

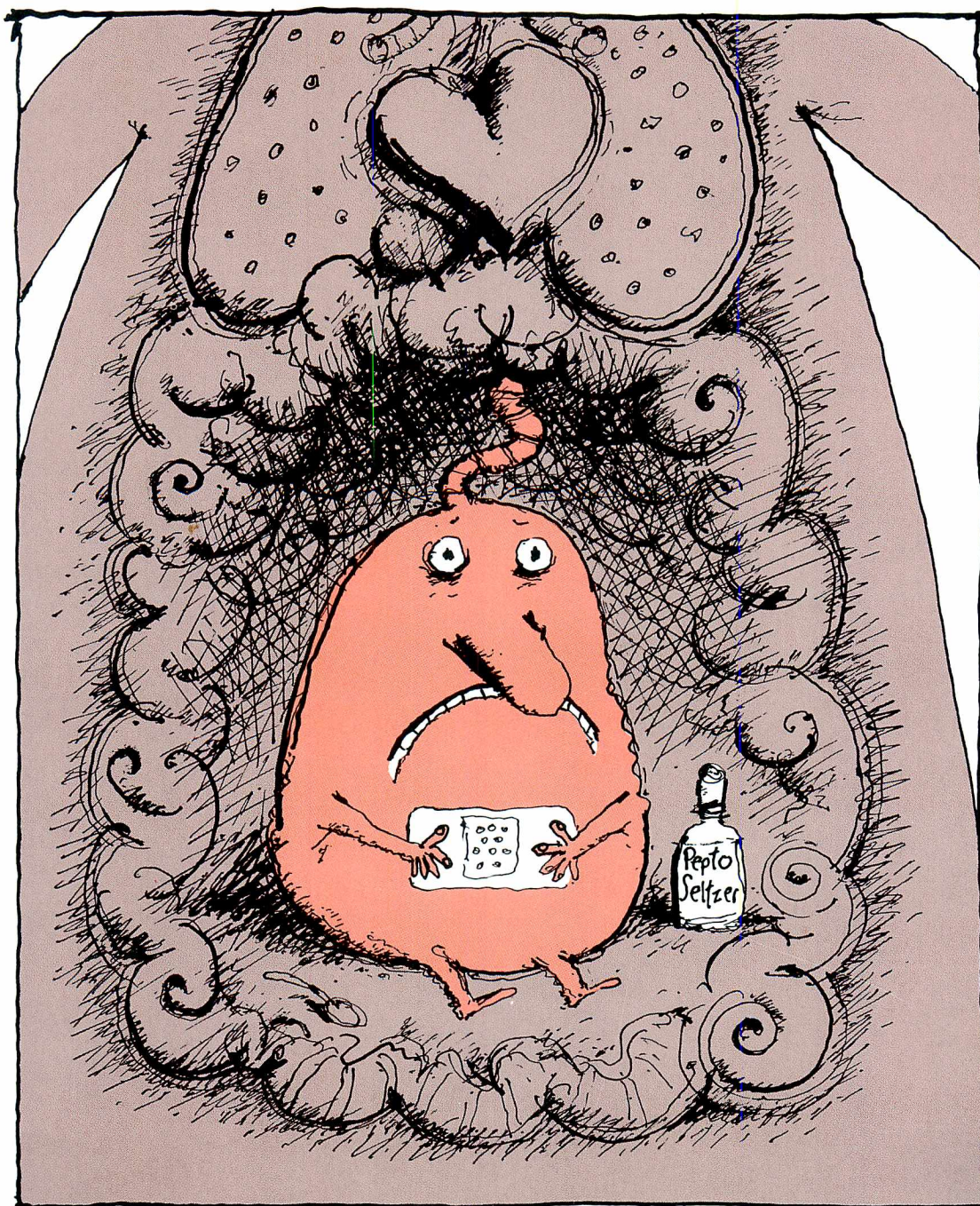
FDA CONSUMER

• VOL. 23 NO. 5

JUNE 1989 •

ULCERS

Screaming Or Silent, Watch Them With Care





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

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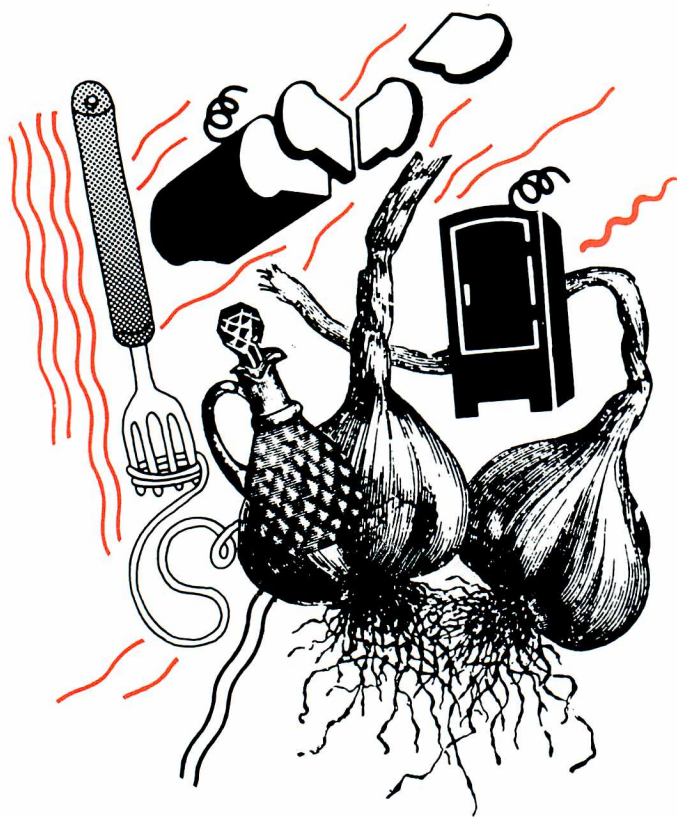
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Inside Front Cover Photo:

Only six weeks after conception, a human embryo has a beating heart and is forming a brain, blood vessels, a spine, and tiny arms and legs. But the road ahead can be risky. For information on how drugs can affect the developing fetus and how to avoid harm to the baby, see page 7.

(Photo courtesy of Photo Researchers, Inc.)



Get Rid of the Garlic, FDA Says

People who eat certain commercial or homemade chopped garlic-in-oil mixes that are left at room temperature risk getting botulism—a type of food poisoning that can be fatal, according to FDA.

Last April, the agency told manufacturers to stop making any garlic-in-oil mixes that require refrigeration for safety, and urged consumers to promptly discard any garlic-in-oil mixtures that do not contain microbial inhibitors. FDA also informed manufacturers that to be safe they must add microbial inhibitors or acidifiers such as

phosphoric or citric acid to prevent the growth of *Clostridium botulinum* bacteria in garlic-in-oil mixtures that they manufacture in the future. The bacteria produce botulin, the toxin that causes botulism.

FDA first issued a warning to consumers in March after three New Yorkers were hospitalized with botulism after eating bread that was spread with a commercial chopped garlic and oil mix that had not been kept refrigerated.

Investigation by New York health officials implicated “Colavita Chopped Garlic in Extra Virgin Olive Oil.” The manufacturer recalled the product but told New York officials that distribution was stopped more than a year ago. The mix was marked “Keep Refrigerated.”

Botulism is a potentially fatal food poisoning characterized by blurred or double vision, speech and breathing difficulty, and progressive paralysis. Without prompt diagnosis and appropriate treatment, one-third of those diagnosed may die.

Approval Criteria for Cancer Drugs

Safety and effectiveness assessments of new cancer drugs must factor in therapeutic gains other than lengthened survival, FDA said in agreeing with key recommendations developed by a National Cancer Institute advisory committee. The committee was organized after NCI’s Division of Cancer Treatment’s Board of Scientific Counselors met with FDA Commissioner Frank E. Young, M.D., Ph.D., and other FDA staff to discuss the agency’s drug approval process.

In evaluating a cancer drug’s efficacy, the committee said, patient survival should not be the only consideration. A drug that significantly improves symptoms and quality of life should be considered for approval, even if there is substantial toxicity. FDA and the committee agreed, however, that these gains should not come at the expense of “very much” survival.

FDA also agreed with the committee’s recommendation that although randomized, controlled trials comparing a new drug to a standard therapy are preferred, other study



designs are acceptable—especially in cancers that do not respond to standard therapy.

The recommendations basically reflect current approval practices for cancer drugs, the agency said.

Hypoallergenic Baby Formula? Maybe Not

FDA has notified three infant formula manufacturers that labeling their products as hypoallergenic could be false and misleading.

The agency asked Carnation (maker of Good Start), Bristol-Meyers (Nutramagen and Pregestimil), and Ross Laboratories (Alimentum) to submit sound scientific evidence that the products are hypoallergenic as claimed, or face misbranding charges.

All the products are safe and wholesome formulas, conforming to the agency's requirements for nutrient levels in infant formulas. Label claims that they are useful in managing severe food allergies, sensitivity to intact protein, and galactosemia (the inability to metabolize one milk sugar) are, however, unsubstantiated, the agency said.

In letters to the companies in January and February 1989, FDA cited flaws in several studies submitted in support of hypoallergenic claims for the companies' products. The supporting evidence was found to be inadequate.

Carnation has since announced it is changing the Good Start label by removing "hypoallergenic" from the front of the package.

Bristol-Meyers and Ross Laboratories have submitted more information to FDA for review.

Juiceless Apple Juice Convictions Overturned

Convictions of the two top executives involved in the largest case ever tried under food, drug, and cosmetic laws have been overturned on a technicality.

Beech-Nut Nutrition Corp., Canajoharie, N.Y., and its president, Niels L. Hoyvald, vice president, John F. Lavery, and two suppliers were found guilty in 1988 of more than 800 violations of federal law in the manufac-



ture and sale of millions of containers of sugar, water and flavoring marketed as "100 percent" apple juice (see "Juiceless Baby Juice Leads to Full-Strength Justice" in the June 1988 issue of *FDA Consumer*).

Hoyvald and Lavery were each sentenced to a year and a day in prison, but were freed on bail pending the outcome of appeals. Now, the U.S. Court of Appeals for the Second Circuit in New York has ruled that the Eastern District of New York federal court in Brooklyn, rather than the Northern District of New York federal court in Albany, should have been the location for the three-month-long trial.

"It was a very technical ruling and does not address their guilt or innocence," U.S. Attorney Andrew Maloney of Brooklyn said.

Prosecutors indicated further legal action is likely.

Progress Reports in the Battle Against Acquired Immune Deficiency Syndrome

FDA Panel Reviews New Data On Drug to Prevent Blindness

In May, FDA's Anti-Infective Drugs Advisory Committee reviewed new information on the safety and effectiveness of a drug that may be critical to the sight of many AIDS patients. The review will help the agency decide whether to approve the drug.

In the meantime, recognizing the need for patients to have access to the drug, the agency, the drug's manufacturer, and the National Institute of Allergy and Infectious Diseases have been working to ensure the drug is available to greater numbers of patients.

The information under review comes from studies FDA approved last November to evaluate the drug ganciclovir in treating cytomegalovirus (CMV) retinitis, an infection that can lead to blindness. CMV retinitis is one of several "opportunistic" diseases that plague AIDS patients because their weakened immune systems cannot fight certain organisms that healthy people ward off. The study designs were developed by ganciclovir's manufacturer, Syntex Corp. of Palo Alto, Calif., and the National Institute of Allergy and Infectious Diseases (NIAID) in response to a recommendation in October 1987 by the advisory committee, citing the need for additional controlled clinical studies to evaluate the safety and effectiveness of the drug.

Under the terms of the studies, patients at immediate risk of blindness from CMV retinitis were given ganciclovir. Patients whose retinitis was not immediately sight-threatening were enrolled in controlled trials: Some received immediate treatment; others had to wait for treatment, receiving it later if their condition worsened.

Pending a final decision on whether or not to approve ganciclovir for CMV retinitis, FDA is working with NIAID and Syntex to ensure that all patients with any stage of the disease can have access to the drug through an "open use" proto-

col. In this study, doctors must carefully monitor their patients and submit medical status reports to the sponsors on a regular basis. Physicians seeking information on any current ganciclovir protocols can call the Ganciclovir Study Center at (301) 497-9888.

New AIDS Treatment Studies

FDA recently authorized clinical testing of two experimental treatments—a vaccine and an anti-viral drug—for people infected with the AIDS virus (HIV).

VaxSyn HIV-1, which in August 1987 became the first experimental vaccine to be cleared for clinical testing to prevent AIDS infection, will now be studied as a means for bolstering the immune systems of HIV-infected people who have not yet shown symptoms of the disease. The genetically engineered vaccine contains a protein found on the surface of the AIDS virus. Its developer, MicroGeneSys Inc. of West Haven, Conn., will sponsor this new study, which will be conducted at Walter Reed Army Medical Center in Washington, D.C.

An anti-viral drug, SC48334, will be tested as a treatment for people with AIDS or advanced AIDS-related complex. The clinical studies, sponsored by the drug's manufacturer, G.D. Searle & Co. of Chicago, Ill., will be conducted at six test centers around the country.

New AIDS Blood Test Licensed

In March, FDA licensed the first filter paper procedure for use with an antibody test for the AIDS virus. With this procedure, small blood samples—usually drawn from finger or heel pricks—are collected on filter paper. This eliminates the need for drawing larger blood samples from the subject's vein and storing them in test tubes. Developed by Genetic Systems Corp. of Seattle, Wash., the procedure will be used in conjunction with the company's approved AIDS antibody test kit.

New AIDS Screen Voted Down

FDA's Blood Products Advisory Committee voted 8 to 1 against recommending licensing of an AIDS antigen test to screen blood donors. At a meeting on March 23, 1989, the committee concluded that the test—developed by Abbott Laboratories of Abbott Park, Ill., to detect the presence of proteins (antigens) found on the AIDS virus—is not significantly more reliable than the AIDS antibody tests already in use.

The committee also voted 8 to 1 against recommending licensing the test for screening blood plasma donors. According to the committee, current AIDS antibody tests and processing procedures to inactivate the AIDS virus in products made from plasma, such as Factor VIII concentrates (blood-clotting preparation used to control bleeding in hemophilia patients), already ensure safety.

In a 6-to-3 vote, however, the committee recommended that FDA license the antigen test for diagnostic and prognostic use in people known to carry the AIDS virus.

The advisory committee's recommendations, while not binding on FDA, will be considered by the agency in its review of the test.

No Risk of AIDS from Plasma

Universal screening of blood plasma for AIDS antibodies, combined with processes to destroy any AIDS virus in the plasma, has virtually eliminated the risk of transmitting AIDS through transfusion of blood-clotting preparations used to control bleeding in hemophilia patients. That is the reassuring message of studies presented at a meeting on March 9 and 10, 1989, cosponsored by FDA and the National Heart, Lung, and Blood Institute.



Health Talk With Dr. Frank Young

Product Labels: First-Line Protection from Harm

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

When safety concerns force a drug or a medical device off the market, many people recognize that FDA has done exactly what it's supposed to do. For example, when reports of liver failure associated with the blood pressure drug ticrynafen (Selacryn) and allergic shock caused by the pain reliever zomepirac sodium (Zomax) led to their removal from the market in the early 1980s, the general reaction was that FDA had taken the only appropriate action to protect the public.

