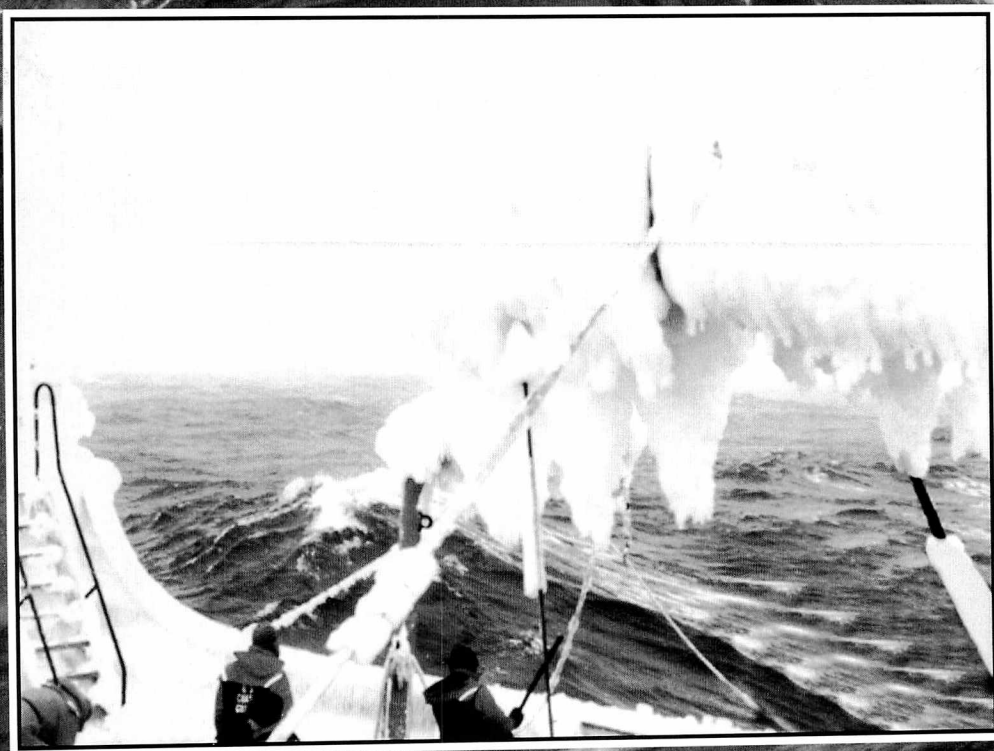


# FDA CONSUMER

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

• VOL. 30 NO. 10

DECEMBER 1996 •



Inside FDA

## *Hazardous Duty in the Bering Sea*





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(Photo courtesy of UroMed Corporation)

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## Public Can Comment on Animal Organ Transplants

The public has until Dec. 23 to submit written comments on a proposed guideline about xenotransplantation—the transplantation of animal organs and tissue into humans.

FDA, the national Centers for Disease Control and Prevention, and the National Institutes of Health developed the guideline to reduce public health risks while not impeding medical innovation.

People may send comments to FDA's Dockets Management Branch, HFA-305, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

The recommendations include:

- Taking appropriate safety measures for pre-transplant animal screening to keep as low as possible any chance that animal diseases may be transmitted to human recipients.
- Archiving biologic samples, such as plasma and tissues, from source animals

and human recipients for potential public health investigations.

- Selecting xenotransplant team members for their expertise in providing adequate safeguards and in conducting research that will yield useful data.
- Having local review boards evaluate the operations to assess infectious disease risks.
- Monitoring patients after xenotransplants for infectious agents, including not yet recognized animal organisms that may cause diseases in humans.

The three agencies are collaborating with the Health Resources and Services Administration to develop a pilot program for a national registry to provide a central database for public health research and investigations.

The guideline was published in the Sept. 12, 1996, *Federal Register*. To obtain a copy, send a self-addressed adhesive label with your order to FDA's Manufacturers Assistance and Communications Staff, HFM-42, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852-1448; or fax your order to (1-888) 827-3844. The guideline is also available on the World Wide Web at <http://www.fda.gov/cber/cberftp.html>; by file transfer protocol at <ftp://ftp.fda.gov/CBER/>; and by E-mail at [Xeno@al.cber.fda.gov](mailto:Xeno@al.cber.fda.gov).

A copy of an FDA backgrounder, "Fact Sheet on Xenotransplantation," may be ordered by writing to FDA, HFI-40, Rockville, MD 20857, or faxing your order to (301) 443-9057. Include the publication number: BG 96-6.

## Policy Change for Emergency Treatments

Promising experimental therapies may now be used in life-threatening situations to treat patients who can't give their consent. This change in policy is reflected in a new FDA final rule and a companion document by the National Institutes of Health.

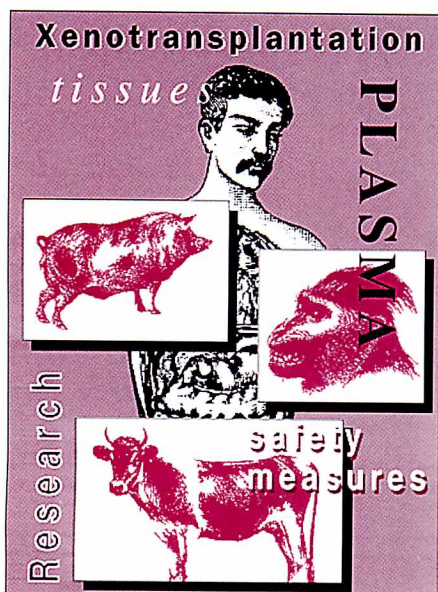
Before, patients in a life-threatening situation could not take advantage of experimental therapies if they were unable to provide the required informed consent or did not have a family member or other legal representative readily available to provide it. But in the new rule, published in the Oct. 2 *Federal Register*, FDA establishes the criteria under which such patients may receive, without consent, treatment with promising experimental drugs and medical devices.

The new policy is expected to offer critically ill, unconscious patients who cannot be successfully treated with conventional therapies the benefits of experimental intervention.

FDA's rule allows patients to be enrolled in clinical trials without their consent provided that an independent doctor and an institutional review board, or IRB, agree that the clinical trial addresses a life-threatening situation and that other criteria are met. An IRB is a committee of experts and lay people established to review research.

Also, patients may receive the experimental therapy only if:

- available treatments are unproven or unsatisfactory
- research cannot otherwise be carried out to determine whether the therapy is safe and effective





- it is not feasible to obtain informed consent from the patient or the patient's legal representative
- risks and benefits of the experimental procedure are reasonable, compared with those associated with the patient's medical condition and standard therapy.

The rule also includes additional protections, such as consultation with the community, public disclosure of study design and attendant risks before the study's commencement, and public disclosure of study results when the study is completed. Also, FDA reviews protocol design and other information on the proposed therapy before the study can proceed.

The NIH companion document, "Emergency Research Consent Waiver," applies to all agencies in the Department of Health and Human Services. Both FDA and NIH are part of the department. NIH's document reaffirms the government's policy of protecting human research subjects. It contains the same criteria as FDA's final rule.

### **New Device for Degenerative Disc Disease**

A new implantable medical device for stabilizing and fusing the spine is the first of its kind to receive FDA approval as a treatment for certain people with degenerative disc disease. It provides an option for doctors to treat patients who do not respond to nonsurgical treatment.

The BAK Interbody Fusion System was approved only for people who need surgical fusion of adjacent vertebrae above and below a diseased disc. The device is a hollow metal cage about an inch long that is implanted into disc space between two vertebrae to stabilize



the spine and to allow for fusion of the vertebrae. The device is not intended for people with general back pain.

In degenerative disc disease, discs between the vertebrae break down and cause lower back and leg pain. Conventional treatments include back braces, physical therapy, and, in some people, surgery to remove the disc. Fusion with hooks and rods has been used in some cases.

When implanting the BAK system, the surgeon removes bone from the patient and packs it inside the implant. Over time, the bone can grow through the holes in the wall of the cage and around the outside of the cage, fusing the vertebrae and often reducing back pain.

In a clinical study, the device was implanted in 947 patients aged 21 to 65 who needed spinal fusion surgery for degenerative disc disease.

After two years, 254 patients were evaluated. The device was successful in 184 patients (72 percent). For this group, the spine had fused, pain was decreased, and there was no loss of muscle strength

or function—the ability to sit, walk, or put on shoes. Complications were similar to those reported from conventional surgery and included damage to the nerve and blood vessels, infection, and the need for more surgery to further stabilize the spine.

As a condition of approval, the manufacturer must conduct postmarketing studies to determine the device's long-term effectiveness and to examine any devices removed from patients for any reason. The company also must provide information that would help potential patients make informed decisions about the surgery.

Spine-Tech Inc., of Minneapolis, makes the BAK Interbody Fusion System.

### **New Brain Cancer Treatment**

A recently approved implantable wafer is the first technology to deliver an anticancer drug directly to the site of a surgically removed brain tumor in recurrent brain cancer.

Gliadel wafers were approved by FDA on Sept. 24 to treat glioblastoma multiforme, an aggressive type of brain cancer in the malignant glioma class of cancers. Glioblastoma multiforme, which occurs mainly in adults, has been extremely difficult to treat effectively with cancer therapies such as surgery, radiation, and traditional chemotherapy.

Implanted into the cavity of the brain created when a tumor is removed, the wafers—seven or eight of them, depending on the cavity's size—deliver the anticancer drug BiCNU (carmustine) directly to the affected area of the brain. The direct delivery lessens the exposure



of the rest of the body to the drug.

In a study of 222 patients with recurrent malignant glioma who had been initially treated with surgery and radiation, the six-month survival rate in those with glioblastoma multiforme who received Gliadel was 56 percent, compared with 36 percent for those who received a placebo. In patients with diagnoses other than glioblastoma multiforme, Gliadel did not affect survival rates. A small 32-patient study supported these results.

Patients should be monitored closely after implantation for possible complications such as seizures, infections, abnormal wound healing, and brain swelling.

Approval followed a June 15, 1996, recommendation for approval by FDA's Oncologic Drug Advisory Committee. Since October 1995, Gliadel had been available under a Treatment IND to patients with recurrent malignant glioma.

Gliadel is manufactured by Guilford Pharmaceuticals Inc., of Baltimore.

### New Bronchial Device

A new device to detect bronchial tissue abnormalities in patients with previous, current or suspected lung cancer has been approved by FDA.

The Xillix Life-Lung Fluorescence Endoscopy System uses a tube inserted through the mouth into the bronchi (tubes leading from the trachea to the lungs) to deliver a blue laser light to the bronchial tissue. The laser light elicits a fluorescence from the tissue, which projects an image on a video monitor. Normal tissue appears green; abnormal tissue appears reddish-brown. A biopsy of suspicious tissue can then identify

cancer or another abnormality.

The system was approved last Sept. 19 for use with conventional white light bronchoscopy, in which a white light is used to illuminate lung tissue to help physicians identify abnormalities. The new system detects more tissue changes than can be seen with the white light alone.

The manufacturer, Xillix Technologies Corp., of Richmond, British Columbia, sponsored a study that examined 700 spots on the bronchial tubes of 173 patients at seven medical facilities in the United States and Canada. Patients first underwent white light bronchoscopy and then, with the bronchoscope still in place, the fluorescence endoscopy. The patients either had symptoms or x-ray findings indicating possible lung cancer or had previously had the disease.

Subsequent biopsy of all 700 suspicious lesions found that 75 patients had one or more abnormal spots. Of those, 28 patients, or 37 percent, were correctly identified by white light bronchoscopy as needing biopsy. The fluorescence system combined with white light correctly identified 56 patients, or 75 percent, as needing biopsy—twice as many as white light alone.

Few adverse effects were associated with the new system. However, the fluorescence exam generated 196 additional biopsies, of which only 60 proved to have significant cellular abnormalities.

As a condition of approval, which was based on the study data and on the recommendation of FDA's Ear Nose and Throat Devices Panel, the manufacturer must conduct a postmarketing study to see if doctors will generally agree on which images are positive and which are negative.

### Recall of Factor Used To Treat Hemophilia A

One lot of Monoclate-P, an antihemophilic factor (factor VIII) used to treat hemophilia A, has been voluntarily recalled by the manufacturer, Centeon L.L.C. of King of Prussia, Pa.

The recalled lot is P72304, with an expiration date of April 12, 1998. It was recalled in early October as a precautionary measure. At press time in October, FDA had not received any reports of illness associated with this product.

Individuals or institutions who have any vials of the recalled lot should return the product immediately to the manufacturer. The company's customer support telephone number is (1-800) 683-1288.

The recall of the lot of Monoclate-P was prompted by the possibility that it had been damaged and possibly contaminated as a result of a manufacturing problem. Similar manufacturing problems may be related to reports linking one lot of Centeon's human albumin, Albuminar-25, to septicemia, a life-threatening blood infection. This lot was recalled by the manufacturer last Sept. 23, followed by the recall of nine other lots.

On Oct. 9, as a precaution, Centeon L.L.C. voluntarily recalled all Albuminar brand human albumin and Plasma Plex brand plasma protein products, distributed under the Centeon and Armour labels. Because these products are typically administered in hospitals and other health-care facilities, it is unlikely that consumers have any. Health-care professionals with questions may



call the company's medical information line at (1-800) 551-0210.

FDA is asking health professionals to report any adverse events associated with these products to MEDWATCH, the agency's adverse event reporting program, at (1-800) FDA-1088, and to the company.

### Medical Devices to Have Preproduction Quality Controls

Firms that make medical devices posing a medium or high risk to patients must now incorporate quality controls in the products' design, according to a new FDA rule. Such controls before production will save lives and greatly reduce risks from unrecognized design flaws.

The quality system rule, published in the Oct. 7, 1996, *Federal Register*, requires that manufacturers:

- establish performance requirements for a device before production
- ensure that device components are compatible with each other
- select adequate packaging materials
- when appropriate, do a risk analysis.

For example, when designing defibrillators for emergency use in hospitals and ambulances to restart the heart, firms must consider all aspects of use in the ambulance as well as in the hospital. Firms must consider such ambulance-related factors as storage temperature, road shock and vibration, two-way radio interference, and electrical noise generated by the siren. They must review their design throughout development to make sure it is meeting all requirements.

In a review of medical device recalls over six years in the 1980s, the Govern-

ment Accounting Office found that design defects accounted for about 44 percent of the products' quality problems and that proper design controls could have prevented the problems. Design-related defects have been found in critical products such as heart valves, catheters, defibrillators, pacemakers, ventilators, patient chair lifts, and laboratory tests.

The quality system rule will make standards for U.S. medical devices consistent with quality system requirements worldwide. The rule's standards closely follow the international standard, ISO 9001, fulfilling a mandate of the Safe Medical Devices Act of 1990 to harmonize these requirements. The rule also includes purchasing and manufacturer servicing controls and clarifies requirements of FDA's current good manufacturing practices. Firms may develop their own methods for meeting the objectives of each control tool.

The rule takes effect June 1, 1997, but FDA will not enforce the design control provisions until after June 1998, when equivalent provisions become mandatory in Europe.

A subsequent proposal and final rule will cover firms that service or refurbish devices outside the original manufacturer's control.

### Calls to FDA Office Now Free

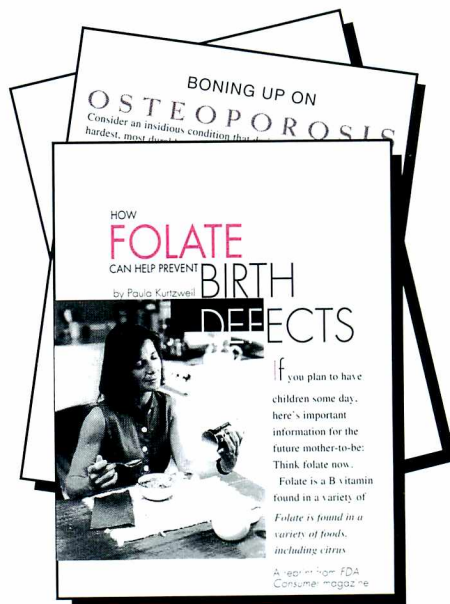
The Office of Consumer Affairs at FDA has a new free telephone number for consumer inquiries: (1-800) 532-4440 (in the D.C. metropolitan area, call (301) 827-4420). Inquiries about breast implants, previously directed to the breast implant information line, should be directed to this number.

