

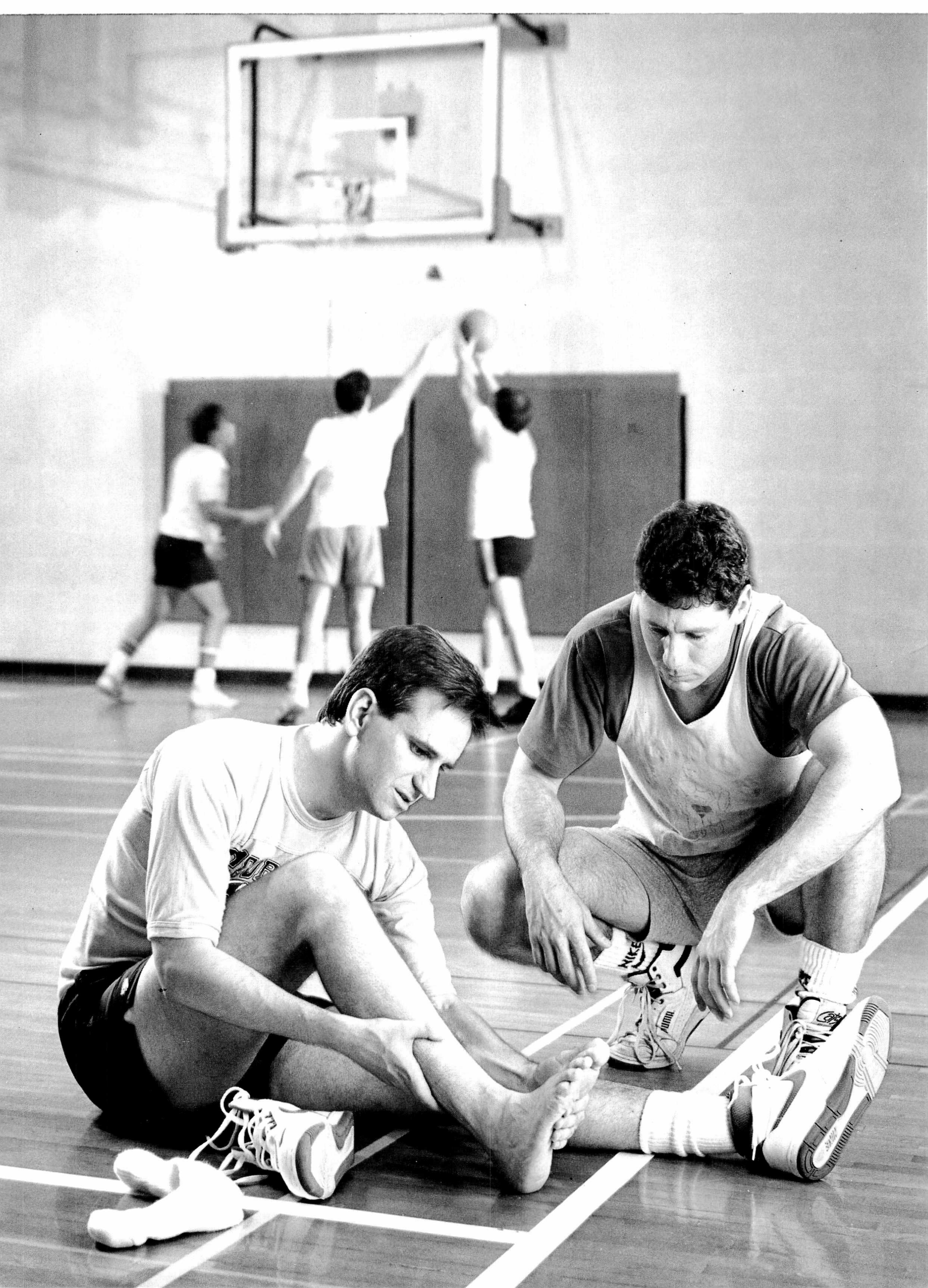
FDA CONSUMER

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MAY 1989 •

It's Spring Again and Allergies Are in Bloom





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

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The war on AIDS is being fought on new fronts with new research funds earmarked for clinics, doctors' offices, and health maintenance organizations in patients' own communities. This new approach, says FDA Commissioner Frank Young, is clearly an avenue of research whose time has come.

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Occasional bed-wetting in young children usually is no cause for worry. But persistent bed-wetting after age 5 could, in rare cases, signal an underlying health problem deserving medical attention. Help is available in many forms.

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SPECT is not a secret foreign spy outfit; it's one of the new ways doctors can "see" inside the body without X-rays. FDA Consumer takes a look at SPECT and other non-X-ray techniques as it concludes its series on medical imaging.

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Pollen is only one of many culprits that get the nose sneezin' and the lungs wheezin'. Antihistamines and decongestants can help relieve symptoms, and better allergy shots may be on the way, too.

Anaphylaxis: An Allergic Reaction That Can Kill 21

For some people at risk of allergic reactions to bee stings, penicillin, and certain other substances, "Be Prepared" is more than just a motto—it's a potential life-saver.

Exercise with Care—Fitness Is Not Risk-Free 24

Getting back in shape is an admirable goal. But when your morning jog ends with a twisted ankle, you need to know how to make it better, not worse. Some simple steps pave the way to proper healing.

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The first rule in treating sports injuries is to just stop the activity. When you twist your ankle coming down from that jump shot, get off the court and check it out. For guidance on how to properly treat—and prevent—common sports mishaps, see page 24.



Pesticide Residues Safe for Children, Too

Pesticide residues in food, including baby food, are safe, despite recent allegations by a consumer group that the legal limits for residues are too high to protect children.

Last winter, the Natural Resources Defense Council, Inc., a consumer advocacy group based in Washington, D.C., stated that the legal limits, or tolerances, set by the U.S. Environmental Protection Agency for pesticide residues in food are too high to protect infants and children. But food sampling by FDA shows that any pesticide residues detected, particularly in baby food, are generally far below the tolerances. Other factors, too, help ensure that pesticide residues in food do not pose a health risk to youngsters:

- A tolerance may be considerably below the actual maximum safe level since EPA sets the tolerance no higher than needed for the pesticide's intended use. Also, a tolerance represents the maximum *legal* residue level in a food, not the *expected* level; actual detected residues, in fact, are almost always much lower.
- In its annual Total Diet Study, FDA buys 234 food items at supermarkets in each of four geographical areas, prepares them (washing and cooking as appropriate), and analyzes them for residues of pesticides and contaminants. Daily intakes of detected residues are calculated for various ages, including children 6 to 11 months, 2 years, and 14 to 16 years. Not only are detected pesticide residues below EPA limits, dietary intakes of residues are less than 1 percent of intakes deemed acceptable by the United Nation's Food and Agriculture Organization and World Health Organization. In some 800 samples of commercial baby foods analyzed since 1982 in the Total Diet Studies, most showed no pesticide residues. Of the 43 percent in which FDA found detectable residues, the highest average level was for permethrin, in an amount about one-thirtieth the EPA tolerance.
- In over 25 years of additional special testing of infant and toddler foods—including thousands of samples of formula, cereal, fruit, juices, vegetables and desserts—FDA has found that only about a quarter of the samples had detectable residues, all within EPA tolerances.

• There also has been concern about the use of daminozide (trade name Alar) on apples to increase firmness, enhance color, and extend storage life. Alar once was used on 40 percent of apples, but now its use is down to about 5 percent. On the basis of results of ongoing animal cancer studies, EPA may halt this use entirely. Two years ago, major baby food firms began prohibiting their suppliers from using Alar. Current analyses of food made from apples, including applesauce and apple juice for children, show no residues or residues well within EPA tolerances.

FDA continually modifies its sampling programs to expand coverage, reflect new pesticide use patterns, or answer newly raised questions. Others who monitor foods for pesticide residues are the U.S. Department of Agriculture—which enforces EPA tolerances for meat and poultry—the states, food firms, and private groups.

For more information about pesticides, see "Setting Safe Limits on Pesticide Residues" in the October 1988 *FDA Consumer*.

Aflatoxin in Corn

Even though last year's drought caused an increase in contamination of the nation's corn crop with aflatoxin, a natural carcinogen, there is plenty of "clean" corn for human consumption, and early tests of corn flakes, corn chips, and other food products don't show contamination.

Aflatoxin is produced by a type of mold that grows well under the conditions of last year's drought. The presence of aflatoxin in corn, especially corn from the Midwest, has caused concern about milk, cheese and other products from dairy cows (which feed on corn), as well as foods made of corn and cornmeal (corn chips, bakery items, breakfast cereals, grits, and tacos).

Last October, FDA notified state health officials to continue monitoring milk for levels exceeding 0.5 parts per billion (ppb) of aflatoxin. The states and the state-supported National Conference on Interstate Milk Shipments have been vigilant in detecting and enforcing this limit. Recently, some milk in Texas, Minnesota, Iowa, and southern Illinois tested higher than 0.5 ppb for aflatoxin. The milk was dumped, so it did not reach con-

sumers. That dumping also served as a reminder to farmers to seek assurances that the corn they buy for dairy cattle is within safe levels.

Not only farmers but food processors, too, risk having to destroy their products if they are found to be contaminated. The agricultural problem has encouraged food processors to test the corn they use for cornflakes, muffins and popcorn.

FDA has found that about 6 percent of field corn in areas with known or potential problems contained more than 20 ppb of aflatoxin, the limit for grain intended for direct human consumption. But in a recent test of finished, ready-to-eat products like cereals and chips, FDA found no aflatoxin. About 2 percent of corn flour and cornmeal, however, were found to be above 20 ppb in FDA's tests. Although FDA's policy is to remove such products from the market, the agency says that the amount of aflatoxin would also be greatly reduced by cooking the grits, corn flour, or cornmeal.

Corn-on-the-cob does not seem to be affected by the contamination problem. FDA recently tested sweet corn—including canned and frozen—and found no aflatoxin. This probably is because sweet corn, including that sold at roadside stands, is harvested before the sugar in the kernels is converted to starch, on which the aflatoxin mold thrives.

FDA permits corn with higher aflatoxin levels to be used for nondairy animals, such as beef cattle and poultry. Studies have shown that such FDA-approved levels did not harm the animals and did not result in significant amounts of aflatoxin in meat or eggs.

Sleep-Aid Standards Set

If worrying keeps you awake at night, at least one thing about which you can now rest assured is that your non-prescription sleep-aids are safe and effective. FDA is stopping the sale of those that are not.

Scientific review of over-the-counter (OTC) sleep-aids has shown that the antihistamines diphenhydramine hydrochloride and diphenhydramine citrate—ingredients in Compoz, Nervine, Nytol, Sleep-eze-3, Sleepinal, Sominex, and Sominex-2—are safe and effective sleep

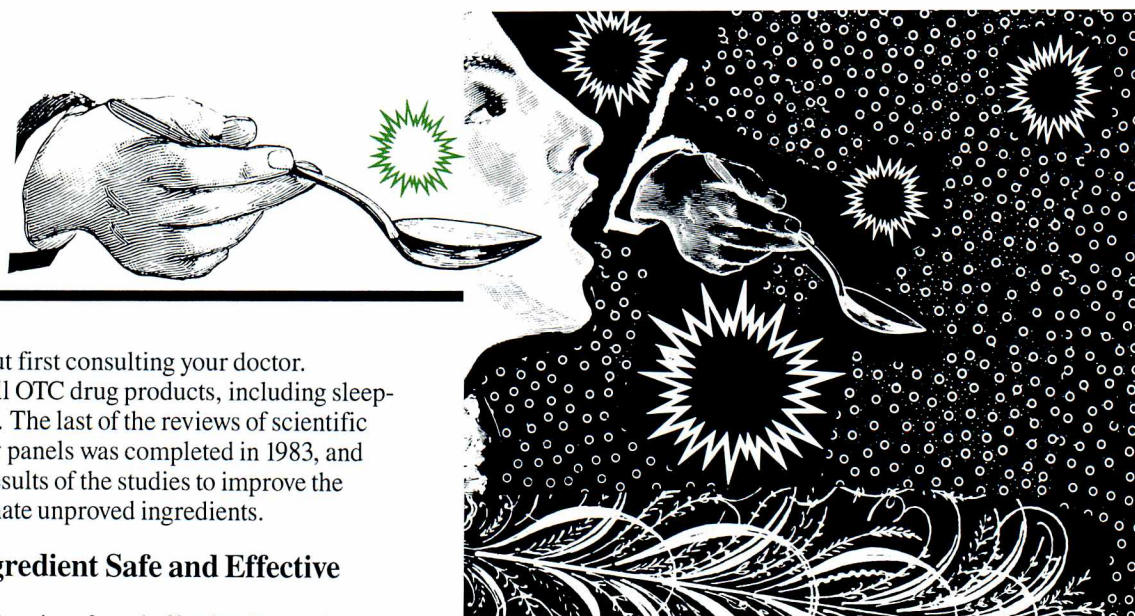


inducers. FDA also has approved doxylamine succinate, another antihistamine, used in Unisom, Doxysom and Ultra Sleep.

But the agency found that some other ingredients that have been in limited use in nonprescription sleep-aids are not effective. Products containing pyrilamine maleate, potassium bromide, sodium bromide, and scopolamine hydrobromide will have to be reformulated or their sales halted.

In publishing its standard in the Feb. 14 *Federal Register*, FDA also stated that approved nonprescription sleep-inducing medications must include the following warnings on labels:

- Do not give to children under 12.
- If sleeplessness persists continuously for more than two weeks, consult your doctor. Insomnia may be a symptom of serious underlying medical illness.
- Do not take this product if you have asthma, glaucoma, emphysema, chronic pulmonary disease, shortness of breath, difficulty in breathing, or difficulty in urination due to enlargement of the prostate gland, unless directed by a doctor.
- Avoid alcoholic beverages while taking this product.
- If you are taking sedatives or tranquilizers, do not take



this product without first consulting your doctor.

FDA review of all OTC drug products, including sleep-aids, began in 1972. The last of the reviews of scientific studies by advisory panels was completed in 1983, and FDA is using the results of the studies to improve the labeling and eliminate unproved ingredients.

One Cough Ingredient Safe and Effective

Only one ingredient is safe and effective for use in non-prescription cough and cold medicines to help loosen phlegm, according to a recent standard published by the Food and Drug Administration. All other expectorant ingredients—about 20 in all—must be taken off the market.

The one useful ingredient—guaifenesin (pronounced gwy-uh-FIN-uh-sin)—is a chemical compound that increases sputum or phlegm volume, makes it less sticky, and makes it easier to cough up. Guaifenesin is the expectorant ingredient most widely used by makers of non-prescription cough and cold medications, including Benylin Expectorant, Robitussin, Sudafed Cough Syrup, Triaminic Expectorant, and Vicks Formula 44-Multi Symptom Cough Mixture. It also is approved as a prescription drug for use by patients with stable chronic bronchitis, to help loosen phlegm and to thin bronchial secretions.

In announcing its regulations on over-the-counter (OTC) expectorants in the Feb. 28 *Federal Register*, FDA said it is also requiring that the following warnings be included on labels of these products:

- Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, chronic bronchitis, or emphysema, or when cough is accompanied by excessive phlegm, unless directed by a doctor.
- A persistent cough may be a sign of a serious condition. If cough persists for more than one week, tends to recur, or is accompanied by fever, rash or persistent headache, consult a doctor.

Claims such as the following will be permitted on labels:

- Helps loosen phlegm (sputum) and thin bronchial secretions to rid the bronchial passageways of bothersome

mucus, drain bronchial tubes, and make coughs more productive.

Expectorants are among the drug products that have been under FDA review since 1972. For information about other OTC cough and cold medicines, see "Modern Pharmacy's Answer to Chicken Soup" in the November 1988 *FDA Consumer*.

No Known Risks from Electric Blankets

FDA has found no conclusive evidence that electric blankets are a health hazard, despite claims to the contrary by a recent network television program. The program, "Killer Electric Blankets," which aired last February on the Fox television network, alleged that the use of electric blankets may be linked with a number of ill effects, including cancer.

Electric blankets—like many other home appliances, including toasters, vacuum cleaners, and computers—produce low-intensity electric and magnetic fields. For the past decade, FDA and other scientists have been investigating whether magnetic fields affect human health. A study conducted in Colorado in 1979 suggested a relationship between exposure to electromagnetic fields and childhood cancer, but a similar study conducted in Rhode Island did not show such a relationship. And a 1988 study in Los Angeles County found no association between the use of electric blankets and adult leukemia. Animal studies have also proved inconclusive.

Based on current information, FDA sees no reason for people to stop using electric blankets. FDA will continue its research in this area and will monitor the research of other organizations.

Progress Reports in the Battle Against Acquired Immune Deficiency Syndrome

Market Grows for Immune Disease Diagnostic Tests

While sales of diagnostic tests for AIDS are expected to climb to almost \$200 million by 1992, the market for diagnostic tests for other immune system disorders is expected to grow even more rapidly, more than doubling its 1987 level, according to a New York-based market research firm.

The entire market for immune disease diagnostic tests is expected to reach \$293.7 million by 1992, up from \$167.2 million in 1987, according to a recently published report, "U.S. Markets for Immune Disease Diagnostic Products," by Frost & Sullivan, Inc.

Standing alone as by far the largest segment of the market are products used to test for the AIDS viruses, HIV and HIV-2, and a close relative, HTLV-1. Frost & Sullivan predicts that the sales of AIDS diagnostics will go from the 1987 figure of \$118 million to \$199 million in 1992, the rise credited to blood bank testing for HIV-2 and HTLV-1. Other increases forecast for the 1987-1992 period include: autoimmune disorders diagnostics—from \$11.2 million to \$25.4 million; allergy diagnostics—\$10.1 million to \$17.1 million; immunoglobulin assays—\$10.7 million to \$17.2 million; and lymphokine assays—\$200,000 to \$1.8 million. (Lymphokines are substances released by lymph cells to play several roles in immunity.)

Broader Use of Methadone Proposed to Fight AIDS

The federal government has proposed allowing broader use of the heroin substitute methadone in an effort to help combat AIDS among intravenous drug abusers.

Heroin users often share needles and in doing so risk transmitting the AIDS virus, not only to other drug abusers but to their sex partners and unborn children. (An AIDS-infected mother can transmit the virus to her child in the womb or during delivery.) Methadone, which helps relieve an addict's craving for heroin without the "high," is taken by mouth, eliminating the risk of AIDS from virus-contaminated needles.

Until now, federal regulations have only allowed methadone to be given to addicts enrolled in a comprehensive treatment program. But some treatment clinics have six-month waiting lists. So FDA and the National Institute on Drug Abuse have proposed a regulation to permit clinics to provide methadone to heroin users in "interim" programs while they wait to get into comprehensive treatment. Counseling on how to avoid getting or transmitting AIDS would be part of the interim programs.

Under the proposal, published in the March 2 *Federal Register*, methadone could be given at clinics and other locations to those in an interim program, but would not be provided for "take-home" use. A pilot interim program in operation at Beth Israel Medical Center in New York City since February 1987 appears to have reduced the use of needles among participants: While 87 percent of addicts in a control group that did not get methadone continued to use needles, only 33 percent of those in the methadone group continued to do so.

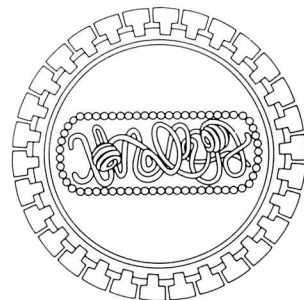
Study Finds Poor Absorption Of Oral Dextran Sulfate

Preliminary results of a study on a proposed treatment for AIDS suggest that not enough of the drug is absorbed by the body to be effective.

The study—conducted by FDA, the National Institute of Allergy and Infectious Diseases, and the Johns Hopkins University Medical Center—found that when rats and human volunteers took the drug dextran sulfate by mouth, very little was absorbed. Such low levels of absorption would indicate that not enough of the drug reached the bloodstream to have an effect on the AIDS virus. Since these data are still preliminary, FDA will compare the results with those of other current studies.

Dextran sulfate has been marketed in Japan for many years as a treatment for reducing blood cholesterol. Many people infected with the AIDS virus have arranged to import small amounts of dextran sulfate into this country for personal use—a practice permitted by FDA in the case of products that are not commercialized and not hazardous.

Although these results are not promising, there is interest in seeing whether dextran sulfate given intravenously or subcutaneously will help control AIDS. However, AIDS patients should not inject the drug themselves. Unlike taking the drug by mouth, which does not cause any dangerous side effects, injecting the drug can completely block the blood's ability to clot and could lead to serious, even fatal, bleeding.