But market withdrawal is certainly not the only way FDA can address such problems. In fact, most of the time we can ensure that the public safety is protected—which is our highest responsibility—by less dramatic but far more appropriate measures. Often we can resolve the problem through changes in the warnings and other information in the product's labeling. In

recent years, new labeling warnings have allowed a variety of valuable medical products to remain on the market, under conditions of safe use. Among recent examples: a drug to treat severe acne, another to control glaucoma, and a powerful medical device that allows physicians to "see" inside the body without potentially harmful X-rays.

These changes in product labeling—the FDA-approved information that doctors receive about a drug or device—are an important part of the agency's effort, not only to protect consumers, but also to improve the quality of health care.

In our work at FDA, labeling means a great deal more than just the information on the product's bottle or box. Where FDA-regulated prescription products are concerned, labeling includes detailed information that tells physicians and other health professionals exactly what the product is, how it works, what side effects it can produce, how it should be used, and who should—and should not—use it.

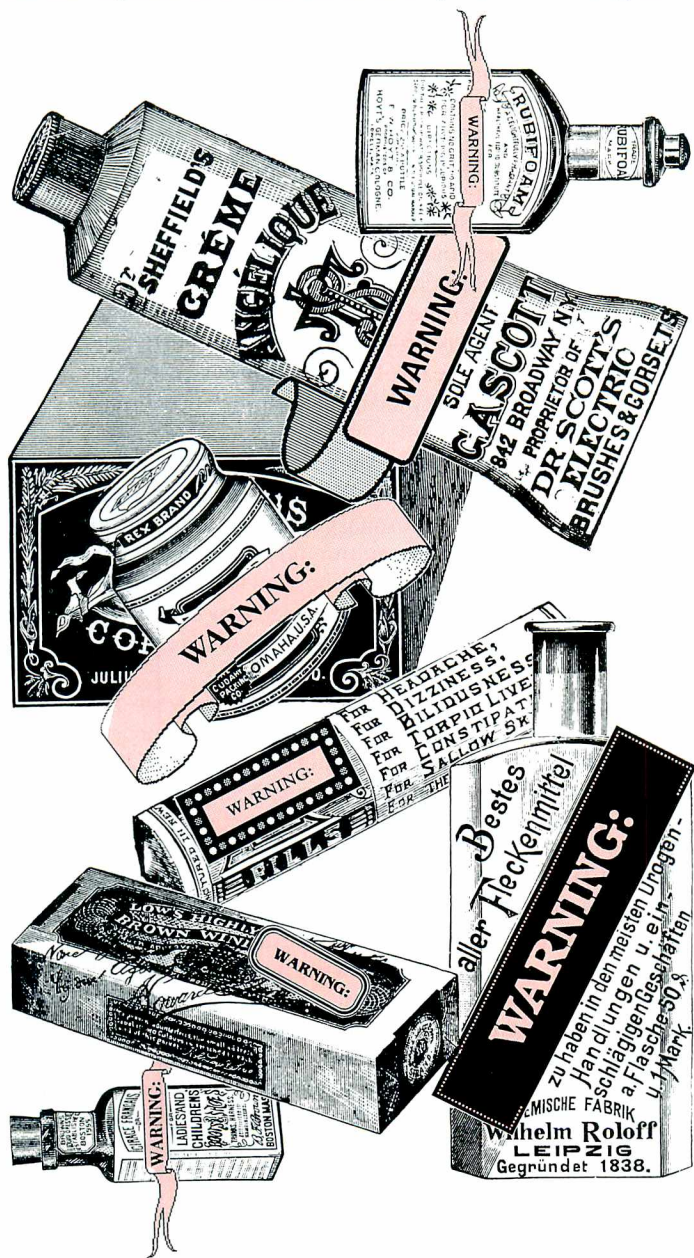
Before FDA approves a new drug or medical device for marketing, our scientists and health professionals work with the product's manufacturer to develop its official labeling. The labeling summarizes the results of scientific research on the product, including studies in humans to assess safety and effectiveness. But these studies, which seldom involve more than a few thousand people, can't generate a perfect picture of how a drug or device will behave when it's used by hundreds of thousands or millions of people. As a result, it's often hard to anticipate all adverse effects—those that may occur only once in 10,000 or more uses, for example, or those that will only be seen in children, pregnant women, or the elderly—groups not usually included in drug or device studies.

That means, of course, that in addition to being as sure as possible that a product is safe and effective before it is approved, FDA has to have in place systems to continue to monitor the safety of approved drugs and devices *after* they come into general use. As those systems disclose safety problems, we are able to take corrective action. And that usually is accomplished not by ordering a product off the market, but by making changes in the warning section contained in the product's labeling.

Let me use the drug monitoring system to illustrate how the process works, though a similar program applies to medical devices as well.

Since 1962, sponsors of drugs newly approved for marketing have been required to notify FDA of all reports of adverse reactions to their products. And since 1985, serious adverse reactions that are not mentioned in the approved labeling must be reported to FDA within 15 working days. A serious reaction is one that results in death or severe or permanent disability, requires hospitalization or prolongs the stay of someone already hospitalized, or is life-threatening. Reports of overdose as well as reports indicating the drug as a cause of cancer or birth defects are always considered serious.

In addition to mandatory reports forwarded by drug sponsors, FDA receives adverse reports directly from physicians and other health professionals. We encourage direct reporting because experience has shown it to be more complete and



more timely than reports channeled through drug sponsors. In 1988, the agency received some 52,000 drug adverse reaction reports, about 10 percent of which came to us directly from health professionals.

Each of those reports was checked against the agency's computerized adverse reaction reports data base. That not only tells us how many times a specific reaction has been reported, but also something about its rate. Is it occurring in one patient out of a hundred? A thousand? Ten thousand? Is it an adverse reaction that *is* described in the product labeling but is being seen more often than expected or under circumstances that the labeling doesn't mention? Or is the reaction one that the labeling doesn't mention?

If adverse reaction reports tied to a specific product accumulate, we are faced with an important question: Is the problem so serious that the product has to come off the market, or can we deal with it responsibly by adding a warning to the labeling or taking other steps to inform doctors and patients of the need to guard against the hazard? The recent history of an acne drug illustrates how serious and complex that question is.

When isotretinoin, or Accutane, was approved in 1982 for treating severe cystic acne unresponsive to other therapy, the labeling warned against its use by pregnant women. The reason: Animal studies had shown that the drug could cause birth defects. Soon after it came into general use, however, we began to receive reports of human birth defects associated with the drug. About 1 out of every 4 fetuses exposed to the drug was injured by it. Clearly, the warning against use by pregnant women was not being well heeded.

The labeling for Accutane was changed several times to strengthen the warning against use in pregnancy. The drug's manufacturer sent letters to physicians reminding them of the risk of fetal injury, and the *FDA Drug Bulletin*, which is mailed to more than 1 million health professionals, published articles advising physicians that Accutane should not be given to women of childbearing age who were not using birth control. *FDA Consumer* magazine also warned about the drug's risks. (See "New Warnings About Accutane and Birth Defects" in the October 1988 issue.)

We also sought expert advice from dermatologists, obstetricians, pediatricians, other federal agencies, and consumers. Opinion was sharply divided on whether Accutane should remain on the market. But it was our responsibility to decide. And we did decide—not to remove the only effective drug for the treatment of a serious, potentially disfiguring, and emotionally damaging disease, but to redouble efforts to alert health-care providers and the public about the risk of Accutane used by pregnant women.

The professional labeling for Accutane is again being revised to highlight the birth defect risk and spell out precisely the conditions for safe use of the drug in women of childbearing age. In addition, the patient labeling for Accutane is being modified to include a stronger warning, accompanied by an explicit illustration showing the kinds of birth defects that the drug can cause. We mean this as a powerful deterrent to women who might underestimate the drug's risk. The message that Accutane carries a 1-in-4 risk of fetal injury is emphasized in the patient labeling and in the consent form that both physician and patient must sign when the drug is being prescribed.

Labeling changes and other forms of information dissemination to address safety concerns are seldom as dramatic or as publicized as in the case of Accutane. Nevertheless, last year alone, adverse reaction reports reviewed by the agency flagged 52 possible safety problems with marketed drugs. Most of these were earmarked for continued close monitoring, but thus far, 26 have necessitated labeling changes. For example:

- The labeling for amiodarone, used to control irregular heartbeats, was changed to warn of the risk of inflammation of the testes and a lowering of the platelet count.
- Captopril, a drug for treating hypertension, was relabeled to alert doctors and patients that it could dangerously lower the sodium content of the blood.
- A broad-spectrum antibacterial drug, norfloxacin, was relabeled when it was found to cause inflammation of the small intestine and colon.
- A drug for gastric ulcers, famotidine, was relabeled because of its association with liver damage and anaphylaxis (an allergic reaction that can produce life-threatening shock).

Including such warnings prominently in the professional labeling enables doctors to watch for these adverse effects and modify the prescribed treatment if necessary.

Thanks to adverse reaction monitoring and evaluation in past years, drugs such as trazodone (Desyrel), used to treat depression, and timolol eye drops (Timoptic), to control glaucoma, have been relabeled to spell out newly discovered safety problems, and these valuable drugs continue to be available.

Medical devices, too, are monitored to detect and correct hazards. Although safety problems associated with devices are very different from those involving drugs, we have had important successes in meeting safety challenges through design and labeling modifications.

For example, in mid-1984, FDA received reports that two youngsters, aged 17 months and 23 months, had been strangled when the security top of a hospital crib failed to close properly. FDA and the crib manufacturer promptly notified hospitals of this potential hazard. We also collaborated to revise the crib's labeling so that hospital personnel would know exactly how to prevent the problem. To our knowledge, there have been no further accidents.

In a bizarre tragedy that occurred in 1985, a 63-year-old man was injured during examination in a magnetic resonance imaging (MRI) device. The powerful magnetic field generated by the MRI device dislodged tiny metal fragments embedded in one of the patient's eyes as a result of a previous occupational accident. He was blinded in that eye. To guard against a recurrence of this kind of mishap, FDA had the MRI device manufacturer relabel the equipment cautioning personnel to check for metal particles before patients are exposed to the MRI's powerful magnetic fields.

Our goals in requiring new label warnings instead of removing products from the market are, first and foremost, to be sure that the public health and safety are protected and, second, to allow useful products to remain available under conditions that promote their safe use. No drug or device is without risk. Recognizing that, we at FDA strive to be sure that risks are well disclosed when a product is approved for marketing and as it takes its place in normal health care. Patient safety is always our highest priority. ■

Drugs and Pregnancy: Often the Two Don't Mix

by Evelyn Zamula

In the summer of 1986, a group of scientists gathered in Boston to discuss — and to commemorate — an event that ruined lives, tore families apart, and left thousands of women with unbearable feelings of anguish and guilt. The occasion was the 25th anniversary of the recognition that the drug thalidomide was a potent producer of birth defects.

One of the speakers at the conference was a young Canadian scientist who had first-hand knowledge of the effects of the drug. Because his mother took the sedative during her pregnancy, he was born with no feet and was missing fingers on both hands. He once asked his parents a disturbing question: If prenatal diagnosis had been available at the time of his birth and could have detected his malformations in the womb, would they have chosen abortion? They answered, “yes,” that based on doctors’ opinions at that time, they would have aborted. But now they were glad they hadn’t because, besides their love for him and pride in his accomplishments, they had gained an empathy with those less fortunate than he.

If that was a bright note in the thalidomide epidemic, there were few others. Although U.S. babies were almost entirely spared thalidomide’s devastating effects—FDA drug reviewer Frances O. Kelsey, M.D., did not approve the manufacturer’s

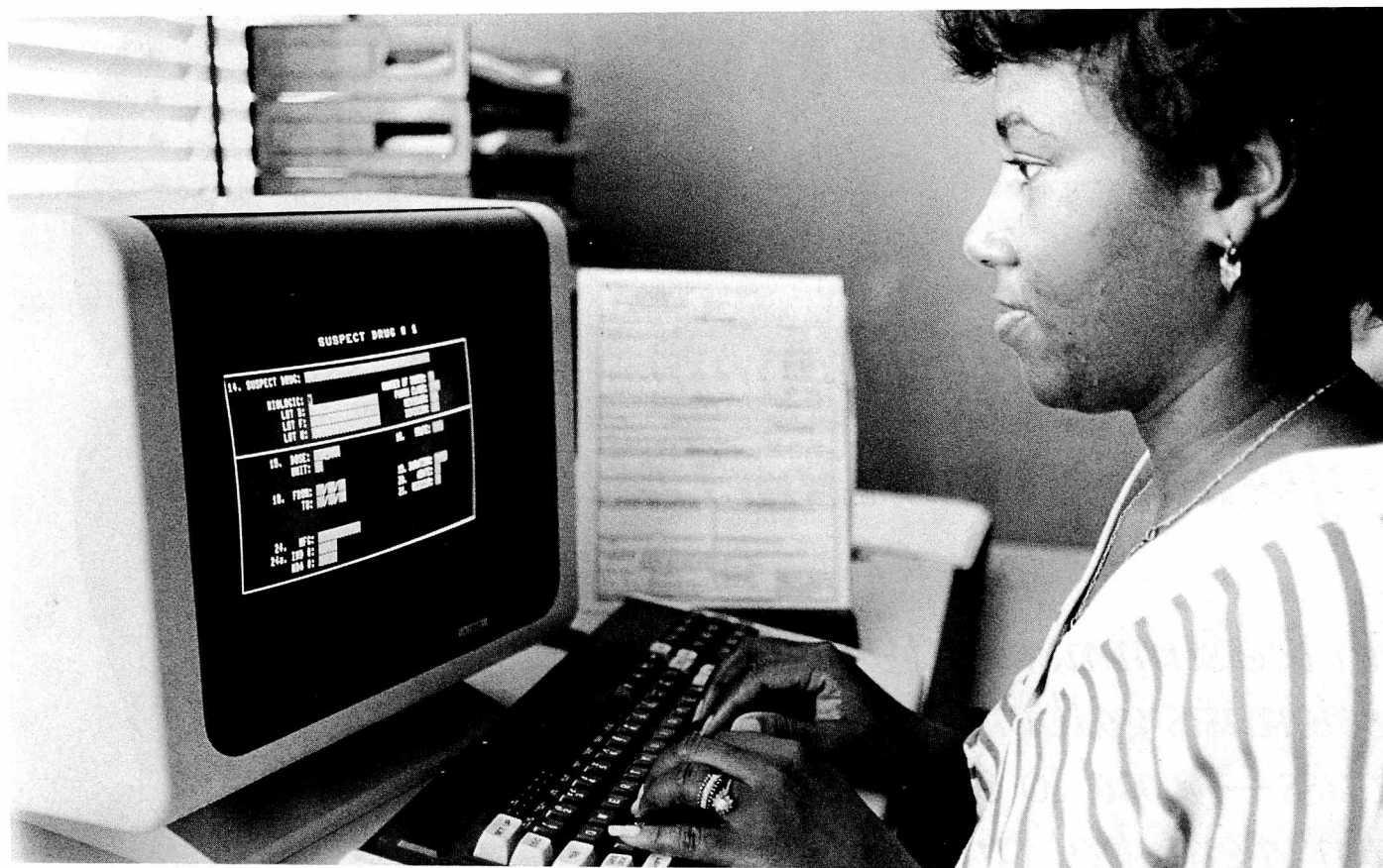
application to market the drug here—in some countries deformed children were abandoned by their families to be raised in institutions, and it is believed that some were even left to die. About 40 percent of the nearly 6,000 known cases of thalidomide children—born between 1956 and 1963—have already died.

