

# FDA CONSUMER

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

• VOL. 26 NO. 2

MARCH 1992 •

**Erasing  
Skin Marks  
With  
Lasers**









Louis W. Sullivan, M.D.  
Secretary of Health and  
Human Services

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

Gary E. Fendler  
Associate Commissioner for  
Public Affairs

Judith Levine Willis / Editor

Patricia N. Edwards / Art Director

Michael L. Herndon / Production Manager

Carol L. Ballentine / Copy Editor

Cover Design: Jack Pardue

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**Unproven Cancer Treatments: Hope or Hoax?** 10  
*Cancer patients who are lured by the inflated promises of unscientific therapies take a double risk. They face unknown hazards from these dubious "cures" and may also be missing out on new options—and real hope—offered by mainstream medicine.*

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**Monitoring High-Risk Pregnancy** 34  
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#### Inside Front Cover Photo:

*Monitoring blood glucose at home is one way to help women with high-risk pregnancies deliver healthy babies. For other ways, see page 34.*





## FDA Requests Moratorium On Silicone Gel Breast Implants

New information on the safety of silicone gel breast implants led FDA last January to request a moratorium on the use of these devices until an independent advisory panel to the agency could review the new data.

At its last meeting, in November 1991, the General and Plastic Surgery Devices Panel recommended that, despite a lack of sufficient safety and efficacy data to approve the implants, the devices remain available under certain conditions while the manufacturers collected additional data.

Since that time, however, the agency received new information about the implants that amplified concerns about their safety.

"Much of the new information provides additional evidence that implants could possibly cause autoimmune or connective tissue disorders," said Kessler, adding that, "The panel looked at this issue in November. However, the new information seems to underscore safety concerns in this area."

There are also new data about silicone leakage, local inflammatory reactions, and implant rupture.

Kessler asked surgeons to stop implanting the devices until the new information could be thoroughly evaluated and said that, "Because of these unanswered questions, we believe the products should not continue to be marketed until this new information is reviewed."

The agency did not recommend removal of implants in women who already have them, unless they are having problems with them. On the other hand, a woman who is having symptoms she thinks may be related to her implants should see her doctor for advice about what to do. Periodic examinations are also recommended to detect problems such as implant rupture.

Saline-filled implants were not included in the January moratorium and remain available to patients.

## Facilities Must Report Device Problems

Health-care facilities must report deaths and serious injuries or illnesses related to medical device use to manufacturers or to FDA, according to a new law that took effect Nov. 28, 1991. To enforce the law, the agency

published a tentative final rule in the Nov. 26 *Federal Register*.

A serious injury or serious illness is defined as one that is life threatening, results in permanent impairment of a body function or permanent damage to the body, or necessitates immediate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

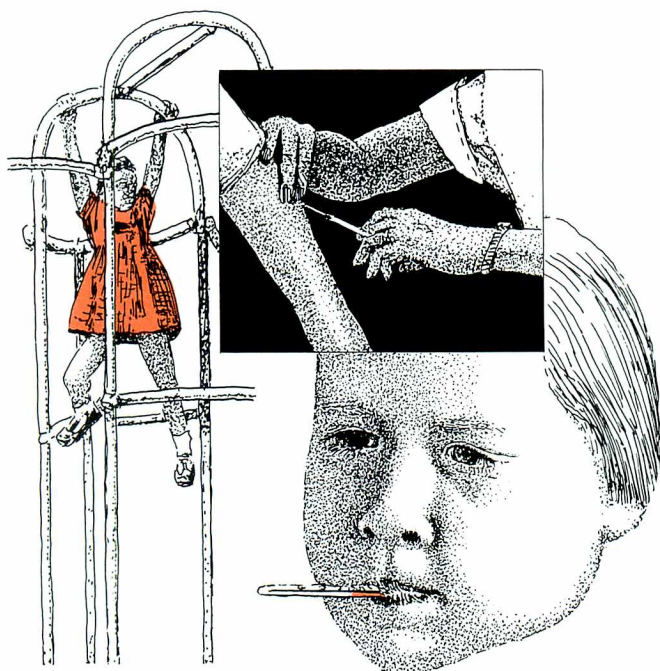
FDA since 1984 has required manufacturers to report device-related injuries and deaths. But Congress mandated this new reporting under the Safe Medical Devices Act of 1990 out of concern that health-care facilities and health professionals often did not report serious device problems to firms and that as a result FDA did not know of the problems.

The General Accounting Office estimated in 1986 that hospitals reported only about half of device problems occurring there, that they reported fewer than 1 percent of the problems directly to FDA, and that the more serious the problems, the less likely it was that hospitals would report them.

The agency has provided interim reporting guidance and a copy of the test reporting form to hospitals, nursing homes, ambulatory surgical facilities, and other outpatient facilities. (Physicians' offices are exempt.) The Safe Medical Devices Act required facilities to begin reporting device-related problems as of Nov. 28, 1991, regardless of whether FDA had issued regulations. Until final regulations are published, facilities may rely on the detailed Nov. 26 tentative final rule in submitting the reports required by the new law. In general, facilities must:

- report incidents in which a medical device was probably the cause or contributed to a serious injury, serious illness or death
- report deaths to both the device manufacturer and FDA
- report serious injuries or serious illnesses to the manufacturer or, if the firm is unknown, to FDA
- submit reports within 10 working days (Monday through Friday, except holidays) of the incident
- include information such as the reporting facility's name, a description of the event, the manufacturer's name (if known), and the medical device's name, model, and serial number
- submit summaries of all reports to FDA twice a year.





## New Whooping Cough Vaccine

A new whooping cough vaccine licensed by FDA last Dec. 17 may cause fewer side effects in children.

"This vaccine may be very useful in getting more children protected," said James Mason, M.D., head of the Public Health Service and director of the National Vaccine Program. "Important as it has been in preventing a difficult and sometimes fatal disease, the old pertussis or whooping cough vaccine has caused more complaints of sore arms, fever, and occasionally more severe effects than most of the other childhood vaccines. As a result, some children never get their full series of shots."

The most common side effects reported in clinical trials of the new vaccine—brand name Acel-Imune—included tenderness, redness and swelling at the injection site, fever, drowsiness, fretfulness, and vomiting.

With diphtheria and tetanus components in addition to the pertussis vaccine, Acel-Imune is licensed for the fourth and fifth DTP shots; the old pertussis vaccine will con-

tinue to be used for the first three shots that constitute primary immunization. The new pertussis vaccine appears as effective as the old one in older children, and research is under way to determine its effectiveness in primary immunization in infants.

Whooping cough is so contagious it infects up to 90 percent of exposed household members who are not immune. Routine U.S. vaccination has brought a drop in case reports from 120,000 with 1,100 deaths in 1950 to an annual average in recent years of 3,500 with 10 deaths. However, in the wake of the largest U.S. measles outbreak in 20 years, with more than 27,600 cases and 89 deaths reported in 1990, the federal government is emphasizing early childhood immunizations. (See "A Responsibility to Remember: Childhood Vaccines" in the September 1990 *FDA Consumer*.)

The old pertussis vaccine is made from the whole pertussis organism, while the new one is made from only part of the organism and, thus, is called acellular. Availability of an acellular vaccine is a significant step forward in infectious disease control, said Gerald Quinnan, M.D., acting director of FDA's Center for Biologics, which evaluated and licensed Acel-Imune.

Takeda Chemical Industries Ltd. of Osaka, Japan, produces Acel-Imune's pertussis component, and Lederle Laboratories of Wayne, N.J., makes the diphtheria and tetanus portions and will distribute the product in the United States.

## Parent Plays Part in Revision Of Corticosteroid Labeling

The efforts of one parent played a role in a labeling revision for corticosteroid drugs, commonly prescribed for children to treat chronic conditions such as asthma, allergies, and juvenile arthritis.

Rebecca Cole of Jacksonville, N.C., informed FDA of her 12-year-old son Christopher's death from complications of chickenpox while he was undergoing treatment for asthma the first time with methylprednisolone, a commonly prescribed corticosteroid.

The agency became concerned that the medical community and many parents may fail to recognize that people taking corticosteroids who become infected with common



viruses may be at risk for serious complications. After reviewing other reports of severe illnesses and deaths in children taking corticosteroids who became ill with chickenpox, FDA last Dec. 2 asked manufacturers of oral, injected and inhaled corticosteroids to include within 90 days the following statement in the "Warnings" section of the physician labeling:

"Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example can have a more serious or even fatal course in children on immunosuppressant corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered."

In addition, FDA requested that the following be added to the "Precautions" section of the physician labeling, also within 90 days:

"Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice."

FDA Commissioner David A. Kessler, M.D., a pediatrician, said, "Many children need these drugs, and stopping them without medical supervision may be very dangerous. But it is also important that parents be alert to the risks if their children are exposed to or get chickenpox or measles while taking corticosteroids. This awareness will hopefully cause them to seek their doctor's advice and treatment."

### **Synthetic Hormone Treats Precocious Puberty**

A synthetic hormone called histrelin acetate was approved by FDA on Dec. 30, 1991, to treat central, or unexplained, precocious puberty, in which young children develop the sexual characteristics of adolescents.

About 6,000 American children have this condition, with 2,000 new cases diagnosed each year. Histrelin acetate was developed as an orphan product by Ortho Pharmaceuticals of Raritan, N.J., and will be marketed under the brand name Supprelin. Orphan status provides incen-

tives to companies to develop products for use in conditions that afflict fewer than 200,000 people.

In idiopathic central precocious puberty, the most common form of precocious puberty, sexual development occurs without known cause before age 8 in girls and age 9 in boys. (In other forms, factors such as injury may be involved.) These children at first grow faster than normal, but their bones mature only to a certain state, after which no growth occurs, often with failure to reach full adult height. They also tend to have emotional problems commonly associated with adolescence. Their intellectual development, however, matches their actual age.

Supprelin is given at home by a parent as a daily injection, similar to the way insulin is given to juvenile diabetics. The drug causes hormone levels to return to normal, development of sexual characteristics to stop, and skeletal maturation to decelerate. Full adult height then becomes attainable. Physician labeling and a patient information brochure stress the need to give the injection at the same time each day. Directions warn that puberty will not be controlled if the drug is not administered consistently.

Injections can be stopped when a child reaches the appropriate age for onset of puberty.

In clinical trials involving 183 children, the most frequent adverse effects associated with the drug, occurring in 5 percent of patients, were skin reactions at the injection site such as redness, swelling and itching. In 22 percent of the girls, light vaginal bleeding occurred during the first month. Other infrequent effects included headache, nausea and vomiting.

### **New Warnings for Sleep Aid**

Stronger written warnings and new packaging are being provided for the prescription sleeping medication Halcion (triazolam) because of concern about the drug's side effects.

The Upjohn Company of Kalamazoo, Mich., agreed last November to make the changes in response to a request by FDA. The British Committee on Safety of Medicines suspended marketing of the drug in the United Kingdom in October 1991, saying that Halcion had a higher frequency of psychiatric side effects than other sleep-aid drugs, including memory loss and depression.

Halcion has been prescribed in more than 90 countries since its introduction in Belgium in 1977. It went on the



market in this country in 1983.

The changes made by the Upjohn company include:

- revised physician labeling emphasizing appropriate use in treating insomnia and information about side effects and dosage
- a patient package insert that includes explicit information about the risks and benefits of Halcion
- "unit-of-use" packaging containing 10 tablets per package to help physicians more closely monitor patients' use of the drug.

Because there have been more adverse behavioral side effects reported for Halcion than for other sedative hypnotic drugs, FDA in September 1989 asked a committee of outside experts to examine the data for the drug. The committee concluded that the reports alone were not necessarily evidence of excess risk, since they could represent the larger number of prescriptions being written for Halcion or differences in reporting practices. Therefore, the committee recommended only that the labeling for Halcion be modified to state that the drug has a greater potential than some other similar drugs to induce temporary amnesia.

FDA plans to ask manufacturers of four similar sleep aids on the market to revise the labeling for their products, prepare patient package inserts, and develop unit-of-use packaging. The agency is also reviewing the data submitted in the original marketing application for Halcion and is investigating a dosing study of Halcion in prisoners in which safety data were reported inaccurately.

## Relief for Hangovers, Gluttony

Consumers and others have until April 22 to comment on an FDA-proposed regulation for nonprescription products to treat hangovers and stomach upsets. The proposal, published in the Dec. 24, 1991, issue of the *Federal Register*, sets conditions under which such products would be classified as safe and effective.

If the rule is made final, the products will be considered safe and effective if they contain the following active ingredients and list them on their labels:

- **for upset stomach:** antacids, certain internal analgesic-antacid combinations, and products containing bismuth subsalicylate
- **for hangover symptoms:** antacid-internal analgesics and stimulant-internal analgesic combinations such as caffeine and aspirin or caffeine and acetaminophen.



Acetaminophen, aspirin and antacids are safe and effective for both upset stomach and hangover products, according to the proposal.

FDA's proposal states that some products, such as those that contain both an antacid and caffeine, are not safe and effective for hangovers because the ingredients counteract each other.

Hangover products containing activated charcoal have not been studied enough to determine their effectiveness, FDA said. If the rule is finalized, manufacturers will have to remove hangover relief claims from these products' labels until more data are submitted to FDA.

FDA previously reviewed products to prevent alcohol inebriation and found none to be safe and effective. No such products are on the market.

Review of these products was part of an ongoing comprehensive review of nonprescription drug products.

In addition to the April 22 public comment deadline, manufacturers and others have one year to submit new data. If new data are submitted, there will be an additional



two months for public comment. Comments should be sent to: Dockets Management Branch (HFA-305), FDA, Room 1-23, 12420 Parklawn Drive, Rockville, Md. 20857.

### **Cholera Bacteria in Ships' Ballast Water**

When foreign ships carry cargo to American ports, they may also harbor disease-causing cholera bacteria, U.S. health officials fear.



Last fall, FDA found cholera bacteria in the ballast and holding tank water of two freighter ships from Latin America, where the disease has been epidemic since January 1991.

Ballast water stabilizes a ship at sea, while the holding tank stores sewage and waste water.

FDA began testing additional ships in November to see if they might have brought the bacteria to U.S. waters. Cholera was found in four seafood samples taken from Mobile Bay, Ala., last summer. The strain of bacteria was the same as that causing the epidemic in Latin American countries.

Cholera is a potentially deadly intestinal disease that is easily treated and fully preventable with good sanitation. Largely because of poverty conditions, the disease has spread throughout 12 Latin American countries, causing about 3,000 deaths.

At the time FDA discovered cholera in Mobile Bay seafood samples, the beds were closed to fishing. No other samples have contained cholera bacteria since then, so the beds have been reopened.

No cases of cholera have been reported in Alabama, and none have been associated with American seafood. Nevertheless, consumers should not eat raw oysters or other raw seafood. Thorough cooking kills cholera bacteria.

Alabama state health officials have asked that all foreign ships entering the Port of Mobile exchange their ballast water twice while on high seas before entering the harbor.

Ships are not allowed to discharge holding tank water into U.S. navigable waters, but vessel operators may either discharge on the open ocean or to a shoreside reception facility.

The U.S. Coast Guard and the national Centers for Disease Control have worked with FDA in testing the ships. The Coast Guard can deny entry of a ship to U.S. ports if it carries cholera bacteria.

### **Don't Eat Internal Organs of Certain Crabs**

Consumers should not eat internal organs, or viscera, of Dungeness crabs from the coast of California, Oregon and Washington because of the possible presence of domoic acid, a toxin produced by marine plankton, FDA advised last Dec. 27. Some ethnic recipes call for viscera.

"The crab meat itself is safe," said FDA Commissioner David A. Kessler, M.D. "No crab samples from the three states have shown any significant levels of domoic acid in the meat. The levels found in the crab meat . . . have been well below the permitted limit of 20 parts per million."

Conditions that cause plankton to produce domoic acid are unknown, but intake of high levels of the toxin can cause amnesic shellfish poisoning. Abdominal cramps, diarrhea, and nausea may appear within 24 hours. In severe cases, neurological symptoms such as headaches, dizziness, disorientation, seizures, breathing difficulty, and



memory loss may appear within 48 hours.

The three states and FDA have been monitoring various fish and shellfish species for several months after reports of 11 cases of amnesic shellfish poisoning. No problems with domoic acid have been found in Dungeness crabs from waters off Alaska and British Columbia, where there is also harvesting.

### **Patients Want to Know More About Prescriptions**

There is a gap between what patients need to know about the medicines their doctors prescribe and what they actually learn from their physicians, pharmacists or nurses, says FDA Commissioner David A. Kessler, M.D.

He believes that the best way to close that gap is "cooperation among consumer groups, health-care providers, and the FDA to improve patient education."

In an article in the Dec. 5, 1991, issue of the *New England Journal of Medicine*, Kessler called on physicians and pharmacists to voluntarily renew efforts to educate patients about the proper and safe use of prescription drugs.

"FDA is ready to assume a supportive role," he says. "FDA cannot ignore the large-scale inappropriate use of drugs whose safety and efficacy are its responsibility."

Improper use of medications is commonly believed to be "an underlying cause of many adverse drug reactions," he says, adding that "evidence suggests that inadequate communication about drugs is one of the principal reasons why 30 to 55 percent of patients deviate from their medical regimens."

Health professionals opposed a mandatory patient package insert program in the early 1980s for 10 classes of drugs. But complaints that the inserts would require considerable storage space and constant reprinting due to changes in medical knowledge are no longer valid, according to Kessler, because of the rapid expansion of computer technology. The system Kessler advocates involves easily updated software that allows the pharmacist to print the needed patient information while filling the prescription.

"Ideally, each [printout] should describe the general purposes of the medication and summarize the risks, precautions, drug interactions, contraindications, and side effects; it should include a description of adverse events se-

rious enough to warrant calling a physician, pharmacist or nurse," says Kessler.

Kessler stresses that patient counseling by both physicians and pharmacists must accompany the printed information. A 1990 federal law requires pharmacists, beginning Jan. 1, 1993, to offer counseling to anyone having a Medicaid prescription filled. At least 21 states have adopted a requirement that pharmacists offer to counsel all patients.

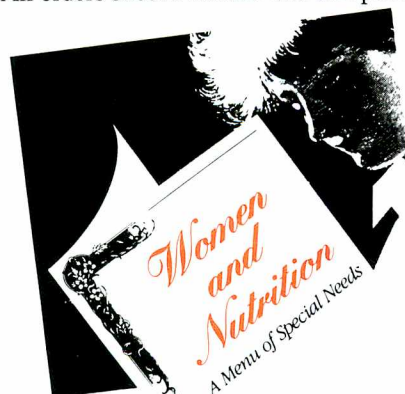
### **Free Pubs**

Several new FDA publications—including one in Spanish—are available free.

They include the Spanish translation of the brochure "Food and Drug Interactions" (OM 89-3023S), which was produced jointly by FDA, the American Pharmaceutical Association, the Food Marketing Institute, and the National Consumers League.