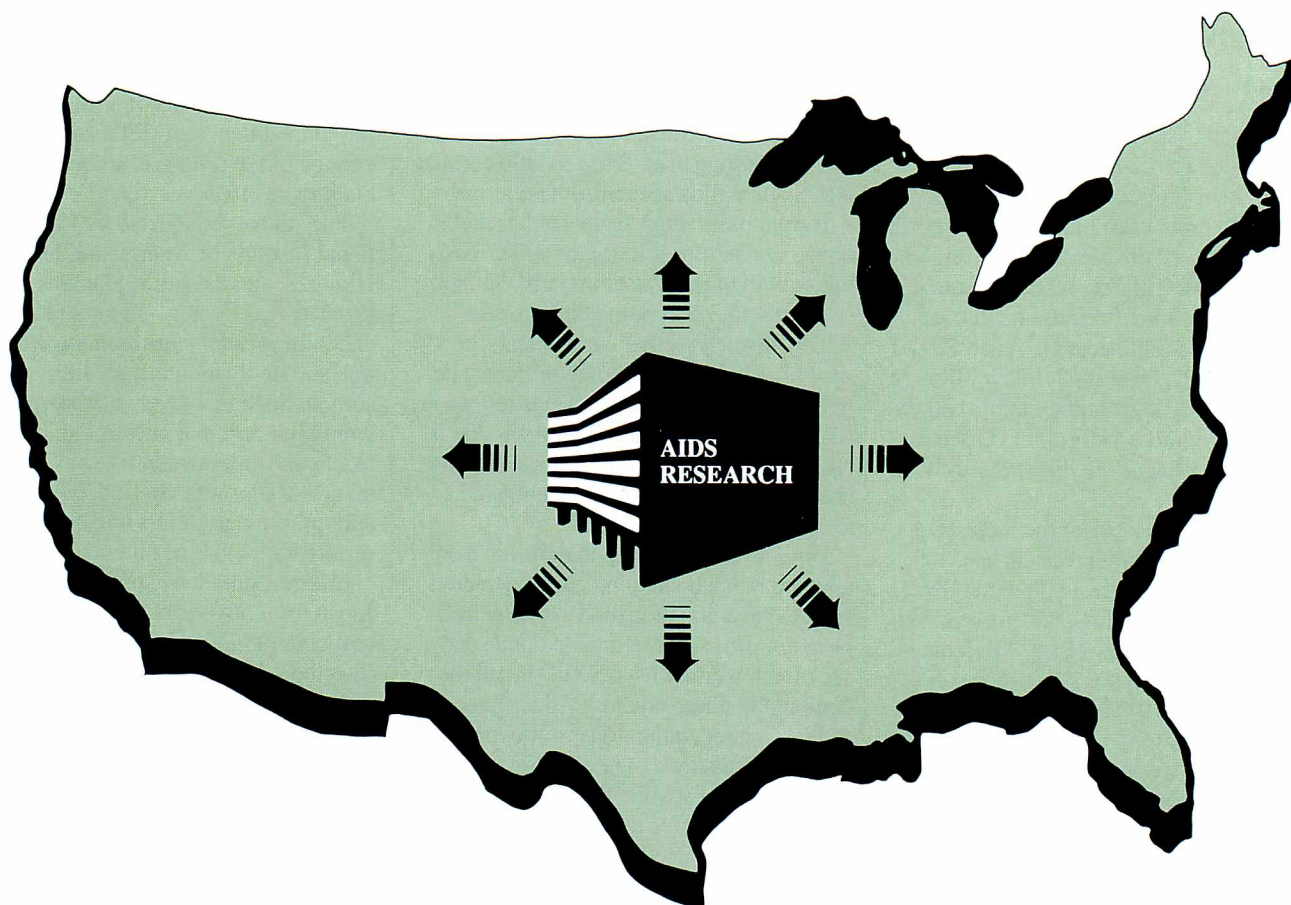




Health Talk With Dr. Frank Young

AIDS Research Comes to Patients' Home Towns

by Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs



The nation's war against acquired immune deficiency syndrome received a significant boost late last year, when Congress passed legislation authorizing federal funding of more AIDS studies in local communities around the country. The potential benefits of community-based AIDS research are twofold: First, such research can bring promising but still experimental drugs to more patients than can be served by existing studies, conducted mainly at universities and large hospitals. Second, with the larger patient population and resulting data base afforded by properly conducted community-based research, AIDS therapies that prove to be safe and effective can be identified and brought to the market more quickly. By the same token, unsuccessful therapies can be eliminated earlier. In addition, by systematically monitoring their patients, community physicians may help generate ideas for treatment that can be further tested in more formal research.

We at FDA, together with the National Institute of Allergy and Infectious Diseases, will do our utmost to make this new system work. As the number of AIDS cases rises, we must find new ways to increase patient access to experimental drugs. This is especially critical since we are dealing with a fatal disease for which no cure

yet exists.

Increasing the role of community-based AIDS research is clearly an avenue whose time has come. In the early years of the AIDS epidemic, patients were cared for mainly in large teaching hospitals and medical centers. But that changed as the number of cases grew (86,157 as of Feb. 13) and as more and better information on patient care reached a wider medical community. Today, the care of many AIDS patients is centered not in a few major academic medical centers, but in clinics, private doctors' offices, and health maintenance organizations in the patients' own home communities. With this trend, more physicians have developed greater expertise in treating AIDS patients and a willingness to participate in clinical research.

NIAID, a part of the National Institutes of Health, is in charge of implementing the new legislation on community-based AIDS research, and FDA is actively involved as well. The new law calls for NIAID to fund community-based clinical studies on experimental AIDS treatments approved by FDA for investigational use. These studies—to be conducted at doctors' offices, clinics, community hospitals, drug addiction treatment centers, and other

primary care settings—will provide a substantially greater number of AIDS patients with a measure of hope. In particular, they will offer greater treatment access for groups of AIDS patients that have not always had full opportunity to participate in existing studies: intravenous drug users, blacks, Hispanics, women (including pregnant women, whose babies are at risk of being born with AIDS), and those not living near major research facilities.

Community-based research already has proven successful in studying new treatments for pain, cancer and arthritis (albeit without the strong patient initiative that we see with AIDS). For example, many of the nonsteroidal anti-inflammatory drugs available today to treat arthritis had been widely researched in numerous small, community-based studies. And, several community organizations are, in fact, already doing AIDS research, including the New York-based Community Research Initiative and the San Francisco County Community Consortium. The latter, a group of about 300 doctors treating people with AIDS, recently studied use of an aerosolized version of the drug pentamidine to help prevent a potentially deadly form of pneumonia that often afflicts AIDS patients. Based on the study results, FDA approved wider use of the promising drug (see “Wider Use of Pneumonia Drug Approved” on the AIDS Page of the April 1989 *FDA Consumer*). These research findings on aerosolized pentamidine clearly demonstrate the positive contribution that community-based research can make in the war against AIDS.

A second research group is being formed in San Francisco, and others are being established in Chicago, Atlanta, Boston, Washington, D.C., and other cities around the country.

NIAID expects to award its first contracts under this new program this summer. Six million dollars will be available this year to hire researchers and administrators; train community physicians, nurse practitioners, and other health professionals in research methods; and carry out administration, data collection, and record management.

NIAID plans to contract with organizations that have already shown an ability to do AIDS research, as well as those that have never done AIDS studies before. In either case, the main criteria will be access to a substantial number of AIDS patients and the capability to compile clinical data on potential therapies *without* specialized equipment or tests such as those used in major research centers. Drugs (or combinations of drugs) that have enough data to support safe investigation in community settings will be considered for study. In addition, drugs or therapies currently in wide use—whether they’ve been formally studied or not—are also candidates for NIAID contracts.

Studies may include not only patients with AIDS—the most severe form of infection with human immunodeficiency virus (the virus that causes AIDS)—but also those who are infected but have less severe symptoms or no symptoms at all.

As the community researchers demonstrate expertise in conducting these studies, additional research funds are expected to come from drug companies developing potential AIDS therapies. The American Foundation for AIDS Research also is awarding grants to community-based research groups.

The locations of the community-based studies will be well publicized to AIDS patients. Another provision of the health bill passed last fall by Congress calls for the government to set up a registry of AIDS clinical trials, so that patients and doctors can more easily find out the locations of AIDS studies, who’s conducting them, and what drugs are being tested. Community-based studies will be included in that registry. (I’ll have more to say about plans for the registry in a future column.) NIAID and FDA will take other steps as well to publicize the studies, as will local and national AIDS groups.

To help ensure that these studies produce the kind of scientific information needed to gain marketing approval for a new drug, FDA is actively assisting in their design and implementation. We have already begun advising community-based research organizations in matters where our expertise on the design and conduct of clinical studies can be useful, and we are exploring ways to expand these technical assistance efforts. By the time you read this, we will have conducted a pilot workshop to familiarize those who have already expressed an interest in community research with how to design a clinical study, how to properly obtain informed patient consent, what is required of an institutional review board (a local group that oversees the study to ensure it is ethical and properly safeguards patients), how to design and carry out the study so the results will be scientifically valid, and what FDA looks for in its inspections of study facilities and records. We expect to provide this same information to other interested parties around the country. We will also provide written guidance materials such as pertinent agency regulations.

NIAID also will conduct workshops on specific clinical research issues; FDA will take an active role in these efforts as well.

These efforts break important new ground for the agency: They mark the first time FDA has taken such intensive steps to educate and inform clinical investigators about the drug study process. There is no doubt in my mind that the magnitude of the AIDS crisis demands such an active role by this agency.

I believe the educational programs, conferences and workshops—and other efforts in conjunction with NIAID—will help community researchers contribute valuable clinical information and will foster humane and ethical treatment. For if community-based research achieves its goals—and I have every reason to believe it will—it will be an important step in bringing hope and help to the thousands of desperate persons now suffering from AIDS. Additionally, it will enable us to determine what works and how active involvement of FDA in protocol design may extend to other medical problems as well. ■



CHILDHOOD BED-WETTING: Cause for Concern?

by Dixie Farley

During grade school, Patsy (not her real name) never asked friends to spend the night. When invited to birthday party "sleep-overs," she declined. She worried about the possible lingering odor in her room. And she hated the plastic sheet that accompanied family vacations. Then, shortly after entering middle school, Patsy no longer had her "problem": bed-wetting.

Fourteen percent of 5- to 13-year-olds wet the bed, according to a recent population study. For many such children, like Patsy, the consequences are humiliation and damaged self-esteem. Fortunately, this common childhood affliction, known medically as "primary enuresis," usually disappears on its own, and proper treatment can often hurry it on its way.

Bed-wetting is considered normal up to age 5. When the problem persists, however, a visit to the doctor is in order. Bed-wetting rarely signals a health problem, but daytime wetting—which often occurs with bed-wetting yet may be overlooked if it's only a dribble—*can* represent serious illness. Indeed, if the wetting disorders known as dysfunctional voiding (see "When Potty-Training Goes Awry," page 9) go untreated, kidney failure—even death—can result.

Delayed Development and Other Causes

The precise cause of bed-wetting is unknown. Most cases appear to be due to delayed physical development. Bladder capacity may be less than half what is considered normal for the child's age. Bed-wetting is up to three times more common in boys than girls—linked, perhaps, to boys' slower rate of maturation. Some researchers, in fact, have argued that boys aren't normally dry at night until age 8.

Several studies point to a genetic link in enuresis. When both parents had the problem as youngsters, 77 percent of the children in these studies developed it. But the figure dropped to 44 percent when only one parent had wet the bed in childhood. By contrast, when neither parent had enuresis, only 15 percent of the children did.

A frequent cause of bed-wetting is constipation. In fact, treatment of constipation in enuretic children often resolves the wetting, report Sean O'Regan, M.D., and others of the Pediatric Research Center, University of Montreal. In the March 1986 *American Journal of Diseases of Children*, they explained that, in chronically constipated children, the rectum is probably never empty so the rectal sphincter muscle remains contracted to hold back stool. This, in turn, can dilate the rectum, which then presses on the small, immature bladder to cause the enuresis.

Attempts to hurry toilet training may backfire and actually contribute to bed-wetting; experts advise letting a child develop blad-

der control at his or her own pace. Other contributing factors include hospitalization (especially between ages 2 and 4), arrival of a baby, loss of a parent, and entering school.

In rare cases, emotionally disturbed children may respond to their illness with loss of bladder and bowel control, according to Gordon McLorie, M.D., and D.A. Husmann, M.D., of Toronto's Hospital for Sick Children, in the October 1987 *Pediatric Clinics of North America*. But in other cases, they wrote, "emotional disturbances may be primarily a result of the enuresis."

Urinary tract infection also can result in bed-wetting. These infections often cause additional symptoms, such as painful urination, foul-smelling urine, and daytime wetting.



A Velcro patch on the child's pajamas holds this battery-powered buzzer in place where it's easy to hear. A cord connects the buzzer to a tiny sensor in a pocket sewn on the underpants. The first sign of wetness triggers the alarm to waken the youngster, who can then finish urinating in the bathroom. Other alarms use a bed pad. Costs vary from about \$55 to \$75, all or part of which may be covered by medical insurance. Urinary alarms are not intended for use in ordinary toilet training.

Diaries and Other Diagnostic Tools

Diagnosis at the Center to Assist the Regulation of Enuresis (C.A.R.E.) in Chicago involves use of a diary. Before the first appointment, parents complete a psychological questionnaire and keep a three-day record on their child's diet and wetting pattern (times, duration and volume of daytime urination and times of bed-wetting). The record may suggest a wetting pattern abnormality, recurring urinary tract infection, or unrecognized constipation.

"I do not believe that all children with these complaints merit a full scale urodynamic evaluation," wrote C.A.R.E. director Max Maizels in the April 1982 *Journal of Urology*. (Urodynamic tests use electrodes and flexible thin tubes called catheters to gain information about urinary tract flows, muscle movement, and pressure changes. See "When Potty-Training Goes Awry.") A

(continued on page 11)

When Potty-Training Goes Awry

Sometime between ages 1 and 2, a toddler first senses bladder fullness and, so, starts to hold back urine by contracting the sphincter muscle of the urethra, the urinary tract opening out of the body. As the bladder gradually stretches to hold more urine, increased inner pressure causes the bladder's powerful detrusor muscle to contract to expel its contents. By age 4 or 5, most children learn to suppress detrusor contractions so they can retain urine and to relax the urethral sphincter during detrusor contractions so they can pass urine. Daytime dryness usually comes before nighttime control.

Certain children, however, get stuck in this transition with a condition known as dysfunctional voiding. Some don't learn to coordinate the urinary muscles; others learn coordination, but so persist in holding back urine that the bladder greatly overstretches. In both abnormal patterns, the contained urine becomes stagnant and infected. Dysfunctional voiding reflects neither disease nor physical defect but, rather, a hitch in the child's beginning efforts at bladder control. Such children make up about 40 percent of the outpatient practice of pediatric urologists.

With early detection and muscle retraining, dysfunctional voiding is often cured. Allowed to progress, this abnormal wetting can lead to permanent damage to the urinary tract—even kidney failure and death.

Why do these abnormal wetting patterns develop?

"In a lot of cases, no clear cause can be found," says Terry Allen, M.D., who teaches urology at Southwestern Medical School in Dallas. Allen has studied dysfunctional voiding extensively. "Quite often," he says, "it's related to a broken home, alcoholism, child abuse, or other stress. But it occurs in stable families, too. Some children hold back their urine all day because they've decided the school bathroom is dirty, or they're so hyperactive and busy they don't take time to go. Some fear the potty because they've fallen into it. One child was terrified of the toilet because his father had a bowel disorder and the son associated it with the toilet.

"Also, trying to force children to urinate can push them into a wrong pattern. They aren't clear on what to do so they tighten the wrong muscles. We recommend letting children decide on their own when they want to be potty-trained. The fundamental effect, though, is the same: The child gets into this mode of holding back, instead of learning to relax and empty the bladder completely at regular intervals."

An abnormal wetting pattern can result in several serious problems, says Allen. "As the detrusor and the urethral sphincter



strain against each other," he says, "the weaker sphincter eventually fails, so that the bladder can squirt out urine." Meanwhile, the straining builds very high pressures within the bladder. The detrusor reacts by contracting and, like any muscle given daily workouts, increases in size and strength. Ever stronger contractions become ever harder to control, causing abdominal cramps and more leaking. The bladder fails to empty completely, causing the child to have repeated urinary tract infection. The pressures inhibit urine flow from the kidneys to the bladder, causing the ureters and kidneys to overstretch, which in turn can be damaging.

The overstretched kidneys work hard to push the urine through the ureters into the bladder, but high pressure there provides resistance. So, while the valves at the ureters momentarily open to let urine into the bladder, this excessive pressure may push the urine back up into the kidneys. Over time, the abnormal urine flow can enlarge and distort the valves until they no longer work but allow the urine to move freely back up into the kidneys. To ward off this dangerous situation, proper diagnosis and treatment are vital.

Following are tests that may be used in diagnosis:

- **Intravenous urography (also called I.V. pyelogram)** — to rule out anatomical defects. This X-ray study is made by injecting dye into a vein, filming the movement of the dye, and watching it progress through the kidneys, ureters, bladder and urethra until it is excreted from the body.

- **Voiding cystourethrogram** — also to rule out anatomical defects. Another X-ray study, this procedure is done by filling the bladder with a dye and filming the dye in the bladder and as it moves along the urinary tract out of the body while the patient urinates.

- **Cystoscopy** — to confirm suspicion of serious urinary tract damage or to determine why the child hasn't responded to outpatient treatments. The inside of the bladder and ureters are examined via a lighted, thin tube called a cystoscope that is threaded through the urethra. Some doctors use a general anesthetic for this examination.

- **Urodynamic testing** — to evaluate how well the urinary tract works by examining pressure changes, flow rate, and muscle movement. The physician uses catheters (thin, flexible tubes) to measure bladder pressure and electrodes to measure activity of the urethral sphincter. With the catheters and electrodes attached to a recording monitor, the child urinates into a special receptacle or "potty chair" connected to a flow meter. Thus, bladder pressure, sphincter activity, and flow rate are recorded simultaneously. This takes about an hour and a half.

If the problem is detected before damage requires surgical correction, the child begins a simple retraining program that centers on urinating frequently, completely, and in a relaxed manner. This may require months or even years. The child goes to the bathroom at two-hour intervals, tries to maintain a continuous stream by remaining completely relaxed, and then tries to urinate again and again until unable to pass any more urine. Some investigators suggest intermittent catheterization (a catheter is threaded through the urethra into the bladder for complete emptying) and the use of any of a number of drugs: the tranquilizer diazepam (Valium) to relax the sphincter, the antidepressant imipramine (Tofranil) to help control wetting, and the antispasmodic oxybutynin chloride (Ditropan) to decrease bladder pressure. ■

Defining Enuresis

Primary enuresis (EN-you-REE-sis) is the medical term commonly used for bed-wetting in someone over age 5 who has never gone at least a year without wetting the bed. Secondary enuresis is bed-wetting in a child who has had bladder control. These terms do not apply to wetting problems due to physical illness or anatomical defect. Enuresis is diagnosed in 5- and 6-year-olds who have two or more monthly episodes and in older children who have one or more episodes a month, according to the American Psychiatric Association. The APA definition includes daytime wetting not due to disease or defect. But, generally, "enuresis" is used solely for wetting during sleep, so that is how it's used here. For every child with daytime

wetting, it's reported there are six who wet at night.

Typically, bed-wetting occurs during the first third of sleep. When it takes place in REM sleep, the child may remember dreaming about urinating. (Rapid eye movement, or REM, accompanies the stage of sleep when most dreaming occurs.) It was once believed that wetting took place only during very deep sleep or when sleep moved from one stage to another. Recent studies, though, show wetting occurs in all sleep stages in proportion to the *time* spent in that stage and without relation to arousal patterns.

Some bed-wetting children walk in their sleep or have coexisting sleep terror disorder, in which nightmares waken them to great fearfulness.

