

FDA CONSUMER

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

• VOL. 25 NO. 8

OCTOBER 1991 •



PLAYING IT SAFE AT WORK



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- Never Say Diet?** 8
Trying to lose weight is more complicated than previously thought: Heredity may play a large role, repeatedly losing and regaining weight may be more dangerous than staying fat, and calories from some foods may put weight on faster than others.
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Inside Front Cover Photo: A small circular patch, worn behind the ear, adheres to the skin and releases the drug scopolamine to help prevent motion sickness. For more on new methods of delivering drugs, see page 13.



FDA Watching Prescription Drug Promotion

Promotion of prescription drugs is coming under closer scrutiny by FDA. The agency is particularly concerned about manufacturers encouraging use of unapproved drugs or unapproved uses of approved drugs.

Since FDA began regulating prescription drug advertising in 1962, industry marketing techniques have become increasingly diverse, more widespread, and less traditional. The agency is paying particular attention to activities such as celebrity endorsements of products,



lecture tours by scientists or experts that promote a firm's product or disparage a competitor's, and videos and computer disks of promotional material disguised as news and educational information. FDA would like discussion about investigational treatments to remain free from promotional bias. Both FDA and Congress have become concerned because many such industry-sponsored promotions may not be in the best interest of physicians or patients.

FDA Commissioner David Kessler, M.D., pointed out

that although in past cases of questionable promotions FDA has directed its regulatory actions against the firms, rather than individuals such as physicians or clinical investigators, "it will no longer apply this restraint across the board." Kessler also recommended that physicians on a drug company's payroll try to avoid becoming unwitting participants in a promotional activity.

Panel Proposes Banning Mercury in OTC Antiseptics

There is no proof that mercury compounds are safe or effective in nonprescription antiseptic products, according to an FDA review panel. Any products with those compounds would be banned under an FDA proposal published in the July 22 *Federal Register*.

Manufacturers of mercury-containing products would either have to reformulate the products or remove them from the market once the proposal becomes final.

Other ingredients commonly used for first aid, such as hydrogen peroxide, alcohol, camphorated metacresol, and tincture of iodine, could continue to be marketed as first-aid antiseptics.

The proposal, part of the agency's ongoing review of all nonprescription drugs, also combines three groups of first-aid products—skin wound cleansers, skin wound protectants, and skin antiseptics—into one category to be called "first-aid antiseptics." The new category is defined as "any antiseptic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes and burns."

Under the proposal, labels on these antiseptics would have to read "first aid to help prevent (or decrease) the risk of (or the chance of) infection (or bacterial contamination or skin infection) in minor cuts, scrapes or burns."

The deadline for written comments, objections, or requests for oral hearing on the proposed regulation is Jan. 22, 1992. The address for all correspondence is Dockets Management Branch (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, Md. 20857.

FDA will propose regulations on other nonprescription antiseptic products used as surgical scrubs, health-care personnel handwashes, and patient preoperative skin preparations at a later date.

Proposed Change for Pancreatic Enzyme Products

All pancreatic enzyme products used to treat cystic fibrosis would be sold by prescription only, under a proposal by FDA published in the *Federal Register* July 15, 1991. Currently, some of these products are sold over-the-counter and others are sold by prescription.

Cystic fibrosis is an inherited disease that affects various glands and can lead to insufficient amounts of pancreatic enzymes. (See "Cystic Fibrosis: New Treatments Give Victims Precious Time" in the October 1986 *FDA Consumer*.)

The proposed requirement would reverse a Nov. 8, 1985, proposal in which the agency agreed that these products could be sold as nonprescription drugs. Part of FDA's ongoing review of nonprescription drugs, the proposal would also require all drugs sold to treat cystic fibrosis to have approved new drug applications (NDAs). Not all products currently marketed have NDAs because some of them were on the market before the passage of the 1938 federal Food, Drug, and Cosmetic Act, which requires pre-market approval for drugs.

Although during their long history of use, FDA did not encounter problems relating to their safety and effectiveness, since 1985, published studies and adverse reaction data show that the dosage, formulation, and manufacturing process have an impact on the effectiveness of the active enzyme ingredients in these drugs. The relevant manufacturing information would be part of the NDA.

Pancreatic enzymes are also used to treat patients with chronic pancreatitis, and those who have had their pancreas removed or have had gastrointestinal bypass surgery.

Written comments or requests for oral hearing on the

proposed regulation should be sent by Nov. 12, 1991, to Dockets Management Branch (HFA-305), FDA, Room 1-23, 12420 Parklawn Drive, Rockville, Md. 20857.

Panel Examines Risks of Breast Implants

The cancer risk, if any, from polyurethane-coated breast implants is probably very small, an FDA advisory panel recently concluded. The panel advised women with this type of implant against having them removed at this time, but called for more study to assess the risk. It also called for establishment of a breast implant registry to track data on women with all types of implants.

Surgitek, a subsidiary of Bristol-Myers Squibb, is the sole manufacturer of polyurethane-coated implants. The firm voluntarily suspended marketing of the implants, sold under the brand names Meme and Replicon, in April after questions about a possible cancer risk arose, and wrote to surgeons asking them not to implant the devices.

