only patients but also doctors with a need to know, were not necessarily learning of significant heart device problems."

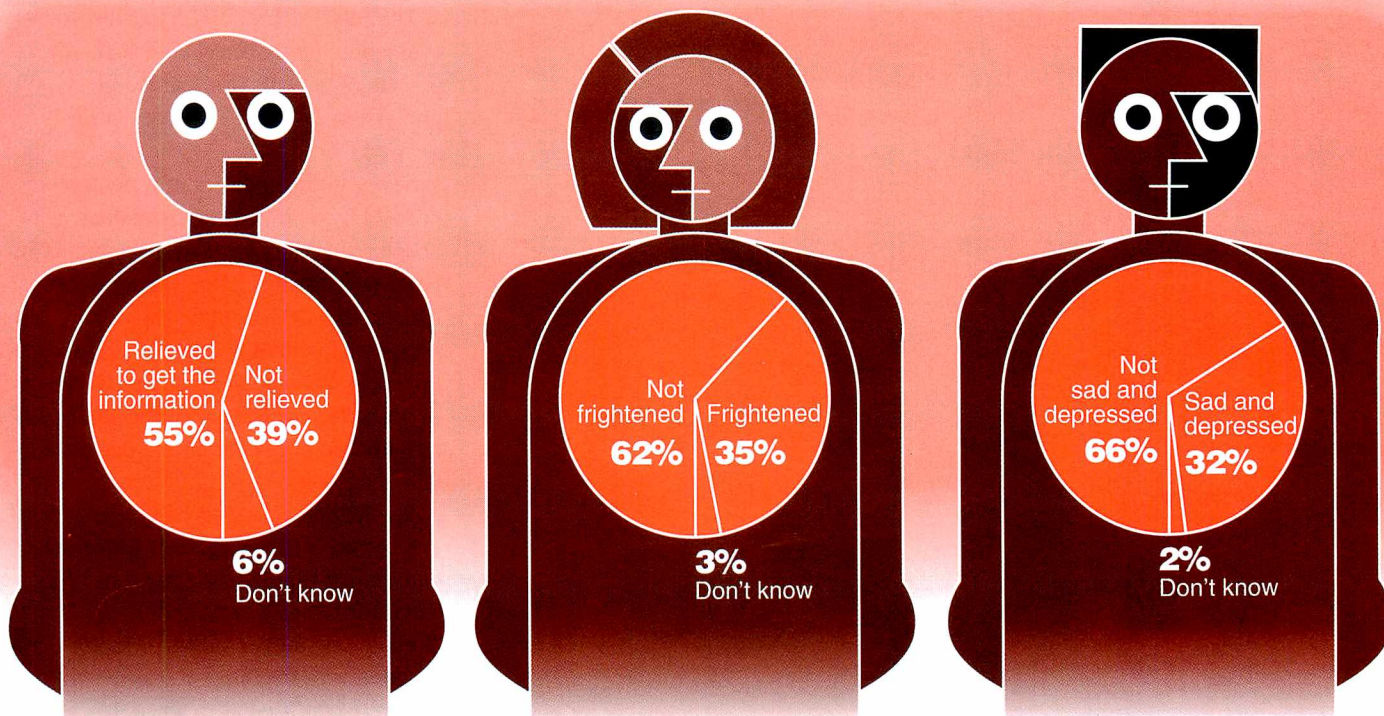
Thus, in March 1990, FDA began holding public meetings on the notification process with heart-device implant recipients and their spouses, patient advocacy groups, health professional groups, and firms that make implantable heart devices. These meetings, and the February 1990 congressional hearing, set the stage for FDA decisions about a Shiley patient notification program, Vetter says. "They molded our ideas on how it should take place, when to notify doctors, when to notify patients, and what information to give each group."

In September 1990, Shiley provided FDA with a specific plan. Shiley would grant \$1.5 million to Medic Alert Foundation, a nonprofit group, to work with health-care professionals to:

- identify and locate patients with C-C valves
- notify patients of the fracture risk, symptoms of possible valve fracture, and actions to take if symptoms appear



# Patient Reactions



What do patients with Bjork-Shiley Convexo-Concave heart valves think about being told they have an increased risk of valve fracture? Many patients apparently deal with this frightening issue quite well, according to these findings from an interim evaluation of the Medic Alert patient notification program.

(Source: Frank N. Magid Associates, Inc.)

- enroll patients free in its International Implant Registry.

The plan called for pretesting the letters with patients, doctors, and risk communication experts. (Shiley also was working on a plan to notify foreign governments about the U.S. program.)

FDA agreed to the plan, and by October the pretesting was completed. Based on the responses, several changes were incorporated into new letters. As the experts suggested, for example, the letter to patients was changed to begin with the positive message about the registry, to cushion the shock of the negative message about the risk.

On Nov. 30, 1990, Medic Alert sent let-

ters to approximately 20,000 U.S. and Canadian heart specialists asking for the names of C-C valve patients. As doctors identified patients, Medic Alert sent the doctors information kits and letters addressed to their patients, and, a few days later, a Mailgram reminder to provide their patients with the letters and discuss the letters with them. (Later, Medic Alert asked hospital administrators to search their records for C-C valve patients.)

Medic Alert's protocol is to call the doctors, several times if needed, to see if they've notified their patients. If not, it notifies the patients by certified mail. It also calls the patients to urge free enrollment in the registry. Each patient who joins (see

box) receives an ID card and a bracelet or neck chain stating the wearer has a C-C valve and providing emergency care information.

## Getting the Message Across

CDRH's Office of Compliance built into its evaluation of the Shiley notification program "mechanisms to continually keep us informed of its effectiveness," says Betty Collins, a consumer safety officer who coordinated Shiley-related activities by different FDA offices. "Monthly reports, a mid-course evaluation, periodic audits by an outside contractor, as well as FDA audits of physicians and patients provided valuable information."



# Valves Replaced in Study

As of Sept. 21, 1993, nine patients in one clinical study have had their "C-C" mechanical heart valves replaced after an experimental x-ray technique identified the valves as probably partially fractured.

That FDA-approved study includes 300 patients whose Bjork-Shiley Convexo-Concave (C-C) heart valves are at high risk of fracture. The Shiley Heart Valve Research Center, of Irvine, Calif., funds this and other studies to detect partially fractured implanted C-C valves that may be prone to catastrophic failure. FDA urged Shiley to expedite such studies, with the agency's consultation and cooperation. Shiley Incorporated, no longer a manufacturer, established the center in 1991.

"Early efforts analyzed the sounds the valve emits during cycling," says Daniel Chwirut, a mechanical engineer with FDA's division of mechanics and materials science. "The theory is these sounds change if the valve starts to fracture. Shiley-sponsored studies in sheep show a valve may function in a partially fractured

condition for months. Detection of this condition would allow for valve replacement before catastrophic failure."

Then Shiley researchers learned of new x-ray equipment that may be sensitive enough to detect separation (see photo) of a single leg on a valve's outlet support strut. After they determined the equipment was both sensitive enough and safe enough in tests with sheep, Chwirut says, they decided to test it with humans in this current clinical study.

Until more is known about the test's accuracy, FDA is maintaining the testing program as an investigational study. The agency is concerned the test might falsely indicate partially fractured valves in patients with intact valves, causing needless surgery—as happened with one patient. Another concern is the test might falsely indicate intact valves in patients with partially fractured valves, preventing needed valve replacement. ■

—D.F.

The July 1991 report on the mid-course evaluation, for instance, indicated only 9 percent of patients first learned of the program from a doctor. The report also showed that:

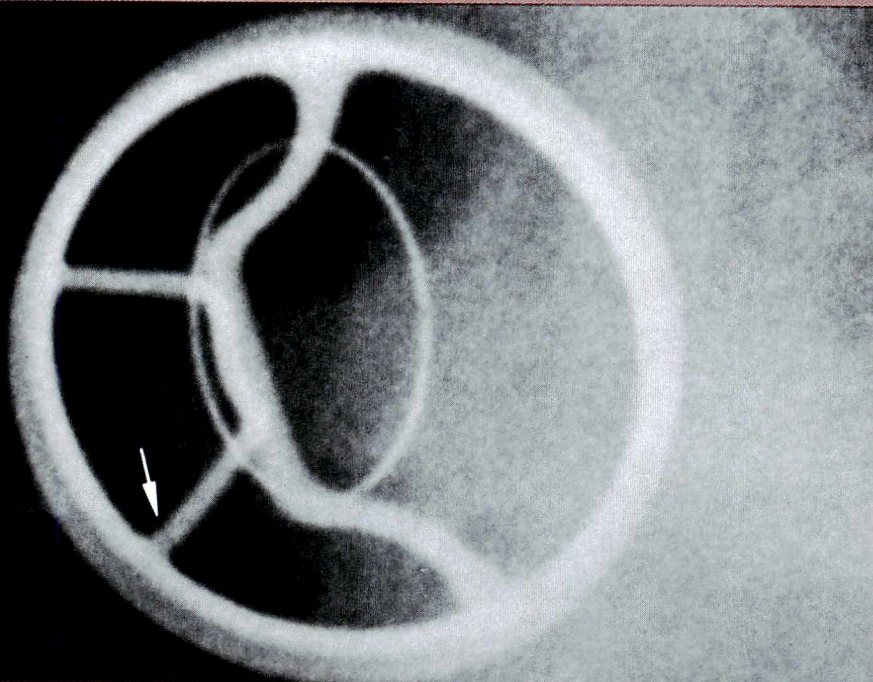
- Seventy-three percent of patients were not told by their doctors about the type of hospital they should go to if symptoms appear, although the "Dear Doctor" letter had advised doctors to do so.
- Forty percent of doctor-patient follow-up discussions did not mention symptoms of possible strut fracture, although the letters advised both doctors and patients to talk about this.

The letters to patients hadn't mentioned symptoms, Vetter says, because when the letter's first draft was pretested in 1990, this information caused confusion. "People said they often had symptoms associated with fracture, such as dizziness, and were confused as to when they should consider it serious."

On the basis of the mid-course evaluation, FDA told Shiley that future letters to patients should explain the symptoms and stress the need for an emergency plan that includes locating the closest hospital with open-heart surgery capability. As directed, Medic Alert gave previously notified patients this information.

An April 1992 report on FDA's own audit revealed that some doctors were still reluctant to participate in the program. It also showed a number of hospitals were not taking part, Collins says, "so we sent them letters encouraging them to participate. We also ordered two hospitals to identify C-C valve patients to Shiley. The number of identified patients soon increased."

That month, Shiley told FDA about new risk estimates in a Dutch study. FDA told the firm to directly notify patients and their doctors that patients with certain valves may have a risk up to four times higher than revealed before, and that patients under age 50 at implantation may be



*The arrow in this x-ray image of an implanted Bjork-Shiley Convexo-Concave heart valve points to a single-leg separation (where one leg of the strut has separated) in the valve's "outlet" strut. The whitish mass in the background on the right is the patient's spine.*

*(Photo courtesy of Shiley Heart Valve Research Center)*



# REGULATORY CHANGES

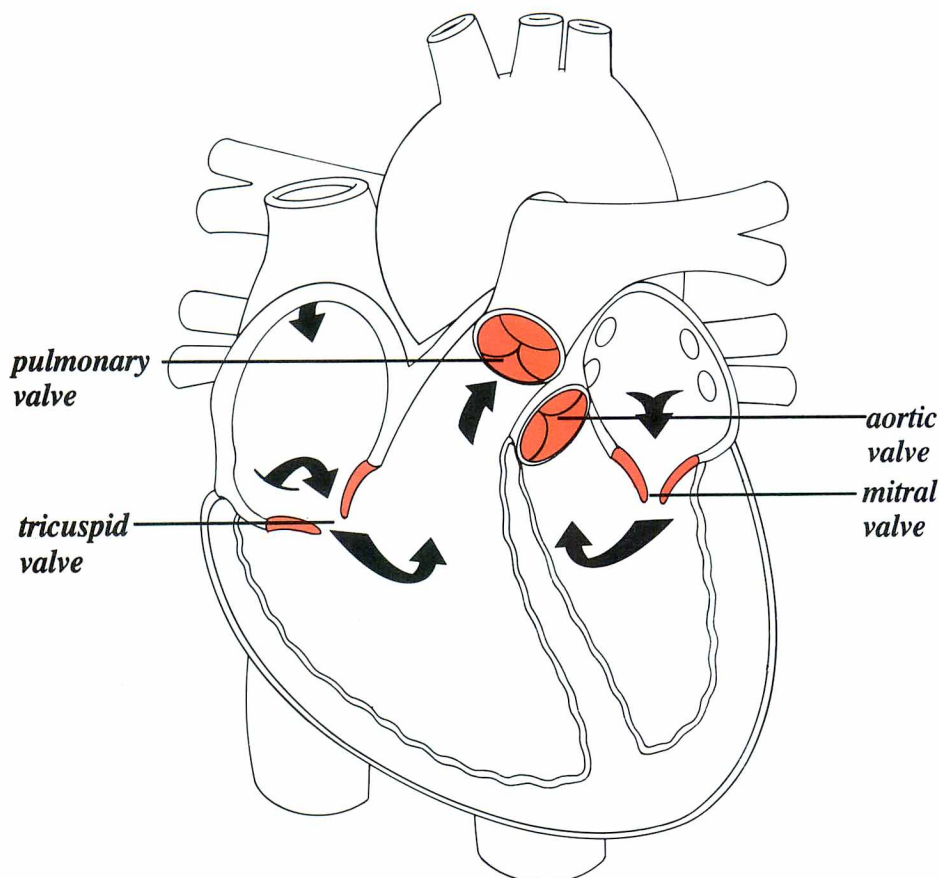
Enactment of the Safe Medical Devices Act of 1990 and stricter FDA enforcement under the Medical Device Amendments of 1976 help reduce health risks to patients from mechanical heart valves and other critical devices—those permanently implanted or whose failure could be life-threatening.

FDA regulatory changes due to these actions include:

- expanding problem reporting on implanted devices by—besides firms—hospitals, nursing homes, and diagnostic and outpatient facilities
- mandatory effective critical device tracking and record keeping by manufacturers to speed patient notification should problems arise
- identifying devices marketed before the 1976 amendments that have potential safety problems, setting priorities in addressing the problems and calling for pre-market approval applications or additional data from manufacturers to justify continued marketing
- strengthening criteria for approving critical devices, such as stringent engineering and preclinical tests as well as the previously required clinical trials on patients
- requiring firms, as a condition of approval, to sign an agreement that specifies conditions under which they must report to FDA; one such condition is making significant manufacturing changes
- expanding FDA enforcement to order recalls of defective devices, apply civil penalties for violations, or temporarily suspend pre-market approval applications of devices with serious health risks.

Before mass-producing a device, a firm may have to prove to FDA by further testing that the product will operate as intended. ■

—D.F.



*As blood is pumped through the heart, the four valves of the heart open and close to allow blood flow in only one direction, indicated by the arrows. The Bjork-Shiley Convexo-Concave (C-C) heart valve (not sold since 1986) had been approved to replace malfunctioning aortic and mitral valves. Some patients have C-C valves in both these positions.*

at higher risk than older patients.

Additionally, as FDA instructed, Shiley directly notified certain C-C valve patients and their doctors in March 1993 of new risk estimates provided by Ronald Brookmeyer, Ph.D., a statistician at Johns Hopkins University, under a Shiley contract. Brookmeyer found a possibly increased risk for men under 50 at implantation, compared with women under 50 at implantation and men 50 or more at implantation. Fracture rates depend on valve position (mitral or aortic), size, and weld date, he found.