Birth Defects Long Connected to Drugs

The unusual deformities caused by thalidomide generated worldwide publicity and focused attention on the fact that certain drugs taken at a critical time in pregnancy had the potential for damaging the unborn baby.

Before thalidomide, most birth defects were thought to be genetic, even though observers in the long-ago past had noticed the connection between drug-taking and birth abnormalities. Some of these ancient men of medicine were also aware that though drugs were most dangerous in the early months of preg-





FDA receives more than 50,000 written reports of adverse drug reactions each year from drug companies and health-care providers. Information about the patient, the suspect drug, and the reaction and its consequences is entered into a computerized data base. FDA scientists use the data to spot patterns of adverse reactions that may call for regulatory action, such as occurred with the acne drug Accutane. Reports of birth defects in children born to women who used the drug while they were pregnant led to strengthened label warnings against its use during pregnancy.



This 8-month-old baby has the characteristic features of fetal alcohol syndrome—narrow eyes, drooping eyelids, short upturned nose, and missing center groove above the upper lip. (Photo courtesy of Streissguth, et al., University of Washington, Seattle)

nancy, the fetus could be affected later, too.

The Greek physician Hippocrates wrote almost 2,500 years ago that for the safety of the fetus, drugs should be administered to pregnant women only from the fourth to the seventh months. In the second century A.D., the Greek physician Soranus of Ephesus warned women not to take drugs at *any* time during pregnancy, but especially during the first trimester. In particular, he maintained that when drugs taken to cause abortion did not produce the desired result, "let no one assume that the fetus has not been injured at all. For it has been harmed: It is weakened, becomes retarded in growth, less well nourished, and in general, more easily injured and susceptible to harmful agents; it becomes misshapen and of ignoble soul." (For an interesting fictional account of just such a case, read Robertson Davies' *What's Bred in the Bone*.)

According to the March of Dimes Foundation, each year more than a quarter of a million U.S. babies—or about 1 out of every 14—are born with birth defects. About one-third of the abnormalities are life-threatening, making birth defects—including low birth weight—the leading cause of infant mortality. A half million more potential lives are lost through miscarriage and stillbirth, usually because of faulty fetal development. About 1.2 million infants, children and adults are hospitalized each year for treat-

ment of birth defects. Birth defects contribute to the death of more than 60,000 Americans of all ages annually.

The causes of birth defects are unknown in about 65 percent to 70 percent of the cases; about 20 percent of the defects are genetic, or inherited. (Infections account for 2 percent to 3 percent of congenital malformations, maternal health problems for 1 percent to 2 percent, and chromosomal aberrations for 3 percent to 5 percent.) It is estimated that 2 percent to 3 percent of birth defects are due to chemicals or drugs, although it is suspected that the percentage may be higher since many women can't recall all the drugs they took during pregnancy. American women take an average of four prescription or over-the-counter drugs during pregnancy, plus vitamin and mineral supplements.

The effects a drug has on an embryo or fetus (the unborn baby is called an embryo up to eight weeks after conception and a fetus from then until birth) depend mainly on whether a drug has the ability to produce abnormalities, how much of it is taken, and at what point in the pregnancy it is taken.

A drug taken by an expectant mother enters her bloodstream and in most instances passes through the placenta to her unborn child. The drug then passes back through the placenta into the mother's circulatory system and is eventually eliminated. The placenta's normal function is to supply oxygen and nutrients to the fetus and to remove its waste products.

Timing Is Important

If a teratogenic (ter-ah-to-JEN-ik) drug—a chemical that can produce birth deformities—is taken in the earliest part of pregnancy (from conception until about 20 days), it will either cause the death of the embryo and subsequent miscarriage, or not affect it at all.

The possibility of harm to normal embryonic development is greatest from the third to eighth weeks, when the organs are forming. In the third week, the brain, heart and blood vessels start to develop and the spine begins to form; the arms and legs appear as tiny buds. By the fourth week, the heart starts to beat, even though the embryo is only a quarter-inch long. At five weeks, the first signs of hands and feet appear. At eight weeks, the arms and legs are separated into upper arm and forearm, thigh and lower leg; the two halves of the hard palate (roof of the mouth) unite.

From then on, the fetus grows and its systems mature. Teratogenic drugs taken after this period usually don't cause major structural defects, but they can affect growth and organ function. Particularly vulnerable is the unborn baby's nervous system, which continues to develop throughout pregnancy and in infancy. For example, the antibiotic streptomycin taken at even late stages in pregnancy may cause hearing damage in the baby. Other systems can also be affected. Tetracycline, another antibiotic, taken during the second or third trimester, when the fetus' teeth begin to calcify, will cause permanent staining of the baby teeth.

In some cases, drugs can have delayed effects. Diethylstilbestrol (DES), a synthetic estrogen widely prescribed in the 1940s to prevent miscarriage and other problems, came to be seen as a time bomb in the children of some of the 4 million to 6 million women who took it during pregnancy. Hundreds of young women who had been exposed to this drug as fetuses developed vaginal cancer after puberty. And a greater incidence of reproductive system abnormalities, such as undescended testes, also occurred in male offspring.

FDA requires that every new drug that may be used by women of childbearing potential be tested in pregnant laboratory animals before it can be marketed. (Because any untested drug presents a risk of harm to the fetus, pregnant women cannot participate in the human drug studies that are also required for pre-market

approval.) But animal testing alone is by no means foolproof; drugs in animals cannot be guaranteed to act the same way in humans. Drugs that cause birth defects in animals may not cause them in people. Conversely, a drug that may be harmful to the unborn baby may not affect animals, or may not affect them to the same degree. For example, humans are 100 times more sensitive to thalidomide than are rats, and 50 times more sensitive than are rabbits. If a drug causes defects in a wide variety of animal species, however, it's almost certain that it will cause them in people, too. (See "The Beginnings: Laboratory and Animal Studies" and "Testing in 'Real People'" in the November 1987 *FDA Consumer*.)

Post-Market Surveillance

After an approved drug is marketed, FDA continues to gather information about adverse effects from a number of sources. Drug manufacturers are required to report to the agency any adverse drug reactions they learn of; doctors do so voluntarily. The U.S. Centers for Disease Control collects reports from hospitals; and large monitoring studies both here and abroad—such as the Finnish Register of Congenital Malformations—gather and analyze information on birth defects. From this data, epidemiologists (scientists who study disease frequency and distribution) can detect a pattern between use of a certain drug and birth defects.

To date, this system has worked so well since its inception that nothing on the scale of the thalidomide tragedy has occurred in the United States, even though potent teratogens do exist. Isotretinoin (Accutane), for example, is an extremely effective treatment for severe cystic acne, but a known teratogen as well. Women are warned not to take the drug if they are pregnant or intend to become pregnant while undergoing treatment. They run a risk of spontaneous abortion and have at least a 25 percent chance of bearing a baby with birth defects, including outer ear malformations, heart and central nervous system abnormalities, and cleft palate.

Since its approval in 1982, Accutane has been labeled in pregnancy category X, meaning it should not be used during pregnancy. (FDA classifies prescription drugs in five pregnancy categories—A, B, C, D and X—based on teratogenic risk. Drugs in category A appear to be least harmful, while those in category X have risks that clearly outweigh the benefits.) Because FDA, CDC, and the manufacturer continued to receive reports of birth defects, warnings against using Accutane in pregnancy were considerably strengthened in 1988. Patients are now required to have a negative pregnancy test before starting therapy and are given a leaflet that contains a drawing of a baby with the birth deformities associated with Accutane.

Fetal Alcohol Syndrome

One drug—alcohol—is so commonly used that some people don't even think of it as a drug. But many experts consider it the most common teratogen in humans. Since more women and teenage girls than ever are drinking now—about 60 percent—and about a quarter of them drink heavily, this has ominous public health implications.

One to three out of every 1,000 newborns, or about 5,000 babies per year, are born with fetal alcohol syndrome (FAS). (A syndrome is a set of symptoms or characteristics that occur together with reasonable consistency.) The syndrome was first described in France in 1967 by a physician who noticed that children of alcoholic mothers shared such distinct characteristics that a diagnosis of maternal alcoholism could be made by just looking at them.

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In 1970, in the United States, a young pediatric resident at the University of Washington Health Sciences Center in Seattle had a similar experience. In reviewing newborns' medical records, she noticed that four babies of alcoholic mothers had abnormally low birth weights. Further search revealed seven more cases. When the 11 children were brought together to the Health Sciences Center for examination, researchers in the birth defects unit were struck by their resemblance to each other. Their heads were abnormally small, and they all had small narrow eyes, drooping eyelids, short upturned noses, and wide upper lips in which the normal center groove was reduced or missing. All were small for their age and all were mentally retarded.

Since FAS children do not usually improve in intelligence even when placed in foster homes, the damage points to alcohol rather than the family environment, which is usually poor. As many as 20 studies in various western countries indicate that FAS surpasses Down's syndrome and spina bifida (a birth defect in which part of the vertebral column is missing) as a cause of mental retardation. FAS children may also have defects of the heart and genital and urinary organs and may have poor coordination, short attention span, and behavioral problems.

Women who drink the equivalent of three ounces of pure alcohol daily—six average mixed drinks or six cans of beer—frequently give birth to babies with the full range of FAS defects. They are also more likely to miscarry or have stillborn children or children who die in early infancy. Those who drink less but still heavily (more than two drinks a day, according to the U.S. Surgeon General) may give birth to babies who have some, but not all, fetal alcohol effects. A new study points out that even two or three drinks a week may trigger spontaneous abortion. Since no one knows at which point in the pregnancy alcohol does the greatest damage or what amount can be consumed safely, pregnant women should drink no alcoholic beverages.

Cigarette Smoking

Among the warnings on packages of cigarettes is a statement that smoking may complicate pregnancy. Still, of the approximately 32 percent of women who smoke cigarettes before pregnancy, 25 percent continue to smoke while pregnant. While no specific malformations are connected with smoking, birth weight of babies born to smokers averages a half pound less than that of babies of nonsmokers. Low-birth-weight babies are 40 times more likely to die in infancy than those of normal weight. It is thought that nicotine, which constricts blood vessels, may reduce placental blood flow, and thus the amounts of nutrients and oxygen to the unborn baby. The March of Dimes states that some research has shown that chest breathing motion in an unborn baby temporarily decreases sharply after its mother has smoked only two cigarettes. Smoking may also increase the risk of miscarriage, stillbirth and death in newborns.

Drug Abuse

And then there are drugs of abuse. Paula Crews, a licensed clinical social worker associated with Sharp Memorial Hospital in San Diego, Calif., works with new mothers and their babies. "About 2 percent of the pregnant women in this area are abusing drugs," she says, "which isn't bad compared to some big city hospitals where it's as high as 30 percent or more.

"Cocaine, 'crystal' [methamphetamine], and heroin are the most popular, in that order, and marijuana is used in conjunction with all of them. Many drug abusers haven't had any prenatal care and walk in off the street to deliver. Some of them are high or drunk during labor and delivery. I feel sorry for their babies. The

minute the umbilical cord is cut, the baby is on its own. It must clear that drug out of its system. The most pitiful cases are the poor heroin babies, who have classic withdrawal symptoms after they're born. They have feeding problems, sneeze, are irritable, and sometimes have seizures. That's a terrible way to start life."

But the baby's problems are just beginning. "Cocaine users don't have much appetite and are malnourished," continues Crews, "so their babies have low birth weight. These mothers are so skinny that they hardly look pregnant even at term. Some don't make it to term, because cocaine users are at high risk for premature delivery. As far as birth defects go, we don't notice any more overt structural abnormalities among cocaine-exposed babies than usual, but they can sustain neurological damage, which is not apparent at birth, but which we pick up later in infancy and childhood. I've been told that some babies exposed to cocaine late in pregnancy have strokes *in utero* [in the womb] that can lead to retardation. When we *do* see malformations, we wouldn't have any idea if a drug is responsible, or which drug is responsible, because many of these women are multiple drug abusers, plus they drink and they smoke, and are often malnourished."

Medicines and Pregnancy

Women who *must* take known teratogens to treat a chronic underlying physical condition present a difficult case for their doctors. Drugs such as anticonvulsants used to treat epilepsy, antibiotics for tuberculosis, oral anticoagulants to prevent blood clots, anti-cancer drugs, drugs to treat an overactive thyroid, and lithium for manic depression are some substances that cannot always be avoided completely. Doctors must advise women taking these drugs—before they become pregnant—of the risk to the unborn baby and how that risk can be reduced. In some cases, it may be possible to withhold the drugs, if only for the first trimester.

For the best outcome, a little prevention is worth a pound of cure. Women who are pregnant or who think they may be pregnant should let their doctors know about their condition when drugs are being prescribed for them. They should take no over-the-counter (OTC) drugs (or prescription drugs left over from another illness) without consulting their doctors. OTC drugs, which look harmless sitting between the candy and housewares departments in drugstores, may not be harmless. Even a drug as commonly used as aspirin can prolong labor and alter bleeding and clotting time if taken in the last three months of pregnancy. Many OTC labels warn: *As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.* It's worth paying attention to those words.

It's often true that the critical period for the development of most organs in the unborn baby is over by the time a woman is sure she is pregnant. Nevertheless, it is comforting to know that even women who have taken a known teratogen during the first trimester have given birth to healthy babies free from deformities. Probably a majority of fetuses whose mothers took thalidomide—one of the most potent teratogens known—resisted the effects of the drug. (A recent British survey reported that babies born to women who had thalidomide-caused birth defects are having normal babies, which was expected.) Timing of exposure to a drug is crucial, of course, but some experts think that other factors yet unknown—though perhaps genetic—appear to determine a fetus' vulnerability to a drug's effects.

For the safest pregnancy, the most sensible course is not to drink or smoke, and to take drugs only if necessary and only on the doctor's advice. ■

Evelyn Zamula is a free-lance writer in Potomac, Md.

'Healthy Tan'—A Fast-Fading Myth



by Cheryl A. Sweet

Americans' rising health consciousness may finally be overriding their obsession to obtain an enviable tan. At the height of poolside-lounging sessions and a host of other sun-drenching activities, we're beginning to realize that soaking up the rays isn't as cheap as it once was. The cost of a bronzed body is growing steeper, as a sometimes-fatal skin cancer becomes alarmingly prevalent. Diagnosed in 1 of every 128 Americans, melanoma killed nearly 6,000 victims last year—a 93 percent increase in the number of cases since 1980. Particularly troubling is the deadly cancer's newest victims: While doctors once rarely saw melanoma patients under age 40, today people in their 20s are commonly treated for the disease.