FDA Commissioner David Kessler, M.D., advised women who are considering getting any breast implants to obtain information on what is known at present about the risks involved and to ask their doctors for the package insert that comes with the devices. They may also request information from FDA by sending a postcard to: Breast Implants, HFE-88, 5600 Fishers Lane, Rockville, Md. 20852.

About 200,000 women—approximately 10 percent of breast implant patients—have polyurethane-coated implants. The polyurethane coating may break down into a chemical called TDA (2, 4-toluenediamine), which has been linked to cancer in laboratory animals. Even though they recognized the uncertainties in the risk assessment, the panel accepted earlier estimates of the small risk from the polyurethane, and concluded that this risk would very likely be outweighed by the surgical risk involved in removing the implants.

Last spring the agency required manufacturers of all silicone gel-filled breast implants to submit data proving their products are safe and effective, as a condition for keeping them on the market. Six manufacturers submit-

ted data for 10 products by last July's deadline. Several smaller firms did not submit data, and the agency is checking to ensure that their products are off the market.

A special team of FDA scientists was set up to review the submitted data within six months, as is required by law. The agency will soon require manufacturers of saline-filled breast implants to submit safety and effectiveness data as well. Approximately 10 percent of women with implants have this type.

In another action, last July, U.S. marshals seized more than 800 Misti Gold brand inflatable breast implants in St. Paul, Minn. The implants, manufactured by Bioplasty, Inc., of St. Paul, were seized because the manufacturer had failed to get FDA approval to market them and, in addition, was making false and misleading medical claims. Bioplasty claimed that Misti Gold implants allow for better mammograms than other implants, making it easier to detect breast tumors. It also claimed that the incidence of capsular contracture and resulting hardening of the breast, a common side effect of implants, is reduced with the Misti Gold devices. Safety was not a factor in FDA's action. Since FDA has not yet reviewed the product, it has no data regarding its safety or the lack thereof.

Task Force Recommends Studies Of Anabolic Steroid Effects

Bulk-building anabolic steroids used illegally by some athletes to enhance performance should be studied further for physical and psychological effects, according to a federal task force.

The task force, made up of representatives from FDA

and other agencies in the Department of Health and Human Services, recommended that steroids be studied for possible links to heart disease, cancer, liver disease, high blood pressure, irritability, mood changes, and aggressiveness.

The group also recommended that studies explore the extent of steroid abuse and that educational programs warn people about the dangers of the drugs.

Anabolic steroids are derivatives of the male hormone testosterone. They can cause genital changes, menstrual irregularities, sterility, fetal damage, liver tumors, heart disease, and death.

Prescription steroids are approved by FDA to treat a small number of diseases. The Drug Enforcement Administration, under the Controlled Substances Act, is responsible for enforcing steroid regulations.

For more information, see "On the Teen Scene: Sports and Steroids Are a Losing Proposition" in the September 1991 issue of *FDA Consumer*.

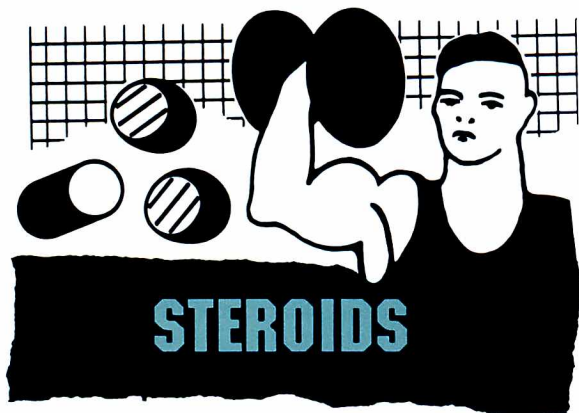
CDC Newly Defines Lyme Disease

The national Centers for Disease Control is urging states to adopt a new standard surveillance case definition when reporting Lyme disease, a tick-borne ailment that became nationally reportable last January.

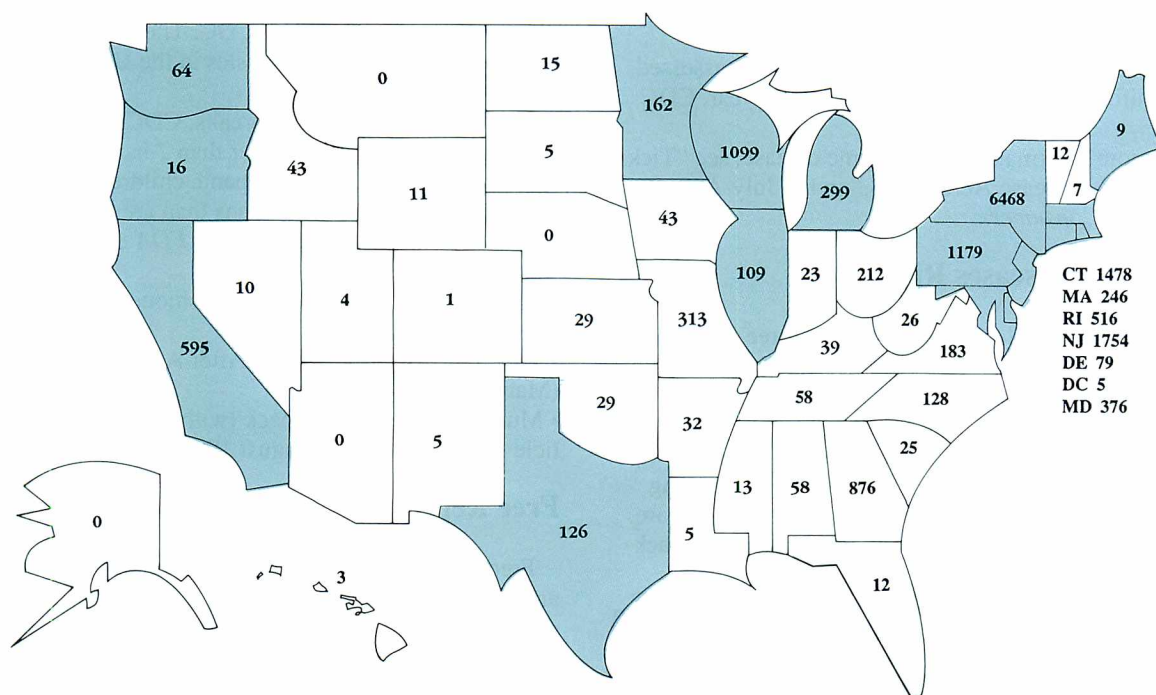
While CDC has been tabulating reports of Lyme disease since 1982, inconsistent case definitions from one state to another have produced unreliable figures. To improve the situation, CDC, the Council of State and Territorial Epidemiologists, and a panel of nongovernment clinical experts developed the new definition.