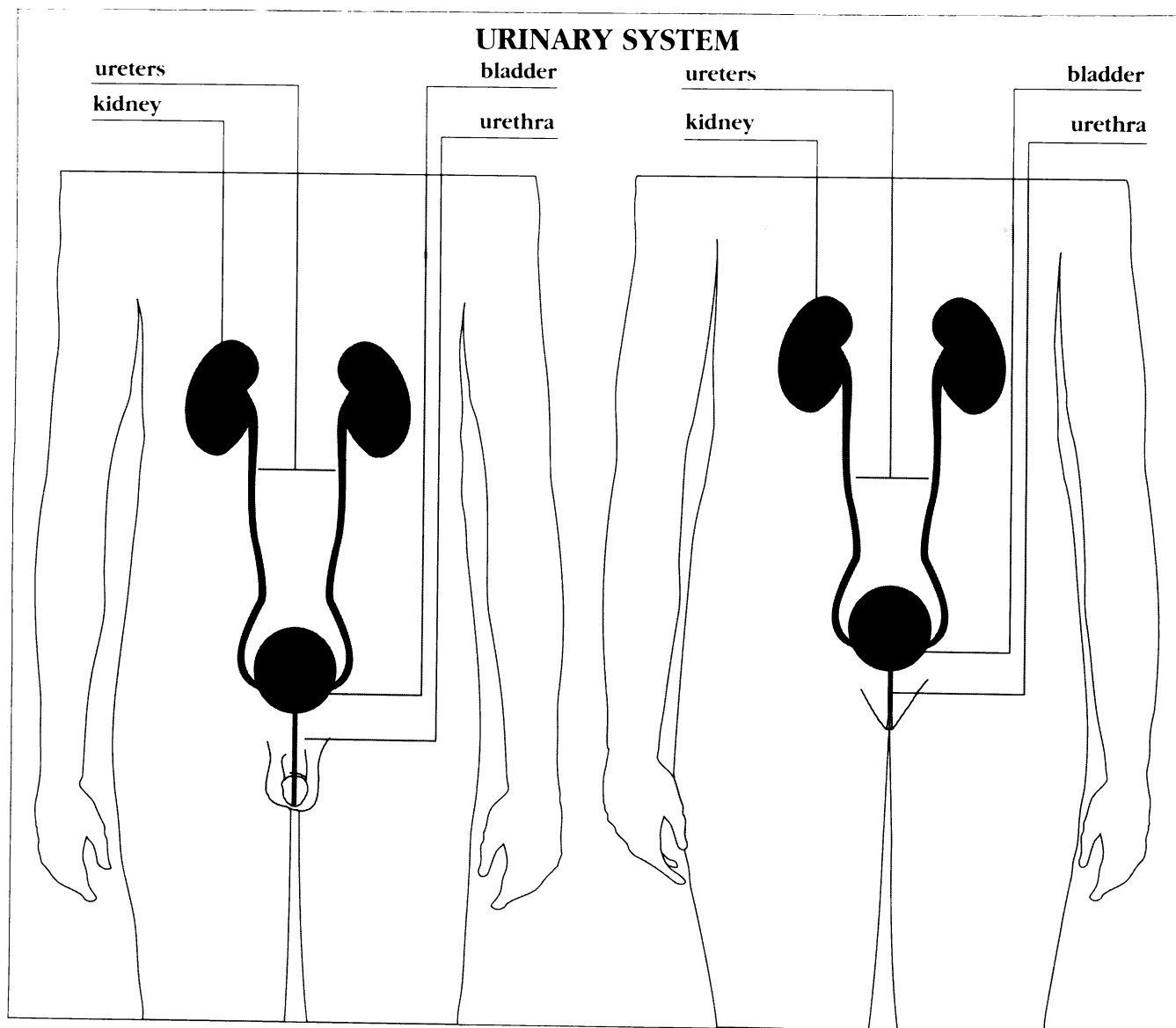
Enuresis affects some 20 percent of children at age 5, 5 percent at age 10, and up to 2 percent at age 15. Only about 1 percent of adults have wet the bed since childhood. ■

For More Information

For more information about bed-wetting and dysfunctional voiding, contact the nearest chapter of the National Kidney Foundation, or write to:

National Kidney Foundation of Texas
Suite 101
13500 Midway Road
Dallas, Texas 75244

Center to Assist the Regulation of Enuresis
Division of Urology
The Children's Memorial Hospital
2300 Children's Plaza
Chicago, Ill. 60614



(Continued from page 8)

"hands off" approach is how Maizels describes C.A.R.E.'s diagnosis and treatment. "I have been content with eliciting a detailed history, performing a physical examination of the genitalia, and observing the voided stream to guide the need for . . . urodynamic evaluation."

What can a patient's history reveal? Compared with youngsters with normal bladder control, bed-wetting children are more likely to have experienced problems while still in the womb, such as maternal illness or bleeding or, after birth, colic or jaundice (skin yellowing from bile pigment buildup in the blood), according to Maizels. "Perhaps these . . . are stresses that later lead to the 'maturational delay' believed responsible for primary enuresis," Maizels and Diane Rosenbaum wrote in the December 1985 *Primary Care*.

A thorough physical examination includes inspecting the rectum for impacted stool, checking the gait and reflexes of the legs and feet for nerve defects, and gently feeling the abdomen, genitals, buttocks, anus and spine for abnormalities. Observing the child's urination is important because different problems may be reflected by the nature of the stream, which may be weak, unusually forceful, intermittent, continuous, spraying, or painful. Intermittent flow, for instance, suggests obstruction.

Flow-rate measurements show how many ounces or milliliters of urine are passed in how many seconds. Ultrasound examination (a painless procedure, made by applying sound waves to the skin) may be needed to check the size and shape of the kidneys and to see how well the bladder empties. Laboratory analysis of urine screens for diabetes, kidney disease, or other disorders.

Among the candidates for further examination with more complicated tests are patients for whom conventional treatment has failed and those with recurrent urinary infection, wetting day and night without an obvious cause, coexisting loss of bowel control, and suspected dysfunctional voiding. Parents should ask questions to be sure they understand why a particular test is recommended and what is involved.

To Treat, or Not

But if the diagnosis is that the nighttime wetting is simply due to an immature bladder, the examination will probably end there. Physician and parents can move on to discussions about treatments. It's reasonable to consider doing no more than being patient and supportive until the child is older. Still, for families facing great stress over the problem and for children feeling shame and low self-worth, there are potentially effective therapies. The choice of therapy and effectiveness of individual treatments depend on the severity of the problem, the child's age and emotional maturity, and the level of commitment of the child and parents. Certainly, scolding and punishment are ineffective and inappropriate.

Behavior Modification

For behavior modification to be effective, child and parents must be highly motivated to follow the physician's instructions exactly and to persist long enough, which may mean several months. It's very easy to become lax or give up. Rewards alone—no punishments—are used. Among the techniques:

- **Responsibility reinforcement training.** The child takes charge of making one last trip to the bathroom, changing and laundering soiled bed linens, and charting progress (dry nights earn rewards). These responsibilities should help improve the child's feelings of self-worth and prevent parental anger over a wet bed. Hints from the Mayo Clinic: Use a plastic mattress pad and pillowcases, and buy lots of inexpensive sheets and blankets for

storage in a tightly sealed plastic bag for weekly washing.

- **Urinary alarm.** Wetting sets off the battery-powered alarm; the child awakens, turns off the switch, and finishes urinating in the bathroom. Eventually, the child is supposed to learn to wake *before* wetting. Lightweight pajamas are best because thick ones slow down the time between the first drops of urine and the sounding of the alarm. It's a good idea to replace batteries at set intervals because weakened ones may not trigger the alarm and may damage the device. The success rate with the alarm is as high as 75 percent, but the relapse rate can be as high as 30 percent. Maizels says that, by combining the alarm with other therapies, he and his colleagues can correct about 80 percent of wetting within the first month or two, with a relapse rate of only around 13 percent.

Another treatment often reported involves retaining urine to enlarge bladder capacity. But Terry Allen, M.D., urology professor at Southwestern Medical School in Dallas, says "this is bad policy because it puts undue pressure on the urinary tract."

Drugs Have Drawbacks

The Food and Drug Administration has approved one drug as safe and effective for bed-wetting: imipramine (Tofranil), an antidepressant. It can immediately produce dry nights, but there are drawbacks. It can cause a number of side effects, including blood pressure changes, irregular heartbeat, anxiety, insomnia, dry mouth, blurred vision, nausea, vomiting, diarrhea, dizziness, drowsiness, and headache. Bed-wetting often resumes when treatment stops. And, while the drug is safe at recommended dosages, an overdose can cause convulsions, coma and death. "One third of the physicians who use the drug do not recognize its toxic potential," wrote Betsy Foxman of the University of Michigan School of Public Health, Ann Arbor, and others in the April 1986 *Pediatrics*. The researchers were commenting on the results of the Rand Health Insurance Experiment, a population study. "We suggest that physicians explore less hazardous alternatives before relying on pharmacologic [drug] treatment for this generally benign condition," they concluded. The April 1987 *Mayo Clinic Health Letter* advised: "We rarely recommend this drug for children with enuresis."

If the decision is nevertheless made to use imipramine, parents should take extreme care to give it exactly as prescribed, to keep it in a locked cabinet out of reach of children, and to seek immediate medical help in case of overdose. Any substance potentially poisonous to a child should be labeled with warning stickers, such as "Mr. Yuk." These are available from regional poison control centers (not emergency rooms), listed with emergency numbers at the front of the telephone directory.

Physicians are investigating enuresis treatment with oxybutynin chloride (Ditropan). The drug is approved by FDA for certain nerve-related bladder disorders, but its safety and effectiveness for bed-wetting remain unproven.

Counseling and Other Treatments

Some physicians may recommend psychological counseling or hypnosis. In the C.A.R.E. program, fluids are not restricted at bedtime, but patients are advised to drink nectars, apple juice, cranberry juice, and water rather than carbonated drinks. "As these beverages may be less interesting," says Maizels, "children tend to drink more for thirst than for recreation."

Dealing with bed-wetting can be frustrating, even traumatic. It might help to keep in mind that nearly every child will outgrow the problem. ■

Dixie Farley is a member of FDA's public affairs staff.

A Primer on Medical Imaging—Part Two

by Egon Weck

This month FDA Consumer offers the second of two articles on the wide array of radiological techniques that physicians can use to help them “see” inside the body. The first article, in last month’s issue, covered techniques that use X-rays, though often in ways far different from the traditional X-ray machine. Part two covers non-X-ray techniques, some of which work without potentially hazardous ionizing radiation.

Advances in X-ray technology have vastly increased the range and precision of medical imaging. Meanwhile, research scientists have developed entirely new imaging technologies, some of which enable physicians to look inside the body without subjecting it to potentially harmful ionizing radiation, such as X-rays. They also enable doctors to “see” beyond the capabilities of X-rays. And in some instances, they can be used to study body functions such as metabolism as well as anatomical features.

Sound Waves from the Navy

The Navy has long used sonar, a system of underwater detection based on ultrahigh frequency sound waves, to locate sub-

marines and other underwater objects. Like sonar, ultrasound medical imaging, or sonography, relies on the echoes of inaudible, high-frequency sound waves.

Medical sonography has been in use in the United States since the early 1960s. To make sonograms (sound “pictures”), ultrasound waves are transmitted from a wand-like probe called a transducer, which is passed back and forth in contact with the skin over target areas such as the liver or a kidney. The ultrasound waves bounce off the internal organs and echo back to the transducer. Other equipment converts the echoes electronically into a picture on a TV screen where they can be monitored, recorded on videotape, or photographed.

Sonograms can’t provide fine structural details, but they can show the size and shape of an organ. And they can reveal cysts and tumors as well as abnormalities of the heart.

Ultrasound, however, is ineffective in imaging the lungs, bones or brain. And obesity or large scarred areas pose obstacles to ultrasound imaging.

Obstetricians have turned to ultrasound as a safe alternative to X-rays. However, while no harmful effects on the human fetus have been documented, experts recommend that it be used only in cases of clear medical necessity. For example, some question the use of ultrasound if the sole motive is to predict the baby’s sex. From fetal sonograms, obstetricians can often predict twins, locate the placenta, identify abnormalities, help prepare for a Caesarean birth, and tell the position and age of the fetus.

Sonograms are used in other applications:

- to identify aneurisms—dangerous outpouchings of the aorta or other arteries;
- to locate blocked bile ducts, gallstones and liver disorders, such as cysts, tumors and abscesses;
- to identify abnormalities and diseases of the pancreas, kidneys and thyroid.

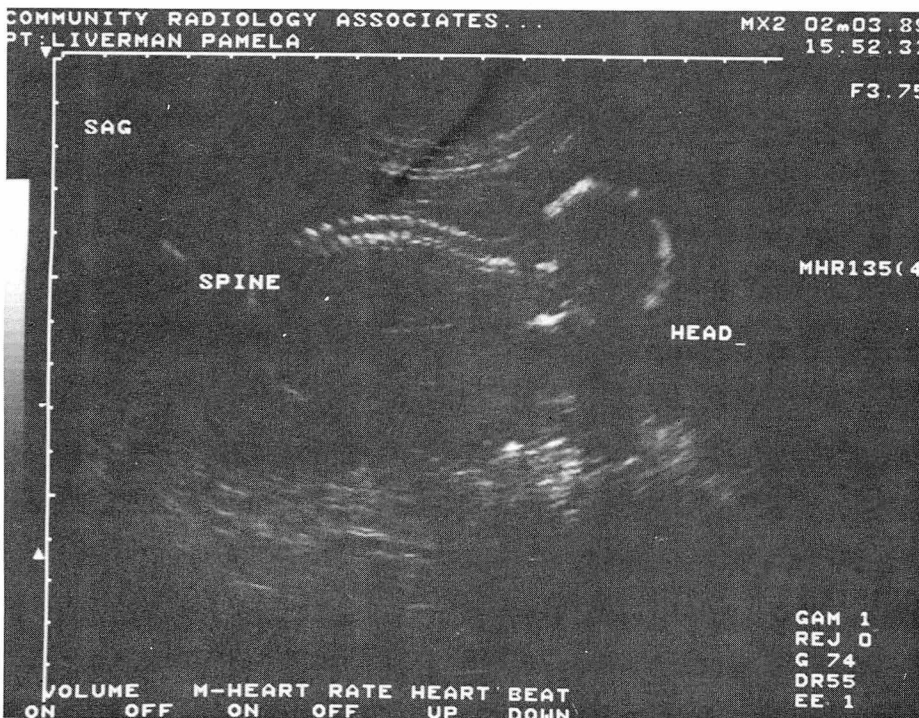
With a technique called Doppler ultrasound, specialists can detect abnormal rates of blood flow that betray blockages or narrowing of blood vessels and blood clots.

Newer ultrasound probes can be used inside the vagina for a closer look at a fetus, or inside the rectum to detect signs of colon cancer, or to view the prostate gland. Specialized ultrasound probes have also proven useful in diagnosing the cause of female infertility.

Radiation from the Inside Out

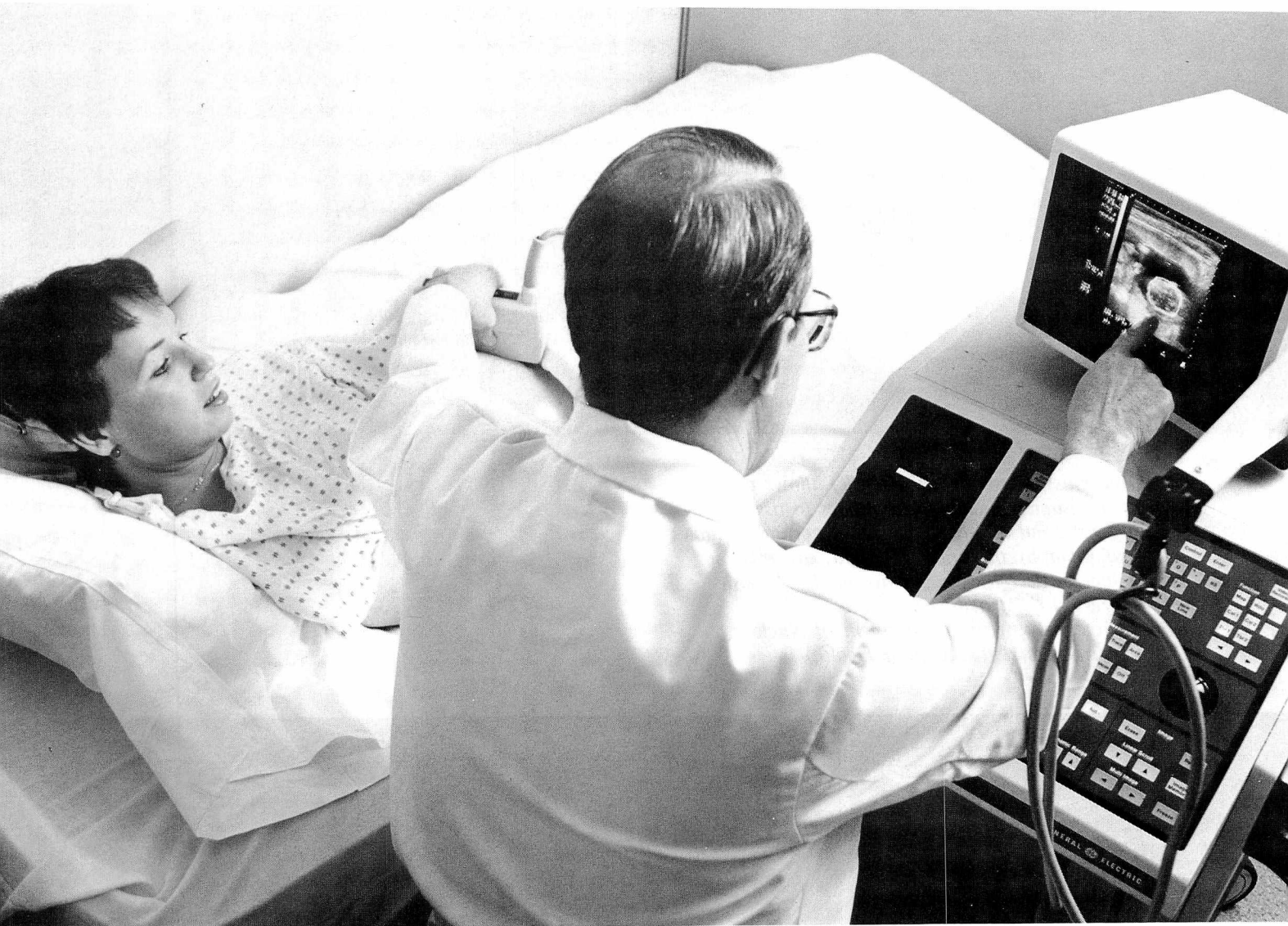
Nuclear medicine emerged after World War II when radionuclides (radioactive isotopes, which emit ionizing radiation) became available. At first, radiation from radionuclides was used to destroy cancerous tissue inside the body. In 1963, however, a body scanner using radionuclides was developed. Unlike an X-ray machine, which beams radiation at the body from outside, a nuclear scan places the source of radiation inside the patient.

(Continued on page 15)



This ultrasound image, or sonogram, was done on a 29-year-old woman to determine the age of the fetus. Doctors needed to know if the pregnancy had progressed beyond the 16th week in order to perform another test that could not be done before then. The sonogram showed that the fetal age was 17 weeks.

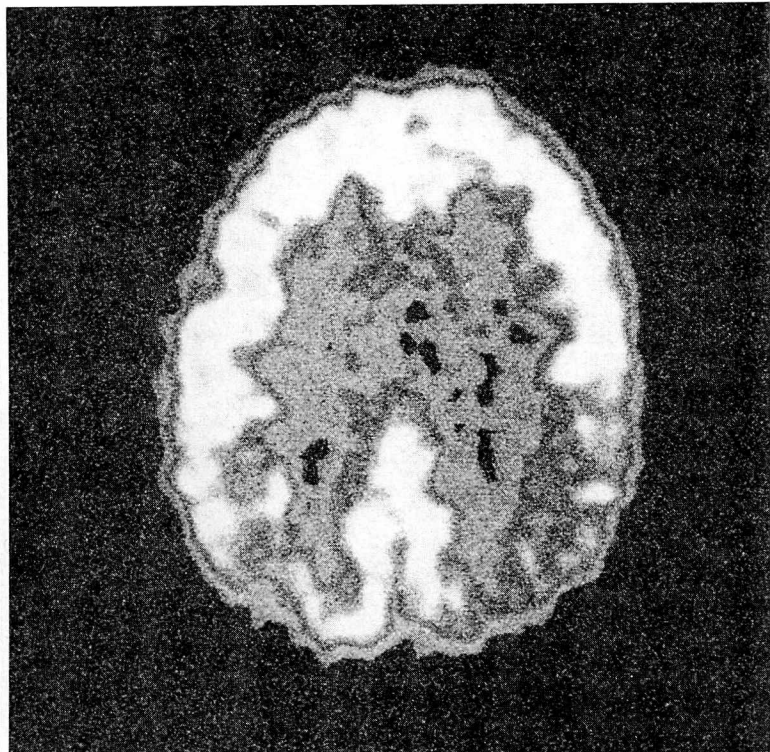
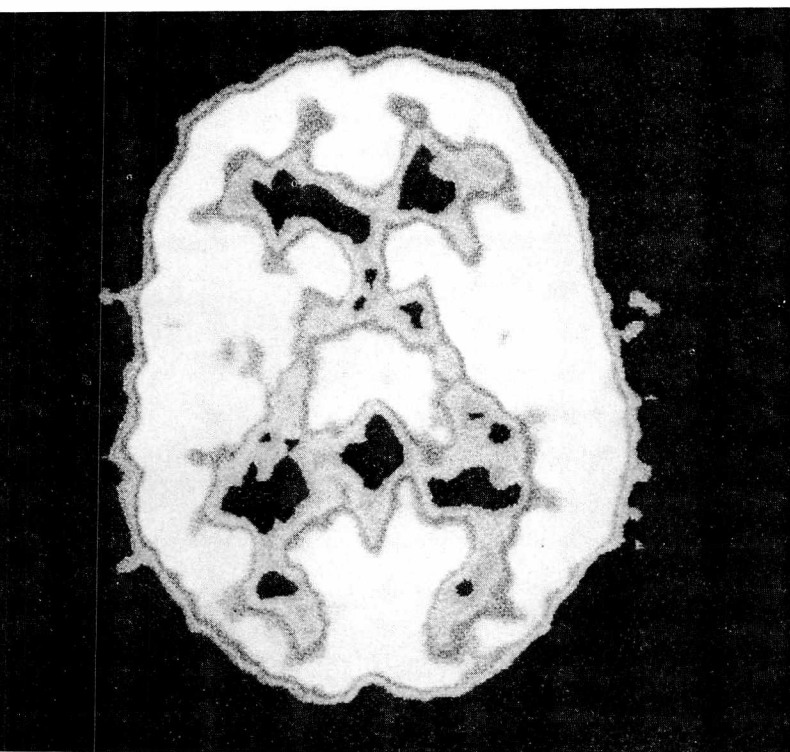
(Photo courtesy of Community Radiology Associates, Bethesda, Md.)