### Three Free Reprints

The following *FDA Consumer* reprints, listed with their publication numbers, are available free from FDA:

- Boning Up on Osteoporosis (FDA) 96-1257
- How Folate Can Help Prevent Birth Defects (FDA) 96-2306
- Adults Need Tetanus Shots, Too (FDA) 96-9017.

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



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



# FDA And Medical Devices

## *After 20 Years, a Look Back, a Look Ahead*

by Tamar Nordenberg

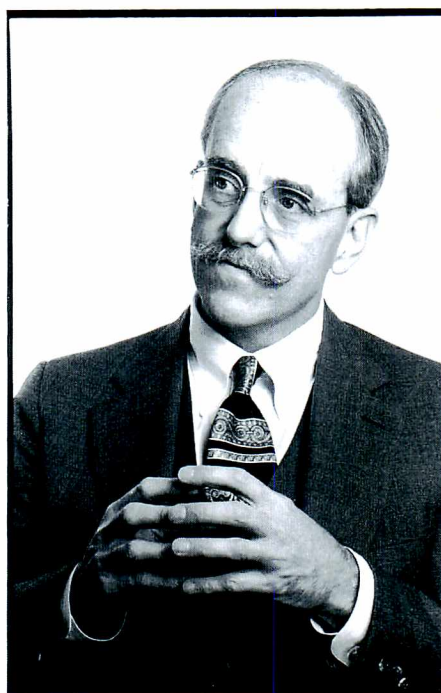
FDA has just marked the 20th anniversary of the Medical Device Amendments to the Food, Drug, and Cosmetic Act.

Until 20 years ago, FDA was ill-equipped to protect Americans from dangerous or useless medical devices, because the agency had to prove a device was unsafe or ineffective before it could take action to remove the device from the market. In 1976, the landmark Medical Device Amendments were signed into law by President Gerald Ford. The law requires manufacturers of most medical devices—particularly moderate- or high-risk devices—to provide FDA with safety and effectiveness data before marketing.

FDA's Center for Devices and Radiological Health is charged with implementing the device law. The center has many functions, including working with FDA's field force to inspect device manufacturing plants; keeping track of problems with devices already in use and taking prompt action to correct them; and helping manufacturers produce better products by conducting laboratory research on the ways companies test their products and on specific device safety problems.

One of the most visible and important functions of the center is to review devices for safety and effectiveness before they are marketed. The center clears for marketing everything from contact lenses and artificial joints to x-ray machines. More than 550 categories of low-risk medical devices, including surgical gloves and therapeutic massagers, are exempted from premarket approval.

Challenged to speed product approv-



*“Once we have the good science necessary to make a decision, we should go ahead and make it, to reach closure on the issue and move on.”*

als without compromising consumer safety, the center has made some changes in the way it does business. (See “Inside FDA: Agency Changes Include Medical Device Review” in the November 1996 issue of *FDA Consumer*.)

In the following interview, center director D. Bruce Burlington, M.D., talks about what the medical device program has accomplished and what remains to be done.

*Q. Twenty years have passed since enactment of the landmark Medical Device Amendments of 1976. Are Americans better cared for as a result of the amendments?*

*A. I think the American people are significantly better off for having the medical device law. Today, Americans can really rely on devices. When a medical device is used in a doctor's office or hospital, patients can be confident that the operator knows how to use the device well and that it will work for them.*

Americans can count on devices because of the system of pre- and postmarket oversight made possible by the 1976 amendments. To ensure that products are well-manufactured, FDA inspects companies to see that they are following good manufacturing practices, keeping appropriate records on the design and manufacture of products, and maintaining a system for handling complaints.

Before a product even goes to market, a company must present data to FDA showing not only that it will be well-manufactured, but also that it is safe and effective—that it won't harm people and



will deliver its expected benefits. And if a product causes unforeseen problems, there's a feedback loop, a requirement that manufacturers report any serious problems to FDA so rapid action, including a product recall if necessary, can be taken to protect people from a faulty device.

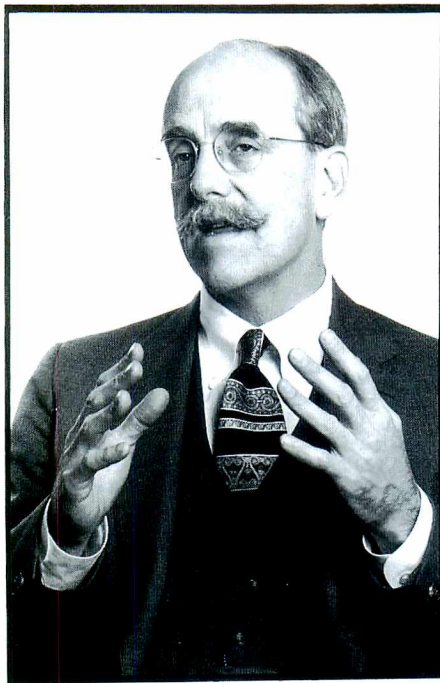
There is yet another vital benefit of our regulation of devices under the medical device law: information. The largest source of risk in using a medical device isn't the product itself, but the interface between the user and the device. It is especially important for doctors to know how and when to use the product. Serving as a reliable, unbiased evaluator of this information may be the most important service FDA can provide to health professionals.

**Q.** *What are some of the most significant accomplishments of the center during your service as director to date?*

**A.** Several breakthrough devices have been approved by the center. One of the most important is our recent approval of the use of implantable defibrillators to prevent sudden death in people who have had heart attacks. This was the first approval for this use in the world, and it should save thousands of lives each year. Also in the area of cardiology, we approved a coronary stent, a cage-like device that's permanently implanted in a diseased coronary artery to expand it and allow normal blood flow. This is really changing the way cardiologists are performing balloon angioplasty to open up clogged arteries feeding the heart, making the procedure available to many patients who before would have had to undergo major surgery.

To help detect cervical cancer more reliably, we've approved a device that scans all pap smears read as normal by the technologist and identifies suspicious ones for a second review.

Also, we've approved a new microwave device to treat symptoms of enlarged prostate, a condition affecting



***“We at FDA have to understand that new products do bring real benefits, and that delaying availability of a safe, effective medical device can harm people just as much as approving a faulty product.”***

millions of men. This device gives patients an alternative to treatment with drugs or surgery.

Two newly approved devices can potentially help millions of women who suffer from urinary incontinence. One is a disposable balloon-type device that the patient inserts into her urethra, and the other is an adhesive-backed foam pad that's placed over the urinary opening.

Another approval that's been prominent in the news is the use of excimer lasers to treat certain cases of nearsightedness, giving many people an alternative to eyeglasses or contact lenses.

An additional major accomplishment has been the center's recent emphasis on clinical trials—controlled studies in humans—for evaluating the safety and effectiveness of new devices. For 20 years, we'd been concentrating primarily on assuring that devices were well-designed and well-made. It goes without saying that these things are still important. But we've come to realize that for some devices—probably less than 10 percent—we also need clinical data from human studies. This gives us information on how the device will perform in actual patients, and gives the physician information about which patients are likely to benefit from the device and under what conditions. In the long run, I think the focus on clinical trials may have a bigger impact on the public than anything else we're doing.

**Q.** *Government agencies are often criticized for making decisions that don't reflect the interests of the public and the regulated industry. Has FDA taken steps to avoid this pitfall?*

**A.** Yes. To help the agency make decisions on policy matters or on specific devices, we want input from the public and industry. For policy issues, we often have grass-roots meetings—we've had several in the last year—to get suggestions on how to approach an issue. When we have a particular device in



front of us that may be ready for marketing, very often we will have an advisory committee meeting. Most meetings are open, and consumer protection groups and members of the public are welcome to attend and tell us what they expect.

Because I also work as an emergency room physician, I get an additional, hands-on perspective. I can see the devices in action and can learn from patients and other physicians what they expect from the devices and from government oversight. It helps me to know which issues are peripheral so I can focus on the issues that really make a difference.

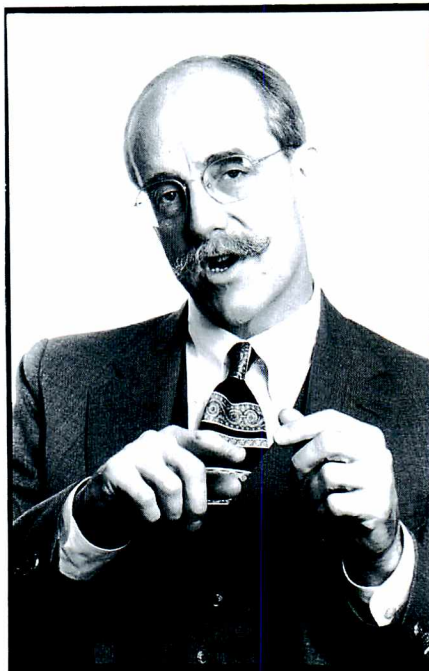
After balancing everyone's input, and with the intent of the law foremost in mind, FDA is ultimately responsible for deciding whether to allow a product on the market and whether it's necessary to take action against a product already on the market. In the end, the government official charged with making the decision is accountable to the public, and he or she must "take the heat" if a decision is criticized.

*Q. Some critics say FDA is too slow in approving medical devices. Is the criticism justified, and what is the agency doing to speed up Americans' access to safe, effective medical devices?*

*A.* We should take seriously those critics who raise valid points, and use their negative appraisals to improve our performance. We at FDA have to understand that new products do bring real benefits, and that delaying availability of a safe, effective medical device can harm people just as much as approving a faulty product.

At the same time, we must bear in mind that our goal is not simply to get products to the market, but to get products that work and that we know how to use. So we can't lose sight of our consumer protection mission as we look at changing the way FDA does business.

A little over three years ago, when I came to the center, we had a mountain



***"The United States has the gold standard for what is expected from companies when they want to bring a product to market."***

of work that had built up over the previous couple of years. We had been through a period of incredibly intense internal scrutiny and external review, and we responded to that review by modifying the way we operate.

We've substantially dug out from under the mountain. Abbreviated applications—applications for a device that's essentially the same as something already on the market—are reviewed on time, usually within 90 days. For more complicated applications, we still have some work to do. We're making real headway, though, towards a record of timeliness.

Some people question whether pa-

tients in other countries get access to new devices sooner than patients in the United States. When it comes to products that are really new—those that represent breakthrough technologies or are the first of their kind—we use a system of expedited review which allows these kinds of devices to go to the head of the queue and receive review very quickly.

Under this system, we've approved several significant new devices in the past few years before they were approved anywhere else in the world. These include a prenatal test for genetic abnormalities, an ultrasound system to speed the healing of bone fractures, a bone growth stimulator for treatment of old, unhealed fractures, and the use of an implanted heart defibrillator to prevent sudden cardiac arrest in patients who have suffered heart attacks.

Of course, we have little control over the time it takes for a company to develop its product and collect data on its safety and effectiveness. But the next step—the company's interaction with FDA—must be productive and efficient. Long, drawn-out decisions aren't necessarily better than prompt ones. We at FDA need to make timely decisions to provide a clear and predictable business climate so that industry can do its job and bring new products to market. But we can't make sacrifices in the quality of data.

Complete, well-prepared applications move through the system more quickly than others. Once we have the good science necessary to make a decision, we should go ahead and make it, to reach closure on the issue and move on. That culture of decisiveness is especially important when we're dealing with the device industry, in which a product's market life often is only a few years.

FDA is committed to doing the best we can with the budget provided. By looking to the experience of businesses across America, we can learn lessons about how to get our job done better and more cheaply.



To make the most efficient use of FDA's resources, we're looking for ways to get the same results with fewer people. The agency has really pushed the envelope regarding abbreviated device applications. We're allowing many products that previously would have required a comprehensive application to now be reviewed under an abbreviated application, which is usually processed in only 90 days.

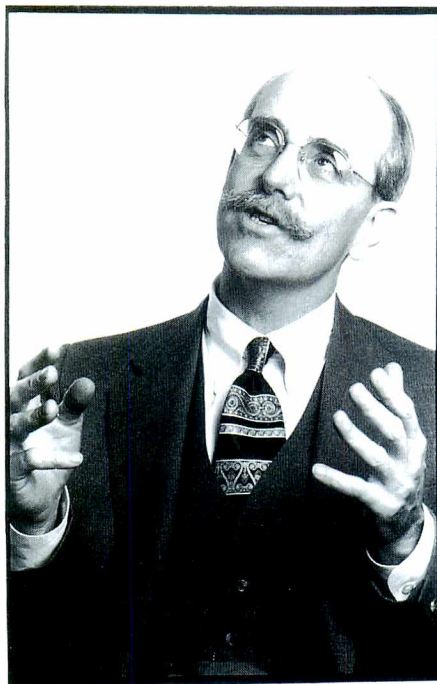
Also, we're pilot-testing a program of third-party reviews, which asks, "Which part of the work does it make sense for the agency to turn over to external parties?" We may be able to reduce review times by allowing carefully selected outside groups to perform the first stage of review of devices that don't present a substantial risk to the American public.

*Q. Is it realistic to think that device regulation could be standardized worldwide to lessen the burden on device manufacturers who want to market their products internationally?*

*A.* Today, medical device manufacturers may have to develop different sets of data for each country in which they seek approval. We are working toward harmonizing standards among countries where we can.

People are much the same around the world, and many of their diseases and injuries are the same. We ought to be able to reach agreement worldwide on what constitutes a safe, well-manufactured product. But the issue of whether a product delivers a sufficient benefit is harder because there are different expectations of the regulatory systems in the United States and, for example, Europe.

The United States has the gold standard for what is expected from companies when they want to bring a product to market, a gold standard not just in terms of knowing how a product is made but also of knowing how it works and under what circumstances it works. In Europe, device regulation focuses on whether devices are well-designed and



***"We can't lose sight of our consumer protection mission as we look at changing the way FDA does business."***

well-made—their mechanical performance characteristics. It doesn't focus on efficacy—on whether the device works on patients—like our system does. We're not prepared to take a step down to a lower standard, and other countries with different expectations of government aren't ready to line up with the American system. So we don't expect to see total harmonization soon, with one reviewing body getting the product to the world market.

*Q. What are the biggest challenges you expect your center to face over the next decade?*

*A.* We have many of the same challenges that people have across government. Given the realities of the federal budget, we have to figure out how to get our job done with tight resources. We have to determine what's most important about what we do, and, where possible, share the public health responsibility with industry, academia, and health-care providers. We've already begun that process through the pilot testing of third-party reviews.

