

# FDA CONSUMER

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

• VOL. 26 NO. 7

SEPTEMBER 1992 •



LATEX ALLERGIES: WHEN RUBBER

RUBS THE WRONG WAY







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# FDA CONSUMER

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Doing research in FDA's pertussis lab, Theresa Finn, Ph.D., streaks a plate with *Bordetella pertussis*, the organism that causes the childhood disease pertussis. For more about FDA's role in this research and for information about a new vaccine, see page 22.





## Device Tracking Reg Final

Manufacturers of certain life-supporting devices and permanent implants such as heart valves and breast implants must track their devices from production through distribution to the patient, according to a new FDA rule mandated by the Safe Medical Devices Act of 1990.

The agency's proposed device-tracking rule, published in the March 27 *Federal Register*, prompted hundreds of comments. As a result, FDA revised it and on May 27 repropose the rule, which became final May 28. Both the reproposal and final rule were published in the May 29 *Federal Register*.

FDA Commissioner David A. Kessler, M.D., said, "Tracking will help FDA protect the public by providing the information necessary to quickly remove dangerous and defective devices from the market. Identifying and following patients who receive these devices is also critical, so that the patients can be notified promptly of any problems."

The requirement only applies to certain permanent implants and to life-sustaining or life-supporting devices not used in medical facilities, the failure of which would be reasonably likely to cause a serious adverse health effect; such devices are difficult to track. FDA could designate additional devices for tracking.

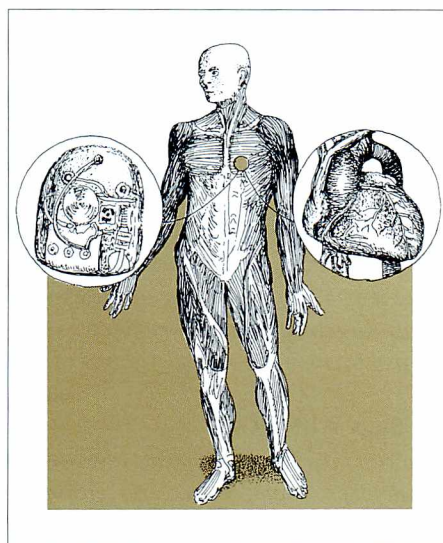
The rule affects 21 types of devices. Of these, 15 meet the statutory criteria for tracking. FDA designated six more, the failure of which also would pose a potential public health risk.

Manufacturers must design a system appropriate to their products to trace, identify and report to FDA, within 10 working days of FDA's request, patient names, device locations, and other information.

Manufacturers have until March 1, 1993, to establish their effective tracking systems.

The portions of FDA's tentative final rule on medical device problem reporting (published in the Nov. 26, 1991, *Federal Register*) applicable to distributors also became final May 28. The reporting rule requires that health-care facilities, and now device distributors, report any death or serious injury or illness related to device use to the manufacturer or FDA within 10 working days of becoming aware of the information.

## Long-Term Studies For Pacemaker Leads



Manufacturers, distributors and importers of all implanted pacemaker leads marketed in the United States since Jan. 1, 1982, are being required by FDA to conduct long-term performance studies, because of concern that leads may wear out prematurely, necessitating their replacement.

A pacemaker is a device surgically implanted in the chest that can sense the onset of abnormal rhythm and sends electrical pulses to the heart to maintain a normal heartbeat. The leads are insulated wires that connect the pacemaker with the heart.

The lifespans of the pacemaker leads vary widely. Some last as long as five years, but others wear out sooner.

"These studies will show whether some pacemaker leads have a tendency to wear out prematurely, needlessly exposing patients to the risk of early replacement," said FDA Commissioner David A. Kessler, M.D. "If this is the case, we will ask the manufacturers to take appropriate action."

The agency announced this requirement on July 1, 1992. FDA is requiring the studies under a provision of the Safe Medical Devices Act of 1990 that allows the agency to require manufacturers to conduct studies of devices already on the market when necessary to protect public health or to provide needed safety or effectiveness data. About 15 firms will be involved in the studies.

## FDA Approves First Drug For Common Prostate Problem

The first drug to treat benign prostatic hyperplasia (BPH), caused by prostate gland enlargement, was approved by FDA last June 19. The drug is named Proscar (finasteride).

"This approval represents a significant improvement in therapy alternatives for a common condition in older men," said FDA Commissioner David A. Kessler, M.D. Previously, the only BPH treatments were surgery and other mechanical procedures to reduce prostate size.



The cause of BPH is unknown. Some doctors believe it may be a reaction to alterations in hormonal balance associated with aging.

The prostate, a walnut-sized gland at the base of the bladder and encircling the urethra, contributes enzymes and acids to semen. As most men age, the prostate gradually enlarges and sometimes blocks the urethra, obstructing the outflow of urine. Prolonged obstruction can damage the kidneys.

In controlled clinical trials, for one year, 1,645 participants received either a placebo or 1 or 5 milligrams of Proscar. Of the patients who received the drug, about 20 percent experienced decreased prostate size, and about 50 percent had increased urine flow and improved symptoms. The most common adverse effects reported with Proscar were decreased libido, ejaculation disorders, and impotence.

Some patients may require treatment for more than six months before they experience the desired increase in urine flow or improvement of symptoms.

Merck and Co., Inc., of Rahway, N.J., manufactures Proscar.

(See also "Prostate Problems Plague Older Men" in the April 1992 *FDA Consumer*.)

### **Prescription Required For Patient Restraints**

Patient restraint devices, used on more than half a million people in nursing homes and hospitals, are now available by prescription only, as a result of a recent FDA action. FDA took this step because, as currently labeled and used, the devices may pose serious risks to patients.

FDA proposed other regulatory changes for the devices, including requiring pre-

market approval, in the June 19, 1992, *Federal Register*.

"When they are necessary, medical restraints provide benefit to many patients and their care-givers," said FDA Commissioner David A. Kessler, M.D. "But if they are used improperly, patients may suffer injuries or even death."

The restraints, which include safety vests, jackets, lap and wheelchair belts, and fabric body holders, are intended to prevent falls or other injuries. Their incorrect use, however, is responsible for an estimated 100 or more deaths each year, mostly due to strangulation. Broken bones, burns, and other injuries have also been reported.

An FDA review of reported incidents shows that inappropriate patient selection, incorrect restraint selection, errors in applying the devices, and inadequate patient monitoring are the primary causes of injuries related to their use.

FDA also proposed that:

- labels for the devices provide clearer directions for use with warnings about potential hazards
- the devices be used under the supervision of a health-care professional or other trained individual
- health-care facilities train their staffs in proper use of the restraints
- alternatives to restraints be used whenever possible
- patients be observed frequently for comfort and safety.

The Health Care Financing Administration already requires distribution of educational information to advise patients that they have a right to refuse restraints and to be informed of facilities' policies regarding their use, and that use of restraints should be monitored and documented by staff specially trained for this purpose.

### **Omniflox Recalled**

Because of serious adverse reactions, including three deaths, the manufacturer of a recently approved antibiotic voluntarily recalled the drug in June and halted distribution.

FDA approved Omniflox (temafloxacin) tablets, manufactured by Abbott Laboratories, Abbott Park, Ill., in January 1992. By June, there were about 50 reports of serious adverse reactions. In addition to the three deaths, reactions were:

- severe low blood sugar, especially in very elderly patients with decreased kidney function
- hemolytic anemia (destruction of red blood cells) and other blood cell abnormalities
- kidney dysfunction, necessitating dialysis in approximately half the cases
- liver dysfunction
- allergic reactions, some of which caused life-threatening respiratory distress.

FDA and Abbott advised consumers who were taking Omniflox to consult their doctors and return unused portions of the drug to the place of purchase.

Omniflox is one of a new class of broad-spectrum antibiotics called synthetic oral fluoroquinolones. They are used to treat a variety of infections, including those of the lower respiratory tract, skin, prostate, and urinary tract.

This pattern and frequency of severe adverse events has not been seen with the other drugs in this class.

Abbott tested Omniflox on 4,200 people before FDA's approval, but did not observe these serious reactions during the clinical studies. However, during the first three months of marketing, about 250,000 people took Omniflox, increasing the



chance of a rare reaction becoming evident.

"This is how the system works," says Bruce Burlington, M.D., a deputy director in the agency's Center for Drug Evaluation and Research. "This is not a failure of drug development. When, over the first months of marketing the number of people taking a new drug increases by fiftyfold or more, it is the first time rare adverse events will show up."

He adds that it is essential for patients to report any unusual symptoms to their doctors, and doctors need, in turn, to contact the manufacturer or FDA. "If the adverse effect is related to the drug, these reports will help us find out early and deal with it promptly," he says.

### Skin Peelers Pose Dangers

Chemical skin peelers that allegedly remove wrinkles, blemishes, blotches, and acne scars are not approved by FDA and may be dangerous, the agency has warned.

FDA issued the warning after it received reports of several injuries caused by skin peelers, including four reports of skin burns from a product called PeelAway. The agency said such products can penetrate the skin too deeply, causing severe burns, swelling, pain, and sometimes permanent scars.

The agency sent a warning letter May 14 to PeelAway manufacturer Global Esthetics of Seattle, Wash., saying it considers the product to be a new drug that cannot be legally marketed without FDA approval. The letter said the product is misbranded and presents a significant health hazard.

In one case, a California woman suffered seizure, shock, and second-degree burns after a beautician applied a skin

peeler to her legs.

Skin-peeling products typically contain acids such as resorcinol, phenol, lactic acid, trichloroacetic acid, salicylic acid, and glycolic acid. Ingredients and strengths vary considerably between products, however. Also, skin reactions to the chemicals vary among individuals.

The products are ordinarily applied to the skin for a short time each day for 6 to 12 days. The skin initially reddens as with a sunburn, then darkens and finally peels away, revealing what manufacturers claim will be "new skin."

Previously, only plastic surgeons and dermatologists carried out skin-peeling procedures. But now cosmetologists, beauticians, and other non-medical professionals do them, sometimes using newly marketed preparations. Several products can be bought by mail. Many have inadequate instructions. None have been approved by FDA as being safe and effective.

FDA will review all skin-peeling products and work with state attorneys general to stop the sale and use of those that are hazardous. The actions are not directed at facial "masks" intended for one-time or occasional use to cleanse the skin.

### 'Pill' Makers Urged To Adopt Simpler Directions

To reduce the number of unplanned pregnancies among women taking birth control pills, FDA asked all oral contraceptive (OC) manufacturers to voluntarily adopt standard simplified directions for use. Such action had been recommended by the agency's Fertility and Maternal Health Advisory Committee on Feb. 8, 1991.

FDA medical personnel, with the help

of consultants, rewrote the current patient directions for use and, last April, sent the new text to all firms making birth control pills.

In an accompanying letter, the agency said, "we believe that our goal of making correct OC use easier—especially when switching from one brand or format to another—will be reinforced by the instructions' standardization among brands as well as by their simplification."

The letter emphasized standardization of two major sections that varied widely from one manufacturer to another: when to start the pill and what to do when pills are missed.

"We have every indication that all companies will comply," says Philip Corfman, M.D., who is with FDA's division of metabolism and endocrine drug products.

Of the 10.7 million American women who take oral contraceptives, more than 250,000 become pregnant each year because they didn't follow the instructions, according to the National Academy of Sciences.

### Committee Recommends Approval of Contraceptive

A drug given by intramuscular injection received unanimous recommendation for approval as a contraceptive from FDA's Fertility and Maternal Health Drugs Advisory Committee last June 19.

If approved for this use by FDA, Depo-Provera (medroxyprogesterone acetate suspension) would be given to women in a single injection, once every three months, to prevent pregnancy. The drug, a derivative of the hormone progesterone, is approved, at a different dosage level, to treat endometrial and kidney cancers.

Upjohn Co. of Kalamazoo, Mich., de-



veloped Depo-Provera in the 1960s and applied for approval of the drug as a contraceptive in 1978. FDA rejected the application because studies showed mammary tumors developed in beagle dogs given the product. Upjohn requested a board of inquiry to reevaluate FDA's decision. The board met in 1983 and upheld FDA's decision. Subsequent studies and recommendations by the World Health Organization (WHO) led FDA to decide in 1991 that



the beagle is not an appropriate model for studies of whether a steroidal (hormonally derived) contraceptive might cause cancer in humans.

Depo-Provera is marketed for contraception in a number of foreign countries. At last June's meeting, Upjohn presented data from a large WHO study showing the relationship between this form of contraception and breast cancer is no greater than that between oral contraceptives and

breast cancer. The advisory committee did not believe the relationship was strong enough to warrant withholding approval of the drug.

New data from Thailand indicates a possible higher risk of low birthweight in babies born to women exposed to Depo-Provera during pregnancy. The committee recommended that the labeling contain a warning that physicians should rule out pregnancy before prescribing the drug.

The committee also evaluated new data from New Zealand showing a possible increased risk of osteoporosis associated with long-term use of Depo-Provera. Committee members suggested that an informed consent document for patients discuss the risk of bone loss, which may lead to osteoporosis. The committee also recommended that post-marketing studies be conducted to address this risk.

When making decisions, FDA seriously considers the recommendations of its advisory committees, which consist of experts outside the agency. However, the agency is not bound by committee recommendations.

### Biotech Food Policy Announced

A policy statement explaining how FDA will regulate new varieties of whole foods developed through biotechnology was announced last May by HHS Secretary Louis W. Sullivan, M.D.

The same standards that govern other foods will be applied to these products. The scientific bases for evaluating and ensuring safety of new varieties of foods produced with any technique, including those of the new biotechnology (such as recombinant DNA or "gene splicing"), are explained in the *Federal Register* of May 29, 1992. This document also explains le-

gal marketing requirements for new food products.

FDA watches over most foods sold in this country under the federal Food, Drug, and Cosmetic Act's provisions on adulterated food. This "post-marketing" authority enables FDA to remove from the market any food or added food component found to injure human health.

However, when substances intentionally added to food through genetic modification raise safety questions, they may be regulated as food additives and require pre-market approval.

FDA anticipates that many substances currently being introduced into new plant varieties will not require its pre-market approval. But to ensure the safe introduction of these substances into the food supply, the agency has included as the core of its policy statement a comprehensive "guidance to industry" to assist companies with their own internal reviews of these foods. The questions companies must resolve while developing foods from new plant varieties include:

- Has the concentration of any naturally occurring toxicants in the plant been increased?
- Has an allergen not commonly found in the plant been introduced?
- Have the levels of important nutrients changed?
- Have new substances been introduced into food that raise safety questions?
- What are the environmental effects?
- Have the genetic material and its "expression products" been well characterized?
- Have accepted, established scientific practices been followed?

The policy developed by FDA is consistent with recent statements and policies adopted by a number of expert panels of



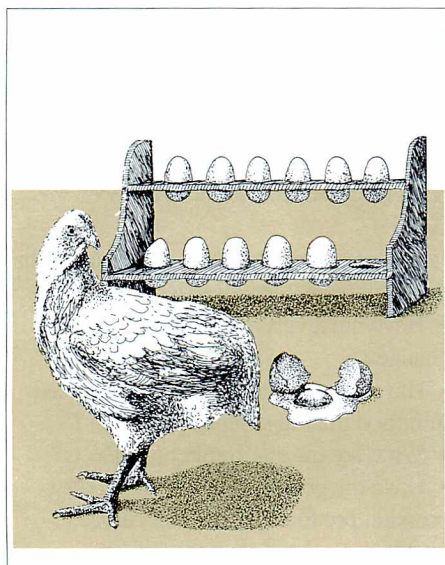
national and international organizations.

FDA developed the policy after receiving requests from manufacturers and others who wanted to know how the biotech foods being prepared for marketing would be regulated. The policy development was expedited by the Biotechnology Working Group of the President's Council on Competitiveness.

(See also "Perspective on Food Biotechnology" in the March 1990 *FDA Consumer*.)

### Agencies Expand Program To Prevent Illness from Eggs

An expanded program to better protect consumers against illness caused by *Salmonella* bacteria in grade A shell eggs is under way.



Announced last May by FDA and USDA's Animal and Plant Health Inspection Service (APHIS), the joint program

includes increased breeder flock testing and enhanced tracking of suspect eggs to the flock of origin. It also includes research and recommendations to consumers, restaurant managers, retail markets, and institutions about storing, handling and cooking eggs. In addition, the agencies pledged support to a pilot *Salmonella* control program with the State of Pennsylvania.

In 1986, the national Centers for Disease Control determined that grade A shell eggs—the kind most commonly sold in cartons in grocery stores—were a significant source of *Salmonella enteritidis*, one variety of the bacteria. To look into the problem and control it, FDA and APHIS each developed programs based on their different authorities and responsibilities.

FDA provides guidance to retail food firms, informs the public how to avoid illness, assists other government agencies, and monitors the marketplace to make sure eggs in interstate commerce are properly handled and labeled. APHIS traces the source of egg-related outbreaks, tests the source flock and works to eliminate infection, and enforces regulations requiring pasteurization of eggs from infected flocks and prohibiting interstate shipment of infected birds.

"The joint program will not eradicate *Salmonella* bacteria or eliminate all risk of disease, but it will help us deal more effectively with the problem and minimize the risk to the public health," FDA Commissioner David A. Kessler, M.D., says.

Salmonellosis, the illness that results from eating food containing *Salmonella*, lasts a day or two in most healthy people. It can be life-threatening, however, in very young children and people with lowered immunity.

### Sleep Aid Safe When Used Carefully

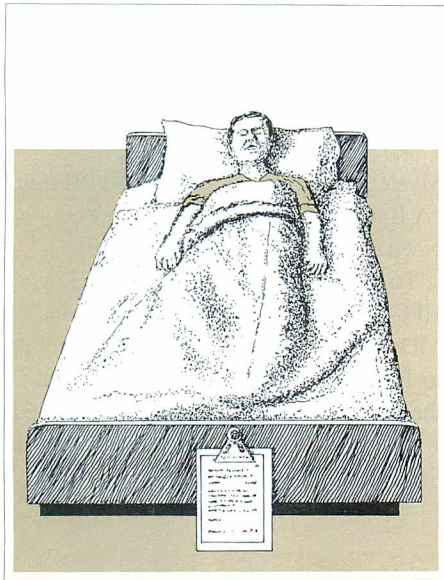
The prescription sleeping aid Halcion (triazolam) is safe and effective when used as the current labeling directs, according to FDA's Psychopharmacological Drug Products Advisory Committee. The committee also recommended further studies and labeling changes to address concerns about the drug's side effects.

For several years, critics have charged that Halcion had a higher frequency of psychiatric side effects—including memory loss and depression—than other sleep-aid drugs. In November 1991, at FDA's request, Halcion's manufacturer, the Upjohn Company, agreed to make changes in the way it marketed Halcion to ensure that both patients and doctors were aware of the appropriate dosage and possible side effects. (See the Updates section of the March 1992 *FDA Consumer*.)

After evaluating current data on Halcion at its meeting last May 18, the FDA advisory committee has recommended:

- Upjohn should conduct further clinical trials to study Halcion's full possible dose range and the relationship of dose to side effects and effectiveness.
- The labeling should emphasize adequately that Halcion should only be used in low doses for a short time and that, although the standard adult dose is 0.25 milligrams, elderly patients or those who weigh 100 pounds or less should take a reduced dose of 0.125 milligrams. The labeling should also emphasize that in clinical trials, some patients experienced anxiety the day after taking Halcion.
- The patient package insert should be revised to include more easily understood guidance on using Halcion. Upjohn had





previously revised the patient package insert to include explicit information about the drug's risks and benefits.

Upjohn announced that it plans to undertake a 10,000-patient clinical trial to compare the safety of Halcion with similar sleep aids.

FDA's advisory committees are composed of outside experts. Although their recommendations are not binding on the agency, they are given serious consideration in FDA's policy and actions.

### Distributor Recalls Products

For Your Health, Inc., Kent, Wash., has recalled certain products, including injectable products and vitamin eye drops, due to possible contamination. FDA announced the recall on June 19 after agency tests found mold in some of the products.

At press time, with testing continuing, FDA tests had found mold in two of the firm's products: intravenous solutions of

"magnesium-ATP" and "Solu-Cortef." (Solu-Cortef is an approved product made and distributed by The Upjohn Co., Kalamazoo, Mich., and there are no known problems with products it distributed. This recall only applies to Solu-Cortef repackaged and distributed by For Your Health Pharmacy.) Injection or intravenous use of these products could cause systemic infections that might be life-threatening in patients with poor health or impaired immunity.

Other products under recall include:

- chromium liquid
- copper liquid
- glutathione
- manganese liquid
- molybdenum liquid
- saline solution
- selenium liquid
- trace mineral
- vanadium liquid
- zinc liquid
- vitamin A and C eye drops.

The vitamin eye drops are in plastic eye-drop bottles, but the other products—all for injection—are in glass vials.

Labeling varies. Some labels may have the name "For Your Health Pharmacy" or "Tahoma Clinic." Some products may not have an attached label.

Because complete records from the firm are unavailable, FDA cannot verify all the consignee names and locations, the quantity of products distributed, or the quantity still on the market.

FDA became aware of the distribution and potential danger of these products on May 6, 1992, when the agency—along with a U.S. attorney and local law enforcement official—executed a search warrant at the firm. FDA conducted sterility testing on drug samples from For Your Health

Pharmacy because the firm's manufacturing facility lacked proper controls to ensure product sterility.

Consumers, physicians, and drug wholesalers and retailers should return these products to For Your Health, Inc., 13215 S.E. 240th St., Kent, WA 98042. People needing further information may telephone the company at (206) 631-0636.

### Study Finds Rx Drug Ads Misleading

A remarkably high proportion of prescription drug advertising from June 1990 contains misleading information and appears to violate FDA regulations, according to a study conducted by the UCLA School of Medicine.

Under the auspices of the HHS Office of the Inspector General, FDA examined the ads and is seeing that the misleading ads are corrected.

The study was reported June 1 in the *Annals of Internal Medicine*, which also contained an editorial on the subject by FDA Commissioner David A. Kessler, M.D. The researchers found that 40 percent of the ads did not contain the required risk/benefit information and 44 percent would lead to improper prescribing if physicians used only the information in the ads. Moreover, the researchers concluded that many ads are deficient in areas for which FDA has explicit standards and that new strategies are needed to ensure that ads follow existing rules and protect consumers.

The study reflects the situation in 1990 before FDA's increased prescription drug advertising review and the pharmaceutical industry's recent increased coopera-



tion. Kessler stated that its publication is important because it heightens awareness of the degree to which misleading information may pervade the “informational marketplace” underlying physicians’ prescribing decisions.

The study’s findings were consistent with FDA’s assessment of the advertising marketplace in 1990, after which FDA’s division of drug marketing, advertising and communications and the division of biometrics started determining what kinds of clinical-statistical problems existed with research cited by manufacturers’ support to their ad claims. In some cases, part of FDA’s responsibility in monitoring ad claims is to evaluate supportive data often

not readily available to physicians who read the ads.

FDA found manufacturers had used study results to show their products were better than their competitors’, even though the studies did not prove such a finding. In some cases, manufacturers had used results from studies designed for one purpose to prove unrelated or accidentally discovered findings.

This increased interest since the agency stepped up its review contributed to addressing many of the problems mentioned in the UCLA study. As a result, FDA believes a pre-approval authority for advertisements is neither necessary nor desirable at this time.