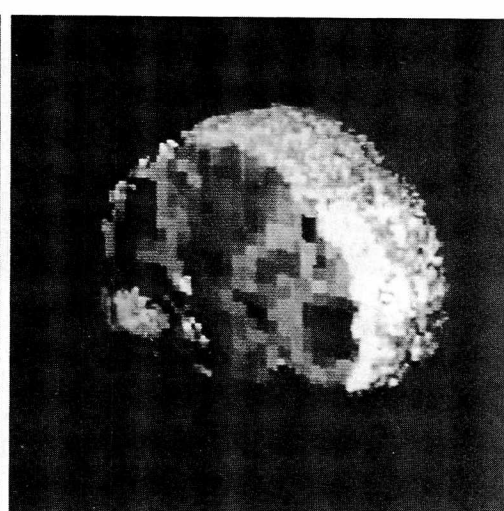
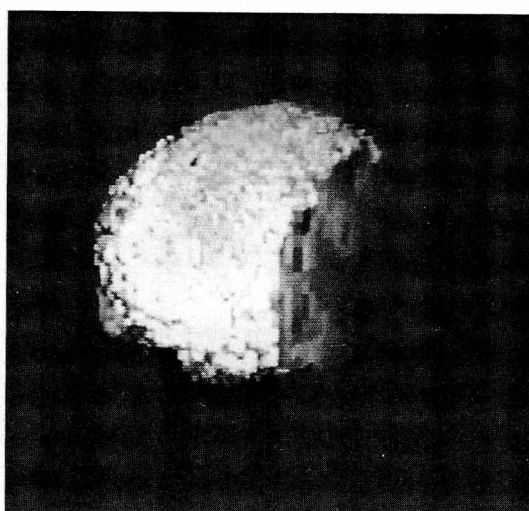
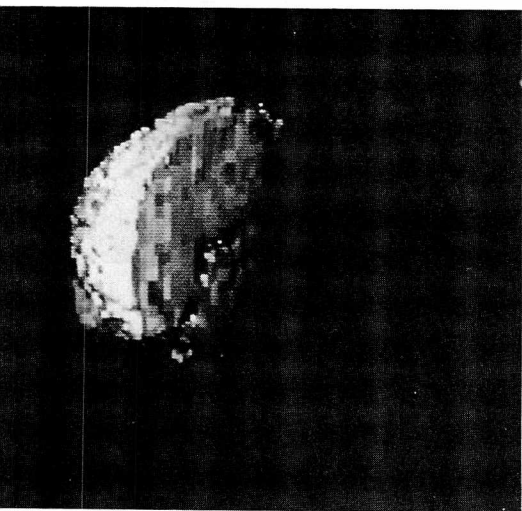
"Yes sir, that's my baby. . . ." Not worth framing, perhaps, but sonograms can tell doctors and expectant mothers a great deal about a developing fetus—its age, whether organs and other structures are developing normally, if a Caesarean delivery may be needed, and if—perchance—it's not just one fetus but two, three, or even more. (Photo courtesy of Georgetown University Hospital, Washington, D.C.)

Positron emission tomography (PET) scanners, like this one at the National Institutes of Health in Bethesda, Md., help doctors evaluate organ function to detect disease. Substances that cells normally use, such as glucose, are altered and combined with a radioactive marker. PET scanning measures the metabolism of the tagged substance and reveals abnormal cell function.





Positron emission tomography (PET) allows physicians to visualize metabolic processes in tissues and organs. Scan at left above shows normal metabolism of sugar by the brain. At right, the gray area indicates decreased sugar metabolism, possibly the result of Alzheimer's disease. (Photos courtesy of the Department of Nuclear Medicine, National Institutes of Health)



Sophisticated computer processing of radiation patterns by SPECT scanning permits the image of this patient's brain to be rotated and sliced, allowing physicians to "see" areas of stroke damage (dark gray) from several angles. (Photo courtesy of the Department of Nuclear Medicine, National Institutes of Health)

(Continued from page 12)

To prepare for nuclear scans (also known as scintigrams), a very small and virtually harmless amount of a radionuclide is administered by mouth, injection or inhalation. A variety of radionuclides, such as technetium and thallium, are available; each has a special affinity for a different organ or part of the body.

A "camera" or scanning device then picks up the radiation being emitted from the body and transforms it into an image. Nuclear scans lack the clear definition of structure visible on an X-ray. But they can reveal areas of an organ, such as the liver, that are not functioning normally.

Some radionuclides that concentrate in diseased areas, such as tumors, show them as hot spots on a scintigram. Others concentrate in healthy, functioning tissues to reveal areas of disease as cold spots.

Nuclear scans of bones can enable doctors to detect bone tumors long before they show up on X-rays. They also aid in diagnosing bone injury, infection, and arthritis. Nuclear scans are also used to locate blood clots in the lungs, and scans of the liver help to diagnose cirrhosis, hepatitis, tumors, cysts and abscesses. In the brain they can uncover tumors and areas damaged by stroke.

SPECT and Stroke

The single photon emission computed tomography (SPECT) scan is a refinement of nuclear scanning. SPECT employs some of the same radionuclides, but it uses a more sophisticated camera to pick up the radiation. SPECT resembles the CAT scan inasmuch as the signals picked up by the "camera" are fed to a computer, which performs countless computations and transmits the results to a TV screen to produce either a slice-like cross-section or a 3-D image.

While some of the radionuclides used in nuclear scans are employed in SPECT, newer ones have been developed especially for SPECT. One new injectable imaging agent, called SPECTamine, is specifically designed to pass intact through the blood-brain barrier (which keeps many chemicals out of the brain). When used by skilled specialists, the new agent can help make quick, accurate assessments of the effects of a stroke, showing which blood vessels have been affected and the nature and extent of brain damage.

A Magnet Stronger Than Earth's

At the heart of a magnetic resonance imaging (MRI) machine is a large cylin-

drical magnet that may weigh many tons. The patient is carefully positioned inside the cylinder. When the machine is turned on, the patient is subjected to a powerful—though apparently harmless—magnetic field thousands of times stronger than the Earth's.

The magnetic field acts on the atomic nuclei in the cells of the patient's body, lining them up like compass needles. The MRI machine then sends out a pulsed radio signal bumping the displaced nuclei out of line. When the radio pulse stops, the nuclei return to their original displaced position. As they do, they emit a faint signal, a phenomenon called nuclear magnetic resonance. Each element emits a distinct signal.

Since 75 percent of the body is composed of water and the water molecule is made up mostly of hydrogen, the hydrogen atom is often the target of MRI. The signals from the hydrogen nuclei differ, depending on the types of tissues the atoms inhabit. The hydrogen nucleus of a water molecule in normal tissue will behave differently than one in cancerous tissue, for example.

The nature, strength and duration of the signals is picked up by MRI's detector coils. The signals are processed by computer, and an image is projected on a TV screen. Like other advanced imaging techniques, MRI scans produce a cross-sectional view, or "slice," through the target area.

By changing the settings on the detector coils, the image can be changed. For example, one setting may image the outline of a tumor. Another will show the insides of the tumor in great detail, offering clues as to whether it is benign or malignant.

Developed in the early 1980s, MRI was first used to image the brain and spinal cord. It has now proved useful in diagnosing many conditions, including:

- disorders of the brain and nervous system;
- bone, joint and muscle disorders;
- tumors;
- heart and blood vessel problems; and
- cancer of the reproductive organs, liver, kidneys, lymph nodes, bladder, pancreas, and vocal cords.

PET for Early Signs

In diseases like cancer, by the time the structural damage shows up on X-rays, it may be too late to effect a cure. So medical investigators are constantly looking for ways to detect early signs of disease.

Another drawback with X-rays is that mental and nervous system disorders sel-

dom produce visible anatomical changes. What is needed is a form of medical imaging capable of visualizing metabolic processes. Enter PET: positron emission tomography.

PET scans employ radionuclides with positrons attached to them. Positrons are subatomic particles that resemble electrons but carry a positive instead of a negative charge. When a positron collides with an electron, the particles are annihilated and transformed into two photons (photons are a form of radiant energy). Because they travel in opposite directions, the source of each pair of photons can be identified with great precision.

As in other forms of tomography, a computer processes the information picked up by a PET scanner and produces an image on a TV screen. The resulting image can be color-coded to differentiate distinct areas of the target.

To prepare for a PET scan, a positron-labeled compound is administered, often by inhalation. The positron tagging is carried out in a machine called a cyclotron, which generates charged atomic particles. The tagged compounds emit their positrons in a matter of minutes, so it takes highly skilled teams working with nearby cyclotrons to perform a PET scan.

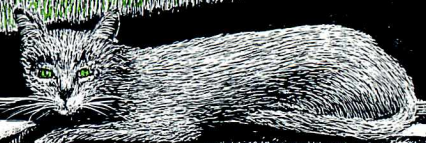
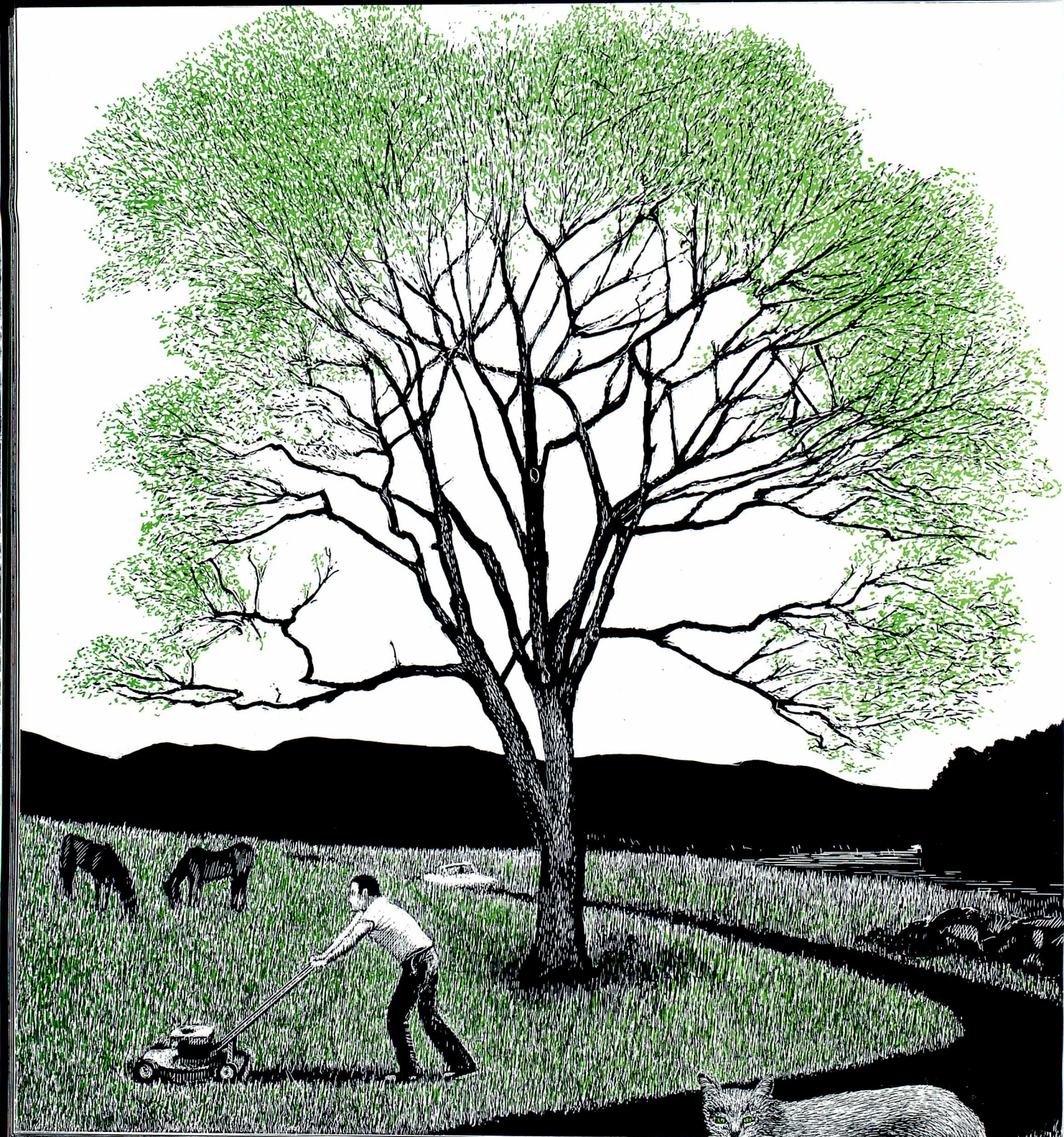
The cost of the skilled teams and the equipment has made the scans very expensive. There are only about two dozen PET scan facilities in the United States, and the technology is still largely under investigation, according to the American College of Radiology.

"PET's great promise rests with the capability of imaging metabolic rather than anatomical detail," notes Dr. Ronald G. Evens, professor and head of radiology at Washington University's School of Medicine in St. Louis. "Processes such as oxygen uptake, blood flow, glucose metabolism, and drug interaction could give us early warning to diseases that produce no anatomical changes.

"For example, we know that cancers start in small metabolic patterns. It would be extremely useful to get a handle on these early signs," Dr. Evens explains.

PET scans are being applied to the study of brain function and disorders such as schizophrenia and Parkinson's disease. In other areas, the scans are giving medical scientists a closer look at the mechanism that causes strokes and heart attacks, and the clogging process that gradually narrows arteries. ■

Egon Weck, a free-lance writer, has written extensively on health and medical issues.



It's Spring Again and Allergies Are in Bloom

by Ken Flieger

Chances are that you would just as soon not think about your nose. As long as it lets air in and out fairly easily, sniffs a nice aroma now and then, and keeps eyeglasses in place, a nose is, well, forgettable.

But for 25 million to 30 million Americans who suffer from seasonal allergic rhinitis—better (if inaccurately) known as hay fever—it is sometimes hard to think of anything but their noses. When a hay fever victim's particular nemesis is in the air, he or she is apt to be preoccupied by a constant struggle against the ailment's classic symptoms—watery nasal discharge, runny eyes, violent fits of sneezing, and itching that can affect not just the nose, but the roof of the mouth and even the Eustachian tubes connecting the inner ear to the back of the throat.

If tree pollen is the culprit, this all-out barrage against the nose and its neighbors usually strikes in early spring. Grass pollen tends to be troublesome in late spring and summer, and the deservedly notorious ragweed pollen is most abundant in the fall. Depending on where they live, hay fever victims who react to all three types of pollen may get a respite only in mid-summer and the dead of winter.

On the other hand, a hay fever sufferer who is allergic to molds, house dust, or animals may have to contend with symptoms the year 'round. So do people whose attacks are triggered by industrial pollutants, cigarette smoke, and other airborne irritants and allergens where they live or work. These unfortunate souls have "perennial allergic rhinitis." Their hay fever never lets up.

If that is the bad news, the good news is that a lot can be done to help hay fever sufferers cope with the disease. Better understanding of the complex events involved in an allergic reaction has made possible substantial improvement in the care of allergy patients, whether they have hay fever, asthma, food allergies, or any of a wide range of distressing and sometimes life-threatening allergic diseases. Medical science cannot cure allergies the way it can pneumonia. But advances in treatment and prevention allow millions of people to avoid the torment that can plague anyone unfortunate enough to "have allergies."

Allergies or a Cold?

Allergists (physicians who specialize in treating allergies) think that a good deal of allergic disease is unrecognized and therefore untreated. One reason is that seasonal allergies can easily be mistaken for a cold. Careful observation and common sense are useful guides to whether a stuffy, runny nose and sneezing signal a cold or an allergy. If the symptoms last more than a week or so, if they go on virtually all of the time, if they start and stop at the same time every year, flare up around cats or horses (principal causes of animal allergy), or otherwise follow a consistent pattern, allergy ought to be suspected. To be more certain, however, appropriate tests should be done by a physician, preferably an allergist.

The diagnosis of allergic rhinitis—the medical term for the inflamed, runny nose that's the main symptom of "allergies"—is based on a detailed patient history and examination of the nose. But the most critical step is skin testing. Tiny, diluted amounts of suspected allergens are injected under the skin or applied to a small scratch or puncture on the patient's arm or back. Within about 15 minutes, if the patient has IgE antibodies (see accompanying article) to an allergen being tested, a small raised area surrounded by redness—the "wheal and flare" reaction—will appear at the test site. The size of the skin reaction indicates how sensitive the patient is to the allergen that caused it.

Paul C. Turkeltaub, M.D., of FDA's Center for Biologics Evaluation and Research, and researchers at the National Center for Health Statistics examined information on allergen skin testing collected between 1976 and 1980 in the Second National Health and Nutrition Examination Survey. Among more than 16,000 people aged 6 to 74, about one in five had skin reactions to at least one allergen. Ryegrass and ragweed pollen each produced reactions in over 10 percent of the people tested, 6.2 percent were sensitive to house dust, and 2.3 percent showed a reaction to cats. More than twice as many people reacted to allergens found outdoors than to those found indoors.

Not everyone who tests positive for specific IgE antibodies necessarily has

allergy symptoms. Nevertheless, many allergists think that allergic disease of one kind or another—hay fever, asthma, drug allergy, or an allergic reaction to certain foods or insect stings—is likely to appear sooner or later in a person who has no symptoms but who has a positive skin test. About 80 percent of people who develop allergic rhinitis do so before the age of 30. But the disease has also first appeared in people in their 70s or 80s.

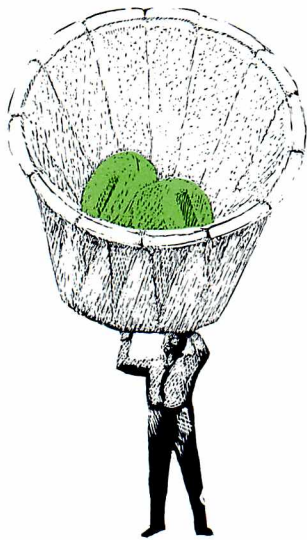
Shots and Other Relief

Before the 1940s brought the general availability of antihistamines, hay fever sufferers could get little help from the pharmacy. A hundred and fifty years ago, the English clergyman, wit, and hay fever victim Sydney Smith—he said his sneezes could be heard for six miles—put opium in his nostrils to relieve "this little upstart disease." Today allergic rhinitis can be controlled by more effective and much less dangerous drugs.

Antihistamines, available both over the counter and by prescription, remain the most widely used agents to treat hay fever symptoms. They can be highly effective in controlling itching and sneezing, but do less well in clearing nasal congestion. Antihistamines are most effective when used regularly rather than sporadically. Their chief undesirable side effects are drowsiness and excessive drying of tissues. Newer antihistamines, such as the prescription medication Seldane (terfenadine), are less apt to cause these side effects.

Nonprescription decongestants that shrink blood vessels in and around the nasal passages may help relieve nasal stuffiness. Decongestants are often sold in combination with antihistamines in the form of tablets, capsules, caplets and liquids. Others are sold as nose drops or sprays. While very effective for short-term use—a few days at most—overuse of nose drops and sprays can cause a "rebound" effect in which the congestion comes roaring back worse than ever. Patients can get caught in a vicious circle of use, relapse, and more use. The only solution is to stop using the drug altogether.

Intal or Nasal crom inhalers (active ingredient cromolyn sodium), available by



prescription, were first used against asthma and are proving useful in treating hay fever as well. For most people, inhaled cromolyn has few if any side effects, but must be taken frequently—every four hours—to be of maximum benefit. The corticosteroids, hormone-like drugs that

suppress the immune response, may also be useful in relieving allergy symptoms. They are usually administered as sprays, but are sometimes taken by mouth. While long-term use of oral corticosteroids can depress the activity of the adrenal glands, resulting in diminished resistance to infection, and cause other serious side effects, the nasal preparations used to treat allergic rhinitis are not thought to have any effect on the body as a whole. Corticosteroids are available only by prescription.

Allergen immunotherapy—"allergy shots"—offers another effective approach to controlling hay fever symptoms. First employed in the 1920s, immunotherapy consists of injecting gradually larger amounts of the allergens that cause the patient's allergic response. At the beginning of the treatment the dose is intentionally much too small to cause a reaction.

The dose is gradually increased to a level that protects the patient from whatever is causing the allergy. It usually takes six to 12 months to reach a protective dose. Once protection has been achieved, patients are given maintenance shots at four- to six-week intervals to keep symptoms under control. Whether or not the patients can successfully stop receiving allergy shots is uncertain. Studies suggest that protection fades if the shots are discontinued. For that reason, some allergy specialists recommend that they be continued indefinitely.

Aiming for Improvements

FDA is actively seeking to standardize the commercially available extracts used in skin testing and immunotherapy to improve their safety and effectiveness. The agency has two main objectives:

Ready Relief from Nasal Warfare: Nonprescription Allergy Medicines

FDA has proposed these ingredients as safe and effective for use in over-the-counter medications to relieve certain allergy symptoms:

Antihistamines (relieve runny nose and sneezing)

Brompheniramine maleate
Chlorcyclizine hydrochloride
Chlorpheniramine maleate
Dexbrompheniramine maleate
Dexchlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Phenindamine tartrate
Pheniramine maleate
Pyrilamine maleate
Thonzylamine hydrochloride
Triprolidine hydrochloride

Decongestants (relieve stuffy nose)

Oral:

Phenylephrine hydrochloride
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate

Topical:

1-Desoxyephedrine
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Racephedrine sulfate
Racephedrine hydrochloride
Naphazoline hydrochloride
Oxymetazoline hydrochloride
Phenylephrine hydrochloride
Propylhexedrine
Xylometazoline hydrochloride

For more information, including labeling claims, dosages and warnings, see the proposed standards published by FDA in the Federal Register:

- Antihistamines: Jan. 15, 1985, and Aug. 24, 1987
- Decongestants: Jan. 15, 1985



An Overachiever Immune System

expanding the availability of single-allergen extracts (individual kinds of pollen, for example, rather than extracts containing mixtures of several allergenic pollens); and standardizing extracts on the basis of how strong a skin reaction they produce. Studies have shown, for example, that weed and grass pollen extracts are more than 10,000 times as potent in producing skin reactions as extracts made from white pine and mountain cedar pollen. The labeling of standardized extracts reflects such differences in terms of "allergy units." Using single-allergen, standardized extracts, physicians are better able to tell precisely what causes a patient's symptoms and to plan, if necessary, the most effective course of allergy shots.