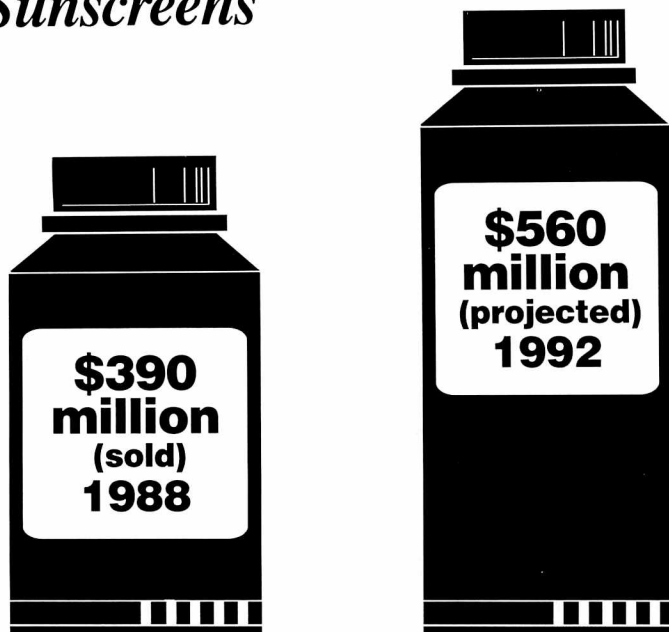
At the current rate, researchers estimate melanoma will strike 1 in every 90 Americans by the year 2000.

This year more than half a million Americans will develop melanoma and other less serious skin cancers, according to the New York-based Skin Cancer Foundation, a nonprofit organization that conducts skin cancer public awareness campaigns. The current skin cancer figure could double to more than 1 million annual cases during the next 25 years. Contributing culprits are unprecedented leisure time for outdoor activities, ozone depletion, skimpier summertime attire, population growth in the sunbelt states, and sunbathing binges.

But we're modifying our sun-worshipping

ways—perhaps in response to the grim cancer projections. According to a survey by the Skin Cancer Foundation and *Health Magazine*, 95 percent of 1,000 Americans interviewed believe repeated sun exposure leads to skin cancer, and 84 percent report using some kind of sun protection. Seventy-three percent say they have limited their sun exposure in the past two years, while only 12 percent report taking no precautions in the sun. A testament to these findings is sales figures on sunscreens, which have replaced tanning lotions as the hottest sellers in the sun-care market. Sunscreen sales hit the \$390 million mark last year, and the market is expected to continue to grow over the next five years—reaching \$560 million by 1992, according to Pack-

Sales of Sunscreens



aged Facts, Inc., a New York market research firm. Analysts say sun-care products now represent about 10 percent to 15 percent of the sales for major cosmetic companies today—at least twice the level of several years ago. Over the years, sun can irreversibly damage the elastin fibers in the skin, causing the sagging, wrinkling, and weather-beaten look associated with years of excessive tanning. But the major threat of excessive sun exposure is skin cancer.

In the early stages of the disease, skin cancer may not look like a growth; it can appear as just a discoloration of the skin. Particular attention should be paid to any changes in the size, color, shape or thickness of moles, birthmarks, or other irregularities. A spot or growth that begins to itch, hurt, crust, scab, erode, or bleed could signal a problem. The American Cancer Society recommends a monthly self-examination to detect early skin cancer warning signs. The best time for this is after a bath or shower, using a full-length mirror and a hand mirror to check moles, blemishes or birthmarks from the top of your head to your toes.

If a self-examination uncovers anything unusual, it is best to consult a physician. If the doctor is suspicious of the lesion, he or she will usually do a biopsy. This involves taking a specimen of the questionable lesion for laboratory analysis to determine whether the growth is benign, precancerous or cancerous. Major treatments for

precancerous and cancerous lesions include:

- **Excisional surgery** — the physician removes the growth and, for a safety margin, a surrounding border of normal skin. The surgical site is then closed with stitches, and the tissue is sent to the laboratory to determine if all the malignant cells have been removed.
- **Electrosurgery** — the diseased skin tissue is scraped with a sharp, ring-shaped instrument. Then an electrical needle is used to burn a safety margin of normal skin around the tumor and at the base of the area that has been scraped. The technique is repeated several times to ensure complete removal.
- **Cryosurgery** — the tissue is destroyed by freezing with liquid nitrogen.
- **Radiation therapy** — X-rays are used to destroy the diseased tissue.
- **Chemotherapy** — treatment with anti-cancer drugs may be used to treat malignancies that have spread to the lymph nodes, for example.

There are three types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. All have been linked to sun exposure. The most common is basal cell carcinoma, comprising about 80 percent of the skin cancers, or some 400,000 cases each year. Characterized by raised translucent nodules that may crust, ulcerate and sometimes bleed, basal cell carcinomas occur most often on the face and other exposed

areas of the body, but can crop up anywhere.

The next most common skin cancer is squamous cell carcinoma, with about 100,000 cases reported each year. The growths look like raised, pink, opaque nodules or patches, which often ulcerate in the center. They may grow anywhere on the body, but, like basal cell carcinomas, most often show up on exposed areas.

The most deadly skin cancer, malignant melanoma, usually appears as a small brown-black or larger multicolored patch, plaque or nodule with an irregular outline. Melanomas may crust on the surface or bleed. Detected early, the Skin Cancer Foundation says, all three skin cancers have at least a 90 percent cure rate. (For more on skin cancer, see "Out of the Bronzed Age," in the June 1987 *FDA Consumer*.)

With increasing awareness of the dangers of excessive exposure to the sun's damaging rays, more people are turning to sunscreens for protection. Sunscreens work by absorbing, reflecting or scattering ultraviolet light, thereby reducing the amount that reaches the skin. While sunscreens traditionally have been aimed at filtering ultraviolet B (UVB) radiation, future products are expected to offer greater protection against ultraviolet A (UVA) rays. UVB rays cause burning, tanning, and increased cancer risks, while UVA radiation penetrates more slowly and deeply into the skin, causing changes in blood vessels, creating sags and bags associated with premature aging, and adding to the cancer risk of UVB rays. Research on mice has shown that animals exposed to both UVA and UVB have a much higher incidence of skin cancer than those exposed just to UVB light.

Choosing a sunscreen is highly subjective. "You just sort of have to use your own judgment," says Jeanne Rippere, a microbiologist with FDA's over-the-counter drug evaluation division. "Look at your skin and know your history. If you burn readily with minimum exposure, you would want to pick a sunscreen with a higher SPF [sun protection factor], especially in a hot climate."

To maximize protection, it's important to apply the right amount of sunscreen. While most labels advise applying sunscreens liberally and often, this can be confusing since lotions, creams, gels, liquids, and sprays all cover the skin differently. Recent studies indicate that most people use only about half as much sunscreen as necessary for full protection. "As a rule of thumb, you'll get the labeled

SPF protection by using about an ounce to cover your entire body," according to a *Consumer Reports* article evaluating sunscreens. It is best to apply a sunscreen about 30 minutes before exposure so it can be absorbed and is less likely to be washed off by perspiration.

Many dermatologists recommend daily sunscreen use to protect against insidious sun damage. Ultraviolet rays don't feel hot, so it's easy to be lulled into a false sense of security if there is a cool breeze or overcast sky. But shade—or even thin clothing—offers little protection. Ultraviolet radiation can also reflect off sand and water, pass through gauzy robes and wet T-shirts, and penetrate several feet underwater.

Although a few cases of skin cancer are caused by overexposure to X-rays and by chronic exposure to chemicals such as arsenic, the chief villains are the sun's ultraviolet rays. Our bodies keep score on the amount of radiation we take in, and when the numbers get too high, the body reacts. Normally, if abnormalities occur during cell division, enzymes repair the damage. Radiation from too much sun, or another source, can put these enzymes out of commission.

Recent sunscreen developments include products that are greaseless, hypoallergenic, waterproof, or PABA-free. PABA, or para-aminobenzoic acid, is a once-popular sunscreen chemical that can irritate skin and stain clothing. The allergic reaction manifests itself as redness and itching about 24 hours after the sunscreen is applied. If you suspect you are sensitive to PABA, apply the sunscreen to a small patch of skin, preferably on the underside of the forearm, and cover the area with an adhesive bandage. After 24 hours, remove the bandage and expose the area to sunlight for 15 minutes. If you're sensitive to PABA, a reaction will appear the next day in the form of redness and swelling. Many sunscreens contain PABA derivatives, so if you're allergic to the chemical, look for PABA-free products with benzophenones and anthranilates. Allergies to these chemicals are less common. Moreover, these agents offer protection against both UVA and UVB rays, while PABA products protect only against UVB.

Marketers are also earmarking more waterproof sunscreens for children, who sweat more heavily than adults and dash in and out of water more frequently, thereby easily removing products that are not waterproof.

To help consumers select products best suited for their skin types, FDA worked

with several sun-care manufacturers from 1974 to 1976 to outline categories and procedures for determining sun protection factor numbers. In 1978, an FDA panel recommended SPF numbers from 2 to 15. The SPF number indicates the amount of protection the sunscreen provides against ultraviolet rays and sunburn. An SPF of 10, for example, enables a person who is likely to sunburn after half an hour's exposure to safely sunbathe for five hours, or 10 times longer than usual.

Until 1986, the highest sunscreen SPF available was 15, which is the highest number currently endorsed by FDA. Today, there are sunscreens with SPF numbers as high as 50. These products do not yet require FDA approval, since the agency is still evaluating whether to endorse higher SPF numbers. "This is a gray area," admits Rippere. "Many SPF numbers are exempt from legal action unless there's a safety problem." Rippere estimates an SPF decision will be reached in two years. Under current FDA consideration are whether higher SPF numbers are really necessary and whether testing procedures accurately determine SPF values, says Rippere. "We're pretty sure that testing procedures can accurately determine an SPF of 8, but we don't know if they can determine the effectiveness of a 30." Sunscreens with SPF numbers higher than FDA's allowable protection factor could ulti-

mately be pulled off shelves, says Rippere.

Meanwhile, debate continues on the necessity and effectiveness of higher SPF numbers. "I think there's possibly some justification for SPF numbers up to 30. For someone with very fair skin, a 15 might not be enough," says Rippere. "But I think you get a diminishing return when you get to higher numbers. SPF numbers of 49 or 50 are absurd, in my view." Besides the still-unanswered question of higher SPF effectiveness, there is concern that higher strengths cause increased irritation among people sensitive to the active ingredients in sunscreens.

Despite an increase in sunscreen use, only time will tell if America will be able to reverse its spiraling skin cancer rate. Some speculate it will take another generation for noticeable cancer reductions. While experts agree the media have done a good job of publicizing the sun-cancer link and some progress is evident, confirmed sun-worshippers nevertheless remain reluctant to forego tanning sessions. Perpetuating the problem is the long-held perception equating a suntan with status and a "healthy" look—a belief that's unlikely to fade as quickly as a tan. ■

Cheryl A. Sweet is a free-lance writer in Phoenix, Ariz.



Ulcers have frequently been the target for humor in describing the stereotypical aggressive, pressured, goal- or career-oriented person. But for those who have them, ulcers are no laughing matter. Peptic ulcers strike 1 out of every 50 Americans each year. There were 4,580,000 new cases in 1987, according to the National Center for Health Statistics.

Peptic ulcers, which are in the stomach and the duodenum (the first part of the intestine leading from the stomach) can occur at any age and affect both men and women. Untreated, sufferers can look forward to a long siege with them. But today's peptic ulcer sufferers have a brighter prospect for relief than did those of even a single generation ago. There's now less than 1 chance in 18 that surgery will ever be necessary. New medications act faster and better to assuage the fires within.

Symptoms Sometimes Silent

Ulcers in your upper digestive tract can be seen through an endoscope (a flexible, tube-shaped device using special light-reflecting properties to allow the doctor to see inside the body). They show up as crater-shaped sores, generally one-quarter to three-quarters of an inch in diameter. Ulcers may feel like little volcanic eruptions to some, but not all ulcers cause pain, particularly duodenal ulcers. Some people, especially the elderly and those who take nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, might never notice pain even though they have serious or repeated ulcer attacks. (See accompanying article, "NSAIDs and Ulcers.")

Once you've developed an ulcer, others are likely to appear in the future. Then, some research suggests, ulcer disease will "burn out," decreasing in severity or disappearing after about 7 to 15 years.

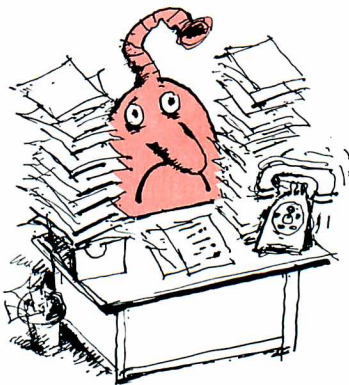
The warning sign of active ulcers you'll most likely experience—if you get any warning at all—is a gnawing discomfort in the middle or upper abdomen that typically comes between meals or in the middle of the night. Food or liquids, including antacids and milk, can provide temporary relief, but milk might not be all that good a remedy since it stimulates production of hydrochloric acid and other digestive juices responsible for the pain.

Antacids, blended from aluminum, calcium or magnesium salts, have long been the nonprescription drugs most people reach for to get quick relief from pains in their stomachs. But, because antacids interfere with absorption of some medications, be sure to tell your doctor you're taking them.

ULCERS

Screaming Or Silent, Watch Them With Care

by Vern Modeland



Don't Take an Ulcer Lightly

You should never ignore any warning signs of ulcers. Ulcer complications are serious and can be life-threatening. If pain persists after more than 10 to 14 days of self-treatment or comes back when self-treatment ends, you should see your doctor. Black or tarry stools, while possibly caused by something else, can be an urgent warning of a bleeding ulcer. Vomiting, or frequent reflux of stomach secretions or recently eaten food, may mean that ulcer scar tissue is blocking the duodenum, stopping food from moving out of the stomach.

Bleeding ulcers can cause anemia or, if the ulcer crater expands into a major blood vessel, a leak can turn into a hemorrhage, with only minutes available for life-saving emergency treatment. Ulcers can also perforate—erode completely through the wall of the stomach or duodenum. If this happens and the stomach's contents flow into the abdominal cavity, severe infection can result. A perforated ulcer is an emergency that requires immediate surgery.

The Causes

There's mounting evidence that something other than smoking, drinking, spicy

meals, or a battle with the boss may be associated with ulcers. It could be a bug that bothers your belly: *Campylobacter pylori*.

C. pylori is an S-shaped bacterium with whip-like appendages (flagella) that it wiggles to scoot about in the slurry-like environment of the stomach's inner surface cells. While rarely found in people under the age of 20, *C. pylori* may infect more than 60 percent of Americans over age 65, researchers say.

The bacteria thrive in clusters among surface cells that line the digestive tract. Irritation caused by the organisms seems likely to lead to gastritis (inflammation of the stomach lining). Whether it also is a precursor of stomach and duodenal ulcers and precancerous conditions is not known for certain. Ulcers appear to be the result of a combination of conditions, the dynamics of which researchers don't fully understand.

Was It Something You Ate Or Something Eating You?

Here's some good news. Spicy pizza and peppery Mexican meals may not pose the risk of long-term damage to your stomach that they've long been blamed for. David Y. Graham, M.D., of Baylor College of Medicine in Houston, Texas, and others studied the effect of spicy foods in a dozen people with normal, healthy digestive systems. They reported in the Dec. 16, 1988, *Journal of the American Medical Association*, that no damage to the digestive tract was observed in the study subjects for up to 24 hours after they had eaten the spicy foods. Current thinking on ulcer diets is this: If a food bothers you, don't eat it. If you favor spicy foods, though, don't assume you have to deny yourself the pleasure just because you have an ulcer.

Another study, published in the February 1988 issue of *Gastroenterology*, reinforces an old but sound idea—that it is not what you're eating but what's eating you that is a major contributor to ulcer disease. This study in Texas and California examined the mix of smoking, drinking alcoholic beverages and coffee, and taking aspirin in a group of men with ulcers. Researcher Pamela Walker, and colleagues concluded that, among those studied, it was emotional stress—"not so much a function of their life events as the unique way that they react to these events"—that distinctly set apart those with ulcers from those without them. The study found no connection between ulcers and coffee or alcohol.