### Reprints Available

Reprints of three *FDA Consumer* articles are newly available.

They are “Arthritis: Modern Treatment for the Old Pain in the Joints” (FDA 92-1190), “Endometriosis: Coping with a Mysterious Disorder” (FDA 92-1191), and “A Burning Question: When Do You Need an Antacid?” (FDA 92-3179).

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## CONSUMER FORUM



### Vegetarian Diets

I recently read a copy of the article “Vegetarian Diets” that appeared in your May issue. I applaud you and the author, Dixie Farley, for attempting to shed light on the vegetarian diet and nutrition. With the increasing evidence of the adverse health and ecological consequences of a meat-based diet, publications such as yours can serve the public well by introducing sound alternatives.

However, I was disappointed in the

slant of the article. Subtitled “The Pluses and the Pitfalls,” the article seemed to steer mostly toward the pitfalls—so much so that I bet readers would be more than happy to fall right back into the diets that are making them sick. . . .

The article raises much concern about the risk of vitamin B<sub>12</sub> deficiency for vegans (pure vegetarians—no animal products or fish), though on the last page . . . the author finally states that the vitamin can be obtained from fortified soy milk and cereals. I appreciate the concern

of the author, for the risks are indeed serious but the preventative measures are so simple. Why not say that up front! Note that only small amounts of this vitamin are thought to be necessary. The average human liver contains several milligrams of the vitamin and can store it for years. . . .

Similarly, the article states that vegetarians may have inadequate vitamin D and calcium, which can contribute to risk of osteoporosis. Please note that studies have shown that vegetarians tend to have denser bones than omnivores, suggesting a lower

than normal risk of developing osteoporosis. In addition, several studies have shown that high-protein intakes cause loss of calcium. (For example, L.H. Allen, E.A. Oddoye, and S. Margen, "Protein-Induced Hypercalcuria: A Longer-Term Study," *The American Journal of Clinical Nutrition*, April 1979; or F.R. Ellis, S. Holesh, and J.W. Ellis, "Incidence of Osteoporosis in Vegetarians and Omnivores," *The American Journal of Clinical Nutrition*, June 1972). . . .

The [*Consumer*] article notes that according to the Institute of Food Technologists and the American Dietetic Association, "if appropriately planned [emphasis the author's], vegan diets can provide adequate nutrition even for children." Then the author quotes an associate professor of food science and human nutrition at the University of Missouri as saying, "My *bet* [emphasis mine!] is those kids will have health problems when they reach 40, 50, or 60 . . . mostly because of imbalances with micronutrients . . . , particularly iron, zinc, and copper." Please note that the professor is only surmising. Studies of vegetarians show that they live much longer and with significantly less incidence of the degenerative diseases (cancer, stroke, and health disease) that plague omnivores. For example, the German Cancer Research Center in Heidelberg found after an 11-year study of 2,000 vegetarians and semi-vegetarians that people who eat little or no meat live significantly longer than meat eaters. Consider as well the long-term studies of Seventh Day Adventists, who are primarily vegetarian (and vegan). Furthermore, evidence shows vegetarian (and vegan) children to be as healthy, if not healthier, than other children. . . . Research by the Centers for Disease Control showed that 404 vegetarian (mostly vegan) chil-

dren were not significantly different in height and weight when compared to meat-eating children. . . .

Regarding the need for the micronutrients, the requirements for these can be easily satisfied by fortified cereals, which most children eat plenty of. Zinc can be obtained from wheat germ; iron can be obtained from legumes, whole grains, potatoes, green vegetables, and dried fruits; copper can be obtained from nuts, legumes, whole grains, and drinking water!

The author states that "nearly every animal food provides all eight of the essential amino acids in the balance needed by humans." All food protein (except gelatin) contains all the essential amino acids. So, even a vegan diet, containing plenty of whole foods, can provide sufficient quantities of these amino acids.

The author mentions Frances Lappe's advocacy of eating complementary proteins to gain the greatest use of all the amino acids (*Diet for a Small Planet*). Lappe has since rescinded this recommendation. Read her latest edition of the book. Many studies that showed protein deficiency of vegetarian diets were done on rodents, whose protein requirements are much higher than that of humans. The largest study of Western diets and colon cancer ever done finds that not only animal fat but meat itself causes the disease. The director of the study, Dr. Walter Willett of Brigham and Womens Hospital in Boston, concluded: "If you step back and look at the data, the optimum amount of red meat you eat should be zero."

The article fails to mention that the Cornell-China-Oxford Project on Nutrition, Health, and Environment, termed by *The New York Times* as "the Grand Prix of dietary studies," confirms with unprecedented authority certain relationships be-

tween diet and health, including:

- Consuming high amounts of fiber can protect against colon cancer.
- Childhood diets that are high in protein, fat, calories, and calcium promote early growth but at the cost of higher breast cancer rates among women later in life.
- A primarily vegetable-based diet is not only completely safe but much more healthful than an animal-based diet.
- Dairy foods are not needed to prevent osteoporosis—the body can get sufficient calcium from plant sources.
- Eating meat is not necessary to prevent iron-deficiency anemia. . . .

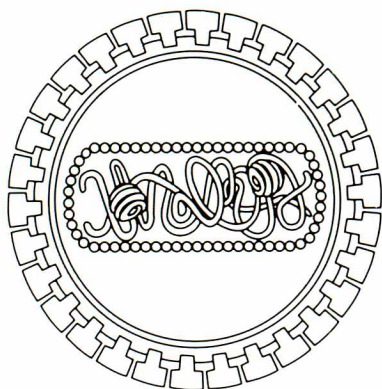
In conclusion, the diet-related diseases plaguing our modern society are not those of deficiency but rather of excess: excess of fat and protein. By turning toward a vegetarian diet, we can eliminate many of these problems. True, changing a meat-centered habit that has been deeply entrenched over many years is not easy. But the consequences of eating meat are too severe to take lightly, and well worth the initial discomforts of change. Health and longevity are very rewarding in themselves!

—Phil Milgram, Warren, Mass.

*Ed. replies: The science on vegetarian diets is evolving and there are many aspects to the discussion. Our intention was to present a balanced article, giving voice to various viewpoints. The additional information Milgram presents is indeed interesting.*

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





### DDC Approved to Treat HIV

Zalcitabine (commonly known as DDC) became the third drug approved specifically to treat HIV infection last June 22. FDA approved the drug for use only in combination with Retrovir (zidovudine, commonly known as AZT) to treat adult patients with advanced infection whose clinical or immunological condition is worsening.

This is in accord with an advisory panel recommendation last April.

Marketed under the trade name HIVID, zalcitabine is the first drug approved under the procedures of FDA's proposed accelerated drug review policy. The policy, designed to speed the review process for drugs intended to treat life-threatening illnesses, also provides for prompt removal of the drug from the market if further review shows it to be ineffective.

"This new drug is not a cure," said James Mason, M.D., assistant secretary for health, "but it constitutes an important addition to the expanding group of antiviral drugs currently available, including AZT and DDI, for treating people with AIDS."

Early clinical studies have shown that patients treated with HIVID and Retrovir

attained higher increases in CD4 immune cells, and sustained them longer, than patients who received Retrovir alone as initial therapy. Studies to date, however, do not show longer survival, fewer opportunistic infections, or slowed progression of disease in patients treated with the two drugs in combination.

The most severe side effects observed in patients taking HIVID have been neurological, sometimes causing tingling and pain in the hands and feet. Other side effects include inflammation of the pancreas, rash, mouth ulcers, decreased blood platelets, and abnormal liver function.

Side effects of combined use of HIVID and Retrovir are about the same as those expected with either drug alone.

HIVID is manufactured and distributed by Hoffmann-La Roche of Nutley, N.J.

### Another Quick HIV Test Licensed

A new 10-minute diagnostic test kit to detect the presence of antibodies to human immunodeficiency virus type 1 (HIV-1) was licensed by FDA last May 22.

The new test kit is designed to be used by health professionals in settings where traditional ELISA kits are either impractical or unavailable, such as doctors' offices, clinics, emergency rooms, small hospitals, or laboratories.

A different rapid HIV test kit, distributed under the trade name Recombigen and licensed by FDA in 1988, uses a latex agglutination test method, in which a sample of whole blood, plasma or serum is mixed with protein-coated latex beads. If AIDS antibodies are present in the sample, they bind to the beads, causing them to clump, or agglutinate. The test requires a trained professional to visually spot the clumping with a bright light.

The new test kit, however, is based on a color reaction. It requires mixing a small amount of a patient's serum or plasma in a test cartridge with an antibody reagent to

which only HIV-1 antibodies will attach. When a special solution is added to the serum or plasma containing the reagent mixture, the window at the bottom of the test cartridge automatically indicates the result: blue if HIV-1 antibodies are present. No special equipment is needed.

"A positive reading still has to be confirmed by the Western Blot or immunofluorescence test," said Jay S. Epstein, M.D., acting deputy director of FDA's division of transfusion science, "but the new kit is a lot easier to use than an ELISA and provides an alternative in settings which require a rapid test."

In clinical trials involving 8,714 specimens collected at 11 test sites, the kit was sensitive to the presence of HIV-1 99.9 percent of the time and specifically identified the presence of HIV-1, as opposed to other antibodies, 99.6 percent of the time.

Murex Corporation of Toronto manufactures the new test kit and will market it under the brand name Murex SUDS HIV-1 Test.

### Hot Line Can Handle More Calls

Beginning Sept. 1, the Center for Disease Control's National AIDS Hotline is able to handle 2,000 more calls a day than its previous daily capacity of 3,500.

A recently installed "voice-port" system gives callers a brief message instead of busy signals when the line is tied up. Tailored to frequently asked questions, the messages might tell about a newly approved AIDS drug, give the address to write for an AIDS publication, or explain how to contact the National AIDS Clearinghouse.

The hot line number is (1-800) 342-AIDS, operating continually day and night. The TDD number for the deaf is (1-800) 243-7889, operating 10 a.m. to 10 p.m. weekdays, including holidays.



# FDA ENSURES EQUIVALENCE OF GENERIC DRUGS

by Jeffrey Yorke

*Pharmacist Jean Limpert in Washington, D.C., helps a shopper compare brand-name and generic products.*

When Stuart Addison goes to the pharmacy in Margate, Fla., he has the pharmacist fill his prescriptions with generic drugs. Addison, a retired federal government auditor, is one of many Americans who are choosing generics when they buy drugs.

"My motivation is to keep the prices down," said Addison, noting that his insurance plan pays for his prescriptions. "My pocketbook is not directly affected, but in the long run, I'm helping to keep down insurance premiums."

Although not all approved drugs are available in a generic version, those that are can offer substantial savings to consumers. For millions of Americans, the less-expensive drugs could mean the difference between getting necessary therapies and not being able to afford proper medical treatment.



Insurance companies' recommendations to policy holders that they choose generics over brand-name drugs whenever possible, coupled with the promotional efforts of large drug chains, have helped heighten consumer awareness of the availability of generics. The result has been that generic sales have been booming most of the years since 1984, when Congress passed the Drug Price Competition and Patent Term Restoration Act. This act expanded the number of drugs eligible to be manufactured as generics. The new rules eliminated the need for duplicate safety and efficacy testing for generics, saving industry time and money. The Food and Drug Administration also developed and issued explicit guidelines for a generic product's bioequivalency (see accompanying article) and stability, ensuring that products retain potency. In addition, products must meet specifications set by the U.S. Pharmacopeial Convention, a private scientific organization that sets standards for drugs and drug products in the United States. Almost 80 percent of U.S. generic drug production is done by brand-name firms in modern manufacturing plants.

In 1991, consumers spent about \$5.5 billion for generics and are expected to spend more than \$15 billion in 1995, according to a report issued earlier this year by Frost & Sullivan International, a health information research organization. The report found that expiring patents on pioneer (brand-name) drugs, coupled with increased attention to containing health-care costs, will play important roles in the growth of the generics industry in the next decade.

Since 1984, there has been a succession of top-selling drugs that have lost their market exclusivity and been challenged for market share by generic brands. An av-

## DRUG TERMS

**Pioneer:** The first version of a drug, which is marketed under a brand name. For example, Valium is the brand name for the first marketed version of the anti-anxiety drug diazepam.

**Generic:** A version of a drug that is equivalent to the pioneer or brand-name drug and is not marketed until the pioneer drug's patent exclusivity has expired. These "copies" are often marketed under just the generic name of the drug—for example, Diazepam. ■

erage of about 15 pioneer drugs lose patent protection annually, and FDA has prepared for an expected explosion of new generic drug applications through the end of 1995. Among the top-selling brand-name drugs scheduled to lose protection are Eli Lilly's anti-infective Ceclor, Marion Merrell Dow's calcium channel-blocker Cardizem SR, and the firm's non-sedating antihistamine Seldane. Also scheduled to lose their exclusive market niche are the anti-inflammatories Anaprox by Syntex and Voltaren by Geigy, hypoglycemics Glucotrol by Roerig and Micronase by Upjohn, and Squibb's antihypertensive Capoten.

### Scandal Rocks Industry

Popularity of the copycat products grew significantly after 1984, when the approval process was widened. But that popularity took a downturn in 1989, when

scandal rocked the industry. Federal investigators uncovered such problems as illegal gratuities, fraud, obstruction of justice, and noncompliance with various manufacturing procedures by some industry officials.

The investigations revealed that several FDA employees had accepted money or other compensation in exchange for information and assistance that gave certain firms an advantage in the approval procedure. Investigators also uncovered submissions of fraudulent data by several manufacturers. In one case, a company submitted the pioneer drug disguised as a generic version with its bioequivalence studies.

Subsequently, FDA investigators rushed to reevaluate data presented in hundreds of generic drug applications. More than 2,550 samples of the top 30 prescribed generic drugs—or about 30 percent of all generic



*The hand on the left holds the brand-name product, Achromycin V, while the other hand holds generic tetracycline.*

drugs on the market—were collected and laboratory-tested. The agency conducted intensive inspections of 36 of the largest generic drug firms and 12 contract laboratories.

### **Agency Steps Up Testing**

In early 1990, more than 300 scientists at 17 FDA labs tested samples from generic drug companies. The agency determined that only 27 samples, or approximately 1 percent of those tested, did not comply with standards of potency, dissolution, content uniformity, product identification, moisture determination, or purity.

FDA also tested 429 samples representing at least three different batches of all 24 then-currently-marketed, narrow-therapeutic-range drugs (those in which the difference between a therapeutic dose and a toxic dose is small) made by 73 brand-name and generic drug manufacturers. The 24 drugs were selected because of their high potential for adverse reactions or therapeutic failure if they lacked bioequivalency. Only five of the samples—all aminophylline tablets, a

bronchodilator—failed to meet USP standards. None of the defects in the generic drugs posed a public health hazard.

Based on these results and the fact that brand-name products experience similar failures at a similar rate, the agency recommended that doctors continue to consider prescribing generic drugs when appropriate, to offer lower-cost products to consumers.

FDA investigators continued to scrutinize operations at dozens of plants, and, in response to government findings, a number of firms made voluntary drug recalls due to manufacturing deficiencies. FDA's Office of Generic Drugs, directed by Roger L. Williams, M.D., is charged with conducting reviews and is responsible for the subsequent approval of the imitator products. The office interacts with a national network of FDA field offices to monitor the production methods of generic makers. Williams said, "the office's increased emphasis on quality, integrity and performance in the development, manufacture and review of generic drugs has led to a strong industry, a better review

process, and better generic products for the consumer."

### **Pre-Approval Inspectors**

In 1990, the agency instituted product-specific, pre-approval inspections of manufacturing sites listed in a sponsor's application. During inspections, FDA reviews the step-by-step manufacturing process and monitors how much and what kind of active ingredients, excipients (material added to make products a suitable consistency), flavorings, and other substances will be used. Sponsors must even identify the type of machinery that will be used in each step of the manufacturing process. Just as it does with brand-name drugs, the agency closely regulates generic makers' production sites and blocks the marketing of any drugs produced in substandard facilities. FDA conducts more than 5,000 inspections at drug plants annually.

Agency inspectors also review on-site production records, examine exhibit batches, and determine whether the plant is capable of producing the drug properly



## WHAT IS BIOEQUIVALENCY?

Generics are not required to replicate the extensive clinical trials that have already been used in the development of the original, brand-name drug. Instead, they must show they are bioequivalent to the pioneer drug and fall into acceptable parameters set for bioavailability, which is the extent and the rate at which the body absorbs the drug.

Scientists measure the time it takes the generic drug to reach the bloodstream. This gives them the rate of absorption (or bioavailability) of the generic drug, which they then compare to that of the pioneer drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream and in the same time as the pioneer drug. Brand-name drugs are subject to the same bioequivalency tests as generics when their manufacturers reformulate them. ■

before giving a satisfactory recommendation for the drug's approval. Plant managers must be able to show that the operation has sterile production facilities where required, acceptable assembly-line procedures, and that labeling procedures are designed to prevent mix-ups. The company must also prove that finished products are kept in a temperature-controlled storage area and that products can be easily identified to prevent drug mix-ups.

Richard Davis, director of FDA's division of field investigation, said new policies and procedures help prevent fraudulent activities and help ensure the availability of safe and effective generic products.

"We believe we have ferreted out virtually all of the fraud that was involved in the scandal," Davis said. "There shouldn't be any reason to be concerned about the equivalency, safety and effectiveness of generic drugs. We now have a very vigor-

ous pre-approval inspection program."

### Other Safeguards

Other safeguards have also been established. In May, President Bush signed into law an act that calls for the mandatory debarment of any individual convicted of a federal felony related to the development or approval of any drug application. The violator will be permanently prohibited from working in any capacity for any individual, partnership, corporation, or association that produces an approved drug and will be fined up to \$250,000. A company convicted of a federal felony related to the development or approval of a generic drug application will be prohibited from submitting applications for 1 to 10 years and fined up to \$1 million.

Todd Dankmyer of the National Association of Retail Druggists credited FDA's swift actions, comprehensive compliance plan, and the subsequent survey after the

generics scandal for restoring the faith of the medical community and consumers in generics.

At the time of the crisis, "physicians were less likely to write prescriptions for generics" because the overall quality and safety were called into question, Dankmyer said. "But it appears to be back where it was before. Pharmacists reevaluated their relationships with suppliers, and if they had been given a clean bill of health by the agency, they continued to sell the company's generic products."

### Applications Increase

From 1984 through 1991, the office received 6,635 applications to manufacture and market generic drugs, called abbreviated new drug applications (ANDAs). (Those for antibiotics are called abbreviated antibiotic drug applications [AADAs]). FDA determined that a little more than half—3,672 applications—completed the agency's requirements and could be marketed. Many others were either dropped by their sponsors or are pending further review by FDA for a variety of reasons. The agency receives thousands more—5,487 in 1991—supplements and amendments to supplements that request changes in strength, dosage form, or manufacturing method.

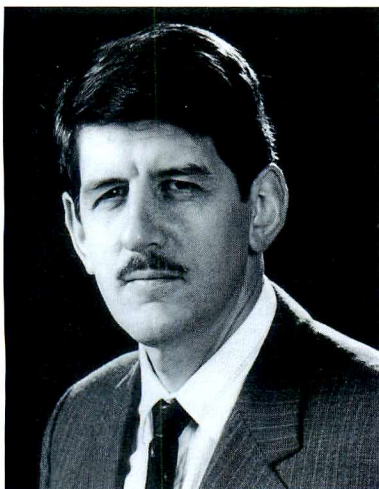
Currently, FDA approves about 200 generic drugs annually. That number is expected to climb to more than 300 over the next several years as more top-selling, brand-name drugs lose patent protection.

Nearly 20 percent of the applications submitted to FDA are rejected within 30 days of submission. The reasons for their rejection range from the firm's failure to provide sufficient stability data, to incomplete sample batch records on bioequivalency testing, to an application that is missing some form of necessary research data.

A staff of nearly 50 chemistry reviewers in the generics office sifts through stacks



## WHEN GETTING YOUR PRESCRIPTION FILLED . . .



Carl C. Peck, M.D.

Before leaving your doctor's office and getting a prescription filled, there are some points to remember and things to consider. First, FDA has taken decisive regulatory action against companies found to be producing inferior products—both brand-name and generic products. And the agency will continue to ensure the safety and effectiveness of drugs on the market.

Second, physicians and their patients should discuss and decide whether a brand-name or generic is the best therapy. There should be an agreement between them, and a physician should be aware of

which drug a patient is taking. If they jointly decide to change a therapy—whether it be a switch between two brand-name products or between brand-name and generic—they should both commit to follow carefully the outcome of that change in therapy.

Third, pharmacists and health-care providers should give careful attention to FDA evaluations of therapeutic equivalence. A drug's therapeutic rating is published monthly in the "Orange Book," *Approved Drug Products With Therapeutic Equivalence Evaluations*. The rating will indicate whether a drug has been judged by the agency to be therapeutically equivalent by meeting the criteria of pharmaceutical equivalents, bioequivalence, labeling, and good manufacturing practices. ■

—Carl C. Peck, M.D., director, FDA's Center for Drug Evaluation and Research

of data submitted by a firm after it has conducted extensive product testing. The applications are reviewed for their scientific content and for such manufacturing procedures as validation methods, raw material specifications, and container and closure systems.

Eight pharmacists review generic labeling. Part of their mission is to anticipate problems of confused or mistaken identity that can arise in drug labeling. In some cases, the pharmacists reject a product's trade name if it is too similar to another product's.

Kent Johnson, the generics office's associate director of labeling and professional support, said that having clearly distinct names is especially important to avoid drug mix-ups in ambulatory-care facilities, institutional settings, and in emergency rooms because there may not be enough time for the staff to closely examine the label.

Pioneer drugs are often protected by several patented indications in their labeling. Labeling for generic products reflects only approved indications that are not patent protected. Generics office pharmacists monitor the labeling and review new labeling as exclusive claims expire and are added to generic labels.

FDA's stepped-up effort to improve and monitor generic drug production, coupled with the industry's revitalized energy, should continue to provide consumers with safe, effective and affordable drugs. ■

*Jeffrey Yorke is a writer in FDA's Center for Drug Evaluation and Research.*



# LATEX ALLERGIES:



# When Rubber Rubs The Wrong Way

by Dori Stehlin

**E**very Thursday, Sue Lockwood's eyes would start to swell. Fridays were always the worst. Sometimes her eyes were so swollen she could hardly see. But, without fail, by the time Monday rolled around, the swelling was gone and her eyes were fine.

"I thought that I was allergic to the sand that I was playing volleyball in every Thursday," says Lockwood, who lives in Grafton, Wis. "The sand would get in my eyes and [I thought] I was breaking out from the sand."

But, although Lockwood quit playing volleyball in August 1991, the problem with her eyes persisted into the fall.

Two ophthalmologists told her that her symptoms didn't indicate an eye infection. Finally, in October she went to see an allergist.

"After interviewing me and getting a medical history he told me he was sure I was latex sensitive. Sure enough, he drew blood and I tested positive."

What were the clues that led to the allergist's conclusion? First, Lockwood is a surgical technician. Like most health-care workers today, Lockwood practically lived in latex gloves at work.

Second, her work schedule was Tuesdays, Wednesdays, and every other Thursday. That explained the miserable Fridays and recovery by Monday.