"Our goal continues to be to get potentially life-saving information to all patients with C-C heart valves," Collins says.

As of May 31, 1993, Medic Alert had located 19,325 American and Canadian C-C valve patients: 7,510 have died (most from causes other than fracture), and 10,919 have intact valves. Another 2,949 patients have been identified, but not yet

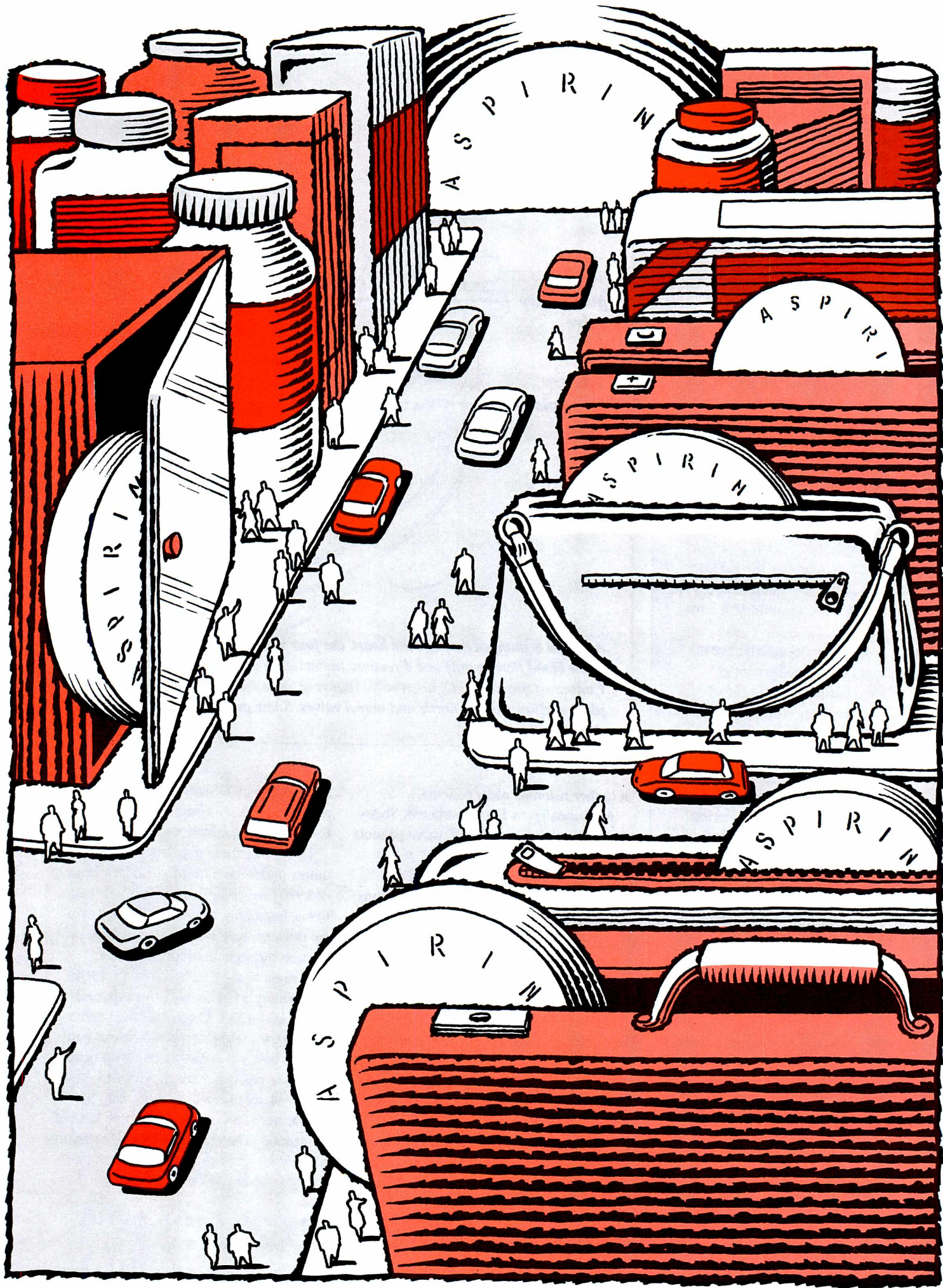
located. Shiley's Sept. 2, 1993, quarterly report to FDA confirms 386 fractures of C-C valves implanted worldwide.

To speed patient notifications, FDA requires under the Safe Medical Devices Act of 1990 (see "Regulatory Changes") that firms, beginning last Aug. 29, track critical devices such as heart valves from production through distribution to users.

"Tragic as they've been, the problems with Shiley's C-C heart valves spurred everyone—FDA, Congress, manufacturers, doctors, and patients—to take a hard look at how we communicate with people about the risks of medical devices," Vetter says. "Many provisions of the Safe Medical Devices Act resulted from that kind of rethinking. These provisions will certainly make it easier to communicate with patients in the future." ■

*Dixie Farley is a staff writer for FDA Consumer.*







# ASPIRIN

## A New Look at an Old Drug

by Ken Flieger

**I**N purses and backpacks, in briefcases and medicine chests the world over, millions of people keep close at hand a drug that has both a long past and a fascinating future. Its past reaches at least to the fifth century B.C., when Hippocrates used a bitter powder obtained from willow bark to ease aches and pains and reduce fever. Its future is being shaped today in laboratories and clinics where scientists are exploring some intriguing new uses for an interesting old drug.

The substance in willow bark that made ancient Greeks feel better, salicin, is the pharmacological ancestor of a family of drugs called salicylates, the best known of which is the world's most widely used drug—aspirin.

Americans consume an estimated 80 billion aspirin tablets a year. The *Physicians' Desk Reference* lists more than 50 over-the-counter drugs in which aspirin is the principal active ingredient. Yet, despite aspirin's having been in routine use for nearly a century, both scientific journals and the popular media are full of reports and speculation about new uses for this old remedy. The National Library of Medicine's main computerized catalog includes more than 2,700 scientific articles about aspirin. And those are only the English language publications that have appeared in the last five years.

Yet aspirin's beginnings were rather unspectacular. Nearly 100 years ago, a German industrial chemist, Felix Hoffmann, set about to find a drug to ease his father's arthritis without causing the

severe stomach irritation associated with sodium salicylate, the standard anti-arthritis drug of the time. In the forms then available, the large doses of salicylates used to treat arthritis—6 to 8 grams a day—commonly irritated the stomach lining, and many patients, like Hoffmann's father, simply could not tolerate them.

Figuring that acidity made salicylates hard on the stomach, Hoffmann started looking for a less acidic formulation. His search led him to synthesize acetylsalicylic acid (ASA), a compound that appeared to share the therapeutic properties of other salicylates and might cause less stomach irritation. ASA reduced fever, relieved moderate pain, and, at substantially higher doses, alleviated rheumatic and arthritic conditions. Hoffmann was confident that ASA would prove more effective than salicylates then in use.

His superiors, however, did not share his enthusiasm. They doubted that ASA would ever become a valuable, commercially successful drug because at large doses salicylates commonly produced shortness of breath and an alarmingly rapid heart rate. It was taken for granted—incorrectly as it turns out—that ASA would weaken the heart and that physicians would be reluctant to prescribe it in preference to sodium salicylate, a drug they at least knew. Hoffmann's employer, Friedrich Bayer & Company, gave ASA the now-familiar name aspirin, but in 1897 Bayer didn't think aspirin had much of a future. It could not have foreseen that almost a century after its development aspirin would be the focus of extensive laboratory research and some of the largest

*Americans  
consume an  
estimated 80  
billion aspirin  
tablets a year.*



clinical trials ever carried out in conditions ranging from cardiovascular disease and cancer to migraine headache and high blood pressure in pregnancy.

### How Does It Work?

The mushrooming interest in aspirin has come about largely because of fairly recent advances in understanding how it works.

What is it about this drug that, at small doses, interferes with blood clotting, at somewhat higher doses reduces fever and eases minor aches and pains, and at comparatively large doses combats pain and inflammation in rheumatoid arthritis and several other related diseases?

The answer is not yet fully known, but most authorities agree

that aspirin achieves some of its effects by inhibiting the production of prostaglandins. Prostaglandins are hormone-like substances that influence the elasticity of blood vessels, control uterine contractions, direct the functioning of blood platelets that help stop bleeding, and regulate numerous other activities in the body.

In the 1970s, a British pharmacologist, John Vane, Ph.D., noted that many forms of tissue injury were followed by the release of prostaglandins. In laboratory studies, he found that two groups of prostaglandins caused redness and fever, common signs of inflammation. Vane and his co-workers also showed that, by blocking the synthesis of prostaglandins, aspirin prevented blood platelets from aggregating, one of the initial steps in the formation of blood clots.

This explanation of how aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) produce their intriguing array of effects prompted laboratory and clinical scientists to form and test new ideas about aspirin's possible value in treating or preventing conditions in which prostaglandins play a role. Interest quickly focused on learning whether aspirin might prevent the blood clots responsible for heart attacks.

A heart attack or myocardial infarction (MI) results from the blockage of blood flow not *through* the heart, but *to* heart muscle. Without an adequate blood supply, the affected area of muscle dies and the heart's pumping action is either impaired or stopped altogether.

The most common sequence of events leading to an MI begins with the gradual build-up of plaque

(atherosclerosis) in the coronary arteries. Circulation through these narrowed arteries is restricted, often causing the chest pain known as angina pectoris.

An acute heart attack is believed to happen when a tear in plaque inside a narrowed coronary artery causes platelets to aggregate, forming a clot that blocks the flow of blood. About 1,250,000 persons suffer heart attacks each year in the United States, and some 500,000 of them die. Those who survive a first heart attack are at greatly increased risk of having another.

### Could Aspirin Help?

To learn whether aspirin could be helpful in preventing or treating cardiovascular disease, scientists have carried out numerous large randomized controlled clinical trials. In these studies, similar groups of

hundreds or thousands of people are randomly assigned to receive either aspirin or a placebo, an inactive, look-alike tablet. The participants—and in double-blind trials the investigators, as well—do not know who is taking aspirin and who is swallowing a placebo.

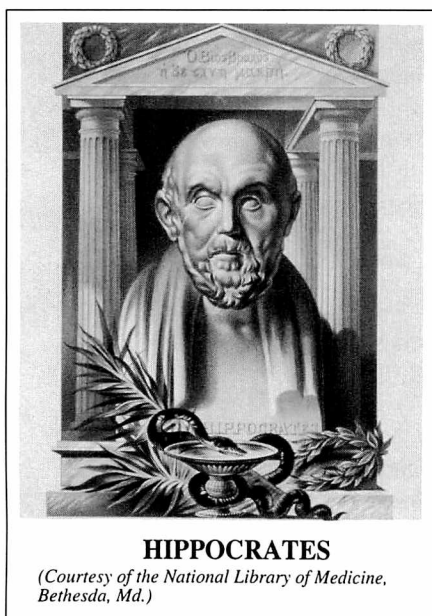
Over the last two decades, aspirin studies have been conducted in three kinds of individuals: persons with a history of coronary artery or cerebral vascular disease, patients in the immediate, acute phases of a heart attack, and healthy men with no indication of current or previous cardiovascular illness.

The results of studies of people with a history of coronary artery disease and those in the immediate phases of a heart attack have proven to be of tremendous importance in the prevention and treatment of cardiovascular disease. The studies showed that aspirin substantially reduces the risk of death and/or non-fatal heart attacks in patients with a previous MI or unstable angina pectoris, which often occurs before a heart attack.

On the basis of such studies, these uses for aspirin (unstable angina, acute MI, and survivors of an MI) are described in the professional labeling of aspirin products, information provided to physicians and other health professionals. Aspirin labeling intended for the general public does not discuss its use in arthritis or cardiovascular disease because treatment of these serious conditions—even with a common over-the-counter drug—has to be medically supervised. The consumer labeling contains a general warning about excessive or inappropriate use of aspirin, and specifically warns against using aspirin to treat children and teenagers who have chickenpox or the flu because of the risk of Reye syndrome, a rare but sometimes fatal condition.

### Aspirin for Healthy People?

Once aspirin's benefits for patients with cardiovascular disease were established, scientists sought to learn whether regular





aspirin use would prevent a first heart attack in healthy individuals. The findings regarding that critical question have thus far been equivocal. The major American study designed to find out if aspirin can prevent cardiovascular deaths in healthy individuals was a randomized, placebo-controlled trial involving just over 22,000 male physicians between 40 and 84 with no prior history of heart disease. Half took one 325-milligram aspirin tablet every other day, and half took a placebo.

The trial was halted early, after about four-and-a-half years, and the findings quickly made public in 1988 when investigators found that the group taking aspirin had a substantial reduction in the rate of fatal and non-fatal heart attacks compared with the placebo group. There was, however, no significant difference between the aspirin and placebo groups in number of strokes (aspirin-treated patients did slightly worse) or in overall deaths from cardiovascular disease.

A similar study in British male physicians with no previous heart disease found no significant effect nor even a favorable trend for aspirin on cardiovascular disease rates. The British study of 5,100 physicians, while considerably smaller than the American study, reported three-quarters as many vascular "events." FDA scientists believe the results of the two studies are inconsistent.

The U.S. Preventive Services Task Force, a panel of medical-scientific authorities in health promotion and disease prevention, is one of many groups looking at new information on the role of aspirin in cardiovascular disease. In its *Guide to Clinical Preventive Services*, issued in 1989, the task force recommended that low-dose aspirin therapy "should be considered for men aged 40 and over who are at significantly increased risk for myocardial infarction and who lack contraindications" to aspirin use. A revised *Guide*, scheduled for publication in the fall of 1994, is expected to include a slightly revised recommendation concern-

ing aspirin and cardiovascular disease but no major change in advice to physicians about aspirin's possible role in preventing heart attacks.

Better understanding of aspirin's myriad effects in the body has led to clinical trials and other studies to assess a variety of possible uses: preventing the severity of migraine headaches, improving circulation to the gums thereby arresting periodontal disease, preventing certain types of cataracts, lowering the risk of recurrence of colorectal cancer, and controlling the dangerously high blood pressure (called preeclampsia) that occurs in 5 to 15 percent of pregnancies.

None of these uses for aspirin has been shown conclusively to be safe and effective, and there is concern that people may be misusing aspirin on the basis of unproven notions about its effectiveness. Last October, FDA proposed a new labeling statement for aspirin products advising consumers to consult a doctor before taking aspirin for new and long-term uses. The proposed statement would read, "IMPORTANT: See your doctor before taking this product for your heart or for other new uses of aspirin because serious side effects could occur with self treatment."

### **The Other Side of the Coin**

While examining new possibilities for aspirin in disease treatment and prevention, scientists do not lose sight of the fact that even at low doses aspirin is not harmless. A small subset of the population is hypersensitive to aspirin and cannot tolerate even small amounts of the drug. Gastrointestinal distress—nausea, heartburn, pain—is a well-recognized adverse effect and is related to dosage. Persons being treated for rheumatoid arthritis who take large daily doses of aspirin are especially likely to experience gastrointestinal side effects.

Aspirin's antiplatelet activity apparently accounts for hemorrhagic strokes, caused by bleeding into the brain, in a small but significant percentage of persons who use

*Better understanding of aspirin's myriad effects in the body has led to clinical trials and other studies to assess a variety of possible uses.*

the drug regularly. For the great majority of occasional aspirin users, internal bleeding is not a problem. But aspirin may be unsuitable for people with uncontrolled high blood pressure, liver or kidney disease, peptic ulcer, or other conditions that might increase the risk of cerebral hemorrhage or other internal bleeding.