Immunotherapy has proven effective in hay fever sufferers and can be little short of miraculous for some patients who cannot get adequate relief either from avoiding allergens or from medication. Allergy shots are, however, time-consuming and costly and entail a slight risk of causing the kind of reaction they are meant to prevent. Because such a reaction can be serious, doctors like to monitor patients for at least 20 minutes after giving the shot.

The best course of action in treating hay fever is to get a careful diagnosis and discuss treatment options with an allergist. Once a hay fever sufferer's problem has been diagnosed, a doctor often can show how symptoms can be controlled by avoidance of the allergen or allergens involved or by the careful use of over-the-counter antihistamines and decongestants. If prescription drugs or immunotherapy are called for, a physician can recommend the most appropriate course of treatment. The important thing is that virtually every hay fever sufferer can be helped by prevention and treatment.

Noses are remarkable. They filter the air we breathe, warm it when it's too cold, and moisten it when it's too dry. They alert us when food might be unsafe to eat, and some noses can even smell a rain storm coming. Yet, with the possible exception of Bob Hope, we would all be grateful if noses went about their impressive variety of tasks unnoticed. For hay fever victims, that would be a blessing. Thanks to medical science, it's a blessing millions of them can enjoy. ■

Seasonal allergic rhinitis—hay fever—is the most common allergic disease. Its medical name means inflammation of the membrane lining the nose caused by exposure to an allergen at specific times of the year. (Hay is almost never its cause, and fever is not one of its symptoms, but the misnomer has stuck since it was coined more than 160 years ago.) Research, most of it in the 20th century, has demonstrated that allergy is actually an altered or exaggerated immune response. In an allergy-prone person the immune system reacts powerfully to foreign substances, such as pollen, that simply do not bother most of us.

The phenomenon of immunity has long been recognized. Ancient scribes reported that survivors of plague seemed to be protected if the disease struck again. Fifteenth century Chinese and Arab physicians tried injecting people with pus taken from smallpox victims. Sometimes the result was a mild case of smallpox that protected against the more serious form of the disease. Sometimes, too, the outcome was severe smallpox and death.

Two centuries ago, an English physician named Edward Jenner successfully immunized a young boy against smallpox by injecting him with a fluid from a cowpox sore—hence the term vaccination—from *vacca*, Latin for cow. But it was not until the late 19th and early 20th centuries that scientists began to explore the immune system and discover that it is responsible for a number of illnesses, including allergies.

The mechanisms by which the human body recognizes its own components and distinguishes them from foreign substances are among the most elegant products of evolution. (See "The Immune System: Your Body's Department of Defense," *FDA Consumer*, March 1988.) Although they do not understand it fully, scientists believe the immune system consists of two main branches. One works through the action of white blood cells called T lymphocytes, or simply T cells. T cells attack foreign materials directly and also produce substances that summon other parts of the immune system to help destroy an invader. A deficit of T cell-mediated immunity is characteristic of acquired immune deficiency syndrome.

The other branch of the immune system is the one we associate with antibodies—highly specialized proteins manufactured by B lymphocytes—and antigens—

enzymes, toxins, or other foreign substances that provoke a response from the body. When B cells encounter antigens, such as those on the surface of bacteria, they multiply and produce antibodies that destroy the invading germ or make it vulnerable to attack by other parts of the immune system. Once B cells have learned to make an antibody against a specific antigen, they go on making it indefinitely. This is why vaccines can induce permanent immunity against some diseases.

Ironically, it is the immune system's ability to maintain constant readiness against a repeat onslaught by an antigen that makes millions of people susceptible to allergic disease. For reasons that are not entirely clear, some antigens cause B cells to make a kind of antibody called immunoglobulin E—IgE for short. (Antigens that provoke IgE formation are referred to as



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Absence Makes the Nose Grow Fonder

allergens because they can cause an allergic reaction.) The first time an allergy-prone person is exposed to an allergen—pollen or house dust for example—the B cells respond by making IgE antibodies tailored to counteract the allergen. These IgE antibodies attach themselves to mast cells that are abundant in the respiratory tract, digestive system, and skin and to basophils, cells circulating in the blood.

The next time an allergen and its IgE antibodies come together, mast cells and basophils release powerful substances called mediators, among them histamine, that cause the allergic reaction. These mediators are fairly rapidly neutralized by the body. But as long as the allergen is present, histamine and other mediators will continue to be released from mast cells and basophils, and the patient's allergy symptoms will persist.

No one knows for sure why some people have allergies while most do not. Genetics appears to play a part; people who suffer from allergies usually have a close relative with similar problems. Susceptibility seems to be related to a person's capacity to produce IgE antibodies. Yet only 30 percent to 40 percent of people with allergic rhinitis have high IgE levels, and individuals with low IgE levels can still suffer from hay fever and other allergies.

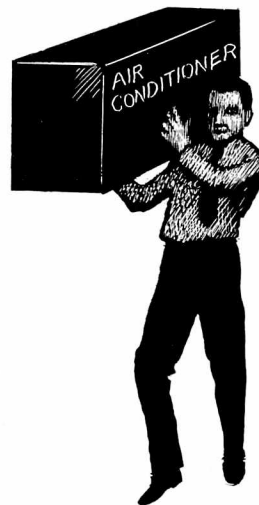
In view of all the grief they cause, you have to wonder if IgE antibodies are good for anything. The answer may well be yes. Studies suggest that several kinds of human parasites provoke the formation of IgE antibodies and are rapidly destroyed by them. (These amoebas and worms are no longer common in this country, but they still cause serious health problems in underdeveloped parts of the world.) Looking at this intriguing discovery, a Swedish immunologist has speculated that "pollen allergy might partly be an undesirable consequence" of modern society's success in ridding itself of parasites and the diseases they cause. ■

Once hay fever has been diagnosed and the responsible allergen or allergens identified, the first line of defense is prevention—avoiding the pollen, house dust, mold spores, scales shed by the skins of animals (dander), or other substances that provoke an allergic reaction.

Sometimes this can be fairly easy. A patient may hate to part with a pet cat or give up horseback riding, but that may be all it takes to be free of symptoms. People allergic to mold spores may solve their problem by keeping out of damp, musty areas. They may also be well advised to avoid foods such as peanuts that may contain mold spores and not to take penicillin and similar drugs that can cause an allergic reaction in mold-sensitive people.

If house dust is the problem, frequent and thorough cleaning of the floors, fabrics such as carpets and curtains, upholstered furniture, and bedding can be beneficial. So can the use of high-efficiency indoor air-filtering devices (not those built into ordinary heating and air conditioning systems) that trap dust particles. (Filtering devices that really help don't come cheap. Beware of inexpensive—and ineffective—substitutes.) Persuasive evidence points to microscopic mites as the prime offenders in house dust allergies. While these spider-like creatures thrive during warm summer months, they may actually be more troublesome in colder weather when fragments of dead mites are more readily dispersed in the air and inhaled.

It is more difficult to avoid pollen and other outdoor airborne allergens. Air conditioning helps in homes, automobiles and workplaces. Simply keeping doors and windows closed can lower the allergen content of indoor air. Hay fever symptoms can be brought on by pollen concentrations as low as 20 grains per cubic meter of air; so during certain seasons, no outdoor area can be assumed pollen-free. Yet it is wise to be especially wary of areas known



to have high concentrations of allergens. Another prudent measure for allergic rhinitis sufferers is to avoid irritants such as tobacco smoke, fumes, polluted air, and hair sprays.

It is seldom helpful to move someplace else to escape hay fever-causing pollen. Every part of the country has varieties of trees, weeds and grasses that shed allergenic pollen. People who try moving to the West Coast to escape ragweed pollen (ragweed does not grow in California, Oregon or Washington) may discover that they are allergic to a pollen found in the new location. Furthermore, pollen grains have been found in air samples collected as far as 400 miles at sea. The adage "you can run but you can't hide" is all too true for most hay fever sufferers. ■



ANAPHYLAXIS ANAPHYLAXIS ANAPHYLAXIS ANAPHYLAXIS

An Allergic Reaction That Can Kill

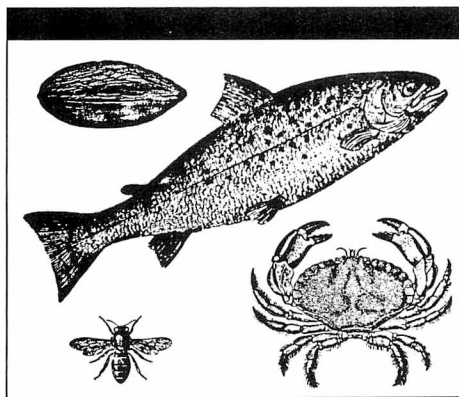
by Marian Segal

One spring day in 1972, Jacki Kwan was quietly working on her research calculations and munching pistachio nuts a co-worker had brought back from the Middle East. After stuffing her body full of pistachios, as she put it, she decided to take a break and go downstairs to pick up her paycheck. Kwan rode the elevator from the 4th floor to the basement and was walking down the hall when she began to feel uncomfortably warm. Then she started to itch. "At that point," she said, "I knew it was the pistachio nuts, because the reaction triggered a vague memory of a problem I had as a child once when I ate pistachio ice cream."

Kwan got her check and went back upstairs. In another 10 minutes she was back at her desk, feeling "really miserable." No wonder: "The itching had become severe and I was getting hives all over my body," Kwan said. "I was flushed and puffy, and started to vomit and have diarrhea at the same time. Everything was getting progressively worse. Finally, I could feel my throat swell up and start to close, and I was having trouble breathing."

Kwan was indeed having an allergic reaction to the pistachio nuts. But her response was not the usual runny nose, watery eyes, sneezing, or itching so many allergy sufferers endure. She was having an anaphylactic reaction—an acute, life-threatening medical emergency. Her symptoms were classic.

Anaphylaxis typically comes on within minutes of exposure to the offending substance, peaks within 15 to 30 minutes, and is over within hours. The first symptom is



usually a sensation of warmth followed by intense itching—especially on the soles of the feet and the palms of the hand. The skin flushes, hives may appear, and the face may swell. Breathing becomes difficult, and the patient may feel faint and anxious. It's not surprising that patients often describe, as Kwan did, a sense of impending doom. Blood pressure may drop precipitously. Convulsions, shock, unconsciousness, even death may follow. Roughly 60 percent to 80 percent of anaphylactic deaths are caused by an inability to breathe because swollen airway passages obstruct airflow to the lungs. The second most common cause of anaphylactic deaths—about 24 percent by one estimate—is shock, caused by insufficient blood circulating through the body.

In the March 1986 *Western Journal of Medicine*, Lawrence M. Lichtenstein, M.D., of Johns Hopkins University School of Medicine described anaphylaxis

as "a dramatic problem which generally has a yes or no outcome: The patient either recovers completely or dies. Fortunately, death is rare."

For Kwan, it was a case of being in the right place at the right time. She was working as a medical technologist in an anesthesiology laboratory at the Washington Hospital Center in Washington, D.C. The doctors in the lab rushed her to a nearby room to lie down and gave her an injection of epinephrine (adrenalin). Kwan recovered quickly and hasn't eaten a pistachio since.

The frightening and life-threatening symptoms of anaphylaxis are caused by the release of substances known as mediators from mast cells and from basophils, a type of white blood cell. Since the skin and the respiratory and digestive tracts are rich in mast cells, the organs of these systems are the ones primarily affected in the reaction.

The cause of anaphylaxis was first explored in the 1920s when horse serum—being used to make antitoxin for diphtheria, scarlet fever, tetanus, and tuberculosis—was found to induce the reaction. Scientists have since discovered that the explosive reaction of anaphylaxis is the culmination of a complicated sequence of events.

Anaphylaxis—like less severe allergic reactions—is an abnormal response to an antigen (a foreign substance, usually a protein) that doesn't bother most people but elicits symptoms in those who have an inherited hypersensitivity to it. Well-known antigens that can cause anaphylaxis

include penicillin, insect venom, pollen extracts, fish, shellfish and nuts.

Initial exposure to the antigen prompts the hypersensitive person to produce immunoglobulin E (IgE) antibodies. Whereas most antibodies (IgG, IgM, IgA, IgD) are primarily protective—helping to fight harmful bacteria, viruses, fungi, and other toxic substances—IgE antibodies are more likely to work against the body, “sensitizing” the affected person for a future allergic response. (See “An Overachiever Immune System” on page 19.)

IgE antibodies attach themselves to mast cells and basophils, priming the body for the allergic reaction. Subsequent exposure to the antigen completes the linkage needed to set off the sequence of events that leads to that “sense of impending doom”: The antigen hooks up to the IgE antibodies bound to the mast cells, causing the cells to “degranulate”—the scientists’ term for an explosive discharge of histamine and other substances from the cell granules. The released mediators cause blood vessels to dilate and leak fluid into the surrounding tissues and cause smooth muscle in the airways to contract. All this activity results in the familiar symptoms of allergy or—in extreme cases—anaphylaxis.

Since the middle of the 20th century, penicillin has been by far the most common cause of anaphylaxis. (Fortunately, most allergic responses to the drug are far

less serious. Some involve only localized skin reactions—hives, rashes or inflammation caused by direct topical administration of the drug. Others are systemic reactions, with wheezing, swelling, redness, and vasculitis—inflammation of blood vessels—but not the life-threatening symptoms of anaphylaxis).

Allergic reactions to insect stings are another major cause of anaphylactic death, almost always caused by the order Hymenoptera—honeybees, bumblebees, wasps, hornets, yellow jackets, and fire ants. Nevertheless, although many millions of people in the United States are allergic to insect venom, and hundreds of thousands of them have allergic reactions to stings each year, the number of deaths reported from these reactions is estimated at only 50 to 100 per year.

Some substances can cause a reaction just like anaphylaxis, but the mast cell degranulation is triggered without IgE. (Some experts refer to these as “anaphylactoid” reactions to distinguish them from true IgE-mediated anaphylaxis. By any name, though, the outcome is the same.) Dyes used in certain diagnostic X-ray tests are the most common cause.

Anaphylactoid reactions can also be incited by physical stimuli, such as cold temperatures or exercise—good news for couch potatoes in search of an excuse to avoid jogging. The reason for mast cell degranulation in these circumstances is

not thoroughly understood.

Some people with exercise-induced anaphylaxis develop symptoms only if they’ve eaten before exercising. This is called “food-dependent exercise-induced” anaphylaxis. Writing in the March 1986 issue of the *Western Journal of Medicine*, Gildon N. Beall, M.D., and his colleagues at Harbor UCLA Medical Center in Torrance, Calif., described the case of a 25-year-old woman who had episodes of food-dependent exercise-induced anaphylaxis. The incidents “only occurred Friday evenings on the dance floor after her escort had treated her to dinner. The patient’s problem resolved when she ate dinner *after* dancing rather than before.” Some people are susceptible to this form of anaphylaxis only if they’ve eaten certain foods (most commonly celery or shellfish).

There are numerous other less common precipitators of anaphylactic or anaphylactoid reactions. Medical reports point to substances as varied as cancer drugs, a hair dye ingredient, topical antibiotics, cornstarch surgical glove powder, milk protein in a diaper rash ointment, cabbage, pig insulin, dextran (used in intravenous drug therapy), muscle relaxants, and wines that contain sulfites. (Because sulfites in foods, wine, beer and drugs can cause severe adverse reactions in some people, FDA has taken steps to curtail the widespread use of these preservatives and to help warn consumers about products that contain them. For more on this, see “Reacting to Sulfites” in the December 1985-January 1986 *FDA Consumer*.)

Despite the numerous foods, chemicals, drugs, and physical precipitators known to cause anaphylaxis, in most instances the cause of a reaction is unknown (idiopathic). Researchers at Northwestern University Medical School in Chicago recently reported on 73 patients with idiopathic anaphylaxis. “Idiopathic anaphylaxis,” the researchers wrote in the February 1987 *Archives of Internal Medicine*, “can be extremely frightening to both patient and physician when no inciting source is found. Patients often attribute their symptoms to foods or food additives, and many patients become increasingly frustrated by the unpredictability of their reactions.” Three patients followed by the scientists became afraid to eat because they feared it would induce anaphylaxis. Reassurance helped rid the fear in two of the three. The third patient consulted another physician who performed laboratory tests and advised her not to eat eggs, soybeans, chocolate, or fish. Despite avoiding these foods, she continued to



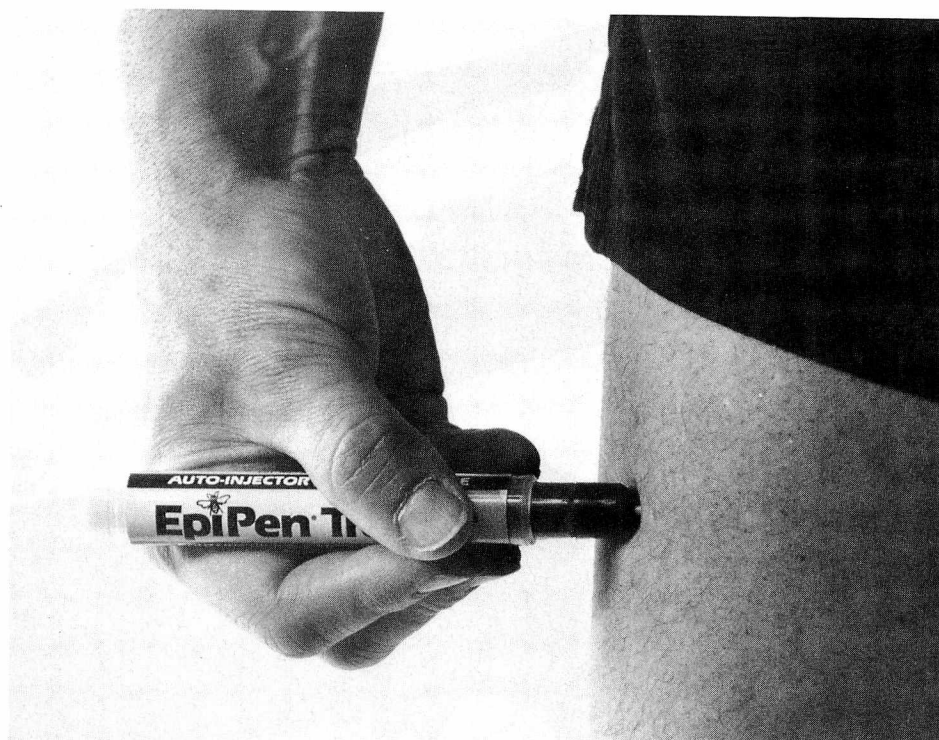
have anaphylactic episodes and lost more than 18 pounds in two years.

In the October 1987 issue of *Obstetrics and Gynecology*, Jay E. Slater, M.D., and his colleagues at the National Institutes of Health in Bethesda, Md., reported a study of five women with recurrent idiopathic anaphylaxis whose episodes were thought to be related to secretion of the hormone progesterone. The researchers speculated that the hormone might somehow foster release of mediators from mast cells. The women were treated with a drug that lowered their progesterone levels by stopping their menstrual periods, and three of the five stopped having attacks. The researchers noted certain common characteristics among the women who responded successfully (such as a history of previous ovarian problems and diagnosis of the problem after age 36), and concluded that the drug would most likely benefit patients with similar characteristics.

When possible, the best course for preventing anaphylaxis is, obviously, to do what Jacki Kwan does: avoid the instigator—in her case, pistachios. Michael A. Kaliner, M.D., of the National Institute of Allergy and Infectious Diseases recommends, for example, that “people with known sensitivity to insect stings should avoid areas where they are likely to encounter stinging insects; always wear shoes when walking in grass; avoid smelling like a flower by using perfumes or other scented products, such as scented soaps, aftershaves, or suntan lotions; and avoid looking like a flower by wearing flowered or brightly colored clothing.” (Dark colors like brown and black may provoke an attack; bees are least attracted to white and light khaki.)

Next best is to be prepared for an attack. Several emergency treatment kits are available by prescription and should always be carried by people who know they are prone to anaphylaxis. All the kits contain epinephrine, which stops the action of the mediators, preloaded in the injecting device. One type contains a notched syringe to ensure the correct dose is given. Richard Nicklas, M.D., an allergist in FDA's Center for Drug Evaluation and Research, cautions that “The patient or another person should be *fully instructed in its use by the prescribing physician.*” Other kits contain a spring-loaded injector that automatically injects a predetermined dose of the drug when it is pressed against the thigh.