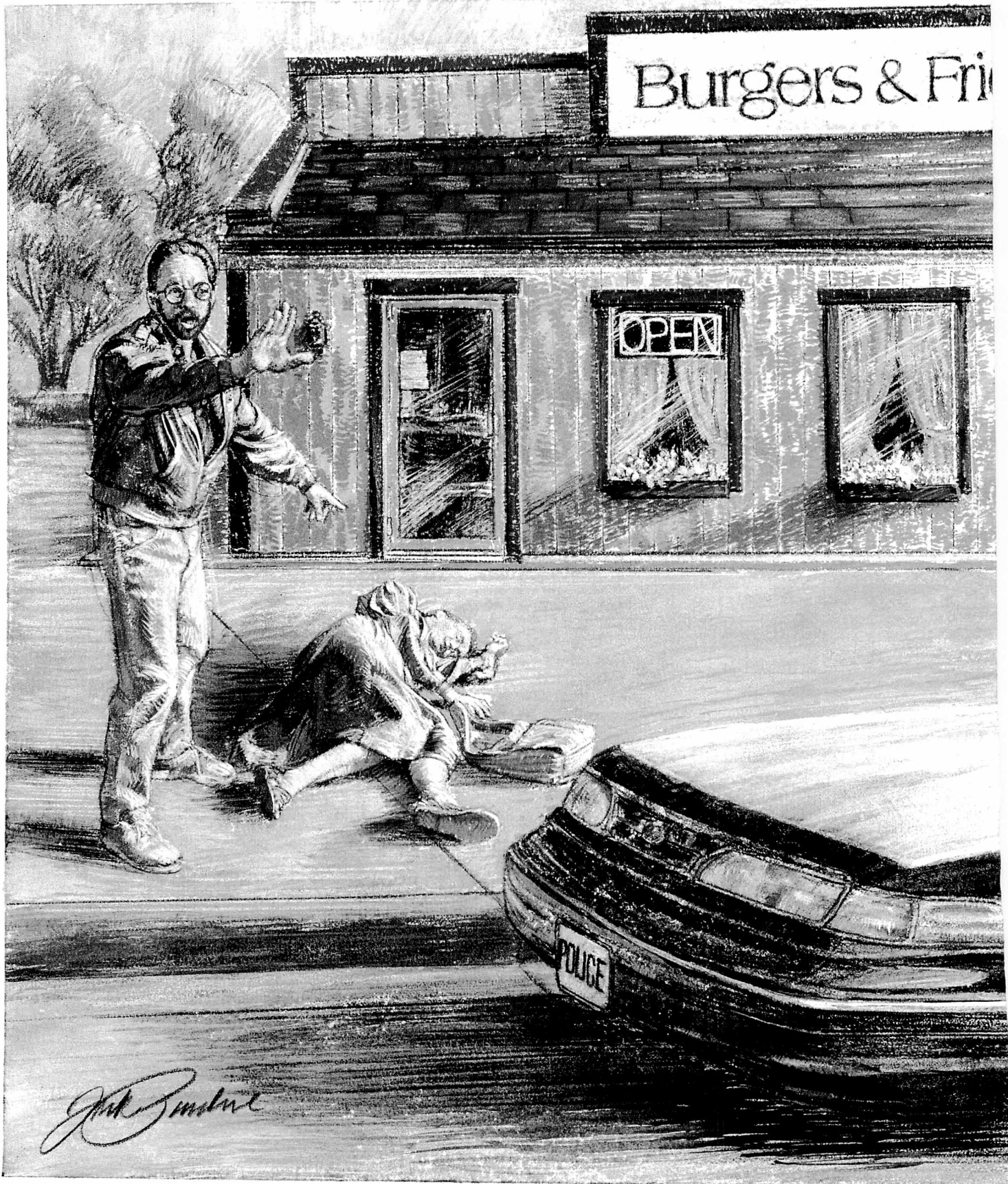
Also, in the last few years there's been a shift from the one-on-one, individual doctor and patient model of health care toward a managed care model where patient care is administered by large organizations like HMOs. With cost-effectiveness considerations playing a much larger role in medical decision-making, health-care organizations will need information for "technology assessment"—information not only on whether a device works, but how it compares to other devices and other forms of treatment.

In some ways this will make FDA's job easier, because every company that wants to market a product will know that its data will not only have to pass review by the agency, but will also have to convince the managed-care organizations that its product really makes a difference.

But this raises questions about FDA's role in this new era. Are we going to continue to evaluate each new device essentially in isolation, simply asking whether the product works and is safe, leaving it to others to do the comparisons? Or will the agency jump into the technology assessment arena? More and more, I think we'll have to focus on how to evaluate products in the context of the whole health-care picture. ■

*Tamar Nordenberg is a staff writer for FDA Consumer.*







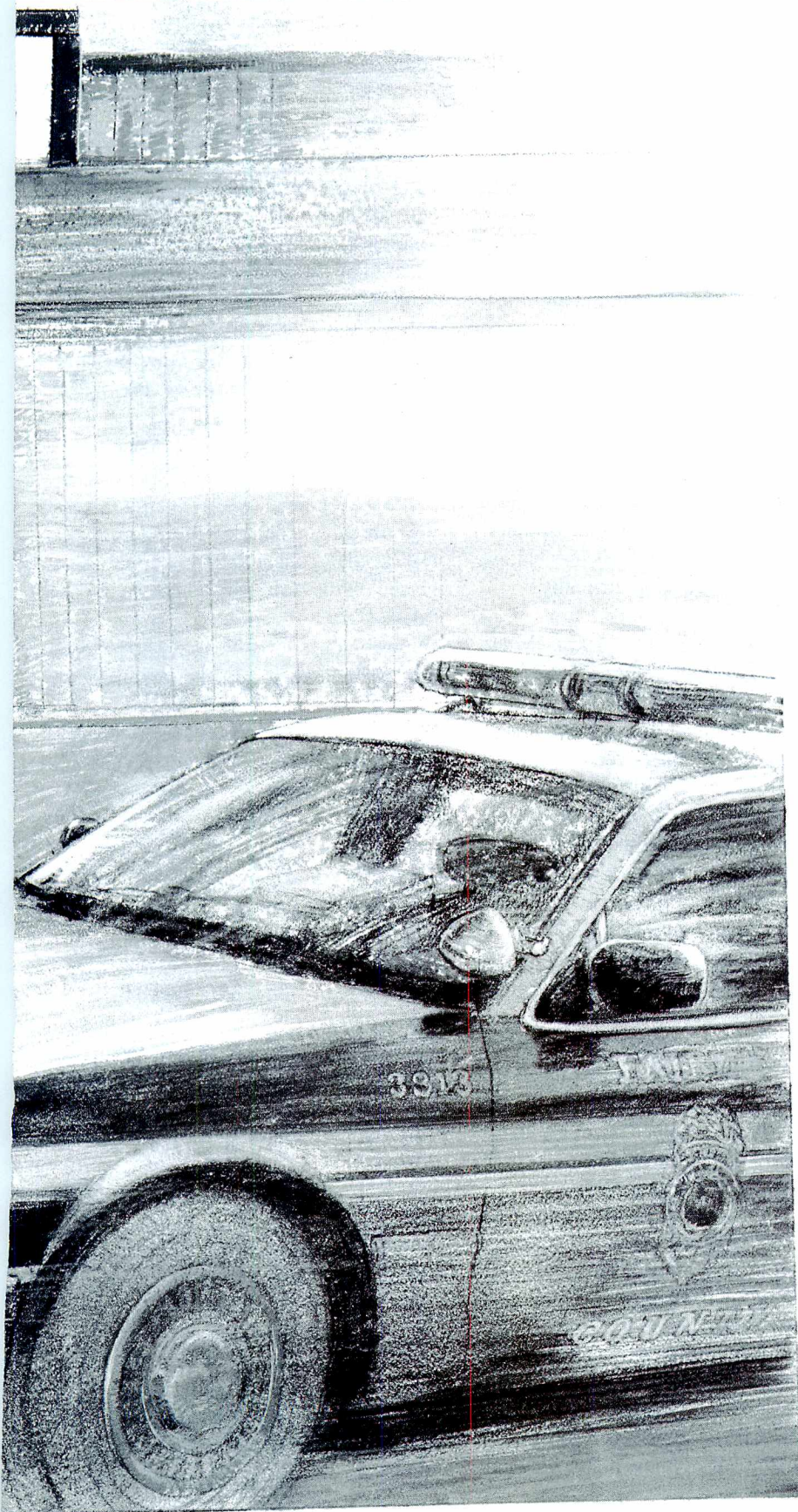
# Sulfites

## Safe For Most, Dangerous For Some

by Ruth Papazian

**I**t wasn't a special occasion—or even a fancy restaurant—but Karen, 37, will never forget that meal:

*My boyfriend and I were at a hamburger joint, and I had a burger and fries. About 10 minutes after we finished eating, my throat began to itch. I grabbed my [asthma] inhaler but I could feel my throat constricting. I couldn't breathe and started to panic. When I passed out, my boyfriend flagged down a passing police car. The officer radioed for an ambulance, and I was rushed to the hospital. I was*





# **FDA** requires that the presence of sulfites be disclosed on labels of packaged foods.

*revived with a massive dose of epinephrine to counteract the reaction caused by the sulfite solution the potatoes had been soaked in before frying.*

*I know enough to stay away from wine, shrimp and other foods that contain sulfites, and take note whenever I don't feel right after eating something. But I never expected french fries to be sulfited. I've had allergic reactions to sulfites before, but this time I came close to dying.*

*I was angry that this happened to me. I felt powerless—I was careful and knowledgeable, and yet I couldn't protect myself. Who ever heard of a lethal french fry? Afterward, I refused to eat out in restaurants for almost two years, and I still can't visit people or go on vacation without knowing there is a hospital nearby.*

The Food and Drug Administration estimates that one out of a hundred people is sulfite-sensitive, and that 5 percent of those who have asthma, like Karen (who asked that her last name not be used), are also at risk of suffering an adverse reaction to the substance. "By law, adverse reactions to drugs must be reported to FDA by doctors or pharmaceutical companies. But with sulfites and other food ingredients, reporting is voluntary so it's difficult to say just how many people may be at risk," cautions FDA consumer safety officer JoAnn Ziyad, Ph.D.

Complicating matters, scientists have not pinpointed the smallest concentration of sulfites needed to provoke a reaction in a sensitive or allergic person. FDA requires food manufacturers and processors to disclose the presence of sulfiting agents in concentrations of at least 10 parts per million, but the threshold may be even lower. The assay used to detect the level of sulfites in food is not sensitive enough to detect amounts less than 10 ppm in all foods (that's 1

part sulfite to 100,000 parts of food—the equivalent of a drop of water in a bathtub) so that's what the regulation has to be based on, explains Ziyad.

"The most rapid reactions occur when sulfites are sprayed onto foods or are present in a beverage, but the most severe reactions occur when sulfites are constituents of the food itself," says Ron Simon, M.D., head of Allergy, Asthma and Immunology at Scripps Clinic and Research Foundation in La Jolla, Calif.

A person can develop sulfite sensitivity at any point in life, and no one knows what triggers onset or the mechanism by which reactions occur. "Doctors believe that asthmatics develop difficulty breathing by inhaling sulfite fumes from treated foods," notes Dan Atkins, M.D., a pediatrician at the National Jewish Center for Immunology and Respiratory Medicine in Denver, Colo. He says that in a severe reaction an overwhelming degree of bronchial constriction occurs, causing breathing to stop. This can lead to lack of oxygen reaching the brain, heart, and other organs and tissues and, possibly, a fatal heart rhythm irregularity.

"We now know that asthmatics who have more severe symptoms and are dependent on corticosteroids, such as prednisone or methylprednisolone, are especially prone to sulfite sensitivity and are most at risk of having a severe reaction," notes Atkins. But it's a chicken-and-egg situation, notes Simon: "We don't know which comes first, the asthma or the sulfite sensitivity, because some people's first experience with asthma is a sulfite reaction, and as their asthma becomes more severe they eventually become steroid-dependent."

Sulfite sensitivity can be tricky to diagnose. Karen went to an internist and two pulmonary specialists without getting to the bottom of her problem.

"People who do experience adverse reactions to sulfites know that it's some-

thing they ate, but might not know what that something is," says Atkins. "I'll ask a patient complaining of an adverse reaction what he or she ate and drank when it occurred. If beer or wine doesn't seem to be the problem, I tend to dismiss sulfite sensitivity. But if I think sulfites may be the culprit, I'll do a challenge [a type of allergy test in which a small amount of the suspect substance is administered in a capsule or in a drink and the patient is monitored to see whether there is a reaction]."

If a person develops hives after ingesting sulfites, the doctor will do a prick test (a small concentration of sulfite is placed on the skin, which is then pricked; the test is positive if a welt develops on the spot). "People who have positive skin tests to sulfites are likely to be allergic to the additive, rather than have a sensitivity. These people, who are usually not asthmatic, are most at risk of anaphylactic shock, [a life-threatening reaction]," says Simon.

## **Regulatory Status in Flux**

Sulfur-based preservatives, or sulfites, have been used around the world for centuries to:

- inhibit oxidation ("browning") of light-colored fruits and vegetables, such as dried apples and dehydrated potatoes
- prevent melanosis ("black spot") on shrimp and lobster
- discourage bacterial growth as wine ferments
- "condition" dough
- bleach food starches
- maintain the stability and potency of some medications.

When the Federal Food, Drug, and Cosmetic Act was amended in 1958 to regulate preservatives and other food additives, FDA considered sulfites to be generally recognized as safe (GRAS). But when FDA reevaluated their safety and proposed to affirm the GRAS status



**“T**he agency continues to have concerns about the safety of sulfiting agents, and plans further action to protect the consumer.”

—JoAnn Ziyad, Ph.D., FDA consumer safety officer



of sulfiting agents in 1982, the agency received numerous reports from consumers and the medical community regarding adverse health reactions. In response, FDA contracted with the Federation of American Societies for Experimental Biology (FASEB) to examine the link between sulfites and reported health problems that ranged from chest tightness or difficulty breathing to hives to fatal anaphylactic shock.

In 1985, FASEB concluded that sulfites are safe for most people, but pose a hazard of unpredictable severity to asthmatics and others who are sensitive to these preservatives. Based on this report, FDA took the following regulatory actions in 1986:

- Prohibited the use of sulfites to maintain color and crispness on fruits and vegetables meant to be eaten raw (for instance, restaurant salad bars or fresh

*Packaged vegetable dips may contain sulfiting agents. If so, they will appear in the ingredient list. So if you're sulfite-sensitive, make sure you check the label.*



# A person can develop sulfite sensitivity at any point in life, and no one knows what triggers onset or the mechanism by which

## reactions occur.

produce in the supermarket).

- Required companies to list on product labels sulfiting agents that occur at concentrations of 10 ppm or higher, and any sulfiting agents that had a technical or functional effect in the food (for instance, as a preservative) regardless of the amount present. (This labeling requirement was extended to standardized foods, such as pickles and bottled lemon juice, in 1993.)

FDA requires that the presence of sulfites be disclosed on labels of packaged food (although manufacturers need not specify the particular agent). This information will be included in the ingredient portion of the label, along with the function of the sulfiting agent (for instance, a preservative).

When food is sold unpackaged in bulk form (as with a barrel of dried fruit or loose, raw shrimp at the fresh fish counter), store managers must post a sign or some other type of labeling that lists the food's ingredients on the container or at the counter so that consumers can determine whether the product was treated with a sulfiting agent.

In 1987, FDA proposed to revoke the GRAS status of sulfiting agents on "fresh" (not canned, dehydrated or frozen) potatoes intended to be cooked and served unpackaged and unlabeled to consumers (french fries, for example), and issued a final ruling to this effect in 1990. However, the rule was held null and void in 1990 after a protracted court battle in which the "fresh" potato industry prevailed on procedural grounds.

This legal setback notwithstanding, "the agency continues to have concerns about the safety of sulfiting agents, and plans further action to protect the consumer," notes Ziyad. Steps the agency is considering include establishing maximum residual levels for specific foods and additional labeling rules.

"The ultimate goal of sulfite regulation is to make sure that there is no higher level of sulfite residues in food

than is absolutely necessary and to encourage the use of substitutes for sulfites in food processing," says Ziyad.

### Sniffing Out Sulfites

Since 1985, FDA's Adverse Reaction Monitoring System has been tracking reactions to sulfites. Over a 10-year period, 1,097 such cases have been reported. However, thanks to regulatory action taken by FDA over the years, coupled with increased consumer savvy, the number of reported sulfite-related health incidents has been dropping steadily. In 1995, just six cases were reported.

Ten years ago, FDA banned the use of sulfites on fruits and vegetables that are to be eaten raw (as with a salad bar)—and the vast majority of those in the food service industry honor the prohibition—but consumers who are sulfite-sensitive "shouldn't take anything for granted," says Ziyad.

Current FDA regulations do not require managers of food service establishments to disclose whether sulfites were used in food preparation. "Consumers continually request FDA to extend the regulation to include food service establishments because either waiters and other staff members didn't know whether the food was treated with sulfites, or gave erroneous information," notes Ziyad. "FDA's position on the issue has been that consumers who see sulfites listed on the label of a packaged food should be able to deduce that the same food sold in a food service establishment would also contain sulfites," she explains.

In addition, sulfites are still found in a variety of cooked and processed foods (including baked goods, condiments, dried and glacéed fruit, jam, gravy, dehydrated or pre-cut or peeled "fresh" potatoes, molasses, shrimp, and soup mixes) and beverages (such as beer, wine, hard cider, fruit and vegetable juices, and tea).

Since sulfites are added to so many foods, someone who is sensitive to the additive must not assume that a food is safe to eat, says Atkins. He recommends these measures to avoid sulfites when buying unlabeled foods at the deli or supermarket and ordering at a restaurant:

- If the food is packaged, read the label. If it is being sold loose or by the portion, ask the store manager or waiter to check the ingredient list on the product's original bulk-size packaging.
- Avoid processed foods that contain sulfites, such as dried fruits, canned vegetables, maraschino cherries, and guacamole. If you want to eat a potato, order a baked potato rather than hash browns, fries, or any dish that involves peeling the potato first.
- If you have asthma, have your inhaler with you when you go out to eat. Similarly, if you've experienced a severe reaction to sulfites in the past (such as breaking out in hives), carry an antihistamine and make sure you have handy a self-administering injectable epinephrine, such as EpiPen, so that if you have a reaction you can stabilize your condition until you get to an emergency room.