Smoking, however, doubles your risk for ulcer disease, many physicians and

researchers have found. Ulcers heal more slowly for smokers, and smokers also have a higher relapse rate.

And you're definitely at risk for ulcers if you take NSAIDs. High-dose aspirin, ibuprofen, naproxen and piroxicam are among NSAIDs in wide use today for many conditions, especially to relieve pain and swelling among the millions of people who have arthritis. These medications can irritate the stomach's lining and cause gastrointestinal bleeding.

What Helps and How

Last December, FDA approved a new medication that targets the dangerous side effects of NSAIDs. It is misoprostol (trade name Cytotec), a synthetic prostaglandin that controls the amount of acid secreted by the stomach and helps replace substances in stomach tissue that are depleted by NSAIDs.

Another category of prescription drugs called histamine-receptor antagonists, or histamine blockers, has helped build a \$2.2 billion business in making antacids and ulcer drugs. Histamine blockers reduce the amount of hydrochloric acid that a billion or so cells in the stomach turn out to digest food. They also affect cholinergic agents, the chemicals that transmit electrical impulses carrying messages between cells, and the secretion of gastrin, which stimulates production of gastric juices. Cimetidine (trade name Tagamet), famotidine (Pepcid), misoprostol, nizatidine (Axid), ranitidine (Zantac), and sucralfate (Carafate) are prescription histamine blockers approved by FDA to treat ulcers.

When No Drug Works, What Then?

Surgery is the "big hammer" medical option in the treatment of what the doctor calls intractable peptic ulcers—ulcers that do not respond to medical treatment. But, thanks to modern medications and improvements in medical management, fewer than 2 out of every 100 Americans who had ulcer disease in 1987 required surgery.

For patients who do require surgery, the most common procedure is a vagotomy. The surgeon severs branches of the vagus nerve that stimulate part of the stomach to make acid.

For more severe or recurrent ulcers, the surgeon may opt to do a gastrectomy in addition to the vagotomy. The surgeon removes as much as two-thirds of the stomach, then attaches the remaining part to the small intestine. The modified stomach will eventually stretch to make room for nearly the same volume of food the patient is accustomed to eating, but

(Continued on page 17)

NSAIDs and Ulcers

"The incidence of ulcers with complications appears to be rising among my older patients, particularly those who take nonsteroidal anti-inflammatory drugs," says Alex Hover, M.D.

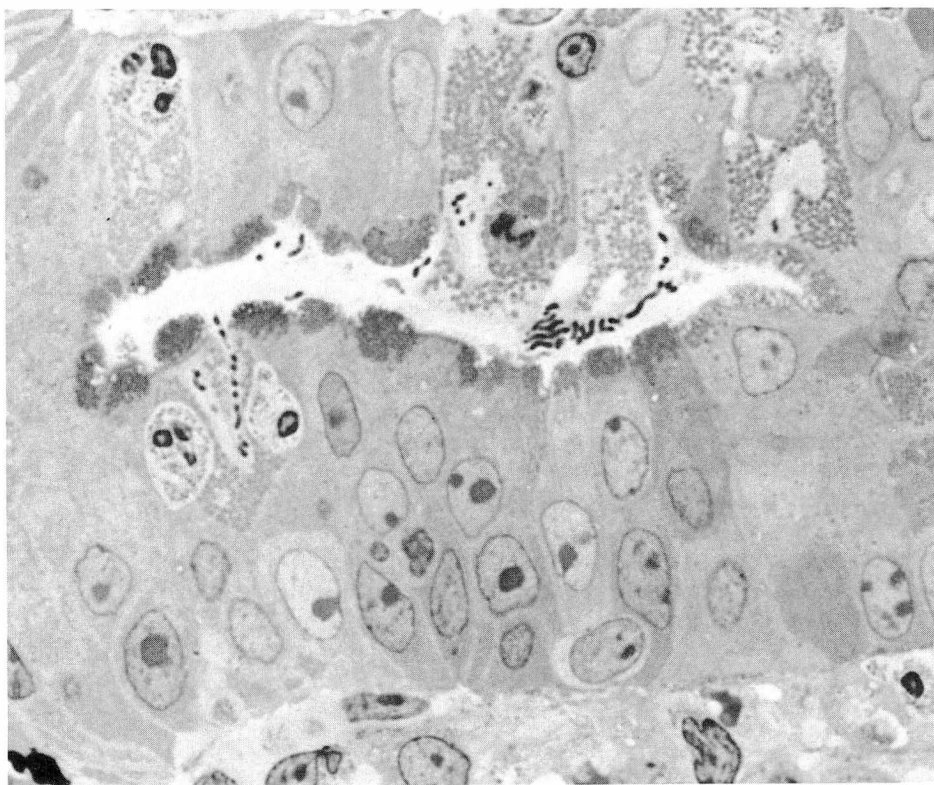
Dr. Hover is a gastroenterologist in Springfield, Mo., where, due to the region's attractions for retirement living, older people are the fastest growing age group. Hover says: "We're seeing more people—mostly the older people—for whom bleeding or perforation is the first sign of their ulcers. It's a major cause for concern."

Nearly 6 out of every 100 Americans take prescription medications for arthritis pain or swelling. They are consuming high doses of nonsteroidal anti-inflammatory drugs—NSAIDs such as aspirin, ibuprofen (Advil, Medipren, Motrin and Nuprin), naproxen (Naprosyn), or piroxicam (Feldene).

The irritation of ulcers from use of NSAIDs tends to be painless. Researchers studying these so-called "silent" ulcers say NSAIDs may be masking the pain signals, or that patients taking NSAIDs may already be used to living with some pain and don't recognize ulcer symptoms.

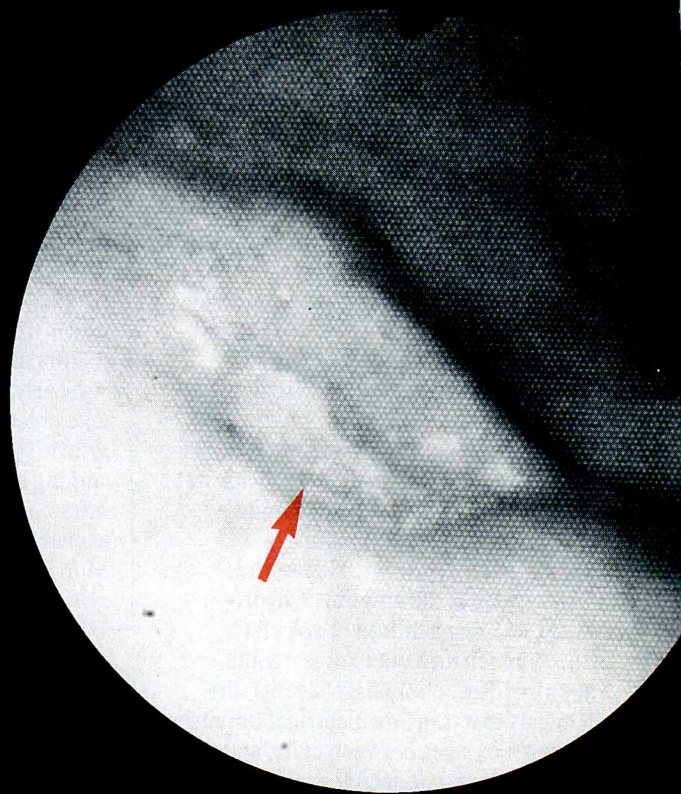
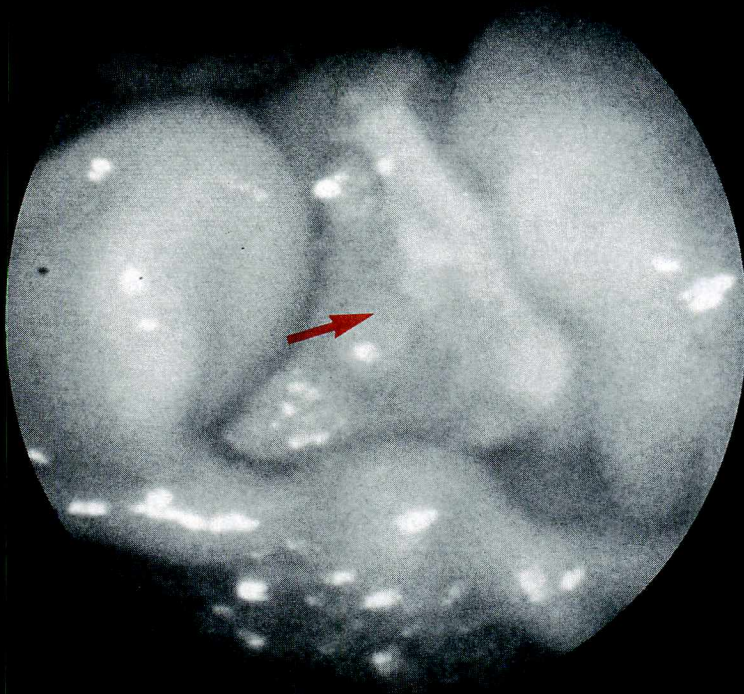
NSAID complications can be serious. As many as 2,000 deaths and 20,000 cases of ulcer-related NSAID side effects are linked each year to the 68 million prescriptions written for arthritis symptoms, according to studies by the Center for Ulcer Research and Education at the UCLA Medical School in Los Angeles.

Earlier this year, FDA revised requirements for labels for all prescription nonsteroidal anti-inflammatory drugs. Labels now must warn that bleeding, ulceration and perforation can occur at any time, with or without symptoms, in people who take these drugs regularly. These serious side effects occur in about 2 to 4 of every 100 people taking NSAIDs, FDA says. ■



Campylobacter pylori (dark specks at the center of the photo) cluster among surface cells in the digestive tract. Irritation from C. pylori infections seems likely to lead to gastritis— inflammation of the stomach lining—and perhaps ulcers.

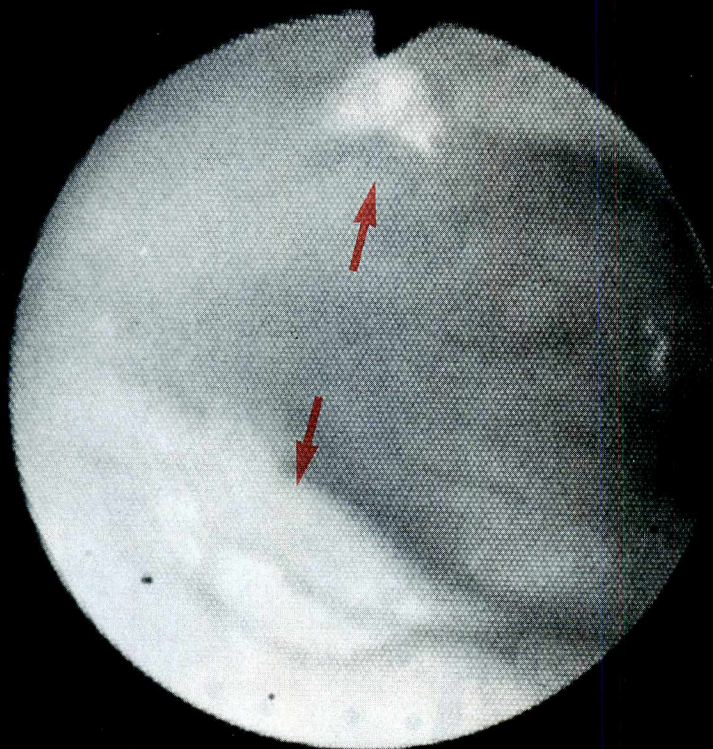
(Photomicrograph courtesy of Lesley C. Alpert, M.D., Department of Pathology, The Methodist Hospital, Houston, Texas)



Physician's-eye view of active peptic ulcers as seen through a fiberoptic endoscope inserted into the stomach through the patient's mouth. Above left: A well-formed ulcer is visible in the mucosal lining of the middle portion of the stomach. Middle: This ulcer is in the wall of the duodenum, the first part of the small intestine leading from the stomach. Right: Double trouble. Two active ulcers appear in this second view of a section of the duodenum shown in the middle photo.

(Photos by Stanley B. Benjamin, M.D., chief, division of gastroenterology, Georgetown University Medical Center, Washington, D.C.)

(Continued from page 15)



removal of the lower part of the stomach reduces its ability to make acid by reducing the number of acid-secreting cells present.

Other surgical modifications can restructure the stomach to make it empty its contents more rapidly into the intestine. Or the surgeon can remove a small part of the stomach where a hormone that stimulates acid secretion is produced. Procedures also have been introduced that stop bleeding by directly injecting drugs that dilate blood vessels in the stomach or by using lasers or heater probes guided by the endoscope to cauterize sites of bleeding.

While surgery can drastically reduce ulcer recurrence, there are infrequent severe digestive side effects that occasionally require follow-up surgery. There also is evidence that ulcer patients surgically treated have a twofold risk of developing stomach cancer 20 years after the operation.

Prevention Possibilities

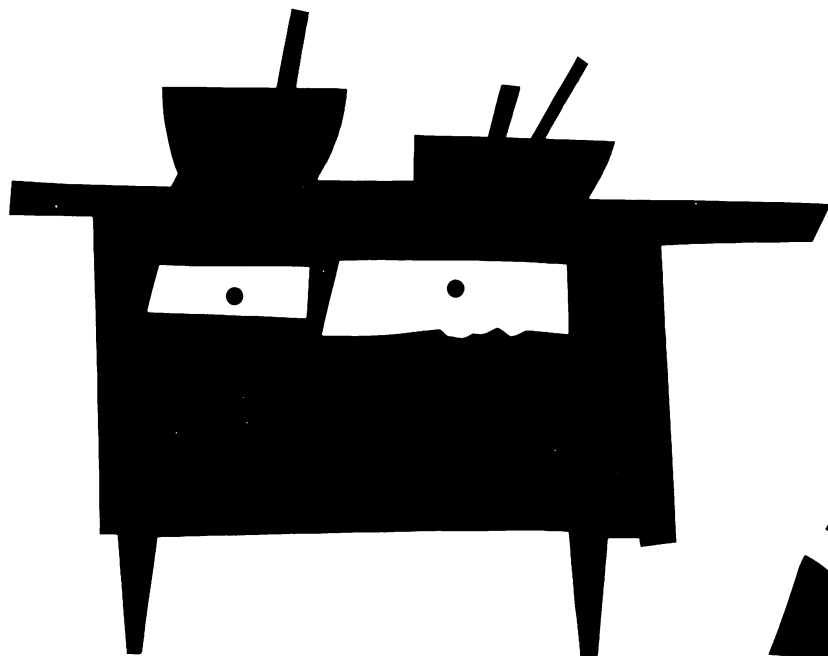
Will diet someday again assume a leading role in your doctor's bag of options for managing ulcer disease? Possibly, according to a 1986 report in the British journal *Gut*.

Reduced incidence and severity of peptic ulcers in the past two decades may be linked to a major concurrent change in our diet. During these 20 years, physicians and nutritionists have been after us to switch from animal fats and tropical oils to plant protein and vegetable fats for cooking. The goal was to reduce serum cholesterol levels for the benefit of our cardiovascular systems. But vegetable oils also may do our digestive systems a favor. Polyunsaturated fatty acids—particularly arachidonic and linoleic acid—promote production of prostaglandins in the stomach and help protect its inner lining and accelerate the healing of ulcers.