And then there was the volleyball. "It turns out she didn't use a standard volleyball," says her allergist, B. Lauren

**Paramedic/firefighter Vicki Freund**

**shows how she would start an IV on an asthma victim while wearing latex gloves.**

**During the 20 minutes Freund wore the gloves for this picture, hives broke out on her wrists and the backs of her hands.**

Charous, M.D. "Her team used a red rubber volleyball."

Latex is the milky sap from the rubber tree *Hevea brasiliensis*. It doesn't cause problems for most people. But, like other things in nature—bee sting venom, poison ivy, peanuts—latex can cause problems for some people. Those problems can range from minor skin irritation to reactions so severe that emergency medical treatment is necessary to prevent death.

For those allergic to the rubber tree's sap the only sure solution is to stay away from it. But latex products are everywhere, especially in health-care settings. It is found in all kinds of medical devices, most notably the ubiquitous surgical and examination gloves that health-care workers wear. Most condoms and diaphragms are made of latex. And latex is found in many everyday items, including balloons, household gloves, underwear, and rubber bands.

Few know better than Lockwood the surprising places latex can show up. "I don't know what I'm going to run into next," she says. She's reacted to the new carpet in her mother's house (the carpet backing contained latex) and to her nieces' and nephews' rubber toys.

## New Problem or Old?

The British first discovered latex in the mid-18th century, but it didn't come into wide use until about 50 years ago. It took several more decades before allergic reactions started to appear.

In 1979, a woman in Great Britain who reacted to her household rubber gloves was the subject of the first report of latex allergy in the medical literature. Between 1979 and 1988, about 50 cases were recorded in European medical journals. Then, things began to change.

In the fall of 1989, the Food and Drug

Administration started receiving reports of patients going into anaphylactic shock during radiologic examinations for lower gastrointestinal tract disorders. The patients had all received barium enemas, so at first the barium was suspected. But in some cases, the patients went into shock after the device, a latex-cuffed enema tip, was inserted but before the barium was administered. In all, 16 people died. The manufacturer of the barium enema tips voluntarily recalled all those on the market and started using tips with silicone cuffs instead. Because that manufacturer dominated the market, at that time FDA felt any further regulatory action was unnecessary.

Then, between March 1990 and January 1991, nine children at a children's hospital in Milwaukee had anaphylactic reactions within 30 minutes after general anesthesia was started but before any surgical incisions had been made. The latex connection was the anesthesia equipment and intravenous catheters. Fortunately, emergency procedures prevented any deaths. Eight of the children, however, required intensive care.

According to Michele Pearson, M.D., an epidemiologist with the national Centers for Disease Control, preliminary results of a nationwide survey of children's hospitals have identified at least 25 other institutions that have reported similar reactions since January 1990. All 75 children who had anaphylactic reactions had either spina bifida or other conditions involving the genitourinary tract. (See accompanying article, "Who's at Risk?")

What was happening? Were the allergic reactions a new phenomenon or just being recognized for the first time?

"I think it is something new," says Jay Slater, M.D., an attending physician in allergy and immunology at Children's National Medical Center in Washington,



# Who's at Risk?

Common to all allergic reactions to natural substances is the body's need to recognize the substance. The more often the body comes in contact with the substance, the greater the opportunity to recognize and react.

For the general public, the risk of an allergic reaction to latex is less than 1 percent. But because of constant exposure to latex, two groups are at greater risk—health-care workers and children with spina bifida and other conditions involving multiple surgical procedures. Because latex-containing medical devices abound in surgical suites, dental offices, and other health-care settings, contact with latex is an occupational hazard for health-care workers. It is also part of daily health maintenance routines (for example, catheterization) and the many surgeries high-risk children undergo.

According to Jay E. Slater, M.D., attending physician in allergy and immunology at Children's National Medical Center in Washington, D.C., the risk is so high for children with spina bifida, "we should treat them as latex-allergic regardless, whether we know that they are or not."

He cites his own research as the basis for his statement. When he tested the blood of 64 spina bifida patients, he

found 25 of the children had antibodies to latex.

"Among those who had the antibody, approximately half had a history of latex-associated reactions," he says. He adds that more and more of these kids will have reactions as time goes on.

Allergic reactions to latex can include:

- skin rash
- itching
- hives
- swollen red skin
- tears
- itching or burning eyes
- swollen lips and tongue with difficulty in breathing, wheezing
- shortness of breath
- dizziness
- fainting
- abdominal pain
- nausea
- diarrhea.

In rare cases, an allergic individual goes into shock; blood pressure plummets, the throat swells, and airways in the lungs constrict. Without immediate treatment, the person will die.

A shot of epinephrine—the same drug used to treat severe allergic reactions to bee stings—will counteract the shock if given immediately. ■

—D.S.

D.C. He explains that the symptoms and the connection to latex use are fairly easy for an allergist to identify, so it would have been noticed earlier if it had been occurring.

"I can't say that it never occurred before 1979, but I certainly don't think it was that much of a problem before '79."

Slater won't speculate about why allergy to latex has increased so dramatically in the last 13 years, but many others consider "universal precautions"—the use of latex gloves to protect against the AIDS virus—the culprit.

"There's lots of health-care technicians using gloves now who didn't use them before," says Jean Reeder, an Army nurse

and immediate past president of the Association of Operating Room Nurses.

"Emergency workers are wearing gloves more often and for longer periods of time," says Jim Paturas, past president of the National Association of Emergency Medical Technicians.

Another possibility is that manufacturers aren't allotting enough time on the production line for washing the latex.

"We assume that more washing will make the latex safer," says Orhan H. Suleiman, Ph.D., chairman of FDA's latex sensitivity task group. Although FDA has no evidence that insufficient washing is an industry-wide problem, in May 1991, the agency outlined in a letter to all manufac-

## Commonly Used Latex Medical Products

- rubber gloves
- elastic bandages
- adhesive tape
- urinary catheters
- electrode pads
- wound drains
- stomach and intestinal tubes
- condom urinary collection devices
- protective sheets
- enema tubing tips
- dental cofferdams
- rubber pads
- fluid circulating warming blankets
- hemodialysis equipment

## Anesthesia Equipment Containing Latex

- rubber masks
- electrode pads
- head straps
- rubber tourniquets
- rubber nasal-pharyngeal airways
- rubber oral-pharyngeal airways
- teeth protectors
- bite blocks
- blood pressure cuffs
- rubber breathing circuits
- reservoir breathing bags
- rubber ventilator hoses
- rubber ventilator bellows
- rubber endotracheal tubes
- latex cuffs on plastic tracheal tubes
- latex injection ports on intravenous tubing
- certain epidural catheter injection adapters

(Source: *Journal of the American Association of Nurse Anesthetists*, October 1991)

turers of latex medical devices a two-step washing procedure—first during a step in the production process called leaching and again after the product is completed—that removes many of latex's allergenic proteins.



## Testing for Latex Allergy

There are two ways to test for latex allergies. With one—the skin-prick test—tiny diluted amounts of latex or one of its proteins are injected under the skin or applied to a small scratch or puncture on the patient's arm or back. If the patient is allergic, a small, raised area surrounded by redness appears at the test site within about 15 minutes.

Laboratory analysis of a blood sample to detect antibodies is the other testing option. (The first time an allergic person is exposed to an allergen, the immune sys-

tem produces a kind of antibody called immunoglobulin E—IgE for short.)

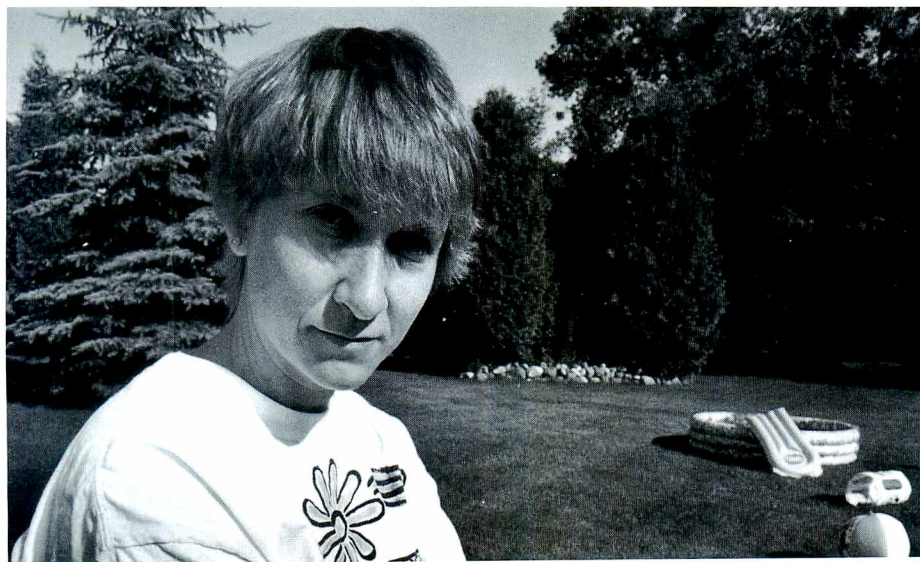
Slater says testing is both very important, and, unfortunately, imperfect. "It is clear that history alone is inadequate to screen some patients," he explains. (Some of the people who died from reactions to the latex barium enema tips had no history of latex allergy.) But, currently there is no FDA-approved extract for the skin-prick test or the blood test. Without an approved standard extract, the accuracy of the test results is not reliable.

The lack of an approved material that

will identify latex-sensitive patients stems in part from latex's complexity. "We're comfortable that at least one of the proteins in latex is the problem," says FDA's Suleiman. But he adds that more than a dozen proteins have been identified in latex. "Which one of these actually initiates the [allergic] reaction? At this time, your guess is as good as mine."

He adds, however, that a tremendous amount of research has been stimulated by questions about latex's proteins.

In addition, latex from some sources, such as different brands of gloves, may cause more severe reactions than that from other sources, according to Harvard dermatology professor Ernesto Gonzalez in



*Sue Lockwood, of Grafton, Wis., sits in her back yard wondering how to avoid latex sources. Her latest challenge: her daughter's pool toys. Her doctor says that although the toys are made of vinyl, there may be traces of latex in the air valves, and they are probably the source of her most recent latex reactions.*

## Why Stick with Latex?

What is it about latex gloves? Why not just switch everyone to something else?

"We can't switch everybody out of latex," says B. Lauren Charous, M.D., chairman of the American College of Allergy and Immunology's task force on latex hypersensitivity. "There's no real reason to. We're still dealing with a very small percentage of health-care workers."

There are, however, real reasons to keep donning latex gloves. The main one is "latex is the barrier of choice [to protect against HIV]," says Orhan Suleiman, Ph.D., chairman of FDA's latex sensitivity task group.

"It's primarily a question of durability," says Thomas Arrowsmith-Lowe, D.D.S., deputy director for health affairs in FDA's Center for Devices and Radiological Health. "Within 15 minutes after putting

on a vinyl glove, it starts to lose its barrier effectiveness. Latex maintains the barrier longer."

Of almost equal importance is latex's ability to stretch and conform to the shape of the hand. "You can stretch it to four or five times its original length and it will not tear," says Barry Page of the Health Industry Manufacturers Association. "There aren't many materials that will do that."

In addition, because latex gloves can be stretched so thin, they don't interfere with the sensitivity and fine manual dexterity required in many medical procedures.

"Latex gloves are better fitting and it's easier to feel veins and start IVs," says Vicki Freund, a paramedic/firefighter with the Montgomery County, Md., fire department. "So, I end up wearing those."

She also ends up with hives on the

backs of her hands. "They itch like crazy." Sometimes her eyes swell up and itch and her nose starts running, too.

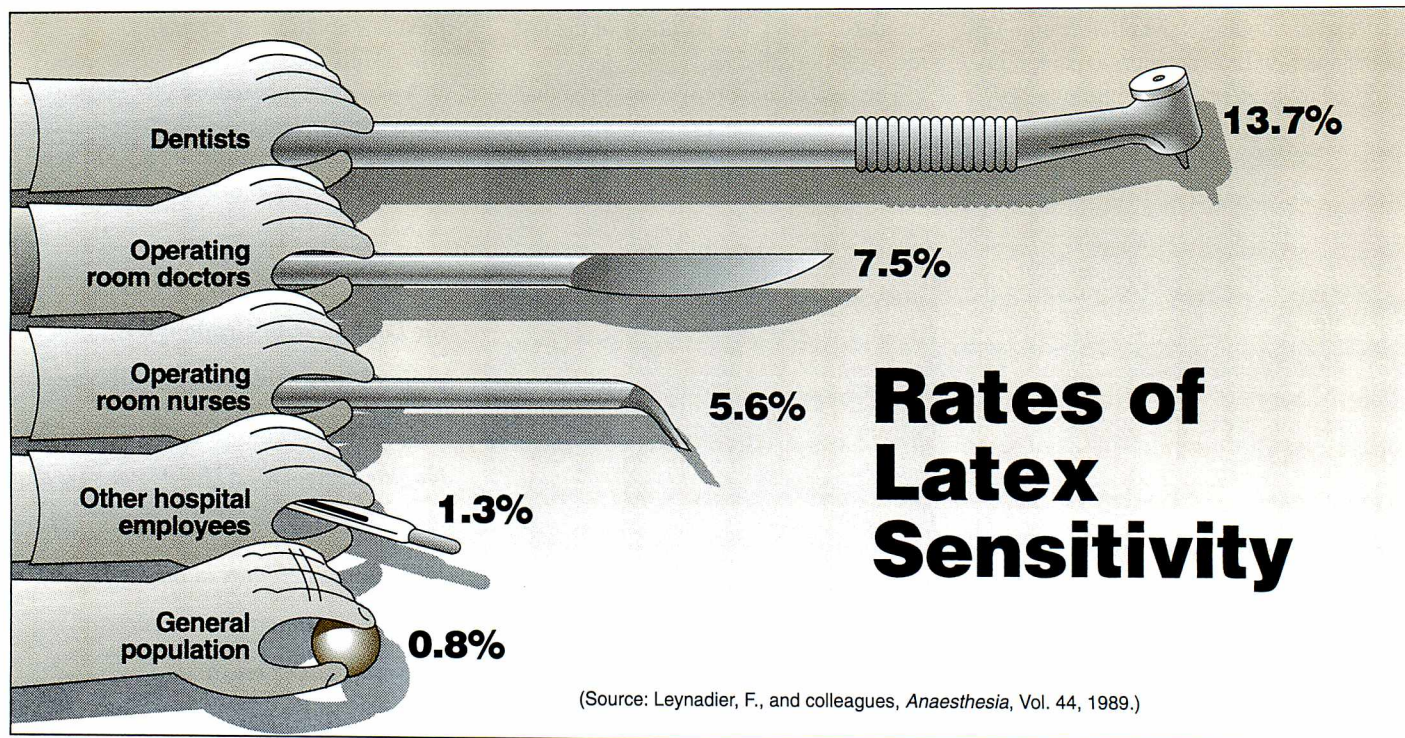
For now, because her reactions are relatively minor, Freund just lives with the problem.

But there are efforts to find an alternative for people like her. Several companies have developed latex-free gloves that the companies claim can stretch like latex and don't impair the wearer's sense of touch. As with all new products that make medical claims, these new gloves have to be reviewed by FDA before they can be sold.

Allergist Charous encourages people with mild reactions to try several different brands of gloves. He adds that "people who have only a history of mild latex glove eczema are not at risk [of a serious reaction] in any immediate sense. I want to emphasize that." ■

—D.S.





the February 1992 issue of the journal *Hospital Practice*.

Still, Slater says people in high-risk groups should be tested if they are concerned, as long as the tests are part of a thorough examination by an allergist who has the background to recognize possible allergens and exclude others based on an individual's history of allergic reactions. "It requires a fair amount of detective work," he says.

In addition, the allergist should be prepared with emergency equipment in case the skin-prick test itself causes a severe allergic reaction.

Slater warns that people shouldn't try to test themselves, by, for example, blowing up a latex balloon.

"That's a lousy idea," he says. "In fact, it's potentially very dangerous." He explains that a truly allergic person could go into shock from such a "test."

Finally, Slater says people who are not

in a high-risk group and who haven't had any history of reactions "need to sit tight."

Suleiman agrees. "Right now, unless someone is already sensitive [to latex] there's no reason to discontinue use. We especially don't want to scare people away from latex condoms."

While approximately 1 billion to 2 billion condoms are used per year in the United States, FDA has received only 44 reports of allergic reactions associated with condom use between October 1988 and the end of 1991.

#### Latex Free

Surgery is nothing new for 7-year-old Paul Reynolds, of Herndon, Va. He was born with spina bifida, and last September's hip operation was his eighth. But, unlike the previous seven, this was his first surgery since he had developed an allergy to latex.

Paul's mother, Adriana Reynolds, says

the doctors assured her the surgery would be latex free "as much as possible. I used to worry about the risks of anesthesia, but now I think this rubber allergy is my greatest concern."

Latex-containing devices fill the average surgical suite, and sometimes even medical professionals aren't aware that a device has a latex component.

"What is needed in the anesthesia world is a list of devices that don't have latex," says Jane McCarthy, a nurse-anesthetist and member of FDA's latex task group. "The clinicians can only attempt at best to provide an environment that's latex free. There's been difficulty in doing that because the devices aren't labeled with or without latex."

In response to that need, several hospitals have developed their own lists of latex-free devices. In addition, two nurse-anesthetists, Charles R. Barton and Cynthia A. Roy, have developed a list of



## Latex Conference Planned for November

FDA and the national Centers for Disease Control are sponsoring a conference on latex sensitivity Nov. 5 to 7, 1992, which will cover:

- latex chemistry
- prevention of sensitization
- protein quantification and identification
- testing for latex hypersensitivity
- clinical studies
- epidemiology of latex hypersensitivity
- prevention of reactions in sensitized individuals
- manufacturers and producers approaches

To register for the conference or to obtain additional information, write Crosspaths Management Systems, Inc., 2 Wisconsin Circle, Suite 660, Chevy Chase, MD 20815, or call (1-800) 527-2847. ■



*Paul Reynolds, 7, of Herndon, Va., plays with his dog, happy to have his latex allergy under control. Doctors attribute his allergy to latex exposure during seven surgeries to correct birth defect problems. Around his neck is a Medic Alert necklace, notifying medical personnel that he's allergic to latex.*

commonly used medical devices that contain latex. (See accompanying chart).

To make sure a patient's latex allergy isn't overlooked, FDA sent a medical alert to approximately 1,000 leaders of health professional organizations in March 1991. The alert advised health professionals to:

- include questions about latex sensitivity when taking a patient's health history. (Asking patients if they've ever experienced itching, rash or wheezing after wearing latex gloves or inflating a toy balloon may be useful.)
- flag the charts of patients who report signs of latex allergy
- counsel patients who have a suspected latex-related allergic reaction while under the professional's care, and recommend a latex allergy test to those individuals.

The agency also recommended that when health professionals are treating a latex-sensitive patient, they should wear a non-latex glove over a latex glove. If both

the health professional and patient are sensitive, triple-gloving—wearing a glove liner or vinyl glove under a latex glove as well as a vinyl glove over the latex—is recommended. (See accompanying article, "Why Stick with Latex?")

To protect themselves, Slater recommends that people allergic to latex:

- carry non-latex gloves (a medium size is their best bet) at all times for health professionals to use during both routine examinations and emergency procedures
- wear a Medic Alert bracelet
- carry an emergency epinephrine kit in case they are accidentally exposed to latex and go into anaphylactic shock (epinephrine immediately counteracts the shock)
- alert all health professionals they deal with about their latex sensitivity.

For Adriana Reynolds, worry over when and if her son could have another reaction is compounded by the lack of knowledge about latex allergies.

"It's all very new," she says. "You tell people that your son has a rubber allergy and they say 'rubber?' I've had to meet with the people at Paul's school several times to convince them that this is serious. I had to buy vinyl gloves for the school nurse [Paul has to be catheterized during the day] and remind them about things like rubber balls in physical education."

For Lockwood, the worst part of her allergy is the loss of her career as a surgical technician. Since she first started reacting to latex more than a year ago, her sensitivity has become so acute that even if she were to wear vinyl gloves during surgery, airborne latex from the rest of the surgical team's gloves would cause her problems.

"There's no way I can work in surgery anymore," she says. "I can't deal with that loss yet. I want my career back." ■

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



# New Pertussis Vaccine Offers Prevention Alternative

by Rebecca D. Williams





**A**s school bells ring this fall, the country's 3.3 million first-graders will clutch new Ninja Turtle lunch boxes and brightly colored backpacks. But before they enter classrooms, many will receive something new at the doctor's office as well—a safer pertussis vaccination.

Approved by the Food and Drug Administration last December, the new vaccine for pertussis, or whooping cough, offers immunity with fewer side effects than the older version, which caused some concern among physicians and parents.

"I think most physicians would like to see all of the reactions eliminated completely," says Donald Schiff, M.D., a spokesman for the American Academy of Pediatrics and a pediatrician at Denver Children's Hospital.

Developed in Japan about 10 years ago, the new vaccine is distributed by Lederle Laboratories of Wayne, N.J.

The pertussis vaccine is given in combination with diphtheria and tetanus vaccines in a series of five DTP shots between 2 months and 6 years of age.

The new vaccine is approved for the last two doses of the series. Children getting it

must be at least 15 months old because it has not yet been tested adequately in younger children.

It is younger children, however, who most often react severely to the old vaccine.

"The new vaccine does not relieve those who are most anxious about it—the parents of infants," says Schiff.

### Fewer Side Effects

In about half of all children, especially infants, the traditional pertussis vaccine causes some uncomfortable side effects, such as swelling and soreness at the site of the shot, fever, and inconsolable crying several hours later.

For a very few others, however, the side effects are much worse. They include shock, convulsions and seizures. The vaccine has even been blamed for some cases of brain damage, but this association has not been proven.

The new vaccine has fewer common side effects. The incidence of severe side effects is still not known, however, since they occur so rarely. Hundreds of thousands of children will have to be vaccinated before doctors can document these.

In theory, the new vaccine should be

much safer. Instead of being made like the old vaccine from whole pertussis bacterial cells that have been killed, the new acellular vaccine is made only from parts of pertussis bacteria that evoke protective immune responses.

Although the new acellular vaccine is available, not all eligible children need it. Many children tolerate the whole-cell vaccine just fine, and it is less expensive than the new one. Parents should check with their children's doctor about which vaccine is right for them.

In any case, children younger than 15 months should still be given the old vaccine unless their doctors recommend otherwise.

"It's important to realize that while there is a new vaccine, the old vaccine is very good, too," says Drusilla Burns, Ph.D., a research chemist in FDA's Laboratory of Pertussis who is involved in pertussis research and helped review the new vaccine.

"The whole-cell vaccine has served us very well," she adds. "It has some relatively minor adverse reactions, but the more severe reactions are still a matter of discussion."





# FDA Leads Research

FDA's Laboratory of Pertussis is a world leader in research on pertussis, also known as whooping cough. Its scientists have made major contributions to the development of new "acellular" pertussis vaccines, so-named because they're made from soluble components, rather than whole pertussis bacterial cells that have been killed.

Through basic research, the laboratory has isolated and characterized virulence factors (the disease-causing substances) from *Bordetella pertussis*, the bacterium responsible for pertussis. These factors are

important components of the various acellular vaccines being clinically evaluated.