Also available are a reprint of the *FDA Consumer* article "Women and Nutrition: A Menu of Special Needs" (FDA 91-2247) and the backgrounders "How to Make a Freedom of Information Act Request to FDA" (BG 91-10.1) and "Reporting Problem Products to FDA" (BG 91-9.1). The backgrounders are available in single copies only.

To order single copies, write to FDA, HFE-88, 5600 Fishers Lane, Rockville, Md. 20857, or call (301) 443-3170. For up to 100 copies of the brochure or reprint, write to FDA, HFI-40, at the same address. Negatives of the women and nutrition article also are available at this address. All orders should include title and publication number.







## Motor Oil and Soft Drink Bottles Don't Mix

The article "What Happens if the Packaging Gets into the Food?" (*FDA Consumer*, November 1991) was a well-written review of an important issue. To the uninformed, however, the inside front cover photo and cutline could be misleading.

The motor oil bottle shown in the photo is made from HDPE. All plastic soft drink bottles are made from a completely different resin, PET. HDPE cannot be recycled into PET and vice versa.

Some plastic soft drink containers—unlike the one in your photo—do have a base cup which is made from HDPE, which most often includes recycled HDPE. The base cup does not come into contact with the product.

Your sidebar on "Recycled Plastics" also correctly notes that when PET is recycled—regardless of what might have been stored in the bottle—the reprocessed PET is perfectly safe for food and beverage use.

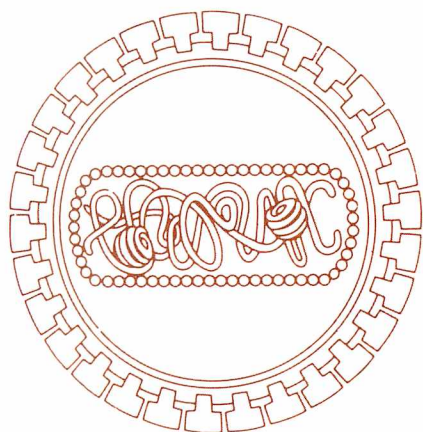
E. Gifford Stack  
Vice President  
Solid Waste Programs and State and Local Affairs  
National Soft Drink Association

*The National Soft Drink Association is correct—a motor oil container made from high-density polyethylene (HDPE) could not be recycled to make a PET soda bottle. PET is polyethylene terephthalate, a completely different resin. The photo showing a motor oil bottle seen through a soda bottle was meant to illustrate the concern that a consumer might use an empty soda bottle to store used motor oil. If the soda bottle were recycled in a manner other than the regeneration processes that FDA has reviewed for PET soda bottles, contaminants could remain. We apologize if the photo is misleading.*

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





### FDA Clears PCP Drug For Treatment IND Use

An experimental drug for fighting *Pneumocystis carinii pneumonia* (PCP)—the leading cause of death in AIDS patients—has been cleared for wider use by FDA under the agency's Treatment Investigational New Drug (IND) program.

The drug, called 566C80, will be available free to AIDS patients (as well as others with compromised immune systems) who cannot tolerate treatment with trimethoprim-sulfa, a standard treatment for PCP.

Many patients can be successfully treated with trimethoprim-sulfa (Bactrim or Septra), but a large number may experience allergic reactions to this drug.

FDA's Treatment IND program allows a company to make an unapproved but potentially lifesaving drug available to seriously ill patients who have no satisfactory treatment alternatives. Treatment IND status was given to 566C80 based on clinical studies indicating that it could be effective for patients with mild to moderate PCP.

Ongoing clinical studies on 566C80 will provide more data on the drug's long-term safety and effectiveness.

The most serious, known adverse effects of 566C80 are severe rashes, but only a small number of patients have had this reaction. Less serious reactions include milder rashes, fever, various digestive problems, and minor blood abnormalities.

The drug's developer is Burroughs Wellcome Co. of Research Triangle Park, N.C.

### OSHA Regs Require Precautions

Physicians, dentists, hospitals, nursing homes, and other employers must require their workers to follow "universal precautions" against contracting infectious diseases such as AIDS and hepatitis B, according to regulations published by the

Occupational Safety and Health Administration (OSHA).

Under universal precautions, blood and certain other bodily fluids are assumed to be contaminated with HIV or other infectious agents. Therefore, workers must wear gloves and other forms of protection while performing activities likely to expose them to blood.

Established by the national Centers for Disease Control in the early 1980s, universal precautions were already being practiced by most doctors and hospitals on a voluntary basis, according to OSHA.

But under regulations taking effect this month, the use of universal precautions is no longer voluntary. The new rules require employers to provide their workers with protective gear, free vaccinations against hepatitis B, infection control training, and medical follow-up after possible exposure to infection.

The regulations, published in the Dec. 6 issue of the *Federal Register*, will affect approximately 4.9 million workers in the health-care profession and another 700,000 workers who routinely come in contact with blood, including law enforcement officers, fire and rescue squad personnel, corrections facility officers, laboratory researchers, undertakers, and people in the linen service industry.

Physicians will spend an average of \$1,179 per year on universal precautions, OSHA estimates, while dentists will spend about \$873.

The new regulations could prevent about 200 deaths and 8,200 blood-borne infections each year, OSHA predicts.



# HOPE

## Unproven Cancer Treatments

by Lenore Gelb

**P**eople who have just been told they have cancer must decide quickly what to do about treatment—their lives may depend on it. When conventional, mainstream treatments don't promise total cures, thousands of cancer patients turn to questionable, untested, possibly fraudulent treatments.

The promises of the practitioners of these treatments can be seductive, not unlike the pitch of the used car salesman offering the "deal of a lifetime." But the stakes are much higher.

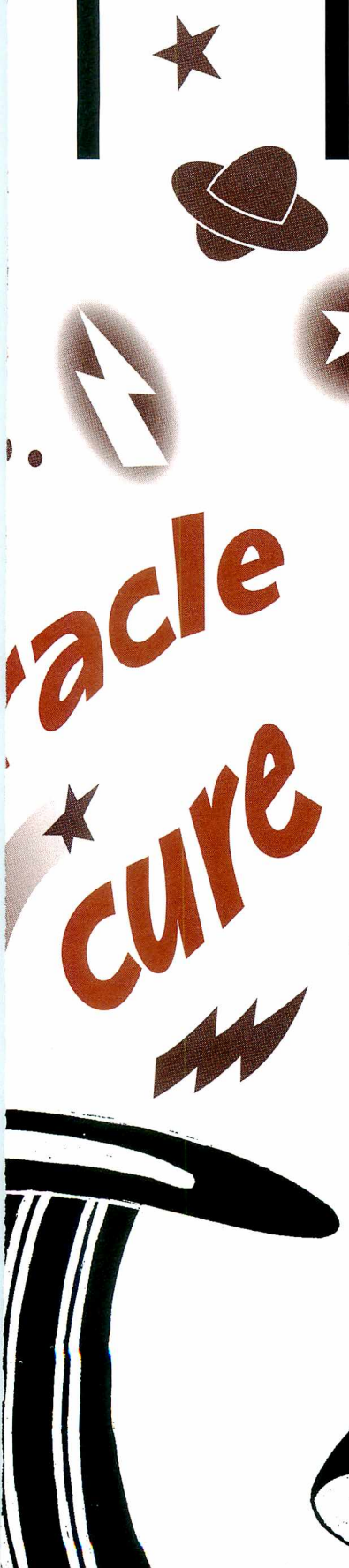
Unproven cancer treatments may sound good at first to patients faced with the possibility of side effects from conventional cancer treatments, including chemotherapy, radiation and surgery. In contrast, promoters often describe questionable,

secret  
natural





# HOAX?



untested treatments outside mainstream medicine as natural, nontoxic and noninvasive. However, while some—such as herbal treatments and some diets—may sound “natural,” others are not, and are made up of unknown substances and possibly toxic contaminants. Others may appear harmless, but, because they are ineffective and cause people to delay or forego beneficial treatments, they, too, are dangerous. Manufacturing standards typically do not exist. Theories underlying the treatments vary widely, but one thing they have in common is the absence of scientific proof that they work.

The Office of Technology Assessment, an agency that serves the U.S. Congress, recently published a report on questionable (or, as OTA calls them, unconven-

tional) cancer treatments, defining them as those treatments that fall outside the bounds of mainstream medicine and have not been proven safe or effective by scientific standards that balance benefit and risk.

This is in contrast to experimental therapies within mainstream medicine, which are new products under investigation or approved products being tested for new uses. These products are tested in a way that allows duplication of the results by others and that controls for other factors that may influence the results. FDA does not test products itself, but permits the human testing of new therapies. Before such testing can begin, the product's sponsor (a pharmaceutical company, private organization, government agency, or individual)





needs to show scientific evidence that the product may work and that precautions will be taken to protect patients on whom it is tested.

Once the results of the clinical trials have been submitted to FDA by the sponsor, FDA must decide whether a treatment's benefits outweigh its risks. For example, cancer drugs often have serious side effects. But the condition they treat is also serious, as cancer patients well know. FDA wants to make sure that new treatments provide benefits outweighing their risks before permitting them on the market. As part of the review process, FDA also approves a labeling insert that accompanies approved products and allows physicians to prescribe the drug safely and effectively at the appropriate doses.

All reviews of new products for cancer (as well as other life-threatening diseases) are done as quickly as possible, with most approval decisions taking a year or less.

Promoters of questionable treatments rarely submit information to FDA about their products, let alone reliable and accurate data. Marketers or promoters of questionable, unconventional treatments for cancer can be prosecuted for violating federal and state laws.

According to Barrie R. Cassileth, Ph.D., of Chapel Hill, N.C., a researcher in the field of unproven cancer treatments, current popular treatments are often lifestyle-oriented remedies with a "do-it-yourself" quality. These treatments may especially appeal to consumers who want an active

role in their own care. They include the popular so-called metabolic therapy, which, depending on the practitioner, may combine special diets, "detoxification" by internal cleanings or enemas, spiritual or emotional "healing," and high-dose vitamins and minerals. Other questionable therapies have names that sound like current mainstream cancer treatments. For example, one questionable treatment is called "immuno-augmentive therapy" (IAT), which sounds like immunotherapy, a mainstream treatment that manipulates a patient's immune system to fight cancer.

### OTA Report

Because of the popularity of many unconventional treatments, Congress commissioned OTA to study them. After four years of research, OTA concluded in a 300-page report that "effectiveness [of unconventional treatments] is unknown, and relevant information on adverse effects is nonexistent." According to OTA, certain psychological and behavioral approaches may have some benefit when they are used *in addition* to mainstream treatments. For example, psychological support groups can benefit those patients who want to try them.

People frightened by a diagnosis of cancer may want to believe in the existence of "a miracle cure." Extravagant claims for questionable cancer treatments are often found in testimonials in the media. These messages can be quite convincing to someone facing the life-and-death issues

of cancer. But people should view claims for questionable cancer treatments with the following in mind:

- If it sounds too good to be true, it probably is.
- Don't believe you have nothing to lose.
- Scientific medicine is accountable.
- Real hope is found in mainstream cancer treatment.

### If It Sounds Too Good to Be True

A recent *Wall Street Journal* cartoon pictured a hiker encountering a guru on top of a hill who tells him, "I found the secret to happiness, but the FDA won't let me release it."

The punchline might have had him say he found a cure for cancer. Such extravagant claims are common for treatments for cancer and other chronic and sometimes fatal diseases for which medical science has yet to find a cure. But real "break-throughs" in medicine are few and far between, and when they do occur, the medical community is quick to take advantage of them.

An example of a claim "too good to be true" is found in the promotional literature for Cancell, a currently popular cancer treatment that looks like a dark brown liquid and is made up of ordinary chemicals, including nitric acid, sodium sulfite, potassium hydroxide, sulfuric acid, and catechol. The literature for Cancell states that the product is nontoxic and has no side effects. Although the Cancell booklet says no claims are made for the treatment, it





also says that the treatment “digests” cancer cells and then, “the cancer no longer exists.” No scientific evidence supports the use of Cancell for any disease, and no data have been submitted to FDA on Cancell’s safety or effectiveness. FDA has conducted numerous regulatory investigations of Cancell, and has taken its promoters to court to try to stop its distribution.

William Jarvis, M.D., professor of Preventive Medicine at Loma Linda University and president of the National Council Against Health Fraud, Inc., says that advocates of unconventional therapies have one major characteristic in common: They exude self-confidence about their treatments. In his opinion, they offer an illusion of effectiveness, like a magician’s act.

Testimonials may seem convincing, but many times, according to Jarvis, the patients quoted never had cancer in the first place. Another important fact is that physicians can’t predict with certainty how long a cancer patient will live. When people live longer than expected, they may attribute their survival to an unconventional treatment, just as people who live to be 100 may claim that a glass of wine a day kept them alive. In reality, the cancer patients may have tried many different treatments, including mainstream therapies, and no one knows why they lived longer than expected. A certain number of people do beat the odds. The people who don’t aren’t around to refute the testimonials.

The choices in conventional cancer medicine—most often involving surgery,

chemotherapy and radiation—do involve risk and discomfort, but in return, the patient has a chance of real, proven benefit.

### Nothing to Lose

Freedom of choice is often mentioned as a reason why cancer patients should have access to any treatment they think might be helpful, especially if no conventional treatments exist that offer much hope for prolonging their lives. However, patients may have a lot to lose.

Jarvis calls it the “Gambler’s fallacy.” He says that “patrons of questionable cancer care expose themselves to incompetent practitioners, unsanitary clinical conditions, improper clinical management that may interfere with the drugs they are taking, and more.” As examples, he cites Laetrile treatment, which exposed patients to possible cyanide poisoning, and coffee enemas, which, when used excessively, have killed patients.

In addition, many of these products are manufactured in a haphazard way without standards to ensure that the ingredients found in them and their amounts are the same each time. For example, an FDA inspection revealed that Cancell was manufactured in the back yard with kitchen utensils.

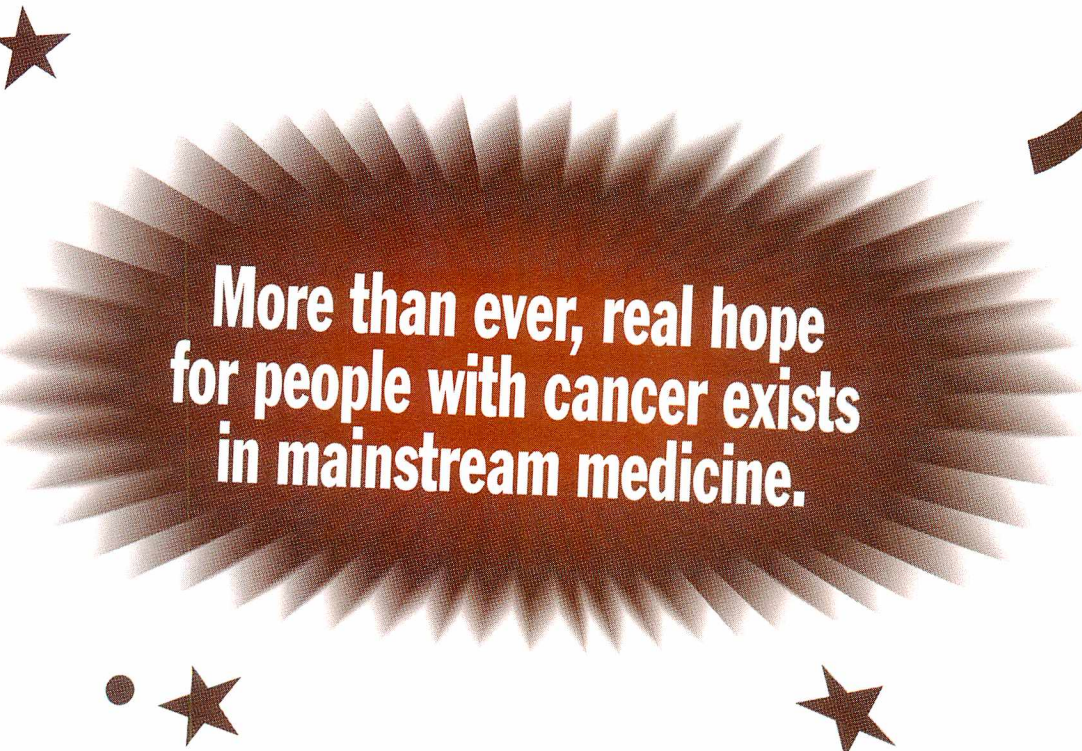
A patient’s quality of life may suffer from unconventional, untested therapies. Cassileth recently compared the quality of life of patients at the Livingston-Wheeler Medical Clinic, an unconventional cancer clinic in San Diego, to that of patients at

the University of Pennsylvania Cancer Center. The Livingston-Wheeler program includes special diets, enemas, and a vaccine that is supposed to boost the immune system. None of the patients was expected to live more than a year, but the researchers thought that quality of life, as measured by a self-report scale, would be better with the unconventional treatment due to an absence of side effects from chemotherapy and other factors. Although survival times between the two groups did not differ, patients at the unconventional treatment center reported a lower quality of life at all times during treatment—the opposite of what was expected.

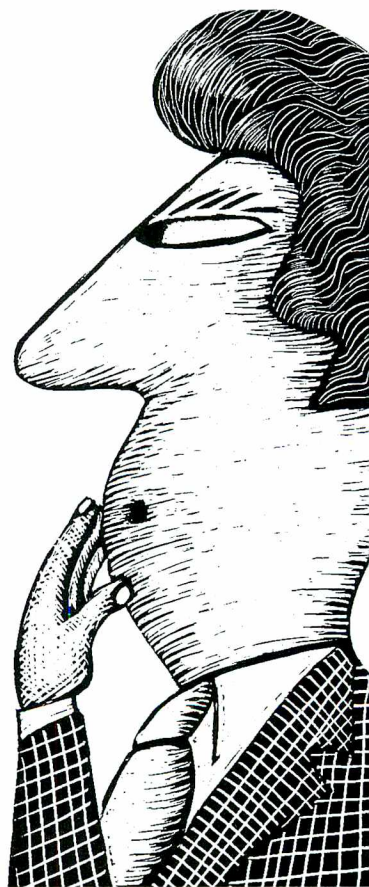
Cassileth points out, in addition, that even seemingly innocuous treatments like vitamin or diet therapies can interfere with the effectiveness of chemotherapy or create nutritional problems.

One of the most dangerous outcomes of some unconventional treatments is that they can discourage or prevent people from using conventional care that offers real hope. Various types of cancer may be symptomless, especially when a person is in remission, and people may feel that an unconventional treatment helped them. This can cause patients to miss the chance of effectively treating the disease with a treatment that has shown real benefit.