The incidence, severity and risk of death from peptic ulcer disease have been declining steadily the past 20 years, according to a summary report on the disease in the June 1988 *American Journal of Gastroenterology*. Stephen Sontag, M.D., and others conclude that dietary therapy may have a place in the future for treating ulcers, but individualized treatment with medications or surgery are today's most practical solutions. ■

Vern Modeland is a member of FDA's public affairs staff.

Mary Mallon's Trail of Typhoid



by Catherine Carey

Salmonella in eggs! Botulism from garlic-in-oil! *Listeria* in cheese! It seems that every day newspapers are shouting headlines about outbreaks of food-borne illnesses. Just within the past year, for example, eggs contaminated with *Salmonella* bacteria have sickened scores of consumers in the northeastern United States, airline food tainted with *Shigella* bacteria brought down members of the Minnesota Vikings football team, and three residents of New York state were hospitalized with botulism after they ate an unrefrigerated garlic-in-oil mix. In fact, FDA scientists estimate that tens of millions of cases of food-borne disease occur every year in this country.

But these recent outbreaks, serious as they are, can't match the 11-year reign of typhoid epidemics caused by one person at the beginning of the 20th century.

Mary Mallon, known to history as "Typhoid Mary," was born sometime around 1870. (Her age, as well as her claim to have been born in the United States, was never verified.) She was the first typhoid carrier identified in the United States who never displayed a single symptom of the disease herself. But before she was captured and quarantined for life, she directly infected at least 51 people,

three of whom died, and indirectly infected countless others.

Typhoid, or typhoid fever, is an acute infectious disease caused by *Salmonella typhi* bacteria. The bacteria enter the body through contaminated food or water, penetrate the small intestine, and thus invade the bloodstream, where they cause blood poisoning and carry infection into other parts of the body.

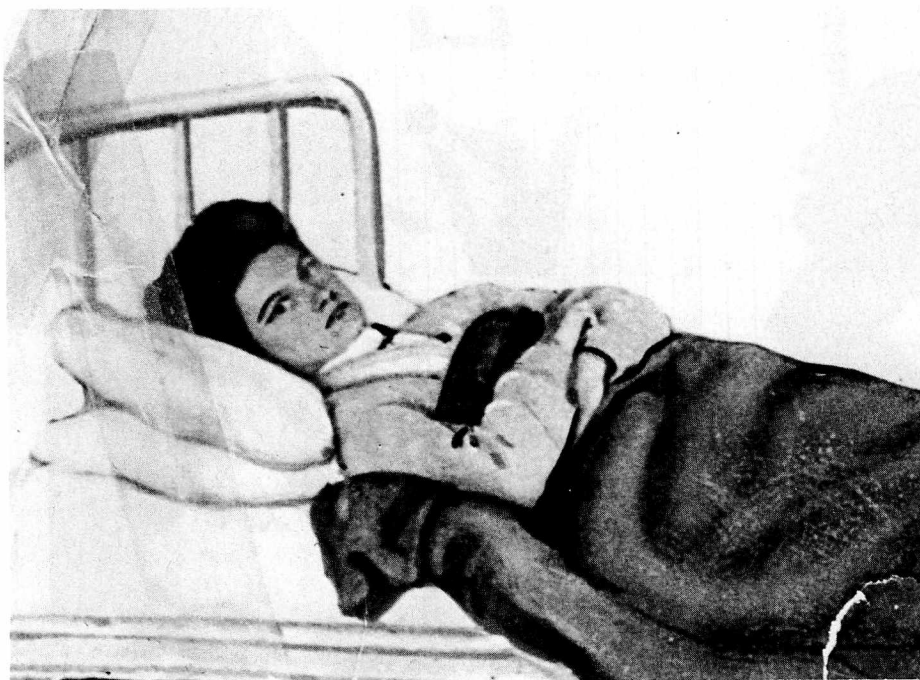
Early symptoms of the disease begin suddenly with headache, general aches and restlessness, coughing, nosebleeds, bloody diarrhea or constipation, and fever. A rash on the torso appears a week or two later. If the victim manages to survive, the fever begins to decline after about four weeks and gradually returns to normal. But if complications arise, such as heart failure and ulceration or perforation of the intestinal wall, typhoid is generally fatal.

About 30 percent of people infected with typhoid remain carriers, excreting the organism in their stool or urine for weeks or months. About 5 percent are long-term carriers, like Mary Mallon, who shed the organism for years. These carriers show no apparent ill effects but harbor the bacteria in their gallbladders and bile ducts. (When health authorities

(Continued on page 20)







Before she was apprehended and quarantined for life, history's most celebrated typhoid carrier, "Typhoid Mary" Mallon, passed her disease to at least 51 people, three of whom died, and probably to countless others. Though she had no symptoms, Mary Mallon was confined to Riverside Hospital for Communicable Diseases on North Brother Island, New York City, in 1915. She died there in 1938. (Photo courtesy of UPI/Bettman Newsphotos)

(Continued from page 18)

urged Mallon to have her gallbladder removed, she refused, claiming it was just a pretext for killing her. But, according to a March 1984 *Science Digest* article by Warren Boroson, Mallon later wrote in an unpublished letter that she was skeptical of having her gallbladder removed because the doctors could not agree on exactly where in her body the bacteria were located.)

Mallon's case came to light in 1904 when an epidemic of typhoid spread through New York's Oyster Bay and adjacent towns on Long Island. A sanitary

engineer with New York City's Department of Health named George Soper was asked to investigate. He found that Mallon had been employed as a cook in each of the stricken households. Even though at that time, it was not widely known that people who were themselves healthy might nonetheless be disease carriers, Soper deduced that Mallon was the source of the outbreaks. When he confronted her with his suspicion and offered medical care at no charge, she vehemently refused, going so far as to threaten the investigator with a rolling pin. She then disappeared.

But a persistent Soper, convinced Mallon

was a typhoid carrier, tracked her for three years. He found her again in 1907, working as a cook in a Park Avenue home in Manhattan. Mallon was brought—literally kicking and screaming—to the Riverside Hospital for Communicable Diseases on North Brother Island, where, upon examination, she was found to be, in Soper's words, "a living culture tube" of typhoid bacteria. The authorities committed her to the isolation center, and, despite a legal appeal that was ultimately denied by the U.S. Supreme Court, she stayed at the center until 1910, when she was released after promising never to work as a food handler again.

But four years later, when typhoid epidemics broke out at a sanatorium in Newfoundland, N.J., and Sloane Maternity Hospital in Manhattan, Soper learned that Mallon had worked as a cook at both places and the search was on again.

She was found at last in 1915 and arrested at a friend's home in suburban Westchester County, N.Y., while making dessert. She was returned to Riverside, where she remained for the rest of her life. In her later years, she worked as a hospital volunteer and did a creditable job. A paralytic stroke led to her slow death in 1938. ■

Catherine Carey is a member of FDA's public affairs staff.

Winning the Battle

Pollution of public water supplies has been responsible for most major typhoid epidemics. However, food and milk may be contaminated by a carrier—like “Typhoid Mary” Mallon—employed in handling and processing them, or by the use of polluted water for cleaning. Shellfish—particularly oysters—harvested from polluted water and fresh vegetables grown in soil fertilized or contaminated by sewage are particularly risky as potential sources of typhoid.

Prevention of typhoid and other food-borne illnesses depends on proper sewage treatment, filtration and chlorination of water, and proper food handling practices among food service workers. (See “Mother Nature’s Regulations on Food Safety” in the April 1988 *FDA Consumer*.) Food handlers should always:

- Wash their hands after every visit to the bathroom.
- Practice good personal hygiene and be in good health.

- Never leave food out unnecessarily. Hot foods should be kept at a temperature of at least 165 degrees Fahrenheit and cold foods at 40 F or colder.
- Wash and sanitize utensils, cutting boards or work areas, and equipment, like blenders, pots and pans, after every use.

Doctors used to be able to treat only the symptoms of typhoid, but after 1948, antibiotics—especially chloramphenicol (accompanied by cortisone)—proved to be effective in killing the bacteria, thus curing the infection. Today, only about 500 cases of typhoid are diagnosed in the United States each year, and over half of those are contracted abroad. Virtually all recover.

In Third World countries, where modern methods of sanitation and sewage disposal aren’t generally practiced, the fatality rate from typhoid remains as high as 10 percent, constituting a serious public health problem.

Travelers to developing countries should avoid drinking untreated water, drinks served with ice, peeled fruits, and other food that is not served hot. They should also see their physicians about being vaccinated before the trip. A typhoid vaccine was developed around the turn of the century. First given to military personnel and people in institutions, it substantially lowered the incidence of the disease. Still, the vaccine provides only partial protection (other vaccines are currently being studied), so even travelers who have been vaccinated should take appropriate food precautions. ■



Artificial Nail Remover Poses Poisoning Risk

by Dale Blumenthal

In late 1987 in Los Angeles, 12 hours after swallowing a mouthful of solvent used to remove sculptured artificial fingernails, a 16-month-old toddler died of cyanide poisoning.

In fall of the same year in Utah, a 2-year-old boy was rushed to the emergency room for rigorous intensive care after his parents found him in bed vomiting, moaning and unresponsive, an open bottle of the same sculptured nail remover by his side. Once again, a child's curiosity had resulted in cyanide poisoning.

Sculptured nails are acrylic artificial fingernails that are glued onto the real nail. It takes a special glue remover to remove these fake long nails. However, some brands of sculptured nail removers are extremely poisonous when swallowed. FDA warns: Keep them out of the reach of small children.

These products contain 98 percent to 100 percent acetonitrile, a chemical that breaks down into cyanide when swallowed. Studies show that 150 milligrams of acetonitrile—about 1/200 of an ounce—will kill 50 percent of laboratory rodents that are given the chemical, says Heinz Eiermann, director of FDA's division of colors and cosmetics.

Toby Litovitz, M.D., who heads the American Association of Poison Control Centers' data collection committee, would like to see acetonitrile-containing sculptured nail removers withdrawn from the market. However, despite the fact that the product is poisonous if swallowed, FDA does not have the authority to restrict its sale unless the injury results from using the product according to directions. Since the product is not *intended* to be swallowed, FDA cannot take it off the market. Regulation falls through the loopholes of federal health and safety laws.

For instance, the Federal Hazardous Substances Act, which covers household products such as cleaners, prohibits the sale of substances that contain concentrations of cyanide greater than 25 parts per million. Acetonitrile contains 4,000 to 80,000 parts per million of a cyanide equivalent, according to Litovitz. But, under the Federal Food, Drug, and Cosmetic Act, sculptured nail removers are not considered household products, but



Keep Out of Reach of Children. *This woman knows that even a small amount of the solvent she uses to remove her artificial nails can be lethal if swallowed. The Consumer Product Safety Commission is considering a requirement that all such products be marketed in child-resistant containers.*

cosmetics. And the Hazardous Substances Act, which is enforced by the Consumer Product Safety Commission, doesn't cover cosmetics. No comparable law exists that would ban a cosmetic that is dangerous for other than its intended use.

Smells Like Grapes

At the very least, Litovitz is calling for child-resistant packaging of sculptured nail removers. The products now come in glass bottles with screw-on caps, easy for a child to open. Also, says Litovitz, she knows of at least one brand that is dyed purple and smells like grapes, further inviting childhood misuse.

Last December, Litovitz and colleague E. Martin Caravati, M.D., published a paper in the *Journal of the American Medical Association* calling attention to poisonings from acetonitrile cosmetics. They cited the two cases mentioned earlier. Since then there have been others, Litovitz says, although none resulted in death: Another 2-year old suffered convulsions after swallowing a small amount of sculptured nail glue remover, and an adult woman became comatose after a suicide attempt involving the substance. At least three others—all children—have escaped with little or no harm after swallowing nail remover containing acetonitrile.

The highly poisonous glue remover is available not just to professionals, but to anyone. In the *JAMA* article, Litovitz and Caravati reported that the "highly toxic, cyanide generating product" was purchased by parents of the victims at wholesale-retail beauty supply outlets. Similar products also are marketed in supermarkets and drugstores.

Read the Label

In January, FDA sent a memo to its district office in Los Angeles, where firms marketing these products are located. The memo instructed investigators to collect samples and labeling of acetonitrile-containing products. Seven sculptured nail glue removers were specifically cited in the memo. "Of special interest," it said, "is any warning or caution statement made in the labeling and promotion of these products."

Scientists in FDA's division of colors and cosmetics in Washington, D.C., have reviewed the samples collected in the



Acetonitrile, a chemical in some glue removers used to take off artificial nails, can break down into cyanide when swallowed. One toddler died and other children became ill from cyanide poisoning after ingesting the nail remover, yet one brand is colored purple and made to smell like grapes. Gaps in consumer protection law make it hard to regulate these products effectively.

field, finding that these products do contain nearly 100 percent acetonitrile.

Labels on the packaging caution: "Poisonous—Do not ingest," "Poisonous & Flammable. Do not swallow or inhale . . . Keep away from children," or "Do not take internally." FDA's Eiermann says that if a nail remover containing acetonitrile "didn't have any cautionary statement, then the agency probably could take action." But the statements on the packages appear "conspicuously as compared to other words" on the label, therefore meeting the minimum requirements of the *Code of Federal Regulations*.

Child-Resistant Packages

The responsibility for requiring child-resistant packaging lies with the Consumer Product Safety Commission under the Poison Prevention Act. Under that law, child-resistant containers may be required for products that can cause serious personal injury or illness because of the way the substance is packaged.

CPSC is reviewing a petition that child-

resistant packaging be required for acetonitrile-containing products, says Alan Brauninger, an attorney at the commission. The petition was submitted by the Cosmetic, Toiletry and Fragrance Association, which represents the cosmetics industry.

Keep Away from Children

Concern about the safety of sculptured nails and their accessories is not new. Last year, *FDA Consumer* published an article warning of possible infections, allergic reactions, fingernail loss, and other problems caused by sculptured nails, especially when used improperly ("Artificial Fingernails: Apply with Caution," February 1988).

FDA continues to monitor sculptured nail products and to warn consumers to read product labels and keep poisonous substances out of the reach of small children. ■

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



The Notebook

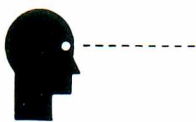
The Notebook: a potpourri of items of interest gathered from FDA news releases, other news sources, and the Federal Register (designated FR, with date of publication). The Federal Register is available in many public libraries.