"It takes some doing, but you can take steps to minimize your contact with sulfites if you are diagnosed with asthma or sulfite sensitivity," says Ziyad. "But you may not even know you have a problem with sulfites until a reaction occurs. Undiagnosed people are at risk because even if they know that sulfites can cause adverse reactions, they often don't associate sulfites with their own health problems," says Ziyad.

"Regulations can go a long way towards protecting people, but there's no substitute for knowledge."

For more information on sulfites, call (1-800) FDA-4010. ■

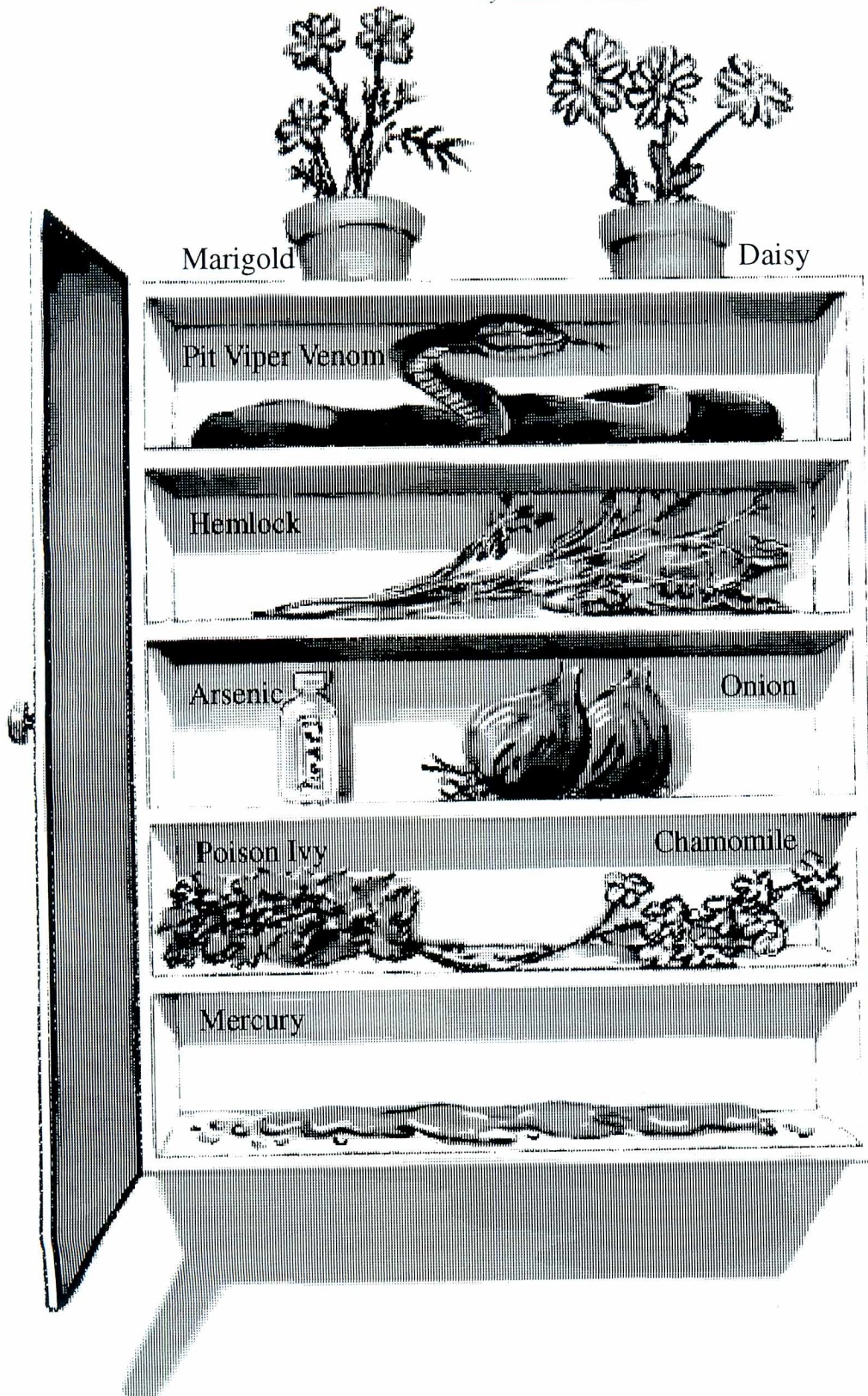
*Ruth Papazian is a writer in Bronx, N.Y., specializing in health and safety issues.*



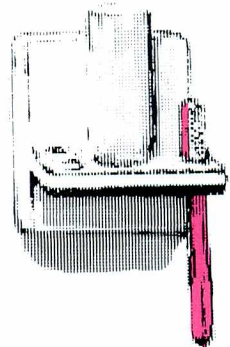
# Homeopathy

## Real Medicine or Empty Promises?

by Isadora Stehlin



Some of the medicines of homeopathy evoke positive images—chamomile, marigold, daisy, onion. But even some of Mother Nature's cruellest creations—poison ivy, mercury, arsenic, pit viper venom, hemlock—are part of homeopathic care.





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# FDA regulates homeopathic drugs in several significantly different ways from other drugs.

Homeopathy is a medical theory and practice that developed in reaction to the bloodletting, blistering, purging, and other harsh procedures of conventional medicine as it was practiced more than 200 years ago. Remedies made from many sources—including plants, minerals or animals—are prescribed based on both a person's symptoms and personality. Patients receiving homeopathic care frequently feel worse before they get better because homeopathic medicines often stimulate, rather than suppress, symptoms. This seeming reversal of logic is a relevant part of homeopathy because symptoms are viewed as the body's effort to restore health.

The Food and Drug Administration regulates homeopathic remedies under provisions of the Food, Drug, and Cosmetic Act.

## **Kinder, Gentler Medicine**

In the late 1700s, the most popular therapy for most ailments was bloodletting. Some doctors had so much faith in bleeding that they were willing to remove up to four-fifths of the patient's blood. Other therapies of choice included blistering—placing caustic or hot substances on the skin to draw out infections—and administering dangerous chemicals to induce vomiting or purge the bowels. Massive doses of a mercury-containing drug called calomel cleansed the bowels, but at the same time caused teeth to loosen, hair to fall out, and other symptoms of acute mercury poisoning.

Samuel Hahnemann, a German physician disenchanted with these methods, began to develop a theory based on three principles: the law of similars, the minimum dose, and the single remedy.

The word homeopathy is derived from the Greek words for like (*homoios*) and suffering (*pathos*). With the law of similars, Hahnemann theorized that if a large amount of a substance causes

certain symptoms in a healthy person, smaller amounts of the same substance can treat those symptoms in someone who is ill. The basis of his theory took shape after a strong dose of the malaria treatment quinine caused his healthy body to develop symptoms similar to ones caused by the disease. He continued to test his theory on himself as well as family and friends with different herbs, minerals and other substances. He called these experiments “provings.”

But, as might be expected, the intensity of the symptoms caused by the original proving was harrowing. So Hahnemann began decreasing the doses to see how little of a substance could still produce signs of healing.

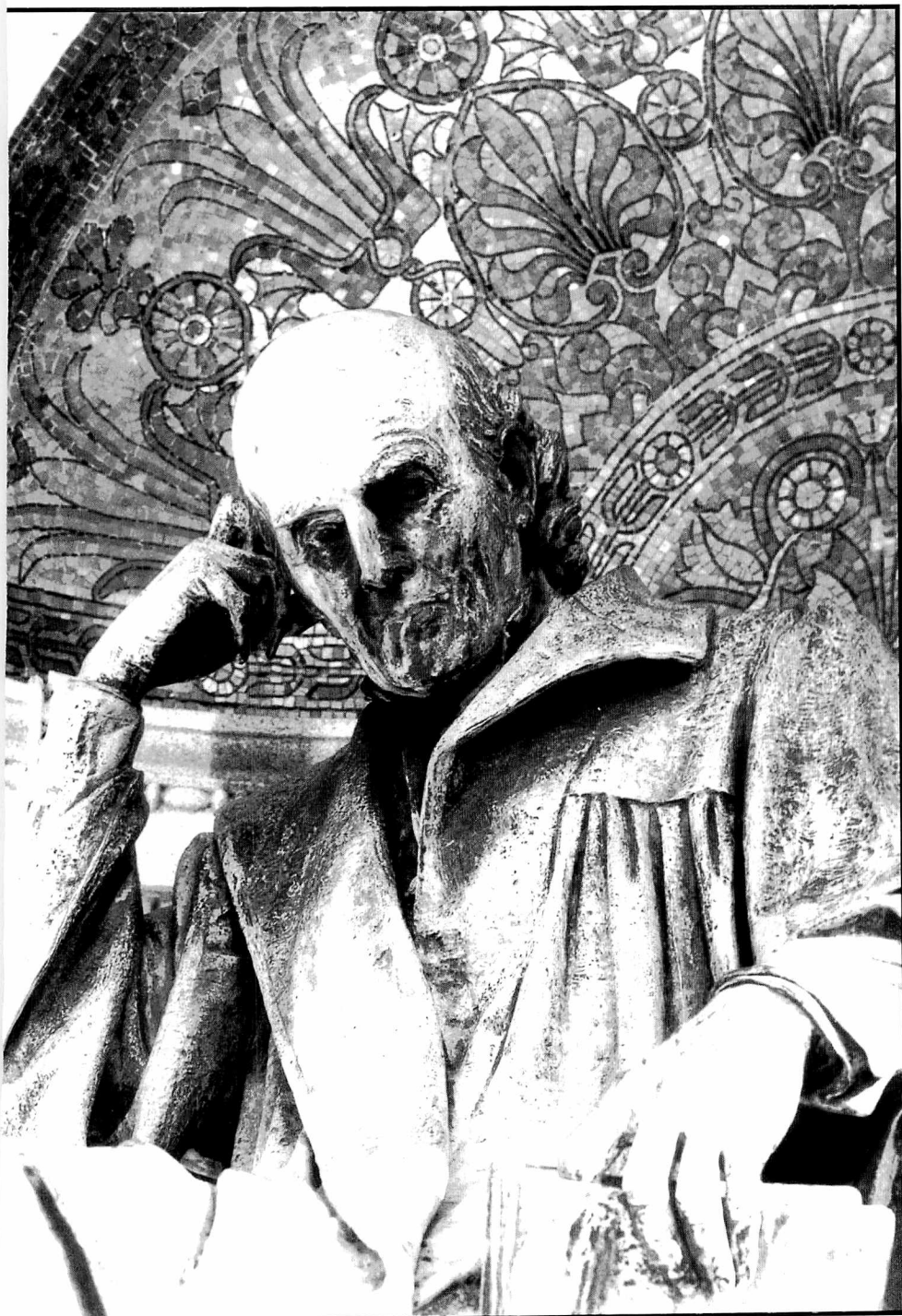
With the minimum dose, or law of infinitesimals, Hahnemann believed that a substance's strength and effectiveness *increased* the more it was diluted. Minuscule doses were prepared by repeatedly diluting the active ingredient by factors of 10. A “6X” preparation (the X is the Roman numeral for 10) is a 1-to-10 dilution repeated six times, leaving the active ingredient as one part per million. Essential to the process of increasing potency while decreasing the actual amount of the active ingredient is vigorous shaking after each dilution.

Some homeopathic remedies are so dilute, no molecules of the healing substance remain. Even with sophisticated technology now available, analytical chemists may find it difficult or impossible to identify any active ingredient. But the homeopathic belief is that the substance has left its imprint or a spirit-like essence that stimulates the body to heal itself.

Finally, a homeopathic physician generally prescribes only a single remedy to cover all symptoms—mental as well as physical—the patient is experiencing. However, the use of multi-ingredient remedies is recognized as part of homeopathic practice.



# Homeopathic drugs are not exempt from all FDA regulations.



*This statue of Samuel Hahnemann, the father of homeopathy, is in Washington, D.C.*

## **FDA Regulation**

In 1938, Sen. Royal Copeland of New York, the chief sponsor of the Food, Drug, and Cosmetic Act and a homeopathic physician, wrote into the law a recognition of any product listed in the *Homeopathic Pharmacopeia* of the United States. The *Homeopathic Pharmacopeia* includes a compilation of standards for source, composition and preparation of homeopathic drugs.

FDA regulates homeopathic drugs in several significantly different ways from other drugs. Manufacturers of homeopathic drugs are deferred from submitting new drug applications to FDA. Their products are exempt from good manufacturing practice requirements related to expiration dating and from finished product testing for identity and strength. Homeopathic drugs in solid oral dosage form must have an imprint that identifies the manufacturer and indicates that the drug is homeopathic. The imprint on conventional products, unless specifically exempt, must identify the active ingredient and dosage strength as well as the manufacturer.

"The reasoning behind [the difference] is that homeopathic products contain little or no active ingredients," explains Edward Miracco, a consumer safety officer with FDA's Center for Drug Evaluation and Research. "From a toxicity, poison-control standpoint, [the active ingredient and strength] was deemed to be unnecessary."

Another difference involves alcohol. Conventional drugs for adults can contain no more than 10 percent alcohol, and the amount is even less for children's medications. But some homeopathic products contain much higher amounts because the agency has temporarily exempted these products from the alcohol limit rules.

"Alcohol is an integral part of many homeopathic products," says Miracco. For this reason, the agency has decided



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# FDA is focusing on preventing problems by educating the homeopathic industry about agency regulations.

to delay its decision concerning alcohol in homeopathic products while it reviews the necessity of high levels of alcohol.

“Overall, the disparate treatment has been primarily based on the uniqueness of homeopathic products, the lack of any real concern over their safety because they have little or no pharmacologically active ingredients, and because of agency resources and priorities,” explains Miracco.

However, homeopathic products are not exempt from all FDA regulations. If a homeopathic drug claims to treat a serious disease such as cancer it can be sold by prescription only. Only products sold for so-called self-limiting conditions—colds, headaches, and other minor health problems that eventually go away on their own—can be sold without a prescription (over-the-counter).

Requirements for nonprescription labeling include:

- an ingredients list
- instructions for safe use
- at least one major indication
- dilution (for example 2X for one part per hundred, 3X for one part per thousand).

Over the past several years, the agency has issued about 12 warning letters to homeopathic marketers. The most common infraction was the sale of prescription homeopathic drugs over-the-counter. “It’s illegal, it’s in violation, and we’re going to focus on it,” says Miracco.

Other problems include:

- products promoted as homeopathic that contain nonhomeopathic active ingredients, such as vitamins or plants not listed in homeopathic references
- lack of tamper-resistant packaging
- lack of proper labeling
- vague indications for use that could encompass serious disease conditions. For example, a phrase like “treats gastrointestinal disorders” is too general,

explains Miracco. “This phrase can encompass a wide variety of conditions, from stomachache or simple diarrhea to colon cancer,” he says. “Claims need to be specific so the consumer knows what the product is intended to treat and the indication does not encompass serious disease conditions that would require prescription dispensing and labeling.”

In addition to enforcement, the agency is also focusing on preventing problems by educating the homeopathic industry about FDA regulations. “Agency representatives continue to meet with homeopathic trade groups to tell them about problems we’ve had, difficulties we’ve seen, and trends we’ve noticed,” says Miracco.

FDA is aware of a few reports of illness associated with the use of homeopathic products. However, agency review of those reported to FDA discounted the homeopathic product involved as the cause of the adverse reaction. In one instance, arsenic, which is a recognized homeopathic ingredient, was implicated. But, as would be expected, FDA analysis revealed the concentration of arsenic was so minute there wasn’t enough to cause concern, explains Miracco. “It’s been diluted out.”

## Homeopathic Treatment

Homeopathy consists of highly individualized treatments based on a person’s genetic history, personal health history, body type, and present status of all physical, emotional and mental symptoms.

Jennifer Jacobs, M.D., who has a family practice and is licensed to practice homeopathy in Washington state, spends at least an hour and a half with each new patient. “What I do is review the lifetime history of the patient’s health,” she explains. “Also I ask a lot of questions about certain general symptoms such as food preferences and sleep patterns that usually aren’t seen as important in



# Some homeopathic remedies are so dilute, no molecules of the healing substance remain.

conventional medicine. In looking to make the match between the person and the remedy, I need to have all of this sort of information.”