Laboratory of Pertussis scientists have proposed vaccine formulations and developed manufacturing methods and laboratory models to evaluate potential vaccines before they are tested in children. They have contributed significantly to clinical studies and to the methods used to measure immunity in vaccinated patients.

"Scientists conducting research basic to the development of the vaccines are better able to advise manufacturers and train public health authorities and employees of

vaccine producers," says Charles R. Manclark, Ph.D., chief of the Laboratory of Pertussis. "In so doing, these scientists expedite the steps to clinical use of new vaccines. But most important of all, basic pertussis research provides tools and knowledge that permit us to reexamine and understand the disease. These studies, for instance, provide information on the role played by older children and adults as reservoirs of disease and sources of infection for the very vulnerable infant."

Related research may help develop vaccines that prevent infection as well as disease, says Manclark, and may change how new vaccines are used. Currently being considered are the use of vaccines in adolescents and adults and the use of maternal antibodies to protect newborns.

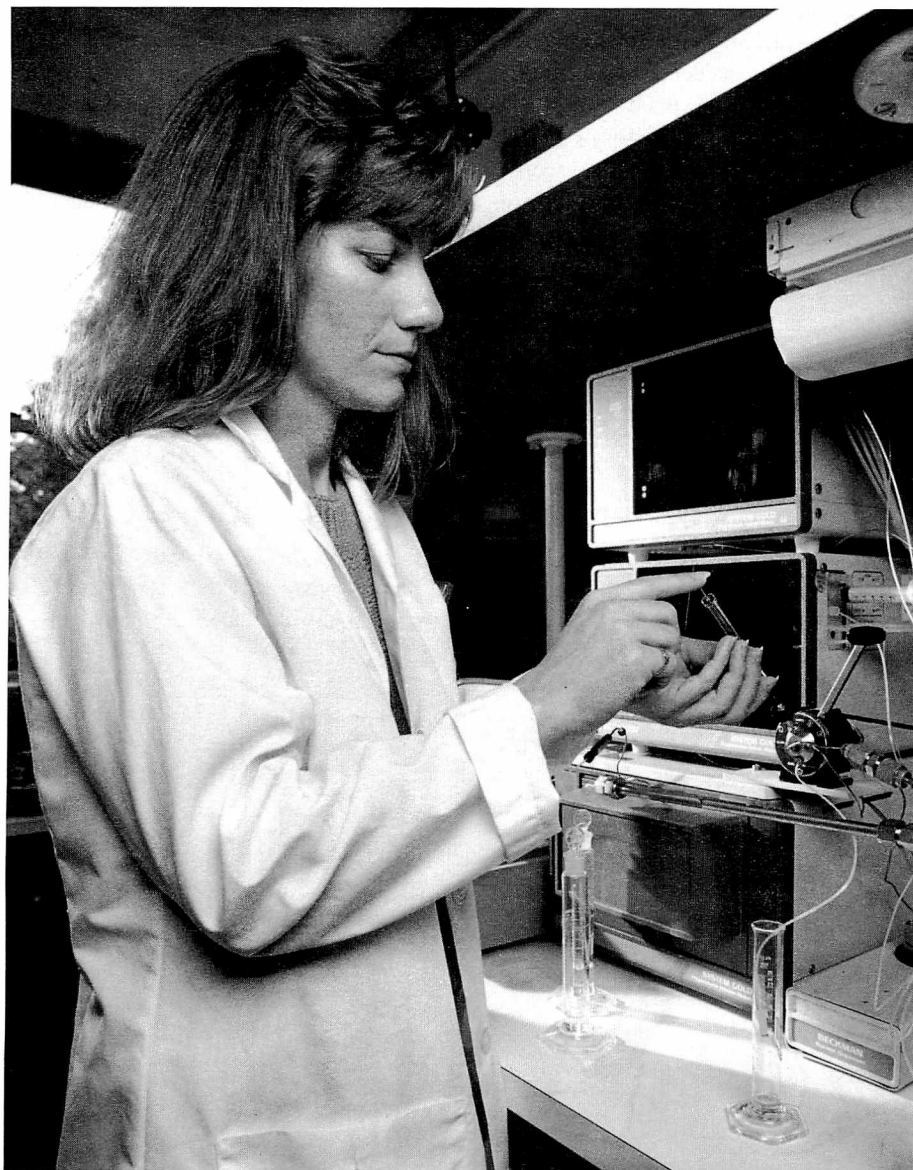
Another area under intensive study in the Laboratory of Pertussis is the concept of oral immunization with living microbial vectors and microencapsulation vectors, substances that carry vaccine components in microspheres and release them gradually. Oral immunization—besides being more acceptable to patients—doesn't require syringes, needles, or highly trained personnel.

"New vaccines used in ways that more effectively disrupt the natural routes to infection, coupled with maternal passive immunity to protect newborns, will probably reduce occurrence of pertussis and may even eradicate the disease," concludes Manclark.

FDA scientists share their knowledge with other researchers by publishing their findings in the scientific literature and by hosting international conferences and workshops on pertussis. The research by Laboratory of Pertussis scientists has resulted in numerous patents, which, because they are held by the federal government, are available to vaccine manufacturers and others who are interested. ■

—R.D.W.

*Julie Hannah, a research microbiologist in FDA's Laboratory of Pertussis, uses high-pressure liquid chromatography to analyze a component of the pertussis organism, one step in research on a pertussis vaccine.*





# Childhood Immunizations



Vaccine	2 months	4 months	6 months	15 months	4-6 years	14-16 years
<b>DTP</b> (Diphtheria, Tetanus, Pertussis)	✓	✓	✓	✓ (or at 18 months)	✓	
<b>OPV</b> (Oral Polio Vaccine)	✓	✓		✓ (or at 18 months)	✓	
<b>MMR</b> (Measles, Mumps, Rubella)				✓ (or at 12 months in some areas)	✓	
<b>Hib</b> (Haemophilus Influenza type b)	✓	✓	✓ (or may not be required, depending on which vaccine)	✓ (or at 12 months depending on which vaccine)		
<b>Td</b> (Tetanus, Diphtheria)						✓ (and every 10 years thereafter)

(Source: Centers for Disease Control)

The American Academy of Pediatrics and pediatric societies in Canada and Great Britain have stated that the vaccine is not a proven cause of brain damage.

And, while the risk of seizures from the whole-cell vaccine is about 1 in 1,750, numerous studies have shown there's no evidence those seizures will permanently harm the child or increase his or her chance of developing other seizure disorders, such as epilepsy, later.

For most children, the benefits of the whole-cell pertussis vaccine far outweigh its risks.

## Deadly Disease

Whooping cough is highly contagious and deadly. It causes mucus to build up in the lungs, making the child gasp and "whoop" for air every few minutes for two to three weeks.

The spasms may bring on vomiting, pneumonia, and sometimes brain hemor-

rhages. Spreading through droplets of moisture expelled by coughing, whooping cough bacteria will infect up to 90 percent of unvaccinated people exposed, especially young children. Both the old and new vaccines protect about 80 percent of children exposed to the disease, and the remainder have mostly mild cases.

Before the first vaccines were developed in the mid-1940s, whooping cough struck about 265,000 children annually in the United States and killed 7,500 of them, more than all other contagious diseases combined. Since then, pertussis cases have dropped drastically in the United States to about 4,500 cases and 10 deaths in 1990, according to the national Centers for Disease Control.

If this country stopped requiring pertussis vaccination, whooping cough would undoubtedly become epidemic again. This happened in the 1970s in Great Britain, Sweden and Japan, where vaci-

nation was either suspended or slowed because of safety concerns.

No completely effective treatment for pertussis exists. According to CDC, about 1 percent of whooping cough victims under 2 months old will die, especially if pneumonia develops.

The key to protecting children from pertussis, then, is vaccination. Studies are under way in several countries to test the new acellular vaccines in younger children and infants.

The hope is that, not too far in the future, when a new school season opens, all children will be vaccinated against pertussis without any ill effects. And whooping cough, once thought of as a common childhood disease, will be remembered only in history books. ■

*Rebecca D. Williams is a staff writer for FDA Consumer.*



# Migraine, Cluster and Tension

## Headache Misery May Yield to Proper Treatment

by Dixie Farley

*"My headaches started when I was taking birth control pills. The pain was intense, first right above my eyes, then spreading below the eyes. It might start on one side and the next day switch to the other side. Nearly every week I'd be sick two or three days like I had the flu—vomiting, aching, and yawning all the time. All I wanted to do was sleep.*

*"After I went off the pill, the headaches were sporadic. I'd go for years with very little trouble. Surprisingly, during my pregnancies, they disappeared. But they returned with a vengeance at menopause, and I was sick more than I wasn't sick. I could hardly stand it."*

Janice Bailey, of Tucson, Ariz., describes her decades-long battle with "sick headaches," the most common symptom of a disabling condition called migraine. Attacks often follow exposure to a trigger—such as birth control pills.

Migraine is only one of 12 headache types (with more than 60 sub-types) classified in 1988 by the International Headache Society for use in diagnosis. Migraine, cluster, and tension-type headaches are the main varieties. Numerous physical disorders underlie the nine other types.

Chronic headaches plague more than 45 million Americans, reports the National Headache Foundation, of Chicago.

Still, the vast majority of headaches are temporary, "requiring no more than an over-the-counter analgesic," says Russell Katz, M.D., deputy director of the Food

and Drug Administration's division of neuropharmacological drugs, which reviews anti-migraine drugs. "Headaches from life-threatening conditions such as tumors are uncommon," he says.

An important tool in diagnosing headache is the patient's medical history, says Stuart Stark, M.D., director of the Headache Program for The Neurology Center in Alexandria, Va.

"The history usually is sufficient to determine the specific type of headache," he says. "But when headaches are debilitating, a diagnostic workup is warranted."

Workups often include taking pictures of the brain with a radiological procedure such as computed tomography or magnetic resonance imaging. To rule out certain causes, further procedures may be needed—blood tests, for instance. "We particularly look at the blood count," Stark says, "to see whether the blood is too thick or too thin. Blood that clots abnormally can be caused by disease, such as lupus [a rheumatic disease]."

### Migraine

Migraine headaches affect 16 million to 18 million Americans, of whom nearly two-thirds are women, the National Headache Foundation says. Since migraine is believed to be mostly an inherited condition, children, even babies, may be "migraineurs," as victims of this headache are called.

"Abdominal colic could be a form of migraine," Stark says. "If the mother or father has had migraines, it's worth considering the colic as a possible prelude to a migraine condition. About all you can treat a baby with is liquid Tylenol, but the colic could alert you to watch for symp-

toms as the child grows."

The two main migraine sub-types are "migraine with aura" (formerly called "classic migraine") and "migraine without aura" (formerly called "common migraine"). Attacks can last from several hours to several days.

About 10 percent of migraine patients have auras—certain neurological (nerve-related) symptoms that precede the headache by 5 to 30 minutes but sometimes persist into the headache phase. Aura symptoms include visual disturbances such as flashing lights or zigzag lines or even temporary vision loss. Others are a pins-and-needles feeling on one side of the face or body followed by numbness, or numbness without the tingling. Less frequent signs are speech problems, confusion, and weakness on one side.

Migraines without auras may be accompanied by vague warning signs, including mood swings, mental fuzziness, and fluid retention.

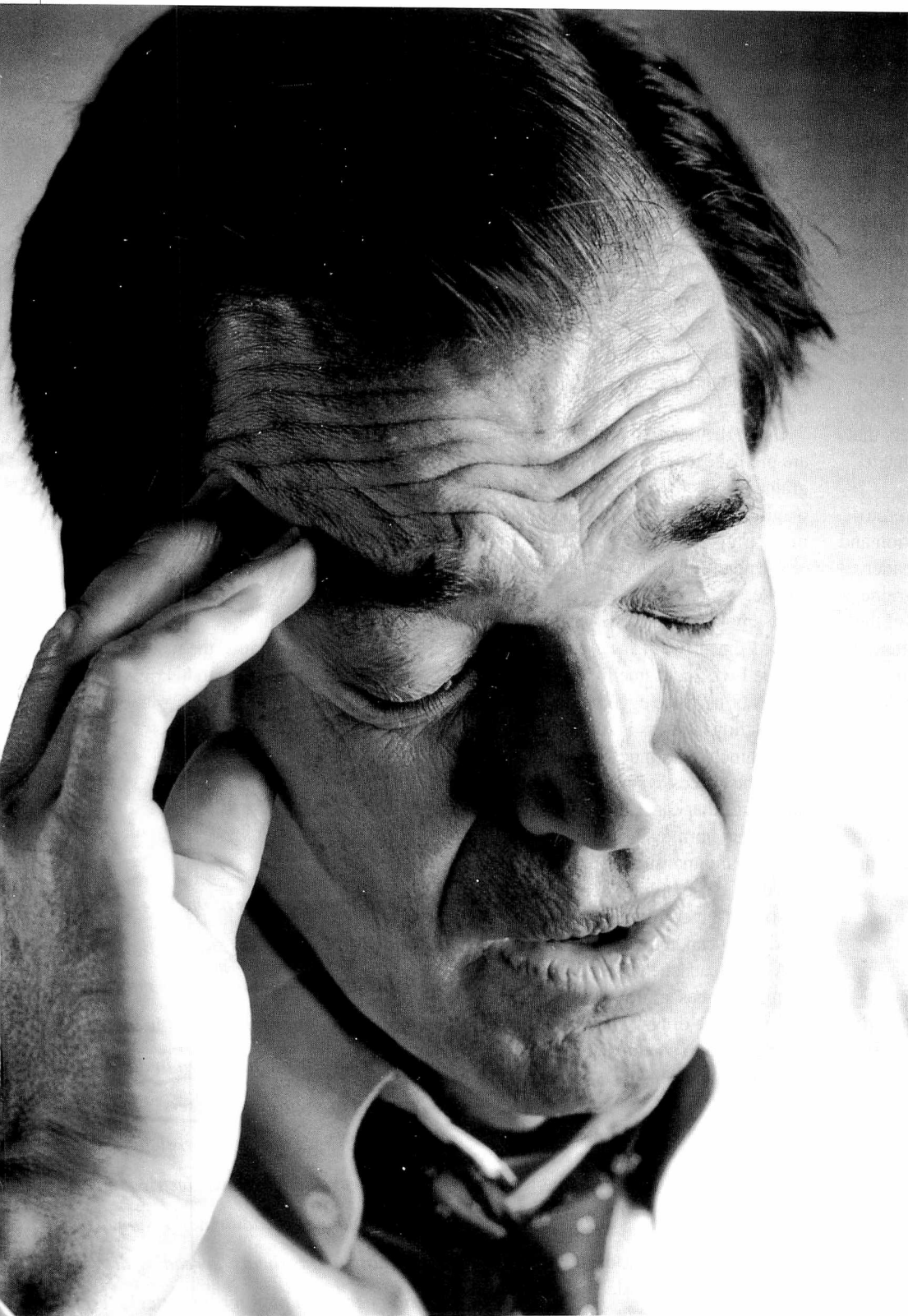
Bailey says she often was very tired before an attack. "I'd yawn and yawn," she says. "But mainly it was just an overall feeling. I'd know I'd better not eat much if I had that feeling."

Patients describe their pain with words such as intense, throbbing, pounding. They feel it in the forehead, temple, ear, jaw, or, like Bailey, around the eye. Most migraines are one-sided. Some start on one side but spread to the other.

Besides headache, symptoms include nausea, vomiting, appetite loss, diarrhea, sensitivity to light and noise, fever, chills, flu-like achiness, and sweats. Attacks range in frequency from several times a week to once every few years.

About 5 percent of migraineurs don't

## ***Most Common Headache Types***



- **Migraine headaches** usually throb and affect one or both sides of the head. Physical activity tends to worsen the pain. Patients also may have nausea, vomiting, light and noise sensitivity, or other symptoms. Some sufferers have warnings, such as visual disturbances. Attacks last from a few hours to days, recurring from several times a week to once every few years. Women get migraines more frequently than men.

- **Cluster headaches** occur as a series of one-sided headaches that are sudden and excruciating and continue for 15 minutes to 4 hours. Cluster attacks last 4 to 12 weeks, followed by remission as long as months or years. Other symptoms on the painful side include nasal congestion, drooping eyelid, and irritated, teary eye. Most cluster patients are men.

- **Tension-type headaches** may last a few hours, a few days, or be chronic. The pain is described as a tight band around the head, but it can affect any scalp, face, neck, and shoulder muscles. Some patients, especially those with chronic tension headaches, also suffer from stress, anxiety or depression. ■

—D.F.



have headaches. "They may have vomiting, dizziness, or ringing in the ears," Stark says. "Since migraine is a condition of the brain, literally any neurologic symptom can occur."

But where does a migraine come from?

A longstanding theory holds that blood vessels in the scalp and on the brain's surface constrict. This reduces the brain's oxygen supply to produce the aura some patients have. The same vessels, reacting to the brain's need for oxygen, open up, or dilate, releasing pain-causing chemicals called prostaglandins, other chemicals that increase sensitivity to pain, and still others that induce painful inflammation and swelling.

Stark is among the neurologists who subscribe to a newer theory that migraine stems from a chemical change deep within the brain, where the body uses the neurotransmitter serotonin abnormally. (Neurotransmitters are chemical messengers that nerve cells use to tell each other what to do.)

Working with other chemicals, serotonin regulates blood vessel constriction and dilation. It can both sharpen and deaden pain. While serotonin's role in migraine isn't completely understood, areas of the brain responsive to serotonin are often involved in migraine. The hypothalamus, for instance—which regulates involuntary bodily functions such as menstruation, sleep and hunger—has cells sensitive to serotonin. Such cells also appear in large amounts in the stomach and intestinal walls. Certain serotonin cells stop "firing" during sleep, which often ends a migraine attack.

"Serotonin acts on the electrical impulses sent out by nerve cells in and around the blood vessels in the brain," Stark explains. "We believe that in a migraine attack, the serotonin isn't properly used for some reason, so that the electrical wave of impulses becomes diminished, or depressed. The wave, called 'spreading depression,' reduces blood flow through the vessels leading to the back of the brain.

"This is when the aura occurs. The symptoms depend on which areas of the brain are included in the wave. Spreading depression is believed present in all migraine attacks, even in people who don't have auras.

"After the spreading depression subsides, the blood vessels start leaking fluid, inflaming the outside of the vessels. The inflammation causes the pain, which can extend to all the nerve cells supplying the blood vessels, not just those in the area of the spreading depression."

The spreading depression correlates with the aura, but not the headache, Stark says. In other words, a depressed wave limited to one side of the head can lead to pain on both sides.

Also, some scientists believe a disturbance in the brain's trigeminal nerve contributes to migraine headache by causing the release of "substance P," which causes inflammation.

If these theories are correct, changes in the head's blood vessels, impulses deep within the brain, and the pain pathway in the trigeminal nerve may all play a part in migraine pain.

Given the theory that most migraineurs are predisposed to their condition, migraine has been described as a cocked gun waiting to go off—except that this gun has many triggers.

A trigger for Bailey was cigarette smoke. "At a party where lots of people were smoking and there wasn't good air flow, I'd nearly always get sick," she says. "Once I was sick, smells such as glue, pesticides or perfume egged it on."

Reaction to stress is a common trigger. Others include fatigue, lack of sleep, glaring lights, excessive noise, weather, certain drugs that cause blood vessels to swell, and hormonal fluctuation—as happens around menstruation, at menopause, and during use of birth control pills.

Foods trigger migraines, too. Keeping a food diary can help identify sensitivities.

As for headache prevention and treatment, FDA has approved a number of anti-migraine drugs. Their benefits vary from person to person and must be weighed against the risks, some of which are serious.

"One preventive drug is Inderal [propranolol]," says FDA's Katz. "It was initially approved to treat high blood pressure and heart problems, and only accidentally found to prevent migraine. It's not useful after the headache begins." FDA approved Inderal, a beta blocker, for preventing migraine in 1979. It's the only beta blocker with this indication. Inderal's

effect in migraine is not well-understood.

The other drug approved for preventing migraine is Sansert (methysergide), one of several ergot drugs, which constrict blood vessels. Sansert can't be given continuously for more than six months, so its use is limited.

"Effective drugs to stop a particular attack of migraine once it has started," Katz says, "include analgesics and ergotamines. Whichever is used, it must be taken early in the attack to be most effective." For occasional mild migraines, he says, over-the-counter pain relievers or prescription drugs with a low dose of codeine are usually adequate.

"Isometheptene combined with dichloralphenazone and acetaminophen—Midrin or Isocom—may also be helpful early in an attack," Katz says. "Anti-emetics can relieve the associated nausea and vomiting in migraine."

OTC analgesics for headache include aspirin, Tylenol (and other brands of acetaminophen), and Advil, Motrin IB, and Nuprin (and other brands of ibuprofen). Ergot drugs include Ergomar, Ergostat, Cafergot, Wigraine, and D.H.E. 45.

### Cluster Headache

"This piercing pain," the man cries to his wife. His hand goes to his right eye, which is teary and red with irritation.

## Migraine Aura and 'Spreading Depression'

*Tingling on one side of the face or body and visual sensations such as flashing lights and zigzag lines are the most common symptoms of the migraine aura, a pre-headache phenomenon in about 10 percent of migraine sufferers. Many scientists believe the aura correlates with a brain wave of depressed electrical impulses called spreading depression. According to this theory, spreading depression occurs in all migraine attacks, even those without auras.*





Spreading  
Depression reduces  
Blood flow to the  
Back of brain

Depression of  
electrical  
impulses  
starts here.

Tingling

Wm. C. C. C.



**Migraine has been described as a cocked gun waiting to go off—except that this gun has many triggers.**

For a half hour, the man has been pacing, unable to keep still. Pausing to stub out his cigarette, he clenches and unclenches his fists, then wipes sweat from his right brow with a tissue. He blows his nose.

Finally, the pain is over. He collapses in a chair to wait, fearing the pain will return yet a fourth time today.

The patient is a fictitious composite of symptoms and behavior typical of cluster headache sufferers.

Cluster headache is so-named because it recurs in clusters, several times a day, for several weeks or months. A cluster may start at a certain time of year, perhaps with a change of season. Each headache lasts from 15 minutes up to 4 hours, but the cluster attack—repeated headaches—can go on for weeks or months. When the cluster series is over, in 90 percent of patients, it won't recur for months or years. The cause is unknown.

Nearly a million Americans have cluster headaches, the National Headache Foundation reports. Most cluster patients are men, usually smokers. Cluster has been called the "suicide headache," "demon of headaches," and, because it often awakens the person, "alarm clock headache."

Nearly always, only the blood vessels of one carotid artery are affected, making the intense, steady pain one-sided—usually centered behind the eye and in the temple.

Also, the pupil on the pain side may constrict, the eyelid may droop, and the brow may sweat. Nasal congestion may lead the person to suspect a sinus infection, but sinus headaches don't start and stop several times a day. Unlike migraineurs, who want to curl up in bed, cluster victims can't sit still.

## Help for Headache Sufferers

In addition to over-the-counter products, a number of prescription drugs are available to treat headaches. Some migraine preparations also are approved to treat cluster headaches. One labeled as only "possibly" effective for migraine is approved for tension headache.