Lyme disease is caused by *Borrelia burgdorferi* bacteria transmitted to people in the bite of infected *Ixodes dammini* or *Ixodes pacificus* ticks. These ticks require animal hosts, mainly the white-footed mouse and white-tailed deer. Up to 80 percent of people with Lyme disease develop a characteristic bull's-eye rash called erythema migrans. Additional symptoms mimic other illnesses, such as arthritis and heart disease.

According to CDC's June 28, 1991, *Morbidity and Mortality Weekly Report*, a drop last year in reports of Lyme disease suggests a plateau in the trend of rapid annual rise. Reports increased from 497 in 1982 to 8,803 in 1989—nearly doubling each year from 1986—but then fell to 7,997 cases in 1990.



Reported U.S. Lyme Disease Cases



Despite widespread reporting of human Lyme disease cases, the highlighted states are the only ones where Lyme disease is either known to occur (because the organism has been isolated from ticks, animals or people there) or is likely to occur (because tick species

occurring there have transmitted Lyme disease in nearby states), according to the national Centers for Disease Control. No cases have been reported in Alaska.

(Source: Centers for Disease Control)

"The reasons for this apparent plateau are unknown," says Roy Campbell, M.D., Ph.D., a CDC expert on Lyme disease. "One factor may be that there's less publicity about the disease today than in previous years, particularly in 1988-1989, and there may be less interest in reporting of cases by physicians. Another factor that may explain some of the apparent plateauing is the use of the more stringent national case definition by some states beginning in 1990."

The surveillance definition is not intended for use in

clinical diagnosis and patient management, Campbell says. Accordingly, a case would be *reported* as Lyme disease if the patient has:

- erythema migrans at least 5 centimeters in diameter, or
- at least one recent symptom of musculoskeletal, nervous, or heart and blood vessel system involvement *and* laboratory confirmation of infection.

The new definition may have accounted for increased reports in some states but decreased reports in others. Last year, Connecticut, for example, following the defi-

nition at CDC's request, defined cases by a rash of 5 centimeters or larger, thereby excluding 15 percent of cases with smaller rashes that would otherwise have been counted. On the other hand, New Jersey's use of the definition broadened its criteria for reporting, including more cases.

Impact of the new definition can be further assessed after uniform use by all states for at least a year, CDC stated.

For more information about Lyme disease, see "Ticks Carry Lyme Disease Across U.S." in the July-August 1988 *FDA Consumer*.

Three Old Diseases Rise Anew

Syphilis, tuberculosis and measles—three infectious diseases that have for years been held to a minimum in the United States—are on the rise, according to the national Centers for Disease Control.

Syphilis, a sexually transmitted disease, has risen 75 percent since 1985, mostly in urban areas and among drug users and those with limited access to health care. Incidence of the disease rose 126 percent among black



men and 231 percent among black women, while rates for whites declined or stayed the same.

The rise in syphilis has important implications for the AIDS epidemic, since open sores caused by syphilis can allow the AIDS virus to enter the body.

Tuberculosis, a lung disease, rose 4.7 percent from 1988 to 1989, with the largest number of cases among immigrants infected before entering the United States. AIDS patients also have a higher incidence of the dis-

ease because their immune systems are too weak to fight off TB bacteria.

Measles rose more than 52 percent between 1989 and 1990, according to CDC. Most cases occur among children under 5 who have not been vaccinated against the disease as recommended by CDC. There were more than 27,000 reported cases of measles in the United States in 1990, with 89 deaths.

In areas with measles outbreaks, CDC said as few as 50 percent of children younger than 2 have been vaccinated, and that black and Hispanic children are less likely to receive vaccinations than are white children.