And questionable treatments can be very expensive. Practitioners of these treatments often charge exorbitant fees for them. But patients cannot be charged for treatments under investigation within



**More than ever, real hope  
for people with cancer exists  
in mainstream medicine.**







**"I found the secret to happiness, but the FDA won't let me release it."**

*(Reprinted by permission of Cartoon Features Syndicate)*

mainstream medicine: Researchers must supply them free.

### **Scientific Medicine Is Accountable**

Another difference between scientific medicine and unconventional therapy is accountability.

Jarvis asks: "What advice can we give to a patient who is struggling with decisions about whom to trust?"

His answer is to use accountability as the criterion. People or institutions whose work is done openly and who are prominent medical specialists can be ruined if they use deceptive practices. They are required to tell patients about possible side effects and risks, not just possible benefits.

The American Cancer Society publishes information that explains in detail how

proponents of unproven cancer treatments can be identified by their lack of accountability. For example, they are often isolated from established scientists and claim that mainstream medicine and the government conspire against them. Their clinical and scientific record-keeping is weak to nonexistent. They often maintain that their treatments are "secrets," or secretly prepared. They may have multiple, unusual degrees from obscure institutions. Their chief supporters are usually outside mainstream medicine.

In contrast, experimental therapies within mainstream medicine are critically reviewed within the medical community and held up to scientific scrutiny as they are being evaluated for safety and effectiveness. The results of studies are published in established medical journals after review by other scientists. The study methods are outlined in the report so that others can try to verify the results by duplicating them.

Though the burden of proof is on manufacturers to show FDA that a given drug is safe and effective, Helene Brown, at UCLA's Jonsson Comprehensive Cancer Center, says proponents of unconventional therapies try to put the burden of proof on others to show that their therapies don't work. They are not willing to submit data for FDA to review. As Brown says, "It's like putting you in a dark, windowless room and asking you to prove that it's not





raining outside.”

Contrary to claims of some proponents of questionable treatments, FDA welcomes applications from product sponsors who want to investigate new drugs, and the National Cancer Institute is willing to investigate promising new therapies from researchers whether or not they are affiliated with major institutions.

### Real Hope

More than ever, real hope for people with cancer exists in mainstream medicine, with increasing reports of new treatments either being approved or being studied under strict scientific conditions.

For example, in 1991 FDA approved a genetically engineered biologic product, G-CSF, that reduces the number of infections in cancer patients undergoing chemotherapy. Late in 1990, FDA gave permission for the National Cancer Institute to begin using human gene therapy for advanced melanoma, a skin cancer that is difficult to treat. And scientists announced in May 1991 a new cancer diagnostic test, developed through genetic engineering, to identify a gene in urine that, when present, may signal the onset of many types of cancer. This discovery may help in prevention and early treatment of cancer.

Under its “treatment IND” (investigational new drug) program, FDA makes certain experimental drugs available to cancer patients before final approval. For

example, more than 40,000 patients received levamisole before it was approved in 1990 as a combination therapy along with fluorouracil, a drug previously approved for other conditions, as a therapy for Dukes’ C colon cancer. The combination therapy was shown by NCI clinical trials to reduce the death rate by about one-third and the recurrence rate by about 40 percent. Based on the data it had, FDA allowed the manufacturer to make the drug available to many patients before the FDA review process was complete.

A diagnosis of cancer can make people

feel as if they don’t have control over their lives and bodies. Prevention and early, effective treatment often can be the key to a good outcome. Time is a precious commodity, especially for cancer patients—and it is sad when it’s wasted on unproven treatments with questionable benefits that may cause harm. Effective, safe, innovative care is best found within mainstream medicine. ■

*Lenore Gelb is editor of the FDA Medical Bulletin, a publication for health professionals.*

## Get the Facts

For reliable information about therapy options for cancer patients, contact:

National Cancer Institute  
Office of Cancer Communications  
Bethesda, Md. 20892  
Call toll-free: 1-800-4-CANCER

Upon request, NCI will send the booklet *What Are Clinical Trials All About?*, which explains how clinical trials work for patients considering experimental treatment. Other cancer publications are also available.

Information on currently popular unconventional treatments is available from:

American Cancer Society  
1599 Clifton Road, N.E.  
Atlanta, Ga. 30329  
Call toll-free: 1-800-ACS-2345, or your local chapter.











*Despite New Clues,*  
***Alzheimer's***  
***Mystery***

*Remains Unsolved*

*by Ken Flieger*

***"He would just wander off."***

*Sometimes I'd find him in the neighborhood, as though he'd gone for a walk and got lost. Other times I'd get a phone call from a total stranger saying my husband was clear across town and would I please come and take him home."*

*Helen Stone (not her real name) is talking about her late husband, who died of Alzheimer's disease*



## ***Alzheimer's is rare in persons under 50, but strikes about 10 percent of people over 65 and nearly half of those 85 or older.***

more than a decade ago in his mid-80s. She is past 90 now, but she recalls her husband's last years vividly. "At first he couldn't remember things—where he'd left his book, what day it was, the names of people and things, even something he'd just said. Then it got worse."

Personality and behavior changes began to appear. Edgar Stone became irritable and depressed, but he resented and resisted offers of help. Within a couple of years, when she could no longer take care of him at home, Helen found a nursing home that would take her husband. Edgar spent the last months of his life there—bedridden, unable to speak, unable to recognize his wife or children.

The Stones' experience is typical of both the pattern of Alzheimer's disease in the population and the course it follows in individual patients. Alzheimer's is rare in persons under age 50, but the results of a large survey conducted by scientists at the Harvard Medical School show that Alzheimer's disease strikes about 10 percent of people over 65 and nearly half of those 85 or older. Memory loss, especially for recent events, is usually the first sign, followed by more profound and debilitating mental, behavioral, and bodily control impairments. If no other cause intervenes, Alzheimer's patients usually die after having infections, such as pneumonia, or other complications 3 to 20 years after the first signs appear.

Despite the devastating impact of Alzheimer's disease on patients, caregivers, and society at large, as recently as two decades ago the public and most health professionals were largely unfamiliar with the condition. Even today, with increased awareness fueled by frequent magazine and newspaper articles heralding "major" research advances against Alzheimer's, the full extent of Alzheimer's disease is difficult to calculate. Studies in the mid-1970s suggested that 2.5 million Americans had Alzheimer's. Now, the National Institute on Aging, one of the National Institutes of Health located in Bethesda, Md., believes as many as 4 million people in the United

States may be afflicted.

The Alzheimer's Association, a Chicago-based nonprofit research and support organization, estimates that more than 100,000 Americans die of Alzheimer's each year, which would make it the fourth leading cause of death among adults in the United States, after heart disease, cancer, and stroke. Dr. Creighton Phelps, the association's senior vice president of medical and scientific affairs, points out that Alzheimer's deaths are probably substantially underreported—attributed to pneumonia or cardiac arrest, when in fact Alzheimer's disease is the underlying cause of death.

The national Centers for Disease Control in Atlanta agrees. In an analysis of death certificate data, CDC investigators found a pronounced increase in the annual rate of Alzheimer's deaths—from 0.4 per 100,000 in 1979 to 4.2 per 100,000 in 1987. The CDC report noted that such a dramatic increase could have been caused by a genuine rise in the number of Alzheimer's patients, by more accurate reporting of Alzheimer's as the cause of death, or a combination of the two. It pointed out, significantly, that similar increases in Alzheimer's death rates have been reported from England, Australia, Norway, and Canada. But CDC cautions that, in conditions such as Alzheimer's disease that are often misdiagnosed and not recognized as the cause of death, figures on annual death rates may not reflect the extent of the public health problem.

### **Dead and Dying Brain Cells**

Many people continue to believe that confused, forgetful, and often bad-tempered elderly people are "senile" or suffering from hardening of the arteries of the brain, a condition that health professionals long accepted as a normal result of aging. If the signs of what is now recognized as Alzheimer's disease occurred in a person under 65, the patient was said to be suffering from pre-senile dementia—literally, mental deterioration before the onset of senility. That was what a German neurologist, Dr. Alois Alzheimer, described early

in this century in a 51-year-old woman who was forgetful, paranoid, and given to bizarre behavior. When he examined her brain at autopsy some four and a half years later, Alzheimer found not the signs of hardened arteries, but striking neurological changes not associated with any known illness.

Scientists now know that, unlike other dementing conditions, such as those caused by strokes, Alzheimer's disease has little if anything to do with the circulatory system. It results instead from massive damage to and loss of nerve cells in the brain. The cause or causes of this damage remains a mystery. Indeed, although it is generally believed that Alzheimer's is a specific disease and not a specific consequence of aging, it is not yet clear whether that is actually the case.

Robert Temple, M.D., director of FDA's Office of Drug Evaluation I, explains: "Certainly Alzheimer's is not an inevitable function of aging, and a small percentage of cases seem to have a familial or genetic component. But the same is true of many conditions that become more common with advancing age."

Temple points out, "With age, athletic skills decline, skin tone and subcutaneous tissue diminish, bone density falls, arteriosclerotic change occurs [influenced by diet], osteoarthritis progresses, cataracts develop, and hearing declines. But these changes take place at very different rates in different individuals. In many people they never occur. We really don't know yet whether Alzheimer's disease is a wearing out—a degenerative process—like those other changes, or a specific illness with, one would hope, potentially a specific way of preventing it.

"Sometimes it's hard to tell the difference between a specific disease and a consequence of aging, because people age at different rates. But anything that affects 50 percent of people over 85 is starting to look pretty 'natural.' Of course, even degenerative changes can be influenced by such things as diet, exercise, replacement therapy, etc., so that, whatever Alzheimer's disease really is, effective



treatment may indeed be possible.”

Whether or not Alzheimer’s is a specific disease or a function of aging, Americans today are more aware of the condition, because an aging population has undoubtedly brought a sharp increase in the number of people at risk of, or correctly diagnosed with, Alzheimer’s disease.

Studies in the mid-1970s suggested that 2.5 million Americans had Alzheimer’s. Now the National Institute on Aging estimates that 4 million people in the United States may be afflicted, and the Alzheimer’s Association calculates the cost of care for Alzheimer’s patients at between \$80 billion and \$90 billion a year. Those numbers could more than triple by the year 2050 if no way is found to prevent or cure the disease and if, as demographers predict, increasing millions of Americans survive into the eighth and ninth decades of life or beyond.

### Looking for Answers

Alzheimer’s can only be positively diagnosed by examining brain tissue. People who have symptoms of Alzheimer’s are evaluated—and clinically diagnosed—on the basis of medical history, physical examination, laboratory tests to identify other possible causes of dementia, and neurological examination that includes tests of mental performance. Although a standard diagnostic procedure—a blood or skin test, for example—has yet to be developed, clinical evaluation is believed to give a correct diagnosis in a high percentage of cases.

The sharply rising numbers of patients and heightened awareness of the terrible impact of this disease have given rise to vastly expanded efforts to determine what causes Alzheimer’s and discover what, if anything, can be done to control, cure or prevent it. These studies have added much new information but so far no breakthroughs.

In recent years, laboratory and clinical research has revealed a detailed picture of the devastation that Alzheimer first described in 1906—a picture of brain cells gripped in a kind of lethal chaos. The in-

ner workings of the brain are still largely hidden territory, but neurologists and other scientists know a good deal more about the brain’s architecture and chemistry than they did only a few years ago. Their work is also beginning to clarify the nature of Alzheimer’s disease.

The billions upon billions of brain cells (neurons) that manage everything from moving a finger to balancing a checkbook accomplish these wonders by a complex sequence of chemical reactions and interactions. When neurons are excited—for example, when a sensory nerve notifies the brain of a pinprick—they release chemicals that move across the spaces between neighboring cells (synapses). These chemical neurotransmitters stimulate adjacent neurons to “fire,” releasing their own chemical messengers. In an instant, the process is repeated along hundreds or thousands of nerve pathways, enabling the brain to interpret an incoming signal and direct an appropriate response. (Higher or-

ders of brain activity, such as memory, though vastly more complicated, work essentially the same way. (See “Memories Are Made of This,” *FDA Consumer*, September 1989.)

In Alzheimer’s disease, the orderly functioning of brain cells falters and eventually fails. The brains of Alzheimer’s disease patients examined at autopsy show two distinctive abnormalities: Nerve fibers are twisted into tangles that render them useless; and the tips of decaying and dead neurons are mired in a blob of an abnormal protein, called beta amyloid, to form “plaques.” Both plaques and tangled nerve fibers are present to a limited extent in the brains of some older persons who don’t have Alzheimer’s disease. But in Alzheimer’s patients the destruction is massive and causes the progressive loss of intellectual and motor control functions characteristic of the disease’s advanced stages.

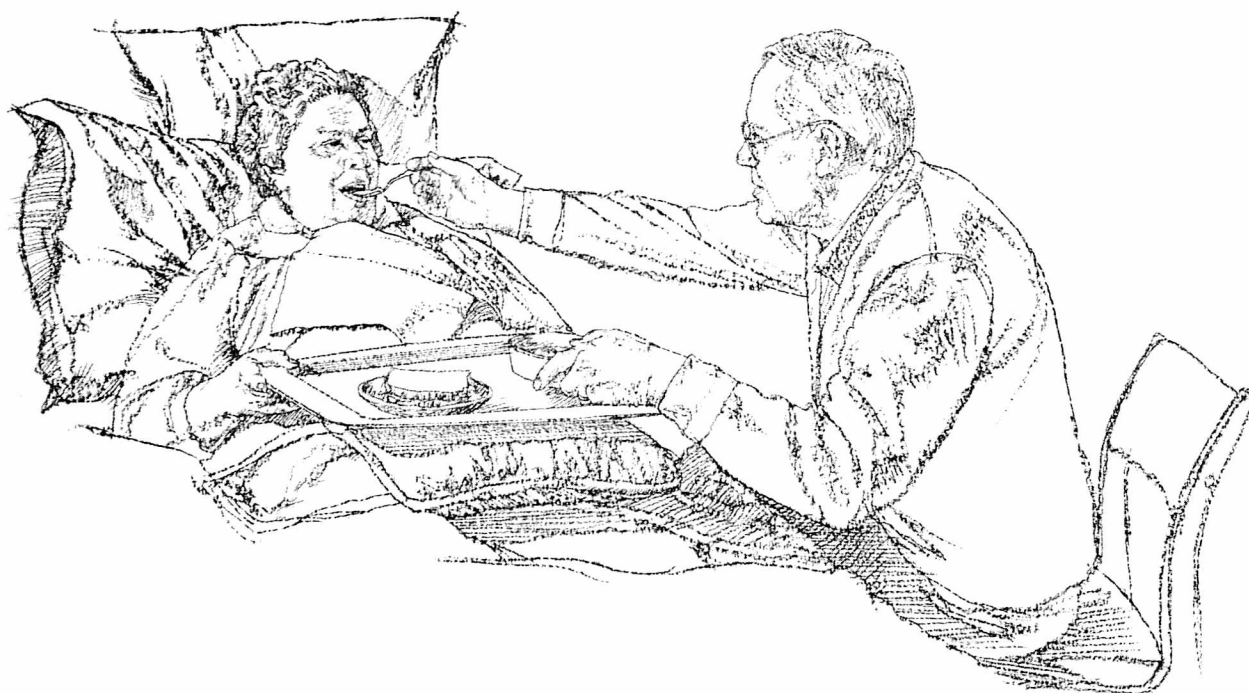
The tangles and plaques of Alzheimer’s



*The brain of a patient with Alzheimer’s disease has specific areas riddled with “plaques” (shown here as orange dots). These plaques form at the tips of dead and decaying neurons and are composed of an abnormal protein called beta amyloid.*



## Help for Helpers



Each case of Alzheimer's disease has at least two victims, the patient and the person or persons who serve as caregivers. It's been said that Alzheimer's care-givers put in a 36-hour day in an ordeal that may continue—and become progressively more demanding—for many years.

In the last stages of their illness, Alzheimer's patients require hospital or nursing home care, but the Alzheimer's Association estimates that 70 percent of care is provided at home by a family member, often aided by trained home-care workers. Finding support, helpful information, and ways to get a break from the continuous demands of caring for an Alzheimer's patient is vital for patients and care-givers alike. One of

the first things an Alzheimer's care-giver needs to do is find out where such help can be found. Here are some places to turn:

- Alzheimer's Disease and Related Disorders Association, Inc., 919 N. Michigan Ave., Suite 1000, Chicago Ill. 60611; telephone (1-800) 272-3900.

The Alzheimer's Association is a non-profit organization devoted to research, information and education, and support activities. It has 210 chapters, 1,600 support groups, and 30,000 members nationwide.

- "Confused Minds, Burdened Families: Finding Help for People with Alzheimer's and Other Dementias." A detailed discussion and inventory of sources of help for Alzheimer's vic-

tims, published in July 1990 by the U.S. Congress's Office of Technology Assessment. Contact the U.S. Government Printing Office, Washington, D.C. 20402.

- The National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20892. Two NIH components, the National Institute on Aging and the National Institute of Neurological Disorders and Stroke, have major research programs relating to Alzheimer's disease and information about advances in scientific understanding that can lead to better care for Alzheimer's victims. ■

—K.F.



disease are associated with a pronounced decline in levels of the neurotransmitter acetylcholine. Although the role of acetylcholine in Alzheimer's disease remains unclear, when its loss is minimal in the early stages of the illness, patients are only mildly impaired. But as more neurons are destroyed, acetylcholine levels can fall to 20 percent or even 10 percent of normal. By then, virtually all cognitive and sensory brain function is lost—not just memory, but speech, thought processes, motor coordination, and bladder and bowel control.

Efforts to pinpoint the cause of Alzheimer's disease are moving on several paths. The observation that some families have higher-than-expected numbers of cases (especially in persons under 65)—so-called “familial Alzheimer's disease”—has prompted speculation that an altered gene may be responsible. Research so far has not confirmed the gene theory. Other theories implicate aluminum, which is sometimes found in unusually large concentrations in the brain cells of Alzheimer's patients, or a virus that triggers the onset of Alzheimer's after lying dormant for decades. None of this work has produced conclusive findings about the cause—or causes—of Alzheimer's.

### Seeking Treatments

The search for one or more explanations continues, and some authorities are confident that the effort will eventually succeed. But even if it doesn't, as FDA's Temple points out, “We have effective drugs for a good many diseases whose fundamental cause we still don't understand. It would help, of course, if we had an animal model of Alzheimer's to work with. That could aid drug research tremendously.” As matters now stand, Temple says, “efforts to develop anti-Alzheimer's drugs that make a significant difference have been frustrating. Still, there is a lot of enthusiasm for trying.”

Some of the symptoms of Alzheimer's disease—depression, anxiety, agitation, insomnia—can be treated with a variety of drugs that are available by prescription. But there is no specific treatment for the

disease itself. Studies of drugs intended to affect neuron destruction or plaque formation and of agents to restore intellectual capacity, such as memory and reasoning ability, are under way at industrial and academic facilities throughout the United States and in Europe. A number of investigational agents are undergoing clinical trials, and more are in the preclinical stages of the drug development “pipeline.”