Anti-migraine drugs should be taken under medical supervision. Though they provide benefits, they can cause side effects, some of which are serious. Scientists don't know exactly how they work. The drugs' names, approved formulations and uses, and *probable* ways they achieve their effects are:

- **Ergotamine tartrate** (Ergomar, Ergostat) tablets, dissolved under the tongue, are used short-term to prevent cluster headaches in some patients and to treat migraine and cluster. This drug constricts blood vessels and inhibits pain-causing fluid leakage from vessels in the brain's outer membrane. It interacts with brain "receptors" for serotonin (a chemical messenger that nerve cells use to tell each other what to do).
- **Ergotamine tartrate/caffeine** (Cafergot, Cafermine, Ercaf, Ercatab, Ergo-Caff, Gotamine, Lanatrate, Migergot, Wigraine) tablets and/or suppositories are used to treat the same headaches as ergotamine alone. Caffeine increases ergotamine's effect, reducing the amount of ergotamine needed.
- **Dihydroergotamine mesylate** injection (D.H.E. 45), an ergotamine derivative, is used like ergotamine. However, it can be injected in a muscle or given intravenously and may be more effective for a given attack.
- **Methysergide maleate** (Sansert) tablets are used to prevent vascular headaches that occur once or more a week or are uncontrollable by other treatments. Thus, it is not used once an attack begins. It should not be taken continuously longer than six months. Sansert blocks serotonin transmission.
- **Isometheptene mucate/dichloralphenazone/acetaminophen** (Amidrin, I.D.A., Iso-Acetazone, Isocom, Midrin, Migratine, Migrazone, Migrex, Mitride) capsules are used to treat tension headache and, the labeling says, "possibly" migraine. (FDA recognizes a potential benefit in migraine but requires more research to prove it is fully effective.) Isometheptene constricts vessels, dichloralphenazone mildly sedates, and acetaminophen relieves pain.
- **Propranolol hydrochloride** (Inderal) tablets are used to prevent migraine. This drug may block communication between certain nerve cells.

FDA is reviewing data to support marketing of a migraine preparation called Imitrex (sumatriptan succinate), formulated as an injection patients can administer. The drug acts on serotonin receptors.

Last fall, an advisory panel to FDA on nervous system drugs recommended unanimously that Imitrex be considered approvable for treating migraine headaches. The panel concluded that more evidence was needed to prove safety and efficacy for use in cluster headaches. ■

—D.F.



## Danger Signals

Sometimes a headache can signal a serious condition requiring prompt medical attention. According to the National Institute of Neurological Disorders and Stroke in Bethesda, Md., a doctor should be consulted if a headache:

- is accompanied by confusion, unconsciousness or convulsions
- involves pain in the eye or ear
- is accompanied by fever
- is accompanied by nausea
- occurs after a blow to the head
- is persistent in someone previously free of headaches
- is recurrent, especially in children
- interferes with normal life.

For more information, contact the Neurology Institute, P.O. Box 5801, Bethesda, MD 20824; telephone (1-800) 352-9424; or the National Headache Foundation, 5252 N. Western Ave., Chicago, IL 60625; telephone (1-800) 843-2256. (NHF offers a list of headache clinics and a state list of National Headache Foundation physician members interested in treating headache.) ■

—D.F.

Why these symptoms accompany cluster headache has not been established.

One theory suggests involvement of the nerves supplying that area, according to Seymour Diamond, M.D., executive director of the National Headache Foundation and head of the Diamond Headache Clinic in Chicago.

One hundred percent oxygen inhaled through a mask for 8 to 15 minutes often stops an attack, Stark says. Painkillers tend not to work, he says. Drugs such as Cafegot lessen some acute attacks. Sansert is sometimes prescribed for prevention.

"We aren't certain how drugs work in cluster," Stark says.

### Tension-Type Headache

The tension-type headache usually involves increased tension in the scalp and neck muscles. It has also been called "muscle contraction headache," "psychogenic headache," "stress head-

ache," "ordinary headache," and "tension headache."

As some of those names suggest, tension-type headaches are the commonest, accounting for 90 percent of headaches not due to disease, and are most often caused by anxiety and stress—for instance, a mile-long traffic tie-up, work deadlines, standing sixth in a grocery check-out line, money worries.

Others susceptible to tension-type headache, Katz says, are people with poor posture, beauticians and others who move their neck and shoulders a lot, and people who work at stationary, repetitive tasks, as on an assembly line.

The pain often involves most of the head, from the forehead to the nape of the neck, and feels like a dull ache, as though the head were being pressed in a vise. Neck and shoulder muscles may be tense. The pain may go away after an hour. It may last several days.

"Usually, OTC pain relievers, hot

*Cluster headache has been called the "suicide headache," "demon of headaches," and, because it often awakens the person, "alarm clock headache."*

packs, and relaxation will relieve occasional tension headaches," Katz says.

Patients with chronic tension-type headaches often are depressed. The depression may result from the pain itself, wrote Stephen Silberstein, M.D., and Marsha Silberstein, M.D., in recent articles in *Pain Management*. For these patients, some doctors prescribe antidepressants.

Other headaches are associated with physical problems, including dysfunction of the temporomandibular joint (which connects the jaw to the skull), brain disease, a blow to the head, arthritis, whiplash, metabolic disorders such as an overactive thyroid gland, and dental, sinus or ear infection. Treatment is based on the underlying cause.

Thanks to increasing knowledge about headaches, most headaches can be prevented or treated, if not cured. Bailey, for instance, has been treated with Inderal since 1983. Does she still have sick headaches?

"I don't know," she says. "I haven't quit taking my medicine long enough to find out." ■

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



# New Drugs, New Alternatives

## *Understanding Leukemia*

by Eleanor Mayfield

**O**tteau Christiansen of Minnetonka, Minnesota, was a 27-year-old television film producer and father of two when, like a bolt from the blue, he learned he had leukemia. His doctors told him he had 6 to 10 weeks left to live. Even with aggressive chemotherapy, they said, his chance of survival was 1 out of 5.

That was in 1983. Today, Christiansen is a successful independent film and video producer who swims, water skis, and goes wilderness camping with his children. He takes no medication and sees his doctor only for routine follow-up. He is cured.

Otteau Christiansen is one of the lucky ones. According to the National Cancer Institute (NCI) and the Leukemia Society of America, about 28,000 Americans will be diagnosed with leukemia in 1992. Fewer than 35 percent of them are likely to be alive in five years.

Survival is strongly linked to age at diagnosis. Physicians are now claiming cure rates of up to 80 percent for some types of childhood leukemia. Adults under 40 probably now have around a 40 to 50 percent chance of long-term survival. But leukemia is most common—and most likely to be fatal—in the elderly.

All forms of leukemia can be treated, and several new drugs have recently been approved by the Food and Drug Administration, while others are being tested in clinical trials. However, leukemia specialists say the best hope of a breakthrough that will significantly increase cure rates lies in understanding and controlling the aberrant molecular processes that lead to development of leukemia.

### **Not a Single Disease**

Leukemia is not a single disease, but a group of malignancies in which the bone marrow and other blood-forming organs produce excessive numbers of white blood cells. The extra cells, which are usually immature or abnormal, suppress the production of normal white blood cells, the function of which is to protect the body against infection.

Malignant cells “take over” the bone marrow and prevent it from producing red blood cells, which transport oxygen around the body, and platelets, which help blood clot. They also invade other organs, such as the liver, spleen, lymph nodes, genitals, and brain.

Leukemias are classified by the type of white blood cell that is proliferating abnormally and by how fast the disease is progressing. Acute leukemia can be fatal in weeks or months without aggressive treatment. Chronic leukemia progresses more slowly and may be “indolent”—producing no symptoms—for 20 years or longer.

A patient with leukemia may go to the doctor feeling extremely sick, complaining of recurrent infections, bleeding, bruising, bone tenderness, fever, chills, sweats, weakness, fatigue, headaches, or swelling in the neck, armpits or groin.

*Otteau Christiansen, who defied his doctor's prediction and survived leukemia, gets ready to waterski near his Minnesota home.*





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# ***Leukemia is most common—and most likely to be fatal—in the elderly.***

On the other hand, the patient may have no symptoms at all and the disease may be discovered by chance from a routine blood test.

A normal blood smear contains many red cells and platelets and a few white cells. In leukemia, the blood usually contains many abnormal white cells and not enough red cells and platelets. Such an abnormal blood count is the physician's first clue that the patient may have leukemia, but it is not sufficient for a diagnosis.

The next step is a bone marrow aspiration and biopsy. Marrow is withdrawn from the body by suction, using a large needle and a syringe, and microscopically examined. This crucial diagnostic test is followed by more laboratory tests to identify what type of leukemia the patient has. A precise diagnosis is important because different types of disease respond to different therapies.

If the diagnosis is chronic leukemia and the patient has no symptoms, treatment may not be required for months or even years. "I have some patients in my clinic who have had chronic lymphocytic leukemia for well over 20 years," said Bruce Cheson, M.D., who heads the medicine section of NCI's cancer therapy evaluation program. "Two patients in particular only required therapy at 23 years and 22 years after diagnosis."

Patients with some types of chronic leukemia may be treated with splenectomy, or surgical removal of the spleen. This or-

gan, located behind the stomach, sometimes becomes enlarged after leukemic cells invade it.

## **Acute Leukemia**

A diagnosis of acute leukemia usually means immediate hospitalization. Patients are given antibiotics, or other appropriate therapy, for infections and other symptoms. Because leukemia patients need frequent transfusions of blood and blood products, they must be treated at medical centers with access to large quantities of such products.

Chemotherapy for acute leukemia involves two phases: an induction phase, in which the patient is aggressively treated with a combination of powerful drugs in an effort to kill all the leukemic cells, and a consolidation phase, using either the same or different drugs, which begins once the disease has gone into remission.

The two main types of acute leukemia are acute lymphocytic leukemia and acute myelogenous leukemia. Currently approved drugs to treat acute lymphocytic leukemia include vincristine (Oncovin), prednisone (Deltasone), asparaginase (Elspar), cyclophosphamide (Cytosan, Neosar), and cytarabine (Cytosar). Approved drugs for acute myelogenous leukemia include daunorubicin, also called daunomycin (Cerubidine), and cytarabine (Cytosar).

These drugs are cytotoxic, which means they kill not only cancerous cells but also normal cells, particularly in the bone marrow. The patient's immune system—already malfunctioning because of the proliferation of leukemic cells—is completely knocked out, leaving the individual defenseless against bacterial and fungal infections.

"The major period of trouble runs three to five weeks, when the normal blood counts are markedly suppressed," said Peter Quesenberry, M.D., professor of hematology and oncology at the University of Virginia School of Medicine and a medical adviser to the Leukemia Society of America.

"The dominant problems are infections and bleeding. Patients get pneumonia, high fever, and mouth sores. You get a bacterial infection—we treat that. Then you get a fungal infection. Early on, vomiting is a problem, although we do much better at controlling that now."

## **Remission: Relapse or Cure?**

About 50 to 80 percent of patients with acute leukemia achieve remission following an aggressive regimen of induction chemotherapy. Remission, however, is not cure.

"It's a period of stability and return to normal, short of cure," said Edward Henderson, M.D., a medical officer in the division of oncology at FDA's Center for Drug Evaluation and Research. Patients feel better, and their blood and marrow counts return to normal. But doctors know from experience that if treatment stops at this point, the disease will make a comeback in a matter of weeks or months—hence the need for remission maintenance therapy.

Remission maintenance therapy generally continues one to two years. After that, treatment stops. The patient still may not be cured, "but you know from experience that additional treatment is just going to add toxicity and it's not going to add therapeutic value," said Henderson. Sometimes remission maintenance therapy is given at higher doses for a shorter period.

Most patients do eventually relapse, usually within two years. One of the most frustrating aspects of treating leukemia, according to specialists like Cheson and Henderson, is the difficulty of predicting which patients will relapse and which ones won't.

"All cures go through a period of remission, but all remissions don't lead to cure," said Henderson. In leukemia, as in other forms of cancer, cure is usually defined as five or more years of disease-free survival.

There have been no major breakthroughs in chemotherapy for acute leukemia for about 20 years. "It's been an evolution, not a revolution," said Henderson.



## Bone Marrow Transplants Controversial

The role of bone marrow transplantation in leukemia therapy remains somewhat controversial. The technique involves first injecting a patient with near-lethal doses of chemotherapeutic drugs and then "rescuing" the patient from the drugs' toxic effects by injecting healthy bone marrow from a matched donor.

Transplantation used to be done almost automatically if a patient had a suitable donor, said Bruce Cheson, M.D., head of the medicine section of the National Cancer Institute's cancer therapy evaluation program.

"Then we realized we were curing people with chemotherapy alone, and some patients were dying from bone marrow transplantation who might have been cured by chemotherapy." Between 5 and 10 percent of patients die of complications of the transplantation procedure.

Other specialists are more positive about the role of bone marrow transplantation. "I've seen very few cures in acute leukemia with just chemotherapy—and we treat aggressively," said Peter Quesenberry, M.D., professor of hematology and oncology at the University of Virginia School of Medicine and a medical adviser to the Leukemia Society of America. "We've finally begun to see cures in our transplant program."

The approach likely to produce the highest percentage of cures is to treat patients with chemotherapy first and transplant those who relapse early, said Edward Henderson, M.D., of the oncology

division at FDA's Center for Drug Evaluation and Research.

But transplantation is still considered too risky for patients over 50, and its use in younger patients is limited by a shortage of suitable donors. Traditionally, a tissue-matched sibling has been considered the ideal donor, although recent advances in tissue typing—and in drug treatment to suppress rejection of the transplanted marrow—have permitted transplants of marrow from unrelated donors.

The major complication of bone marrow transplantation is graft versus host disease (GVHD), in which the transplanted marrow cells attack the patient's own immune system. The development of the immunosuppressive drug cyclosporine (Sandimmune) has enabled doctors to control GVHD, said Henderson. But physicians have also learned that patients who suffer mild GVHD do better in the long run than patients who do not experience the complication, he said.

"It's been shown beyond a doubt that if there is no reactivity to the transplanted marrow, the patient is more likely to relapse. We know this because marrow from an identical twin is only about half as effective in long-term disease control than a graft from a non-identical sibling."

The reason is that the identical twin's marrow cells are too similar to the patient's, said Henderson. "It seems that a low level of immunoreactivity is necessary for the graft to mount a suppressive reaction against the leukemic cells surviving the intensive pre-transplantation therapy."

Bone marrow transplantation using marrow donated by another individual is known as *allogeneic* transplantation. Another approach, which is still considered experimental, is *autologous* transplantation, in which a portion of the patient's

own bone marrow is removed, treated with drugs to purge it of leukemic cells, and given back to the patient.

In June 1991 FDA authorized the drug 4HC (Pergamid) to be used as a bone marrow purging agent under Treatment IND regulations. These regulations provide a way for drug developers to make investigational therapies for life-threatening illnesses available to patients before marketing under certain circumstances.

Pergamid may be used to treat patients with acute myelogenous leukemia who have achieved two or more remissions with conventional drug therapy. The drug—a form of the approved chemotherapeutic drug cyclophosphamide (Cytosan, Neosar)—kills leukemic cells in the bone marrow without destroying the marrow's capacity to generate new blood cells after it is reinfused in the patient.

Clinical studies have shown that patients with acute myelogenous leukemia in a second or later remission who receive autologous bone marrow transplants that have been treated with Pergamid may have a better chance of survival than similar patients who receive standard chemotherapy alone. ■

—E.M.

"The approach has shifted toward more aggressive treatment, backed up by bone marrow transplantation." (See accompanying article.)

Recently, however, some physicians and researchers have become excited about a new compound that appears to be extraordinarily effective at achieving remission in patients with a rare form of acute leukemia called acute promyelocytic leukemia.

The compound is ATRA (all trans retinoic acid), a form of vitamin A. It is currently classified by NCI as a Group C experimental drug, available to physicians only through the institute. Clinical studies in China, France, and most recently the United States have found that ATRA brings about complete remission, with few side effects, in about 80 percent of patients with acute promyelocytic leukemia.

In acute promyelocytic leukemia, immature white blood cells called promyelocytes do not mature normally. Instead, masses of abnormal, immature cells accumulate in the blood and bone marrow and produce chemicals damaging to surrounding tissues. Scientists think ATRA works by inducing these cells to grow normally again.

But for reasons scientists do not yet fully understand, ATRA eventually stops working. "It disappears after a patient has been on it for a while," said Cheson. "You can no longer detect it in the blood, even though the patient is still taking it. We're trying to figure out why that is and how it can be reversed."

### New Drugs for Chronic Leukemia

Most of the recent advances in drug therapy for leukemia involve compounds effective against chronic leukemia, particularly chronic lymphocytic leukemia (CLL), the most common form of adult leukemia in the United States. It is a slowly progressing disease that usually affects people over 50.

Treatment for chronic leukemia is generally less aggressive than for acute leukemia and is often given on an outpatient basis. The current standard therapy for CLL is cyclophosphamide or chlorambucil (Leukeran), sometimes in combination with prednisone (Deltasone) or

prednisolone (Hydeltra, Pediapred). While these drugs can relieve symptoms, many patients experience significant side effects and eventually stop responding.

Fludarabine (Fludara) was approved by FDA in April 1991 to treat patients who do not respond to other therapies for CLL. In NCI-sponsored clinical trials involving such patients, 32 to 48 percent responded to fludarabine and 13 percent achieved complete remission.

Researchers think fludarabine works by inhibiting reproduction of abnormal lymphocytes, a type of white blood cell. The drug belongs to a unique class of medications known as purine analogues. Purines are nitrogen-based molecules used as building blocks of DNA, the basic genetic material of living organisms.

Another type of chronic leukemia is chronic myelogenous leukemia (CML). Currently approved drugs for CML are busulfan (Myleran) and hydroxyurea (Hydrea).

In January 1992, FDA approved pentostatin (Nipent) for treating patients with a rare form of chronic leukemia called hairy cell leukemia who do not respond to alpha interferon, the standard therapy. In clinical trials, 70 percent of patients taking pentostatin achieved complete, long-term remission. The drug is a derivative of *Streptomyces antibioticus*, a fungus from which many antibiotics, including tetracycline, are derived.

An experimental drug, 2CDA, has also shown results against hairy cell leukemia, achieving long-term remissions in 80 to 85 percent of patients treated in clinical trials. This drug is currently available under FDA's Treatment IND regulations. (IND stands for investigational new drug.) Under these regulations, desperately ill patients who do not respond to conventional therapy can receive promising experimental drugs before completion of the review needed for full approval.

Last June, FDA's oncologic drug advisory committee recommended that FDA approve 2CDA for the treatment of hairy cell leukemia. At press time, the agency had not reached a decision on the drug's approval.

2CDA is an antimetabolite, one of a group of drugs that prevent cell growth by

interfering with essential enzyme reactions. A major difference between 2CDA and pentostatin, said NCI's Cheson, is that a complete course of 2CDA can be given in one week, while treatment with pentostatin extends over a six-month period.

Fludara, Nipent and 2CDA, Cheson said, all have fewer side effects than other drugs currently in use. "There is surprisingly little nausea, vomiting, generally no hair loss, and they are very well tolerated. The biggest side effect is immunosuppression." Suppression of the immune system puts patients at risk for infections.

One curiosity of cancer treatment, observed both Henderson and Cheson, is why breakthroughs tend to occur more often in rarer forms of a disease. Leukemia is no exception: ATRA, Nipent and 2CDA all are targeted to rare forms of leukemia.

"The rare tumors tend to be the ones that respond," said Henderson. "It may be that they are even further differentiated from normal, with special characteristics that make them more susceptible to treatment if you push the right button."

Future progress will be made against all forms of leukemia, Cheson predicted, "when we become smarter than the leukemias. . . . We need to overcome the various cellular mechanisms of drug resistance." As scientists learn more about the molecular biology of leukemia, he said, they will be able to develop compounds that can halt or reverse cancerous changes at the cellular level.

"Biotechnology is the hope and promise of the future," said Henderson. "If we can identify specific genetic defects, we can then look for ways of correcting those defects. The product of those genes can be switched on or off, or drugs can be given to switch off a signal that shouldn't be given or provide one that's missing.

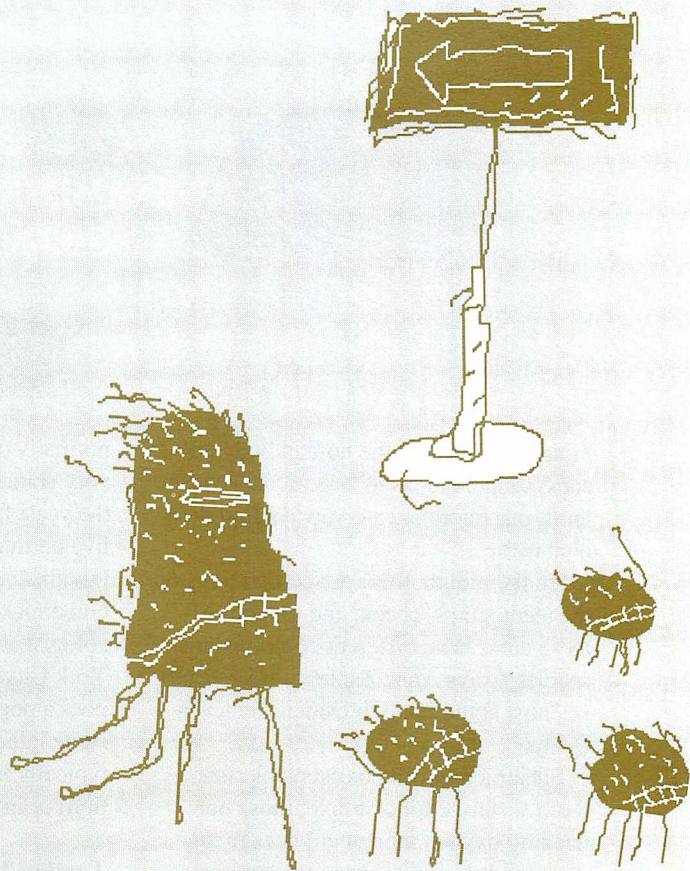
"It's the most optimistic time for that sort of approach that there's ever been," he said. "I have no real doubts that leukemia will be cured—but whether it will take a few years or a few decades is hard to say." ■

*Eleanor Mayfield is a freelance writer in Silver Spring, Md.*



# The Bugs Within Us

by Ricki Lewis, Ph.D.



They're found in predictable places, where bends in the body create warm, moist pockets, and where the body is exposed to the outside.

A microscopic zoo inhabits our armpits and groins, our eyes and ears, the entrances to our respiratory tracts, and the exits from our urinary tracts. Our digestive systems are continuous tubes along which bacteria congregate. Our urine, sterile as it collects from our kidneys, picks up bacteria as it leaves our bodies. The contents of our colons harbor 10 billion microbes per gram.

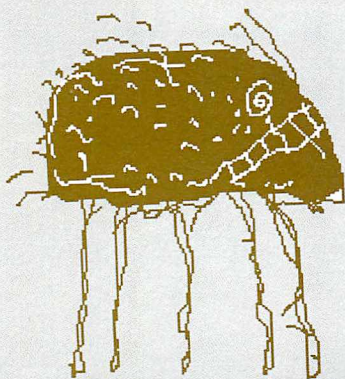
From between our fingers to between our toes, many microbes call the healthy human body home.