Why does someone trained in conventional medicine turn to homeopathy? “With chronic illnesses such as arthritis and allergies, conventional medicine has solutions that help control the symptoms but you don’t really see the patients getting better,” says Jacobs. “What I have seen in my homeopathic work is that it really does seem to help people get better. I’m not saying I can cure everyone but I do see where people’s overall health is improved over the course of treatment.”

Jacobs’ hasn’t abandoned conventional medicine completely. “My daughter is 17 and she’s never taken antibiotics, but I would have no hesitation to use antibiotics if she had pneumonia, or meningitis, or a kidney infection,” says Jacobs.

About a third of Jacobs’ practice is children, and ear infections are one of the most common problems she treats. “Ear infections are something that seems to respond well to homeopathy,” she says. “Of course, if a child is not better within two or three days, or if the child develops a high fever, or if I feel that there’s a serious complication setting in, then of course I will use antibiotics. But I find that in the majority of cases, ear infections do resolve without antibiotics.”

In addition to treating patients, Jacobs has conducted a clinical trial the results of which suggest that homeopathic treatment might be useful in the treatment of acute childhood diarrhea. The results were published in the May 1994 issue of *Pediatrics*. In the article, Jacobs concluded that further studies should be conducted to determine whether her findings were accurate. A subsequent article appearing the November 1995 issue of *Pediatrics* indicated that Jacobs’

study was flawed in several ways.

Although *Pediatrics* is published by the American Academy of Pediatrics, Jacobs’ study and several others published in such journals as *The Lancet* and the *British Medical Journal* are considered “scanty at best” by the academy. “Given the plethora of studies that are published [on other topics] in scientific journals, I wouldn’t say there are a lot of articles coming out,” says Joe M. Sanders Jr., M.D., the executive director of the academy. “Just because an article appears in a scientific journal does not mean that it’s absolute fact and should be immediately incorporated into therapeutic regimens. It just means that the study is [published] for critique and review and hopefully people will use that as a stepping stone for further research.”

More studies are under way. For example, the Office of Alternative Medicine at the National Institutes of Health has awarded a grant for a clinical trial of the effects of homeopathic treatment on mild traumatic brain injury.

Even with the dearth of clinical research, homeopathy’s popularity in the United States is growing. The 1995 retail sales of homeopathic medicines in the United States were estimated at \$201 million and growing at a rate of 20 percent a year, according to the American Homeopathic Pharmaceutical Association. The number of homeopathic practitioners in the United States has increased from fewer than 200 in the 1970s to approximately 3,000 in 1996.

When looking for a homeopathic practitioner, it’s important to find someone who is licensed, according to the National Center for Homeopathy. Each state has its own licensing requirements. “Whether that person is a medical doctor or a physician’s assistant or a naturopathic physician, I feel that anyone who’s treating people who are sick needs to have medical training,” says Jacobs.

## Real Medicine or Wishful Thinking?

Many who don’t believe in homeopathy’s effectiveness say any successful treatments are due to the placebo effect, or, in other words, positive thinking.

But homeopathy’s supporters counter that their medicine works in groups like infants and even animals that can’t be influenced by a pep talk. Jacobs adds that sometimes she mistakenly gives a patient the wrong remedy and he or she doesn’t get better. “Then I give the right remedy, and the person does get better,” she says. “So it’s not like everybody gets better because it’s all in their head. I think it’s only because we don’t understand the mechanism of action of homeopathy that so many people have trouble accepting it.”

The American Medical Association does not accept homeopathy, but it doesn’t reject it either. “The AMA encourages doctors to become aware of alternative therapies and use them when and where appropriate,” says AMA spokesman Jim Fox.

Similarly, the American Academy of Pediatrics has no specific policy on homeopathy. If an adult asked the academy’s Sanders about homeopathy, he would tell that person to “do your own investigation. I don’t personally prescribe homeopathic remedies, but I would be open-minded.”

That open-mindedness applies only to adults, however. “I would have problems with somebody imposing other than conventional medicine onto a child who’s incapable of making that decision,” he says.

Even professionals who practice homeopathy warn that nothing in medicine—either conventional or alternative—is absolute. “I’m not saying we can cure everyone [with homeopathy],” says Jacobs. ■

*Isadora Stehlin is a member of FDA’s public affairs staff.*



# Non-Hodgkin's Lymphoma

Becomes More Common, More Treatable

by Margie Patlak

**Non-Hodgkin's lymphoma is now the sixth most common cancer in the United States.**



*The late Jacqueline Kennedy Onassis*

PUBLISHERS DEPOT / © , 1978



*Senator Paul Tsongas*

PUBLISHERS DEPOT / © RICK FRIEDMAN, 1991



## Because NHL can develop wherever in the body lymphocytes can be found, the cancer can crop up nearly anywhere.

**M**ary Relles of Philadelphia never heard of non-Hodgkins lymphoma until her father was diagnosed with it in 1990. Since then, three of her friends—and Relles herself, 49—have developed this relatively unknown yet deadly cancer of the immune system.

Non-Hodgkins lymphoma (NHL) has become more common in the last few decades and is now the sixth most common cancer in the United States, according to the National Cancer Institute (NCI). Striking such luminaries as Jacqueline Kennedy Onassis, Senator Paul Tsongas, and the Shah Mohammed Reza Pahlevi of Iran, NHL has increased 75 percent over the last 20 years, making it the most rapidly rising cancer after lung cancer and melanoma, according to NCI. Although recent studies have provided some intriguing clues, the cause of what some experts call the “NHL epidemic” is not known. (See accompanying article.) Fortunately, advances in treatment seem to be keeping pace; the five-year survival rate for NHL rose from 31 percent to 51 percent over the past 30 years, according to NCI.

### Cancers of the Immune System

NHL is a collection of more than a dozen different cancers of the lymphatic system, which generates the body's immune defenses. This system includes a network of channels akin to blood vessels through which lymphocytes—important white blood cells of the immune system—patrol the body for invading microbes. Along these lymphatic routes in the neck, armpits, abdomen, and groin are clusters of bean-shaped lymph nodes that house platoons of the infection-fighting lymphocytes. These cells also cluster in areas that serve as gateways to the body, including the mucous membranes lining the respiratory and digestive tracts, and the skin. Lymphocytes travel in the bloodstream, as well. The lymphatic system also includes such organs as the spleen, thymus and tonsils.

Because NHL can develop wherever in the body lymphocytes can be found, the cancer can crop up nearly anywhere. Symptoms can vary widely, depending on the cancer site. The most common symptom is a noticeable, usually painless swelling of a lymph node. NHL in the digestive tract can cause nausea, vomiting, or abdominal pain; in the chest, shortness of breath or cough may develop. If the brain is involved, patients may have headaches, vision changes, or seizures. If the bone marrow is affected, lymphoma cells may crowd out red blood cell precursors, causing anemia. Reddened patches on the skin can occur when lymphoma cells there prompt localized inflammation.

Because NHL can foster a hyperactive immune response, it often causes symptoms that develop when the body is fighting an infection, such as fevers, night sweats, tiredness, and weight loss. Another NHL symptom is widespread itching, apparently triggered by immune cells' release of histamines, the same compounds that cause itchiness in allergic reactions.

NHLs can affect people of all ages, although the incidence of NHL increases with age. About half of all cases are in people aged 60 and older.

The treatments for NHL include drugs and radiation therapy regulated by the Food and Drug Administration.

### Diverse Group of Cancers

To diagnose NHL, doctors remove a small sample of the tissue thought to be cancerous. This procedure, known as a biopsy, is usually done with a local anesthetic. A pathologist examines the tissue under a microscope to look for cancer cells. The appearance of these cells and the proteins on their surfaces helps the pathologist determine the type of NHL the cancer is. The various types have distinctive appearances, carry different prognoses (predicted outcomes), and have different treatments. Whereas one



## Doctors tailor treatment of NHL to the type of tumor, the stage of the disease, and the patient's age and general health.

type may be extremely deadly, another may be highly curable.

NHLs are classed as low-, intermediate- and high-grade. This classification scheme accurately predicts the survival of untreated patients, but is not as reliable in predicting outcome after treatment. Low-grade lymphomas are slow-growing tumors, and some patients can survive for more than a decade without treatment. Although chemotherapy often can shrink low-grade lymphomas, the cancer usually recurs within five years. Recurrent tumors can also be treated with chemotherapy or radiation, but over time, low-grade NHLs tend to become more aggressive and less responsive to therapy. Consequently, these types of lymphomas are not cured with currently available treatment.

In contrast, intermediate-grade and high-grade lymphomas are fast-growing tumors that, without treatment, generally are fatal within a year or two of diagnosis. Chemotherapy may cure many types of these lymphomas.

Doctors determine the stage of the cancer according to the number and location of tumors. This information, which also affects prognosis, is obtained from a physical exam, blood tests, and x-rays, CAT-scans, or ultrasound scans of various organs and tissues. Biopsies of the bone marrow and lymph nodes often are necessary. Regardless of NHL type, patients have a better prognosis with appropriate therapy if they have:

- the cancer in only one lymph node area or in only one area or organ outside the lymph nodes
- no tumors more than 10 centimeters in diameter
- no systemic symptoms, such as fevers or night sweats.

Younger patients also usually fare better than older ones.

A number of studies have pinpointed the genetic flaws that characterize different types or subtypes of NHL. Experts predict that this information will soon foster a new classification scheme that more accurately predicts outcome.

## Tracking the Cause of a Cancer Increase

Medical researchers have been trying to find a reason or reasons for the rising incidence of non-Hodgkin's lymphoma, which has been increasing in this country since the 1950s. Suspects include: pesticides, hair dyes, AIDS, immune-suppressing therapies, and improved diagnosis.

Studies on a possible relationship between pesticides and NHL were prompted by two observations. First, the central part of the United States, which is predominantly an agricultural area, has been a hot spot for NHL since 1950. Second, NHL incidence also has been increasing more rapidly in rural areas than urban areas. These findings suggest certain pesticide exposures might cause NHL in some people. The National Cancer Institute's Sheila Zahm, Sc.D., and others found a two- to eightfold increase in NHL incidence among farmers who frequently used phenoxy herbicides such as 2,4-D, which are widely used on crops such as wheat, corn, oats, rye, barley, and sugarcane. These herbicides are also commonly used to rid lawns of weeds. More research needs to be done, however, to assess the possible link between NHL and pesticides.

Researchers are also examining the potential for hair dyes to cause NHL. The largest study on this, conducted by the American Cancer Society and reported in 1994, found women who used black hair dye for 20 years or more were more than four times as likely to develop NHL than women who didn't use hair dye. This finding confirms those of other studies.

But because only a small fraction of women who dye their hair use black hair dye, this alone cannot contribute significantly to the increase in NHL in recent years.

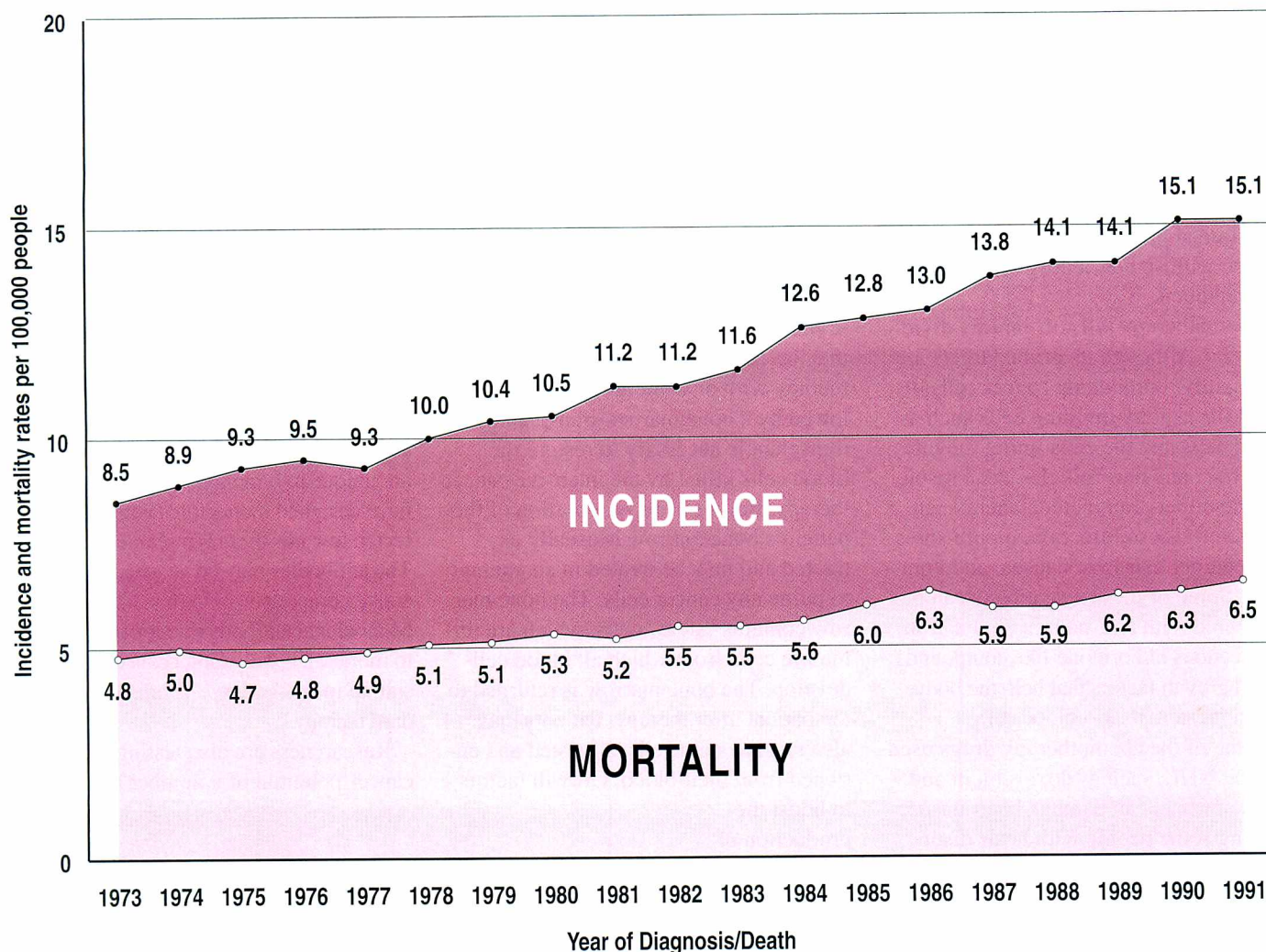
According to Carol Palackdharry, M.D., of the Medical College of Ohio, changes in diagnostic criteria can account for only about 10 to 15 percent of the current cases of NHL. A similar percentage of cases can be attributed to AIDS, researchers M.H. Gail and colleagues estimated in a 1991 issue of the *Journal of the National Cancer Institute*. The immune suppression AIDS induces makes people more susceptible to NHL. The increased use of immune-suppressing therapies to prevent rejection of organ transplants, and to treat rheumatoid arthritis, cancer, and other disorders might also account for a small percentage of NHL cases, according to Palackdharry.

Further research is needed to fully explain the rising incidence of NHL. As Dan Longo, M.D., formerly at NCI and now at the National Institute on Aging, sums up in the August 1994 issue of the journal *Oncology*, "... it appears that lymphoma incidence is a building tidal wave. What remains unclear is whether we can rapidly learn enough about the various causes to implement successful prevention strategies that will enable us to diminish the damage done by the coming wave." ■

—M.P.



## Non-Hodgkin's Lymphoma Incidence and Mortality Rates



(Source: National Institutes of Health, National Cancer Institute)

■ Incidence Rate  
□ Mortality Rate

### Treatment Varies

Doctors tailor treatment of NHL to the type of tumor, the stage of the disease, and the patient's age and general health. Most patients receive chemotherapy, radiation therapy, or both.

Because low-grade lymphomas usually grow slowly and cause few symptoms but eventually become resistant to treatment, doctors may postpone treatment until the cancer shows signs of spreading, or causes systemic symptoms (such as fevers or weight loss), or until the tumors become excessively bulky or threaten vital organs such as the kidneys or lungs. NCI researchers and others

have shown that delaying treatment does not adversely affect long-term survival and may actually improve patients' quality of life, as the treatments themselves can be debilitating. A substantial proportion of patients with low-grade NHL have spontaneous remissions, although these disease-free periods rarely last for long.