For more information, see these *FDA Consumer* articles:

- Syphilis and Gonorrhea: Old-Fashioned VD Still Flourishing (April 1986)
- Tuberculosis: Still Striking After All These Years (March 1991)
- Mumps Makes a Comeback (with accompanying article on measles, July-August 1989)

Free Reprints

Free reprints of the following *FDA Consumer* articles are now available:

- Feeding Baby: Nature and Nurture (Spanish version, FDA 91-2236S)
- Getting Information from FDA (FDA 91-1167)
- How to Take Your Medicine: Penicillins (Spanish version, FDA 91-3184S)
- Modern Diagnostics Help Detect Cancer Early (FDA 91-1173)
- Planning a Diet for a Healthy Heart (FDA 91-2220)
- Sweetness Minus Calories Equals Controversy (FDA 91-2205)

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



Guidelines Set for HIV-Infected Health Workers

Physicians, dentists, and other health-care workers who are infected with HIV, the virus that causes AIDS, should not perform "exposure-prone" medical procedures unless they have received guidance from an expert review panel, according to new guidelines issued by the U.S. Department of Health and Human Services.

Although the states, not the federal government, regulate the practice of medicine, the federal guidelines are expected to strongly influence professional standards and requirements.

Specifically, the guidelines advise health-care workers who perform exposure-prone procedures to be tested for HIV and for the hepatitis B virus. If infected with HIV or the most virulent form of hepatitis B, they should not perform exposure-prone procedures unless they seek guidance from an expert review panel. The review panel will advise them under what circumstances, if any, they may continue to perform these procedures. In such cases, at a minimum, the infected health-care worker must notify prospective patients about the infection before performing an invasive, exposure-prone procedure.

"Exposure-prone" procedures are those in which the health-care worker's blood might come in contact (through a cut, scratch, or other injury) with a patient's body cavity, mucous membranes, or subcutaneous (under the skin) tissues.

Examples of such procedures include abdominal, gynecological and heart surgery, and root canals and tooth extractions.

The vast majority of medical activities involve no risk of AIDS transmission.

The new guidelines were developed by the national Centers for Disease Control after two days of public hearings in Atlanta and a 30-day public comment period. In addition to their primary recommendations concerning invasive procedures and patient notification, the guidelines encourage other safety practices, including:

- scrupulous precautions against infection—including sterilizing equipment, handling needles and other sharp instruments carefully, and wearing gloves when appropriate

- increased hepatitis B vaccination for health-care workers who are likely to be exposed to blood
- more research to find ways of reducing the chances of injury to health-care workers that might result in patient exposure.

CDC is distributing the new recommendations as a supplement to its *Morbidity and Mortality Weekly Report*. The recommendations will be distributed widely to physicians, dentists, nurses, professional schools, and other interested parties. They may be obtained by calling the AIDS Hotline, 1-800-342-AIDS.

Sale of Unapproved Test Kits Stopped

Two firms that were selling unapproved AIDS test kits stopped those sales a week after FDA sent them letters warning of severe regulatory action if they continued selling them.

On July 5, 1991, Epitepe Inc., of Beaverton, Ore., and Home Office Reference Laboratory, Inc., of Lenexa, Kan., agreed to stop selling OraSure saliva collection kits for AIDS antibody testing. Although Epitepe was seeking FDA approval of the devices, the agency had not yet determined the safety and efficacy of the kits nor approved them for marketing. Home Office Reference retrieved the devices from insurance firms that had purchased them to screen potential policy holders for evidence of antibodies to the AIDS virus.

Medical devices require pre-market approval by FDA before they can be commercially marketed. To date, no AIDS antibody test kit using any human body fluid other than whole blood, dried blood spots, plasma, or serum has been approved.

FDA is also investigating reports of other unapproved specimen collection devices being used for AIDS antibody testing.

Human Trials of Procysteine Begin

A new agent to fight AIDS is being tested on HIV-infected patients.

FDA in July allowed Clintec Nutrition Company of Deerfield, Ill., to begin phase I testing of the drug, Procysteine, in humans. (Phase I tests are conducted in small numbers of patients to determine a product's safety.)

According to Clintec, procysteine stimulates the body to produce glutathione, a combination of amino acids critical for maintaining normal cell function. In laboratory tests, glutathione has been shown to inhibit replication of the HIV virus.

Interest in procysteine as an AIDS-fighting drug followed the discovery by scientists at the National Institutes of Health in Bethesda, Md., and the Institute for Immunology and Genetics in Heidelberg, Germany, that AIDS patients have considerably reduced intracellular levels of glutathione.

Procysteine has not been studied directly for laboratory evidence of anti-HIV activity, but has been found to increase intracellular glutathione levels after administration. Its effectiveness in humans can only be determined by Phase II testing.

Clintec Nutrition Company is a joint venture between Baxter Healthcare Corporation and Nestle S.A., both of Deerfield, Ill.



N E V E R S A Y

DIET?

by Ruth Papazian

Like millions of her fellow Americans, talk show host Oprah Winfrey has known the thrill of weight loss and the agony of watching the pounds creep back on. Some three years after losing 67 pounds on a liquid formula diet, Oprah lost her battle to stay a size 10 and has sworn off dieting forever.

Considering that weight-loss programs, pills and potions typically slim the wallet but not the dieter, Oprah may be on to something. And, with research pointing to genetic and metabolic differences between stout and slim people, obesity experts are now debating whether dieting can achieve permanent weight loss.