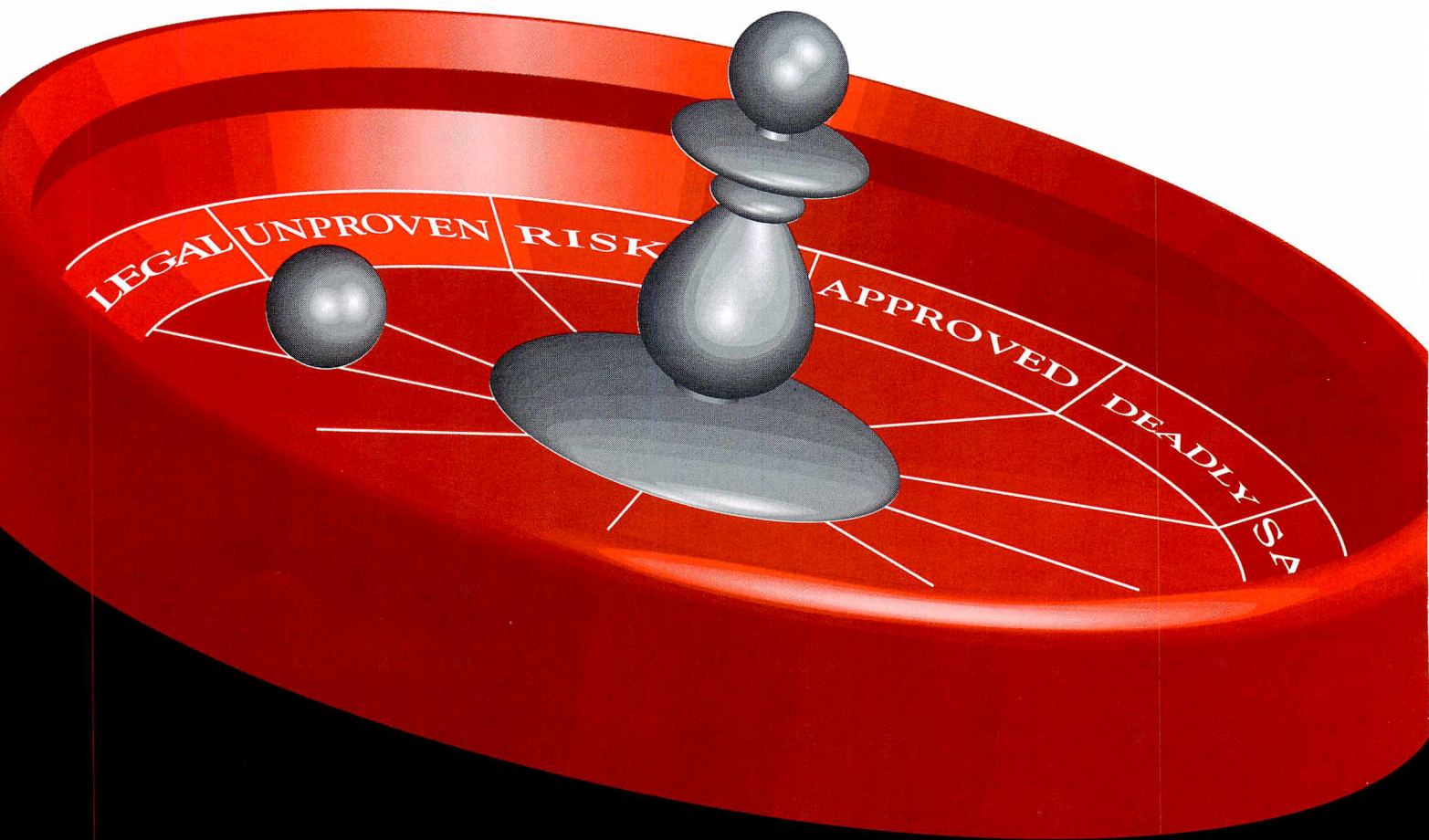
New understanding of how aspirin works and what it can do leaves no doubt that the drug has a far broader range of uses than Felix Hoffmann and his colleagues imagined. The jury is still out, however, on a number of key questions about the best and safest ways to use aspirin. And until some critical verdicts are handed down, consumers are well-advised to regard aspirin with appropriate caution. ■

*Ken Flieger is a writer in Washington, D.C.*



# Buying 'Off-Shore' Drugs May Be Risky Business

by Kevin L. Ropp



*"Self-medication with potentially dangerous  
prescription drugs without professional  
consultation truly is  
pharmaceutical roulette."*

*Donald Leggett, FDA compliance officer*



**J**ohn Hoxsey had a horse. One of the horse's legs developed a sore, which the local veterinarian decided was cancerous. Several months after putting the horse out to pasture, John noticed the sore disappeared.

John then gathered all the plants the horse had eaten from and rubbed against in the pasture and combined them into his "Hoxsey Herbal Formula."  
—Hoxsey Family Folklore

No one knows for sure if this story is true, but Hoxsey's formula is being sold by mail order throughout the United States as an alternative cancer therapy, according to Donald Leggett, a compliance officer in the Food and Drug Administration's Center for Drug Evaluation and Research.

International mail-order drug firms, known as offshore or overseas pharmacies, sell virtually any drug, treatment or therapy, including the Hoxsey Herbal Formula.

While most mail-order pharmacies within the United States operate within the law, the offshore mail-order pharmacies are known to sell many products, especially unapproved therapies, that are potentially dangerous, even deadly.

Some of these firms may offer, unknown to the customer, counterfeit or bogus drugs, dangerous controlled drugs, and drugs used in "alternative" therapies.

"We have found such drugs to include anabolic steroids, addictive drugs, and long discredited drugs associated with the treatment of serious disease conditions, like Laetrile or Hoxsey therapy for cancer," says Leggett.

The World Health Organization estimates that 5 percent of the world market of drugs is counterfeit. "But the United

States is not affected at the same high rate," Leggett says. "International counterfeiters have been quick to exploit Third World countries, especially those with inadequate laws to protect consumers."

Offshore pharmacies often advertise their products in direct-mail catalogs and in what have become known as "alternative therapy publications"—magazines and newsletters that promote health and healing through use of herbs, spices, and unapproved and unproven drugs.

One offshore pharmacy sells products with unproven claims for enhancing memory and intelligence, boosting the immune system, treating cancer, multiple sclerosis, Parkinson's disease, and arthritis, and arousing sexual desire. They include Laetrile, Adrenal Cortex Extract, Coenzyme Q-10, Gerovital H-3, Thymus, Thyroid, and Zumba.

They sell the Hoxsey Herbal Formula, too. The firm's catalog states: "This time-honored herbal remedy is actively used in many major alternative cancer therapy clinics throughout the world. . . . Once a proprietary formula, we can now offer you this all-purpose cancer fighter for your home use. . . . The ingredients include Red Clover, Burdock Root, Barberry Bark, Licorice Root, Buckthorn, Prickly Ash, Chaparral, Stillengia, Cascara Amarga and Potassium Iodide"—all for just \$50 per 16-ounce bottle.

On Dec. 10, 1992, FDA warned consumers to stop using chaparral—an ingredient in the Hoxsey Herbal Formula—because it can cause acute toxic hepatitis and possibly permanent liver damage or death.

Leggett says, "Some of these pharmacies have been involved in shipping drugs that have no active ingredient and may be deemed counterfeit. More often, these drugs may be superpotent or subpotent. For example, one drug was found to con-

tain 300 percent of the active ingredient declared on the label, and that amount was 450 percent higher than the highest dosage approved for use in this country. Other products have been found to contain potentially dangerous adulterants."

### Pharmaceutical Roulette

FDA requires all drugs sold in the United States to undergo extensive clinical testing for safety and effectiveness. In addition, the agency inspects the manufacturer's facilities, evaluates its manufacturing methods, and may collect drug samples for testing before releasing the products for sale.

These requirements, and some even more stringent, are rarely required for drugs manufactured overseas and sold by offshore pharmacies.

Says Leggett: "We know little or nothing about the manufacture of those drugs, the firm's manufacturing practices, the controls used in their manufacturing. In many cases, when we've attempted to follow up, the government authority is not able to provide this information. All we have is a name on a label."

Another consideration with offshore drugs, he says, is "that, when the drug reaches these shores, there is no requirement for pretesting before the customer receives it. We can offer no guarantees the drug is safe, nor can the customer seek a remedy if he or she becomes ill."

A buyer can't even be assured that the order will be filled. Recently, a Canadian operation that used various names and addresses was shut down by government authorities after enticing thousands of American citizens to order products that were never delivered. Often, buyers from such sources have little recourse to recover their money.

"It's been our experience," says



***Offshore mail-order pharmacies  
are known to sell unapproved  
therapies that are potentially  
dangerous, even deadly.***

Leggett, "that these establishments frequently change their name, address, and their toll-free telephone numbers. If you spent hundreds of dollars trusting a firm you knew nothing about and then never got your order filled, in all likelihood your own government couldn't protect you."

And, even if the customer receives the drug, Leggett says, often the labeling lacks adequate directions for use.

"The consumer determines how it's going to be used, in what quantity, and what other drugs might be used in conjunction with it. Normally, the safe, effective use of any prescription drug involves close monitoring by a physician to make sure dangerous side effects do not interfere with the treatment.

"Self-medication with potentially dangerous prescription drugs without professional consultation truly is pharmaceutical roulette," Leggett says.

The American Medical Association (AMA), which represents approximately 300,000 (nearly 41 percent) of the nation's physicians, has many of the same concerns as FDA.

"We are opposed to our patients seeking their pharmaceuticals outside of the United States," says Robert E. McAfee,

M.D., AMA president-elect and a practicing general surgeon in Portland, Maine. "The reason for this is primarily one of patient safety. We have no way of assuring the purity, the dose, the manufacture, or the safety of any of those pharmaceuticals, even though they may be packaged in a similar fashion.

"The reason for purchasing in this country is because agencies such as FDA concern themselves with assuring pharmaceutical efficacy and, therefore, safety to the patient of drugs that fall under their domain," McAfee says.

#### **What To Do**

Even though FDA has only limited options when dealing with offshore pharmacies, the agency still needs to know about these firms.

"FDA needs to know what promotions are being made," Leggett says. "The first time we hear about it is from the consumer."

Anyone who receives promotional material from a suspected offshore pharmacy and considers purchasing a drug should first consult a physician, Leggett says. Then they should contact the FDA office in their area. FDA offices are listed in tele-

phone book blue pages under "Federal Government."

Once FDA knows about a firm, the agency can take some action.

"When we find firms that are operating contrary to our policies and essentially exploiting the marketplace," Leggett says, "we send them a warning letter even though they are outside this country.

"We provide that firm, and FDA's counterpart in the host government, information about the acts we feel violate our law and potentially endanger the lives of our citizens. We ask that the firm voluntarily desist and the host government's law enforcement agency assist us in whatever needs be done in order to ensure our citizens aren't endangered in the future," he says.

Some people say they feel the risks involved in purchasing drug products from offshore pharmacies outweigh the sometimes substantial cost savings.

McAfee says people should carefully look at the possible outcomes of such risky actions. "If you don't get the appropriate drug or if you do not take the drug the doctor thinks you are taking, your illness may not be cured or it could be prolonged. The additional expense is rather substantial, and so what looked to be a good buy at first may not turn out that way."

Leggett adds, "Consumer tax dollars contribute to the protections given by the Food and Drug Administration. It is extremely foolish when consumers drop that protection by going into the international market with firms that are not within our enforcement powers. They risk not receiving the goods they pay for or, even worse, getting something that might be extremely hazardous." ■

*Kevin L. Ropp is a staff writer for FDA Consumer.*



# Inflatable Penile Implants Under Scrutiny

by John Henkel

**F**or Ed Shoebridge, the options were clear: He could have a device surgically inserted into his genitals or say goodbye to the sex life he and his wife once knew.

Like a quarter million U.S. men since the early 1970s, he opted for an inflatable penile implant, a device that treats impotence by mechanically creating an erection. It was a choice that "appealed to me right away," says the 72-year-old Seneca Falls, N.Y., resident, who became impotent following 1974 prostate cancer surgery.

His options were more limited than many men's because the cancer operation had severed blood vessels and nerves needed for an erection. He considered nonsurgical impotence treatments but decided against them. In 1976, he obtained a device he says allowed him "to be made whole again." Inflatable penile implants had been on the market only three years then, and experience with them still was limited. Shoebridge says he received one of the earliest.

During the next 17 years, Shoebridge had three of the devices implanted. The first two were "less than perfect," he says, and failed after working reliably for two and eight years, respectively. He has had no complications with a third one, implanted in 1986, which continues to function dependably, he says.

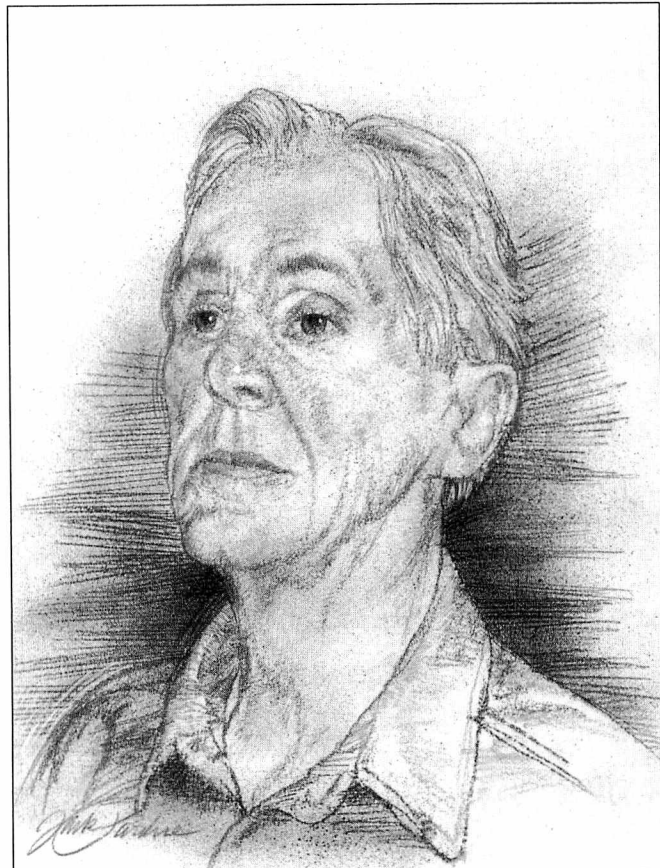
Experiences with faulty implants haven't dulled Shoebridge's zeal for the devices. Despite repeat surgeries to correct defects, he endorses penile implants vigorously. As a participant in and speaker for impotence support groups nationwide, he's met numerous fellow inflatable implant users. He says he and many other men accept the fact that things can go wrong. "Let's face it," he says, "with an implant, you've got a foreign body in your

body, and nothing lasts forever."

Made of silicone rubber or polyurethane rubber, penile implants are now coming under FDA scrutiny, following reports of problems. The agency is stepping up its regulatory review of the several kinds of inflatable devices available to impotence patients.

One, a three-piece unit, creates erections on demand when the user gently squeezes a pump implanted in the scrotum. This causes fluid from a bulb-like reservoir implanted in the lower abdomen to surge into two cylinders located in the shaft of the penis. The cylinders inflate, giving the penis firmness adequate for intercourse. Pushing a release valve on the pump sends fluid back to the reservoir, returning the penis to normal. The devices typically are implanted through a single small incision above the base of the penis or at the point where the penis and scrotum join.