Tacrine, or THA, a drug to increase levels of acetylcholine, is the only drug treatment for Alzheimer's disease for which a

favorable effects,” said Dr. Kessler, “the effects were very small and of uncertain real benefit, and there is still concern about possible liver toxicity.”

The treatment IND protocol for tacrine allows for the treatment of up to 3,000 patients beginning at a daily dose of 40 milligrams for six consecutive weeks. Patients who show no liver toxicity at that dose will receive 80 milligrams per day for six more consecutive weeks. The daily dose then may be increased to 120 milligrams per day for six weeks. Researchers hope

**“While it's clear that tacrine had some favorable effects [in clinical studies], the effects were very small . . . and there is still concern about possible liver toxicity.”**

**—FDA Commissioner David A. Kessler, M.D.**

marketing application is currently under review by FDA. The agency approved a “treatment IND” program for tacrine last December, to begin in February. Treatment IND regulations allow patients with serious or life-threatening conditions to be treated with experimental drugs (drugs under study but not approved) for which a certain amount of safety and efficacy information has been obtained.

Announcing the treatment IND for tacrine, FDA Commissioner David A. Kessler, M.D., said, “FDA has approved expanded use of tacrine based on evidence that the drug produced a small improvement in mental function in some patients taking the drug during controlled clinical trials and evidence that larger doses might have a greater effect.”

THA causes liver damage in many patients that may outweigh its benefits. “While it's clear that tacrine had some fa-

that the study might eventually include a 160-milligram daily dose.

Apart from the desire to ease the burden of Alzheimer's disease on patients, their families, and the health-care system, drug developers are motivated by the potential market for an effective Alzheimer's drug, estimated at \$1 billion a year in this country alone.

A drug or drugs that make a substantial difference in the lives of Alzheimer's disease patients and their care-givers may not be around the corner. According to Temple, detecting small effects of such drugs can be difficult. But he adds, “When an Alzheimer's drug with a good-sized effect does come along, clinical investigators and FDA reviewing scientists should have no trouble identifying it.” ■

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







# Erasing Skin Marks With *LASERS*

by Ricki Lewis, Ph.D.

**P**ort-wine stains can make life difficult for people of all ages. Donna Arnds, a 23-year-old from North Los Angeles, has marks on her nose, eyelids and lips. In high school, she never attended a dance because, she says, no one wanted to be seen with her. Anne Plescia, 40, of Ithaca, N.Y., was often mistaken to be mentally retarded because of her facial birthmarks. "I've been in conversations where they will only address my husband, assuming I have no intellect," she says.

Thousands of parents have agonized as their birthmarked children approach school age "when the kids are old enough to be cruel," notes Linda Margalith of Beverly Hills, Calif., mother of 3-year-old Alexa.

For Gina Brass of Escondido, Calif., the suffering was even worse. Many people who saw the marks on her 6-year-old daughter's cheek and chin would accuse her of physically abusing the child, causing her "bruises." These and many other people with birthmarks have been helped by a new type of treatment using laser devices, which are regulated by the Food and Drug Administration. The treatments for benign (noncancerous) skin lesions possible with lasers extend beyond birthmarks, to include liver spots, spider veins, residual redness following plastic surgery on the nose, and even tattoo removal.

The temporary redness, swelling, and a bruised appearance that can occur after la-

ser treatment of the skin are preferred by some patients to the discomforts of older methods, which include freezing tissue with liquid nitrogen, electrosurgery, scraping off (curettage) the affected area, treating the area with chemicals such as Retin A (tretinoin) or acids, or masking marks with make-up. When used by physicians who are trained in the use of a laser, results can be quite dramatic. But in less well-trained hands, a laser can cause damage and scarring, just as traditional surgery or scraping can.

Lasers used in these treatments include: carbon dioxide, argon, continuous tunable dye, ruby, copper vapor, and flashlamp-pumped pulsed dye (see accompanying article). Here is a rundown on what these new lasers can do when applied to the skin.

## Port-Wine Stains

A beet-colored mark splashed across a small face can be the butt of many children's jokes.

"Reaction depends on the individual child, but especially when one hits school age, the teasing is unbelievable," says Tina Dawn, president of the National Congenital Port-Wine Stain Foundation in New York City. "I've known children to throw their eyes out of whack because they constantly keep their heads down to hide the stain," she adds. For these children, successful treatment can literally turn their lives around.

Because the idea of a laser can be frightening, the staff at the University of Massa-

chusetts Medical Center in Boston gives each patient a Raggedy Ann or Raggedy Andy doll that has a matching mark made in red crayon. The doll receives a laser treatment to show the child how the mark disappears, and to quiet fears.

To remove a port-wine stain, a small area on the patient's arm is first tested, and then the mark is treated. Anesthesia is not used unless the area to be treated is extensive, and then local anesthesia is used.

The laser feels like a small rubber band being snapped against the skin. For the first 24 hours, the area swells and reddens, the signs of the body's immune response to the vaporized blood vessels in the birthmark. The area turns a bluish-gray with purplish-red spots for 7 to 10 days. The spots fade, and the treated area continues to lighten over the next eight weeks.

But it may be difficult to locate a physician who is experienced with this relatively new procedure. "The average dermatologist has yet to have a laser available, but more and more are getting them," says Dawn. "Now, only specialized medical centers and some dermatologists have them."

Using the flashlamp-pumped pulsed dye laser to treat port-wine stains requires more sessions to fade the mark than with other lasers, and bumpy lesions do not respond well.

Still, this type of laser is currently the one recommended to treat children—and the sooner the lesion is treated, the better the results. Blas Reyes, M.D., and Roy Geronemus, M.D., of the New York Uni-



***T***he laser feels like a small rubber band being snapped against the skin.



*The photo at the far left shows a port-wine stain on a woman's neck before laser treatment. At left, the same area after laser treatment.*

*(Photos courtesy of Robert Hutcherson, M.D., St. John's Hospital, Santa Monica, Calif.)*

versity Medical Center, treated port-wine stains in 73 patients between the ages of 3 months and 14 years, and discovered three reasons to zap a port-wine stain as soon as possible:

- the skin thickens up to age 20, when it becomes more difficult to treat
- the extraneous blood vessels are smaller in diameter in a youngster
- the stain itself occupies a smaller area in the young.

### **Spots, Freckles, Moles, and Spiders**

A cousin to the "vascular lesion laser" used to treat port-wine stains is a pigmented lesion laser, which FDA cleared for use in May 1991. It is used to treat lentigines (also known as age, sun or liver spots), moles, freckles, and brown birthmarks, which millions of people have. This laser zeroes in on melanin, the pigment found in the epidermis, the outer skin layer.

The pulse delivered by the pigmented lesion laser lasts one-third of a millionth of a second, and covers an area the size of a pea. It, too, feels like a rubber band snap. Two weeks after treatment, the skin peels away and is replaced from beneath with a new, unblemished epidermis.

"Many people develop solar lentigines early in adult life, particularly people from the Southwest. Not only are these lesions unsightly, but they are associated with old age. Removing the lesions seems to enhance people's self-confidence significantly," says Joseph Morelli, M.D., assistant professor of dermatology and pediatrics at the University of Colorado School of Medicine in Denver.

Too much sun is linked to a number of types of skin lesions. "Exposure to the sun thins the skin, making it more transparent. It also causes enlargement of the blood vessels on the skin's surface, which in turn makes these vessels more visible. Plastic surgeons refer to these red, unsightly vessels as telangiectasias, or 'spiders,'" says Joel M. Noe, M.D., assistant professor of plastic and reconstructive surgery at Harvard Medical School.

Often, spiders are caused by chronic overexposure to the sun, but they may also result from liver disease or occur in pregnancy due to a change in the way the body processes estrogen. In addition, they can be a side effect of oral contraceptives or prolonged use of topical corticosteroid drugs. They may also occur with a little-understood condition called rosacea, in

which the middle third of the face is affected.

"These conditions responsible for red blood vessels on the face are incredibly common in our society, especially among the fair-skinned who have had lots of sun exposure," Noe adds.

He uses argon or pulsed dye lasers to treat spiders. "It can be done in the doctor's office using local anesthesia. The treatment produces a mild sensation of heat and a feeling like pinpoints lightly touching the skin," he says. Usually one or two treatments are needed.

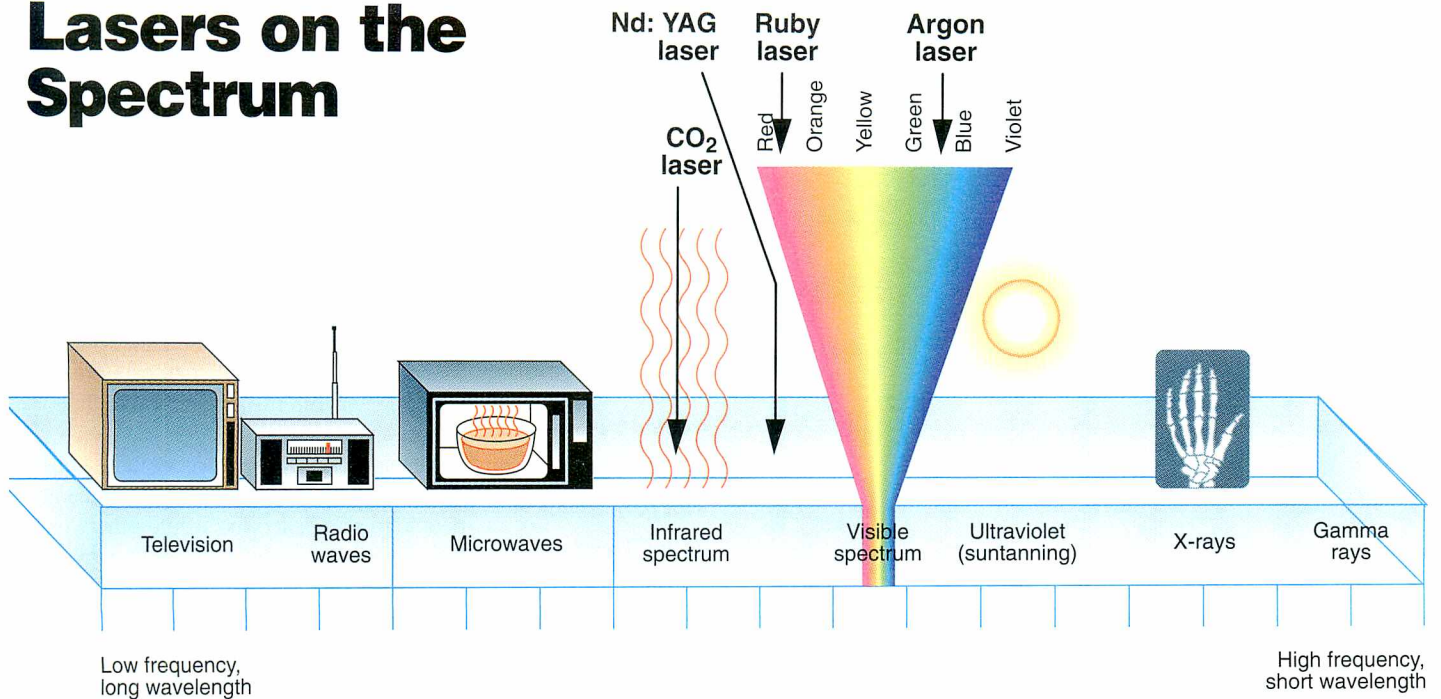
Ultraviolet exposure from excessive sunning can wreak havoc on recovery from plastic surgery on the nose, producing redness called "post-rhinoplasty red nose" as new blood vessels appear on the bridge of the nose. This is part of the healing process and is preventable by minimizing sun exposure. It can be covered with make-up, or treated with an argon laser, says Noe.

### **Bleaching Cream Backfires**

A 53-year-old black woman had used an over-the-counter "skin whitener cream" to even out her complexion for three months when she noticed just the opposite



# Lasers on the Spectrum



*Carbon dioxide and Nd:YAG lasers emit infrared energy. The tunable dye and argon lasers emit blue light, and the ruby laser emits red light.*

## Laser Basics

Since the mid-1960s, lasers have proven to be powerful surgical tools. The word “laser” is actually an acronym for “light amplification by stimulated emission of radiation,” which means that the intense and narrow beam of light is of one wavelength. Ordinary “white” sunlight, in contrast, is a continuum of light of many wavelengths, corresponding to the colors of the spectrum plus the infrared (heat) and ultraviolet wavelengths that sandwich them.

A medical laser device includes a source of electricity, mirrors to direct the beam, a crystal or gas that is stimulated to emit the light, and tubing to deliver the energy. Design of the instrument is tailored to specific uses.

“The diameter of the light beam is picked to match the diameter of the area to be treated,” says Joel M. Noe, M.D., assistant professor of plastic and reconstructive surgery at Harvard Medical School. “For example,” he explains, “to treat a blood vessel 1 millimeter in diameter, you would use a 1-millimeter handpiece. If the target is a group of vessels, you would use a larger diameter handpiece.”

About 5 percent of the nation’s 10,000 plastic surgeons use lasers, says Noe.

FDA regulates lasers, including those for medical uses. “FDA evaluation is of the device itself. We try to find out if the

device to be marketed is equivalent to another device on the market. It does not have to be superior. We look at safety and efficacy,” says Sankar Basu, Ph.D., a physicist with FDA’s surgical devices evaluation branch.

The radiation a laser emits depends on the chemical through which it passes. A carbon dioxide (CO<sub>2</sub>) laser, for example, emits energy that can heat water; it can vaporize watery tissue near the body’s surface. In dermatology, CO<sub>2</sub> lasers are used to remove warts, lip lesions, and ingrown toenails. CO<sub>2</sub> lasers, however, have no effect on blood, which permeates tissue beneath the skin’s outer layer.

The blue-green emission of an argon laser is suited for tissue with a lush blood supply. It passes right through watery tissue, but is absorbed by hemoglobin, the vibrant red protein in red blood cells that carries oxygen to the body’s tissues. In a port-wine stain, hemoglobin courses through the abnormally numerous blood vessels in the underlying skin layer. An argon laser can destroy these extra vessels, lightening the marks in 80 percent of adult cases. But a child’s delicate skin can be badly scarred by the powerful argon laser.

A gentler laser for benign skin conditions is a flashlamp-pumped pulsed dye laser, which FDA cleared for use in 1987. The device consists of a dye (rhodamine

in methanol) that is excited by high-intensity flashlamps to release photons, which are tiny subatomic packets of light energy. Like an argon laser, the wavelength of the pulsed dye laser is absorbed by hemoglobin, but it is less powerful. When aimed at the skin, a few brief pulses safely zap away the blood vessels. The trick is to apply the light pulses faster than the blood vessels can dissipate the heat. A pulse of this laser takes 360 to 450 microseconds, and the blood vessels need about 3 milliseconds (equal to 3,000 microseconds) to recover. In contrast, an argon laser pulse typically takes five-hundredths of a second, long enough to damage much more than the stain, and thereby cause a scar to form.

The ability of the flashlamp-pumped pulsed dye laser to treat port-wine stains was first reported in the Feb. 16, 1989, *New England Journal of Medicine* by Oon Tian Tan, M.D., and colleagues, of the Boston University Medical Center. Since then, other studies have confirmed their findings—and some 60,000 persons have had their birthmarks removed worldwide, according to the Candela Laser Corp. in Wayland, Mass., which markets the device and keeps track of its use. ■

—R.L.





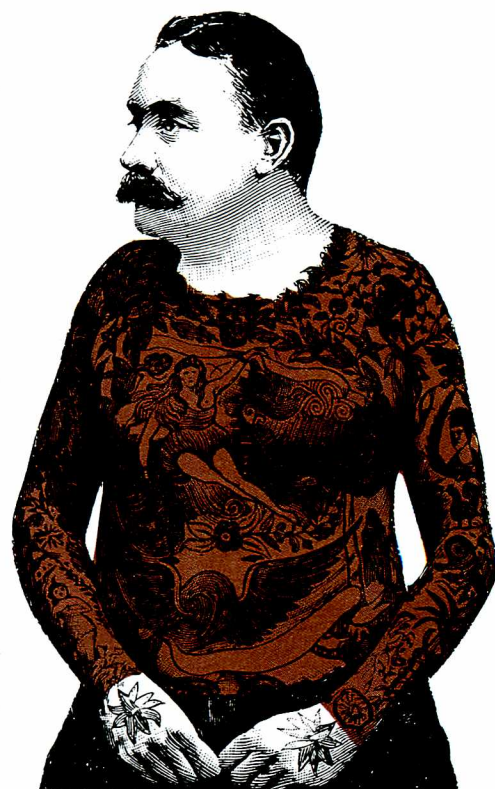
*A physician uses a pulsed dye laser called the Candela Vascular Lesion Laser to remove a port-wine stain from a woman's cheek. (Photo reprinted with permission of the Worcester Telegram & Gazette. Copyright 1989)*

pigments used in tattoos. The skin initially turns white for 10 to 20 minutes, then swells and turns red, feeling like a sunburn. Although the skin stays red for one to three weeks, healing takes 10 to 14 days, and fading continues for months. There are no open wounds. The researchers treated 163 tattoos on 80 patients and found that black and blue tattoos more than 10 years old responded best to the treatment.

The success of laser surgery in treating benign skin lesions has encouraged many people to seek help who would otherwise have relied on disguising or hiding their blemishes. Lasers have also helped thousands of others who were unhappy with the results of more traditional treatments. In the future, this kind of laser surgery may become more common for an increasing number of people with problems that are more than skin deep. ■

*Ricki Lewis, a writer in Scotia, N.Y., teaches biology at the State University of New York at Albany.*

***Since 6000 B.C., people have had their skin tattooed—and then later regretted it.***



effect—a sooty, bluish-black raised area on her face. Her doctors first tried to lighten the area by treatments with the acne drug Retin-A, cryosurgery with liquid nitrogen, and finally by peeling off the skin pigment with trichloroacetic acid. These dermabrasion procedures worked on parts of her face, but not on the thin-skinned areas near her eyes and nose. She consulted Edgar Smith, M.D., and his colleagues at the University of Texas Medical Branch in Galveston, who had reported success with a carbon dioxide laser.

Sooty marks resulting from lightening creams are due to the ingredient hydroquinone, which can cause pigmented fibers to be gradually laid down in the dermis (the underlying skin layer). In the mid 1970s, doctors in South Africa began reporting the mysterious dark spots on the faces of black people who had used products containing 6 to 8 percent hydroquinone, and, as a result, the amount was limited in many countries, including the United States, to 2 percent. Still, in the 1980s, cases were reported among U.S. blacks.

So far, only blacks have been reported

to be affected, and their skin responses range from redness and mild pigmentation, to dark coloration, to the appearance of nodules. Although the CO<sub>2</sub> laser is now the only one used on these blemishes, Smith suggests that a ruby laser may work even better, considering the recently reported success of this type of laser in removing tattoos.