Defining Obesity

Obesity is associated with such health problems as diabetes, gallstones, hypertension, and heart disease. Obesity is also linked to colorectal cancer and to breast, uterine and ovarian cancer in women and prostate cancer in men. But how many extra pounds does it take before a person crosses the line from overweight to obese? It depends on whom you ask: The definition of obesity is currently in a state of flux.

Traditionally, obesity was defined as 20 percent or more above an optimal weight for height derived from actuarial statistics that correlated with lowest death rates. Now, some health experts

say that the weight-for-height yardstick is both imprecise and overly restrictive.

Recent research suggests that more important than the amount of extra weight a person carries is where it is located.

"Rather than weight-for-height, obesity should be defined in terms of waist-to-hip ratio," says C. Wayne Callaway, M.D., associate clinical professor of medicine at George Washington University in Washington, D.C., and a leading authority on obesity.

Waist-to-hip ratio can be calculated by dividing the number of inches around the waistline by the circumference of the hips. For example, someone who has a 27-inch waist and 38-inch hips would have a ratio of 0.71. A woman whose ratio is 0.8 or higher would be at high risk of weight-related health problems, as would a man whose ratio is 0.95 or above.

Numerous studies show that fat in the hips and thighs is less health-threatening than abdominal fat. While other fat cells empty directly into general circulation, the fatty acid contents of abdominal fat cells go straight to the liver, by way of the portal vein, before being circulated to the muscles. This process interferes with the liver's ability to clear insulin from the bloodstream. As blood levels of insulin increase, muscles and other cells become insulin-resistant, and blood glucose levels rise as a result. In response, the pancreas cranks out more insulin, prompting the autonomic nervous system (which controls heart rate, blood pres-

sure, and other vital signs) to produce norepinephrine, an adrenalin-like chemical that raises blood pressure. This sets the stage for the development of diabetes, hypertension, and heart problems.

Callaway also points out that weight tables do not take age-related weight gain into account (as people age, fat cells become less metabolically active, so one can weigh more and still be healthy) and "arbitrarily" assign lower weights to women at a given height than to men. "There is no evidence showing that women live longer if they weigh less than men of equal stature," he says.

To be a more useful indicator of health risks, experts advocate broadening the definition of obesity to meet three criteria: weight for age and height rather than for gender and height, waist-to-hip ratio, and presence of such weight-related health problems as hypertension.

Food or Fate?

As researchers try to figure out why some people get fat and others don't, it is becoming increasingly apparent that obesity has a variety of causes—heredity, environment, metabolism, and level of physical activity—and, therefore, no single "cure."

Adipose tissue (fat cells) stores energy in the form of fat to meet the body's energy needs when other sources, such as glucose, are unavailable or depleted.

The body has an almost limitless capacity to store fat. Not only can each fat cell balloon to more than 10 times its

Product Bans and Controversies

In the wake of last year's House Committee on Small Business hearings on the \$33 billion weight-loss industry, FDA and the Federal Trade Commission separately announced investigations into the safety and efficacy of diet pills and programs, and how they are promoted in advertising. FDA also moved to pull dangerous or ineffective products off store shelves.

In the fall of 1990, FDA proposed a ban on 111 ingredients in over-the-counter (OTC) diet products, including amino acids, cellulose, grapefruit extract, and kelp. The agency had given manufacturers of these products an opportunity to provide data from clinical tests showing they were effective in promoting weight loss, but did not receive adequate information to support advertising claims, according to William Gilbertson, Pharm.D., director of FDA's OTC Drug Review Program. "Many of these ingredients had been marketed before 1962 [when an amendment to the 1938 Food, Drug, and Cosmetic Act was passed requiring drugs not only to be safe, but also effective] and had never been evaluated for efficacy," Gilbertson explains.

He says that manufacturers wanting to market weight-loss drugs using the banned ingredients will have to get prior FDA approval—which means fil-

ing a new drug application and supplying data from clinical tests to support claims.

FDA also recalled Cal-Ban 3000, a heavily advertised diet pill containing guar gum (a vegetable gum that swells when it absorbs moisture, providing a feeling of fullness, according to advertising claims) after receiving a number of consumer complaints of adverse reactions. In a number of cases, the tablet caused gastric or esophageal obstruction, and one person died as a result of complications following surgery to remove the mass of gum blocking his throat.

The most widely used ingredient in OTC diet pills, phenylpropanolamine hydrochloride (PPA), an appetite suppressant that is chemically related to amphetamines, has been the subject of a decade-long medical dispute. Though clinical tests yielded conflicting results (often due to defects in study design), an FDA panel concluded in 1982 that enough data existed to support the efficacy of PPA in curbing the appetite to qualify it as an OTC weight-loss aid. However, a controversy developed over PPA's safety. The drug can cause small elevations of blood pressure at recommended doses, and there are a few reports of marked blood pressure elevation and intracranial bleeding associated with its use. Whether such events are truly drug-related and can occur at recommended doses is the subject of debate.

In May, FDA held a public meeting to explore such issues as whether PPA can cause such central nervous system damage as stroke when taken at (or over) the recommended dosage, whether the drug poses a health hazard to teenagers, and whether PPA is especially hazardous to those with eating disorders.

For its part, FTC has begun to look

into advertising claims of 14 diet programs. "We are concerned with programs that go beyond promising weight loss and claim to be able to keep the weight off," says Richard Kelly, assistant director of FTC's division of service industry practices. Additionally, FTC is looking into whether diet companies are touting the safety of their programs while playing down such health risks as the development of gallstones or loss of muscle tissue. Kelly expects the FTC investigation to be completed by the end of the year.