The bacteria, protozoa, viruses, and fungi that live within us come in two basic varieties: residents and transients. "Normal resident flora" are always present and include, for example, the microbes of the digestive system. "Transient flora" come and go, vanquished by bathing, flushed out in sweat, urine, tears, and feces, only to reestablish themselves repeatedly.

So diverse and numerous are the "normal flora" that







biologists consider the human body an ecosystem. And, as in large-scale ecosystems, our microbial stowaways find their own niches.

"In the mouth, there are certain bugs on the teeth, gums, cheek, and tongue. All these areas have different combinations of species," says Anne Tanner, Ph.D., senior scientist at the Forsyth Dental Center in Boston.

Bacteria requiring oxygen colonize tooth surfaces, for example; those not needing oxygen inhabit crevices in the gums and minute folds on the surface of the tonsils.

Researchers in the department of periodontology at the University of Helsinki compared bacteria and fungi in healthy mouths to those in mouths of 51 denture-wearers. One fungus was notably missing in the denture group, presumably because its home, the teeth, was gone.

Microbes first inhabit our bodies as we are born, hitching a ride in the birth canal. Within 12 hours, several species are present in the intestinal tract, transferred from the mother, from food, and from the baby's fist should it contact the mouth. These are not necessarily hazardous to the baby and in fact are beneficial in stimulating the infant's natural immunity. Immunologists even suspect that a parent's instinctive kissing and nuzzling of the newborn introduces bacteria that rev up the child's immune system.

Throughout our lives, normal flora benefit us. "They manufacture nutrients—biotin, pantothenic acid, pyridoxine, vitamin B<sub>12</sub>—stimulate the immune system to recognize threatening microbes, and stake out a territory that might otherwise be occupied by pathogenic [disease-causing] organisms," says Holly Ahern, a microbiologist at the State University of New York at Albany. Resident microbes are also behind such embarrassing problems as intestinal gas, bad breath (halitosis), and body odor.

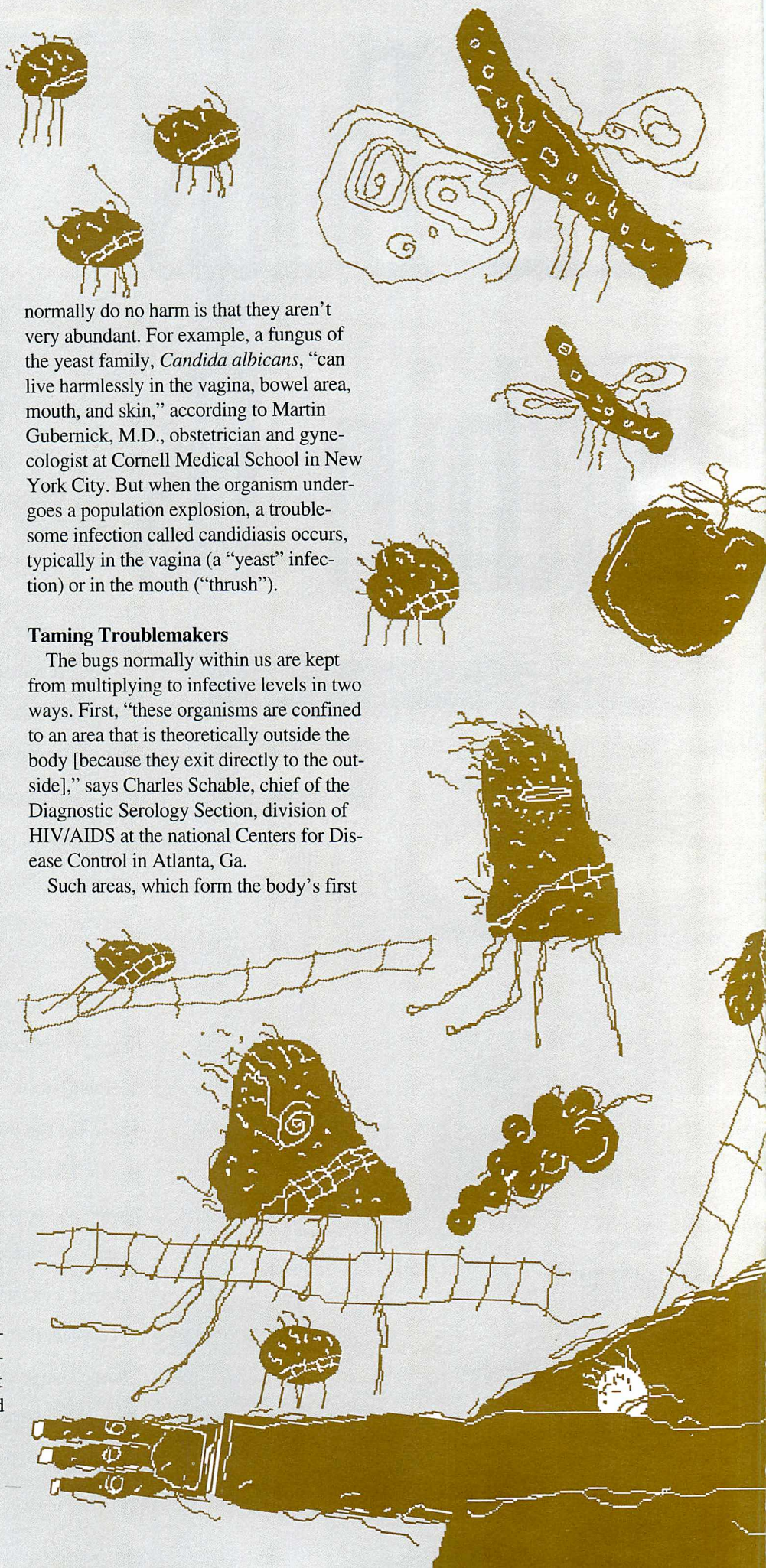
One reason why the bugs within us may

normally do no harm is that they aren't very abundant. For example, a fungus of the yeast family, *Candida albicans*, "can live harmlessly in the vagina, bowel area, mouth, and skin," according to Martin Gubernick, M.D., obstetrician and gynecologist at Cornell Medical School in New York City. But when the organism undergoes a population explosion, a troublesome infection called candidiasis occurs, typically in the vagina (a "yeast" infection) or in the mouth ("thrush").

### Taming Troublemakers

The bugs normally within us are kept from multiplying to infective levels in two ways. First, "these organisms are confined to an area that is theoretically outside the body [because they exit directly to the outside]," says Charles Schable, chief of the Diagnostic Serology Section, division of HIV/AIDS at the national Centers for Disease Control in Atlanta, Ga.

Such areas, which form the body's first









# Microbe Hang-Outs

**Skin:** Bacteria (*Staphylococci*, *Streptococci*, *E. coli*, and diphtheroids) and fungi (*Candida albicans* and *Cryptococcus*) congregate in warm, hairy, moist areas, such as the groin and armpits, but steer clear of dry, calloused areas, such as the palms and soles. They also grow on the scalp and near sweat and sebaceous (oil) glands. Transient microbes dwell in mucus secretions near body openings, such as the mouth, nose, eyes, and vagina, vanquished only temporarily by washing. Bacteria return from the environment and from populations that live deep down in oil gland ducts.

**Ear:** The outer ear is home to a varied collection of bacteria, yeasts and molds. The middle and inner ears are normally free of microbes, but can become occupied—and infected—by persistent coughing, sneezing, and nose-blowing. These actions open the eustachian tubes, permitting microbes to enter the ears. The three major middle ear pathogens—*Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Branhamella catarrhalis*—are more prevalent in children with recurrent middle ear infections, even when they are healthy, than in children who do not have frequent ear infections.

**Eye:** Several types of bacteria live in and around the eye, over the opening, in the conjunctiva (the eyelid lining), and in tears. They include species of staphylococcus, streptococcus, diphtheroids, and *Neisseria*. Visual structures are protected from these microbes by partitioning membranes, and by lysozyme, an antibacterial substance in tears.

**Respiratory System:** Many microbes live in the nose and throat, but the lower respiratory structures—the larynx (voice box), trachea (windpipe), bronchi, bronchioles, and alveoli (the microscopic air sacs in the lungs)—have built-in barriers. The narrowing of the tubes keeps some bugs out, and the numerous waving, hairlike cilia that fringe the cells lining the tract propel bugs up and out. One of the dangers of

cigarette smoking is tobacco tar's destruction of the protective cilia, which provides a gateway for bacteria from the nose and throat to the lungs.

**Mouth:** The mouth harbors the most bacteria of any body part. One resident, *Streptococcus mutans*, causes dental caries (cavities), but only under certain conditions. Sticky foods, such as candy and raisins, enable the bugs to cling to teeth, where they produce acids that eat away at tooth enamel. "You can carry the bug but not have decay until you eat the wrong foods," says Anne Tanner, Ph.D., senior scientist at the Forsyth Dental Center in Boston.

"One of the good guys in the mouth is *Strep sanguis*," says Jeffrey Hillman, D.M.D., of the University of Florida at Gainesville. "It's a hydrogen peroxide producer and this prevents the outgrowth of potentially pathogenic organisms."

**Digestive Tract:** Swallowed microbes perish as they splash into the stomach's acid contents, where only those organisms protected in the mucus-rich lining survive. Microbe populations grow in the upper part of the small intestine (the duodenum), but bile, a greenish substance produced in the liver and stored in the gallbladder, inhibits their growth. In the lower portions (the jejunum and ileum), as the effects of stomach acid and bile dissipate, bacterial populations bloom. Most nutrients are absorbed into the bloodstream in the small intestine, leaving waste, toxins and microbes galore as the normal state of affairs in the large intestine.

The further down the digestive tract, the more populous the bacteria, ranging from an estimated 1,000 to 100,000 per gram of contents in the stomach to 10 billion per gram in the large intestine. By the time the contents are excreted in a bowel movement, there are commonly 100 billion bacteria per gram.

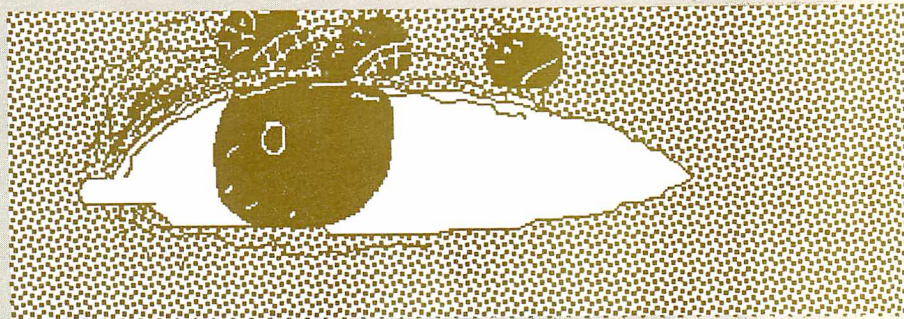
**Urinary Tract:** Urine dripping from the microscopic kidney tubules, into the ureters to the bladder, is sterile. But bacteria, yeast, viruses, and fungi come on board in the urethra, because this tube leads from the bladder to the outside. Although the acidic urine routinely flushes microbes out, they can return. Healthy urine on its way out of the body may harbor up to 1,000 bacteria, of several types, per milliliter. More than 100,000 bacteria per milliliter of a single type is a sign of a urinary tract infection.

Women are more prone to urinary tract infections than men because the urethra is closer to the bacteria-laden rectum, and it is shorter. (See also "Urinary Infection: The Unwelcome Night Visitor," in the March 1985 *FDA Consumer*.)

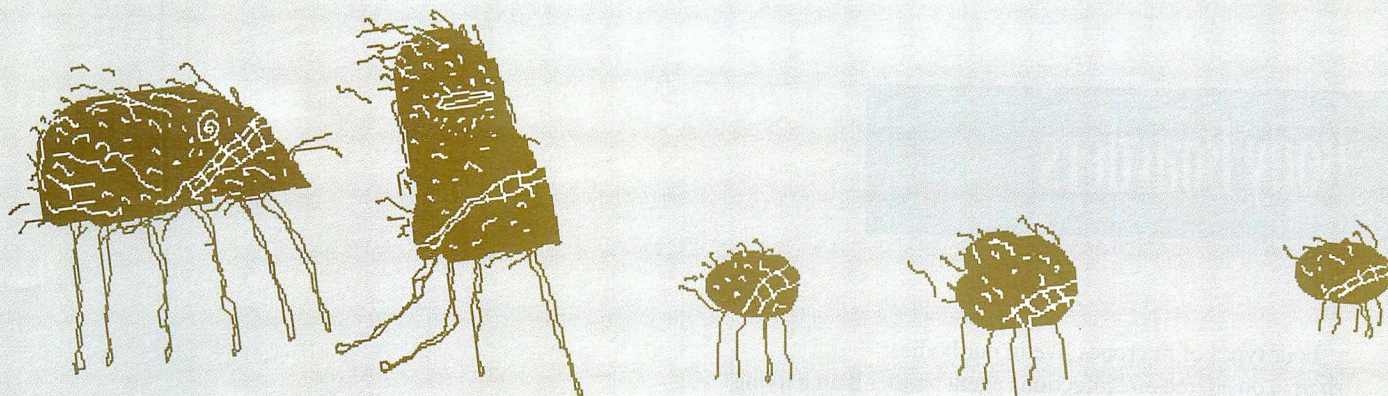
**Vagina:** The vagina is lined with what biologists call a "bacterial biofilm," consisting of a dozen types of microbes. Some, such as strep and staph germs, easily wash away in a tub bath. Others, such as certain lactobacilli, hold fast. The microbial environment of the vagina varies as the pH (acidity or alkalinity) of secretions shifts with the changing hormonal milieu as a woman ages.

These pH ups and downs affect which microbes inhabit the vagina. When secretions are alkaline, before and after the childbearing years, *E. coli*, diphtheroids, streptococcus, and staphylococcus predominate. During the childbearing years, when secretions are acidic, lactobacilli become abundant, and different strains of streptococcus and staphylococcus live. One common cause of vaginal inflammation, or vaginitis, is infection by *Trichomonas vaginalis*, a protozoan with a characteristic flipperlike tail. *Neisseria gonorrhoeae*, the bacterium responsible for the sexually transmitted disease gonorrhea, can survive the acid environment. ■

—R.L.







line of defense, include the skin, digestive system, and genitourinary and respiratory tracts. The lining of the small intestine, for example, forms a barrier that keeps organisms out of body areas where they could cause disease. "If these intestinal microbes were in the blood, you'd be in deep trouble," Schable adds. One normal gut bacterium is *Escherichia coli*. When a wound provides *E. coli* access to the abdominal cavity outside the intestines, a severe infection, peritonitis, results.

Should normal flora escape to an unfamiliar place, they still may not cause harm, because they are attacked by cells and biochemicals of the body's second line of defense, the immune system. But when immunity fails, microbes normally present in low numbers flourish, causing opportunistic infections, so-named because the bugs seem to take advantage of the slip in immune surveillance.

"If the immune system is impaired due to AIDS or chemotherapy to treat cancer, for example, organisms the body normally fights off with ease can spread. An example is *Pneumocystis carinii*, which can reside harmlessly in the throats of normal healthy people. The immunocompromised have a tough time fighting it off," says Schable of the lung infection that is often the first serious sign of AIDS.

Infections resulting from normally resident microbes growing out of control are typically treated with antibiotics. FDA evaluates and approves a wide range of these products, from over-the-counter antibiotic creams used topically to treat minor skin infections, to a number of prescription oral antibiotics, to prescription antibi-

otics that must be administered intravenously or intramuscularly for very serious or hard-to-treat infections.

### Paving the Way for Pathogens

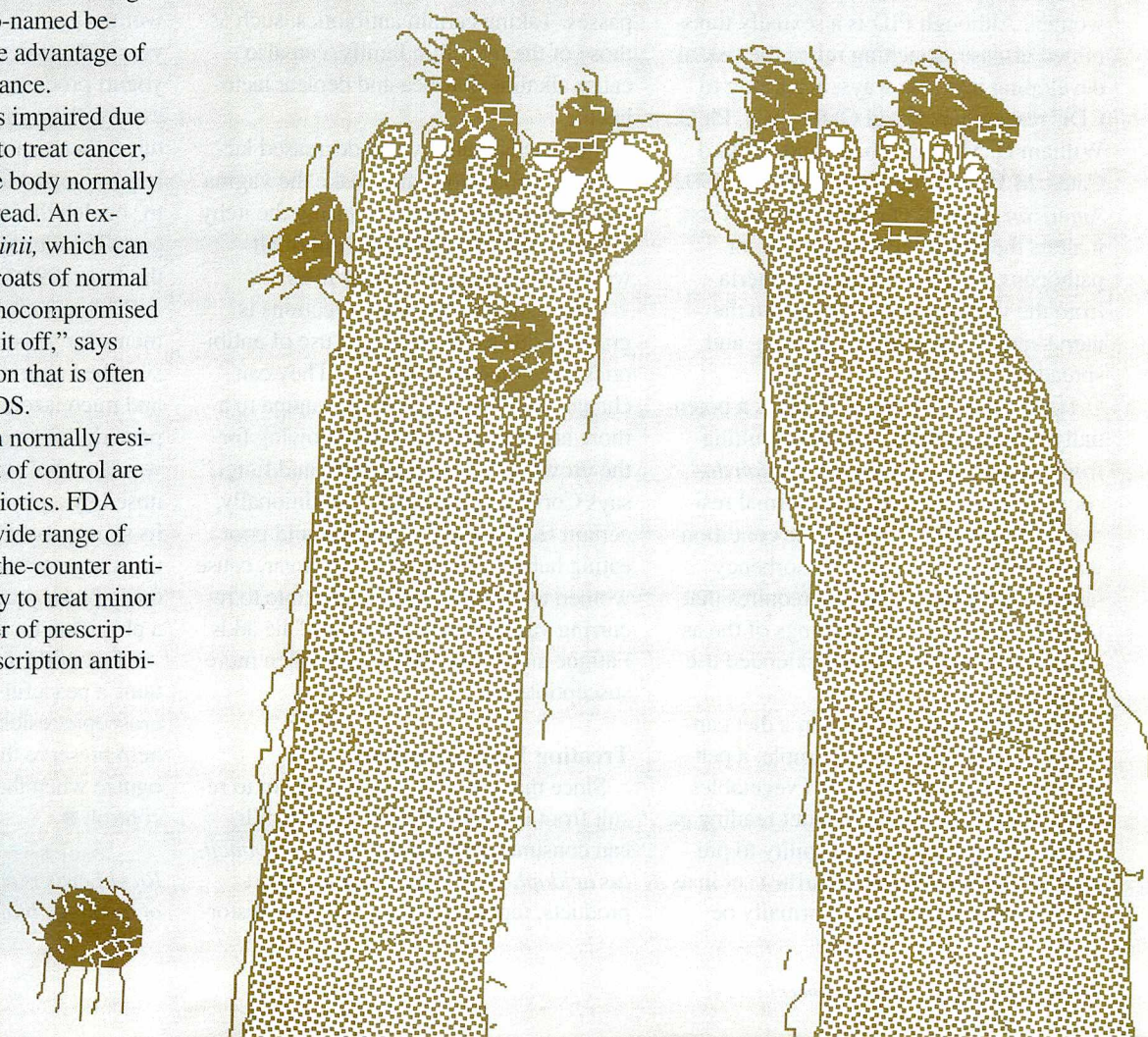
In a more subtle way, the normal microbes in our bodies can also usher in infection when their numbers fall. "This can happen when something in their environment changes, such as the moisture, temperature, availability of oxygen, or the pH," says Ahern. The pH is a measurement of acidity or alkalinity, with a value of 7 representing neutral, below 7 acidic, and above 7 alkaline.

Often, changes in microbial habitats result from something we do. Consider the ancient practice of douching, cleansing the

vagina. It is practiced by 37 percent of American women, finds the most recent National Survey of Family Growth, a survey of 8,450 women of reproductive age conducted regularly by the National Center for Health Statistics.

Advertisers for douche products capitalize on the reputation of microbes as disease-carriers, using such phrases as "natural," "clean" and "healthy," claiming that a douche can make a woman feel "as fresh as a summer rain," as one such pitch goes. So it is not surprising that many women who douche do so because they think it is a healthy practice.

It may be just the opposite. Douching is a known risk factor for pelvic inflammatory disease (PID), a severe infection of





# Body Boarders

Four types of microbes live in our bodies:

**virus:** considered an “infectious agent” rather than a living thing by many biologists, a virus is simpler than a cell, built of a nucleic acid (DNA or RNA) surrounded by protein.

**bacteria:** among the simplest of cells, bacteria come in a variety of forms. They are distinguished by their growth requirements, shape (round are cocci, spiral are spirilla, rods are bacilli, and curved rods are vibrios), and whether their cell walls stain purple (Gram positive) or not (Gram negative).

**protozoa:** microscopic organisms built of a single, complex cell, often distinguished by the way they move.

**fungi:** organisms built of complex cells, lacking nervous systems (which animals have) and lacking the ability to extract energy from sunlight (which plants have). Yeasts are single-celled fungi. ■

—R.L.

the upper reproductive structures in women. Although PID is a sexually transmitted disease, douching raises the risk of developing it in two ways, according to CDC researchers Sevgi Okten Aral, Ph.D., William D. Mosher, Ph.D., and Willard Cates, M.D., writing in the February 1992 *American Journal of Public Health*. First, it alters the pH of the vagina to favor pathogens. Second, it flushes bacteria from the vagina and cervix up into the uterus and fallopian tubes, seeding and spreading infection.

Toxic shock syndrome (TSS) is a potentially life-threatening disorder resulting from production of a toxin by *Staphylococcus aureus*, a sometimes normal resident of the vagina. In 1980, the condition was linked to certain high-absorbency tampon products. FDA now requires that tampon packages bear warnings of the association between TSS and extended use of tampons.

Drastic changes in a person's diet can affect resident flora. For example, a person who never eats fruits and vegetables may start taking fiber pills after reading an article saying fiber has the ability to prevent cancer. Cramps and diarrhea set in as the intestinal bacteria that normally oc-

cupy the digestive tract are hastened out of the body by the sudden barrage of fiber.

Emotional upset can cause diarrhea too. Diarrhea caused by stress has a higher pH and fewer acid-producing bacteria (lactobacilli). Lack of lactobacilli typically leads to population explosions of yeasts.

Normal conditions return when the trauma passes. Taking certain antibiotics, such as those of the penicillin family, can also cause alkaline diarrhea and deplete lactobacilli.

Increased alkalinity and decreased lactobacilli populations also make the vagina more hospitable to yeast, causing the itchy infection that affects 75 percent of all women at some time in their lives.

“The incidence of yeast infections is growing due to the increased use of antibiotics and oral contraceptives. They can change the pH balance of the vagina to a more alkaline environment, allowing for the growth of harmful bacteria and fungi,” says Cornell's Gubernick. “Additionally, certain factors such as diabetes and poor eating habits, like diets rich in sugar, cause women to become more susceptible to recurring vaginal yeast infections,” he adds. Fatigue and stress can make women more susceptible too.