Some kits also contain a tourniquet and an antihistamine. But *an antihistamine is not an effective emergency treatment.* It is included in the kit to reduce symptoms that



This pressure-activated device delivers a set dose of epinephrine for temporary emergency treatment of anaphylaxis. This device, or another type of epinephrine delivery system, is included in any of several emergency treatment kits available by prescription.

may continue after treatment with epinephrine. *Anaphylaxis must be treated immediately with epinephrine.* The tourniquet is for use in the case of an insect sting on an arm or leg. First the stinger should be flicked. The tourniquet should be applied above the site of the sting and loosened every 10 minutes to allow sufficient blood circulation. If possible, a cold pack should also be applied. The cold causes the blood vessels to constrict, which slows venom getting into the bloodstream.

Emergency kits are not a substitute for professional medical help. They are intended for patients to use until they can reach a doctor or hospital. The patient should not hesitate, however, to use the medication immediately, as directed by the physician.

Finally, treatments to reduce sensitivity in a patient (allergen immunotherapy), or to completely desensitize a patient (desensitization therapy), are effective for some patients. Immunotherapy involves injecting the allergen, such as insect venom, in increasing amounts over a period of years. The injected allergen stimulates production of IgG antibodies, which confer protection from the substance.

Desensitization is done in patients who need treatment with a life-saving drug to which they are allergic—usually penicillin—and for which there is no

effective substitute. Unlike allergen immunotherapy, desensitization is done in the hospital over a short period, beginning with extremely diluted solutions of the allergen. The patient is watched carefully as the dose is gradually increased and may be treated with antihistamines or other medicines if symptoms occur.

Experts disagree about whether certain individuals are predisposed to anaphylaxis. Many feel that people with a history of allergies are more likely to have an anaphylactic episode; others are unconvinced that this or other factors—such as age, sex, race or geographic location—predispose a person to it. One thing is clear, though: Previous exposure to the allergen usually precedes the anaphylactic reaction. Sometimes people will notice that an allergen makes them feel bad in some way—perhaps mild itching or upset stomach. This *may* indicate that future exposure will produce a more severe reaction.

Whatever the reason for anaphylaxis—as Johns Hopkins' Lichtenstein says, its outcome is generally a yes or a no. Patient awareness, preparedness, and prompt action can help raise the tally in the yes column. ■

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



Exercise with Care—Fitness Is Not Risk-Free

by Nancy Karkowsky

Early one morning you're out jogging along your favorite path, getting the heartbeat going a little faster and feeling good, when suddenly, your ankle twists and your leg gives way. You groan in pain and mutter something about that hole you stepped in not being there yesterday.

What next?

Should you walk on that sore ankle? Should you rush to a doctor, or treat the injury yourself? Should you apply heat or cold to the injury? Should you take something for the pain? Which medications are safe? Which are helpful?

First, just stop, advises Gabe Mirkin, M.D. According to this author of several books on physical fitness and sports medicine, pain is a way your body talks to you. Stopping whatever you are doing prevents further damage and allows you to assess the situation.

Robert Nirschl, M.D., assistant professor of orthopedics at Georgetown University, in Washington, D.C., offers this advice: "Look for signs of inflammation such as swelling, redness, tenderness, fever—generalized or local—or pain that persists with or without continued activity." Any of these signs—or others, such as decreased mobility or weight-bearing ability of the affected limb, or a "popping" or "snapping" sound—indicates the need for immediate treatment.

Mirkin advocates the "RICE" program for a traumatic injury: **Rest-Ice-Compression-Elevation**. Stop the activity, cool the injured area with ice or a coldpack, wrap an elastic bandage around it, and elevate the injury above the head to reduce swelling.

There are exceptions to the RICE regimen. Ice or coldpacks should not be used on people who have problems with arteriosclerosis (hardening of the arteries), or on an extremity that may become gangrenous, such as a foot injury in someone with poor blood circulation.

But aside from those exceptions, the RICE treatment should begin immediately after an injury occurs to reduce swelling to the area and promote healing.

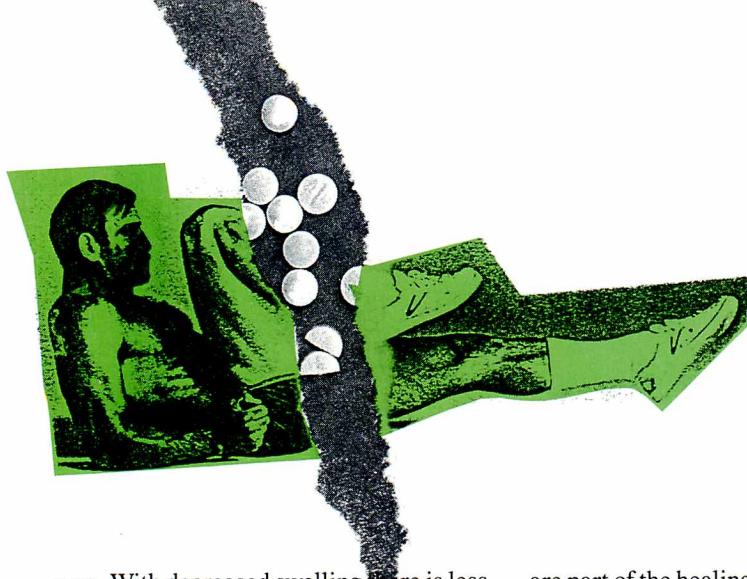
Writing in *The Sports Medicine Book*, Mirkin and Hoffman advise consulting a physician after beginning RICE if one or more of the following conditions exists:

- traumatic injury to a joint;
- severe pain;
- pain in a joint or bone that persists for more than two weeks;
- infection, signaled by pus, red streaks, swollen lymph nodes, or fever; or
- injury that *you* feel should be checked.

As Mirkin and Hoffman point out, these are only guidelines. Your own intuition is often better and more relevant to the particular situation than anything in a book or magazine. When in doubt, have it checked out. It is far better to consult a physician needlessly than to hesitate and suffer permanent injury.

In general, cold is highly recommended for treating sports injuries. By constricting the blood vessels, cold decreases swelling by inhibiting blood flow to the injured





area. With decreased swelling there is less inflammation, and more rapid healing.

Heat has the reverse effect and therefore should be avoided in case of traumatic injury. The hot bath that feels "oh so good" relaxes the walls of the blood vessels, increasing the flow of blood and fluid to the injured area, making the inflammation worse. "If there is swelling," cautions Nirschl, "no heat, no warmth, until the injury is healed."

Over-the-counter pain relievers for minor sports injuries get a rather mixed review. Vincent Karusaitis, M.D., a medical review officer in the Food and Drug Administration's Center for Drug Evaluation and Research, explains that aspirin and related drugs are helpful for short-term relief for minor sports injuries.

"Aspirin and aspirin-like compounds reduce temperature and inflammation, and relieve pain," says Karusaitis. "Some people, however, are allergic to aspirin, so they can take an analgesic that doesn't contain aspirin, such as acetaminophen, to reduce the pain and fever, though it has no anti-inflammatory action."

Lee Geismar, a chemist with FDA's division of over-the-counter drug evaluation, voiced concern over any medication's potential to "cover up" pain and allow people to ignore a serious injury. Geismar explains, "That's why the label says '10 days.' After 10 days, if you still feel pain, it's not a minor injury. It might be serious, and should be seen by a doctor."

Mirkin went even further in cautioning injured athletes about using pain relievers at all. "They stop the pain," he explained, "but the prostaglandins that cause the pain

are part of the healing process. There have been studies indicating that blocking prostaglandins may inhibit healing. . . . You're better off taking nothing." He recommends rest and keeping in shape during recovery with a sport that stresses uninjured parts of the body.

A warning note: Aspirin—even children's aspirin—should not be given to children and teenagers suffering from or recovering from flu, chicken pox, or other viral illness. Use of aspirin in such cases has been associated with Reye syndrome, a rare but serious—and sometimes fatal—condition.

Experts are even less enthusiastic about topical treatments such as creams, ointments and liniments in treating injured muscles. FDA categorizes these treatments as "topical counterirritants": "externally applied substances that cause irritation or mild inflammation of the skin for the purpose of relieving pain in muscle, joints, or viscera distal to the site of application." In other words, the burning of your skin takes your mind off your aching muscles. As Geismar puts it, "It's like pinching your big toe so that you forget about your headache."

There is no scientific proof that topical treatments, even those that contain aspirin, ease aching muscles, though the rubbing or massaging of the area can itself be soothing. Since the medications often contain irritants, such as menthol, the label's caution against bandaging the applied area tightly or for too long.

If your sports injury is a blister, be sure to keep the top layer of skin in place for faster, less painful healing and to lessen the chance of infection. *The Complete Sports Medicine Book for Women*, by Mirkin and Mona Shangold, M.D., recommends removing the fluid by making a small hole at the edge of the blister with a sterilized needle, gently pressing the fluid out, applying antiseptic ointment, and bandaging the area. If redness or pus develops, consult a doctor.

Whatever treatment you choose, fitness experts are unanimous in agreeing that the injured area must be rested until the pain is gone, then gradually rehabilitated back to normal. "Unless the area of the injury is properly rehabilitated," cautions Nirschl, "you are at high risk for the same problem recurring."

With foresight, planning and care, you can prevent most sports injuries and treat some yourself. Sooner than you think, you can be out jogging on that favorite path once again, cautiously avoiding that pesky hole. ■

Nancy Karkowsky is a free-lance writer in Silver Spring, Md.



Getting Off on the Right Foot

"To thine own self be true," Shakespeare wrote, and a long, hard look at yourself is the first recommendation of experts in preventing athletic injuries. Determining realistic goals, choosing appropriate activities, starting out slowly, progressing gradually, and taking the time for proper warm-ups and cool-downs can prevent a lot of sports injuries. So will a few short and easy preventive measures.

"Before you start any exercise, sports, or fitness program, you need to educate yourself," advises Neil MacDonald, director of the Sports Medicine Center in Baltimore, "and the first thing to educate yourself about is yourself. A person has to realize that he's 35 years old and 20 pounds overweight, not a high-school athlete."

After having a complete physical examination, including a stress test and a family history, you can plan a fitness program that is suited to your individual needs and preferences. Anyone can benefit from a thorough check-up, but certainly if you are over 40 and have a history of heart disease or problems with overweight, smoking or drinking, a complete evaluation is essential before beginning a regimen of vigorous exercise. In addition, your attending physician might have some good ideas on how best to carry out your fitness program.

Before you can accomplish, or even begin, a fitness program, experts say, you must choose realistic goals: You must identify what you want to accomplish and tailor your exercise program to

those long-range aims. According to Robert Nirschl, M.D., assistant professor of clinical orthopedics at Georgetown University and medical director of the Virginia Sports Medicine Institute in Arlington, "Don't take up a sport to get into shape; get into shape to take up a sport. A 50-pound overweight man with an arthritic knee should get rid of the fat and strengthen his muscles to protect that weak knee before he takes up weekend racquetball, football or jogging."

Once you have set reasonable goals, you'll avoid a lot of injuries by starting out modestly and progressing slowly. "Going too far too fast is self-defeating," explains Nirschl. "You may get some short-term benefits, but you can't sustain that kind of performance, [and you might] get an injury; your whole fitness program ends in three days."

So, "you have to walk before you can run" is a good motto, both figuratively and literally. Indeed, MacDonald recommends walking rather than jogging to a lot of people these days, and even then he has them work up slowly. Even 10 minutes of vigorous exercise per day can help you maintain your health, though you can improve your condition substantially by working up to 30 minutes every other day.

MacDonald points out that non-athletes achieve maximum cardiovascular benefits from exercising vigorously for at least 30 minutes three to four times a week. Working out every day increases the "risk-benefit" ratio: The risk of injury may outweigh the fitness benefit gained.

Gabe Mirkin, M.D., advocates 48-hour recovery periods between strenuous workouts, and stopping activity if there is discomfort. An "alternate day" exercise program—allowing the body 48 hours to recover from workouts—can be accomplished in various ways, explains the fitness author and columnist. A young, athletic person might work out "hard/easy"—push himself or herself hard one day, easy the next. An older person might alternate sports, so as not to constantly stress the same parts of the body; someone over 50 might work out every other

day, and just rest or do some gentle stretching on alternate days.

Not only should your entire fitness program start out slowly and progress gradually, but each day's regimen should include a warm-up that gently brings your body up to a level where it can do vigorous exercise, and then a cool-down to return to a normal activity level. A few minutes of walking, for example, might be a good way to begin and end each session of jogging. Stretching after warm-ups and cool-downs is also generally recommended.

Though most of us are busy and want to accomplish a lot in a short time, warm-ups, cool-downs, and stretching add only minutes to the regimen. In fact, if you are strapped for time, fitness experts recommend reducing the amount of time spent on vigorous exercise, rather than cutting out warm-ups, cool-downs, or stretching. They not only help prevent injuries, but help the body exercise and function more efficiently in the long run.

Michael McGinnis, M.D., deputy assistant secretary for the U.S. Office of Disease Prevention and Health Promotion, suggests some general measures to help prevent sports injuries:

- Wear properly fitting shoes.
- Walk or run on familiar, well-known routes.
- Drink plenty of fluids.
- Don't run in the heat of the day.
- Don't run at night or twilight, or, if you must, wear reflectors and light-colored clothing.

Also, wear clothing appropriate to the weather. Simply wearing more or fewer layers of clothing can prevent hypothermia—the extreme loss of body heat—or hyperthermia—too much body heat.

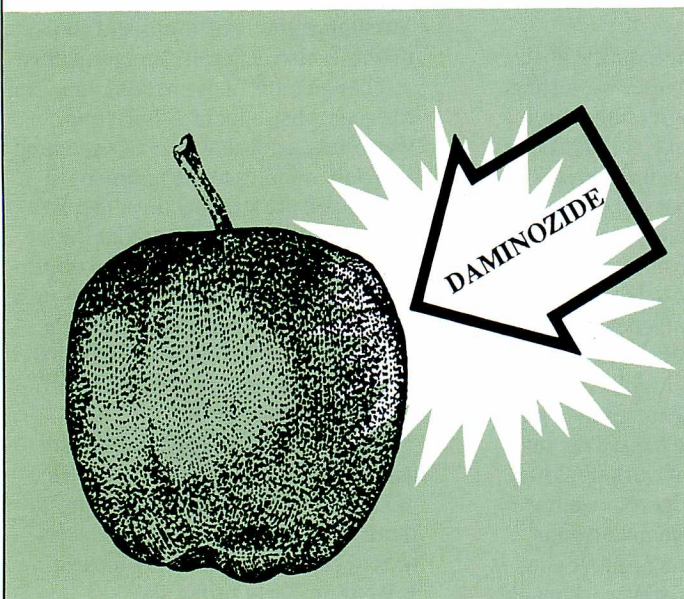
Wearing clothing with no seams or soft seams can prevent chafing and irritation of the skin. Wearing properly fitting shoes and the right thickness of socks can also prevent blisters, another common sports injury. ■



The Notebook

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

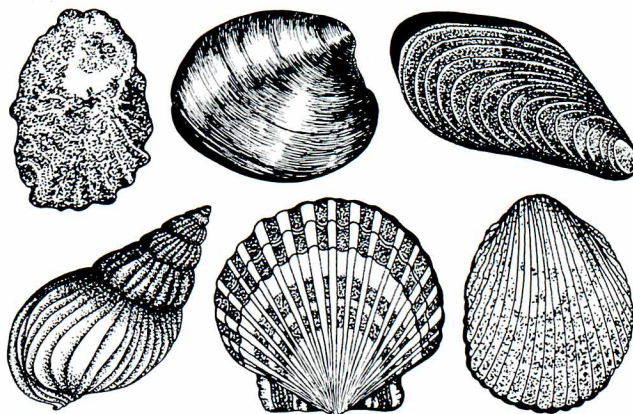
- The Environmental Protection Agency has proposed banning the use of **daminozide**, trade name Alar, which has been used to enhance the growth and appearance of apples.



- Diagnostic medical devices using **magnetic resonance imaging** technology have been reclassified by FDA from Class III (need pre-market approval) to Class II (must meet performance standards) (FR Feb. 1).
- After Feb. 2, 1990, packaging for two-piece hard gelatin capsules sold over the counter must have at least two **tamper-resistant** package features (FR Feb. 2).
- The National Aeronautics and Space Administration has petitioned FDA to amend food additive regulations to allow **radiation processing** of beefsteaks for use in space flight meals (FR Feb. 6).
- Standards of identity for **pasteurized process cheese** spreads have been amended to allow use of nisin as an antimicrobial agent (FR Feb. 8).
- A list of **new animal drugs** approved before last year's enactment of the Generic Animal Drug and Patent Term Restoration Act is available from the Industry Information Staff, Center for Veterinary Medicine, HFV-12, FDA, 5600 Fishers Lane, Rockville, Md. 20857 (FR Feb. 13).

Also available from that office is a new FDA compliance policy guide, covering conditions in which regulatory letters will be issued in the illegal sale of veterinary prescription drugs (FR Feb. 21).

- The Lastac System, a **catheter using laser energy**, made by GV Medical, Inc., Minneapolis, has been approved by FDA for surgical removal of arterial plaque as an alternative to conventional angioplasty (FR Feb. 13).
- A list of the names, approved uses, and makers of **orphan drugs and biological products**, is now available from the Dockets Management Branch (HFA-305), FDA, 5600 Fishers Lane, Rockville, Md. 20857 (FR Feb. 16).
- Revisions made during 1988 to the *National Shellfish Sanitation Program Manual of Operations, Parts I and II*, are available for \$100 from the Interstate Shellfish Sanitation Conference, P.O. Box 32777, Phoenix, Ariz. 85064 (FR Feb. 17).



- Mono- and diglycerides, diacetyl tartaric acid esters of mono- and diglycerides, monosodium phosphate derivatives of mono- and diglycerides, glyceryl monosterate, glyceryl monooleate, triacetin (glyceryl triacetate), and tributyrin (glyceryl tributyrate) have been approved for use as **food ingredients** (FR Feb. 21).

Minute Shrimp

by Dale Blumenthal

Usually an FDA investigation into a faulty product results in removal of that product from the market because it poses a hazard to health. But one recent investigation took a different twist. Some FDA microbiologists, acting on a scientific hunch, came to find that what appeared to be a problem was not. The product in question—fresh shrimp—was OK after all, as long as it was properly cooked.

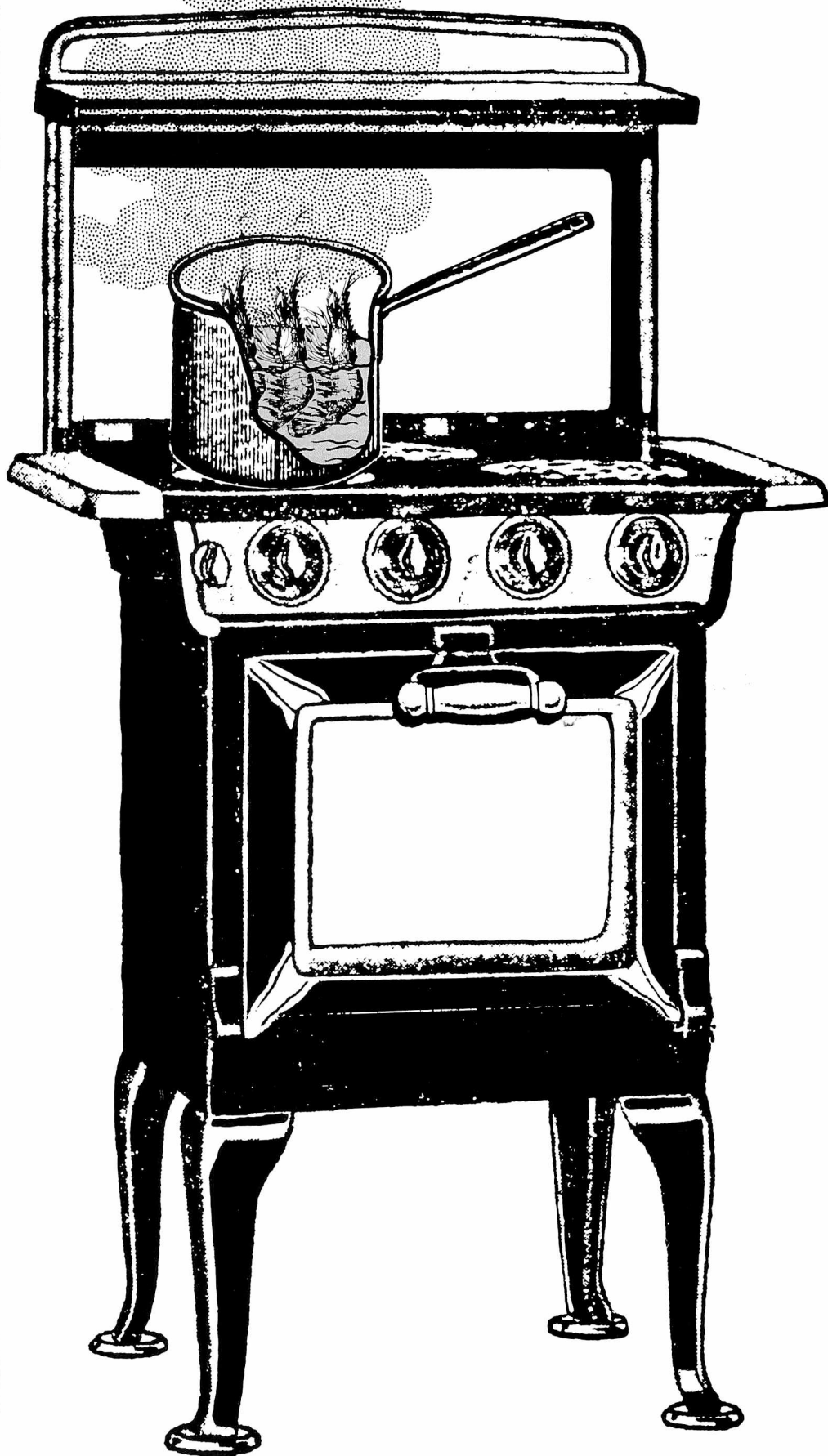
Steve Weagant, a member of the Seattle team, says that scientific curiosity prompted them to test a sample of imported raw shrimp for *Listeria monocytogenes*. Although the researchers had never before tested for this bacteria on raw seafood and had no reports of problems with *Listeria*-contaminated shellfish, they had reason to suspect it might show up in raw fish.