#### **Tattoos Skidoo**

Since 6000 B.C., people have had their skin tattooed—and then later regretted it. Unfortunately, treatments to remove the marks often marred the skin further. Ronald Wheeland and co-workers of the University of California at Davis reported in the December 1990 *Journal of Dermatological and Surgical Oncology* that a preliminary study indicated treatment with a ruby laser to remove tattoos is “vastly superior” to standard methods, such as dermabrasion and surgical removal.

The ruby laser works much the way the pigmented lesion laser does, and also feels like a rubber band snap. The laser light is absorbed by melanin and the carbon-based



On the  
*Teen Scene*

# EaTiNg DiSORDERS

## Require Medical Attention

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

*by Dixie Farley*



**F**or reasons that are unclear, some people—mainly young women—develop potentially life-threatening eating disorders called bulimia nervosa and anorexia nervosa. People with bulimia, known as bulimics, indulge in bingeing (episodes of eating large amounts of food) and purging (getting rid of the food by vomiting or using laxatives). People with anorexia, whom doctors sometimes call anorexics, severely limit their food intake. About half of them also have bulimia symptoms.

The National Center for Health Statistics (NCHS) estimates that 10,000 bulimia cases and 11,000 anorexia cases were diagnosed in 1989, the latest year for which statistics are available. Studies indicate that by their first year of college, 4.5 to 18 percent of women and 0.4 percent of men have a history of bulimia and that as many as 1 in 100 females be-



## Disorders' Definitions

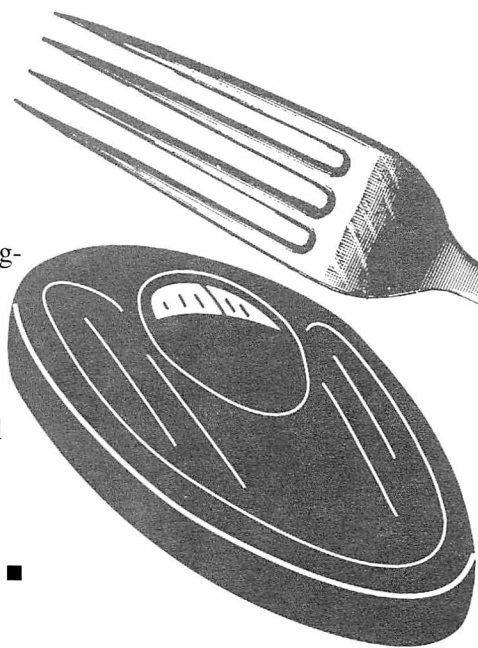
According to the American Psychiatric Association, a person diagnosed as bulimic or anorectic must have all of that disorder's specific symptoms:

### ***Bulimia Nervosa***

- recurrent episodes of binge eating (minimum average of two binge-eating episodes a week for at least three months)
- a feeling of lack of control over eating during the binges
- regular use of one or more of the following to prevent weight gain: self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise
- persistent over-concern with body shape and weight.

### ***Anorexia Nervosa***

- refusal to maintain weight that's over the lowest weight considered normal for age and height
- intense fear of gaining weight or becoming fat, even though underweight
- distorted body image
- in women, three consecutive missed menstrual periods without pregnancy. ■



tween the ages of 12 and 18 have anorexia.

Males account for only 5 to 10 percent of bulimia and anorexia cases. While people of all races develop the disorders, the vast majority of those diagnosed are white.

Most people find it difficult to stop their bulimic or anorectic behavior without professional help. If untreated, the disorders may become chronic and lead to severe health problems, even death. NCHS reports 67 deaths from anorexia in 1988, the latest year for which it has figures, but does not have similar information on bulimia.

As to the causes of bulimia and anorexia, there are many theories. One is that some young women feel abnormally pressured to be as thin as the "ideal" portrayed by magazines, movies and television. Another is that defects in key chemical messengers in the brain may contribute to the disorders' development or persistence.

### **The Bulimia Secret**

Once people begin bingeing and purging, usually in conjunction with a diet, the

cycle easily gets out of control. While cases tend to develop during the teens or early 20s, many bulimics successfully hide their symptoms, thereby delaying help until they reach their 30s or 40s. Several years ago, actress Jane Fonda revealed she had been a secret bulimic from age 12 until her recovery at 35. She told of bingeing and purging up to 20 times a day.

Many people with bulimia maintain a nearly normal weight. Though they appear healthy and successful—"perfectionists" at whatever they do—in reality, they have low self-esteem and are often depressed. They may exhibit other compulsive behaviors. For example, one physician reports that a third of his bulimia patients regularly engage in shoplifting and that a quarter of the patients have suffered from alcohol abuse or addiction at some point in their lives.

While normal food intake for a teenager is 2,000 to 3,000 calories in a day, bulimic binges average about 3,400 calories in 1 1/4 hours, according to one study. Some bulimics consume up to 20,000 calories in binges lasting as long as eight hours. Some spend \$50 or more a day on food and may resort to stealing food or money

to support their obsession.

To lose the weight gained during a binge, bulimics begin purging by vomiting (by self-induced gagging or with an emetic, a substance that causes vomiting) or by using laxatives (50 to 100 tablets at a time), diuretics (drugs that increase urination), or enemas. Between binges, they may fast or exercise excessively.

Extreme purging rapidly upsets the body's balance of sodium, potassium, and other chemicals. This can cause fatigue, seizures, irregular heartbeat, and thinner bones. Repeated vomiting can damage the stomach and esophagus (the tube that carries food to the stomach), make the gums recede, and erode tooth enamel. (Some patients need all their teeth pulled prematurely). Other effects include various skin rashes, broken blood vessels in the face, and irregular menstrual cycles.

### **Complexities of Anorexia**

While anorexia most commonly begins in the teens, it can start at any age and has been reported from age 5 to 60. Incidence among 8- to 11-year-olds is said to be increasing.

Anorexia may be a single, limited epi-





*Once people begin  
bingeing and purg-  
ing, the cycle easily  
gets out of control.*

sode with large weight loss within a few months followed by recovery. Or it may develop gradually and persist for years. The illness may go back and forth between getting better and getting worse. Or it may steadily get more severe.

Anorectics may exercise excessively. Their preoccupation with food usually prompts habits such as moving food about on the plate and cutting it into tiny pieces to prolong eating, and not eating with the family.

Obsessed with weight loss and fear of becoming fat, anorectics see normal folds of flesh as "fat" that must be eliminated. When the normal fat padding is lost, sitting or lying down brings discomfort not rest, making sleep difficult. As the disorder continues, victims may become isolated and withdraw from friends and family.

The body responds to starvation by slowing or stopping certain bodily processes. Blood pressure falls, breathing rate slows, menstruation ceases (or, in girls in their early teens, never begins), and activity of the thyroid gland (which regulates growth) diminishes. Skin becomes dry, and hair and nails become brittle. Lightheadedness, cold intolerance, constipation, and joint swelling are other symptoms. Reduced fat causes the body temperature to fall. Soft hair called lanugo forms on the skin for warmth. Body chemicals may get so imbalanced that heart failure occurs.

Anorectics who additionally binge and purge impair their health even further. The late recording artist Karen Carpenter, an

anorectic who used syrup of ipecac to induce vomiting, died after buildup of the drug irreversibly damaged her heart.

#### **Getting Help**

Early treatment is vital. As either disorder becomes more entrenched, its damage becomes less reversible.

Usually, the family is asked to help in the treatment, which may include psychotherapy, nutrition counseling, behavior modification, and self-help groups. Therapy often lasts a year or more—on an outpatient basis unless life-threatening physical symptoms or severe psychological problems require hospitalization. If there is deterioration or no response to therapy, the patient (or parent or other advocate) may want to talk to the health professional about the plan of treatment.

There are no drugs approved specifically for bulimia or anorexia, but several, including some antidepressants, are being investigated for this use.

If you think a friend or family member has bulimia or anorexia, point out in a caring, nonjudgmental way the behavior you have observed and encourage the person to get medical help. If you think you have bulimia or anorexia, remember that you are not alone and that this is a health problem that requires professional help. As a first step, talk to your parents, family doctor, religious counselor, or school counselor or nurse. ■

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

## ***For More Information***

If you want more information about bulimia and anorexia, send your request and a stamped, self-addressed, business-size envelope to:

American Anorexia/Bulimia Association,  
Inc.  
418 E. 76th St.  
New York, N.Y. 10021  
(212) 734-1114

Bulimia, Anorexia Self-Help  
6125 Clayton Ave., Suite 215  
St. Louis, Mo. 63139  
(1-800) 227-4785

National Association of Anorexia Nervosa  
and Associated Disorders, Inc.  
P.O. Box 7  
Highland Park, Ill. 60035  
(708) 831-3438







NO

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Bottom

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Treating

Hemorrhoids

*by Dori Stehlin*

Say the word “hemorrhoids” to just about anyone and they will either roll their eyes, moan or both. Invariably they will want to change the subject.

According to the National Institutes of Health, about half the U.S. population over 50 have hemorrhoids.

“Hemorrhoids are one of the most common complaints a physician must evaluate,” agrees Lee E. Smith, M.D., director of the division of colon and rectal surgery at the George Washington University Medical Center, Washington, D.C.

Common, but rarely a serious risk to health, hemorrhoids are the result of too much pressure on the hemorrhoidal veins in the rectum. The strain of constipation, diarrhea and pregnancy can cause the veins to swell. Other factors such as obesity and liver disease can also increase pressure and cause hemorrhoids.

There are two kinds of hemorrhoids—internal and external [see illustration]. Frequently, the only sign that internal hemorrhoids exist is bright red blood that appears on the surface of the stool, in the toilet bowl, or on the toilet paper. But, if the pressure and swelling continue, the hemorrhoidal veins may stretch out of shape, sometimes so much that they bulge through the anus to the outside of the body.

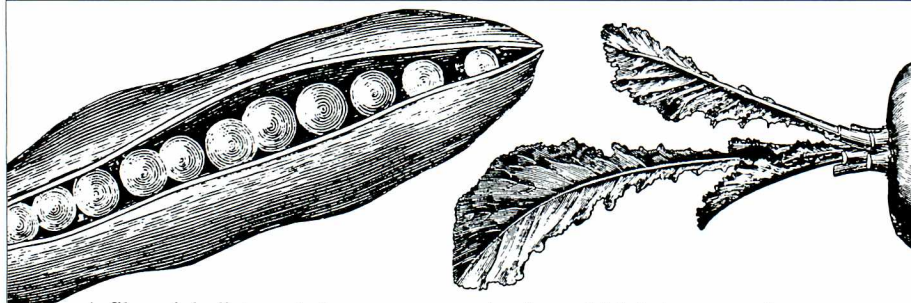
The veins around the anus can also become swollen, causing external hemorrhoids. These swollen veins bleed easily, either from straining or rubbing, and irritation from draining mucus may cause itching in the anal area. If blood clots form in these hemorrhoids, the pain can be severe.

“If you see blood, it’s probably hemorrhoids,” says Smith. Hemorrhoids are the most common source of bleeding from the rectum and the anus. However, if the bleeding lasts for more than a couple of days, it’s important to see a doctor for an exam. Smith stresses that a “thorough physical exam, not just talking about the symptoms” is essential.

“The unfortunate thing is every year I see somebody who has been seeing blood and they were treated as hav-



# Preventing Constipation



A fiber-rich diet can help prevent constipation, which is important because the strain caused by constipation is how many hemorrhoid problems begin.

Good sources of fiber include:

- potatoes
- beans—kidney, navy, lima, pinto
- whole-grain breads
- bran
- fresh fruits
- vegetables, especially asparagus, brussels sprouts, cabbage, carrots, cauliflower, corn, peas, kale, and parsnips.

It will also help to limit these low- or no-fiber foods: ice cream, soft drinks, cheese, white bread, and meat. ■

ing hemorrhoids without really being examined, and they had a cancer,” he says.

Treatment for hemorrhoids depends not only on the severity of the symptoms, but also on the patient’s reaction to those symptoms.

“Hemorrhoids don’t cause cancer; they’re a nuisance,” says Smith. “Rarely do they cause severe anemia and rarely do they cause something that is hazardous to health. If the patient doesn’t mind, then let them live with the hemorrhoids.”

Even though he’s a surgeon, Smith considers surgery an option only after everything else has failed.

## Relieving the Pressure

The first step in treating hemorrhoids is to relieve the pressure and straining. This can often be done by controlling constipation with a high-fiber diet, according to Barbara Frank, M.D., director of the division of gastroenterology at the Crozer-Chester Medical Center, Chester, Pa.

Eating the right amounts of bran (the outer coating of grains, available mainly as cereals), as well as fruits, vegetables, and whole grains results in a soft, bulky stool that is easily eliminated without strain or pressure on the hemorrhoidal

veins. (See box for list of good fiber sources.)

“Bran is the cheapest way to go,” says Smith, who also recommends bulk stool softeners (brand-name products include FiberCon, Metamucil, Citracil, and Serutan) as a way to relieve pressure and straining.

Lots to drink, as long as it isn’t alcohol, which can actually cause dehydration, is also important for the regularity that can relieve hemorrhoids you already have and prevent new ones.

People should drink “several glasses [of liquid] a day, and it doesn’t have to be just water,” says Marilyn Stephenson, a registered dietitian with FDA’s Center for Food Safety and Applied Nutrition. “Fruits and vegetables are high in fluids, too.”

“Several” may seem a little too fluid an amount, but people’s needs vary, sometimes daily, depending on things like the weather or exercise.

“Especially in hot weather, a glass [of water] every couple of hours is very reasonable,” says Smith.

One thing to avoid when trying to relieve constipation is any laxative other than a stool softener, says Smith. Other laxatives frequently cause diarrhea, which

can be just as rough on the hemorrhoidal veins as straining due to constipation, he explains.

Besides an improved diet, other simple steps to relieve the irritation some hemorrhoids cause include:

- warm soaks (sitz baths) three or four times a day
- cold packs
- good hygiene. (Be gentle about cleaning, though. Frank recommends using a soft, moist pad or even rinsing in the shower as an alternative to wiping.)

## OTC Remedies

If necessary, there are several nonprescription drugs available that can help relieve certain symptoms of hemorrhoids. FDA’s review of those drugs, published in August 1990, found 33 active ingredients safe and effective for protecting the skin, reducing swelling, or relieving discomfort, itching and inflammation. At the same time, however, FDA banned more than 30 other ingredients that have not been proven safe and effective.

Most of the approved ingredients are for external use on the skin, but some may also be used on mucous membranes just inside the rectum. The best drug depends on the particular individual’s symptoms, and it may be advisable to consult a doctor or pharmacist about which one to buy, says William E. Gilbertson, director of FDA’s division of over-the-counter drug evaluation.

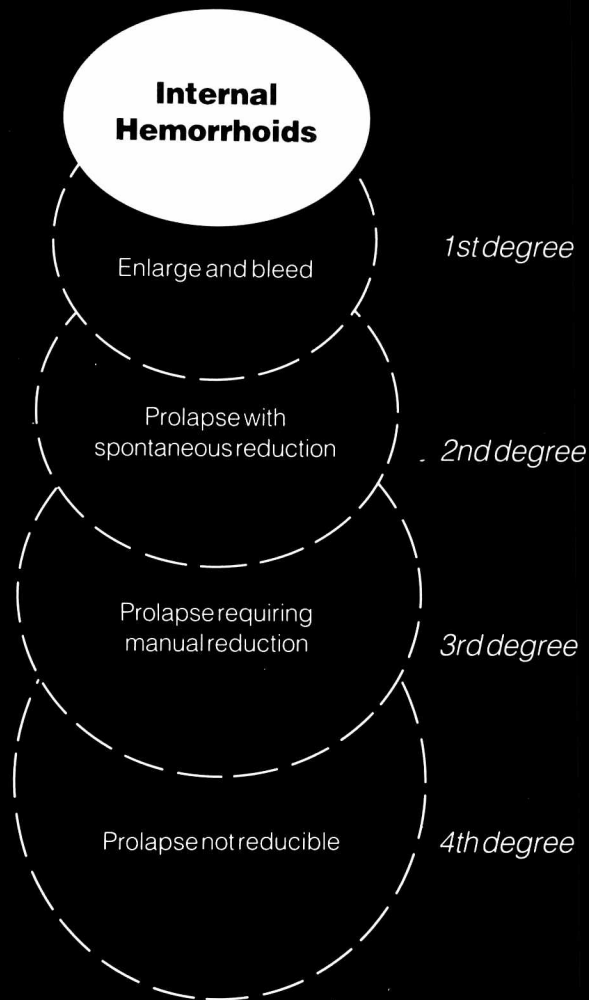
No ingredients to relieve pain, soreness and burning were approved for internal use because there are no nerve endings inside the rectum.

Internal hemorrhoids “don’t hurt and they don’t itch,” says Smith. “Pain means a fissure [break in the skin] or a thrombosed [blood-clot-filled] external hemorrhoid, but it doesn’t mean internal hemorrhoid problems.”

Manufacturers had until August 1991, when the FDA regulations went into effect, to reformulate products that contained ingredients for pain, soreness and



## Degrees of Hemorrhoids



*Pressure and swelling can cause internal hemorrhoids to stretch out of shape (first-degree hemorrhoids). As the stretching worsens, straining and pressure causes the hemorrhoidal veins to prolapse (fall down) and bulge outside of the body. At first the prolapsed hemorrhoids will spontaneously reduce (pull back up) inside the body (second degree). However, with continued pressure and straining, spontaneous reduction may no longer occur (third and fourth degree).*

nine urea, sodium morrhuate, or phenol in oil) is injected into the hemorrhoid, which causes inflammation and eventual scarring that eliminates hemorrhoidal symptoms.

Third- and fourth-degree hemorrhoids may have to be surgically removed, either with traditional scalpels or with lasers.

Complications such as infection and incontinence are possible with all of these techniques.

burning or relabel with the statement "for external use only" and a warning not to put the product into the rectum.

In addition, nonprescription hemorrhoid remedy labels must include the statement "If condition worsens or does not improve within seven days, consult a doctor." Two other warnings—"Do not exceed the recommended daily dosage unless directed by a doctor" and "In case of bleeding, consult a doctor promptly"—must also be on the label.

### Surgical Options

Occasionally, some form of surgery may be necessary to remove or destroy the hemorrhoid.

One of the most common surgical methods is rubber band ligation. A tiny rubber band—diameter 1 millimeter (about one-twenty-fifth of an inch)—is fitted onto a

special gun-like device. When the trigger is pulled, the rubber band is forced onto the base of the hemorrhoid. Because there are no nerve endings in the rectum, no anesthesia is necessary.

It takes about a week for the strangled tissue to slough off and a scar to form. Rubber band ligation works best on first- and second-degree hemorrhoids. (See illustration.)