Some inflatable devices on the market are two-piece units that combine reservoir



**Ed Shoebridge**  
(Drawn by Jack Pardue)



***One recurring criticism of penile implants is that patients are inadequately informed about proper device use, limitations, and risks.***

and pump in the scrotum. Others are one-piece implants that house all components within the penis only. With these, the user gently squeezes the tip of the penis to activate fluid flow into the cylinders.

Still other types of implants are non-inflatable and have flexible or malleable rods that make the penis firm enough for intercourse but flexible enough to be unnoticeable.

Though Shoebridge says inflatable penile implants have worked out well for him, he advises men to consider alternatives before undergoing the operation. "Not everyone is an ideal candidate," he says. Equally important, he adds, is sensitivity toward one's partner. At first, his wife, Elsie, resisted the implant idea. But she now agrees that the device "has worked out well" for their sex life.

#### **Horror Stories**

Not all recipients embrace the devices as enthusiastically as Shoebridge. Some have horror stories that have prompted lawsuits and media coverage. Since 1984, FDA's Center for Devices and Radiological Health, which regulates penile implants, has logged more than 6,500 reports of problems with inflatable devices—"a large number for a medical device," says John H. Baxley, reviewer in FDA's urology and lithotripsy branch. Complaints run the gamut from infection, migration of device components, and tissue hardening to leaks, breaks, and mechanical failures. Improper surgical techniques have created other difficulties, causing a relatively high rate of corrective surgery and patient discontent.

Some users complain that sex is not as enjoyable after implants or that the penis is not as firm or large as expected. Others have more serious grievances, such as a Missouri man whose implant had to be removed when the device's pump protruded through his scrotum, or a Massachusetts recipient whose implant developed a leak that resulted in numerous repeat surgeries.

Like breast implants and many other

devices, inflatable penile implants already were on the market when the Medical Device Amendments of 1976 gave FDA authority to regulate these products. Over the years, FDA allowed penile and other "pre-amendment" implants to stay on the market with the provision that device manufacturers ultimately would have to confirm safety and effectiveness.

That time is here. FDA is scrutinizing not only inflatable penile implants, but testicular prostheses, saline-filled breast implants, and other devices. This action follows on the heels of the agency's 1992 removal of silicone-gel breast implants from the market for general uses.

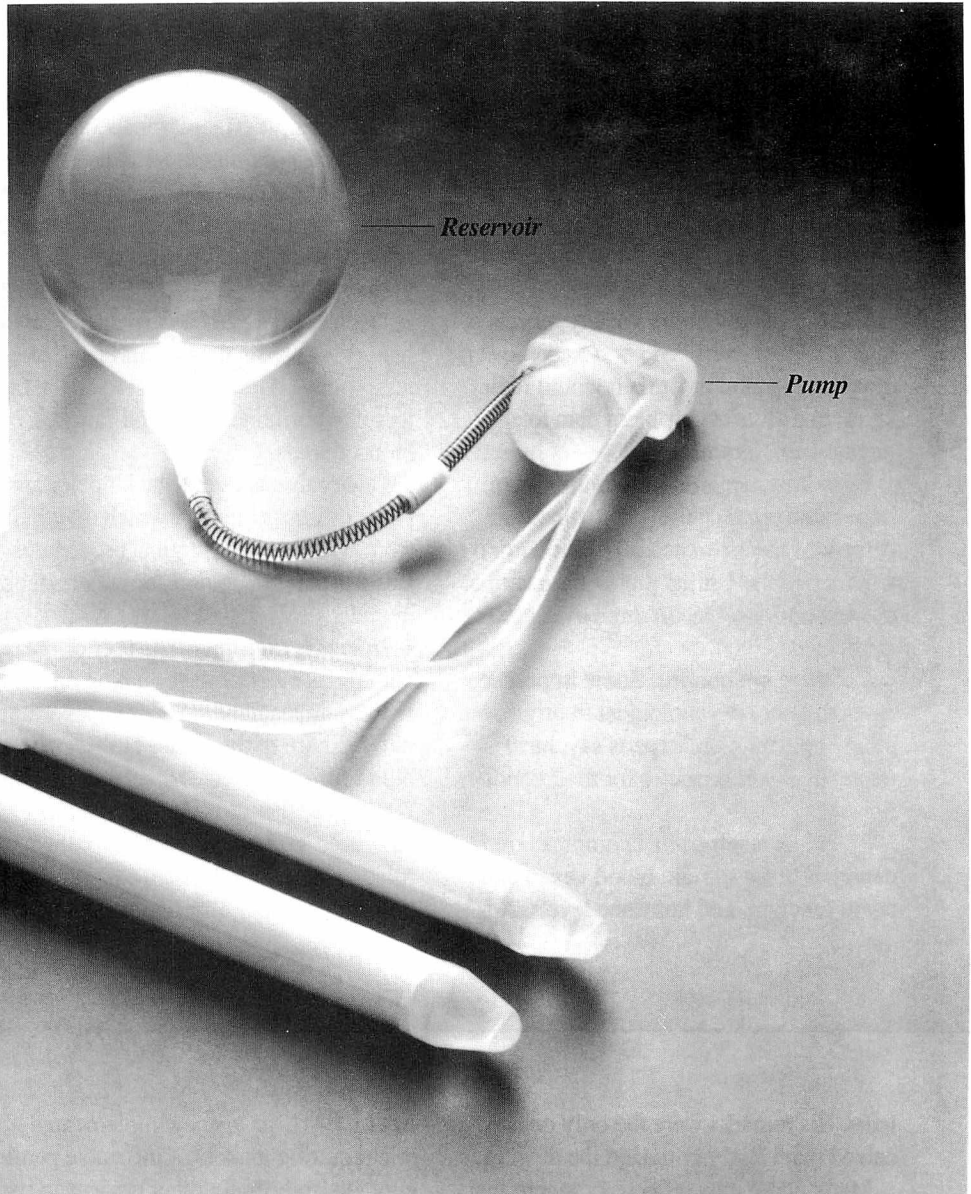
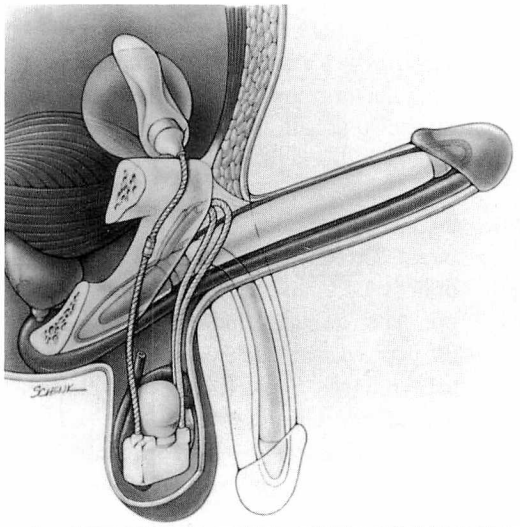
#### **Tightening Controls**

On April 28, 1993, FDA published a proposed rule in the *Federal Register* that would require inflatable penile implant makers to file pre-market approval applications (PMAs) for their products. In these, FDA requires manufacturers to report details of device production such as chemicals used and composition of components. Results of tests on device materials—including compatibility in the human body, toxic effects, and degradation—must be included.

PMAs also must contain data from clinical studies and long-term follow-up to support claims. In other words, PMAs place the burden on manufacturers to prove their devices work properly and are safe. The draft rule affects only inflatable penile implants, not the simpler non-inflatable types, for which the agency has fewer safety concerns.

During the comment period for FDA's proposed rule, the agency received 27 submissions. Many came from urologists experienced with implants who claimed few or no past patient problems with inflatable implants and touted the devices as generally safe and effective. But comments also included a letter from a Brooklyn, N.Y., man who wrote that he had undergone four operations related to his penile implant and must have a fifth to correct prob-





*This three-piece penile implant is one of several types available to men with impotence. The user squeezes the pump (implanted in the scrotum) several times, sending fluid from the reservoir (implanted in the abdomen) into two cylinders (implanted in the shaft of the penis). The cylinders inflate, creating firmness adequate for intercourse. A valve release on the pump sends fluid back to the reservoir, returning the penis to a flaccid state.*

*(Photo and illustration courtesy of American Medical Systems)*



# Treating Impotence

"Go see a shrink."

Until the early 1980s, that is the advice impotence sufferers often received.

Doctors then typically were perplexed about impotence and how to treat it, says J. Douglas Trapp, M.D., medical director of the Osborn Foundation, an impotence education and research organization. Prevailing attitudes assumed impotence stemmed largely from psychological problems. Consequently, impotent men often suffered in silence.

"Unfortunately in our society, psychological illness is looked upon as some sort of weakness, and most men would rather admit to a physical problem than to a mental one," Trapp says.

Even now, according to figures from impotence organizations, only about 5 percent of the estimated 30 million impotent men in the United States are aware of therapy options. One in three over age 60 is affected.

Yet there are options. Some impotence cases truly are psychological in origin, but most impotent men, experts say, have treatable physical causes for their condition.

Erections result from a complex combination of brain stimuli, blood vessel and nerve function, and hormone levels. Ad-

verse effects on any one can cause impotence.

Treatment begins with a medical history, says Myron I. Murdock, M.D., a Washington, D.C.-area urologist and medical director of the Impotence Institute of America. "You look for specific conditions such as cardiovascular disease or diabetes" that could be causing the problem. Smoking and drinking, as well as prescribed or illegal drugs, can influence potency.

Doctors then gather the patient's sexual history. A physical exam and laboratory tests follow, Murdock says, to check factors like hormone levels and function of blood vessels.

Once cause is established, doctor and patient discuss therapy, which may range from counseling to surgical procedures. Besides penile implants, treatment options include:

- **Injection therapy**—The user or his partner injects blood-vessel-dilating drugs such as prostaglandin E1 or papaverine into the base of the penis. This increases blood flow and creates an erection within 20 minutes that lasts up to two hours. However, prolonged erections, called priapism, can result. Also, patient education about proper injection technique is

crucial. An estimated 300,000 men a year in the United States use this method.

Drugs used in penile injections are approved by FDA for other uses, but not specifically for impotence therapy. However, doctors may use approved drugs for unlabeled uses if, in their judgment, the patient will benefit.

- **Vacuum devices**—The user places over the penis a cylinder with an attached pump. This device creates a vacuum that draws blood into the penis. The user then puts a constriction band around the base of the penis, causing an erection that lasts up to 30 minutes. Some 100,000 men choose this treatment each year.

- **Vascular surgery**—can be effective for impotence caused by narrow or blocked arteries.

Murdock says urologists sometimes differ in how they present therapy options to patients. But, he says, he and many of his colleagues opt first for nonsurgical treatments.

This concurs with a December 1992 National Institutes of Health consensus statement on impotence that declared, "As a general rule, the least invasive or dangerous procedures should be tried first." ■

—J.H.

lems. His remarks were the only ones received that clearly criticized the devices.

Many comments reflected concern that the proposed rule is too stringent. For example, one device maker expressed uneasiness about FDA's proposal to require psychological testing of patients and partners as part of the PMA's clinical data provision. Other comments praised FDA for identifying potential risks but complained that device benefits have been understated. FDA will respond to these comments in the final rule.

The agency is tightening oversight of penile implants in other ways. In August 1993, as part of the Safe Medical Devices

Act of 1990, the agency implemented a rule requiring makers of inflatable penile implants and certain other devices to track their products from distribution to the device user. In its letter to companies explaining the rule, FDA wrote that tracking would "ensure that manufacturers can expeditiously locate and remove dangerous and/or defective devices from the market." FDA plans to monitor companies' tracking procedures closely.

## Patient Information Inadequate

While experts say there is no single reason why inflatable penile implants have drawn so many complaints, one criticism

seems to recur: Many patients receive inadequate information about proper device use, device limitations, and potential risks. Poor doctor-patient communication and deficient device labeling can contribute to this problem, says FDA's Baxley. The labeling provision in FDA's proposed rule would require that prospective penile implant recipients be informed about risks and benefits of the procedure. Risks include:

- **Infections**—These usually result in implant removal and, in extreme cases, could lead to gangrene or penile amputation.
- **Migration/erosion**—The implant may move to another location or injure nearby tissue or organs.



## For More Information...

Many organizations and support groups offer information for impotence sufferers.

Here are a few:

- **Impotents Anonymous**—will send callers “Answers to the Most Often Asked Questions About Impotence” and a list of doctors in their area specializing in impotence; telephone (1-800) 669-1603.
- **Impotence Information Center**—sponsored by American Medical Systems,

a manufacturer of penile implants, the center has a brochure, “Impotence Answers.

Where to Go. What to Ask,” and other printed background information; telephone (1-800) 328-3881.

- **The Osbon Foundation**—will send callers fact sheets, article reprints, and booklets on impotence treatments and women’s perspective on impotence; telephone (1-800) 433-4215. ■

- **Capsule formation**—Scar tissue around the fluid reservoir or pump can cause spontaneous erection or prevent an erection from softening.

- **Mechanical malfunctions**—The implant may inflate without warning, overinflate, underinflate, or inflate unevenly. Corrective surgery often is required.

- **Patient dissatisfaction**—Chronic pain, sensory loss, and disappointment in appearance or firmness of the penis are among complaints. Dissatisfaction results in a high reoperation rate.

- **Possible risks of cancer, immune-related connective tissue disorders, and reproductive problems**—FDA says not enough is known about these possibilities and they should be studied. Also unknown are long-term effects of the silicone or polyurethane rubber of which the devices are made.

Though it’s noble to aim for trouble-free implants, risks are inherent in all invasive treatments, says J. Douglas Trapp, M.D., a

urologist and medical director of the Osbon Foundation, an impotence education and research organization. “There’s a complication rate with every surgical procedure you do,” he says. “You do the procedure enough and you’re going to see complications.” He emphasizes that doctors should be responsible for detailing these risks to patients.

“It is important to let patients know about factors such as possible infections, mechanical failures, and the potential that the device can move around,” says Myron I. Murdock, M.D., medical director of the Impotence Institute of America. However, he says, overemphasis on risks, coupled with the bad publicity inflatable implants have received in recent years, might frighten patients into rejecting an implant when it might be their best therapy option. Murdock has seen a recent drop-off in the number of implanted devices in his own Washington, D.C.-area urology practice. Cases plunged from 150 annually

just a few years ago to 35 last year.

Still, an estimated 24,000 men nationwide opt for inflatable implants yearly. Recent medical literature suggests the devices are improved over earlier versions and are lasting longer with fewer problems.

Then there are the legions of satisfied inflatable implant users whose devices have allowed them to repossess the sexuality that otherwise may have been lost. “You won’t hear a lot from these folks” because good experiences with medical devices “tend to be taken for granted,” says implant user Shoebridge, adding, “The happy ones stay in the background.”