FTC also monitors advertising claims for diet aids on an ongoing basis and takes legal action to get companies to stop making unfounded claims. Among the agency's recent targets: Fat-Magnet, a pill that claimed to break up into thousands of tiny "fat-attracting" particles that "flush" fat from the body, and FibreTrim, a high-fiber supplement that its manufacturer claimed could aid in weight reduction.

FDA's ban of ineffective diet drugs could make future FTC action easier. "The FDA says these products are not efficacious, which is a good piece of evidence to have when we go to trial," says Judy Wilkenfeld, assistant director of FTC's advertising practices division.

Consumers can get a list of ineffective diet aids by writing to: FDA, HFE-20, 5600 Fishers Lane, Rockville, Md. 20857. ■

—R.P.

Research indicates that obesity may be linked to the proportion of fat in the diet rather than to the amount of calories consumed.

original size, but should the available cells get filled to the brim, new ones will propagate. As the body stores more fat, weight and girth increase.

A number of studies have shown that genetics may be the most important determinant of how much you weigh. Some people are more prone to weight gain than others even when caloric intake is the same, according to a study of 12 pairs of identical male twins aged 19 to 27 conducted at Quebec's Laval University and reported in the May 24, 1990, issue of the *New England Journal of Medicine*. After eating an extra 1,000 calories six days a week for 100 days, some of the twins gained 9 pounds apiece while others gained as much as 29 pounds each—in some twin pairs, the extra calories were stored as fat while others used up the excess calories by building muscle tissue. The twins in each pair gained the same amount of weight and in the same places, suggesting that as-yet unidentified genetic factors influence the amount of weight gain and its distribution.

The same issue of the *New England Journal of Medicine* also reported on a study comparing the body mass of 673 pairs of identical and fraternal Swedish twins who had been raised together or apart to determine how much influence heredity had over obesity (identical twins have the exact same genetic makeup whereas fraternal twins do not; twins who were raised together were subject to the same environmental influences while those who were raised apart were not). Even if they had grown up together, the fraternal twins were less likely than the identical twins to share a similar pattern of body weight whereas identical twins—even when raised apart—did not vary significantly in weight. The researchers concluded that genetic factors, apart from diet or lifestyle, strongly influence how much a person weighs.

Previously, researchers at the University of Iowa found evidence of a recessive obesity gene (the child needs one copy of the gene from each parent to have the tendency towards overweight). A study of 277 schoolchildren and their families showed a pattern

of obesity that followed the classic model for recessive inheritance.

However, it is likely that a number of genetic mechanisms exert influence on weight, among them genes that dictate metabolism and appetite. One that is being investigated actively is the gene that codes for lipoprotein lipase (LPL), an enzyme produced by fat cells to help store calories as fat. If too much LPL is produced, the body will be especially efficient at storing calories.

LPL is partly controlled by reproductive hormones (estrogen in women, testosterone in men), so gender-based differences in the activity of the enzyme also factor into obesity. In women, fat cells in the hips, thighs and breasts secrete LPL, while in men the enzyme is produced by fat cells in the midriff region. Fat cells in the abdominal area release their contents for quick energy, while fat in the thighs and buttocks are used for long-term energy storage. Thus, a man can often pare his paunch more readily than a woman can shed her saddlebags.

LPL also makes it easier to regain lost weight, according to a study conducted at Cedars-Sinai Medical Center in Los Angeles and reported in the April 12, 1990, issue of the *New England Journal of Medicine*. Nine people who lost an average of 90 pounds had their LPL levels measured before dieting and after maintaining their new weights for three months. The researchers found that levels of the enzyme rose after weight loss, and that the fatter the person was to start with, the higher the LPL levels were—as though the body was fighting to regain the weight. They believe that weight loss activated the gene producing the enzyme. This may be one reason why it is easier for a dieter to regain lost weight than for someone who has never been obese to put weight on.

Set for Life?

This study supports the much-debated "set point" theory, which holds that inner mechanisms set a person's weight at a predetermined level and if anything is done to change the weight, the body will adjust to restore fat content to the set point.

"I regard body temperature, which stays around 98.6 degrees F, to be a set point. Weight doesn't have a set point in that sense," says Xavier Pi-Sunyer, M.D., director of the Obesity Research Center at St. Luke's-Roosevelt Hospital Center in New York.

If there is a set point for weight, it generally seems to move in one direction—that is, the body will not make adjustments to counteract a large weight gain but will fight efforts to lose the weight. "When a person gains weight and stays at that weight a while, the body will defend that weight. It becomes the new 'set point'," explains Pi-Sunyer.

Aside from the action of LPL, the body uses other adaptive mechanisms when food intake is reduced. To cite just two of them: Dieting depresses the metabolic rate so that calories are burned more slowly, and as fat cells shrink, they become more responsive to the action of insulin and do not release their contents as readily.

"The body is very good at defending itself from the danger of underweight, but is not really equipped to handle overweight. Throughout the ages, people have not had a problem with having too much to eat. That's a modern problem," says Pi-Sunyer.