## Treating Yeast Infections

Since many health problems seem to result from lowered levels of lactobacilli, can consuming live cultures of *Lactobacillus acidophilus*, found in some yogurt products, replace the harmful bugs, restor-

ing the low (acidic) pH? Eating yogurt containing live bacteria has recently received some scientific support. In the March 1, 1992, issue of the *Annals of Internal Medicine*, Eileen Hilton, M.D., of the Long Island Jewish Medical Center reported on 13 women with recurrent vaginal yeast infections. The women ate eight ounces of yogurt with live *Lactobacillus acidophilus* a day for six months, then no yogurt for six months. They had fewer infections while on the yogurt regimen, and had higher levels of the apparently protective bacteria in their vaginas and rectums at this time.

But in an accompanying editorial, David J. Drutz, M.D., of St. Michael's Medical Center in Newark, N.J., cautions women against trying to treat a vaginal yeast infection with yogurt alone. Many yogurt products lack live lactobacilli. And even with yogurt that contains live cultures, there isn't enough scientific data to rely on yogurt alone. Medication is needed to squelch the infection. (See also “Yogurt: The Curds and Whey to Health?” in the June 1992 *FDA Consumer*.)

FDA recently altered the status of treatments for yeast infections. The agency switched clotrimazole (Gyne-Lotrimin) and miconazole nitrate (Monistat 7) from prescription to over-the-counter, because a woman who's had a yeast infection diagnosed by a physician can easily recognize its symptoms. Packages of both medications urge women who have not previously had a yeast infection to first consult a physician for an initial diagnosis.

Most of the time, the human body maintains a peaceful coexistence with its microscopic residents and visitors. We can help preserve the peace by learning to recognize when the bugs within us get out of control. ■

*Ricki Lewis is a geneticist and the author of a college biology text.*

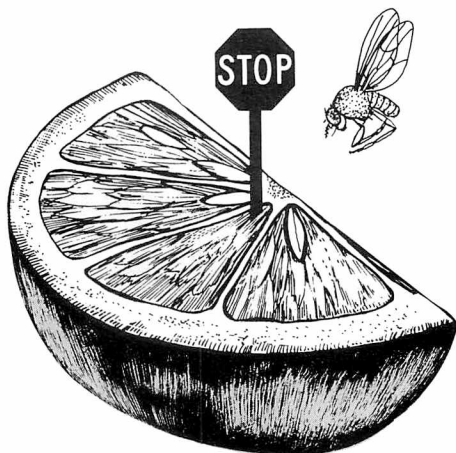




*The Notebook: a potpourri of items of interest gathered from FDA news releases, other news sources, and the Federal Register (designated FR, with date of publication). The Federal Register is available in many public libraries.*

■ **New animal drug applications** using a variety of computer systems are now being accepted by the Center for Veterinary Medicine. The center no longer restricts computer-assisted submissions to floppy disks compatible with existing computer systems. More information is available from Robert C. Livingstone, Center for Veterinary Medicine (HFV-100), FDA, 7500 Standish Place, Rockville, MD 20855; telephone (301) 295-8620. (FR May 28)

■ **Citrus fruit** grown in South Australia has been proven free of insects and can be imported into the United States. U.S. Department of Agriculture officials initially denied entry because they were concerned that fruit flies and other insects would enter the country with the fruit. South Australia's Department of Agriculture has since taken steps to ensure the fruit is insect-free. (FR May 28)



■ **The flu vaccine** for the winter of 1992-93 should include protection against the Texas, Beijing and Panama flu viruses, an independent committee recommended to FDA. Flu vaccines are made differently from year to year to combat the strains health officials predict will cause the most illness. (*Morbidity and Mortality Weekly Report*, May 8)

■ **A certified drug-testing labs list** is updated in the *Federal Register* the first week of each month. This list includes only labs that have been approved to test federal agency employees for drug abuse. More information is available from Denise L. Goss, National Institute on Drug Abuse, Room 9A53, 5600 Fishers Lane, Rockville, MD 20857; telephone (301) 443-6014. (FR June 1)

■ **Prostate cancer deaths** are on the rise, especially among black men, according to the national Centers for Disease Control. From 1980 through 1988, prostate cancer deaths increased 2.5 percent for white men and 5.7 percent for black men despite improved early detection methods. Prostate cancer is the second leading cause of cancer deaths among American men. (*MMWR* June 12)

■ **Breast cancer incidence** increased 36 percent from 1973 to 1987, but deaths from the disease only increased 1 percent, according to the Centers for Disease Control. There were 26.9 deaths per 100,000 women in 1973, compared with 27.1 in 1987. Among American women, breast cancer is the most common cancer and the second leading cause of death. (*MMWR* April 24)

■ **Baby bean bag pillows** were banned July 23, 1992, by the Consumer Product Safety Commission because their use caused 35 deaths and one serious injury in infants. (FR June 23)

■ **Infant carrier seat accidents** accounted for 26 deaths in children between January 1986 and October 1991, according to the Centers for Disease Control. In most cases, the infants were strangled by the seat's straps or smothered when the seat turned over. CDC stressed that infants should never be left unattended in carrier seats. (*MMWR* April 24)

■ **A campaign against smokeless tobacco**, aimed primarily at boys 10 to 12 years old, has been launched by the Little League International Congress. About 14 percent of tobacco chewers are between 12 and 17. Most of them began chewing tobacco at around age 13. (*American Medical News*, May 4)

■ **Firearms** are the second leading cause of death among 15- to 19-year-olds. The leading cause of death is motor vehicle crashes. Five times as many teenagers are killed by guns in metropolitan counties (13.7 deaths per 100,000 population) than in non-metropolitan counties (2.9 per 100,000). (*JAMA* June 9)





# Mother Goes to Jail for Baby Food Tampering

by Dori Stehlin

A South Carolina woman who put more than 460 pieces of glass in a jar of baby food and then fed several spoonfuls to her 13-month-old son is going to jail for 33 months with no chance for parole.

On April 30, 1992, Elese M. Johnson, 39, of Hartsville, S.C., was sentenced on a charge of violating the federal Anti-Tampering Act. Besides the prison term, Judge Dennis W. Shedd, U.S. District Court for the District of South Carolina, sentenced Johnson to three years supervised probation. The conditions of the probation prohibit Johnson from living with her son and 4-year-old daughter unless a South Carolina family court issues an order granting Johnson custody.

FDA first learned of the tainted baby food from the Hartsville police department, which notified the agency's Atlanta district office on the evening of May 2, 1991.

The police told FDA that Johnson had brought her son to Hartsville's Byerly Hospital emergency room earlier that evening. She claimed she had discovered glass in two jars of Gerber baby food and in her son's mouth. The emergency room doctor could not detect any cuts or other injuries from the glass, but told Johnson to have her son examined by his pediatrician the next morning.

The Atlanta office immediately notified the agency's Columbia, S.C., office, where Investigator Tamera Smith was assigned to the case.

The next morning, Smith left for Hartsville—about 100 miles east of Columbia—and met with Hartsville police officer Lt. Timothy Kemp. Kemp gave her the two jars of baby food from which Johnson had fed her son and two other unopened jars Johnson had purchased at the same time. Smith and Kemp then went to the Piggly Wiggly grocery store where

Johnson had bought the baby food and collected samples with the same lot numbers. (In case there were more tainted jars, the store had pulled all Gerber baby food jars from the shelves.)

After visiting five other grocery stores and interviewing the emergency room doctor, Smith and Kemp met with Johnson at her home. Smith asked Johnson to retrace her steps leading up to the discovery of the glass.

"She told me she opened two jars of food, bananas with tapioca and green beans, and spooned some of both onto a saucer," says Smith. "She said she fed her son a few spoonfuls before hearing a crunching noise."

In an affidavit, Johnson said she placed

her finger in her son's mouth and found a small piece of glass. "I started looking in the saucer, and found more slivers of glass."

Johnson also told Smith and Kemp her son's pediatrician had found a small cut on the baby's tongue earlier that morning.

Smith and Kemp left Johnson and went to interview the pediatrician. While they were there, Johnson arrived with a stool sample from her son that contained pieces of glass.

The following morning, Smith drove to FDA's Southeast regional laboratory in Atlanta with the jars of baby food collected from Johnson, those from the grocery store, and the stool sample. FDA chemist David Jordan analyzed the two





opened jars. In addition to the 460 pieces in the jar of bananas and tapioca, Jordan found 72 pieces in the green beans.

It had to be tampering, according to Jordan. "There's just no way it happened at the manufacturer," he says. First, he explains, if it had happened during production, it would be unlikely that any more than two or three fragments would fall into any one jar. Plus, the glass was in two different foods, with different lot numbers and, according to Gerber records, produced six months apart.

On May 6, Smith and Hart went to Johnson's apartment again. "I told her that we were pretty sure that this was tampering and not the fault of Gerber," says Smith. "She just stuck with her story. But

then as we started to leave, she said, 'What would happen if I told the truth?' All I could tell her was, 'If you want to say something to us, now is the time to say it.' "

Johnson confessed to putting glass in the two jars of baby food and feeding it to her baby. "I really did not want to hurt [my baby], I just needed money," Johnson said in her affidavit. She said she hoped she could get money from both the manufacturer and the grocery store.

After confessing, Johnson was arrested and her children were placed in the custody of the local department of social services. The children are now living with Johnson's sister.

On Aug. 7, 1991, a federal grand jury

indicted Johnson on two counts of violating the Federal Anti-Tampering Act. After a one-day trial on Nov. 12, a federal jury found Johnson guilty on one count—lying about the cause of the tampering of a consumer product. (On the government's motion, the judge dismissed the second count, which deals directly with the act of tampering, because, under his interpretation, it only applied if Johnson had put the tampered food back on the grocery store shelf.)

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

## Michigan Mayor Sentenced In Prescription Drug Sales

Mary Donnelly used to have two jobs—sales representative for a North Carolina drug manufacturer and mayor of Bay City, Mich. But she was fired from the first and had to resign from the second because she broke federal law.

On April 16, 1992, Donnelly was sentenced to five years' probation, with the first five months to be spent in a Saginaw, Mich., halfway house, for illegally selling and offering to sell to a pharmacist samples of the ulcer drug Zantac 150 between July 1988 and April 1990. In addition, she was ordered to pay \$1,000 to the drug manufacturer and perform 300 hours of community service.

In March 1992, the pharmacist pleaded guilty to misbranding a prescription drug. At press time, no sentencing date had been set.

Donnelly had pleaded guilty on Oct. 24, 1991, in the U.S. District Court for the

Eastern District of Michigan, to violating the Prescription Drug Marketing Act (PDMA), which prohibits selling, buying, trading, or offering to sell, buy or trade prescription drug samples. Under the provisions of the plea, she agreed to cooperate with FDA and FBI investigators looking into other potential violations of the act. (For more on PDMA, see "Sales Rep Convicted for Selling Prescription Drug Samples" in the October 1991 *FDA Consumer*.)

FDA first learned of Donnelly's illegal sales from Glaxo Pharmaceuticals, Research Triangle Park, N.C., the manufacturer of Zantac and Donnelly's employer. In a letter received Aug. 16, 1990, FDA's division of drug quality evaluation learned from Glaxo that Donnelly had sold samples and that Glaxo had fired her on Aug. 7.

The drug quality division called FDA's Detroit district office that same day, and Jim Mundo, an investigator with FDA's local office in Saginaw, Mich., initiated

the government's investigation on Aug. 29. Mundo interviewed Glaxo's security chief, who told him that the case against Donnelly began in December 1989 when an employee at a pharmacy in Bay City told another Glaxo sales representative about the illegal sales. At first, the sales representative didn't take the complaint seriously. But, when the employee complained again five months later, the representative notified Glaxo headquarters.

The security chief told Mundo that he confronted Donnelly with the accusations on Aug. 7. Although she denied selling the samples, she was unable to account for 80 missing bottles of Zantac in her drug inventory. This led to her being fired.

Mundo also spoke to the pharmacy employee, who told him that Donnelly brought the samples into the store in a briefcase or a bag and "once even a plastic trash bag full." The sales were usually between \$300 and \$700. The largest sale, in November 1989, was for \$800.

On Aug. 31, Mundo and a representa-



tive from the Michigan Board of Pharmacy interviewed the pharmacist, Martin Howard. After 45 minutes of denying any wrongdoing, Howard finally admitted to buying samples of Zantac from Donnelly for half the wholesale price.

Howard agreed to give FDA copies of his purchase and sales records for Zantac. According to those records, he had sold approximately 3,825 more pills than he had purchased through legal channels between 1987 and 1990.

Mundo continued to interview other witnesses during the next three months. During the spring and summer of 1991, the U.S. attorney's office for the Eastern District of Michigan, with assistance from FDA and the FBI, prepared the case against Donnelly for trial.

On March 17, 1992, Howard pleaded guilty to a misdemeanor charge of misbranding a prescription drug. He admitted that he had removed the Zantac he had purchased from Donnelly from the sample packaging and put the drug in his own glass vials. He faces a maximum of one year in prison and a \$100,000 fine.

—Dori Stehlin

## Proplast Devices Seized

Bone degeneration, immune reactions, painful tumor-like growths—these are just some of the reactions caused by jaw implants coated with Proplast, a porous substance made by a medical device company in Houston, Texas.

Vitek, Inc., of Houston stopped selling one of its Proplast devices—the Interpositional Implant—in 1988 because of mounting lawsuits against the product. The founder of Vitek, Charles A. Homsy, invented Proplast.

FDA revoked approval of the device and took several other actions to keep

other kinds of Proplast implants, all made in violation of numerous safety standards, off the market.

From March 1989 to April 1992, FDA conducted four inspections, initiated five seizures, and was involved in a trial and several other court actions concerning Proplast. In the end, an estimated \$2 million worth of Proplast devices were condemned and destroyed.

Problems with Vitek date back to the early 1980s. "Basically, we had problems with the firm going back 10 years," said FDA compliance officer Elaine Crosby, who supervised the investigation and the enforcement actions in the Dallas district. "They had a lot of regulatory problems."

The Interpositional Implant was intended to repair jaw joints damaged by temporomandibular joint syndrome, a commonly diagnosed degenerative jaw ailment. These implants were made in part with Proplast, a substance that was supposed to promote bone and tissue ingrowth so that the implant would become stable and restore joint function.

The Proplast component caused many problems, however, breaking down in patients' jaws and causing immune disorders and tumor-like growths. After some 400 lawsuits were filed against Vitek, the firm filed for bankruptcy in June 1990. Altogether, approximately 3,000 claims have been filed in bankruptcy court due to failures of the Interpositional Implant.

Homsy formed two spin-off companies to take over production of other face, hip and jaw implants, as well as the Proplast itself. NovaMed, Inc., had been formed in November 1988, and Oral Surgery Marketing, Inc. (OSMI), was incorporated the same day Vitek filed for bankruptcy. Both operated out of Vitek's building with the same employees and manufacturing equipment. NovaMed and OSMI also had

many of the same violations of FDA standards that had plagued Vitek.

The following violations were found during investigations of the three companies between 1989 and 1991:

- The companies did not keep track of and report to FDA hundreds of complaints about the implants, including infection and bone degeneration, many of which resulted in serious injury.
- Proplast that had failed quality control tests was used in the implants.
- The companies did not validate several key Proplast manufacturing processes, such as mixing, filtering, sintering, leaching, and drying the material.
- Some devices were marketed and exported without FDA approval.

The companies failed to file required medical device reports (MDRs) of serious injury caused by Proplast devices. In March 1989, FDA's Southwest regional medical device specialist, Cheryl A. Boyce, conducted a comprehensive inspection of Vitek and NovaMed. Boyce found numerous violations of FDA's good manufacturing practice (GMP) and MDR regulations. She also discovered that Vitek was distributing an unapproved device intended to replace the total jaw joint. FDA thereafter issued a regulatory letter to Homsy, advising him of the deficiencies.

Homsy promised to correct the GMP and MDR violations, but argued that he didn't need to follow FDA's pre-market notification requirements for the total joint replacement device (known as the V-II) because it was covered by another previously approved device. FDA disagreed with Homsy's position.

Boyce and Investigator Cheryl Crosier from the Houston FDA office inspected NovaMed and OSMI again in late July and August 1990 and again found extensive GMP and MDR violations.





The investigators also determined that Homsy continued to sell the V-II jaw implant without pre-market notification and had shipped several of the devices to an oral surgeon at Humana Hospital in Dallas.

At FDA's request, the Texas Department of Health placed the jaw implants under state embargo. The devices were later seized under FDA sanctions.

Boyce also discovered during the inspection that NovaMed continued to manufacture and export a Proplast-coated hip prosthesis for which FDA had revoked approval. During the inspection, a NovaMed employee told Boyce that some hip implants had secretly been removed from the facility shortly after the inspection began. The employee said that Homsy planned to take the implants to the Netherlands in the next 48 hours.

Crosby and supervisory investigators James Lahar and Jim Jones quickly arranged for U.S. Customs officials to meet Homsy at Houston's Intercontinental Airport on Aug. 1, where they seized a dozen

hip prostheses they found in his suitcase.

So that Homsy couldn't order more implants sent from the factory, Crosby and Investigator Carlos Dixie asked the Texas Department of Health to detain the illegal hip and jaw implants at the company.

The implants seized at the company's facility and airport were valued at about \$1 million.

Boyce and Crosier again inspected the companies in December 1990 and February 1991, finding continuing MDR and GMP problems. The agency asked the U.S. attorney's office in Houston to initiate a mass seizure of all remaining Proplast devices, components and raw materials at NovaMed and OSMI. The U.S. Marshal's Service seized an estimated \$1 million worth of Proplast products in March 1991.

In March 1992, following a week-long trial, Judge David A. Hittner of the U.S. District Court for the Southern District of Texas condemned all Proplast materials seized in March 1991. In June 1992, Judge Hittner ordered the devices destroyed.

Acting on a tip from an informant, Crosby requested FDA's Cincinnati office to investigate a physician's office in Columbus, Ohio. Cincinnati investigators Steve Kilker and Fred Schultz discovered that the physician was continuing to buy and use the total jaw replacement, the Interpositional Implant, and chin implants made with Proplast. U.S. marshals in Ohio seized those devices in October 1991, and they were turned over to the government in January 1992.

All of the Proplast implants seized previously from the manufacturer, as well as from the oral surgeon in Dallas and at Houston's Intercontinental Airport, were also condemned and have either been destroyed or placed in the government's possession.

The doors of NovaMed and OSMI, meanwhile, are closed, and Proplast products are no longer being made in the United States.

—Rebecca D. Williams

## Food Warehouse Closed After Repeated Violations

After investigations and legal actions spanning nearly two decades, FDA and the U.S. Attorney's Office for the District of Massachusetts shut down a food storage company with a long history of public health violations.

On Feb. 5, 1992, Alfred G. Maroun, owner of Maroun Brothers, Inc., of Lawrence, Mass., was fined \$5,000 and sentenced to three years' probation and 2,000 hours of community service, with the provision that further violations of the Food, Drug, and Cosmetic Act would be a direct violation of his probation. No fine was imposed against the corporation, because it was insolvent at the time of sentencing.



According to Robert Crowell, acting director of investigations for FDA's Boston district, "This was a remarkable case. Usually when a firm has a problem they will correct it. Here was a case with repeat violations."

FDA's problems with the firm went back to 1973 when investigators from the Boston district office noted extensive sanitation problems during a routine inspection of the Maroun Brothers warehouse. They found extensive insect and rodent contamination in pallets of macaroni, flour, candy, shortening, and pet food. They also uncovered structural problems in the building, including holes in floors and walls that allowed insects and rodents access to the food storage areas.

Uncorrected violations noted at the first inspection and follow-up visits a month later led to government prosecution of the firm and Maroun. The defendants pleaded guilty to three charges each and were fined \$1,800 in June 1974.

FDA investigators visited the firm again in October and November 1974. These inspections showed no improvements in the conditions, and Maroun was warned about the continuing problems. Another inspection in 1975 revealed greatly deteriorated conditions. Insect and rodent infestation and contamination were extensive, and the structural problems had not been corrected.

In early 1976, the corporation and Maroun were again indicted on several charges of violating the FDC Act. Again, they pleaded guilty. The court fined the corporation \$4,000. Maroun was fined \$2,000 and given a three-month suspended sentence.

Over the next 10 years, FDA and the State of Massachusetts monitored conditions at the warehouse. State and federal inspections in 1988 showed the violations were worse than in the past.

During a December 1988 inspection, FDA investigators Richard L. Licari,

Richard Wright, Paralumen Leonin, Wendy Hollet, and Diane Prince made their way through pallets of food products, some of which were misbranded and covered with mold. Pallets of flour, dry milk, baby cereal, soup mixes, pasta, salt, cookies, and candy showed evidence of insect and rodent infestation.

The problems were further aggravated by the extensive state of disrepair outside the building. Overgrown vegetation provided excellent breeding grounds for vermin, and holes in the building's walls and floors gave them access to food storage areas.

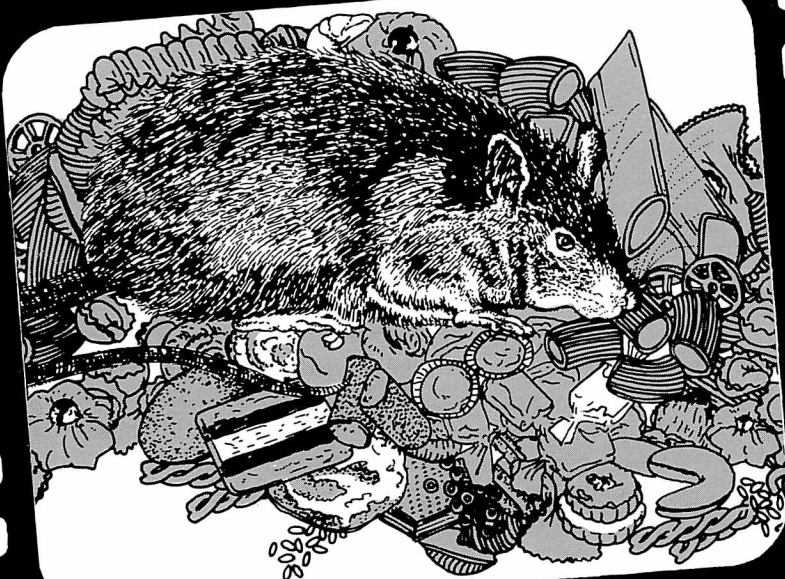
"I spent the better part of one morning just documenting the structural defects with 35mm photographs," Licari said. "The company was located in an old mill building, and it was cold, dark and badly illuminated inside. There was a great amount of rat feces in the food storage areas. Our discussion with management [about the conditions] lasted six hours."

The government filed an indictment against Maroun and the corporation on Feb. 12, 1990, that included eight felony counts of adulterating food products by holding them under insanitary conditions.

After almost two years of legal activities by FDA, the U.S. attorney's office and the U.S. District Court for the District of Massachusetts, Maroun pleaded guilty to three counts. The corporation, which was by then bankrupt, pleaded guilty to all eight counts.

On Feb. 5, 1992, Chief Justice Joseph L. Tauro sentenced Maroun and warned him against repeat violations, adding, "I consider crimes against the food supply to be of a serious nature. If I see him [Maroun] again, I will deal with him most severely."