As for FDA’s role, Baxley says the agency’s actions will establish once and for all how safe and effective inflatable penile implants are, as well as ensure a savvy patient population. ■

*John Henkel is a staff writer for FDA Consumer.*

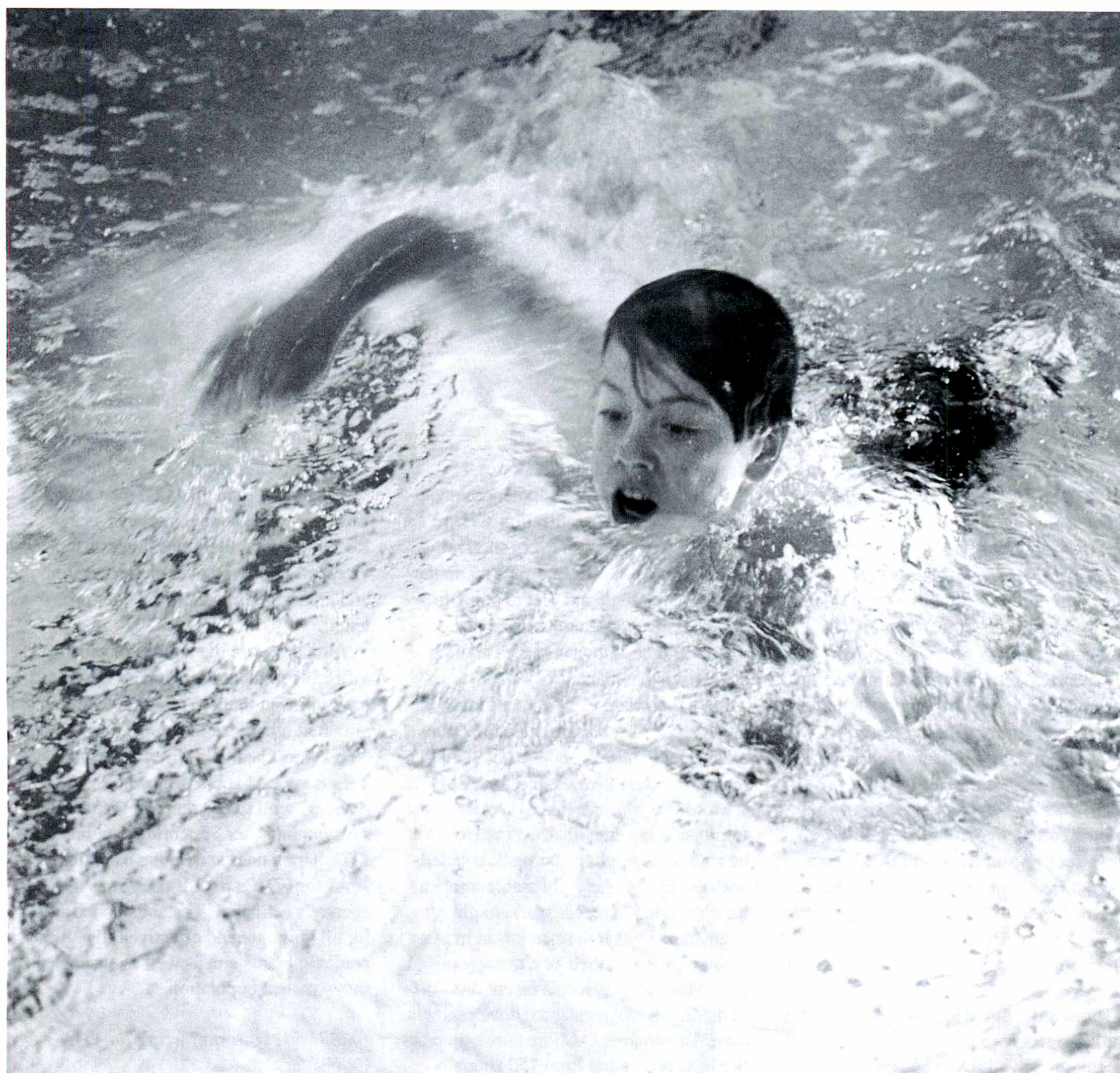


*On The Teen Scene*

# Being A Sport With

## **EXERCISE-INDUCED ASTHMA**

*by Ruth Papazian*





*This article is part of a series with important health information for teenagers.*

You wouldn't call Nicholas, 16, a jock. He harbors no dreams of Olympic glory, has no intention of trying out for a school sports team, and has faked more injuries to get out of gym class than even he can count. His hobbies run more to the creative and intellectual—playing bass guitar in a garage band and fooling around on his computer.

But Nicholas (who asked that his last name not be used) didn't always avoid sports. At one time, he was an avid basketball player. But all that changed about four years ago.

"We were supposed to run a mile in gym, and about halfway through, I started coughing, wheezing and felt nauseous. I told the teacher I couldn't go on, but he said that he didn't like quitters. I tried to finish, but I couldn't," he recalls. Nicholas went to the doctor and found out he had exercise-induced asthma.

"My friends stopped inviting me to play B-ball or soccer after school because they were afraid that I would have an attack in the middle of a game. Some of the kids called me 'wheeze boy,'" Nicholas says. "After a while, I decided they were right, so even though I loved sports, I gave up on all physical activities."

Asthma is a lung disease that is either inherited or may develop as a severe allergic reaction to pollen, viruses, dust, cigarette smoke, and other "triggers" (but not everyone with allergies develops asthma and not every asthmatic has allergies). Exercise-induced asthma (EIA) is a common form of asthma. It occurs only when a person exercises. People who have chronic asthma, on the other hand, can develop symptoms whenever they are exposed to a trigger.

About 80 to 90 percent of people who have chronic asthma also have EIA. But

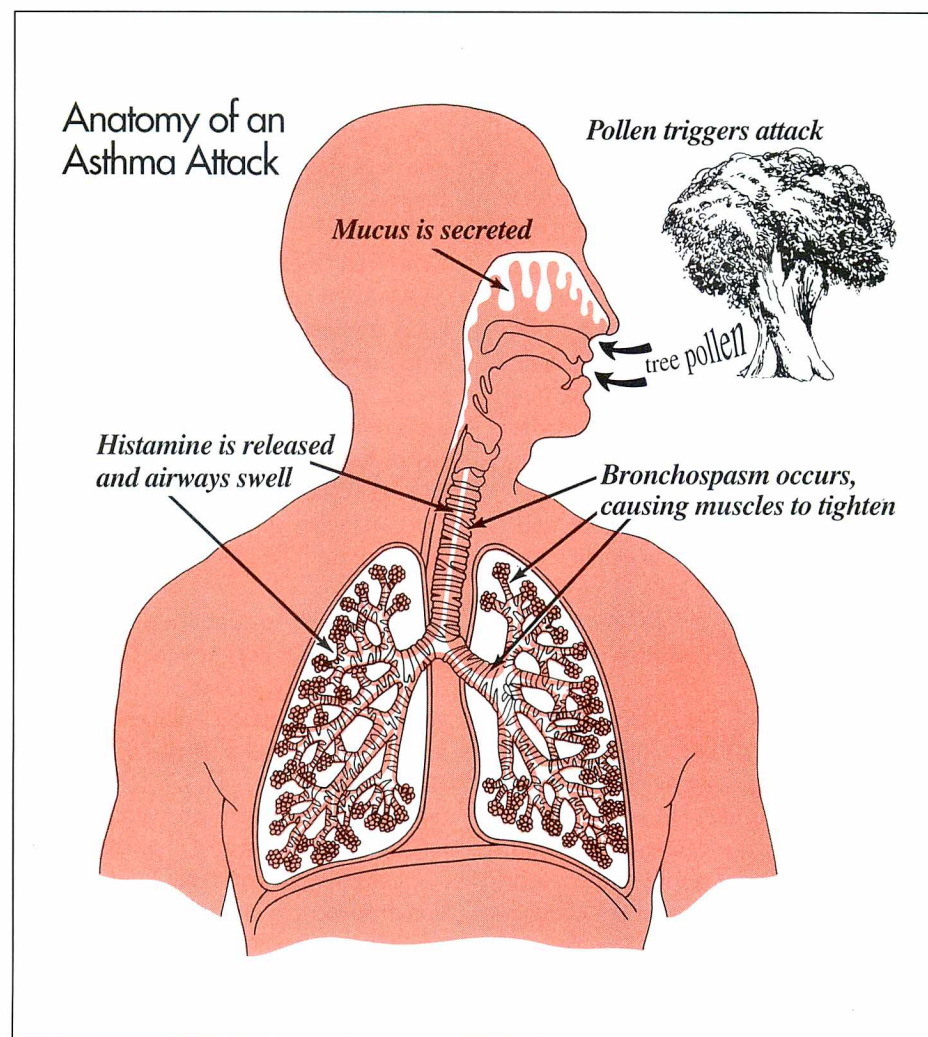
you can have EIA even if you don't have chronic asthma. Nicholas is among the 35 to 40 percent of people with seasonal allergies who have EIA, and his symptoms are always worse during the spring and fall when gym classes are held outdoors.

### How an EIA Attack Happens

During an asthma attack, the bronchial airways (the large and small tubes that bring air into the lungs) become partly blocked. A trigger, such as pollen, causes immune system cells in the lungs to re-

lease histamine and other chemicals. These chemicals cause the lining of the airways to swell, making them narrower. At the same time, tiny rubberband-like muscles wrapped around the outside of the bronchi (the two large tubes that branch out from the windpipe into the lungs) tighten in what is known as "bronchospasm." Completing the process, mucus cells in the airways produce secretions that plug up the works even more.

In about half of chronic asthmatics, the initial attack (known as "early response")







*Using a bronchodilator from five minutes to an hour before strenuous exercise, such as soccer, can prevent an exercise-induced asthma attack.*

is followed by a delayed reaction (“late response”). This delayed reaction happens because lung inflammation makes the airways and lungs extremely sensitive to irritation. Some asthma specialists believe that EIA differs from chronic asthma because exercise-induced bronchospasm (another name for EIA) does not cause lung inflammation, so there is no late response.

With asthma, the problem isn’t getting air into the lungs, but exhaling air out through the obstructed airways. (People who don’t have asthma can get an idea of what an asthma attack feels like by taking a breath and holding it for a second, then trying to take another breath without exhaling first.)

Cold, dry air is believed to trigger EIA. So, exercising outdoors in the winter or breathing through your mouth during heavy exertion is likely to set off an attack. (Breathing through your nose warms and moistens the air before it reaches the lungs.) EIA symptoms typically occur after three to eight minutes of strenuous activity, and can last 20 to 30 minutes. They can range from mild to severe, and include coughing, wheezing, tightness or pain in

the chest, shortness of breath, and reduced stamina.

### **EIA Need Not Bench You**

“Many people who have EIA don’t know it because they blame their symptoms on being out of shape,” notes John Weiler, M.D., a professor in the department of internal medicine at the University of Iowa Hospitals and Clinics in Iowa City. Others may experience symptoms only when they push themselves to the “max” or exercise outdoors when air quality is poor.

But if you’re susceptible to it, EIA can affect you, regardless of your fitness level or athletic ability. In fact, according to various studies, 10 to 12 percent of athletes have EIA. At the 1984 summer Olympics in Los Angeles, 67 of the 597 members of the American team had EIA; among them, they won 41 medals.

Obviously, EIA need not limit participation or success in vigorous activities. Today it can be medically managed and its effects minimized.

“In the past, doctors discouraged people with asthma from exerting themselves to

avoid triggering an attack. But the current thinking is that it is important for asthmatics to engage in regular exercise to condition and strengthen their lungs,” says Stanley Szefer, M.D., director of clinical pharmacology at the National Jewish Center for Immunology and Respiratory Medicine in Denver.

Swimming in an indoor pool may be the ideal exercise for asthmatics because the warm, humid air keeps the airways from drying and cooling. However, “with proper management, virtually no sport is off-limits,” says Szefer.

Proper management of EIA, Szefer says, includes monitoring air flow with a peak-flow meter, avoiding allergic triggers, and using medication before exercise.

Asthma symptoms can change a lot. They are often worse at night than during the day. They may be worse in the winter or during “allergy seasons” when pollen counts are high. The new National Heart, Lung, and Blood Institute guidelines recommend that people 5 years or older who have moderate to severe asthma use a peak-flow meter twice a day (morning and evening).

A peak-flow meter measures how fast you blow air out of your lungs. When a person blows into the device—which looks something like a kazoo—a slide indicates the force of the exhaled air. The farther the slide is pushed, the greater the peak flow.

“Peak-flow meters can help asthmatics monitor their symptoms so attacks can be better anticipated,” explains Michael Gluck, D.Sc., chief of FDA’s anesthesiol-



## Tips on Coping with EIA

- Start with a 15-minute warm-up to allow the lungs to adjust to the increased demand for oxygen.
- In cold weather, cover your mouth and nose with a scarf to help warm the air before it gets to the lungs.
- Avoid triggers that may cause or worsen EIA (for example, don't exercise outdoors when pollen counts are high).
- End with a 15-minute cool-down rather than stopping abruptly.
- Follow your doctor's instructions about using medication before or after exercise. If you're on a team, let your coach know about your doctor's instructions.
- If you have symptoms, use a bronchodilator right away. Remember, cromolyn and corticosteroids are not recommended during an asthma attack because they do not immediately open the airways. ■

—R.P.

ogy and respiratory devices branch.

Once a doctor determines normal peak flow, a treatment approach can be tailored just for you. For instance, your doctor may instruct you to take more medicine than usual if your peak flow drops a certain amount, say 70 percent of normal, or to get medical help right away if it falls to 30 percent of normal.

"In the past, a vague sense of not feeling well was the only indication a person had that an asthma attack was imminent. By that time, it was often too late to head off the attack," says Gluck. "Peak-flow meters give you . . . a much earlier indication of an oncoming attack."

"Drugs that relax the muscle spasm in the walls of the bronchial tubes to open them are often the first line of treatment in preventing EIA," says Tunde Otulana, M.D., a medical reviewer in FDA's oncology and pulmonary drugs division. Such drugs are called bronchodilators. They are typically prescribed in aerosol (inhalant) form. They are sprayed into the mouth and breathed directly into the lungs. Doctors recommend using the medication from five minutes to an hour before exercise. If breathing problems develop during exercise, you may need to take another dose. The most common side effect of bronchodilators is feeling jittery, says Otulana.

Cromolyn sodium is often prescribed to treat athletes who have EIA. This drug, which is also an inhalant, prevents the lining of the airways from swelling in response to cold air or allergic triggers, explains Otulana, and must be taken on a regular basis for the treatment of asthma. Cromolyn sodium can be used up to 15 minutes before engaging in physical activity.

Cromolyn has few side effects, according to Otulana. "The most common complaint is that it leaves an unpleasant taste in the mouth for a few seconds. Some people may experience coughing due to dryness and throat irritation and, in rare instances, patients have become nauseated."

In addition to bronchodilators and cromolyn, which are used primarily to head off an attack of EIA, the National Heart, Lung, and Blood Institute treatment guidelines recommend the use of inhaled corticosteroids for patients with moderate to severe chronic asthma. "Instead of using a 'rescue' approach to treat episodes of breathlessness, doctors are now focusing on the big picture and using a preventive approach to treat airway inflammation, which is the underlying cause of asthma," says Szefer.

"Corticosteroids work by reducing swelling in the bronchial tubes and by enhancing the action of bronchodilators. They are meant to be used as preventive medication, usually on an ongoing basis," says Otulana.

Corticosteroid inhalants can occasionally cause throat irritation and thrush (a fungal infection in the mouth), says Otulana. (He advises gargling with warm water after using the inhaler to help avoid both side effects.) Prolonged use of very high doses may increase the risk of the same type of health problems associated with the drug in pill form: high blood pressure, diabetes, and softening of the bones.

"It is very difficult to recognize EIA, especially when exercise is the only trigger for asthma," says Weiler. "If you can't keep up with the other kids, can't seem to be able to 'get into shape' no matter how much you exercise, or experience problems after exercise that your classmates don't, EIA may be to blame."