Other surgical techniques for these less severe hemorrhoids include:

- **infrared photocoagulation**—A specially designed device uses infrared light to create a small tissue-destroying burn around the base of the hemorrhoid.
- **laser coagulation**—The laser causes a minor burn, which seals off the blood vessels. This results in the hemorrhoid being retained in a non-prolapsed position.
- **sclerotherapy**—A solution (either qui-

### External Hemorrhoids

Blood clots in external hemorrhoids are "like a black eye," says Smith. "Even if the patient does nothing, the clots will eventually disappear." Treating the pain and irritation with sitz baths, bulk stool softeners, and pain medication may be all that's necessary, he says.

Sometimes, however, the clots are so painful the patient can't bear to wait, and traditional surgery to cut out the clots is necessary.

But even surgery is only a temporary solution. If a person's diet isn't improved, the hemorrhoid may return. And even in the best of cases, in the end, "hemorrhoids don't go away, they just get better," says Smith. ■

*Dori Stehlin is a staff writer for FDA Consumer.*



# *Monitoring High-Risk*

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# Pregnancy

by Deborah M. Bash



Pregnancy is usually a serene time in a women's life. However, sometimes it can be complicated by unexpected illnesses or medical conditions. When this happens, the pregnancy becomes high risk.

Fortunately, with the development of medical technology, pregnant women can be carefully monitored for signs and symptoms of high-risk pregnancies.

In the following fictionalized example, several real-life experiences are combined to explain how home devices, regulated by the Food and Drug Administration, can help monitor a high-risk pregnancy.

## Gestational Diabetes

Sharon, 27 and expecting her first baby, was in her 18th week of pregnancy and feeling fine when her obstetrician told her that the routine blood screening test for glucose levels she had taken the week before identified her as a gestational diabetic.

If an expectant mother cannot metabolize (process) glucose (a form of sugar) properly, her fetus can receive too much glucose and grow too large. Glucose metabolism is altered during all pregnancies, but in women with gestational diabetes, erratic glucose metabolism is harmful to the fetus, causing problems during the pregnancy as well as during labor and delivery.

Because Sharon had always been healthy, she was shocked when her obstetrician told her that she was now considered a high-risk patient and would have to be closely monitored until her baby was born.

A team—including Sharon's obstetrician, the hospital's perinatal specialist, and a certified diabetic educator—began to work with her. They taught her how to monitor her glucose at home herself with a blood glucose monitor that she bought in

*As part of home health care in a high-risk pregnancy, author Deborah M. Bash, a certified nurse-midwife, listens to fetal heart tones through a fetoscope. Resting a part of the instrument against the practitioner's forehead bone magnifies the sound of the baby's heartbeat.*





her local pharmacy. Sharon was instructed in the principles of using the diabetic exchange diet. Although in Sharon's case diet alone was sufficient to control her condition, if it had not been, she would have been instructed how and when to inject insulin at home.

Infants of uncontrolled gestational diabetes often grow larger than full-term infants but are in other ways physically immature. The mother's placenta, the lifeline to the fetus, may not produce adequate nutrition for the infant to mature according to size. To monitor the growth and well-being of her fetus, Sharon was sent to the maternal-fetal radiologist for ultrasonic screening. Measurements of fetal movements and breathing patterns by the sonographer helped to ensure that the fetus was growing appropriately and appeared healthy.

During the last four weeks of her pregnancy, Sharon's perinatal team met weekly to discuss her case. They talked about the possibility of inducing labor if her fetus began to grow too large. Sharon had carefully followed her prescribed diet and had gained only 22 pounds. She had

also monitored her blood glucose levels daily and adhered to a moderate exercise program throughout her pregnancy.

At 39 weeks gestation, one week before her expected delivery date, Sharon went into spontaneous labor. After a normal six-hour labor and vaginal delivery, she gave birth to a healthy 8-pound, 2-ounce son.

Like most women with gestational diabetes, Sharon's blood sugar levels returned to normal after she gave birth. On the third day after the birth, Sharon went home with her newborn son.

Almost all pregnant women are now screened for gestational diabetes during their second trimester, usually between 24 and 28 weeks gestation, because normal pregnancy causes a "diabetic-like" state in all pregnant women.

Some pregnant women can handle the imbalance of glucose and insulin while others cannot. When a pregnant woman develops diabetes during pregnancy, this medical condition is superimposed on the added stresses and physiologic changes that a normal pregnancy produces. Women with gestational diabetes must be carefully monitored for possible additional

*As Trish Mooney gives her 7-month-old daughter Leslie a lift, the days of high-risk pregnancy seem far behind her.*

medical problems such as high blood pressure, vascular problems, and pre-term labor.

### **Pre-Term Labor**

A woman who has a medical condition complicating pregnancy may be more likely to have an early labor and delivery. Smoking, poor nutritional habits, drug and alcohol abuse, and other poor health practices during pregnancy also increase the risk of early delivery and birth of stillborn or sick infants. Early in pregnancy, health professionals try to identify women who are at risk for pre-term labor and delivery so they can be monitored more frequently for early signs of the problem.

The usual length of a pregnancy is 38 to 40 weeks after the first day of the last menstrual period. Premature or pre-term labor is defined as labor occurring after 20 weeks and before 37 completed weeks of pregnancy. Although there is no firm data,

estimates on the incidence of pre-term delivery suggest that 6 to 10 percent of all births in the United States occur between the 20th and the 37th week of pregnancy.

According to Robert K. Creasy, M.D., chairman of the department of obstetrics, gynecology, and reproductive sciences at the University of Texas Science Center at Houston, prematurity accounts for over 50 percent of the neurologically handicapped children in this country and is the greatest single cause of newborn illness and death.

Unfortunately, it is difficult to predict which women are at risk for pre-term labor. Since pre-term labor can occur in all age groups and within all social settings, researchers continue to explore what lifestyles and risk factors are common to women who experience pre-term labor.

Sometimes women mistake a certain type of contraction for labor. As early as six weeks into all pregnancies, the uterus, which is a large muscle, begins to contract rhythmically. These contractions (called Braxton Hicks contractions) are usually irregular and painless, and, because they usually do not cause the cervix to dilate, they do not threaten the pregnancy.

Braxton Hicks contractions that tend to increase in frequency and intensity toward the end of the pregnancy may be misinterpreted as contractions of labor and are sometimes referred to as "false labor" contractions. Women are not usually aware of cervical dilatation, the stretching and opening of the entrance to the uterus, and cervical dilatation can only be measured by a health practitioner during a pelvic examination.

Trish Mooney of Takoma Park, Md., has had two high-risk pregnancies. During the first one, however, she didn't recognize the symptoms. Her son Isaiah was born after only 34 weeks' gestation, weighing 5 pounds, 8 ounces. During her second pregnancy, her contractions were recognized and, due also to her history of previous pre-term birth, she was put on bed rest. She also developed gestational diabetes. She was closely monitored and last May, after a full-term pregnancy, gave birth to her daughter Leslie, who weighed in at 8 pounds, 4 ounces.

### What to Do

A pregnant woman experiencing contractions, either painful or painless, anytime during pregnancy, that occur more

## Baby Talk

Health-care professionals may use the following terms when discussing high-risk pregnancy:

**Braxton Hicks contractions:** intermittent contractions that occur throughout pregnancy. When these contractions do not cause cervical changes they are called "false labor" contractions.

**Cervix:** the lowermost portion of the uterus that dilates during labor, permitting the fetus to pass from the uterus through the vagina or birth canal during birth.

**Contractions:** the rhythmic firming of the uterine muscle, which may or may not be painful. Contractions associated with labor usually cause the cervix to open.

**Gestational diabetes:** diabetes occurring during pregnancy when the woman's body is unable to properly process glucose, a form of sugar.

**High-risk pregnancy:** a pregnancy in which the woman or fetus has a higher-than-average chance of experiencing medical complications or death.

**Perinatal:** the period during pregnancy up to the 28th day past birth.

**Pre-term labor:** labor that occurs after 20 weeks but before 37 completed weeks of pregnancy.

**Sonogram:** an image made through ultrasound scanning technology. When done during pregnancy, the image can give information about the fetus.

**Tocolytic medication:** a drug that inhibits labor.

**Uterus:** a hollow muscular organ that nourishes and houses the developing fetus until birth. It is sometimes called the womb. ■

than four times an hour or are less than 15 minutes apart should report this activity to her physician or midwife, and be prepared to answer the following questions:

- When did the discomfort start?
- What is the type and frequency of the contractions?
- What were you doing when the symptoms began?
- Do you have any other signs or symptoms such as:
  - menstrual-like cramps that may come and go
  - abdominal cramps with or without diarrhea

- backache that is dull and may radiate around toward the abdomen

- vaginal discharge increase or a noticeable change in color
- pelvic pressure that is constant or intermittent.

While waiting for her provider to return her call, the woman should:

- lie down with her feet elevated
- drink two or three glasses of water or juice.

These two activities sometimes cause contractions to subside. If symptoms do not lessen within one hour and the woman is not able to get in touch with her health-



care provider, she should go to the nearest hospital for further evaluation.

### Home Monitoring

Home monitoring of the mother-to-be who has signs of pre-term labor may be ordered by her health-care provider, especially if she must be on bed rest for a significant time (often 20 weeks or more). Home care, although quite expensive itself, may help reduce costs and continue to provide a safe and satisfactory means of monitoring the pregnancy. Some insurance companies cover the cost of home care visits and some aspects of home monitoring equipment. Not all insurance companies cover home uterine activity monitoring.

In the fall of 1990, FDA approved for marketing the Genesis Home Uterine Activity Monitoring System to monitor uterine activity in women past their 24th week of pregnancy who have histories of previous pre-term births. The purpose of such monitoring is the early detection of uterine activity, which can cause cervical dilation and pre-term labor.

Wearing an elastic belt around her waist, the expectant mother places the transducer attached to the belt on her abdomen. The transducer is a small, flat, pressure-sensitive recorder that looks like a "compact" or a small "beeper" and detects uterine contractions. A computer program transfers the data reporting the uterine activity over the telephone lines to communication centers such as the obstetrician's office, the home health service office, or a hospital relay station. Some women complain of skin irritation from the belt and the transducer because the belt is worn for two hours a day, usually one hour in the morning and one hour in the evening.

### Drug Treatment

Pregnant women at risk for premature labor are often placed on medications that can stop contractions and give the fetus more time in the uterus. Such medications are called tocolytic agents. The word is derived from the Greek words *tokos*, meaning birth, and *lysis*, meaning dissolution.

The following fictionalized example, based on several real-life examples, explains the benefits of tocolytics.

Robin believes her 6-month-old daughter is alive and well today because of the tocolytic drug treatment Robin received in her 22nd week of pregnancy. Hospitalized

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## *Many communities have home health-care services specializing in pregnancy.*

for painful uterine contractions, Robin received tocolytic medication intravenously. After one week, she was sent home on strict bed rest, oral medication to prevent contractions, and a regimen of careful monitoring.

The only tocolytic medication approved by FDA for use in pre-term labor is Yutopar (ritodrine hydrochloride). Yutopar can be prescribed if labor begins between 20 and 36 weeks gestation and if the fetus weighs between 500 and 2,499 grams (1 to 5 pounds). The initial dose of Yutopar is usually given intravenously. Once the best dose for the patient is found, she may receive the medication by oral or intramuscular route. The amount and frequency of subsequent dosages depend on the woman's response to the initial therapy.

Yutopar should not be used in women who have cardiovascular disease, pregnancy-induced high blood pressure, intra-uterine infection, vaginal bleeding, or uncontrolled diabetes. Nor should it be used if the woman is in active labor or has a history of repeated miscarriages due to an incompetent cervix, or if the fetal membranes have ruptured.

Side effects include: heart palpitations, excessively rapid heartbeat, tremors, anxiety, headaches, vomiting, and fever.

Low blood sugar, bowel problems, and a low level of calcium in the blood have been reported in infants of mothers who were given tocolytics such as Yutopar. The labeling instructs physicians to carefully weigh the risks and benefits of administering the drug to women who are more than 32 weeks pregnant because of its possible effect on the fetus.

An electrocardiogram is recommended before starting Yutopar therapy. Before and often during tocolytic therapy, the patient may be monitored for serial blood glucose and blood electrolyte levels.

When a woman in pre-term labor also has diabetes or heart disease, she may be placed on magnesium sulfate to reduce uterine activity. Magnesium sulfate is approved for magnesium deficiency states

but not specifically for use in pre-term labor. However, because there is extensive literature and clinical data on this use, some physicians prescribe it. The most uncomfortable side effect of magnesium sulfate is a feeling of warmth and flushing when the drug is first administered. Women must also be carefully monitored for respiratory or cardiac complications during the therapy.

Terbutaline sulfate, a drug approved for asthma and other lung disorders, has been used by some physicians to treat pre-term labor. However, it has not been approved by FDA for this use, nor has the agency been asked to review an application for marketing terbutaline sulfate for treating pre-term labor. The labeling for terbutaline sulfate was revised in 1988 by the drug's manufacturer to specify that it is not approved for treatment of pre-term labor.

Health professionals hope that proper use of home monitoring will lead to more appropriate and effective use of tocolytics.

### Home Health-Care Services

Many communities have home health-care services specializing in pregnancy. Nurses from these services provide specialized care for pregnant patients at home, including evaluation of:

- weight
- urine
- blood pressure
- blood glucose levels
- bed rest compliance
- psychological status
- uterine contractions
- fetal heart tones using a fetoscope, a stethoscope-like instrument.

Home services also provide medication therapy as prescribed by a physician.

Gestational diabetes and pre-term birth are two serious medical conditions that cause parents-to-be much concern and worry. High costs of hospitalization and the rate of illness and death in newborns are factors in the increased use of home monitoring for women who have high-risk pregnancies due to these conditions. Educating expectant mothers to get early prenatal care, eat nutritionally sound diets, stop smoking, practice stress reduction, and detect signs of pre-term labor can go a long way towards lowering the incidence of infant mortality and illness. ■

*Deborah M. Bash is director of the Nurse-Midwifery Education Program at Georgetown University in Washington, D.C.*



*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.*

■ **FDA's infant formula regulations** are being amended to ensure the retention of all records relating to various subjects, including records pertaining to microbiological and nutrient testing, compliance with quality control procedures, and consumer complaints. The purpose of the amendment is to ensure a safe and sanitary source of nutrition for infants. The amendment becomes effective April 22. (FR Dec. 24)

■ **Over-the-counter drug products** to treat dandruff, seborrheic dermatitis, and psoriasis are covered in a final rule issued by FDA. The rule establishes conditions under which the products are generally recognized as safe and effective and not misbranded. The rule is part of FDA's ongoing review of OTC drug products. (FR Dec. 4)

■ **Funding for conferences on HIV transmission** is being provided by the national Centers for Disease Control, which is making approximately \$255,000 available in fiscal year 1992. The money will be divided among 10 to 15 recipients. For additional written information, call (404) 332-4561. Refer to Announcement Number 201 when requesting information. (FR Dec. 13)

■ **"Osteoporosis Research, Education, and Health Promotion,"** a new report published by the Department of Health and Human Services, is now available to health professionals. Single copies of the report are available from: HHS Osteoporosis Report, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Box AMS, 9000 Rockville Pike, Bethesda, Md. 20892; telephone (301) 495-4484 or facsimile (301) 587-4352.

■ **"Pesticides and Ground-Water Strategy,"** a document describing the Environmental Protection Agency's goals, policies, management programs, and regulatory approaches for protecting the nation's ground-water resources from risks of contamination by pesticides, is available free from EPA's Public Information Center (PM-211B), 401 M St. S.W., Washington, D.C. 20460; telephone (202) 260-2080. (FR Nov. 6)

■ **Smoking** is more common among divorced and separated persons than among those who are married, widowed, or never married, according to a 1988 Centers for Disease Control survey. (*Morbidity and Mortality Weekly Report*, Nov. 8)

■ **Use of alcohol and other drugs** is associated with the leading causes of death and injury (such as motor vehicle crashes, homicides, and suicides) among teenagers and young adults. Nearly half of all deaths from motor vehicle crashes in this age group involve alcohol use. (MMWR, Nov. 15)

■ **Male high school students** are more likely to consider themselves either the right weight (68.8 percent) or underweight (16.5 percent) than are female students (58.5 percent and 7.2 percent), according to a report from the Centers for Disease Control. Female students are more likely to report currently trying to lose weight (43.6 percent) than are male students (15.3 percent). Black students of both sexes are less likely to consider themselves overweight than are white and Hispanic students. (MMWR, Nov. 1)

■ **Obesity** tends to be more than twice as prevalent among women who watch four hours or more of television daily than among women who view less than an hour every day, according to research published in the July 1991 issue of *American Journal of Public Health*.