—Joseph Raulinaitis  
FDA Boston district office







## SEIZURE ACTIONS

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

**PRODUCT:** **Chow Mein noodles**, at Malden, E. Dist. Mo.; Civil No. S90-0114-C.

**CHARGED** 9-4-90: When shipped after manufacture by Chinese Maid, Inc., Chicago, Ill., the article labeled "Parade . . . Chow Mein Noodles . . . Packed For National Brand Sales, A Division of Federated Foods, Inc., Arlington Heights, IL." had been prepared and packed under insanitary conditions, and the article contained insect and rodent filth—402(a)(3), 402(a)(4).

**DISPOSITION:** Consent—ordered destroyed. (F.D.C. No. 65916; S. No. 90-526-688; S.J. No. 1)

**PRODUCT:** **Crab meat, pasteurized**, at Reading, E. Dist. Pa.; Civil No. 91-5221.

**CHARGED** 8-14-91: While held for sale after being imported, the article contained a decomposed substance and was unfit for food because it was in swollen cans—402(a)(3).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66244; S. No. 91-569-835; S.J. No. 2)

### *Food/Economic and Labeling Violations*

**PRODUCT:** **Lobster tails, frozen**, at Seattle, W. Dist. Wash.; Civil No. C91-1195.

**CHARGED** 8-27-91: When shipped by Sysco Intermountain, Salt Lake City, Utah, the article labeled "Moon Lake Brand . . . Frozen Slipper Lobster . . . Tails . . . Sun Wah Marine Products . . . Co., Ltd. . . . Hong Kong" contained decomposed lobster tails—402(a)(3); excessive glaze (ice) had been added to increase the article's bulk and weight—402(b)(4); and the article lacked an accurate net quantity-of-contents statement (i.e., the article was labeled to contain a net weight of 5 pounds per package, but contained less than 4 pounds after removal of the excessive glaze)—403(e)(2).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66242; S. No. 91-534-071; S.J. No. 3)

### *Food Additives*

**PRODUCT:** **Linseed oil**, at Fountain Hills, Dist. Ariz.; Civil No. 88-0896PHX-CAM.

**CHARGED** 6-3-88: When shipped from Canadian Health Reform

Products, Burnaby, Canada, the article labeled "Bio-San . . . C-Leinosan . . . All Organic Virgin Linseed Oil. Imported from Canada . . . Imported by ND New Dimensions Fountain Hills, Ariz." was a nonconforming food additive, since there was no regulation prescribing the conditions under which the additive might be safely used for its intended use—402(a)(2)(C).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 65411; S. No. 88-446-470; S.J. No. 4)

### *Drugs/Human Use*

**PRODUCT:** **Chlordiazepoxide and amitriptyline HCl tablets**, at Wallington, Dist. N.J.; Civil No. 91-3747.

**CHARGED** 8-22-91: when shipped by Pharmaceutical Basics, Inc., Denver, Colo., the articles' labeling ("phi . . . Chlordiazepoxide and Amitriptyline Hydrochloride Tablets, USP 5 mg/12.5 mg [or "10 mg/25 mg"] . . . Mfd. by Pharmaceutical Basics, Inc.") was false and misleading because it failed to reveal that data contained in marketing applications for the articles were false or fraudulent—502(a).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66194; S. No. 91-588-673; S.J. No. 5)

**PRODUCT:** **Oxygen, U.S.P., in cylinders**, at Pella, S. Dist. Iowa; Civil No. 90-0294B.

**CHARGED** 5-30-90: While held by Midwest Medical Supplies, Inc., Pella, Iowa, the circumstances used for the article's manufacture, processing, packing, and holding failed to conform with current good manufacturing practice—501(a)(2)(B).

**DISPOSITION:** A consent decree authorized release of the article to the dealer for bringing into compliance, and also required the discontinuance of the dealer's drug operations until certain conditions were met if, within five years, a DHHS representative advised that any of its drugs were again adulterated under 501(a)(2)(B). (F.D.C. No. 65857; S. No. 90-551-940 et al.; S.J. No. 6)

**PRODUCTS:** **Retinoic acid cream**, and **clotrimazole and hydrocortisone combination cream**, at Arlington Heights, N. Dist. Ill.; Civil No. 91-C-4532.

**CHARGED** 7-19-91: When shipped by Syosset Laboratories Co., Inc., Syosset, N.Y., the articles were new drugs without effective approved New Drug Applications—505(a); and the articles' labeling lacked adequate directions for use—502(f)(1).

**DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66084; S. No. 91-612-058 et al.; S.J. No. 7)



**PRODUCT:** **Yohimbe-royal jelly-herb combination tablets**, and **Slim 'n Clenz capsules**, at Valparaiso, N. Dist. Ind.; Civil No. H-91-0258.

**CHARGED** 7-26-91: While held by Palko Distributing Co., Valparaiso, Ind., the articles labeled "Manhood Plus Potent Formula (with . . . Yohimbe . . . Royal Jelly) . . . Tablets . . . Distributed By: N.I.S.M., Inc., . . . Rochelle Park, NJ" and "Slim 'n Clenz . . . Capsules . . . Vital Edge Products, . . . Santa Barbara, CA." were new drugs without effective approved New Drug Applications—505(a); the articles' labeling (including the dealer's catalogs) contained false and misleading claims suggesting that the articles were safe and effective for the prevention or treatment of disease (e.g., to treat impotence, reduce cellulite, and eliminate parasites)—502(a); and the articles' labeling lacked adequate directions for use and the articles were not exempt due to their new drug status—502(f)(1). **DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 66234; S. Nos. 91-956-010/011; S.J. No. 8)

## Medical Devices

**PRODUCT:** **Cardiac pacemakers, explanted, and metal prosthetic implants, used**, at Bothell, W. Dist. Wash.; Civil No. C87-1035D.

**CHARGED** 7-31-87: The articles, which were held by Implant Technologies, Inc., Bothell, Wash., for reprocessing, export and re-implantation, lacked labeling bearing adequate directions for use for their intended purposes and lacked labeling bearing adequate warnings against unsafe uses—502(f)(1), 502(f)(2). In addition, the pacemakers were Class III devices and, as explanted devices, did not have in effect pre-market approval applications—501(f)(1)(B).

**DISPOSITION:** The articles were claimed by the dealer, who denied the charges and asserted that the articles had not been shipped in interstate commerce and were exempt because they were intended for export only and were not sold or offered for sale in domestic commerce.

Subsequently, a consent decree of permanent injunction and a consent decree of condemnation were filed. Pursuant to agreement of the parties, 269 specified cardiac pacemakers were released to the dealer and were made subject to the separate decree of injunction. The metal prosthetic implants were ordered destroyed, and the remaining 1,187 pacemakers were authorized to be released to the claimant for reconditioning for use in animals, or alternatively subjecting them to destructive research and testing or using them for destructive demonstration or display purposes. The specified 269 pacemakers were held by the claimant under the decree of injunction that enjoined the claimant from any interstate shipment, including export, unless and until it obtained FDA approval of a pre-market approval application for such pacemakers or unless and until it obtained FDA approval to export such pacemakers. Following the claimant's bankruptcy filing, the pacemakers were delivered to FDA for exhibition and/or destruction. (F.D.C. No. 65222; S. No. 87-335-688 et al.; S.J. No. 9)

## CONTEMPT ACTIONS

**DEFENDANTS:** **Albany Pecan Sales Co., Inc.**, and **Henry LeRoy Wilkerson Jr.**, Sylvester, M. Dist. Ga.; Civil No. 87-165-ALB-AMER.

**PETITIONED** 7-29-91 for civil contempt: That defendants should show cause why they should not be found in willful contempt of the court's decree of permanent injunction entered in November 1987.

**DISPOSITION:** The court issued the requested show-cause order. The defendants appeared and consented to a consent decree for enforcement of the permanent injunction. The consent decree ordered that all shelled nuts under the defendants' control should be inventoried, coded, tested, and reconditioned (if necessary) prior to their movement or sale, and that the defendants would come into full compliance with specified decree provisions before shelling pecans in the upcoming pecan season. Other provisions prescribed the following: maintenance of specified methods, facilities and controls, the deposit of \$1,000 in escrow to be forfeited at the rate of \$100 per day as a civil penalty for failure to remain in compliance, and the recovery by the government of \$1,000 in costs from the defendants.

**PETITIONED** 11-27-91 for civil contempt: That the defendants had failed to comply fully with the terms of the consent decree for enforcement of the permanent injunction; and, accordingly, the government prayed for the court to issue an order that the defendants show cause why they should not be held in civil contempt.

**DISPOSITION:** The court issued a show-cause order; and, after a hearing, the court found the defendants in contempt of the consent decree, but allowed 30 days during which the defendants could come into full compliance and be purged of their contempt. The court also awarded the government \$1,000 in direct costs, plus an additional \$1,000 representing forfeiture of the escrow sum.

After expiration of the 30-day period, the defendants presented testimony that they had done nothing more since December to bring their operations into compliance, although they thought they had done enough to satisfy FDA. The government moved for an order awarding additional costs and directing that the defendants' operations be shut down.

At a subsequent hearing, the court discussed the findings of an approved expert retained by the defendants to inspect their operations and help bring them into compliance. The court found that the defendants had failed to purge themselves of contempt within the time permitted and had willfully ignored the requirements of previous orders of injunction. The court directed the defendants to come into compliance immediately and to take measures to ensure continued compliance. Also, the court ordered that the defendants were not to ship any pecans or pecan products until FDA inspected their plant and confirmed full compliance with applicable laws and decrees, and that the defendants should hold the first 10 lots of finished pecans until representative sampling results had been received from an approved laboratory. The court also directed payment of the previously assessed cost of \$2,000 as well as an additional \$2,000. (Inj. No. 1175-A; S. No. 90-585-484 et al.; S.J. No. 10)



## INJUNCTION ACTIONS

**DEFENDANTS:** **Marshall Warehouses, Inc.,** and **Charles P. Marshall,** president, Jerome, Dist. Idaho; Civil No. 91-0329-S-HLR.

**CHARGED** 7-18-91 in a complaint for injunction: That, at Jerome, Idaho, the defendants held and shipped in interstate commerce various foods, including pink, pinto, Great Northern, and red beans and soft white wheat; and that such foods contained filthy substances and had been held under insanitary conditions—402(a)(3), 402(a)(4). The complaint for injunction also asserted that FDA inspections had revealed extensive rodent and bird activity throughout the defendants' warehouse, rodent, insect or bird activity in, on and around stored food products, and that FDA analyses revealed rodent filth in samples of such food collected at a recent inspection. The defendants were well aware that their activities were in violation of the law; and the government believed that, unless restrained by the court, the defendants would continue to violate the law.

**DISPOSITION:** A consent decree of permanent injunction enjoined the defendants from the complained-of violations. The decree also enjoined the interstate shipment of any food received or held at the defendants' warehouse facility unless and until a number of specified conditions were met, including the following: the cleaning and renovation of such facility; the establishment of a written pest control program; the certification by an expert that the defendants had implemented adequate methods, facilities and controls; and the examination of all foods on hand and the destruction or otherwise bringing into compliance of all contaminated food. (Inj. No. 1250; S. No. 91-590-515 et al.; S.J. No. 11)

## MISCELLANEOUS ACTIONS

**SUBJECT:** **Divalproex sodium tablets (a drug having as its active moiety valproic acid), and denial by FDA of 10 years of marketing exclusivity for Depakote (divalproex sodium) tablets,** Washington, Dist. Columbia; Civil Nos. 88-0174 and (upon appeal) 88-0474-OG.

**PETITIONED** 2-23-88 by Abbott Laboratories, North Chicago, Ill., against FDA Commissioner Dr. Frank E. Young, in a suit for declaratory and injunctive relief: That FDA had under active consideration the approval of Abbreviated New Drug Applications (ANDAs) of Abbott's competitors for generic copies of Abbott's Depakote; that Abbott was entitled to 10 years of market exclusivity for Depakote under the Drug Price Competition and Patent Term Restoration Act of 1984 (the DPC/PTR Act); that Abbott had filed with FDA a Citizen Petition opposing approval of such ANDAs and a related Petition for a Stay, which petitions had been denied; that the DPC/PTR Act granted 10 years' exclusivity if the product's "active ingredient (including any salt or ester of the active ingredient)" was not previously approved in a New Drug Application (NDA). However, if such active ingredient had been previously approved, the period of market exclusivity was *two* years—a period that had

expired for Depakote. Abbott asserted that the active ingredient of Depakote in its final dosage form was divalproex sodium, and that neither divalproex sodium nor a salt or ester of divalproex had been approved in an NDA prior to Depakote's approval; and thus Depakote was entitled to 10 year's market exclusivity.

Abbott asserted that FDA had conceded that the original grounds for the denial of 10 years exclusivity were wrong and that FDA had offered three alternative interpretations, as follows: a) After ingestion divalproex sodium undergoes a chemical reaction that leaves it identical to a previously approved drug product [i.e., Abbott's Depakene (valproic acid)]; b) the 10-year exclusivity did not apply to drugs whose active ingredients were salts or esters of a previously approved drug [valproic acid]; and c) FDA claimed to have discretion to deny the 10-year exclusivity to any compounds not representing either substantial investments in research and development or significant therapeutic innovations. Abbott also charged that FDA had improperly determined that divalproex sodium was itself a salt of a previously approved drug [Abbott's valproic acid], that Abbott would be adversely affected by the approval of the pending ANDAs, and that any such approvals would violate Abbott's statutory right to market Depakote exclusively.

**DISPOSITION:** *District Court*—The government moved for summary judgment, and Abbott filed a cross-motion for summary judgment. The court granted the government's motion, and denied Abbott's cross-motion. The court noted that FDA's decision was based on the finding that divalproex sodium was simply a salt of valproic acid, but could not accept FDA's conflicting interpretations of the term "active ingredient" (i.e., that, as used in the ANDA subsection, the term "active ingredient" was to be construed narrowly to exclude drugs not truly the same as previously approved drugs, but, with respect to the exclusive marketing subsection, the term was to be defined broadly to restrict the exclusive marketing privilege to drugs that were genuinely new chemical entities). The court concluded as follows: There was a conflict between subsections (i) and (v) of 21 U.S.C. 355(j)(4)(D), which was resolved by reference to the purpose of the DPC/PTR Act; and that, because "Depakote was approved entirely upon the clinical investigations conducted for Depakene, Congress' purpose is served only by restricting Depakote to two years of exclusive marketing." Accordingly, the government's motion for summary judgment was granted. Abbott Laboratories appealed.

*Court of Appeals*—The court thought that both Abbott's and the government's interpretations of the DPC/PTR Act were unreasonable. The court noted that it was suggested in an FDA letter, subsequent to FDA's decision in Abbott's case, that the phrase "active ingredient" itself, even without the parenthetical phrase of "including any esters or salt of the active ingredient", could be interpreted to include active moiety, notwithstanding that FDA construed the term narrowly in another section of the act. However, because FDA had not employed this theory in its decision on Abbott's application, the Court of Appeals could not consider whether "active ingredient" was a term that was permitted to be



interpreted differently in two separate sections of the statute, as was permitted under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 838 (1984). The Court of Appeals concluded that the language of the statute was ambiguous as it related to the issue; it rejected FDA's interpretation of the statute as not being possible linguistically; and it found that Abbott's interpretation was possible linguistically but failed to serve any conceivable statutory purpose. The court held that the statute was ambiguous, that the government's reliance on an unreasonable construction of the including clause ("including any salt or ester of the active ingredient") was misplaced, and that Abbott's interpretation of the statute was unreasonable. Accordingly, the court remanded the case to the district court with instructions, in turn, to remand it to FDA. (Misc. No. 860; S.J. No. 12)

**SUBJECT: Generic equivalents of Maxzide and FDA 180-day statutory delay of effective date of approval of a generic equivalent**, E. Dist. N.Y.; Civil No. CV 87-3826.

CHARGED 11-10-87 by American Therapeutics, Inc., Bohemia, N.Y., against the Department of HHS, the Food and Drug Administration, and FDA Director of Office of Drug Standards Peter H. Reinstein, M.D., in a suit for judicial review and voiding of 21 U.S.C. 355(j)(4)(B)(iv): That American Therapeutics, Inc. (ATI), had filed an Abbreviated New Drug Application (ANDA) for a generic equivalent of the listed drug Maxzide (triamterene and hydrochlorothiazide) in tablet form, which was the subject of a New Drug Application (NDA) of Mylan Pharmaceuticals, Inc. (Mylan), and which was the subject of Mylan's U.S. Patent No. 4,444,769 (Mylan Patent); that, when FDA notified ATI that its ANDA was acceptable, ATI certified to FDA that the Mylan patent was invalid or was not infringed and provided Mylan with suitable information to confirm that ATI's drug and method of manufacture did not infringe the Mylan patent. Mylan responded that it would not bring an infringement action during the 45-day period contemplated by the Drug Price Competition and Patent Term Restoration Act of 1984 (DPC/PTR Act). ATI asserted that Mylan's decision not to sue ATI confirmed ATI's certification that the Mylan patent was invalid or not infringed and that, in the event marketing exclusivity was being awarded for a generic drug, ATI's drug approval should be effective immediately and ATI should be entitled to a 180-day period of marketing exclusivity as against other submitted ANDA's for generic equivalents of Maxzide. ATI asserted that a patent that had issued prior to the Mylan patent and had subsequently expired had disclosed and claimed the specific combination of active ingredients found in Mylan's Maxzide; and that the claims of the Mylan patent did not and could not cover the active ingredients of Maxzide so as to exclude ATI from making, using and selling ATI's generic equivalent of Maxzide. However, although FDA had issued an approval letter for ATI's generic drug indicating that ATI had satisfied all of the safety requirements of FDA's statute and regulations, FDA had delayed the effective date of approval of the ANDA for 180 days from the date on which a final judgment was entered in a patent suit by Mylan against Vitarine Pharmaceuticals,

Inc. (Vitarine). ATI asserted that, although FDA had determined that Vitarine had submitted the first ANDA containing the required paragraph IV certification, Vitarine's ANDA, at the time of filing, lacked the required bioavailability or bioequivalence studies and, therefore, should be identified by FDA and by legislative history, as a "sham ANDA".

In addition ATI asserted: that FDA had arbitrarily, capriciously and wrongly determined that ATI's ANDA for its drug was the same as Vitarine's ANDA and had improperly applied clause IV because FDA had interpreted "a drug" in clause IV as being the active ingredients of the listed drug; that the Mylan patent was a process and product by process patent (not claiming the drug or method of using the drug) and FDA had arbitrarily and capriciously refused to consider whether the Mylan patent was of the type excluded from being listed; and that 21 U.S.C. 355(j)(4)(B)(iv) was unconstitutionally vague and indefinite because it empowered FDA to enforce the statute in an arbitrary fashion, since, as evidenced by FDA's ANDA Approval Letter, FDA was not capable of interpreting the statute in accordance with the literal language of the statute or the express congressional purpose, and because literal interpretation of the statute produced absurd and unintended results and FDA's interpretation of the statute also produced absurd and unintended results. **DISPOSITION:** The court issued an order to show cause and a temporary restraining order restraining FDA from issuing an effective date of approval for a generic Maxzide to any manufacturer or other third party that was earlier than the effective date of approval issued to ATI. A hearing was held on ATI's motion for a preliminary injunction, and the court denied such motion.

Meanwhile, Vitarine moved for leave to intervene and was recognized by the court as a party to the suit opposing ATI. In opposing ATI's motion, FDA had asserted the following: that, at the time ATI submitted its ANDA, three other companies had already submitted their own ANDAs and two of these companies had submitted ANDAs for the drug a full year earlier and had been, during that time, engaged in patent litigation with the holder of the Maxzide patent; that 21 U.S.C. 355(j)(4)(B)(iv) rewards the first ANDA applicant who submits an application containing a paragraph IV certification and who is subsequently sued for patent infringement; and that the same law requires FDA to delay the effective date of any subsequent ANDA for 180 days. FDA asserted that Vitarine qualified for the statutory period of exclusive marketing, that ATI had not established such irreparable harm as to tip the balance of hardship in its favor, that Congress intended that patent questions would be settled in a private action between the person challenging a patent and the patent holder, and that ATI could have sought a declaratory order that the Mylan patent was a process patent as provided by 21 U.S.C. 355(j)(4)(B)(iii), but that ATI had not done so.

Because ATI had shown neither a probability of success on the merits nor sufficiently serious questions to make a fair ground for litigation, the court denied ATI's motion for a preliminary injunction, and ATI voluntarily dismissed the action. (Misc. No. 854; S.J. No. 13)



# Take the Guesswork Out of *Good Nutrition*

The new food labeling regulations call for food retailers to voluntarily provide shoppers with nutrition information about fresh produce, meat and seafood. This chart is one of a series developed by the Food Marketing Institute and other trade associations to help meet this goal.

## MEAT NUTRITION INFORMATION CHART ■ BEEF & VEAL

### ■ BEEF

	Total Calories	Protein	Carbohydrate	Total Fat	Saturated Fatty Acids	Cholesterol	Sodium	Vitamin A	Vitamin C	Calcium	Iron
3oz, edible, cooked, closely trimmed of fat	kcal	g	g	g	g	mg	mg	% U.S. RDA			
<b>Brisket, Point Half</b> , braised	222	24	0	13	5	77	65	*	*	*	13
<b>Chuck, Arm Pot Roast</b> , braised	183	28	0	7	3	86	56	*	*	*	18
<b>Chuck, Blade Roast</b> , braised	213	26	0	11	4	90	60	*	*	*	17
<b>Ground Beef, Regular</b> (73%) broiled, med.	246	20	0	18	7	76	70	*	*	*	12
<b>Ground Beef, Lean</b> (83%) broiled, med.	217	22	0	14	5	71	59	*	*	*	11
<b>Loin, Sirloin Steak</b> , broiled	165	26	0	6	2	76	56	*	*	*	16
<b>Loin, Tenderloin Steak</b> , broiled	179	24	0	9	3	71	54	*	*	*	17
<b>Loin, Top</b> , broiled	176	24	0	8	3	65	58	*	*	*	12
<b>Rib, Large End Roast</b> , roasted	201	23	0	11	4	69	62	*	*	*	13
<b>Rib, Small End Steak</b> , broiled	188	24	0	10	4	68	59	*	*	*	12
<b>Round, Eye</b> , roasted	143	25	0	4	2	59	53	*	*	*	9
<b>Round, Bottom</b> , braised	178	27	0	7	2	82	43	*	*	*	16
<b>Round, Tip Roast</b> , roasted	157	24	0	6	2	69	55	*	*	*	14
<b>Round, Top Steak</b> , broiled	153	27	0	4	1	71	52	*	*	*	14

### ■ VEAL

3oz, edible, cooked, closely trimmed of fat	kcal	g	g	g	g	mg	mg	% U.S. RDA			
<b>Cutlets</b> , unbreaded, pan fried	156	28	0	4	1	91	65	*	*	*	4
<b>Loin Chop</b> , roasted	149	22	0	6	2	90	82	*	*	2	4
<b>Rib Roast</b> , roasted	151	22	0	6	2	97	82	*	*	*	5
<b>Shoulder, Arm Steak</b> , braised	171	30	0	5	1	132	76	*	*	3	7
<b>Shoulder, Blade Steak</b> , braised	168	28	0	6	2	135	86	*	*	3	7

\* Contains less than 2% of U.S. RDA

**Serving Size:** 3 oz.—well trimmed of fat—cooked portion roasted, baked, broiled/grilled, stir fried, braised or cooked in liquid without additional fat, salt, sodium or sauces.

(Data Source: USDA)