Chemotherapy for NHL usually involves several different drugs given at the same time. Some drugs, such as chlorambucil (marketed as Leukeran), are given by mouth; others, such as cyclophosphamide (marketed as Cytosan), are injected into a vein or muscle. To

treat disease that has spread to the brain, chemotherapy may be delivered to the fluid that surrounds the brain through a needle in the spine. Chemotherapy is usually given in cycles: a treatment period followed by a rest period, then another treatment period, and so on.

A frequently used chemotherapy regimen for NHL combines cyclophosphamide, doxorubicin hydrochloride (marketed as Adriamycin), vincristine (marketed as Oncovin), and the anti-inflammatory drug prednisone. Although used for about 20 years, recent studies suggest this regimen is as effective and has less serious side effects than some of



the newer drug combinations, according to Alan Aisenberg, M.D., of Massachusetts General Hospital.

An experimental NHL chemotherapy compound is a drug called fludarabine. FDA approved this drug as Fludara in 1991 for treating a type of leukemia, and, according to NCI's Bruce Cheson, M.D., early studies suggest that more low-grade NHL patients go into complete remission when they are treated with fludarabine than when they are treated with standard drugs such as chlorambucil.

Chemotherapy kills off rapidly dividing cells. Although its prime targets are the rapidly reproducing cancer cells, it also kills healthy dividing cells such as blood cells and the cells lining the intestinal tract and hair follicles. As a result, its side effects can include anemia, an increased risk of infection, mouth sores or bleeding, hair loss, nausea, and vomiting. Some of these side effects can be countered with anti-nausea medication or injections of hormone-like compounds called growth factors that help the body quickly restore its lost blood cells.

Some of the chemotherapy drugs used to treat NHL, such as doxorubicin and mitoxantrone, can damage heart tissue, making some people with heart disorders unable to tolerate this treatment. These patients may be given alternative kinds of chemotherapy and radiation therapy. Radiation therapy alone may be the treatment of choice for some patients, especially those who have only a single, small tumor. Some types of NHL respond best to chemotherapy followed by radiation therapy.

Radiation therapy uses high-energy x-rays to damage cancer cells and stop their growth. Radiation therapy is directed to the areas of the body known to harbor cancer cells. As an extra precaution, radiation may be directed to a broader area, such as to all the lymph nodes in the region of a known cancerous site. The treatment is generally given on an outpatient basis.

Radiation therapy can cause fatigue and red or dry skin in the treated area. Radiation directed to the chest and neck can cause patients to have a dry, sore throat and some trouble swallowing. Patients may also have shortness of breath or a dry cough. Radiation therapy

to the abdomen may cause nausea, vomiting or diarrhea. Some patients who receive radiation to the spine may also have tingling or numbness in their arms, legs and lower back.

The chemotherapy used to treat NHL can cause sterility as can radiation directed to the pelvis. NHL treatments may also make patients more susceptible to other cancers, including those of the lung, brain, kidney, bladder, skin, and blood.

### **Bone Marrow Transplants**

NHL patients with a poor prognosis may be candidates for high-dose chemotherapy with or without radiation followed by a bone marrow transplant. The transplant is necessary to restore the blood cells killed by the intensive cancer therapy. Before therapy, a portion of the patient's bone marrow is usually extracted and may be treated in an attempt to purge any cancer cells. The bone marrow contains "stem" cells, which are immature cells from which all blood cells develop. The bone marrow is returned to the patient after therapy. Patients may also receive stem cells harvested and enriched from their blood. Growth factors to boost the production of blood cells are also used in conjunction with bone marrow transplants.

Intensive radiation or chemotherapy followed by a bone marrow transplant has a number of potential serious side effects, including life-threatening infections, bleeding, damage to the liver, kidneys, lungs or heart, and subsequent leukemia. Although FDA has approved the chemotherapy drugs and growth factors most commonly used in conjunction with bone marrow transplants for cancer therapy, it does not regulate the procedure itself, just as it does not regulate other surgery and medical procedures considered "practice of medicine."

Studies provide strong evidence that bone marrow transplants improve the

long-term survival of patients with intermediate- or high-grade lymphomas that have relapsed but are still sensitive to chemotherapy. There is little, if any, evidence of patients with low-grade lymphomas benefiting from the procedure, according to NCI's Cheson. Also, bone marrow transplants are usually not effective in NHL patients whose tumors do not respond to chemotherapy. NCI is supporting more research to assess the value of bone marrow treatment for different types of NHL.

Research is also under way to evaluate the safety and effectiveness of monoclonal antibody therapies in NHL patients. Monoclonal antibodies are synthetic antibodies that latch onto specific substances called antigens. Some antigens are unique to lymphoma cells. Researchers have designed monoclonal antibodies directed towards these lymphoma antigens. The antibodies may be attached to radioactive compounds or toxins that kill cells. Monoclonal antibody therapy is designed to more selectively target cancer cells, resulting in less severe side effects than standard therapy.

Researchers are also testing the anticancer potential of a number of com-

## **Patient Information**

*Patients who wish to participate in research evaluating experimental NHL treatments should contact the National Cancer Institute at (1-800) 4-CANCER. ■*

pounds produced by immune cells. These compounds, which include interleukin 2 and alpha-interferon, are usually given in addition to standard chemotherapy or radiation therapies.

"We're at an exciting time in lymphoma research," said Cheson. "There are a lot of promising new drugs on the horizon." And people are eyeing that horizon more intently as NHL becomes more common. ■

*Margie Patlak is a writer in Elkins Park, Pa.*



# Inside FDA

## HAZARDOUS DUTY IN THE BERING SEA

by John Henkel

*This is one in a series of articles on FDA activities and concerns.*

Snow was blowing horizontally that January day as the wind whipped into a 50-mile-an-hour frenzy. Out in the Bering Sea, some 60 miles off Alaska, two FDA investigators wrapped up their inspection of a floating seafood processor.

Temperatures had dipped below freezing, and the sea was crashing with 15-foot waves. The investigators climbed down a rope ladder onto a 16-foot boat that was to carry them to a Coast Guard cutter about a quarter mile away.

After the small boat got under way, the pilot radioed the cutter that he wasn't sure the craft could make it through the severe weather. But he forged on, finally reaching the cutter and delivering the two to safety.

"We barely made it back," says Janelle Main, investigator in FDA's Puget Sound [Washington] resident post, who shared the adventure with investigator Elizabeth Sheller. "It was really, really rough out there."

Another typical day in the life of an FDA investigator? Well, not exactly. But it does illustrate the dangerous situations these folks can find themselves in while on duty. Main is one of seven investigators from FDA's Seattle district who have volunteered to inspect floating processors. These vessels, 65 to 300 feet long, actually are "factories" that catch, process, and prepare for market various types of fish while at sea. More than 85 of the processors, registered in the United States, operate off the coasts of Alaska, Washington and Oregon.

**Inspecting processors in Alaskan waters poses major hazards largely due to the risk of hypothermia—a dangerous lowering of body temperature—from the icy seas.**



*Crew members chop away at ice that has accumulated on the deck of a Coast Guard cutter, a chilling reminder of the hazards of working in the Bering Sea.*



**"I'm confident that the program is worthwhile and that conditions are better on the processors because we have a presence out there."**

**—Janelle Main, FDA investigator**

Inspecting processors in Alaskan waters poses major hazards, says Main, largely due to the risk of hypothermia—a dangerous lowering of body temperature—from the icy seas. "If you fall into the Bering Sea, you've got about two minutes to be pulled out or there's a good chance you could die," she says. When the seas are choppy, riders could be thrown overboard from the small boats. Or the boats could capsize.

Getting into the boats is a trick in itself. Boarding a floating processor usually involves descending a rope ladder from a Coast Guard cutter and taking a small boat to the processing vessel. Riders then must step—or sometimes leap—from the boat to another rope ladder.

Going up this ladder, which may be as long as 30 feet, is not easy, especially in rough seas. "I've fallen off the rope before," says Main, "but fortunately I fell into the boat and not the water." She injured her knee in that incident and had to undergo physical therapy.

Why put your life on the line for this work? Because, Main says, it is important to ensure that floating processors, like seafood factories found on land, provide products that are safe for consumers. This means the processors must adhere to strict procedures for sanitation, storage and refrigeration.

In the past, FDA relied on Alaska state officials to inspect floating processors while they were docked. But because

these ships don't process fish when in port, the state inspections didn't look at operations while they were going on.

In 1994, former Seattle investigator Debra DeVlieger set up a joint inspection program with the Coast Guard that allows FDA investigators to ride along on cutters as the Coast Guard conducts its own inspections of vessel safety and seaworthiness.

In August 1994, FDA boarded the first processing vessels under the program during hake season off Washington and Oregon. Since then, Chris Rezendes, FDA supervisory investigator, has expanded the program into Alaska. Investigators have gone into the Bering Sea during pollack A (January and February) and pollack B (August and September) seasons.

An investigator can inspect as many as 11 processors during a trip, which usually lasts two weeks. "Some trips have been less fruitful," says Main. "Because of weather, only two or three boardings could be made." Also, the cutters are sometimes diverted to search-and-rescue missions.

Main calls the joint inspection program "a good use of taxpayers' money." The Coast Guard does not charge FDA for lodging on board the cutters and charges only about \$5 a day for meals. By comparison, an air flight to Alaska can cost as much as \$800. "We've saved many thousands of dollars," says Main.

She adds that the program has paid dividends in other ways. Though the inspections have resulted in some warning letters, FDA investigators have set up "a really good relationship" with processors. In the off-season, FDA holds meetings to discuss concerns with quality control officials and others representing processors. By sharing information about what FDA is looking for in inspections, the agency receives a high degree of compliance and cooperation.

"I'm confident that the program is worthwhile and that conditions are better on the processors because we have a presence out there," Main says.

Besides Main and Sheller, the other FDA volunteer investigators are Jody Robinson, Gretchen Weber, Jim Vik, Gordon Wales, and Bob Williams. ■

*John Henkel is a member of FDA's public affairs staff.*



*An FDA investigator carefully steps down a rope ladder dangling from the side of a Coast Guard cutter. On the sea below, a small boat awaits to take the investigator to a floating seafood processor.*





*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.*

■ **The infant formula regulations** comment period has been extended to Dec. 6 by FDA. Revisions the agency is proposing include:

- setting standards for current good manufacturing practice
- amending requirements on quality control procedures, notification, records, and reports
- requiring infant formulas to contain, and be tested for, certain nutrients.

Written comments should be submitted to the Dockets Management Branch (HFA-305), FDA, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857. (FR Sept. 23)

■ **Folic-acid-fortified grain products** marketed before Jan. 1, 1998—when fortification becomes mandatory—do not have to be labeled as containing folic acid unless a health claim for the nutri-

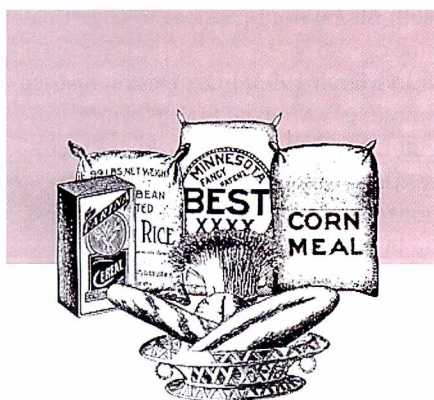
ent is made, according to an FDA final rule. FDA originally had required fortification before Jan. 1, 1998, to be indicated on labeling. But the agency reconsidered after receiving a letter from the March of Dimes pointing out that though manufacturers want to fortify earlier than the deadline, many are holding off because they could not use existing label stocks. FDA mandated folic acid fortification because of evidence that the nutrient can reduce the risk of neural tube birth defects such as spina bifida. (FR Sept. 5)

■ **Blood collection and distribution facilities** must quarantine whole blood and blood products taken from a donor who initially tests negative for HIV antibodies but later tests positive, according to a final FDA rule. Facilities also must prepare and follow written standard operating procedures that define steps to be taken when screening tests show later batches of a donor's blood to be reactive to HIV antibodies. Facilities then must perform a licensed, more specific HIV antibody test. (FR Sept. 9)

■ **Administering streptokinase** to stroke victims more than three hours after the stroke is not helpful and may cause more serious problems, according to Australian research. Streptokinase is a blood-clot-dissolving drug. The study of

340 patients sought to determine if giving the drug within four hours of the onset of acute ischemic stroke (insufficient blood supply to the brain) would reduce disability or death. The trial was stopped early because of unacceptably high complication rates. The researchers say larger trials are needed to test further the effectiveness of therapy given within three hours. They add that public education may be needed to increase the number of patients who seek treatment early after a stroke. (*Journal of the American Medical Association*, Sept. 24)

■ **High school students** who drink alcohol or use illegal drugs, including anabolic steroids, are more than twice as likely as teenagers who don't use drugs to carry a weapon or get into a fight. A survey of more than 12,000 high school students in the United States shows the increased risk of violence is similar among adolescents regardless of gender. (*Archives of Pediatrics and Adolescent Medicine*, 1996)

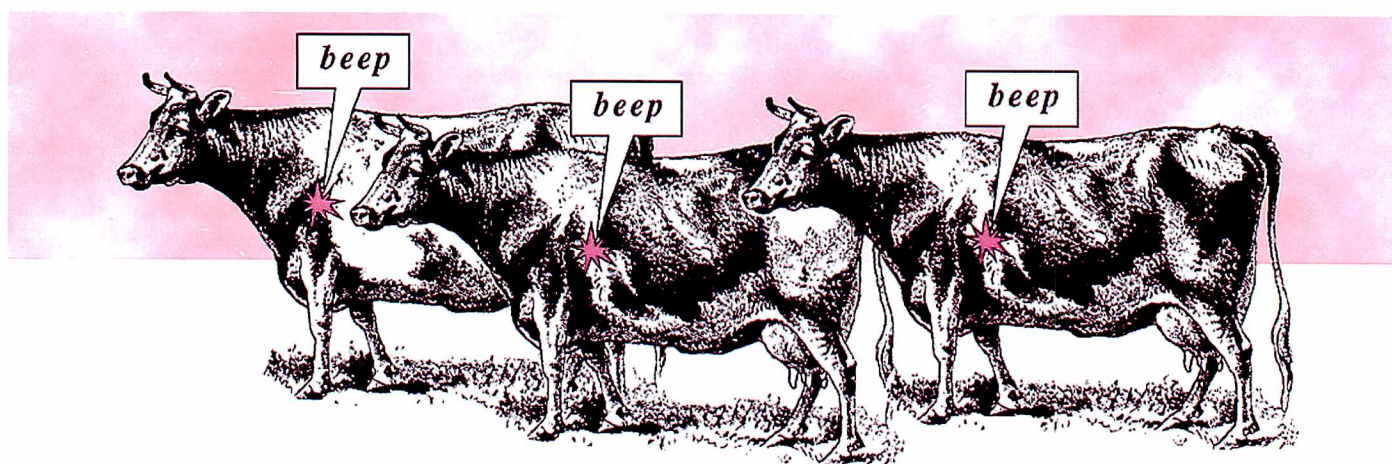






# Undercover Cows Help Get Guilty Pleas

by Tamar Nordenberg



For the first time in FDA history, beeper-carrying cows were used in an undercover investigation to track down evidence against two cattle dealers who sold medicated livestock for use as human food.

The cattle dealers were brothers Richard Eugene Gorr and Jeffery Lee Gorr, owners of Gorr Livestock of Petersburg, Mich. Both pleaded guilty July 18, 1996, in the U.S. District Court for the Eastern District of Michigan to buying and selling cattle between 1988 and 1994 that contained illegal levels of drugs. Cows headed for slaughter with signal-emitting beepers in their stomachs and FDA agents close behind helped secure the guilty pleas.

Both brothers were sentenced Oct. 10, 1996. They were each fined \$25,000—five times higher than the recommended sentencing guidelines—because of the extent of their conduct and their profit-making motive. Also, each must serve

three years' probation and perform 150 hours of community service.