- The Environmental Protection Agency proposes **banning captan** as an ingredient in fungicides except in specific applications where benefits outweigh risks. Animal studies suggest an increased risk of cancer in humans exposed to captan and captan-treated crops (FR Feb. 24).
- A revised edition of "Guidance on the Use of Methadone in Maintenance and Detoxification Treatment of Narcotic Addicts," reflecting changes in **methadone regulations**, is available free from the FDA Legislative, Professional and Consumer Affairs Branch (HFD-365), 5600 Fishers Lane, Rockville, Md. 20857 (FR March 2).
- Guidelines for phased submissions of **new animal drug applications** are outlined in the "Guide 1240.3040 to the CVM Policy and Procedures Manual." Free copies are available from the Industry Information Branch (HFV-11), Center for Veterinary Medicine, FDA, 5600 Fishers Lane, Rockville, Md. 20857 (FR March 14).
- Applications to **export unlicensed human biological products** should be sent to Boyd Fogle Jr., Center for Biologics Evaluation and Research, FDA, Room 217, 7520 Standish Place, Rockville, Md. 20855 (FR March 14).
- FDA has denied approval of 36 **applications for new animal drugs** that contain sulfamethazine, sulfaquinolaxaline, sulfamerazine, sulfathiazole, sulfapyridine, or sulfanilamide (FR March 15. Also see FR Sept. 15, 1988).
- After investigation by the Council of Better Business Bureaus, Redken Laboratories, Inc., Canoga Park, Calif., stopped using advertising claims stating that 79 percent of users of Vivagen Hair Treatment experienced "**decreased hair loss.**"
- Revised "**Guidelines for Preparing Compressed Gases for Medical Use**" are available free. Write: Legislative, Professional and Consumer Affairs Branch (HFD-365), Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, Md. 20857 (FR March 22).
- A "Guide to Acceptable Market Names for Food Fish Sold in Interstate Commerce" (**The Fish List**) is now available for \$2.75 per copy from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. Ask for GPO Stock No. 017-012-00341-9 (FR March 24).

■ Polyvinylcyclohexane has been approved for use in the manufacture of certain **plastics** intended for use in **food packaging** (FR March 27).

■ FDA has **amended animal drug regulations** for safe residue levels in beef of the implanted drug trenbolone acetate (FR March 28).





Biggest Drug Research Fraud Case In FDA History

Doctor Gets Jail Term for Faking Drug Tests

by Judy Folkenberg

After pleading guilty to pocketing nearly \$2 million from pharmaceutical firms for experimental drug tests that he never performed, prominent New Jersey physician Robert A. Fogari was sentenced to four years in prison on Feb. 2. He was also fined \$2 million and ordered to make financial restitution to the drug companies he defrauded. After serving his prison sentence, Fogari will be placed on probation for five years.

"This is one of the worst cases I've ever seen, and I would not have believed it if I had not seen it," said Judge Garrett Brown of the U.S. District Court for the District of New Jersey, who presided over the trial. "What you did was worse than dealing in drugs and murder," he told Fogari. "You betrayed the public trust. Our system of drug testing relies on honesty."

The judge said the sentence was as compassionate as possible considering the circumstances.

Fogari's case is believed to be the biggest investigational drug fraud case in the history of FDA, according to Alan B. Lisook, M.D., chief of FDA's clinical investigations.

At the beginning of his trial last Sept. 27, Fogari, an arthritis specialist, had pleaded not guilty to 20 charges of fraud and obstruction of justice. But seven days into what was expected to be a month-long trial he changed his plea and admitted guilt on four counts: conspiring to falsify drug test data, making two false statements to FDA, and obstructing justice by having a false affidavit submitted to FDA.

Fogari also admitted that he concealed the deaths of two patients "enrolled" in the bogus drug studies because he wanted to "maintain a favorable impression" with the pharmaceutical companies that had hired him, according to assistant U.S. attorney Paul Weissman, who prosecuted the case. However, Fogari said the deaths

were not related to the experimental drugs, and FDA had no evidence to contradict him. (Although Fogari never conducted any formal research, he may have used the experimental drugs in a haphazard fashion.)

Between 1977 and 1985, pharmaceutical companies that were seeking FDA approval for anti-inflammatory arthritis drugs paid Fogari to conduct clinical studies. Payment was based on the number of patients enrolled, the number of office visits, and the number of procedures performed during the study. According to Weissman, Fogari submitted thousands of falsified reports to drug companies.

During the week-long trial, former employees, who were given immunity, testified that Fogari instructed them to list the names of persons who were not enrolled in the study, make up patients, and continue to include patients who had dropped out of the study. Fogari also failed to conduct urine, stool, and blood tests necessary for the study. Under questioning from Weissman, Fogari admitted to forging the signatures of radiologists and other specialists to documents attesting that X-rays and other tests or exams had been performed.

The most damaging testimony came from Patricia Cunningham Czorniewy, a former assistant to Fogari who admitted under questioning that the doctor had pressured her to sign an affidavit falsely stating that she had invented study data. It was after her testimony that Fogari changed his plea from innocent to guilty. Questioned by Weissman, Fogari admitted it was he who falsified *all* data and that he did not conduct *any* legitimate research during the entire eight-year period.

Fogari participated as an investigator in at least 18 experimental drug studies for nine drug manufacturers, including Ciba-Geigy, Johnson & Johnson, Warner-Lambert, Pfizer, Upjohn, Syntex, and Merck, Sharp & Dohme. The drugs he was supposed to test included Voltaren, Maxicam, Seldene, and Naprosyn. How-



ever, Anthony Panzica, director of FDA's compliance branch in the Newark district office, emphasizes that the drug manufacturers deleted Fogari's data from their marketing applications after they were notified of his disqualification. Panzica said that most of the drugs have not yet been approved by FDA, and those that were did not depend on his data for approval.

"His research did not influence decisions to put any drugs on the market,"

said Panzica.

Fogari was first investigated by FDA in 1983 after officials at Ciba-Geigy became suspicious because his data were "too perfect," said Weissman.

Fogari's sentence angered many patients and former patients. He had a "great following among his patients, and people couldn't believe what had happened," said Diane Kolaitis, a compliance officer in FDA's Newark office. He was known as a

kind doctor, and long lines of patients were a familiar sight at his office, according to newspaper accounts.

Fogari can no longer practice medicine since the New Jersey State Board of Medical Examiners revoked Fogari's medical license as of March 17, according to Deputy Attorney General James F. Lafargue.

Judy Folkenberg is a member of FDA's public affairs staff.

Another Case of Fraud

As New Jersey physician Robert Fogari faced trial in the biggest case of fraudulent drug research in FDA's history (see preceding article), a board-certified urologist pleaded guilty in the U.S. District Court of Massachusetts on charges of faking research data.

On July 14, 1988, Constantine I. Kostas pleaded guilty to one count of making a false statement to a federal agency and one count of mail fraud.

Although he faced a maximum penalty of 10 years in prison and a \$500,000 fine, Kostas instead received a one-year suspended prison sentence, was fined \$30,000, and was ordered to perform 400 hours of community service.

Miles Pharmaceuticals of West Haven, Conn., had hired Kostas as a clinical investigator to test the drug ciprofloxacin (brand name Cipro) for treating urinary infections. The firm's officials became alarmed when, during a routine audit, serious discrepancies—such as giving antibiotics instead of Cipro to some patients—were discovered in Kostas' data. When the firm informed Kostas it intended to conduct a full audit, he confessed that only 15 of the 85 subjects listed in the study had actually received the experimental drug.

In addition, Kostas included in the study patients who did not meet the medical criteria of the research protocol, and he faked results of nonexistent lab tests and office examinations.

Kostas admitted that he thought the study would be easy to conduct, but he had been dogged with problems from the start. The physician said he pressured himself to continue the study and "wouldn't admit that he couldn't do it," according to Ed Warner, assistant regional director for operations for the northeast region. Kostas' study had no bearing on FDA's



approval of the drug.

According to his probation officer, Kostas fulfills the community service obligations of his sentence by giving physical exams to people who go before court at the Peabody District Court Clinic. He retains his medical license and continues to practice medicine in Peabody, Mass.

Snaring Smugglers Of Animal Drugs

A former veterinary drug company executive pleaded guilty in January to charges of illegally importing and selling unapproved animal drugs. The plea followed a four-year investigation by FDA, the U.S. Customs Service, and the Justice

Department into a nationwide bulk veterinary drug business with international connections. More than 30 tons of animal drugs, with a wholesale value of more than \$600,000, were seized in Illinois and Nebraska in connection with the case. The former executive, Jeffrey A. Engel, was president and general manager of Custom Feed Blenders, Fort Dodge, Iowa.

The investigation followed a growing number of complaints from legitimate veterinary drug sources about the availability throughout the country of illegal bulk drugs. Investigators eventually uncovered an illegal path of distribution that reached from Eastern Europe and China, where the drugs were produced, to Canada, then Iowa, and, from there, across the United States. The drugs were smuggled into the United States by tractor-trailer truck, concealed under loads of hay or wood chips, investigators said. The operation began in May 1983 and ended in October 1988, although Custom Feed Blenders closed in the spring of 1986 while under investigation.

Custom Feed Blenders made and distributed drugs for sale to veterinarians, farm supply outlets, and farmers throughout the nation, according to the Justice Department. Engel and the company were linked to the illegal operation in 1984 along with 13 others. They were charged with working together—or, in some cases, separately—to import, manufacture or sell high-potency, unapproved bulk animal drugs, and with making false statements to federal agents.

Others pleading guilty in the case were Rex J. Blunk of Callender, Iowa; Gary Van Dusen of Mississauga, Ontario, Canada; Jon L. Engel of Omaha, Neb., brother of Jeffrey Engel; Timothy J. Hoffman of Omaha; Bradley Langmo and Gregory S. Langmo of Litchfield, Minn.; Ronald L. Nissen of Fort Dodge; James Rhodes of Fort Dodge; Wesley J. Thoreson



of Ellsworth, Iowa; Larry Tipton of Winona, Minn.; and Dana Wolf of Fort Calhoun, Neb. As of April 1, Hoffman had been fined \$9,000, Thoreson \$2,500, and Wolf \$4,500. At press time, the others, along with Jeffrey Engel, were awaiting sentencing.

In addition, Heinz G. Dall of Ossining, N.Y., and Robert M. Clack of Pittsfield, Ill., were charged with 25 counts of illegally importing and distributing animal drugs. They pleaded not guilty after being indicted last November by a federal grand jury in Cedar Rapids, Iowa, and are awaiting trial.

Two businesses dealing in the smuggled veterinary medicines—International Manufacturing and Sales of Omaha, Neb., and Zetapharm Corp., New York—were charged with misbranding and adulteration of animal drugs since the drugs were made under conditions that presented no assurance as to their safety or strength. International Manufacturing has been fined \$40,000. Fines of up to \$100,000 to \$250,000 per count are possible.

The unapproved animal drugs included amprolium, carbadox, chloramphenicol, chlortetracycline, dimetridazole, ipronidazole, levamisole, nitrofurazone, oxytetracycline, potassium penicillin, rifampin, spectinomycin, tetracycline hydrochloride, tylosin, and other antibiotics. Unapproved drugs pose a threat to an animal's health because their safety and effectiveness have not been scientifically determined. They may also endanger humans if they leave cancer-causing or otherwise toxic drug residues in meat, milk or eggs from feed animals.



The nationwide investigation is continuing, with more charges expected.

Blood Bank Put on Notice

The American Red Cross Blood Services Center in Albany, N.Y., almost lost its FDA license last March because of continuing problems that led to the release of more than 300 units of potentially contaminated blood—most of which were transfused. The most critical problem was that hepatitis testing was done incorrectly for nearly five months because the center's employees had failed to recognize an inappropriate computer setting. To date, retesting of the 112 donors who gave the blood in question has not shown any hepatitis contamination.

Numerous problems with the Red Cross regional blood banking operations over the past several months had prompted FDA to

step up its inspections of the centers. Indeed, in 1988, the agency visited every FDA-regulated blood bank. During the Albany center inspection, from May 2 to June 6, an investigator from FDA's Buffalo district found a number of deficiencies—notably, the distribution of blood components from five units that hadn't been properly tested for AIDS (acquired immune deficiency syndrome) virus antibodies. The donors are being retested and, so far, all tests have been negative.

Meanwhile, FDA had been working with the Red Cross to remedy such serious deficiencies. On Sept. 14, 1988, the Red Cross signed an agreement to monitor its centers more tightly, to establish uniform blood collection standards that would include improved employee training procedures and auditing procedures, and to analyze computer hardware and software as a further measure to prevent the release of unsuitable blood.

FDA conducted a follow-up inspection of the Albany center from Dec. 6, 1988, to Jan. 18, 1989, to see what changes were in place. Shortly before the inspection, however, the manufacturer of the automated test equipment had conducted a routine check and noticed the computer was in the wrong mode. The center immediately informed FDA. The agency's subsequent investigation confirmed the error and found significant problems in the blood bank's hepatitis testing, including:

- Faulty procedures that caused inaccurate test results from July 12 to Dec. 2, 1988.
- Lack of complete instructions for performing hepatitis testing with automated equipment.
- Failure of supervisors or managers to review original test results so as to ensure technicians were using the correct procedure.
- Some test records that were incomplete or improperly filed.

In a letter dated Feb. 14, 1989, FDA advised the American Red Cross national headquarters that it would revoke the Albany center's license unless the center promptly submitted a plan to bring blood handling procedures into accord with FDA standards and regulations. The Albany Red Cross submitted such a plan on March 1, 1989, and FDA is reviewing it.

— *This small sample of reports from the field was prepared by Dixie Farley, Judy Folkenberg, and Vern Modeland.*



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/Poisonous and Deleterious Substances

PRODUCT: **Swordfish chunks**, at Monterey, N. Dist. Calif.; Civil No. C-84-20140-WAI.

CHARGED 3-1-84: When shipped by the boat "Arista" after being caught in waters outside of the boundaries of California, the article contained the added poisonous or deleterious substance mercury (approx. 1.25 ppm)—402(a)(1).

DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 64178; S. No. 84-324-126 et al.; S.J. No. 1)

Foods/Contamination, Spoilage, and Insanitary Handling

PRODUCT: **Pecan meats**, at Fargo, Dist. N.D.; Civil No. A3-88-62.

CHARGED 5-5-88: When shipped by Pippin Pecan Co., Inc., Albany, Ga., the article contained a filthy substance (*E. coli*) and had been prepared, packed and held under insanitary

conditions—402(a)(3), 402(a)(4).

DISPOSITION: Default—ordered delivered to eleemosynary institution for feeding wildlife. (F.D.C. No. 65458; S. No. 88-472-556; S.J. No. 2)

PRODUCT: **Rice**, at St. Louis, E. Dist. Mo.; Civil No. 88-0153-C-6.

CHARGED 1-27-88: While held for sale, the article had been held under insanitary conditions—402(a)(4).

DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 65375; S. No. 88-526-181 et al.; S.J. No. 3)

PRODUCT: **Rice**, and **other food stocks**, at Chicago, N. Dist. Ill.; Civil No. 88-C-3170.

CHARGED 4-13-88: While held by Golden Country Oriental Food Co., Chicago, Ill., the articles had been held under insanitary conditions, and one lot of rice contained rodent filth—402(a)(3), 402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65441; S. No. 88-503-907 et al.; S.J. No. 4)

PRODUCT: **Rye, in bulk**, at Hereford, N. Dist. Texas; Civil No. 2-88-0069.

CHARGED 4-11-88: While held by Arrowhead Mills, Inc., Hereford, Texas, the article contained insects—402(a)(3).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65422; S. No. 88-517-427; S.J. No. 5)

PRODUCT: **Shrimp "rounds," breaded, frozen, SeaPak**, at Brunswick, S. Dist. Ga.; Civil No. 288-207.

CHARGED 9-19-88: While held by Rich-SeaPak Corp., Brunswick, Ga., who manufactured the article with minced imported shrimp, the article contained decomposed shrimp, and the article's label lacked the required statement "made from minced shrimp"—402(a)(3), 403(a)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65526; S. No. 88-435-797; S.J. No. 6)

Foods/Economic and Labeling Violations

PRODUCT: Cheeses, provolone, and low-moisture mozzarella, at Edison, Dist. N.J.; Civil No. 88-20.