■ **Diabetes mellitus** is the leading cause of leg amputations in the United States, accounting for about 50 percent of all leg amputations not due to injury. In 1987, there were approximately 56,000 such amputations among Americans with diabetes in the United States. (MMWR, Nov. 1)

■ **Financial relationships** between physicians and certain health-care entities is the topic of an interim rule by the Health Care Financing Administration. The interim rule implements a Social Security Act requirement that entities furnishing Medicare-covered clinical laboratory services must provide the agency with information concerning their ownership arrangements. (FR Dec. 3)





# Medical Gas Mix-Up Implicated in Patient Death

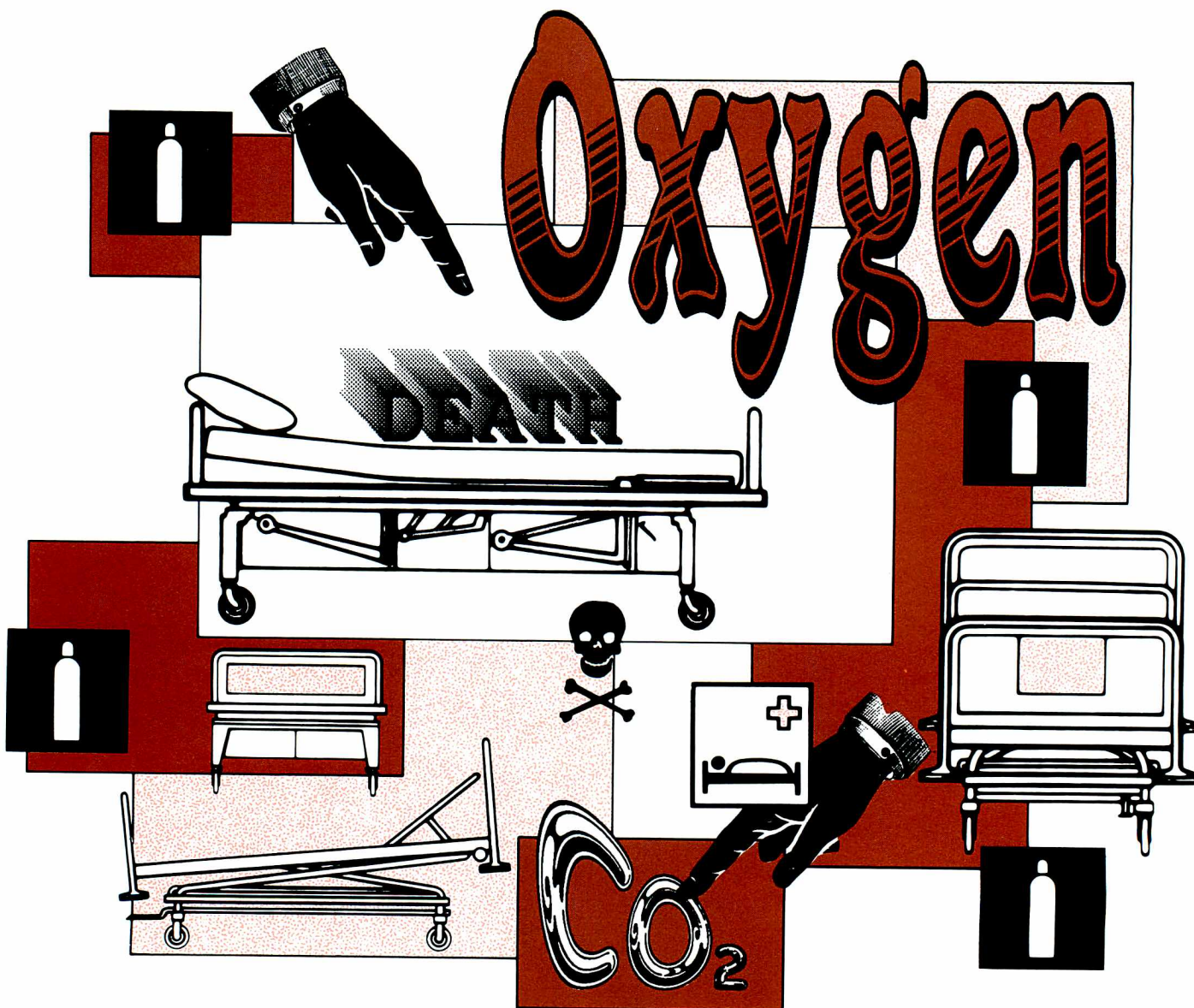
by Marian Segal and Judith Foulke

The death of a hospitalized patient mistakenly given carbon dioxide instead of oxygen prompted an FDA investigation that led to a \$100,000 fine for a New York gas repacking firm. The former president of the company was also fined \$100,000 and was sentenced to three years' probation, the first six months of which will be electronically monitored.

General Welding Supply Corporation of Westbury, N.Y., and its then president, Harry Ruddy, were sentenced Jan. 31, 1992, following guilty pleas entered last July 30 to one count of adulterating oxygen-valved cylinders by substituting carbon dioxide for oxygen. In addition to the fine and sentence, Ruddy was ordered to perform 300 hours of community service.

FDA began investigating the incident April 9, 1987, when the agency received a report from Southside Hospital in Bayshore, N.Y., of a medical gas mix-up that was associated with the death of one patient and injury of another.

The hospital told FDA that in July 1986, it had placed an order with General Welding to refill four of its oxygen cylinders.



After noting problems with two patients given gas from one of the cylinders on Feb. 23, 1987, the hospital had the contents of all four cylinders tested and found that they contained carbon dioxide. All four cylinders were oxygen-valved; that is, the valve system permitted filling only with oxygen. To substitute another gas would require deliberately circumventing the system of holes on the valves that permit use of only an oxygen-filling yoke.

"Basic to good manufacturing practice in any medical gas repacking operation is that a cylinder valved specifically for one gas should not be filled with a different gas, and that no cylinder should be released unlabeled as to its true contents," said FDA attorney Mark Brown.

Nevertheless, that's precisely what happened with the refilled cylinders delivered to Southside Hospital. General Welding's truck driver, who had picked up the empty cylinders for refilling, noted on the paperwork that they were carbon dioxide cylinders even though the word "oxygen" was etched on them and they were oxygen-valved. Also, the pick-up order showed that the hospital wanted oxygen.

The refilled cylinders were returned to the hospital without labels describing their true contents, with the oxygen pin systems intact, and marked only with the word "oxygen" etched on the valves. The accompanying paperwork described them as containing carbon dioxide, and they were accepted as such by the hospital. They were invoiced and paid for by the hospital's receiving department as carbon dioxide.

When oxygen was needed for a patient, however, hospital personnel administered the contents of the carbon dioxide-filled cylinder as oxygen, consistent with the oxygen-dispensing pin system and the valve etching indicating oxygen.

From April 9 to 24, FDA investigators inspected General Welding and concluded that the cylinders were deliberately filled with carbon dioxide, based on the belief of a company employee that the hospital wanted carbon dioxide filled into its oxygen cylinders. Different kinds of yokes were available in the gas filling area, enabling an employee to change the yoke and fill a cylinder with a different gas.

The inspection also revealed that there were not adequate controls to ensure the identity, purity, proper filling, and proper labeling of medical gases. Nor were personnel adequately trained and supervised,

or given well-defined responsibilities for quality assurance or label control. The firm failed during most of 1986 to prepare any filling, testing or labeling records, as required by law. The investigators could not identify the individual who filled the oxygen cylinders with carbon dioxide because proper records were not kept. Nor could the investigators determine whether a supervisor had been present when the tanks were filled.

FDA had inspected General Welding in November 1986 and again in January 1987. At the end of the January inspection, the agency presented the firm with a list of good manufacturing practice (GMP) deficiencies, including failure to test repacked oxygen and to prepare records for repackings from December 1985 to November 1986. At that time, investigators discussed the problems with the company's controller and treasurer, who promised to take corrective actions. On April 1, 1987, the agency sent a regulatory letter to Ruddy, detailing the violations from the November and January inspections.

Following the April 9 inspection and a meeting with FDA representatives on April 16, Ruddy promised to suspend all medical gas filling operations until the general manager obtained training and certification as a pump room supervisor and the firm came into full compliance with good manufacturing practices.

Good manufacturing practices for medical gases require specific procedures to protect against the kind of mishaps that occurred at General Welding. These include:

- separation of each filling operation and each storage area to prevent mix-ups
- adequate control of the labeling operations to ensure that each cylinder is correctly labeled and that no unlabeled container leaves the premises
- inspection of the containers and valves
- testing finished product samples after packaging and labeling to safeguard against errors
- production and control records for each product listing each significant step required
- batch production records identifying the employee performing and the employee verifying each step.

Because of the serious consequences of the gas mix-up at Southside Hospital, the New York district, in December, recommended prosecuting General Welding

Supply Corporation, and in August 1988, FDA asked the Department of Justice to institute criminal proceedings against the firm and its president. On May 17, 1991, the U.S. attorney for the Eastern District of New York filed misdemeanor charges against the defendants on two counts of adulterating a drug and one count of misbranding. Under a plea agreement, General Welding and Harry Ruddy pleaded guilty July 30 to one count of adulterating four oxygen-valved cylinders, and the government agreed to dismiss the remaining two counts.

Other FDA investigations uncovered GMP violations by three Tennessee oxygen repacking firms, leading to seizures of cylinders and bulk tanks of oxygen valued at \$250,000. The firms in violation were Eastern Welding Supply Inc. of Knoxville, Volunteer Welding Supply Inc. of Nashville, and Price Bass Company, also of Nashville.

During routine checks of these manufacturers as far back as 1982, FDA's Nashville district investigators found violations and sent warning letters to the firms.

The violations included:

- failure to test oxygen and repacked oxygen for identity and purity
- incomplete written operating procedures concerning all aspects of repacking medical oxygen
- incomplete production records
- insufficient personnel training
- failure to adequately maintain or calibrate testing equipment
- inadequate procedures for labeling.

In each case, officers of the firms notified the agency by letter that corrections had been made. But the most recent inspections of the firms in 1990 showed that all three continued to violate GMPs.

Because the firms had shown no attempt to correct the problems, U.S. marshals, at FDA's request, seized cylinders and bulk tanks valued at \$250,000 between September 1990 and March 1991. The tanks were returned to the firms after the oxygen was vented.

Eastern Welding Supply has stopped producing oxygen for medical use; Volunteer Welding Supply has come into compliance with GMPs; and Price Bass Company has agreed to make the changes necessary to come into compliance.

*Marian Segal and Judith Foulke are staff writers for FDA Consumer.*





### **Cover-Up Fails; Firm Pleads Guilty**

Managers of a Georgia seafood company who tried to conceal the firm's accidental use of decomposed shrimp pleaded guilty after an investigation uncovered the deception.

In February 1988, Rich-SeaPak Corp., Brunswick, Ga., imported 522 cartons of frozen shrimp from the People's Republic of China. As part of FDA's import responsibilities, FDA investigators took samples of the shrimp. Analysis showed that the shrimp was decomposed, and the agency refused to allow it to be sold in the United States. In early May, Rich-SeaPak decided to destroy, rather than reexport, the decomposed shrimp.

However, the previous month, on April 15, Rich-SeaPak's manufacturing depart-

ment had accidentally used 119 cartons of the decomposed shrimp, along with shrimp from other lots, to manufacture more than 3,000 cases of their extruded (minced and shaped) shrimp product, Round Shrimp 'n Batter. From April 21 until May 20, the firm distributed approximately 1,160 cases of the product. Distribution stopped on May 21 when the company discovered the error.

However, instead of reporting the accidental use of the shrimp to FDA, the company managers, including the president and chief executive officer, Frank W. Holas, and the director of new products, Hamsa A.P. Thota, decided to substitute for destruction 119 cartons of shrimp from a lot imported in December 1987. The firm dumped the remainder of the refused lot with the 119 substituted cases in a landfill on June 7 and signed U.S. Cus-

toms documents certifying that all of the refused shrimp had been destroyed.

The deception came to FDA's attention from an informant who told the agency about the accidental use and subsequent cover-up, and provided copies of records to substantiate the allegations.

On June 21, an FDA investigator visited Rich-SeaPak's facility in Brunswick to investigate the disposition of the refused shrimp. The plant manager repeatedly told the investigator that all the refused shrimp had been dumped and said it would take several days to assemble the documents requested to confirm the destruction of the decomposed lot.

Three days later, Rich-SeaPak's director of quality assurance, Patrick Donahoo, gave the investigator limited records that appeared to confirm that only 10 pallets of the decomposed lot had been dumped,



along with three pallets from another lot received in December 1987.

However, Donahoo told FDA that Rich-SeaPak employees mistakenly put three pallets (119 cartons) from the refused lot in a freezer location reserved for the December lot, and the computer assigned the December lot numbers to those misplaced pallets. All of the decomposed shrimp was then destroyed, according to Donahoo, although three of the pallets had incorrect lot numbers due to the computer mix-up.

However, from a review of the records supplied by the informant and discussions with other plant personnel, FDA confirmed that some of the decomposed shrimp had been used in production. The agency concluded that when the company pulled samples of the refused shrimp for a private laboratory analysis, employees entered a release code into the computer, which allowed them to physically move the three pallets they wanted to sample. After sampling, the pallets were placed back with the rest of the lot, but the release code was never cancelled in the computer. Then, when the manufacturing department checked the computer for lots of shrimp available for production, the three sampled pallets of decomposed shrimp were listed among the available lots.

Based on the records and investigation, the Atlanta district office recommended seizure of the remainder of the April 15 lot of Shrimp 'n Batter still in Rich-SeaPak's possession.

The U.S. marshal's office seized the Round Shrimp 'n Batter on Sept. 22, and the product was destroyed on Oct. 19. FDA asked the U.S. attorney's office for the Southern District of Georgia, Brunswick division, to conduct a grand jury investigation of the company's activities to identify which employees were responsible for the cover-up.

During the investigation, Rich-SeaPak agreed to guilty pleas for the company and several responsible individuals.

Rich-SeaPak pleaded guilty on July 13, 1990, to one felony count of knowingly using false documents to deceive FDA and the U.S. Customs Service. On Aug. 31, Judge Anthony A. Alaimo fined the firm \$78,200 and sentenced it to six months' unsupervised probation.

Holas, Donahoo and Thota each pleaded guilty on July 8, 1990, to one misdemeanor count of receiving and delivering adulterated food in interstate commerce. On Oct. 9, Federal Magistrate

James Graham sentenced each of the individuals to one year probation and a \$750 fine.

FDA has no reports of illness resulting from the Round Shrimp 'n Batter manufactured with the decomposed shrimp.

—Dori Stehlin

## Plasma Collection Facility Closed

A North Carolina plasma collection facility had its license suspended because of operating procedure violations that FDA called "a danger to health."

The Clinical Coagulation Laboratory, Chapel Hill, N.C., was cited by the agency for numerous violations, including inadequate donor screening, bleeding donors more often than legally permitted, and distributing plasma that tested positive for hepatitis.

The facility has about 20 donors, and collects only from people who have blood coagulation factor deficiencies, such as hemophiliacs. Some of the plasma is used for laboratory diagnostic procedures in the North Carolina Memorial Hospital where the laboratory is located, and some is shipped for use in manufacturing laboratory diagnostic products.

It is FDA's policy to inspect blood donor facilities every year to ensure safety to donors and recipients. Atlanta district investigator Erin Hyer, assigned to the Clinical Coagulation Laboratory, said that deficiencies have been noted in almost every inspection since the facility was licensed in 1984.

The last inspection, conducted between July 30 and Aug. 15, 1991, showed many more violations than in previous years, resulting in the license suspension, effective Sept. 3, 1991. For example, a review of the facility's records showed that three donors who admitted to a history of hepatitis, liver disease, or jaundice were regularly accepted for plasma donation. At least two donors were allowed to donate three times in a week, even though the maximum permitted is two donations within a seven-day period. In addition, the laboratory failed to standardize and calibrate equipment used to collect, process and distribute blood components.

On Sept. 3, 1991, FDA sent a letter to the laboratory's director, Katherine A. High, M.D., notifying her that the facility's license was suspended because of the violations noted during the July-August 1991 inspection. It further stated

that she had not fulfilled her responsibilities to exercise control in matters relating to compliance with FDA regulations and to ensure that all personnel were adequately trained to have a thorough understanding of the procedures they performed.

The suspension can be lifted if a reinspection by FDA shows that the facility has corrected all the deficiencies. Otherwise, the license could be permanently revoked. The laboratory is now working with FDA in an effort to correct the violations.

—Judith Foulke

## Food Safety in the Air

With temperatures in the 70s, New York was unseasonably warm last Nov. 14. A catering truck, its front door open, rolled slowly towards an airplane at John F. Kennedy Airport.

Most people looking on would see nothing wrong. But Donald Borges, an interstate travel sanitation specialist with FDA's New York district office, saw a health risk. Through that open door, outside heat would move inside, possibly warming the food to temperatures that could foster the growth of bacteria.

FDA requires foods to be chilled at 7.2 degrees Celsius (45 degrees Fahrenheit) when they are put on interstate vehicles that serve food.

At JFK on a routine inspection of the United Airlines catering service, Borges decided to check out this open door. He followed the truck to the airplane, which he boarded, and began measuring the food's temperatures. A few foods had slightly elevated temperatures, but, because cold air would be circulating around them on the plane, Borges judged they would soon be down to FDA's safety zone.

However, Borges also observed roach infestation and dirty cooking equipment in the dining unit. He saw that workers weren't soaking wiping cloths in disinfectant between uses and that the foods weren't labeled with the ingredients and catering source, as FDA requires. The agency's New York district issued a warning letter, and United's catering representative promised to correct the situation. Borges said he would check back in a month.

The United Airlines food service is among 32 interstate and foreign caterers





Borges inspects on a regular basis every year, with follow-up calls as needed to confirm corrections.

Trains and interstate ships, such as ferries, seldom have temperature violations, Borges says, because their galleys usually are large enough to house refrigerators. Airlines, on the other hand, depend upon chilled food at delivery and the use of dry ice for cooling food during international or long-haul transcontinental flights.

"About 20 to 25 percent of the visits to airlines turn up problems with food," Borges said. "This is particularly true in the summertime with elevated air temperatures, increased numbers of passengers to serve, and weather conditions such as thunderstorms delaying departures. I try to concentrate my airplane inspections from about mid-May until September."

Not all inspections by Borges are routine, however.

Last Sept. 17, while driving home from work, he heard a radio newscast that a communications breakdown had forced the closing of JFK Airport. He immedi-

ately went there and determined the status of flights through the individual airlines operations control offices.

The first airline he checked was United, where a supervisor told him food had been stored the longest on a San Francisco flight. Scheduled to depart at 5:40 p.m., it had been catered about an hour earlier.

"I was on board a little before 9," he said. "First-class entrées tested between 17.2 C (61 F) and 20 C (68 F), and the plane was expected to be on the ground for another two hours. There was no problem with coach meals, because they were stored in carts with dry ice with chilled air circulating through the carts."

Borges notified the supervisors, and they saw that all the first-class meals were removed. The caterer voluntarily removed the same food items off another United flight to Los Angeles.

Next, Borges visited MGM Grand Air, a nonstop flight to Los Angeles, and its meals also had to be removed because of time/temperature deviations. At Pan American Airlines, he found that the ca-

terer, anticipating long delays, had provided extra dry ice as needed. Last, a check of Trans World Airlines determined that flight attendants on the planes awaiting takeoff had served the meals to passengers while the planes were at the gates.

The food service industry has cooperated with FDA for about six years in training airline employees and catering firms on ways to prevent airline food hazards. —Dixie Farley

#### **CORRECTION: Missing AIDS Virus**

Page 42 of the January–February 1992 *FDA Consumer* contained a graphics error. A dot was dropped that illustrated the size of the AIDS virus when compared with the much larger human sperm. The dot, about the size of a typewriter period, was apparently mistaken for dust and deleted in the final stages of magazine production.

# 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 that were alleged to be adulterated or misbranded or otherwise violative of the law when introduced into and while in interstate commerce or while held for sale after shipment in interstate commerce.

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

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

## SEIZURE ACTIONS

### *Food/Poisonous and Deleterious Substances*

PRODUCT: **Fish, whole, frozen**, at Seaside, N. Dist. Calif.; Civil No. C90-1554-DLJ.

CHARGED 5-30-90: When shipped from Ruskin, Fla., the article labeled "J.O. Guthrie Fish Co. Inc. . . . Ruskin, Florida . . . LG Mullet" contained a poisonous or deleterious substance—402(a)(1).  
DISPOSITION: Consent decree authorized release of a portion of the article for scientific testing by FDA and destruction of the balance of the article. (F.D.C. No. 65874; S. No. 90-592-715; S.J. No. 1)

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

PRODUCT: **Mushroom pieces and stems, canned**, at Winchester, Dist. Mass.; Civil No. 89-2296-MA.