As Weagant notes, *L. monocytogenes* thrives in the kind of cold, moist environment that processing conditions for raw fish and some other foods provide. Soft cheese contaminated with the bacteria was responsible for the deaths of 47 people in Southern California four years ago. Other outbreaks of listeriosis, the disease caused by *Listeria*, were associated with consuming contaminated coleslaw and pasteurized milk that became contaminated after pasteurization.

Symptoms of listeriosis include fever, headache, nausea and vomiting. The infection is especially dangerous in elderly people, people with weakened immune systems (such as AIDS patients and those on cancer chemotherapy), and pregnant women (because of risk to the fetus). Weagant and his colleagues felt uneasy about the role of this potentially deadly bacteria in foods and, in June 1987, added a check for *Listeria* to the standard battery of tests run on shrimp.

Listeria monocytogenes was detected in the first test sample—raw shrimp imported from Taiwan. The Seattle scientists then tested frozen seafood products for *Listeria monocytogenes* and found the bacteria in 15 of 57 samples. Two of the positive samples were raw shrimp. (No illnesses were reported from consumption of any of the seafood.)

(continued on next page)



After the Seattle researchers' initial test, FDA scientists in other parts of the country began discovering *Listeria monocytogenes* in raw shrimp. It has turned up in shrimp imported from at least eight foreign countries and also from waters around the United States. Ginger Gipson, a microbiologist in FDA's Dallas district office, says that in the past year two samples of shrimp (one from Texas and one from Nigeria) have tested positive for the bacteria, and FDA microbiologist Miles Motes, from the Fishery Research Branch in Dauphin Island, Ala., said he found the culprit organism on shrimp collected from Eastern states.

Researchers in the Fishery Research Branch went to work to determine how to manage the problem. According to Anthony Guarino, chief of the Dauphin

Island laboratory, the first step was to determine whether *Listeria monocytogenes* was inside the shrimp or just on the surface. If it was inside—for instance in the shrimp's gastrointestinal tract—longer cooking times would be necessary to heat the interior of the shrimp to a temperature high enough to kill the bacteria.

Susan McCarthy, a Fishery Research Branch microbiologist, designed an experiment to compare the boiling time required to kill *Listeria* on contaminated shrimp harvested from the water with the time required to kill the bacteria in shrimp that have been injected with *Listeria* in the laboratory.

The experiment involved boiling both batches of shrimp for various intervals of from one to five minutes. Then, to determine whether any *Listeria* damaged by the

boiling could recover, she incubated cells from the shrimp at temperatures favorable to *Listeria* growth. Bacteria from the injected shrimp were able to recover even after being boiled for five minutes. However, after only one minute's boiling, none of the bacteria in the naturally contaminated shrimp survived.

The shorter time needed to kill the bacteria in the naturally contaminated shrimp suggested to FDA scientists that *Listeria* may be present only on the surface of the shellfish. Based on the laboratory findings, the researchers recommend that consumers only eat shrimp that has been boiled for at least one minute.

Dale Blumenthal is a member of FDA's public affairs staff.

Another Wrinkle in the Wrinkle Cream War

Trying to make a place for itself among producers of skin-care products has gotten St. Ives Laboratories, Inc., Chatsworth, Calif., to a place it didn't anticipate—in trouble with competitors and FDA.

St. Ives was among a number of companies FDA is investigating for promoting and selling products containing the acne-fighting drug tretinoin (a vitamin A derivative) with promotional claims that the products will reduce or reverse skin wrinkles due to aging or too much sunshine. This makes the products drugs, which require FDA pre-market approval. Such approval must be based on scientifically controlled studies that show the products are safe and effective treatments.



Tretinoin is only approved for use as a prescription acne drug. No studies of tretinoin products for wrinkles have been presented to FDA.

St. Ives Laboratories received a regulatory letter from FDA in August 1988 because the labeling on its product Retinyl-A suggested the cream would reduce visible signs of aging. FDA also said the labeling was misleading because of the similarity between the names Retinyl-A and Retin-A, which is Ortho Pharmaceutical Corp.'s FDA-approved prescription acne drug. St. Ives Laboratories agreed to remove from the product label a claim that it "helps reduce the visible signs of aging." It also agreed to play down the Retinyl name and change the label design (logo) of the unapproved product after Ortho and Johnson & Johnson, Ortho's parent company, sued for trademark infringement.

The proliferation of illegal promotions of tretinoin products as skin medications or anti-aging products is being monitored by FDA, state authorities, the U.S. Customs Service, U.S. Postal Inspection Service, and the Federal Trade Commission. Regulatory actions are likely where violations are found.

Not Like Mother Made

A health food it may have been, but a "quality substitute" for mother's milk? FDA said no, and a Michigan company's president has become the first person to be

found guilty and sentenced to prison for violating the Infant Formula Act of 1980.

Michael J. Potter, president of Eden Foods, a Clinton, Mich., health food producer, was sentenced in January 1989 to a year in jail and fined \$25,000 after pleading guilty to one count of violating the Infant Formula Act by misrepresenting the nutritional value of a soy milk health food product. All but 30 days of his jail term was suspended, but Potter will remain on probation for two years. Eden Foods, after pleading guilty on 12 counts, was fined the full \$111,000 permissible under the law.

In 1983, Eden Foods introduced a soybean product it named "Edensoy." The soy drink was described in promotional literature as free of cholesterol, rich in iron, and—under the heading of "Good for Babies"—as a "quality," "easily digested," and "preferred" substitute for mother's milk, suitable for children who could not tolerate dairy milk or other liquid or powdered formulas. By 1985, the new soy drink accounted for one-third of Eden Foods' \$5.5 million annual sales, and 35 percent of sales of all similar products in the nation's health food market, according to industry reports.

In the fall of 1983, an inquiry from the state of Maine first brought Edensoy's use as a food for infants to the attention of FDA. The Maine Department of Human Services was being asked to authorize payment for Edensoy as an infant formula, based on the sales claims. Maine authorities asked FDA's Detroit district office if

Edensoy was approved as a food for infants.

FDA investigators went to the plant in October 1983 and told Potter that his company's promotional claims made Edensoy an infant formula under the Food, Drug, and Cosmetic Act. As such, the product was adulterated because laboratory analysis of samples showed the soy drink did not contain the minimum levels of vitamins, minerals and protein specified for infant formula under the Infant Formula Act of 1980. If used as the only food fed to infants, the soy drink posed a risk of severe malnutrition, even death. Potter said he would stop promoting Edensoy as an infant formula. It appeared the matter was resolved.

But as late as 1985, the claim that Edensoy could be substituted for milk for children was still receiving credence. Based on the information in the original promotional literature, a Canadian pediatrician approved the product as the sole milk substitute for a 6-month-old patient. The baby had to be hospitalized and treated for undernourishment, rickets (vitamin D deficiency), xerophthalmia (eye problems resulting from vitamin A deficiency), and mild iron deficiency. And FDA investigators continued to find the promotional literature in health food stores, where they discovered that clerks were advising customers that Edensoy and similar soy drinks were suitable as food for infants.

Because of the illness in Canada—the

sole report of injury from Edensoy—Eden Foods voluntarily issued a nationwide Class I recall (meaning the product was potentially life threatening) of the promotional pamphlet. The company also agreed to place a warning notice at retail sales outlets, destroy remaining pamphlets, and change the product labeling to emphasize that it was not suitable as an infant formula or as a sole source of nutrition.

The company was charged with selling at least 53,482 cartons of the soy drink illegally as an infant formula between July 1983 and June 1985. The cases against both the firm and Potter were heard in the U.S. Court for the Eastern District of Michigan, in Detroit.

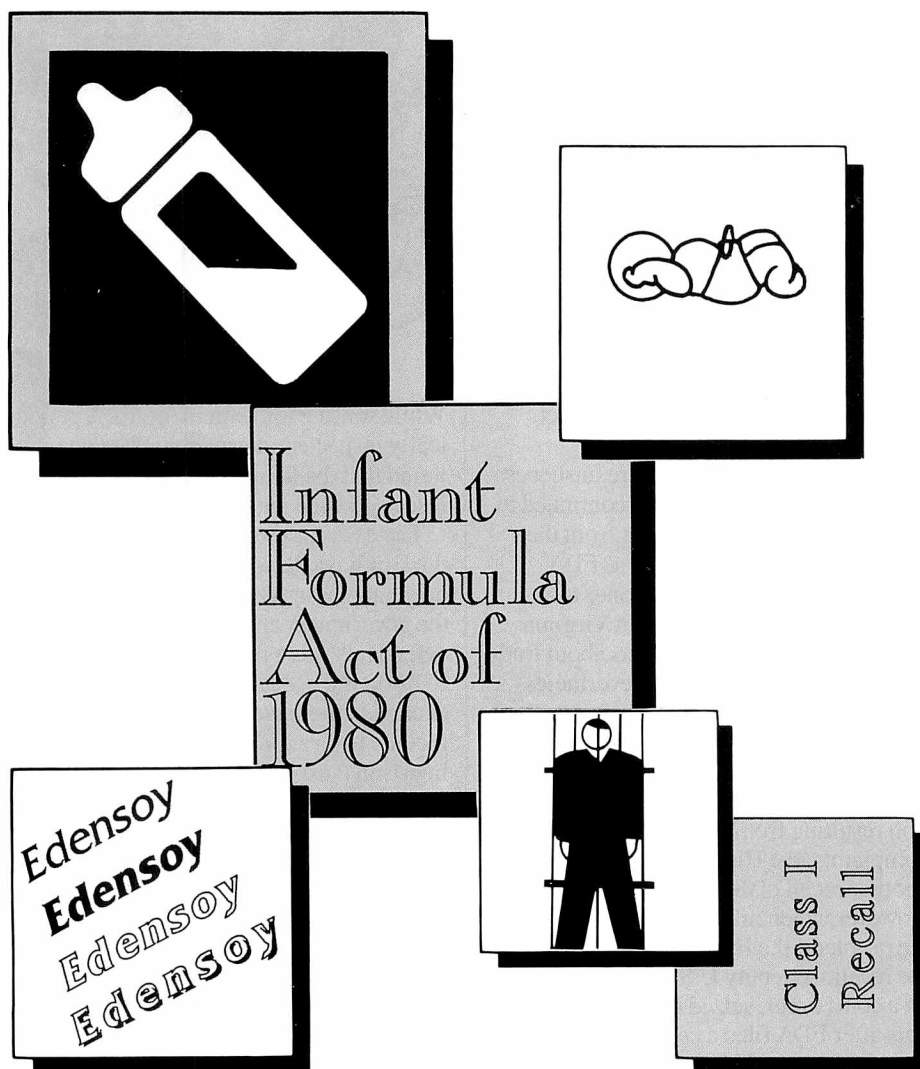
Buggy Nuts

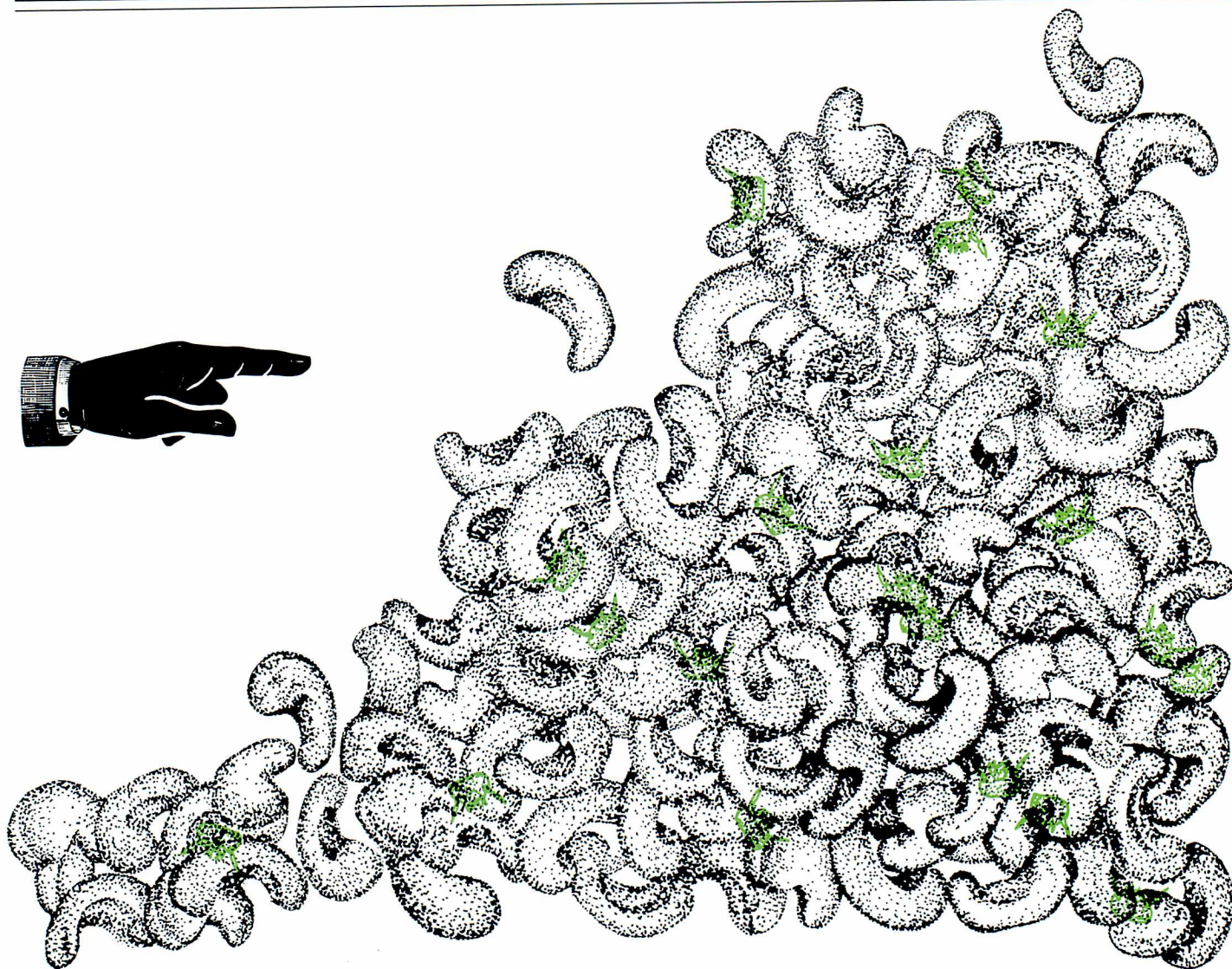
When FDA Boston district inspector Joseph Foley responded to a routine complaint concerning an allergic reaction to canned cashews, he found something unusual at the Massachusetts firm that processed the nuts. And, as the district's compliance officer Robert Crowell notes, "The unusual is what will surely capture the attention of an FDA inspector." The result, after more than four years of regulatory and legal work by FDA, was \$38,000 in fines for the responsible firm and its officers.

It all began in March 1984. During his inspection of the International Nut Corporation of Lowell, Mass. (now located in Billerica, Mass.), Foley found forty-three 25-pound tins of raw whole cashews placed aside, suspiciously wrapped in heavy plastic and electrician's tape, and marked as rejects. Foley learned that the remainder of the original 700-can lot was judged by the firm to be acceptable and had been processed and packaged for sale. He took samples of the rejects and of the finished product.

The problem was, according to Crowell, that "the 'good' nuts were as 'bad' as the rejected nuts." They all contained adult beetles, beetle larvae, insect excrement, insect fragments, and human hair. FDA recommended seizure of the nuts, but withdrew the proposal when the firm agreed to a recall.

Nearly four-and-a-half years later, following a series of inspections that regularly revealed insect filth in cashews produced by International Nut, the firm's officers—president Gregory Hintlian and treasurer Aram Hintlian Jr.—were found





guilty of shipping insect-infested food for sale out-of-state on eight separate occasions.

The violation of the federal Food, Drug, and Cosmetic Act resulted in a \$28,000 fine for the corporation and a \$5,000 fine for each of the Hintlian brothers. In addition, Boston U.S. District Court Magistrate Robert Collings put the company's officers on probation for two years.

Inspections over the four-and-a-half years had yielded an exotic collection of *Tribolium* adult mandibles, *Lepidoptera* cocoons, and *Oryzaephilus* larval heads. These are not field insects, says Crowell, but insects that find their way into food as a result of unsanitary storage conditions. The Hintlians initially expressed the desire to cooperate with FDA by recalling the insect-infested products, tightening quality assurance procedures, and reconditioning the tainted nuts. Reconditioning involves inspecting products for sale and

discarding the nuts that contain insect filth.

These efforts, however, were unsuccessful. The *Oryzaephilus* beetle continued to rear its larval head in cashews from the International Nut Corporation. FDA inspectors were not the only ones to notice. The agency's offices in Virginia received consumer complaints about finding bugs in the firm's nuts. Nevertheless, the 1984 complaint of an allergic reaction was the only illness reported in association with the nuts.

In April 1986, following another inspection resulting from one of the consumer complaints, the Hintlians agreed to another recall of the insect-infested nuts. However, when informed of the extent of the problem, the Hintlians later blocked the recall. A deputy U.S. marshal, acting on a court order, seized the contaminated nuts after FDA filed a complaint for seizure through the U.S. Attorney's Office.

While waiting for settlement, FDA periodically inspected International Nut and found that the firm continued to process insect-infested nuts.

The case came to court in June 1988, and the Hintlians decided to plea bargain. The original plea agreement reached between the government and the attorney for the defendants was a recommendation for the \$38,000 fine. Magistrate Collings expanded the sentence, however, to include two years' probation and one year in prison (suspended) because of the length of time over which the unsanitary conditions persisted. Collings warned the Hintlians that further violations could result in jail sentences.

— This small sample of reports from the field was prepared by Dale Blumenthal, Vern Modeland, and Gordon Scott.



Summaries of Court Actions

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

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

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

SEIZURE ACTIONS

Foods/Contamination, Spoilage, Insanitary Handling

PRODUCT: **Crab meat**, at Savannah, S. Dist. Ga.; Civil No. CV 488-141.

CHARGED 7-22-88: When shipped by South Coast Seafood, Inc., Berwick, La., the article had been prepared, packed and held under insanitary conditions—402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65512; S. No. 88-520-210; S.J. No. 1)

PRODUCT: **Peanuts, shelled**, at Boykins, E. Dist. Va.; Civil No. 87-851-N.

CHARGED 12-4-87: While held by Aster Nut Products, Inc., Boykins, Va., the articles contained rodent and insect filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65345; S. No. 88-500-615 et al.; S.J. No. 2)

PRODUCT: **Rice, and garlic**, at Mayaguez, Dist. Puerto Rico; Civil No. 86-1827 (JAF).

CHARGED 11-26-86: While held by Super Cash Food Center, Inc., Mayaguez, Puerto Rico, the articles contained rodent filth and had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65074; S. Nos. 87-512-121/2; S.J. No. 3)

PRODUCT: **Shrimp, headless, frozen**, at Pascagoula, S. Dist. Miss.; Civil No. S 87-0650.

CHARGED 10-16-87: When shipped by Matrix Seafood, Inc., Miami, Fla., the article, labeled "Product of Ecuador . . . Buckdix Pack Packed by: Estemar S.A.," was decomposed—402(a)(3).

DISPOSITION: The article was claimed by Sysco Corp., Houston, Texas, who denied the charge. The claimant served a request for documents on the government. Pursuant to stipula-

tion, post-seizure sampling of the article was authorized. After the article was sampled, a consent decree of condemnation ordered the article destroyed. (F.D.C. No. 65273; S. No. 87-494-553 et al.; S.J. No. 4)

Foods/Economic and Labeling Violations

PRODUCT: **Various syrups in retail jars and in unlabeled bulk cans**, at Seattle, W. Dist. Wash.; Civil No. C87-1070.