Today, Nicholas carries a bronchodilator with him and uses cromolyn 20 minutes before gym class. Although he still dislikes exercise, he doesn't cut gym now that he can keep up with the other kids. "If I premedicate, I have no problems," he says. "Asthma can be a setback, but it doesn't have to be—if you learn how to deal with it." ■

*Ruth Papazian is a health and medical writer in the Bronx, N.Y.*





*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.*

■ **An urgent warning about playpens** marketed as "Home and Roam" playpens has been issued by Baby Trend, Inc., Pomona, Calif., in conjunction with the Consumer Product Safety Commission. Additional Home and Roam playpens were sold under the Baby Express label. The playpens pose a strangulation risk if the top rails are not locked properly. For more information, call Baby Trend toll free at (1-800) 234-1879. When calling, provide model and lot numbers located on the playpen's foot.

■ **Very-low-calorie diets (VLCD)** helped 90 percent of participants in a recent study lose significant weight, but only one-third of the patients maintained that loss, according to a report in the October 1993 *Archives of Family Medicine*. Researchers

studied 255 patients enrolled in a widely advertised 26-week VLCD program in Florida. (*Archives of Family Medicine*, October)

■ **Polio** may soon be eliminated from the Western Hemisphere, according to Frederick C. Robbins, M.D., from the International Commission for Certification of Eradication of Polio in the Americas. The last case of paralysis due to wild poliovirus occurred in Peru in 1991. The United States has had no polio cases, except those from live vaccine and importation, since 1979. Argentina, Chile, Paraguay, Uruguay, and the Caribbean islands have had no cases for four years or more. (*Journal of the American Medical Association*, Oct. 19)

■ **Leprosy scientific literature** from 1913 through 1991 has been compiled by the Leprosy Research Foundation and is available on compact disk for researchers. The disks are available for \$20 from the Leprosy Research Foundation, 11588 Lawton Court, Loma Linda, CA 92354; facsimile (909) 824-1361. (*Public Health Reports*, September-October)

■ **Illegal drug use** among Americans 12 and older declined 11 percent in 1992 to 11.4 million, down from 12.8 million in 1991, according to the Substance Abuse and Mental Health Services Administration's National Household Survey on Drug Abuse. The survey is based on a nationwide sample of 28,832 people over 12. (*Public Health Reports*, September-October)

■ **Aluminum** does not contribute to Alzheimer's disease, according to FDA's

Jean Pennington, Ph.D., R.D. "While there may be high levels of aluminum in the brains of some people with Alzheimer's disease, there is no evidence to suggest that dietary exposure to aluminum correlates in any way with onset of the disease," said Pennington, who presented her findings at the American Dietetic Association's 76th Annual Meeting Oct. 28. For more information, write to the American Dietetic Association, 216 West Jackson Blvd., Suite 800, Chicago, IL 60606-6995.

■ **Infant mortality** in the United States dropped to a U.S. record low in 1992 of 8.5 infant deaths per 1,000 births, according to provisional data from the National Center for Health Statistics. "Births, Marriages, Divorces, and Deaths for 1992" reports that infant mortality declined 4 percent from 1991 to 1992. There were an estimated 34,400 deaths of infants younger than 1 year in 1992 among an estimated 4,084,000 births. (*Public Health Reports*, September-October)

■ **Health-care organization meetings** this March include:

- American College of Cardiology, March 13-17 in Atlanta; telephone (301) 897-5400
- American College of Preventive Medicine, March 19-22 in Atlanta; contact John McCrohan at (301) 443-2436
- American Pharmaceutical Association, March 19-23 in Seattle; contact Betty Palsgrove at (301) 443-5470.

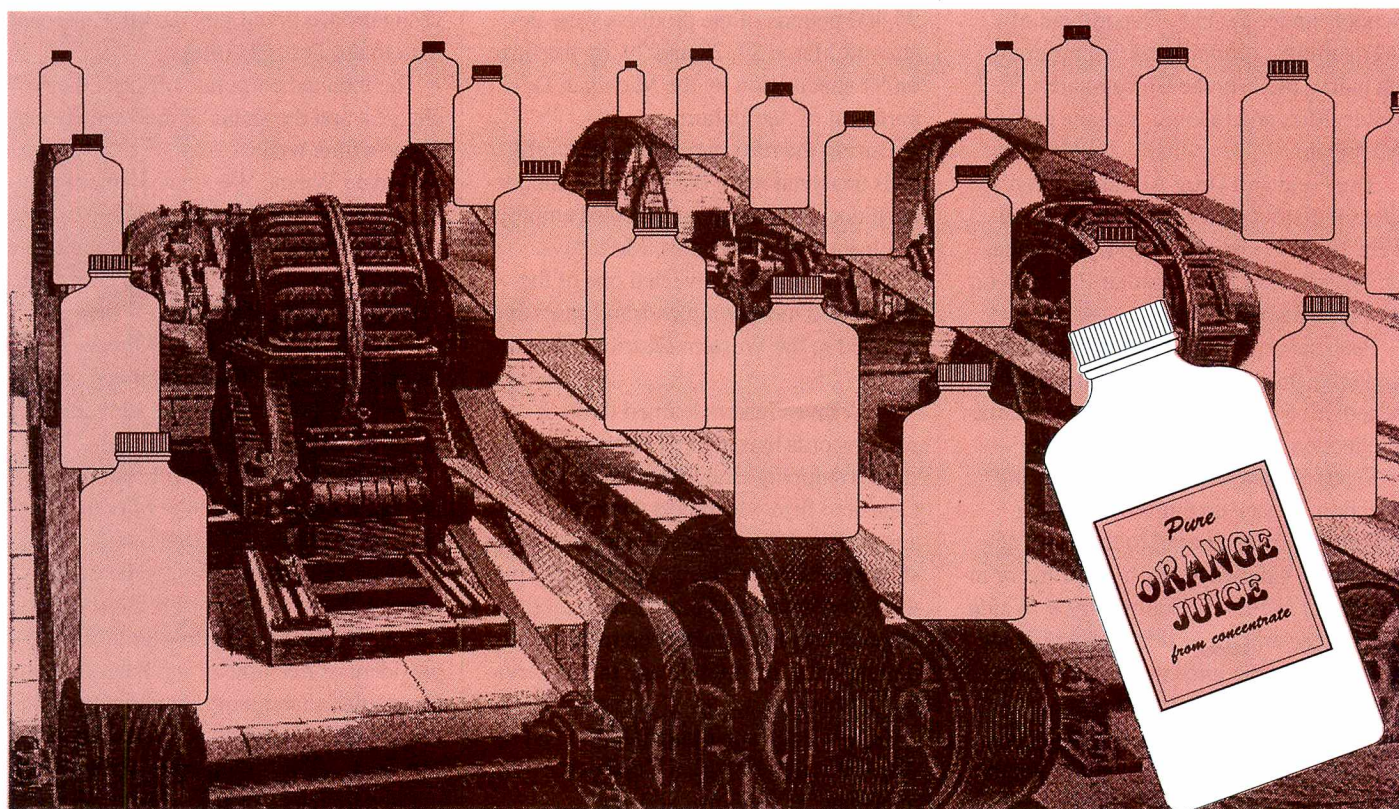






# Juice Maker Cheats Consumers of \$40 Million

by Kevin L. Ropp



An orange juice manufacturer and 11 corporate officers pleaded guilty to defrauding consumers of more than \$40 million by selling products containing low-cost, inferior ingredients but labeled as pure orange juice from concentrate.

Flavor Fresh Foods Corp., Chicago, pleaded guilty in the U.S. District Court for the Western District of Michigan last Sept. 1 to 32 felony counts, including conspiring with another firm, which was also indicted, to adulterate and misbrand food products shipped in interstate commerce, and mail and wire fraud. Flavor Fresh is awaiting sentencing.

Peninsular Products Company, Lansing, Mich., the other indicted firm is no longer in business. As a result, all charges against it were dismissed.

The two firms sold over 40 million gallons of adulterated orange juice from 1979 to February 1991. Flavor Fresh sold its juice under the Flavor Fresh brand, while Peninsular sold its orange juice under the Orchard Grove label and numerous private labels. Distributors of the private label brands didn't know the orange juice was adulterated, according to the Department of Justice.

Adulterated juice concentrates from Flavor Fresh contained between 55 and 75 percent beet sugar. Flavor Fresh added other adulterants in an attempt to conceal

the substitution of sugar for orange juice. Flavor Fresh shipped the adulterated juice to Peninsular, which knowingly added the adulterated concentrates to other orange juice, added other adulterants, and sold the product as 100 percent pure orange juice from concentrate.

The products were sold in at least 25 states, including Illinois, Indiana, Kansas, Kentucky, Michigan, Minnesota, Missouri, Nebraska, Ohio, Pennsylvania, and Tennessee.

The juice was also sold through both chain and independent stores and supplied



to hospitals, nursing homes, preschools, schools, and colleges. It was sold to schools under the U.S. Department of Agriculture's school breakfast program, including those in the Chicago area, St. Louis, Mo., and in Ohio, Indiana and Michigan.

The Food and Drug Administration's Detroit district office first got involved Feb. 19, 1991, when it sent Lyle Wajda, an investigator, to Peninsular Products on a routine inspection.

Peninsular produced a variety of milk and juice products. The firm alternated schedules for its products, using the same production lines for milk and juices.

While Wajda was conducting his inspection, he saw an employee adding something from a barrel to the juice, according to Charles Moss, a supervisory investigator in FDA's Detroit office. Wajda learned the employee was adding orange pulp wash to the juice that was to be labeled orange juice from concentrate.

Pulp wash is the residual orange pulp left after squeezing the oranges to get the juice. It isn't permitted in pure orange juice.

On March 5, after obtaining a court-ordered search warrant, FDA Detroit district employees accompanied U.S. Marshal's Service officials when they seized Peninsular's records and computers, which contained records.

On March 7, the Michigan Department of Agriculture seized all Peninsular's orange juice products made on Feb. 19. On

March 22, Peninsular began recalling its juice products still on the market. About 94,400 pounds of the products were destroyed March 27, 28 and 29, by the firm under supervision by the Michigan Department of Agriculture.

During the next two years, FDA officials analyzed more than 500,000 subpoenaed documents and interviewed employees from both companies, Moss says. "This investigation revealed one of the largest and most complex fraud cases ever handled in the Western District of Michigan."

FDA investigators learned through company records that in 1983 Peninsular started shipping Brazilian orange juice to a Canadian firm where beet sugar was added. From there, the sugared juice was shipped to Flavor Fresh, which added pulp wash and amino and citric acids and then shipped it to Peninsular. Peninsular added orange juice, pulp wash, and the preservative natamycin.

At first Peninsular purchased the preservative through Friedrich Kohlbach in Germany and, at that time, added it to the batches of juice after pasteurization through a special machine which he designed, Moss says. "Later, they started buying from another supplier but the natamycin clogged the machine, so they had to add it by hand and mix it in."

Adding the natamycin allowed Peninsular to extend the shelf life of the orange juices from 24 days to as much as 49 days. Natamycin's only approved human food use is on the surface of cut and sliced cheeses to inhibit mold growth.

Under the Food, Drug, and Cosmetic Act, beet sugar, pulp wash, amino and citric acids, and natamycin are each considered an adulterant to pure orange juice from concentrate. FDA knows of no cases of illness resulting from drinking the adulterated orange juice products.

On the basis of the evidence FDA's Detroit office gathered during its two-year investigation, a grand jury issued a 33-count indictment Feb. 18, 1993.

The indicted corporate officers, their charges, and the status of their sentencing at press time were:

- Donald Wayne Wagoner, former Peninsular president and chief executive officer—one count of conspiracy to adulterate orange juice with illegal ingredients; five years in prison and a \$100,000 fine
- James R. Marshall, Flavor Fresh owner—one conspiracy count and one felony count of orange juice adulteration; awaiting sentencing
- Wilhelm Denner, Flavor Fresh chemist—a misdemeanor charge of orange juice adulteration; a \$5,000 fine
- Edward B. Crouse, Peninsular owner; James E. Benton, Flavor Fresh president; Jeffrey K. Bennett, Peninsular's vice president of manufacturing; Saad A. Alhir, Peninsular's laboratory director; and Friedrich R. Kohlbach, a German citizen—one felony count each of adulterating orange juice; awaiting sentencing
- George R. "Pete" Reynolds, Peninsular vice president of sales; William Kruger, Peninsular vice president; and William Laviolette, Peninsular vice president of finance—one misdemeanor count each of adulterating orange juice; awaiting sentencing.

*Kevin L. Ropp is a staff writer for FDA Consumer.*



## Firm Agrees to Correct Misleading Promotion

A New Jersey drug manufacturer recently signed a consent decree with FDA in which the firm agreed to undertake an extensive campaign to correct misleading promotion and advertising for one of the firm's drugs. The decree was reached in conjunction with FDA's filing of a complaint for injunction.

In the decree, signed in the U.S. District Court for the District of New Jersey on Aug. 2, Kabi Pharmacia Inc., Piscataway, N.J., and president and chief executive officer Anders Wiklund, agreed to stop illegal promotion of Dipentum (olsalazine sodium), a drug used to treat symptoms of an inflammatory bowel disease known as ulcerative colitis.

Ulcerative colitis causes inflammation in the inner mucous membranes lining the colon, which may lead to bleeding, fever, muscle aches, heavy sweating, and poor appetite. A frequent, urgent need to move the bowels may interrupt sleep, meals, and other activities.

FDA approved Dipentum in 1990 for only one use: to maintain periods of remission of ulcerative colitis in adults. Moreover, because of concerns about the high incidence of diarrhea that occurs with Dipentum, the agency restricted its approval to patients who can't tolerate

sulfasalazine, marketed generically and under the brand name Azulfidine.

In its approval letter, FDA specifically told Kabi that Dipentum was not approved to treat patients with active disease or children under any circumstances.

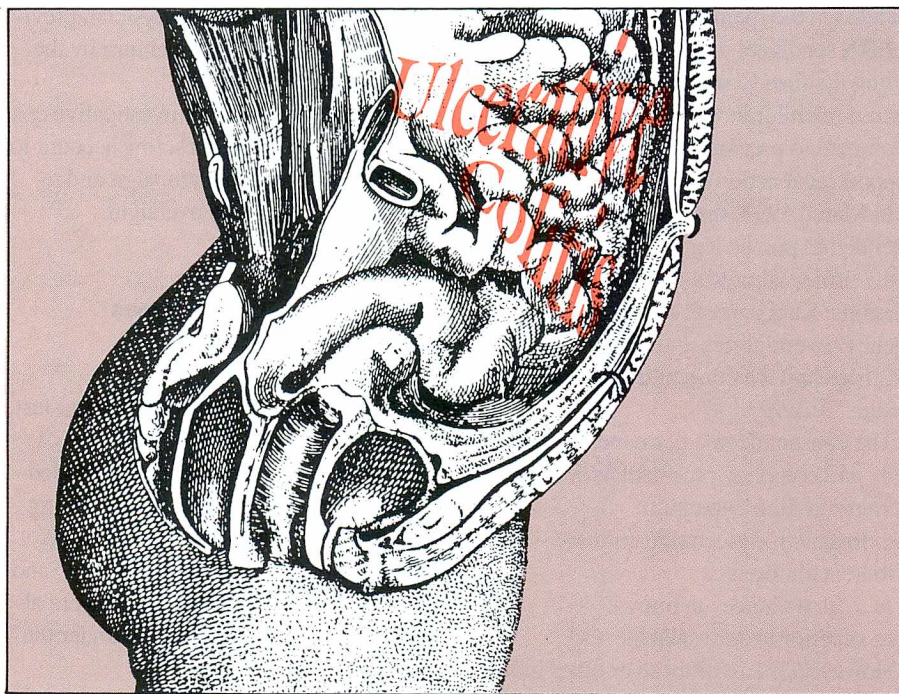
However, in December 1991, FDA received information, which it verified, that Kabi was directing its sales force to promote Dipentum to physicians for unapproved uses. Although physicians may prescribe approved drugs for unlabeled uses if, in their judgment, such use is medically appropriate, the Federal Food, Drug, and Cosmetic Act does not allow manufacturers to promote drugs for uses not included in the approved labeling.