No injuries were attributed to the Gorr cattle, but cows with illegal drug residues can pose significant health hazards if the cows are used for human food, according to FDA. People allergic to antibiotics can suffer severe, even fatal, allergic reactions to the residues. Also, illegal antibiotic residues can cause diarrhea and other stomach and intestinal problems, vitamin deficiencies, and resistance to antibiotic medications.

To ensure a food is free of harmful drug residues when eaten, FDA requires a "withdrawal period" between the time an animal is medicated and the time it is slaughtered for human food. This gives the drug time to metabolize.

FDA's undercover investigation revealed that Gorr Livestock bought sick, old cattle that were often treated with antibiotics and other drugs—either by the farmers who sold the cattle to the

Gorrs or by the Gorrs themselves—and sold the cattle without regard to the withdrawal periods.

FDA first became aware of the extent of the Gorrs' violations in 1992, when a Michigan Department of Agriculture inspector traced slaughtered dairy cows with illegal drug residues to Gorr Livestock.

In March 1993, FDA Detroit district employees Michael Owens, an investigator, and Judith Jankowski, a tissue residue monitor, went to slaughterhouses in western Michigan to follow up on reports of about 300 violative tissue samples in the Gorr Livestock area. The violations had been reported to FDA by the U.S. Department of Agriculture, which collects cattle tissue samples from slaughterhouses, tests them for antibiotics and other drugs, and reports illegal drug residues to FDA.

In Michigan, Owens interviewed



farmers who were believed to be the source of animals with violative residues. The interviews revealed that in many cases, the animals didn't really come from their farms. In one case, a farm thought to be the source of a violative dairy cow didn't even keep dairy cows—only steers.

The discrepancies led FDA to suspect the Gorrs of widespread violations, including switching the medicated cows' identifying tags so they couldn't be traced to Gorr Livestock.

"It became clear the Gorrs did this a lot—selling medicated cattle with the hope that USDA wouldn't test the cattle and detect the illegal residues," says Ross Parker, an assistant U.S. attorney in Detroit who prosecuted the brothers.

Between September 1988 and February 1996, FDA and the Michigan Department of Agriculture warned Gorr Livestock about findings of 36 illegally medicated cattle. In addition, USDA warned the Gorrs in writing 12 times about illegal drug residues.

To get proof that the Gorrs were violating animal drug laws, FDA's Office of Criminal Investigations conducted three "sting" operations, in June, August and November 1994.

OCI special agents, with the help of Owens and Jankowski, began by observing the Gorrs' daily routine, including the days they usually took their cattle to auction or to slaughterhouses. Then, the agents posed as cattle dealers in southeastern Michigan, observing the Gorrs' illegal activities and document-

ing them on audio- and videotape.

For each sting operation, the agents obtained a cow headed for slaughter. With the assistance of the Michigan Department of Agriculture, they placed a transponder, or beeper, in the cow's stomach. The beeper was inserted through the cow's throat using a speculum, the way a cow is given medication.

Because transponders allow authorities to track an animal without a telltale mark like an ear tag, they have been used in Africa to catch poachers, according to investigator Owens. "But Gorr Livestock was a unique case," he says. "It was the first time FDA had ever used a transponder in a cow for a criminal investigation."

Each beeper-carrying cow was placed on a farm with other animals. Posing as a farmer, an OCI agent told the Gorrs he wanted to get rid of a sickly cow, but he wasn't sure it could pass USDA inspection because it had been medicated recently. The cows were not actually medicated, though.

All three times, the Gorrs bought the cow, and the agents watched the brothers and waited, sometimes for up to a week. The beepers allowed FDA to track the cows to slaughter. The agents kept a receiver in their car. When the Gorrs loaded cows on a truck to transport them to an auction or slaughterhouse, the agents drove past the truck. If the receiver picked up a signal, they knew their cow was on the truck, and they followed the truck to its destination.

The Gorrs sold all three cows without

waiting until the withdrawal period expired. "The more quickly they moved them, the more money they made," says an OCI agent. "Otherwise, they would have had to feed and take care of them."

The FDA investigators followed each beeper-containing animal to slaughter and retrieved the beeper, which cost several hundred dollars. "I had to cut open the slaughtered cow's stomach and stick my hands in to fish around for the beeper," Owens says.

The stings came off with only one minor hitch. After the first buy, a steer belonging to the farm FDA agents were using broke down the farm fence and eluded agents for over a mile, until they recruited a local cowboy to lasso the animal.

Armed with the evidence collected by FDA, the U.S. Attorney's Office for the Eastern District of Michigan obtained a search warrant on Jan. 20, 1995, and FDA special agents seized the Gorrs' records and drugs.

In their plea agreements, the Gorrs agreed to cooperate with law enforcement agencies in related investigations into other farmers' illegal practices. Also, they agreed to keep detailed records about their livestock.

After sentencing, FDA will closely monitor Gorr Livestock's record keeping.

*Tamar Nordenberg is a staff writer for FDA Consumer.*

## Unapproved Dental Drug Goes Up in Smoke

Root canal filler containing a toxic substance was destroyed under court order at FDA's request because it was an unapproved drug whose safety and ef-

fectiveness had never been established. An environmental services company burned the product in an incinerator.

Harvey Altholtz, D.M.D., president of the Connecticut firm that distributed the filler, had asserted that because his White One-Step Endodontic Formula

was widely used, it was generally recognized as safe and effective and therefore not a new drug requiring FDA approval. But a U.S. district judge ruled that adequate and well-controlled studies are required to establish drug safety and effectiveness and, since study data on the



root canal filler had never been submitted to FDA, ordered the product destroyed.

Stephen Souza, an investigator with FDA's Hartford, Conn., resident post, inspected Altholtz's Dental Clearing House, in Simsbury, Conn., on Jan. 18, 1992, following numerous complaints from health professionals that advertisements claimed the one-step formula "meets FDA standards" and was "FDA sanctioned." Agency records showed no approved new drug application (NDA) on file for the product.

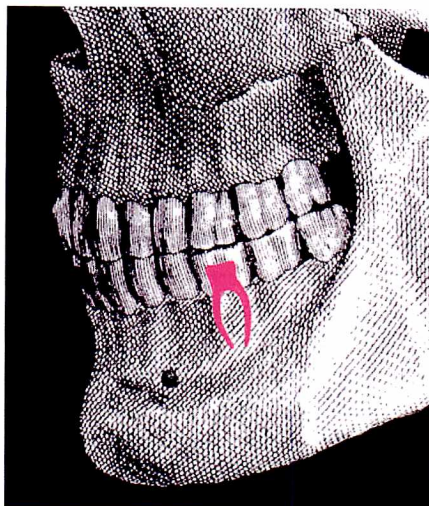
Souza found Altholtz was distributing the formula in 60-gram (2-ounce) bottles of white powder and 30-milliliter (1-oz.) bottles of liquid. One bottle of each was to be mixed at the ordering dentist's office to create the filler.

"Altholtz had the powder and liquid made to his specifications at contract laboratories," Souza says. "The records showed that the liquid contained an approved dental analgesic-antiseptic, eugenol, and some inert ingredients. But the active ingredient in the powder was paraformaldehyde, a toxic preservative that has no approved use in drug products."

A month later FDA wrote to Altholtz, warning him that seizure or other legal action might ensue if he didn't stop selling the unapproved drug and advertising it with statements that imply approval, such as "meets FDA standards."

Altholtz wrote back, saying that an FDA official had told the formula's original owner in a 1982 letter that the agency would take no regulatory action until it reviewed the product to determine its safety and effectiveness.

"If the FDA now feels it is not a safe and efficacious product," he wrote, "I think you should poll some of the dentists who have used it and also the patients who have benefitted from its effectiveness so that you will have a total picture of its place in the modern dental



world." He said FDA had suggested the precise formula at that time "so that we would be able to market in interstate commerce without requiring a prescription. ... Our boasting that this is a 'sanctioned' formulation is nothing more than a way of giving credit to the man and the agency which suggested its very makeup."

In an April 2, 1992, letter to Altholtz, FDA pointed out that while the agency official had indeed indicated FDA would defer action until after reviewing the product, the official also had informed the original owner that the product had no approved NDA on file with FDA. "This product still does not have an approved NDA," the agency stated in the letter, "and is in violation of the Food, Drug, and Cosmetic Act when introduced or delivered for introduction into interstate commerce."

The letter further explained that FDA does not "poll" users to determine drug effectiveness. "The responsibility for determining this rests with the drug manufacturer and must have some basis in science not testimonials," the letter stated, adding that adequate and well-controlled studies provide the basis for the agency's evaluation of a drug. The letter also explained that the agency had not suggested the precise formula but had quoted it from a letter from the

original owner. "We strongly object to reference that this product is FDA sanctioned because not only is it misleading, it is entirely false." FDA warned, "Continued marketing of this unapproved new drug is at your own risk."

A year later, FDA still had no approved NDA on file for the White One-Step Endodontic Formula. On July 22, 1993, Souza inspected the firm again to determine the product's marketing status.

From the firm's records, Souza learned that in August and September 1992—despite FDA's warning that the formula was an unapproved product—Altholtz had ordered about 3,000 units of the powder, which at the firm's current sales rate amounted to a six-year supply.

"I asked Dr. Altholtz if he was aware that his product did not have an approved NDA," Souza recalled. "Dr. Altholtz explained he thought someone had applied for an NDA, but he wasn't sure." Souza explained to Altholtz that he must apply for his own NDA and that this generally involves animal and clinical testing to prove the product is safe and effective.

Altholtz replied that this would be too costly. He then showed Souza FDA's 1982 letter to the original owner of the formula and claimed that the FDA official's statement about not taking regulatory action until reviewing the product allowed him, Altholtz, to market the product. Souza reiterated that Altholtz needed his own NDA.

Souza collected product samples and promotional literature, noting that, as required for approved drugs, no additional labeling, insert or instructions accompanied the product. He noticed, however, that Altholtz had removed references to FDA in the promotional literature.

On Feb. 25, 1994, at FDA's request, the U.S. attorney in Hartford filed in the U.S. District Court for the District of



Connecticut a complaint for forfeiture and a warrant for the arrest of the White One-Step Endodontic Formula. U.S. marshals seized the product March 22 at the Dental Clearing House and ordered the company to detain the product until further court order.

On March 28, 1996, U.S. District Judge Janet Bond Arterton ordered the seized unapproved new drug condemned, forfeited and destroyed and ordered Dental Clearing House to pay all costs.

On June 20, 1996, Russell Sinni, supervisory deputy U.S. marshal, and Patricia Murphy, FDA consumer safety officer, met Altholtz at the site of his now defunct Dental Clearing House to identify the seized product. Jesse McCool, of Clean Harbors Environmental Services, Bristol, Conn., placed the bottles into a 5-gallon drum and sent the drug by truck to Natick, Mass., to be processed. From there, the product was sent to a toxic-waste disposal site in Nebraska, where it was burned in an incinerator and buried.

—Dixie Farley

### **Ex-Bard Executives Sentenced to Prison**

Three former executives of the first company approved to market balloon heart catheters in this country were sentenced to 18 months in prison each for conspiring to defraud FDA by selling illegal catheters. They received the maximum sentence allowed under sentencing guidelines.

The former executives for C.R. Bard Inc., of Murray Hill, N.J., and Bard's U.S.C.I. Division, in Billerica, Mass., approved the illegal activities in the late 1980s to boost company profits and maintain Bard's market share in an increasingly competitive field, according to the U.S. Attorney's Office, which prosecuted the case. Bard is a major

medical device manufacturer. U.S.C.I. produces the company's heart catheters.

Chief Judge Joseph Tauro of the U.S. District Court for the District of Massachusetts sentenced the three men Aug. 8, 1996, almost one year after the three were convicted following an eight-week jury trial. In addition to prison, he sentenced them to two years of supervised release and assessed them a \$50 special fee.

Bard pleaded guilty to similar charges in 1993, and agreed to pay what was at that time the highest penalty ever imposed in a health-care fraud case—\$61 million. Bard also had to implement numerous measures to prevent such illegal activities from occurring again.

The government estimated that total sales of the illegal catheters amounted to \$77 million.

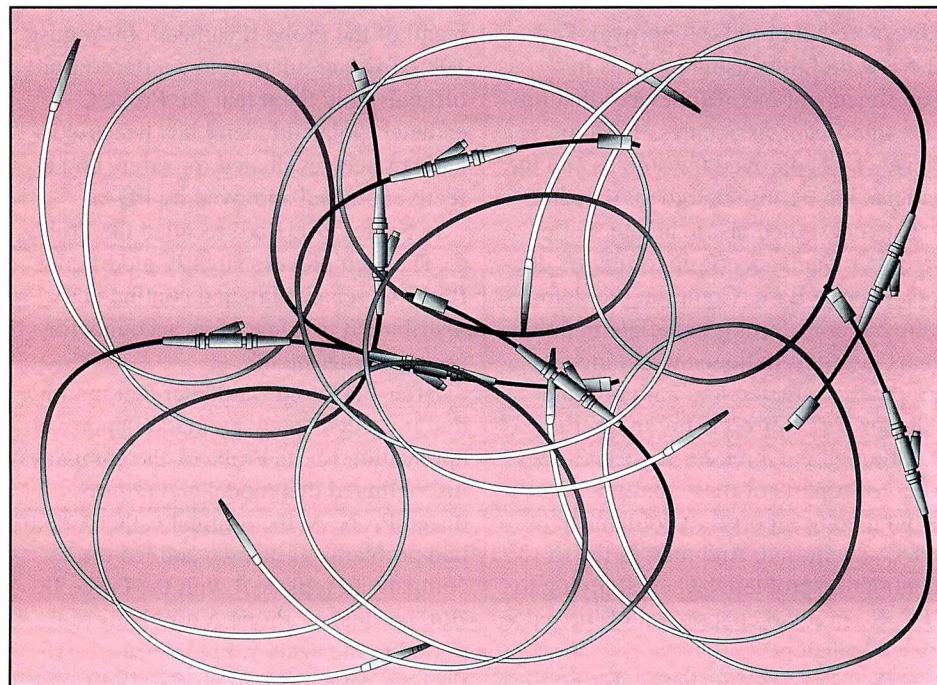
Catheters now made by Bard's U.S.C.I. Division have been approved by FDA.

The former Bard executives are appealing their conviction and sentence. They are David Prigmore, 56, of Natick,

Mass.; John Cvinar, 50, of Winchester, Mass.; and Lee Leichter, 46, of Fort Myers, Fla. Prigmore was a corporate executive vice president responsible for the U.S.C.I. Division. Cvinar was U.S.C.I. president, and Leichter was U.S.C.I. director of regulatory affairs and quality assurance.

Bard was the first company to obtain FDA approval to market a balloon angioplasty catheter in the United States and remained the only U.S. distributor of heart catheters from about 1980 to 1985, after which other U.S. companies began developing and marketing their own.

Heart catheters are used in angioplasty, a procedure to clear clogged arteries. The device, a wire with a balloon-like tip, is threaded into a clogged heart artery, where the balloon tip is inflated to flatten the clogging material against the vessel wall and then deflated and removed from the artery. The procedure helps widen the path for blood to flow to the heart muscle, thus reducing the risk of heart attack.





Investigators with FDA's New England district office collected evidence during a four-month investigation of the company in 1990. That evidence, introduced in the 1995 trial, showed that the company, with the defendants' approval, redesigned heart catheters already approved by FDA and sold them before obtaining FDA approval. The redesigning began about 1987, partly to address problems that doctors reported having with the original catheters.

Under medical device regulations, companies must file applications for premarket approval and receive approval from FDA before they can market their devices in the United States. Supplements for premarket approval applications also are required for changes made to approved devices, when the changes affect the device's safety or effectiveness. Such was the case with the Bard heart catheters.

By allowing the catheters to be put on the market, the executives essentially allowed the devices to be used experimentally in humans without patients' consent or knowledge, without doctors' knowledge, and without FDA approval. Federal law prohibits using humans in experiments of medical devices that present significant risks unless FDA has reviewed and approved the studies and the patients have consented to participate.

The redesigned heart catheters often malfunctioned, according to reports doctors made to Bard. Common problems were balloons failing to deflate in patients' arteries, balloons wrapping around the catheter, and balloons and catheter wire tips breaking in arteries.

Although the three former executives received reports of these malfunctions, they failed to report the problems to FDA, as required. And they failed to mention the problems when applying to FDA for premarket approval of the redesigned catheters.