CHARGED 1-5-88: When shipped by Sun-Re Corp., Sunbury, PA., the articles, labeled "Mamma Mia . . . Whole Milk—Low Moisture Mozzarella Dist. By Marlboro Foods . . . Mfg at Plant #42-264" and "Mamma Mia . . . Midget Provolone . . . Manufactured By Sun-Re Cheese . . . Plant #42-264," had had the valuable constituent milk fat omitted in part from the articles—402(b)(1); the articles' labels lacked the address of the distributor and/or manufacturer—403(e)(1); the articles' labels lacked an accurate quantity of contents statement in terms of weight—403(e)(2); and the articles failed to conform to the definition and standard of identity for low-moisture mozzarella cheese and provolone cheese, because the articles contained less than 45 percent milk fat and more than 45 percent moisture—403(g)(1); and the articles' labels lacked the name of the food ("cheese") specified in the definition and standard and lacked the common names of all the articles' ingredients—403(g)(2).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65363; S. Nos. 88-438-153/4; S.J. No. 7)

PRODUCT: Fish fillets, "flounder," frozen, at Charlotte, W. Dist. N.C.; Civil No. C-C-88-72-M.

CHARGED 2-11-88: While held for sale, after shipment by Greenwood Packing Corp., Middletown, N.Y., who had relabeled "Cape Haddie" fillets as "flounder" fillets, the article had had an unknown fish (labeled with the fictitious name "Cape Haddie") substituted for flounder—402(b)(2); the article's labeling falsely and misleadingly claimed that the only fish in the article was flounder—403(a)(1); the article was offered for sale under the name of another food, flounder—403(b); the label of the article lacked the name and place of business of the manufacturer, packer or distributor—403(e)(1); and the article's label lacked the common or usual name of the article, because "flounder" was not the article's common or usual name—403(i)(1).

DISPOSITION: Consent—ordered destroyed or constructively destroyed by donation to a bona fide charitable organization. (F.D.C.

No. 65381; S. No. 88-423-685; S.J. No. 8)

PRODUCT: Fish fillets, "flounder," frozen, Middletown, S. Dist. N.Y.; Civil No. 88 Civ. 1107 (JMW).

CHARGED 2-18-88: While held by Greenwood Packing Corp., Middletown, N.Y., the article (which the dealer had had labeled "IQF Flounder Fillets Prod. of Canada" using an unknown fish—not flounder—that had been previously labeled with the fictitious name "Cape Haddie") had had an unknown fish substituted for flounder—402(b)(2); the article's label was false and misleading in claiming that the fish in the article was flounder—403(a)(1); the article was offered for sale under the name of another food, flounder—403(b); the article's label lacked the name and place of business of the manufacturer, packer or distributor—403(e)(1); and the article's label failed to bear the common or usual name of the food, because "flounder" was not the article's common or usual name—403(i)(1).

DISPOSITION: Default—ordered constructively destroyed by donation to a charitable organization. (F.D.C. No. 65379; S. No. 88-423-685; S.J. No. 9)

PRODUCT: Fish pieces, frozen, at Brooklyn Park, Dist. Minn.; Civil No. 3-87-350.

CHARGED 5-26-87: While held for sale, the label of the article (which was being sold as "Pacific Ruffie") failed to bear the common or usual name of the food (grouper)—403(i)(1).

DISPOSITION: Default—ordered constructively destroyed by donation to a charitable organization. (F.D.C. No. 65207; S. No. 87-445-698; S.J. No. 10)

Food Additives

PRODUCT: Betel nuts, at Los Angeles, C. Dist. Calif.; Civil No. 88-02134 WMB (Ex).

CHARGED 4-19-88: While held for sale, the article contained the nonconforming food additive arecoline, and no regulation prescribed conditions for use of the additive—402(a)(2)(C).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65438; S. No. 88-300-009; S.J. No. 11)

PRODUCT: Calcium orotate tablets, and tablets and capsules of other salts of orotic acid, at Oceanside, E. Dist. N.Y.; Civil No. 88-1517 (Mishler).

CHARGED 5-13-88: While held for sale, the articles contained the nonconforming food additives salts of orotic acid—402(a)(2)(C). **DISPOSITION:** Default—ordered destroyed. (F.D.C. No. 65420; S. No. 88-424-163 et al.; S.J. No. 12)

Drugs/Human Use

PRODUCT: ImmuVir topical analgesic ointment, at Lake Oswego, Dist. Ore.; Civil No. 88-341-FR.

CHARGED 3-28-88: When shipped by Bio Pharmaceuticals Corp., Portland, Or., the article (which was represented for use in the cure, mitigation or treatment of diseases, including herpes) was a new drug without an effective approved New Drug Application—505(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65403; S. No. 88-423-046; S.J. No. 13)

PRODUCT: Parenterals, small-volume, in ampules and vials, at Rosemont, N. Dist. Ill.; Civil No. 88C-5784.

CHARGED 7-6-88: When shipped by LyphoMed, Inc., Orlando, Fla., the circumstances used for the articles' manufacture and processing failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: The articles were claimed by the shipper. Pursuant to stipulation of the parties, five similar seizure actions in Florida, Georgia, New Jersey, California and Texas were consolidated for trial with this action. Subsequently, a consent decree condemned the articles and ordered the destruction, reconditioning, or other specified disposition of the articles in each action. In addition, all of the shipper's potassium chloride injection of lot no. 480099 (including the seized articles, recalled articles, and not-seized but on-hand articles) was to be destroyed, as were all seized aseptically filled articles. Additional provisions covered articles subsequently found to be non-sterile and articles of terminally sterilized products, and covered the Florida plant (which was then closed) where the

drugs had been manufactured. (F.D.C. No. 65503; S. No. 88-443-906 et al.; S.J. No. 14)

PRODUCT: Parenterals, small-volume, in ampules and vials, five seizure actions, at Orlando, M. Dist. Fla.; Stone Mountain, N. Dist. Ga.; Edison, Dist. N.J.; Vernon, C. Dist. Calif.; and Carrollton, N. Dist. Texas; Civil Nos. 88-573-Civ-ORL-18, 6-88-CV-1489 JTC, 88-2971, CV 88-04112-IH, & CA 3-88-1591-G. **CHARGED 7-5-88, 7-12-88, 7-6-88, 7-6-88 and 7-7-88:** When shipped or while held by LyphoMed, Inc., Orlando, Fla., the circumstances used for the articles' manufacture and processing failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: Upon stipulation of the shipper and the government, the five seizure actions were consolidated for trial with a similar seizure action in the Northern District of Illinois (see the preceding S.J.). Subsequently, a consent decree of condemnation was entered in the consolidated actions, which ordered specified destruction and salvaging of specified articles. (F.D.C. Nos. 65499, 65500, 65001, 65502 and 65504; S. No. 88-443-906 et al.; S.J. No. 15)

PRODUCT: Sunscreen creams colored orange, yellow, pink, green, blue or red, at Fairlawn, Dist. N.J.; Civil No. 87-2829.

CHARGED 7-15-87: While held for sale after some of the articles had been imported from Australia and some of the articles had been manufactured locally from interstate color ingredients, the articles (both drugs and cosmetics, which were labeled "Le Zink Advanced Formula High Protection Sunscreen . . . perfect sun protection for all outdoor sports" and which contained Rhodamine 6G, C.I. Solvent Yellow 135, C.I. Fluorescent Brightener 61, and an unidentified red color) contained nonconforming color additives—501(a)(4)(A), 601(e); the articles were processed, packed and labeled in an unregistered facility—502(o); the articles' labels lacked a statement of active ingredient—502(e); the labels lacked a statement of the place of business of the manufacturer, packer or distributor—502(b); and the articles' labeling lacked adequate directions for use—502(f)(2).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65200; S. No. 87-438-121 et al.; S.J. No. 16)

PRODUCT: **Tanning lotions (with sun protection factors of 15, 8, 5 and 0), Coco-LoCo**, at Honolulu, Dist. Hawaii; Civil No. 87-0376 VAC.

CHARGED 5-9-87: When shipped by Basjian Distributing, Tukwila, Wash., the articles (with sun protection factors 15, 8 and 5) were drugs which had been manufactured and processed under circumstances that failed to conform with current good manufacturing practice; and those drugs had been processed, packaged and labeled in an unregistered facility; their labeling contained the false and misleading claim that the drugs contained no mineral oil; their labels lacked a statement of the active ingredient para-aminobenzoic acid; and their labeling lacked adequate directions for use—501(a)(2)(B), 502(o), 502(e), 502(f)(1); the article with sun protection factor 15 was a new drug without an effective approved New Drug Application—505(a); all of the articles (including the article with sun protection factor zero) were cosmetics and their labeling contained false and misleading declarations claiming that the articles were a blend of all natural coconut ingredients, representing that the articles did not contain mineral oil or any synthetic ingredients, and suggesting that BHT/BHA were required—602(a); the articles were also in violation of the Fair Packaging & Labeling Act, since the cosmetics' label failed to bear, with prominence and conspicuousness, an accurate ingredient statement, since the partial ingredient declaration was not visible to consumers under conditions of retail sale, and since some ingredients (e.g., mineral oil and propylene glycol) were not declared—15 U.S.C. 1456.

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65156; S. No. 87-450-03 et al.; S.J. No. 17)

Medical Devices

PRODUCT: **Condoms**, at Savannah, S. Dist. Ga.; Civil No. 488-171.

CHARGED 8-30-88: The article, which Okamoto U.S.A., Inc.,

Stratford, Conn., had initially attempted to import through Port Newark, N.J. (but the article was rejected), and subsequently had attempted to import at Savannah, Ga., and which were labeled "Lubricated—Skinless Skin - Harmony Manufactured by Okamoto Industries, Inc., Tokyo, Japan," had a quality that fell below its purported quality since the article contained an excessive number of holes—501(c).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65527; S. No. 88-161-801 et al.; S.J. No. 18)

PRODUCT: **Condoms**, at Brooklyn Center, Dist. Minn.; Civil No. 3-88-595.

CHARGED 9-1-88: The quality of the article, which was packaged by Mentor Corp., Brooklyn Center, Minn., and labeled "Mentor Safety-Seal No-Slip Condoms . . . Mentor Health Care Products Minneapolis, Mn.," fell below the article's purported quality, since the article contained excessive holes—501(b); and its labeling for prevention of disease was false and misleading because the article contained holes—502(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65528; S. No. 88-562-786 et al.; S.J. No. 19)

INJUNCTION ACTIONS

DEFENDANTS: **Bleyhl Farm Service, Inc., Fred L. Harris**, general manager, **Robert L. Eucker**, feed department manager, and **Ollie M. Dodd**, feed mill manager, Grandview and Granger, E. Dist. Wash.; Civil No. C-87-349-AAM.

CHARGED 5-26-87 in a complaint for injunction: That defendants, at their Granger, Wash., feed mill, manufactured, processed, packed, labeled, stored, held for sale, and distributed in interstate commerce various medicated feeds containing interstate components; that such medicated feeds had been manufactured, processed, packed and held under conditions which failed to conform with current good manufacturing practice—501(a)(2)(B); that such medicated feeds (such as those containing amprolium, lincomycin and monensin in combination, monensin and chlortetracy-

cline in combination, and monensin, chlortetracycline and sulfamethazine in combination) contained new animal drugs, and no approvals of New Animal Drug Applications were in effect with respect to the use and intended use of such drugs—501(a)(6); that the purity and quality of certain medicated feeds fell below, or their strength differed from, their purported strength and quality, because they did not contain their represented amount of drug—501(c); the labeling of certain medicated feeds represented that the feeds contained a drug or drugs different from those actually used in manufacturing the feeds—502(a); that FDA inspections and FDA laboratory analyses documented various violations; and that the defendants were well aware that their activities violated the law.

DISPOSITION: A consent decree of permanent injunction enjoined the complained-of violations and enjoined interstate medicated feed operations, unless and until a number of specified conditions were met, including adherence to current good manufacturing practice and adherence to New Animal Drug Applications for the medicated feeds. (Inj. No. 1172; S. Nos. 87-420-004 et al.; S.J. No. 20)

DEFENDANTS: **Odessa Union Warehouse Co-op, Cecil A. Schell**, secretary-treasurer of the corporation at Odessa, E. Dist. Wash., **Edward Sewall**, agent-manager at the Harrington, Downs and Moher stations, **Gary L. Schmauder**, agent-manager at the Davenport and Rocklyn stations, and **Marvin Kleyn**, agent-manager at the Ephrata station; Civil No. C-86-608-AAM.

CHARGED 7-20-86 in a complaint for injunction: That the defendants prepared and held for sale quantities of wheat at their grain elevator stations; that, when shipped, such wheat was, in part, moldy and insect damaged, and contained insect and rodent filth and had been held under insanitary conditions; that FDA inspections of the defendants' elevator facilities had disclosed numerous insanitary conditions and abundant evidence of food adulteration; and that the defendants had continued to ship wheat without sanitary and adequate food warehousing and storage procedures—402(a)(3), 402(a)(4).

DISPOSITION: *District Court*—The government moved for a preliminary injunction. In response to the filing of the action and prior to the hearing on the government's motion, the defendant firm

acted to improve the sanitation at its facilities by cleaning and fumigating wheat, destroying rodent tunnels, sealing the elevators to prevent future infestations, and employing a sanitation expert. The District Court denied the government's motion, since the court felt that a preliminary injunction should issue only "when the circumstances truly permit no other course, when the crisis is current or at least appears to be recurrent, that the response of the respondent is recalcitrant and clearly so, and that the total impact of the Order must be assessed."

Court of Appeals—The government appealed the denial of its motion for a preliminary injunction. The Court of Appeals reversed and remanded, because the District Court's standard was far too restrictive compared with the standards applicable to the issuance of an injunction authorized by a statute of the United States to enforce and implement Congressional policy. The Court of Appeals stated the following: that, once Congress, exercising its delegated powers, has decided the order of priorities in a given area, it was for the courts to enforce them when asked; that the District Court should have presumed that the government would suffer irreparable injury from a denial of its motion; and that, because of presumed irreparable injury, the District Court needed only to find some chance of probable success on the merits.

As to the elements of the balancing of hardships and the likelihood of recurring violations, the Court of Appeals noted that the public interest in the purity of its food was so great as to warrant imposing the highest standards on distributors, and that Odessa's progress towards improvement must be weighed in light of Odessa's extensive history of violations because an inference rose from Odessa's past violations that future violations were likely to occur. *District Court Upon Remand*—A consent decree of permanent injunction was entered, even though the parties agreed—and the court found—that the defendants' facilities were in compliance at FDA's last inspection. The defendants were enjoined for two years from receiving, preparing, packing or holding food at their facilities unless and until a number of specified conditions (including the purchase and installation of equipment for applying insecticides and for detecting rodent and insect activity, as well as the employment of a sanitarian to monitor conditions) were met. (Inj. No. 1147; S. No. 85-463-828 et al.; S.J. No. 21)

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In the form of verbal abuse at home. If that's been happening to you,
you've got to work to change things. Words can hit a child as hard as a fist.
And leave scars you can't see. Think about what you're saying.
Stop using words that hurt. Start using words that help.**

stop using words that hurt.



For helpful information, write: National Committee for Prevention of Child Abuse, Box 2866E, Chicago, IL 60690.