CHARGED 8-5-87: When shipped by Southern Farms Syrup Co., Inc., Philadelphia, Miss., and while held by Northwest Distributing Co., Inc., Seattle, Wash., who was repacking and relabeling unlabeled bulk syrups, the articles labeled "Pure Black Strap Molasses [or "Pure Ribbon Cane Syrup" or "Pure Sorghum Table Syrup"] . . . Made By Magnolia Syrup Co. . . . Magnolia, Miss." had had a sweetener from sources other than cane or sorghum substituted for the molasses, cane syrup, and sorghum syrup; such articles were offered for sale under the name of other foods; and the labeling of such articles was false and misleading because it represented that the foods consisted wholly of molasses, cane syrup, or sorghum syrup—402(b)(2), 403(a)(1), 403(b); the labeling of such articles and the other labeled articles (i.e., the article labeled "Pecan Table Syrup . . . Made By The Magnolia Syrup Co. . . . Magnolia, Miss." and the article labeled "A Gourmet Gift Package of Table Syrup . . . Made By The Magnolia Syrup Company . . . Magnolia, Miss.," which comprised a carton containing three jars of different table syrups) lacked required nutritional labeling information, and falsely represented that the foods were made by "The Magnolia Syrup Company . . . Magnolia, Miss." when such a company did not exist—403(a)(1); the unlabeled syrups in bulk cans lacked labels containing the name and place of business of the manufacturer, packer or distributor, and lacked an accurate quantity of contents statement—403(e)(1), 403(e)(2); certain labeled lots of syrup lacked accurate quantity of contents statements, since the label statements "Net Wt. Approx. 29 Fl. Oz." and "Net Wt. Approx. 16 Fl. Oz." were approximations for articles packed in containers of 17.2-fluid-ounce capacity and 12.7-fluid-ounce capacity respectively—403(e)(2); the quantity of contents declarations for the labeled articles was not in terms likely to be understood under customary conditions because such statements were unclear as to whether the net contents were expressed in terms of weight or fluid measure; and the label declarations of the manufacturer's name and place of business was inconspicuous because the declarations were in a type size less than 1/16 inch high—403(e)(2), 403(f); the lots of syrup labeled "cane syrup" and "sorghum syrup" failed to conform to the definitions and standards of identity for cane and sorghum syrups, since they consisted wholly or in large part of syrups from other sources—403(g)(1); the lots of syrup labeled "pecan syrup" and "Gift Package of Table Syrup" failed to conform to the definition and standard of identity for table syrups because their labels declared the presence of "pecan syrup," which was not the common or usual name of any food—403(g)(2); and the labeled lots of syrup were also in violation of the Fair Packaging and Labeling Act since the quantity of contents statements for all of those articles was not expressed, as prescribed by regulation,

in fluid ounces followed in parentheses by a declaration of the largest units of net quantity of contents, and since the quantity of contents statements appearing on the principal display panels were in a type size less than the prescribed 1/8 inch high—15 U.S.C. 1453(a)(3)(A)(i), 15 U.S.C. 1453(a)(3)(C)(i).

DISPOSITION: Default—ordered destroyed (constructive destruction by donation to charitable or government organization authorized). (F.D.C. No. 65230; S. No. 87-422-951 et al.; S.J. No. 5)

Drugs/Human Use

PRODUCT: Aspirin-combination capsule-shaped tablets, at Santa Fe Springs, C. Dist. Calif.; Civil No. 87-03682-JMI(Tx). **CHARGED 6-5-87:** The article, which contained no naproxen (Naprosyn), although it had been repacked by Stat-Pak Pharmaceuticals, Inc., Santa Fe Springs, Calif., with labels reading “Naprosyn . . . Tabs . . . Dist. By Stat-Pak Pharmaceuticals, Inc., Santa Fe Springs, CA . . . MNFD. BY: Syntex Puerto Rico, Inc.,” was a counterfeit drug, in that the tablet of the article and the article’s labeling, without authorization, bore the trademark, trade name, imprint, or likeness of a drug manufactured by other than the actual manufacturer—201(g)(2); and the labeling of the article falsely claimed Naprosyn as the active ingredient, when the article contained a mixture of aspirin and acetaminophen that were not listed as ingredients on the article’s labeling—502(a).

DISPOSITION: Default—ordered constructive destruction by turning over to FDA. (F.D.C. No. 65209; S. No. 87-412-813; S.J. No. 6)

PRODUCT: Nafrinse sodium fluoride tablets, Nafrinse unit-dose mouth rinse, Nafrinse powder packets, Premier sodium fluoride gel, and Premier prophylaxis paste, at Philadelphia, Pa.; Civil No. 87-4990.

CHARGED 8-10-87: While held by Medical Products Laboratories, Philadelphia, Pa., who manufactured the articles using interstate sodium fluoride, the articles had been manufactured and processed under circumstances that failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: Consent decree authorized release of the articles to the claimant (the manufacturer) for bringing the articles into compliance or for the articles’ destruction or disposal. The consent decree also provided that the claimant was to discontinue drug manufacturing upon FDA notice, if within two years there were certain specified failures of current good manufacturing practice, and that the claimant was then not to resume manufacturing until specified conditions were met. Ultimately, the seized articles were destroyed. (F.D.C. No. 65229; S. No. 87-458-981 et al; S.J. No. 7)

PRODUCT: “Pipracil” antibiotic for injection, at Cincinnati, S. Dist. Ohio; Civil No. C-1-86-1225.

CHARGED 12-9-86: When diverted from shipment to Honduras and relabeled with a counterfeit English label, the article (which

had originally been manufactured in Puerto Rico and labeled in Spanish, under the brand name “Pipril,” for distribution in Central and South America) was a counterfeit drug, since the article’s labeling bore without authorization the trade mark, brand name, and other identifying marks of Lederle Piperacillin, Inc., and since such labeling falsely purported that the article was labeled by that firm—201(g)(2); and the label’s control number (lot number) was incorrect and, thus, incapable of yielding the required manufacturing history of the article—502(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65073; S. Nos. 86-513-684/5; S.J. No. 8)

PRODUCTS: Shampoo kits and topical oil kits, each kit containing a bottle of shampoo or a bottle of emollient oils with a capsule of fluocinolone acetonide, at Orlando, M. Dist. Fla.; Civil No. 87-656-Civ-Orl-18.

CHARGED 7-17-87: When shipped by Mikart, Inc., Atlanta, Ga., the articles, labeled (carton) “FS Shampoo [or “Derma-Smoothe/FS”] (as dispensed) (Fluocinolone Acetonide) 0.01% Topical Shampoo Cleanser . . . [or “Topical Oil”] Distributed By: Hill Dermaceuticals, Inc. Orlando, Florida . . . Manufactured By: Mikart, Inc. Atlanta, Georgia,” were new drugs without effective approved New Drug Applications—505(a).

DISPOSITION: The articles were claimed by Hill Dermaceuticals, Inc., Orlando, Fla., owner of the articles, who denied the charge and asserted that the articles were generally recognized as safe and effective. Mikart, Inc., Atlanta, Ga., claimed the right to intervene in the action as the manufacturer of the articles. Subsequently, a new drug application for Derma-Smoothe/FS topical oil was approved; and the distributor and manufacturer of the shampoo advised FDA that the commercial manufacture and distribution of the shampoo had been discontinued. Thereafter, a consent decree of condemnation ordered the articles destroyed. (F.D.C. No. 65217; S. Nos. 87-447-667/8; S.J. No. 9)

Drugs/Veterinary

PRODUCT: Penicillin-streptomycin-vitamin veterinary mixture, two seizure actions, at Arab and Gainesville, N. Dist. Ga.; Civil Nos. CV87-C-0817M and C87-075G.

CHARGED 5-18-87 and 6-8-87: When shipped by Litchfield Distributing (Goldberg Industry, Inc.), Litchfield, Minn., the article, which was labeled “Stress Pak (Penicillin-Streptomycin-Vitamin Mixture) Agricultural Code of California: Hazardous,” was a new animal drug, and no approval of a New Animal Drug Application was in effect with respect to its use or intended use—501(a)(5).

DISPOSITION: In the seizure action at Gainesville, Ga., the government moved for and was granted permission to take post-seizure samples for further investigatory purposes. Subsequently, default decrees ordering destruction were entered in both actions. (F.D.C. Nos. 65184 & 65185; S. Nos. 87-508-545 & 87-537-041; S.J. No. 10)

Medical Devices

PRODUCT: Infra-red radiation therapy devices, and accessories, at Inola, N. Dist. Okla.; Civil No. 87-C-1055.

CHARGED 12-17-87: The devices, labeled "CEFCO Inc. Lacer Therapy . . . Lacer Stimulator Model: SSB-83," "Programmable Lacer Stimulator Model: PLS-4A . . . CEFCO," "Lacer R Stimulator Model PLS-2 CEFCO Inc.," "Lacer Stimulator Model: SSB-83A," and "CEFCO Inc. Lacer Stimulator Model: BPL-2," were accompanied by false and misleading instruction sheets making claims for treatment of disease conditions in animals, including reproductive and non-union fractures, acute injuries, cannon bone, edema, bowed tendon, pastern, ankle fetlocks, splints, muscular problems, reproductive (male or female) problems, and postoperative wound and lesions—502(a); and the labeling of the articles lacked adequate directions for use, because adequate directions for the articles' intended purposes could not be written, and the articles lacked the prescription legend— 502(f)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65287; S. No. 87-448-865; S.J. No. 11)

CRIMINAL ACTIONS

DEFENDANTS: Generix Drug Corp., Lewis Michael Orlove, president, and **Gary R. Dubin,** executive vice president, Hollywood, S. Dist. Fla.; Criminal No. 85-6007-Cr-Paine.

CHARGED 1-22-85 by grand jury and by superseding information following a plea agreement of 2-21-86: That the defendants knowingly conspired to defraud the United States and FDA by impairing, obstructing and defeating the FDA's lawful functions, as follows: (a) making and using false records, and (b) obstructing and impeding FDA's investigation and inspections of Generix, and that in furtherance of the conspiracy, a number of specified overt acts were committed by one or more of the defendants, including the removal and hiding of various prescription drugs and the falsification, alteration and hiding of a number of inventory records—18 U.S.C. 371; the president (Count 2), the executive vice president (Count 3), the executive vice president and a warehouse employee (Count 4), and an employee (Counts 5 & 6) were separately charged in counts involving the alteration and falsification of records concerning prescription drugs—18 U.S.C. 1001; and the defendants (Count 7) also knowingly obstructed and impeded FDA inspections of the Generix warehouse—18 U.S.C. 1505.

DISPOSITION: The defendants pleaded not guilty and demanded a jury trial. The defendants made more than 23 pre-trial motions. One of the defendants' motions was a motion for the production of copies of certain grand jury testimony. The government responded that, absent a "particularized need," such transcripts should not be turned over any earlier than they would normally be produced as Jencks Act material. The court denied that motion, and the defendants appealed.

Meanwhile, the government moved for and was granted an order

to compel compliance with outstanding subpoenas.

In another of the defendants' motions, the defendants asked the court to dismiss the indictment on the ground that the government had unfairly and prejudicially taken advantage of the circumstance that an attorney who had represented the defendants for some of the time charged in the indictment had terminated his representation of the defendants and had been hired by FDA. The defendants complained of delay on the part of the government in filing the indictment, and that, because of such attorney's government position, such attorney might be unable or unwilling to testify.

The court noted that disqualification of an entire government department because of a conflict of interest of a government attorney arising from his former employment would not be appropriate, and that dismissal on such grounds would be untenable. The court concluded that the defendants had failed to raise a genuine due-process claim over pre-indictment delay, and denied that motion to dismiss. Other of defendants' motions also denied by the court were the following: a motion for a bill of particulars; a motion to require a search for exculpatory materials by the department of government agencies; a motion for an inventory of rough notes; and a motion to dismiss the indictment due to governmental misconduct.

Subsequently, pursuant to a plea agreement, a four-count criminal information was filed charging only the firm and the president and executive vice president of the firm; and the original indictment was **dismissed** as to all defendants.

The corporation pled guilty to all four counts of the information, and the president and executive vice president pleaded guilty to one count each. The corporation was fined \$40,000, and was ordered to pay \$10,000 for costs of FDA's investigations; the president and executive vice president were each fined \$10,000; and these defendants were placed on probation until such fines and costs were paid. (Misc. No. 709; S.J. No. 12)

INJUNCTION ACTIONS

DEFENDANTS: Baders Dutch Biscuit Co., Inc., and Stephanie A. Chilton, owner and president, Seattle, W. Dist. Wash.; Civil No. C84-1343.

CHARGED 10-5-84 in a complaint for injunction: That the defendants, at their Seattle, Wash., plant, manufactured, packed and held various cookies made using interstate flour, sugar and other ingredients; that the defendants shipped their cookies in interstate commerce; that the defendants' cookies were prepared, packed and held under insanitary conditions—402(a)(4); that FDA inspections had disclosed a number of specified insanitary conditions and FDA analysis had identified insects and rodent filth in samples collected at the defendants' plant; and that the defendants were well aware that their plant was not in compliance with the law. **DISPOSITION:** Consent decree enjoined the defendants from further violations and enjoined the defendants from preparing, packing and shipping any food made using interstate components at

the defendants' plant, unless and until a number of specified conditions were met, including the cleaning and renovation of the plant, the establishment of a sanitation control program, and the examination, analysis and destruction or otherwise bringing into compliance of all food on hand. (Inj. No. 1079; S. No. 84-398-384 et al.; S.J. No. 13)

DEFENDANTS: **Generix Drug Corp.**, **Lewis Michael Orlove**, president, **Gary R. Dubin**, vice president, and **Ofelia Perez**, manager, Hollywood, S. Dist. Fla.; Civil Nos. 79-6655 Civ. NCR; (appeal) 80-5652, 80-5856, and 80-5857; (certiorari) 81-1222.

CHARGED 11-29-79 in a complaint for injunction: That the defendants, at their Hollywood, Fla., plant, were engaged in distribution in interstate commerce of "new drugs" that lacked effective approved New Drug Applications, and were engaged in packing, labeling, storing and distributing various interstate "new drugs" that lacked effective approved New Drug Applications (NDAs); that the circumstances under which drugs packaged and labeled by the defendants were packed, labeled and held failed to conform with current good manufacturing practice—501(a)(2)(B), 505(a); that FDA inspections revealed that significant and continuing deviations from current good manufacturing practice existed despite the defendants' representations that corrections either had been or were being made; and that the defendants had had numerous warnings regarding the marketing of new drugs without approved NDAs and regarding their failure to operate in accordance with current good manufacturing practice.

DISPOSITION: *District Court:* The court held that a generic drug product containing the same active ingredients as a previously approved pioneer drug was a "new drug," requiring an NDA only if there was a reasonable possibility that the differences in excipients between the generic product and the pioneer would make the generic product less safe and effective. The court held that the government was entitled to an order enjoining the distribution of the defendant's "Goldline" generic drugs containing allopurinol, spironolactone, furosemide, chlorothiazide with reserpine, amitriptyline, and diethylpropion hydrochloride, but the government's motion for a preliminary injunction was denied as to the defendants' drug products containing prochlorperazine maleate and chlorthalidone, as was the government's request for a recall. The government appealed.

Court of Appeals: The Court of Appeals vacated the District Court's injunction and remanded with instructions to dismiss the complaint. It held that the statutory prohibition against the sale of a "new drug" without prior approval did not apply to a drug product having the same active ingredients as a previously approved drug product, regardless of any differences in excipients. The Court of Appeals believed that the legislative history suggested that Congress had not intended to create a product-by-product licensing system and since the active ingredients involved in this action had all received approval in pioneer New Drug Applications, the government was entitled to no relief at all. However, the government petitioned and received a writ of cer-

tiorari to the U.S. Supreme Court.

Supreme Court: The statutory text had been misread by the Court of Appeals; that court's proposition that the statutory phrase "any drug" did not include a complete drug product (but only an active ingredient) was "simply untenable"; and the Supreme Court reversed the judgment of the Court of Appeals. The Supreme Court found that the statute's definition of "drug" was plainly broad enough to describe a completed drug product and cited the original 1906 Federal Food and Drugs Act as well as the following sections of the 1938 Federal Food, Drug, and Cosmetic Act: 201(g)(1), 501(a)(4), 502(e)(1), 505(b), and 502(i).

The Supreme Court did not reach the issue of whether two demonstrably bioequivalent products, containing the same active ingredients but different excipients, might under some circumstances be the same "drug." However, a generic drug product is a "drug" within the meaning of 201(g)(1), and is a "new drug" subject to 505 until the product (and not merely its active ingredients) no longer falls within the terms of 201(p).

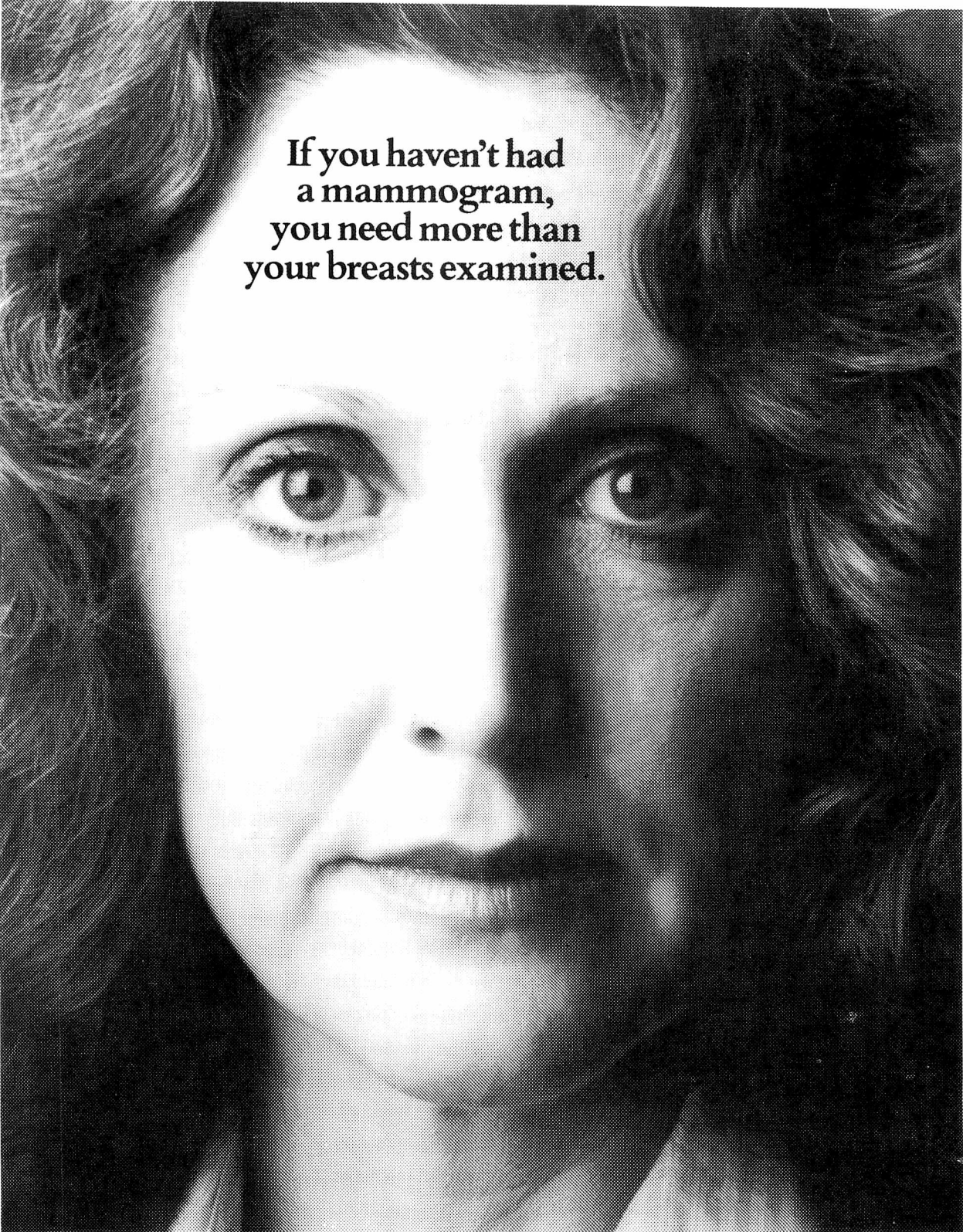
Remand: Upon the remand of the Supreme Court, the case was mandated to the Court of Appeals for further proceedings. The Court of Appeals vacated its earlier judgment, affirmed the District Court's preliminary injunction, and returned the case to the District Court for the fashioning of permanent injunctive relief consistent with the Supreme Court's opinion.

Ultimately, a consent decree of permanent injunction was entered which permanently enjoined the defendants from shipping any drug for which the defendants had received a specified notice that such drug was a new drug. (Inj. No. 918; S. No. 79-166-562 et al.; S.J. No. 14)

DEFENDANTS: **Waters Seafood, Inc.**, and **Clarence Leroy Waters Jr.**, president, Coden, S. Dist. Ala.; Civil No. 86-1030-P.

CHARGED 11-24-86 in a complaint for injunction: That the firm purchased and processed live interstate crabs and sells fresh crab meat to out-of-state customers; that FDA inspections revealed numerous insanitary conditions, including insect infestation, structure defects in the physical plant allowing insect ingress, and insanitary employee practices; that FDA laboratory analyses confirmed the presence of *E. coli* in the defendants' crab meat; and that the defendants had been advised of FDA's inspectional findings—402(a)(4).

DISPOSITION: A consent decree of permanent injunction enjoined the complained-of violation and enjoined continued interstate operations unless and until a number of specified methods, facilities, and controls were established, including the elimination of all insects, rodents and other vermin, the cleaning and renovation of the plant, and the establishment of a sanitation control program. In addition, an expert was to certify to FDA that adequate methods and controls had been implemented, and all food on hand was to be examined for contamination, necessary analyses were to be made, and all contaminated food was to be destroyed or otherwise brought into compliance. (Inj. No. 1161; S. No. 86-376-114 et al.; S.J. No. 15)



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