On Jan. 21, 1992, FDA sent a letter to Kabi requesting documents relating to the marketing of Dipentum. In March, Kabi sent the agency 20 volumes of documents on the marketing of Dipentum, including memos to sales representatives instructing them to promote Dipentum "not just as an alternative to sulfasalazine, but as initial,

first-line therapy for treating inflammatory bowel disease."

In addition, job performance memos from regional sales managers who had accompanied individual sales representatives to physicians' offices also stressed the promotion of Dipentum for unapproved uses in both adults and children. Many of these memos indicated that copies had been sent to the company's upper management, including a vice president.

Of great concern to FDA were memos promoting Dipentum for use in children, especially one from a sales trainer to a sales representative that listed specific dose amounts. According to the FDA division that reviews gastrointestinal drugs,





based on available data, the dose recommended in the memo was ineffective.

FDA sent Kabi a letter in June 1992, telling the firm to stop promoting the drug for use in children. In addition, the agency continued to prepare documentation to support legal action against Kabi.

In March 1993, the agency told Kabi it intended to pursue legal action, and asked if the firm was interested in settlement discussions. Kabi agreed, and met with the agency several times until the complaint was filed and the consent decree entered on July 30, 1993.

The consent decree permanently enjoins Kabi and company president Wiklund from promoting Dipentum:

- to treat active ulcerative colitis
- to treat children
- as a "first choice" therapy
- as superior to sulfasalazine.

However, if any of these or other indications are the subject of a new drug application or supplement that is approved after the date of entry of the decree, the injunction won't apply for the approved indications.

In addition, the consent decree specifically calls for the company to:

- revise, and get FDA approval for, promotional and advertising materials for Dipentum for a period of one year
- destroy existing promotional and advertising materials
- conduct an FDA-approved training program for the company's sales, marketing, regulatory, and legal personnel on how to promote products in compliance with the law
- begin a six-month remedial advertising

campaign in medical journals and send remedial letters to every physician previously contacted about Dipentum by the company's sales force

- pay FDA \$85,000 for investigative costs
- establish a \$300,000 escrow account to pay for the corrective campaign and to reimburse FDA for its oversight.

—Dori Stehlin

### Warner-Lambert Agrees To Stop Production

Warner-Lambert Company agreed last August to stop making a wide range of drug products until it complied with federal regulations for good manufacturing practices (GMPs). A few prescription drugs deemed "medically necessary" and not available from other sources were allowed to remain in production under the agreement.

Under the terms of a consent decree of permanent injunction entered Aug. 16 in the U.S. District Court for the District of New Jersey, the pharmaceutical firm agreed to correct deficiencies in manufacturing practices uncovered by numerous FDA inspections at its plants in Morris Plains, N.J., Lititz, Pa., Rochester and Holland, Mich., and Vega Baja and Fajardo, Puerto Rico. Fourteen of the firm's drug products had been recalled since December 1992 for failing to comply with GMPs and product quality standards. None of the recalled products posed a critical health risk.

The firm also agreed to stop making most of its over-the-counter and prescription products until it complies with GMPs. Prescription drugs that remained in production, under conditions specified in the decree, were Celontin, chloramphenicol injection, Cholelodyl, Dilantin, Humatin, Ketalar, Loestrin 1/20, Lopid, Milontin, Nardil, Nipent, Nitrostat, and Zarontin. The conditions were imposed to ensure the drugs have the identity, strength, quality,

and purity they are purported to have.

More than a dozen FDA inspections of Warner-Lambert plants from 1991 to 1993 revealed numerous repeated violations, which included failure to notify the agency of batches of drugs that failed product stability tests. Other problems found throughout Warner-Lambert's operations included:

- inadequate record keeping
- use of unapproved production processes
- lab workers not adequately trained to use drug analysis equipment or conduct drug tests
- ineffective quality control procedures
- failure to investigate quality control problems
- inadequate equipment cleaning procedures.

Despite the numerous inspections and notices to the company's officers of the problems found, the numerous product recalls, and other warnings by FDA officials, Warner-Lambert's GMP problems persisted. According to an agency official, the firm's responses to FDA observations showed a continuing failure to appreciate the significance of its violations.

Under the consent decree, Warner-Lambert agreed that:

- an independent expert will certify whether each laboratory at each of the facilities complies with the GMPs
- all laboratory personnel will be trained to be fully qualified to perform their assigned duties
- outside experts will certify whether manufacturing processes comply with GMPs
- expert certifications or remedial plans to



correct deficiencies will be reviewed and subject to FDA approval for “medically necessary” products that are not otherwise available.

To ensure compliance, FDA will continue to inspect Warner-Lambert plants and examine production and testing records. Under the terms of the decree, FDA can order the company to recall products whenever the agency deems it necessary. FDA may also require Warner-Lambert to stop manufacturing and distributing any drug product that fails to comply with GMPs. The decree also requires Warner-Lambert to pay damages if it violates the injunction and to pay costs incurred by FDA for continuing oversight of the company’s manufacturing processes.

—Marian Segal

## Devices Seized in Seattle

Approximately \$100,000 worth of pain diagnostic and treatment devices and software were recently seized in Seattle by U.S. marshals. FDA requested the seizure because, despite FDA warnings, the manufacturer continued to market its products while the agency was reviewing violations found during an inspection of the firm.

As the result of a routine inspection of Myo-Tronics, Inc., of Seattle, from Aug. 8 to Sept. 25, 1991, FDA investigators found the firm had not filed the pre-market notifications required by the Food, Drug, and Cosmetic Act for five of its devices:

- Physiotech 4000 EMG Monitoring System (EMG is an abbreviation for electromyogram, used to measure muscle function)

- MS-100 EMG Scanner
- K6-I (head and jaw) Diagnostic System
- J-4 Myo-monitor—a transcutaneous (through the skin) electronic nerve stimulator, or TENS, device
- BNS-40 Home Treatment Unit (a TENS device).

In addition, FDA determined that the brochure and operating guide for the J-4 Myo-monitor and BNS-40 Home Treatment Unit made false and misleading claims, specifically that the products were TENS devices that could effectively relieve head and neck pain and treat conditions such as tinnitus (ringing in the ear), temporomandibular joint disorder (jaw



joint pain), tic douloureux (severe head, neck and facial pain), and Bell’s palsy.

The two misbranded devices and the K6-I Diagnostic System also failed to have adequate directions for use.

On March 23, 1992, FDA sent a warning letter to Robert Jankelson, chairman of the board of Myo-Tronics, instructing him to take prompt action to correct the violations and recommending that he not award contracts for any of the affected products. FDA met with Fray Adib, Myo-Tronic’s vice president of regulatory affairs, at his request. At the meeting, Adib promised to file pre-market notifications for three of the devices and to remove the false and misleading claims of the two others. He also asked FDA to allow him to continue distributing the devices while his pre-market notifications were being reviewed. FDA turned down Adib’s request and warned him that distribution of the devices without permission would be a violation of the Food, Drug, and Cosmetic Act.

An FDA reinspection from June 30 to July 13, 1992, showed that the firm had submitted three pre-market notifications to FDA. However, the firm sold nearly \$500,000 worth of devices from March 23, the date of the warning letter, to June 30, the date of the reinspection.

FDA filed a complaint for forfeiture on Aug. 5, 1993, in the Western District of Washington. On Aug. 9, U.S. marshals seized the K6-I Diagnostic System and the Physiotech 4000 devices, software, and the accompanying literature. FDA has worked with the firm to bring the other three devices into compliance.

—Judith E. Foulke



# SUMMARIES OF COURT ACTIONS



Summaries of Court Actions are given pursuant to section 705 of the Federal Food, Drug, and Cosmetic Act. Summaries of Court Actions report cases involving seizure proceedings, criminal proceedings, and injunction proceedings. Seizure proceedings are civil actions taken against *goods* alleged to be in violation, and criminal and injunction proceedings are against *firms* or *individuals* charged to be responsible for violations. The cases generally involve foods, drugs, devices, or cosmetics which were alleged to be adulterated or misbranded or otherwise violative of the law when introduced into and while in interstate commerce or while held for sale after shipment in interstate commerce.

Summaries of Court Actions are prepared by Food and Drug Division, Office of the General Counsel, HHS.

Published by direction of the Secretary of Health and Human Services.

## SEIZURE ACTIONS

### *Food/Contamination, Spoilage, Insanitary Handling*

**PRODUCT:** Beans of various types, dried, blackeye peas, and chick peas, at Barceloneta, Dist. Puerto Rico; Civil No. 92-2471 (CC).

**CHARGED** 10-20-92: While held by Casera Foods, Inc., Barceloneta, Puerto Rico, one lot of Idaho beans and two lots of light red kidney beans contained insect filth, and all of the articles had been held under insanitary conditions—402(a)(3), 402(a)(4).

**DISPOSITION:** Consent decree authorized release to the dealer for salvaging. (F.D.C. No. 66610; S. No. 92-633-343 et al.; S.J. No. 1)

**PRODUCT:** Ice cream cups, crackers, candies, bubblegums, and sundry food stocks, at Richwood, E. Dist. Ky.; Civil No. 91-101. **CHARGED** 6-27-91: While held by Klee Wholesale Co., Richwood, Ky., the ice cream cups contained rodent filth, and all of the articles had been held under insanitary conditions—402(a)(3), 402(a)(4).

**DISPOSITION:** Default—authorized release to the dealer for salvaging. (F.D.C. No. 66205; S. No. 91-642-112 et al.; S.J. No. 2)

**PRODUCT:** Mandarin oranges, canned, at Jacksonville, M. Dist. Fla.; Civil No. 92-1327-Civ-J-10.

**CHARGED** 12-8-92: While held for sale, the article was unfit for food because the cans were swollen—402(a)(3).

**DISPOSITION:** The article was claimed by The Connell Co., Westfield, N.J., who sought the return of the article to the original foreign supplier. However, no answer to the complaint's charge was filed; and, upon motion of the government, a default decree was entered ordering the article destroyed. Subsequently, the government moved for an order awarding and taxing cost (including all costs of storage and costs incurred in destroying the article) against the claimant. Ultimately, the article was destroyed and the costs paid. (F.D.C. No. 66635; S. No. 92-556-382; S.J. No. 3)

### *Food/Economic and Labeling Violations*

**PRODUCTS:** "Distilled Vinegar," and various "vanilla" flavorings, at Gurabo, Dist. Puerto Rico; Civil No. 92-1022(JP).

**CHARGED** 1-8-92: While held by Productos del Mundo, Inc., Gurabo, Puerto Rico, the articles (labeled "sabor Dorado Distilled Vinegar . . . Packed By Productos Del Mundo, Inc." and "sabor Vanilla Flavor [or "sabor Concentrado De Vanilla" or "sabor White Vanilla Flavor"] . . . Distributed By: Productos Del Mundo, Inc. . . . San Juan, P.R." and manufactured by the dealer using glacial acetic acid and methyl coumarin and vanillin) had glacial acetic acid substituted for vinegar and methyl coumarin and vanillin for vanilla—402(b)(2); labeling of the "Distilled Vinegar" was false and misleading because the article was diluted glacial acetic acid, and labeling of the "vanilla" flavorings was false and misleading because the articles contained vanillin and methyl coumarin—402(a)(3); glacial acetic acid was offered for sale under the name of another food (vinegar); diluted methyl coumarin and vanillin were offered for sale under the name of other foods—403(b); and the "vanilla" flavorings failed to conform to definitions and standards of identity for vanilla flavoring or concentrated vanilla flavoring—403(g).

**DISPOSITION:** A consent decree authorized release of the articles to the dealer. However, the dealer failed to post the required bond; and, upon the motion of the government, the court ordered the articles destroyed. The articles were destroyed. Subsequently, the dealer-claimant failed to pay the \$900.50 due for FDA charges incurred during the destruction process. The government moved the court for an order for the prompt payment of such charges. The court issued such an order, and payment of such costs was received. (F.D.C. No. 66295; S. No. 91-637-511 et al.; S.J. No. 4)



### *Food Additives*

**PRODUCT: Evening primrose oil (with vitamin E) capsules in bulk cartons and in retail bottles,** at Springville and Provo, Dist. Utah; Civil No. 92-C-0584B.

**CHARGED 7-1-92:** While held for sale, the articles contained the nonconforming food additive evening primrose oil—402(a)(2)(C). **DISPOSITION:** The articles were claimed by Nature's Way Products, Inc., Springville, Utah, who denied the charge. After claimant's proposal to export the article pursuant to section 304(d)(1) was rejected by FDA, a consent decree of condemnation authorized release to the claimant to attempt to bring the articles into compliance with the law. Ultimately, the claimant failed to propose a method acceptable to FDA to bring the articles into compliance, the time for review of FDA's determination expired, and the articles were destroyed pursuant to the terms of the consent decree. (F.D.C. No. 66473; S. No. 88-233-183 et al.; S.J. No. 5)

**PRODUCT: Lemon strips, dried, in unlabeled plastic bags,** at Honolulu, Dist. Hawaii; Civil No. 92-00477 ACK.

**CHARGED 6-23-92:** When shipped by Anhing Corp., Los Angeles, Calif., the article labeled (case) "Lemon Strip"—in handwriting—and "Anhing Corp. . . . Los Angeles, CA . . . For Export . . . Tamarind Soup Base Mix" contained the nonconforming food additives cyclamate and saccharin salts—402(a)(2)(C); the article was offered for sale under the name of another food, since its cases were labeled as soup mix—403(b); and the article's label lacked the common or usual name of the food, failed to declare the presence of saccharin or cyclamate, and lacked the required saccharin warning—403(i)(1), 403(i)(2), and 403(o).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66464; S. No. 92-664-531; S.J. No. 6)

### *Drugs/Human Use*

**PRODUCT: Tea-tree-oil antiseptic, lip balm, water-soluble antiseptic, and medicated cream,** at Chesapeake, E. Dist. Va.; Civil No. 2:92cv372.

**CHARGED 5-14-92:** When shipped by Rare Oils of Australia PTY, Ltd., Goonellabah, Australia, the articles (which were labeled "Mela Folia . . . antiseptic [or "medicated lip balm" or "Water Soluble Antiseptic" or "medicated cream"] . . . tea tree oil . . .