Though a definitive study has yet to be done in humans showing that weight gain becomes more likely after each successive diet (the so-called "yo-yo" syndrome), the Cedars-Sinai study strengthens this controversial hypothesis. However, in order to show conclusively that weight loss gets harder each time a person loses and regains weight, the subjects in the Cedars-Sinai study would have to be followed through several cycles of weight gain and loss to determine whether LPL levels kept rising after each diet.

Repeatedly losing and gaining weight may have other health consequences, according to a report in the June 27, 1991, *New England Journal of Medicine*. American and Swedish researchers analyzed weight fluctuations and later health problems over a period of 32 years in more than 3,000 women and men who participated in the Framingham (Mass.)

***R*ather than severely restricting caloric intake, weight-loss specialists now advise moderate exercise as a means of achieving weight control.**

Health Study. The researchers said that people who repeatedly lose and regain weight appear to have an overall higher death rate and to be at greater risk of heart disease and some cancers than those whose weight remains stable (even if overweight) or steadily increases.

Are All Calories Created Equal?

"The body will do what it was programmed to do even if that's not what you want it to do," notes Callaway. For this reason, restricting food intake to 1,000 or 1,200 calories in order to lose weight is "doomed to failure," he says. "For many people, going on one more diet isn't going to solve a weight problem in the long run."

Even well-established weight-loss programs are not individualized enough to account for genetics, past dieting attempts, and a person's activity level, he says.

While Pi-Sunyer agrees that putting everyone on the same prepackaged weight-loss regimen can be counterproductive, he believes that restricting caloric intake is an important weight-control tool. "You can easily cut caloric intake just by restricting the amount of fat and sugar you eat. This might be the only adjustment a moderately overweight person would need to make in order to lose weight."

Research indicates that obesity may be linked to the proportion of fat in the diet rather than to the amount of calories consumed, according to a survey of the diets and exercise habits of 107 men and 109 women reported in the September 1990 issue of *American Journal of Clinical Nutrition*. Researchers at Indiana University in Bloomington found that overweight subjects got 35 percent of their calories from fat and 46 percent from carbohydrates, compared to 29 percent of calories from fat and 53 percent from

carbohydrates for their slender counterparts. A recent University of Vermont study suggests that limiting fat intake to about 20 percent of total calories enabled chronically obese patients who failed to lose weight on a variety of reducing programs to lose an aver-

age of 20 to 30 pounds over the course of a year.

Scientists used to think that all calories were created equal. That is, whether it came from fat, carbohydrates or protein, a calorie produced a certain amount of heat when the body burned it to fuel metabolic processes. Thus, according to "The Dieter's Law of Thermodynamics," mashed potatoes and milkshakes were no more culpable in promoting weight gain than pasta and peas—as long as caloric intake was limited to 1,000 or some other magic number.

Alas, further research has shown this to be an illusion. Calories from carbohydrates, fat and protein are used differently by the body. Virtually all fat calories are immediately stored in fat cells. Carbohydrates and protein are converted into glucose for fuel, with only those calories in excess of the body's energy needs being stored.

Compounding the problem, a gram of fat has 9 calories while an equal amount of carbohydrates or protein has 4. "For the same number of calories, a person can have a much bigger serving of a food that is primarily carbohydrate as one that is high in fat," observes Walter Glinsmann, M.D., associate director for clinical nutrition at the Food and Drug Administration's Center for Food Safety and Applied Nutrition. For instance, a 6.5-ounce baked potato has the same number of calories as 1.5 ounces of potato chips (about 225).

The type of fat in the diet is important as well. Currently, the National Cholesterol Education Program recommends that the diet be limited to 30 percent of calories from fat, with no more than 10 percent of those coming from saturated fats. "Unsaturated fats are precursors of such biologically active molecules as prostaglandins, which are involved in a variety of body processes, including

blood pressure regulation and immune system function. Various types of fat have different roles in health maintenance and disease risk," says Glinsmann.

Exercise the Key

Rather than severely restricting caloric intake and depressing metabolic activity as a result, weight-loss specialists now advise moderate exercise as a means of achieving weight control. "A person not only burns calories while exercising, but if he or she is eating an adequate amount of food, calories will continue to be burned at a higher rate for up to several hours afterward," says Callaway.

"For most people, cutting fat intake and adding moderate exercise can work as well as a commercial weight control program," says Pi-Sunyer. Exercisers are also more likely than sedentary people to keep weight off, whether they use a "do-it-yourself" diet or attend a program.

Unfortunately, weight maintenance is a universal failing of all weight-loss programs, regardless of how expensive or well-established. "If you're going to evaluate weight-loss success, you can't just look at the number of pounds lost. You have to look at long-term weight maintenance," says Callaway.

"Diet programs make money on the weight-loss phase, not the weight maintenance phase. At the time when people need the most help in controlling their weight, many programs cut them off," says Pi-Sunyer. By various estimates, as many as 85 percent of dieters put the weight back on within two years after weight loss.

"Perhaps weight-loss programs should be less focused on weight control and more focused on identifying individual risk factors and dietary patterns associated with obesity, and to modify them where possible," suggests Glinsmann.

"Obesity is not yet well understood," concedes Pi-Sunyer, "and all we can do right now is to tell people to exercise and to cut down on fat intake." However, while genetic predisposition towards obesity can be mitigated by exercise and sensible eating habits, some people will have to work a lot harder at keeping weight at optimal levels than others. "It's like jazz—there's a theme and rhythm and you've got to work within that framework, but you can improvise," says Callaway. ■

Ruth Papazian is a freelance writer in New York City specializing in health and medicine.