CHARGED 10-13-89: When imported from China, the article labeled "Ma Ling Mushrooms (Pieces & Stems) . . . Packed for

China National Cereals, Oils and Foodstuffs Import and Export Corporation, Ningbo . . . China" was unfit for food, since it was held in swollen and leaking containers—402(2)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65757; S. No. 89-599-323; S.J. No. 2)

PRODUCTS: **Oatmeal cereals, cornstarch, flour, spices, coconut flakes**, and **other food stocks**, at Minneapolis, Dist. Minn.; Civil No. 4-90-798.

CHARGED 10-18-90: While held by National Warehouse, Inc., Minneapolis, Minn., the articles had been held under insanitary conditions—402(a)(4).

DISPOSITION: The oatmeal products were claimed by Old Wessex, Ltd., Franklin Lakes, N.J.; certain cornstarch and spice products were claimed by Oziama International, Minneapolis, Minn.; and a consent decree authorized release of such products to the claimants for salvaging. A default decree ordered the remaining articles destroyed. (F.D.C. No. 65958; S. No. 90-572-010 et al.; S.J. No. 3)

### *Food Additives*

PRODUCT: **Candy beads**, at Des Plains, N. Dist. Ill.; Civil No. 90-C-7195.

CHARGED 12-12-90: When imported from China, the article labeled "Cons-Mark's Ping Pongs Candy Beads . . . Distributed By Cosmark Inc. . . . Glenview, Ill. . . . Made in China" contained the nonconforming color additive cochineal red A-402(c).

DISPOSITION: Default ordered destroyed. (F.D.C. No. 66006; S. No. 90-575-998; S.J. No. 4)

### *Drugs/Human Use*

PRODUCT: **Damason-P analgesic tablets**, at Irvine, C. Dist. Calif.; Civil No. 86-5305-SVW(Tx).

CHARGED 8-11-86: While held by Anabolic, Inc., Irvine, Calif., who had manufactured the article using interstate hydrocodone bitartrate, the article labeled "Damason-P . . . Hydrocodone Bitartrate . . . Aspirin . . . Caffeine . . . Manufactured by Anabolic, Inc.,



Irvine, CA . . . and Pharmaceutical Basics, Inc., Denver, CO . . . expressly for Mason Pharmaceuticals, Inc., Newport Beach, CA” was a new drug without an effective approved New Drug Application (NDA)—505(a); and the labeling of the article lacked adequate directions for use and the article was not exempt due to its new drug status—502(f)(1).

**DISPOSITION:** *District Court*—The article was claimed by Mason Pharmaceuticals, Inc. (Mason), Newport Beach, Calif., who denied the charges and raised four affirmative defenses (i.e., (1) Mason had not been offered an administrative hearing on the issue of Damason-P’s new drug status under Part B of FDA’s Compliance Policy Guide 7132c.02; (2) After FDA had notified Mason in a regulatory letter that Damason-P was subject to the same requirements for marketing as Synalogos and Synalogos-DC and was regarded as a new drug, Mason had not received a reply to Mason’s letter of denial, had been denied an opportunity to achieve compliance, and had been denied due process of law; (3) FDA had failed to approve or disapprove of Mason’s petition for an Abbreviated New Drug Application (ANDA) for Damason-P; and (4) Damason-P was exempted by virtue of the “grandfather clause” of the Drug Amendments Act of 1962.) The claimant also filed a counterclaim and a third-party claim. The government moved for summary judgment. Mason opposed such motion. Pending efforts by the parties to settle the action, the court placed the government’s motion in abeyance and ordered FDA and Mason to work together in an effort to get approval of an NDA for the seized article or for a substitute product. After more than two years, the court ordered status reports and learned that Mason’s NDA for the article had been rejected and that Mason had not obtained approval for a substitute product. At the court’s suggestion, the government renewed its motion for summary judgment.

After a hearing on the government’s motion, the court granted summary judgment to the government. The court held that since there were no published, well-controlled clinical investigations of Damason-P, the testimony of Mason’s experts (based on “extrapolation” of studies of other products and of the drug’s individual ingredients) was insufficient as a matter of law to show either that Damason-P was effective as an entity or that each ingredient contributed to its claimed effects. Therefore, Damason-P was a new drug that Mason admittedly had not had approved by FDA.

In addition, a new drug could be exempt from 502(f)(1) only to the extent to which such exemption is claimed in an approved NDA. Thus, a prescription drug such as Damason-P could only be exempt from 502(f)(1) if its labeling had been approved by FDA in the context of an NDA or an abbreviated NDA. Accordingly, the court found that Damason-P was misbranded within the meaning of 502(f)(1).

As to Mason’s affirmative four defenses, the court ruled as follows: (1) FDA’s Compliance Policy Guide neither suggested that manufacturers would be the beneficiaries of any specific procedures (on the issue of whether a product was a new drug) nor suggested that

manufacturers would be able to participate in any such procedures or in FDA’s evaluation of a product’s new drug status; (2) Section 310.6 of 21 *C.F.R.* and the FDA regulatory letter did not suggest that Mason was entitled to an administrative hearing before FDA filed an enforcement action, Damason-P was seized based on its own new drug status and not because it was related to Synalogos, and, finally, Damason-P and Synalogos were “related” as that term was defined in 21 *C.F.R.* 310.6(b); (3) Mason’s defense that FDA had failed to act on Mason’s petition for a ruling of eligibility for an ANDA for Damason-P had become moot because FDA had denied the petition; and (4) Damason-P would not meet two of the requirements for exemptions under the grandfather clause, since the current version of the product was not “unchanged” from the pre-1962 product, and since Mason’s labeling for Damason-P had changed significantly since 1962; and, even assuming that Mason had shown that the formulation and labeling changes had been made to comply with FDA recommendations, no factual issue would be presented for trial, since society’s interest was best served by narrowly construing the grandfather exemption.

As to Mason’s contention that additional discovery concerning a different handling of Synalogos and other facts might enable it to defeat the government’s motion, the court found that “possible instances of FDA’s inconsistent treatment of other products is not material and provides no basis to forestall summary judgment.”

Accordingly, the court condemned the article Damason-P and ordered it forfeited to the government.

Mason filed an appeal of the judgment of the district court. However, pursuant to a stipulation between the parties, the appeal was dismissed. (F.D.C. No. 64950; S. No. 86-324-783; S.J. No. 5)

### *Medical Devices*

**PRODUCT:** **Gloves, latex, for examination**, at Monterey Park, City of Industry, C. Dist. Calif.; Civil No. 90-5632 RSWL(JRx).  
**CHARGED** 10-18-90: The quality of the articles, labeled “Ambidextrous Latex Examination Gloves Non-Sterile UltraMED . . . Made in Malaysia . . . UltraMED San Francisco, CA,” fell below the articles’ purported quality due to excessive holes—501(c); and the articles’ labeling misleadingly declared “UltraMED, San Francisco, Calif.,” which was contrary to fact since the actual distributor was, in fact, Handee (U.S.A.) Inc., Monterey Park, Calif.—502(a).  
**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 65936; S. No. 90-616-168 et al.; S.J. No. 6)

### **CRIMINAL ACTIONS**

**DEFENDANTS:** **Aubrey P. Cullen, M.D.**, clinical investigator, and **Frieda J. Cullen**, research assistant, Houston, S. Dist. Texas; Criminal Nos. H-87 1921 and (upon appeal) 88-2719.  
**CHARGED** 8-6-87: *Count 1*—That the defendants, each aiding and

abetting the other, knowingly devised a scheme to defraud that included the following: false entries would be made on patient cards indicating that various patients had been treated; information on case report forms for the sponsor (a pharmaceutical firm) of the investigational new drug Parafon Forte would be fabricated; certain patients would be represented as participating in such new drug investigation when in fact such patients had no knowledge of and did not participate in such investigation; signatures of such nonparticipating patients would be forged on the required patient consent forms; claims for payment by the sponsor for \$225 per patient would be submitted; and the sponsor's check for \$1,350, addressed to the doctor, would be caused to be delivered by the U.S. Postal Service, when the defendants knew they were not entitled to such payment—18 U.S.C. 1341.

*Counts 2 and 3*—In a matter within the jurisdiction of the Food and Drug Administration, fictitious statements and representations as to material facts in two specified completed case report forms for a study of human subjects purporting to evaluate the performance of the drug Parafon Forte were made and submitted to the sponsor of an investigation of the "new drug" Parafon Forte, when the defendants knew that the case report form contained information of patient experience that was fraudulent—18 U.S.C. 1001.

*Count 4*—In a matter within the jurisdiction of the Food and Drug Administration, fraudulent records were presented during an FDA inspection conducted to determine the authenticity of a study of the "new drug" Parafon Forte, when the defendants knew that the patient records were false and fictitious—18 U.S.C. 1001.

*DISPOSITION: District Court*—After a jury trial, the defendants were found guilty. The doctor was sentenced to three years imprisonment (all but 60 days suspended) and probation for three years. The court sentenced his research assistant to one year of supervision at a halfway house (all but 30 days suspended) and one year of probation.

*Court of Appeals*—The defendants appealed. The doctor subsequently died, and his appeal was consequently dismissed as moot. The surviving defendant contended as follows: that the evidence was insufficient to establish a mail fraud scheme as to her, because the use of the mail in executing such a scheme was unsatisfactory; that the evidence was insufficient to convict her of aiding and abetting mail fraud; and that the evidence was insufficient to convict her of aiding and abetting the presentation of fraudulent records to the FDA investigator. The Court of Appeals reviewed the trial record and found that the use of the mail to cause the study sponsor to send a check that the defendants knew they were not entitled to was a use of the mails that was at least incidental to the defendants' misrepresentations, since it was the means by which the defendants realized gain from their fraud. The court found that, given the evidence that the research assistant made false entries and notes on patient charts, forged signatures on consent forms, and witnessed such signatures, a rational trier of fact could easily conclude that the research assistant

participated in the scheme and did so with the specific intent to defraud. In addition, the research assistant showed the FDA investigator the forged consent forms and the patients' records, including the patient charts on which the research assistant had made fraudulent entries. Therefore, the Court of Appeals affirmed the judgment of the district court. (Misc. No. 824; S.J. No. 7)

*DEFENDANT: Damon Corp.*, Needham Heights, Dist. Mass.; Criminal No. 84-279-T.

*CHARGED 8-28-84:* When implants of DES (diethylstilbestrol) were caused to be shipped from Childress, Texas, to Miami, Fla., for export out of the United States, DES was a new animal drug, and no approved New Animal Drug Application was in effect with respect to its intended use—501(a)(5).

*DISPOSITION:* Guilty plea; \$500 fine. (Misc. No. 633; S. No. 80-211-580 et al.; S.J. No. 8)

*DEFENDANT: David L. Henriquez*, director for international marketing of a veterinary drug firm, Needham Heights, Dist. Mass.; Criminal No. 84-278-S.

*CHARGED 8-28-84 by grand jury:* That the defendant and others conspired to defraud an agency of the United States by impairing and obstructing the function of FDA to determine whether the defendant's veterinary drug firm was causing the violative shipment of DES (diethylstilbestrol). In furtherance of the conspiracy, DES implants were shipped to Childress, Texas, and Miami, Fla.; specified sums of cash were moved from Miami, Fla., to the defendant at Needham Heights, Mass.; and a specified sum of cash was taken from the veterinary drug firm's headquarters to a Needham Heights, Mass., bank, and a treasurer's check was issued by that bank payable to a Childress, Texas, veterinary supply firm—18 U.S.C. 371. In addition, when implants of DES, with intent to defraud and mislead, were caused to be shipped from Childress, Texas, to Miami, Fla., for export out of the United States, DES was a new animal drug, and no approved New Animal Drug Application was in effect with respect to its intended use—501(a)(5).

*DISPOSITION:* The defendant moved to strike portions of the indictment, moved for a bill of particulars, and moved to dismiss the indictment. The defendant also moved for a continuance and moved to enlarge the time for filing pre-trial motions. Subsequently, the defendant pleaded guilty and was sentenced to probation for two years, 52 days of community service, and a \$7,500 fine. (Misc. No. 633; S. No. 80-211-580 et al.; S.J. No. 9)

## MISCELLANEOUS ACTIONS

**SUBJECT: Buprenorphine HCl injectable and date of FDA approval for purposes of the non-patent exclusivity period of Norwich Eaton Pharmaceuticals, Inc., Cincinnati, S. Dist. Ohio; Civil Nos. C-1-85-1914 and (upon appeal) 86-3397.**



CHARGED 12-27-85 by Norwich Eaton Pharmaceuticals, Inc., against HHS Secretary Otis R. Bowen, FDA Commissioner Frank E. Young, M.D., and the Food and Drug Administration (FDA) in a complaint for declaratory judgment: That Norwich was the owner of the approved New Drug Application (NDA) for the analgesic drug Buprenex (buprenorphine HCl) Injectable; that the Drug Price Competition and Patent Term Restoration (DPC-PTR) Act of 1984 made a sweeping change in the new drug approval process for post-1962 new drugs based on a compromise that provided for prospective periods of exclusivity for certain pioneer new drug approvals granted between Jan. 1, 1982, and Sept. 24, 1984; that prior to FDA's approval of Norwich's NDA, buprenorphine had never been approved for marketing or use as a drug in the United States; that while buprenorphine HCl was being tested in the United States and until Feb. 19, 1985, buprenorphine HCl was treated as being automatically controlled under the Controlled Substances Act as a Schedule II drug because it was prepared from thebaine; that clinical studies of buprenorphine established none of the significant physical dependence liability of Schedule II substances such as morphine and codeine and established that the psychological dependence liability of buprenorphine was also very low compared to such drugs; that buprenorphine should be controlled by the Drug Enforcement Administration (DEA), if at all, in Schedule V—the least strictly controlled schedule under the Controlled Substances Act; that Norwich had complied with the FDA and DEA's determination that buprenorphine was automatically controlled in Schedule II until it was rescheduled in a formal DEA rule-making proceeding; that on Jan. 16, 1981, Norwich and FDA corresponded concerning Norwich's NDA and the labeling for Buprenex Injectable; and that the Norwich-FDA correspondence also included the following: an Oct. 14, 1981, FDA letter that concluded "Upon successful completion or agreement of the aforementioned, you will be notified in writing that your application is approved. However, you may not legally market the drug until final rulemaking procedures are enacted by the Drug Enforcement Administration"; a Dec. 29, 1981, FDA letter stating that the Norwich's NDA "is approved" but also stating, "As you know, the Division is preparing documents to affect lesser controls for buprenorphine. This, however, in no way impairs your approval to market buprenorphine in its current controlled substances schedule"; a May 24, 1982, FDA letter rejecting Norwich labeling and commenting that Norwich must comply with labeling requirements, "which will be necessary following control by the Drug Enforcement Agency"; and a June 28, 1985, FDA letter that approved Norwich's final printed labeling. Marketing of the drug began soon after the June 28, 1985, approval of Norwich's labeling.

In view of the above, Norwich charged that its NDA for Buprenex Injectable could not be deemed to have been approved on Dec. 29, 1981, because the draft labeling before FDA did not contain any references to the controlled status of the drug as required by regulation and Norwich had not proposed nor had it accepted any FDA proposal that the drug be labeled and marketed as a Schedule II drug; that its NDA was actually approved on June 28, 1985, when

labeling incorporating a controlled substance designation was finally approved; and, therefore, Norwich was entitled to the five-year exclusivity provided by the DPC-PTR Act of 1984.

Norwich wrote FDA requesting recognition of such "exclusivity"; Norwich submitted a Citizen Petition for recognition of such exclusivity; and, when Norwich's Citizen Petition was denied, Norwich had exhausted its administrative remedies. Norwich further charged that its NDA cannot be deemed to have been approved on Dec. 29, 1981, because the draft labeling pending before FDA and upon which the "approval" was based was not actually approved by the agency; that Norwich was unaware of and was unable to accept or ratify FDA's implied proposal, in the December 1981 letter, that the drug be marketed with labeling reflecting a Schedule II status; and that, if Norwich was deemed to have accepted the implied FDA proposal for marketing the drug as a Schedule II substance, then such acceptance occurred on Sept. 14, 1984, when Norwich first submitted draft labeling reflecting a Schedule II designation.

Accordingly, Norwich prayed that FDA publish a specific reference to the appropriate exclusivity period, and that FDA be enjoined from permitting abbreviated NDAs for the drug before the expiration of the five-year exclusivity period.

**DISPOSITION: District Court**—The district court found that Norwich was entitled to five years exclusivity and enjoined FDA from approving any abbreviated NDAs for the drug. The court noted that the case turned on when FDA approved Norwich's NDA; and, relying upon the stated policy of 21 CFR 314.1(c)(4)(e) not to approve an NDA until the labeling was in its final form, the court found that FDA's approval had been contingent upon and not effective until the approval of labeling in its final form. The government appealed.

**Court of Appeals**—Upon appeal, the Court of Appeals ruled for the government since it could see nothing in either the statute or the regulations that would prohibit FDA from approving a drug based upon proposed labeling as FDA purported to do in December 1981. The court found that the statute, although requiring submission of "specimens of the labeling proposed to be used for such drug" did not specifically require submission of the final labeling and the regulation stating that an "application will not ordinarily be approved prior to the submission of the final printed label" logically implied that, on some occasions, FDA would approve an NDA based on draft labeling. FDA admitted that its letter of Oct. 14, 1981, erroneously indicated that final DEA rule-making would be necessary before legal marketing could occur. Norwich could have marketed the drug at the time of the 1981 approval as a Schedule II drug and Norwich's decision not to do so was a marketing decision, not a result compelled by law. FDA's determination that the drug was approved in 1981 was a reasonable interpretation and was not in conflict with expressed congressional intent. FDA's determination did not violate the statutory prohibitions against arbitrariness and capriciousness. (Misc. No. 795; S.J. No. 10)

# WHY YOU SHOULD OPEN YOUR EYES BEFORE YOU OPEN YOUR MOUTH.

## **SEEING IS BELIEVING**

If you don't examine your nonprescription medicine very carefully before you take it, you're taking a chance. Because even though nonprescription medicines are packaged in ways that help make tampering evident to consumers, nothing—not even state-of-the-art technology—can make a package completely tamper-proof.

## **TO USE AS DIRECTED YOU HAVE TO READ WHAT'S DIRECTED**

Always read the label on over-the-counter medicines to find out what safety seals and other tamper-evident features you should be aware of.

## **LOOK BEFORE YOU LEAP**

Always inspect the outer packaging *before* purchasing.

## **INSPECTION IS PROTECTION**

Never buy packaging that looks suspicious, has cuts, tears or other imperfections. Always examine the medicine itself very carefully when you open the package. And never take any medicine that looks different from the others in the package.

## **LET THERE BE LIGHT**

Never take your medicine in the dark.

## **SILENCE IS NOT GOLDEN**

A product imperfection or irregularity does not necessarily mean that a medicine has been tampered with. However, if you're in doubt, don't use it and don't keep it to yourself. Make sure you inform the store manager who will report it to the proper authorities.

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