Manufactured By: Mela Folia PTY, LTD., Lismore . . . Australia [or "Distributed By: Rare Oils of Australia & Hawaii Inc., Honolulu, Hawaii"]") were new drugs without effective approved new drug applications—505(a); the labeling of the articles contained false and misleading claims for various diseases (for example, arthritis, cystitis, herpes, and varicose veins)—502(a); and the labeling of the articles lacked adequate directions for their intended uses—502(f)(1).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66392; S. No. 91-623-410 et al.; S.J. No. 7)

### *Medical Devices*

**PRODUCT: Eyeglasses, pinhole,** at Manitowoc, E. Dist. Wis.; Civil No. 92-C-0538.

**CHARGED 5-15-92:** The article, which was accompanied by labeling such as (display card) "Aerobic Glasses By Natural Vision International . . . Secrets of Seeing Without Glasses or Contacts," and (eye chart) "The New Way For Better Vision," was a class III device and no approved pre-market approval application was in effect—501(f)(1)(B); the article had been manufactured and processed in an unregistered establishment—502(o); the article was not listed as required—510(j); and information respecting the article had not been provided as required—510(k). The labeling of the article contained false and misleading claims for improving vision—502(a); and the article's labeling lacked adequate directions for use for the article's intended uses, and such directions could not be written—502(f)(1).

**DISPOSITION:** The article was claimed by the dealer, who denied the charges. The government served written interrogatories and requests for admissions on the dealer. A consent decree ordered destruction. (F.D.C. No. 66409; S. No. 92-542-457 et al.; S.J. No. 8)

**PRODUCT: Hearing test device,** at Northbrook, N. Dist. Ill.; Civil No. 91-C-4239.

**CHARGED 7-9-91:** The article (which was labeled "Communidyne Computerized Hearing Test," was accompanied by a pamphlet reading "Facts About Hearing Loss: . . . measures the most common loss," and was being promoted by Communidyne, Inc., Northbrook, Ill.) had not provided the required pre-market notification—502(o); and the article's labeling lacked adequate directions for use—502(f)(1).



**DISPOSITION:** The article was unclaimed, and a default decree ordered its destruction. Then the article was claimed by Communidyne, Inc., Northbrook, Ill., who moved that the default decree be set aside. The court vacated the decree. The parties filed cross-motions for summary judgment. The government moved to strike two affidavits submitted by the claimant, and the claimant sought authorization to export the article. Ultimately, a consent decree of condemnation authorized release of the article to the claimant for salvaging. (F.D.C. No. 66184; S. No. 91-577-369; S.J. No. 9)

**PRODUCT: Photofluorographic x-ray system**, at Zephyrhills, M. Dist. Fla.; Civil No. 92-1350-Civ-T-17C.

**CHARGED** 9-18-92: The article, which had been manufactured and marketed by Industrial Medical Imaging, Inc., Ann Arbor, Mich., was a class III device and it lacked an effective approved pre-market approval application—501(f)(1)(B); the article's labeling lacked adequate directions for use—502(f)(1); and required information had not been filed with FDA—502(o).

**DISPOSITION:** A default decree directed that the system's electronic transducer and the operator's manual be released to FDA for educational and other purposes. The U.S. marshal was directed to dispose of the remaining parts of the system pursuant to law. (F.D.C. No. 66495; S. No. 92-443-320; S.J. No. 10)

**PRODUCTS: Surgical stockinettes**, at Hauppauge, E. Dist. N.Y.; Civil No. CV-92-2805.

**CHARGED** 6-15-92: The articles bore labels such as "Stockinette, Surgical, Stretchable, Rubber Coated, Bacterial Barrier . . . Sterile . . . Etex Co." and had been manufactured by Etex Co. (Division of Eagle Beef Cloth Co., Inc.), Hauppauge, N.Y.; and the circumstances used for the articles' manufacture, packing, storage or installation failed to conform with current good manufacturing practice—501(h).

**DISPOSITION:** A default decree ordered the articles destroyed. However, that decree was vacated, and a consent decree authorized release of the articles to the manufacturer for bringing into compliance. (F.D.C. No. 66047; S. No. 90-546-273 et al.; S.J. No. 11)

### CRIMINAL ACTIONS

**DEFENDANTS: David M. Halpern** (aka David Hall, David Hab, and David Lewis), t/a Emanon, Inc., Tudor Trading Co. (U.S.A.), and D.M.H. Co., **Frances H. Wellgood** (aka Frances C. Halpern and

Frances Gottlieb), purchasing agent, and **Edward Sollisch**, employee, Pebble Beach and Fort Bragg, S. Dist. Calif.; Criminal No. 92-0298-G.

**CHARGED** 3-13-92 by grand jury: *Count 1*—That the above defendants and others conspired: (a) to ship, with intent to defraud and mislead, various drugs not approved for use in the United States; (b) to distribute prescription drugs without a prescription and without adequate directions for use; (c) to conceal various unapproved drugs, knowing that the drugs had been illegally imported; (d) to knowingly ship unapproved drugs by means of false declarations; and (e) to impede FDA's function of evaluating and regulating drugs. Parts of the conspiracy included the following: David Halpern's traveling to England to purchase procaine hydrochloride products from various services; the use by Halpern of foreign firms to purchase and illegally ship Gerovital, other "fountain of youth pharmaceuticals," and other unapproved drugs; the opening by Halpern, Wellgood and others of approximately 20 different "mail drops" in the names of fictitious individuals and sham companies in order to receive smuggled unapproved pharmaceuticals, including cell therapies and other fountain of youth pharmaceuticals; the receipt, advertising and shipment to customers by the defendants of literature which claimed that the unapproved new drugs were effective in the treatment and prevention of old age symptoms, geriatric conditions, premature aging, climacteric disturbances, rheumatism, diabetes, connective tissue weakness, loss of memory, immune reactions, eczema, osteoporosis, and sexual impotence; the instruction of employees by Wellgood and Sollisch that all shipping labels from incoming boxes be cut off and shredded; and the ordering by Halpern and Sollisch, after the government learned of their illegal activities, that all records and other evidence be destroyed—18 U.S.C. 371.

*Counts 2-105*—When shipped from Germany with intent to defraud and mislead, specified drugs (e.g., Regeneresen Thymus—count 10) were new drugs without effective approved New Drug Applications—505(a).

*Counts 106-122*—When shipped from England with intent to defraud and mislead, specified drugs were new drugs without effective approved New Drug Applications—505(a).

*Counts 123-134*—With intent to defraud the United States, false invoices, documents and papers were made out and passed through the customhouse in order to import from England Gerovital H3 (count 123) and other similar unapproved drugs—18 U.S.C. 545.

*Counts 135-160*—With intent to defraud the United States, false



invoices, documents and papers were made out and passed through the customs house in order to import from Germany a number of specified drugs—18 U.S.C. 545.

*Counts 161-198*—With intent to defraud and mislead, specified drugs were knowingly introduced and attempted to be introduced from England (counts 161-172) and Germany (counts 173-198) by procuring the making of false statements as to material matters (e.g., count 161 listed Gerovital H3 with a declared content and value of “8 Glass Figurines/\$38”)—18 U.S.C. 542.

**DISPOSITION:** Guilty plea by Halpern to counts 1, 10 and 123; imprisonment for two years and supervised release for three years. Guilty pleas by Wellgood and Sollisch to counts 1, 10 and 123; imprisonment for eight months each, and supervised release for three years. In addition, Sollisch was fined \$2,000. (F.D.C. No. 66572; S.J. No. 12)

**DEFENDANT:** **Angel L. Rivera Melendez**, dairy farm administrator, Fajardo, Dist. Puerto Rico; Criminal No. 92-72(CC).

**CHARGED 4-1-92** by grand jury: *Counts 1, 2, and 3*—On three specified dates, the defendant, by falsely declaring that bottles of an unapproved new animal drug (Berenil) were for use on personally owned horses only and would be administered by a licensed veterinarian, entered such unapproved drug into the commerce of the United States, when such unapproved drug was intended for resale and for use on dairy cows—18 U.S.C. 542; *Counts 4, 5, and 6*—On three specified dates, the defendant, with intent to defraud and mislead, introduced into interstate commerce bottles of a new animal drug (Berenil), and no approved New Animal Drug Application was on file for such drug—512(a)(1).

**DISPOSITION:** The defendant pleaded not guilty to the indictment and filed a motion to strike various language in the indictment. After a trial, the defendant was found **not guilty** on count 1, was found guilty on the other counts, and was sentenced to imprisonment for seven months, supervised release for three years, and a special assessment of \$175. (F.D.C. No. 66146; S. No. 90-676-228 et al.; S.J. No. 13)

## INJUNCTION ACTIONS

**DEFENDANTS:** **Pennex Products Co., Inc.**, and **Johan A. Mous**, president, Verona, W. Dist. Pa.; Civil No. 92-1164.

**CHARGED 4-30-92** in a complaint for injunction: That the defendants (at their Verona, Pa., manufacturing plant and Youngwood,

Pa., warehouse) were manufacturing, processing, packing, repackaging, labeling, distributing, and holding for sale various drugs [as well as cosmetics]. The defendants’ drugs, which contained one or more interstate components and which were shipped in interstate commerce, had been manufactured, processed, packed, and held under circumstances that failed to conform with current good manufacturing practice—501(a)(2)(B). FDA inspections documented a number of failures to comply with specified current good manufacturing practice regulations. The defendants were unable or unwilling to make changes to their manufacturing processes sufficient to bring them into compliance; and, unless enjoined by the court, the defendants were likely to continue to violate the law.

**DISPOSITION:** The government moved for a preliminary injunction. The defendants generally denied the charges, asserted that the individual defendant, the president, had been appointed less than a year earlier and had not been present at any discussion of the FDA inspector’s observations, and asserted that the relief requested by the government was over-broad, inequitable, and in contravention of the law. In addition, as affirmative defenses, the defendants stated that there was no substantial likelihood of irreparable harm or injury sufficient to form a basis for injunctive relief, that they had cooperated with the government and taken prompt and direct steps to address deficiencies noted by FDA, that they operated their plant and warehouse in accordance with the law, and that the relief requested by the government was over-broad and contrary to law as it related to the corporation and specifically as it related to its president. The defendants moved for a continuance of the scheduled hearing on the preliminary injunction and for a consolidation of that hearing with a hearing on the merits of the action. As grounds for the motion, the defendants represented that the corporation would suffer irreparable harm, that the defendants’ drugs would not pose any health hazards, that consolidation of the hearings would conserve judicial resources, and that fundamental fairness to a new management (which was acquiring the corporation) warranted a continuance.

Meanwhile, after the firm was acquired by an investment group with experience in managing pharmaceutical manufacturing operations, the president of the firm resigned, planned to return to the Netherlands, and planned no future engagement in the pharmaceutical manufacturing business in the United States. The court granted an order **dismissing** Johan A. Mous from the action.

Subsequently, a consent decree of permanent injunction against the corporation was agreed to by the new president of the corporation. The corporation was enjoined from the complained-of viola-



tions. In addition, the firm was enjoined from specified operations involving interstate drugs and drug components (with specified exceptions) unless and until a number of specified conditions were met, including the establishment and operation of the defendant's facilities in accordance with current good manufacturing practice, the certification by an expert of the corporation's compliance with such manufacturing practice, successful validation of cleaning procedures for the corporation's liquid filling lines, successful prospective validation of batches of layered drug tablets, and verification of the stability testing data of drugs. (Inj. No. 1280; S. No. 91-607-241 et al.; S.J. No. 14)

**DEFENDANT:** Robert Rivas, t/a Mexico Cafe Tortilla Co., Mount Vernon, W. Dist. Wash.; Civil No. C-92-696.

**CHARGED** 4-23-92 in a complaint for injunction: That, at the defendant's food processing facility, foods such as corn and flour tortillas and tortilla chips (made using interstate flour and corn) were manufactured, prepared, packed, held for sale, and distributed. Such foods were prepared, packed or held under insanitary conditions—402(a)(4). FDA inspections had consistently revealed insanitary conditions in and around the defendant's facility, and FDA laboratory analysis had found insect and animal filth in samples of food or product residue from food processing equipment. FDA had provided the defendant with prior notice and warning concerning his violative conduct; and, based on continued insanitary conditions, it was apparent that, unless restrained by the court, the violations would continue.

**DISPOSITION:** A consent decree of permanent injunction was filed permanently enjoining the complained-of violations. In addition, the defendant was enjoined from processing and distributing any interstate food unless and until a number of specified conditions had been met, including the cleaning and renovation of the facility and its equipment, the elimination of insect infestation, the establishment of a sanitation control program, and the certification by an expert that adequate methods, facilities and controls have been implemented. (Inj. No. 1285; S. No. 92-667-431 et al.; S.J. No. 15)

## MISCELLANEOUS ACTIONS

**SUBJECT:** Nasal device and FDA refusal to reclassify, Lancaster, E. Dist. Pa.; Civil No. 88-6275.

**CHARGED** 8-15-88 and amended 1-26-89 by Norman M. Lake,

inventor of the Inductive Nasal Device, Lancaster, Pa., against the FDA, HHS Secretary Otis R. Bowen, and FDA Commissioner Frank E. Young: That FDA had classified the plaintiff Lake's nasal device as a class III medical device. The plaintiff had petitioned FDA seeking reclassification of his device from class III to class I. The plaintiff asserted that because his device was substantially equivalent to the "nose clip" already classified by FDA as a class I medical device, FDA had wrongfully determined that his device was not substantially equivalent to the nose clip and had wrongfully relied on a determination, unsupported by scientific evidence and contradicted by the plaintiff's valid scientific evidence, that no medical device could be effective for the treatment of the common cold. The plaintiff also alleged a failure to maintain due regard for professional medical ethics and the interests of patients by the failure to allow the marketing of the plaintiff's Inductive Nasal Device as a device that prevented the common cold and warded off nasal allergies. The plaintiff demanded that the court order the defendants to reclassify the plaintiff's device as a class I medical device, to allow the device's marketing, to submit the plaintiff's petition to a classification panel, and to grant other just and proper relief.






**DISPOSITION:** The defendants moved for summary judgment. After reviewing the history of the plaintiff's efforts to obtain FDA approval to market what essentially was a nose clip, the court granted summary judgment to the defendants. Although FDA had refused to approve the device's sale as a cure for colds and allergies, the court was unpersuaded that FDA's decisions were the product of "impermissible influences," since there was no evidence that Mr. Lake presented valid scientific evidence which FDA ignored. If FDA evidenced some skepticism with respect to Lake's claims, it was because after numerous communications the plaintiff still had failed to provide any evidence of the efficacy of his device.

The plaintiff also argued that FDA made it too difficult to procure reclassification into class I by maintaining that when there was no valid scientific evidence of benefit, the risk was *per se* unreasonable. The court found that FDA's interpretation of section 360(a)(1)(A)(ii) was valid, stating: "We are long past the day when snake oil can be sold with impunity. Plaintiff's reading of the statute would shift the burden of proof to the FDA and that is not how our public health laws are designed to work. When there is no valid scientific evidence of efficacy, and the risks are unknown, the risk is unreasonable." The plaintiff's motion for summary judgment was denied, and the defendant's motion was granted. (Misc. No. 888; S.J. No. 16)



# Beans, beans, good for your heart, the more you eat beans



and other vegetables and fruit  and grains and trimmed lean meats and poultry and low fat milk and  yogurt and Chicken Ratatouille and Catfish Stew and Beef Stroganoff and Homemade Turkey Soup and Sweet Potato Custard and Baked Pork Chops and Garden Potato Salad and Banana Nut Bread  and Chicken Creole and Mocha Cheesecake and a lot of other delicious foods, in moderation of course,  that really can be made so that they're lower in saturated fat and  (cholesterol, the less likely you are to develop high blood cholesterol and heart disease. For recipes, write: The National Cholesterol Education Program, P.O. Box 30105, Bethesda, MD 20824-0105.

A LOW FAT DIET. GOOD FOOD. GOOD FOR YOUR HEART.

National Cholesterol Education Program

National Heart, Lung, and Blood Institute; National Institutes of Health; Public Health Service; U.S. Department of Health and Human Services.