They learned, for instance, during ille-

gal human clinical trials and while the company's Probe B catheter was under FDA review, that the Probe B catheter tip was likely to break off in the arteries in 2 of every 100 patients. Yet, Cvinar and Leichter decided to keep this information from FDA and proceed with plans to commercialize the catheter when approved by FDA without changing the labeling to inform doctors of the risk of catheter tip breakage. FDA approved the device in January 1989, unaware of the tip breakage problem identified by the company during the illegal clinical trials.

Within three months, after receiving 33 reports of tip breakage during angioplasty with the Probe B, Bard redesigned this catheter, calling the new model Probe C. In March 1989, the company began distributing the Probe C without FDA approval for human experimentation.

In June 1989, after learning of catheter malfunctions, FDA met with Bard representatives and informed them that their catheters were illegal and subject to seizure. In June 1989, Bard initiated a recall of the Probe B catheter. In August 1989, FDA regulators, in a letter to Bard officials, told them that the Probe C catheter violated federal law because it had not been evaluated for safety and effectiveness and approved by FDA.

In September, Bard recalled the Probe C. Then, employees slightly modified Probe C, renamed it, and continued to distribute it to a few of its accounts for about another month.

After FDA told Bard later that month that it needed a new premarket approval application for its Probe C, the company discontinued that model and reintroduced Probe A, the original catheter that had problems of its own and led the company to replace it with the Probe B. But, because of Probe A problems reported to the agency, FDA seized 1,815 Probe A catheters on Feb. 22, 1990, and

witnessed their destruction on Nov. 20, 1990.

Another illegal practice in which Bard executives participated was to allow manufacturing of the company's Simplus catheter in a manufacturing facility not yet approved by FDA. In approving class III medical devices, such as heart catheters, FDA also must approve the manufacturing facilities to ensure compliance with medical device good manufacturing practices (GMPs).

In its 1987 premarket approval application for the Simplus catheter, Bard said it would make and package the catheter in its Billerica, Mass., facility, an FDA-approved manufacturing plant. However, by this time, Bard had already begun to make the Simplus catheter at the company's newly acquired plant in Haverhill, Mass. Former company executives determined it would be too costly to shift the manufacturing to the facility approved by FDA. So, the company continued to make, package and eventually distribute Simplus catheters from the unapproved Haverhill plant. When FDA inspected the Haverhill site in March 1988, inspectors identified several GMP deviations.

A grand jury for the U.S. District Court for the District of Massachusetts handed down a 393-count indictment against the three former executives and others in January 1995.

In sentencing the three former Bard executives, Judge Tauro emphasized that corporate entities do not commit crimes, people do, and that executives running other companies who might engage in such conduct should bear in mind the prison terms imposed in this case.

—Paula Kurtzweil

## No Place for Critters

Happy Valley Food was once home for some probably very happy rats—and insects and other animals. Here, accord-



ing to FDA inspections, the critters had free rein in a warehouse filled with bags of rice, flour and other foods.

But not any more. A Sept. 6 inspection by FDA's Baltimore district office found the warehouse finally clean and free of pests.

This came about after Happy Valley Food Inc., Washington, D.C., agreed in a consent decree with FDA and the Department of Justice to clean up its warehouse and recondition all potentially contaminated food.

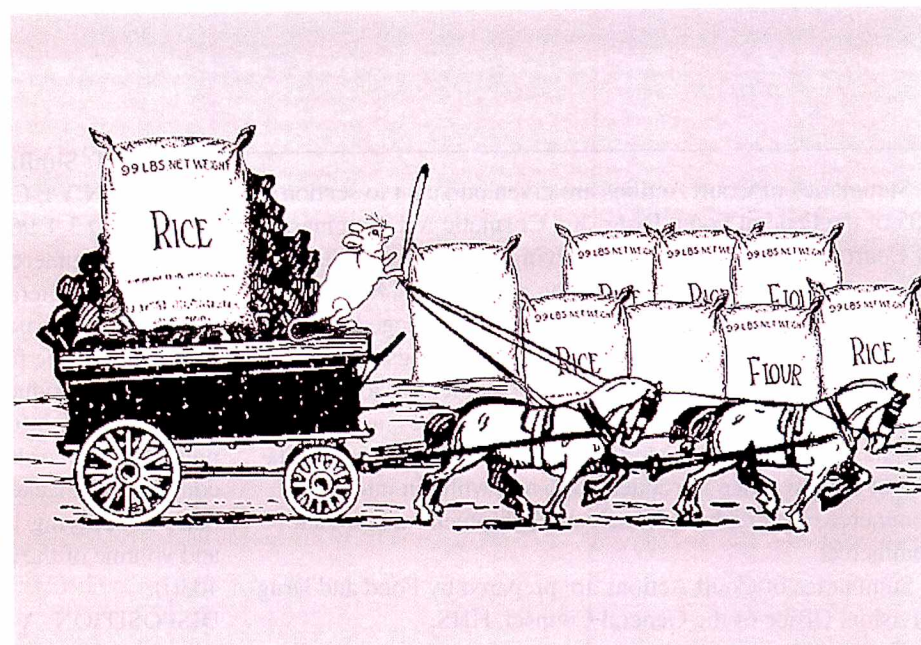
The contamination problem became evident when investigator Linda Hunt of FDA's Baltimore district office inspected Happy Valley's warehouse Jan. 18 through 30, 1996. The inspection was part of the district's 1996 work plan.

Hunt found insects, animals and general filth throughout the warehouse, including five live and eight dead rats, two live cats, a live dog, several rodent nests, and hundreds of rodent excreta pellets. She also found bags of rice, flour, and potato starch with rodent-gnawed holes and noted many holes in the walls where rodents could easily enter and openings along the bottom of closed doors where rodents could hide and build nests.

Hunt took samples of several products, including rice, potato flour, and wheat flour. FDA chemists in the Baltimore district laboratory verified that the samples contained rodent nesting material, urine and excreta, and animal hair.

During the inspection, Johnny C. Chan, president of Happy Valley, told Hunt he would clean up the warehouse, repair structural defects, and withhold from distribution all products that appeared to be rodent adulterated. He also hired an exterminator, who, between Jan. 24 and 30, killed at least 10 rats, according to Chan.

However, when Hunt returned to Happy Valley on March 6, she found that conditions had not improved. Also, some of the food Chan said he wouldn't



sell because of contamination had been sold.

Because contamination was so widespread, on March 12 FDA asked the U.S. attorney for the District of Columbia to file a complaint for seizure of all the company's food products, except for canned and refrigerated products, which showed no evidence of contamination.

The complaint was filed March 15 in the U.S. District Court for the District of Columbia, and on March 19, the U.S. Marshals Service seized food products worth more than \$52,000.

During a visit to the warehouse on March 21 to ensure that the seized products were still intact, Hunt and a deputy U.S. marshal found two cartons missing and the tape used to secure the items torn. They discovered more seized items missing during a visit on March 26.

Tony Chan, vice president of Happy Valley, said employees had mistakenly taken the seized products. To prevent future mistakes, U.S. marshals returned to Happy Valley on April 2 and moved all seized merchandise to a rear storage area of the warehouse where it could be eas-

ily monitored by management.

The consent decree, signed April 30, required the firm to post a \$104,000 bond and established the steps the company would have to take to recondition the food and clean up and repair the warehouse. FDA approved Happy Valley's reconditioning plan, which included looking at each bag and box for evidence of rodent pellets and gnawed material. In addition, the plan called for each bag and box to be examined by a black light for the presence of rodent urine. Those bags and boxes with evidence of contamination had to be destroyed. The company also had to repair all holes in walls and window screens to prevent pests from entering the building. The reconditioning and repairs were done under FDA supervision at the firm's expense.

By Aug. 27, the reconditioning was complete, and Hunt and several deputy U.S. marshals observed the destruction of \$7,500 worth of contaminated food.

—Isadora Stehlin



## 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 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.

### SEIZURE ACTIONS

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

PRODUCT: **Milk, condensed**, at Chicago, Ill. (E.D. Ill.); Civil No. 95C-4148.

CHARGED 7-18-95: While held for sale after shipment in interstate commerce at La Bodega, Inc., in Chicago, Ill., the article was misbranded in that the statement of identity, declaration of net quantity of contents, and the statement of ingredients were not in English—403(f). The article was also misbranded in that the name and place of business of the manufacturer, packer or distributor did not appear on the label in the required type size, and the label failed to bear nutrition information—403(f) and 403(q)(1).

DISPOSITION: A default decree of condemnation, forfeiture and destruction ordered the articles destroyed. (F.D.C. No. 67098; S. No. 94-741-379; S.J. No. 1)

PRODUCT: **Riga Sprats**, at Elizabeth, N.J. (DNJ); Civil No. 95-1148 (AJL).

CHARGED 3-8-95: While held for sale after shipment in interstate commerce at SeaLand Container Service Station, in Elizabeth, N.J., the articles were adulterated in that they were prepared and packed under conditions whereby they might have been rendered injurious to health—402(a)(4).

DISPOSITION: A consent judgment and final order of forfeiture ordered the articles destroyed. (F.D.C. No. 67048; S. No. 95-647-620; S.J. No. 2)

PRODUCT: **Similac infant formula, powdered**, at Deer Park, N.Y. (E.D.N.Y.); Civil No. CV-96-0938.

CHARGED 3-1-96: While held for sale, after shipment in interstate commerce, at Krantor Corp., in Deer Park, N.Y., the article was adulterated in that it failed to bear a lot code—412(a)(3). The article was misbranded in that it was represented to be for special dietary use in that the label declared the product as “infant formula.” And the article lacked nutrient information regarding the product when it was prepared in accordance with label directions for infant consumption, lacked a statement of the number of fluid ounces supplying 100 kilocalories, and lacked the weight and volume of the powdered formula to be reconstituted—403(j).

DISPOSITION: A default decree of condemnation and destruction ordered the article destroyed. (F.D.C. No. 67129; S. No. 96-782-071; S.J. No. 3)

PRODUCT: **Tuna, chunk light**, at Tampa, Fla. (M.D. Fla.); Civil No. 94-609-CIV-T-23C.

CHARGED 4-12-94: While held for sale after shipment in interstate commerce at Winn Dixie Warehouse, in Tampa, Fla., the article was misbranded in that it failed to meet the standard of fill for canned tuna, and the label did not state that the article was below such standard—403(h)(2).

DISPOSITION: A default judgment ordered the articles donated to a charitable institution. (F.D.C. No. 66934; S. No. 93-681-942; S.J. No. 4)

PRODUCT: **Tuna, chunk light**, at Pascagoula, Miss. (S.D. Miss.); Civil No. 1:94cv164RR.

CHARGED 3-29-94: While held for sale after shipment in interstate commerce at Starkist Food, Inc., d/b/a Heinz Pet Products, in Pascagoula, Miss., the article was misbranded in that it failed to meet the standard of fill for canned tuna, and the label did not state that the article was below such standard—403(h)(2).

DISPOSITION: A default judgment ordered the articles donated to a charitable institution. (F.D.C. No. 66927; S. No. 93-651-183; S.J. No. 5)

PRODUCT: **Tuna, raw, frozen, whole**, at Long Beach, Calif. (C.D. Calif.); Civil No. 95-4257 KN.

CHARGED 6-26-95: While held for sale after shipment in interstate commerce at Sea-Land Service, in Long Beach, Calif.,



the article was adulterated in that it consisted of decomposed tuna—402(a)(3).

DISPOSITION: A default judgment ordered the article destroyed. (F.D.C. No. 67095; S. No. 95-714-095; S.J. No. 6)

### *Drugs/Human Use*

PRODUCT: **Exachol, capsules**, at Hastings-On-Hudson, N.Y. (S.D.N.Y.); Civil No. 87 Civ. 7779 (RWS).

CHARGED 5-20-88: While held for sale after shipment in interstate commerce at U.S. Health Club, Inc., in Hastings-On-Hudson, N.Y., the articles were adulterated in that they were unapproved new drugs—505(a). The articles were misbranded in that they failed to bear adequate direction for use—502(f)(1).

DISPOSITION: A consent decree ordered the article destroyed. (F.D.C. No. 65277; S. No. 87-459-661; S.J. No. 7)

### *Medical Devices*

PRODUCT: **Intraocular lenses**, at Azusa, Calif. (C.D. Calif.); Civil No. 93 6928 WDK.

CHARGED 11-18-93: While held for sale after shipment in interstate commerce at Optical Radiation Corp., in Azusa, Calif., the articles were adulterated in that the methods used in, and the facilities and controls used for, their manufacture, packing and storage were not in conformity with current good manufacturing practice requirements—501(h).

DISPOSITION: A consent decree ordered that the articles be destroyed. During an inspection, it was discovered that the firm destroyed some of the articles without FDA's supervision. The firm agreed to pay the value of the destroyed articles. Consequently, FDA released the firm from the rest of the bond. (F.D.C. No. 66754; S. No. 93-663-878; S.J. No. 8)

PRODUCT: **Sharper Image Relaxation Systems**, at North Little Rock, Ark. (E.D. Ark.); Civil No. LR-C-94-563.

CHARGED 9-1-94: While held for sale after shipment in interstate commerce at ABF Freight System, Inc., in North Little Rock, Ark., and at The Sharper Image in Little Rock, Ark., the articles were adulterated in that they were class III devices without an application for premarket approval—501(f)(1)(B). The articles were misbranded in that information regarding the articles was not provided as required—502(o).

DISPOSITION: A consent decree of condemnation was filed. The articles were reconditioned as set forth in the consent decree. (F.D.C. No. 67003; S. No. 94-687-982; S.J. No. 9)

PRODUCT: **Various Articles of Device**, at Seattle, Wash. (W.D. Wash.); Civil No. C94-883R.

CHARGED 6-10-94: While held for sale after shipment in interstate commerce at Synetic Systems, Inc., in Seattle, Wash., the articles were adulterated in that they were class III devices without an application for premarket approval—501(f)(1)(B). The articles were misbranded in that information regarding the devices was not provided as required—502(o).

DISPOSITION: A consent decree of condemnation was filed. The articles were reconditioned as set forth in the consent decree. (F.D.C. No. 66918; S. No. 93-629-464; S.J. No. 10)

PRODUCT: **Viro-Gloves**, at Pompano Beach, Fla. (S.D. Fla.); Civil No. 94 7224 CIV-HURLEY.

CHARGED 12-19-94: While held for sale after shipment in interstate commerce at Knight Industries, Inc., in Pompano Beach, Fla., the articles were adulterated in that the methods used in, and the facilities and controls used for, their manufacture, processing, packing, and holding did not conform to current good manufacturing practice requirements—501(a)(2)(B). The articles were misbranded in that they failed to bear adequate directions for use—502(f)(1).

DISPOSITION: A consent decree of condemnation and destruction ordered the articles destroyed. (F.D.C. No. 67000; S. No. 94-682-477; S.J. No. 11)

### **INJUNCTION ACTIONS**

DEFENDANTS: **Smith Family Farms** and **Paul Steven Smith**, at Clyde, N.Y. (W.D.N.Y.); Civil No. 94 CV 6260T.

CHARGED 6-2-94: The defendants introduced into interstate commerce adulterated cattle and held the cattle for sale after shipment in interstate commerce—301(a) and 301(k). The cattle were adulterated in that they contained an unsafe new animal drug—402(a)(2)(D). The cattle were also adulterated in that they were held under insanitary conditions whereby they might have been rendered injurious to health—402(a)(4).

DISPOSITION: A consent decree of permanent injunction was filed. The defendants later were found in compliance with the decree. (Inj. 1350; S. No. 93-543-575; S.J. No. 12)



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I certify that the statements made by me above are correct and complete.

Judith Levine Willis, editor





Is Your  
Kitchen Crawling with

# DIRTY LITTLE SECRETS?

When it comes to food-borne illness, what you don't know could hurt—or even kill—you. Did you know that millions of cases of food-borne illnesses occur each year from harmful bacteria found in the kitchen? Or that a kitchen that looks clean may not be hygienic?

To help protect your family from food-borne illnesses, the Food and Drug Administration produced an 8½-minute video on kitchen food safety titled “Dirty Little Secrets.” With humor and a quick pace, the video presents information on safe practices to follow when shopping, storing, preparing, and cooking food. Accompanying the video is a Kitchen Food Safety Test that can be used to rate home food safety practices.

Cost: \$8.95.

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