PATCHES, PUMPS, & TIMED RELEASE

New Ways to Deliver Drugs

by Marian Segal

involves "controlled-release" products. Rather than develop new drug entities at great cost, some drug therapies already on the market can be improved simply by controlling the rate at which they enter the bloodstream.

"Virtually all the delivery systems marketed are initially in what we would call 'immediate-release preparations'—things that disintegrate and dissolve in 5 or 10 minutes," says FDA visiting scientist Gordon Amidon, Ph.D. "For some drugs, dissolution may take longer because of drug or dosage form properties, but the controlled release is not designed in."

Timing Is Everything

"Drugs that are released rapidly produce a relatively rapid and high concentration in the body, followed by a sharp decline—a peak and valley effect," says Amidon. "We know that at too low a blood level the drug is not effective, at optimum level it's effective, and at too high a level undesirable effects are produced. The objective is to try to maintain the range in between."

Controlled-release systems deliver a drug at a slower rate for a longer period. The dosage form contains more drug than a conventional tablet or injection,

for example, but delivers the medication far more slowly—over a period of hours, days, or even years, rather than seconds or minutes.

Depending on the mechanism, the delivery system may simply release the drug at a variable, but slower, rate, or release it at a constant rate over the period of release. Sometimes, by decreasing the variability of blood levels, it may reduce side effects.

The Ways to Delay

Milo Gibaldi, Ph.D., dean of the University of Washington's School of Pharmacy in Seattle, writes in *Biopharmaceutics and Clinical Pharmacokinetics*: "The early history of the prolonged-release oral dosage form is probably best forgotten. Products were developed empirically, often with little rationale, and . . . problems were common. Today, the situation has improved; many of the available products are well-designed drug delivery systems and have a defined therapeutic goal. In some cases, the prolonged-release dosage form is the most important and most frequently used form of the drug."

Prolonged-release preparations usually require less frequent dosing. Being able to take a pill once a day instead of four

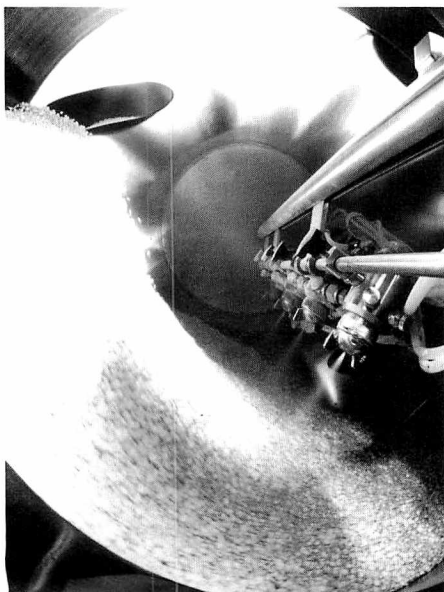
If, 25 years ago, someone tried to sell you an adhesive patch, telling you to stick it behind your ear and it would keep you from getting sick on the high seas, you could make a safe bet that you were being sold up the river by a modern-day snake oil salesman.

Today, however, a similar patch can be legitimately prescribed by your doctor. Technological advances over the last 20 to 30 years have enabled scientists to develop new forms of delivering drugs to our bodies, including a transdermal patch containing the drug scopolamine to prevent motion sickness.

Drug dosage forms are keeping pace with the high-tech times. Indeed, the ubiquitous tablet of 1990 may one day become obsolete, going the way of the spirits, powders and tinctures of a century ago.

What might replace the tablet? How about pills that are pumps and implanted drug-filled devices with or without tiny computers to regulate the time and amount of drug dispensed? These and other unconventional dosage forms already exist, heralding advances in drug delivery that promise even safer and more effective treatments.

One of the most active areas of research and development in drug delivery



High-tech equipment spray coats the rate-controlling membrane on an osmotic system tablet.



Special equipment is used to measure drug release rates from osmotic system tablets.



A worker uses laser equipment to drill a hole in osmotic tablets in the manufacture of oral osmotic systems. (This photo and those on the previous page courtesy of ALZA Corporation, Palo Alto, Calif.)

times or more, for example, can help improve patient compliance. That is, it's often easier and less bothersome for patients to remember to take fewer doses of medications.

There are a number of ways of controlling the rate of delivery of oral medicines. One system uses the principle of osmosis to release the drug. The drug and an osmotic agent are surrounded by a semipermeable membrane pierced by one or more small, laser-drilled holes. As water from the digestive tract is drawn through the membrane, the osmotic layer expands, pushing the drug through the holes.

In other systems, the drug simply diffuses through a polymer coating of the pill. The drug may be contained in a reservoir surrounded by a polymer film, or it may be uniformly distributed through the polymeric material.

"Most of the polymers used in human pharmaceuticals are derivatives of natural products such as gelatin and cellulose, or the synthetic polymer silicone," says Amidon. "When designing a drug

delivery system, you select the polymer best suited for that particular system based on the properties of the specific polymer."

An erosion-controlled release system uses a polymer that is relatively water-soluble with the drug incorporated in it. As the polymer dissolves, it releases the drug. The formulation of Contac's "tiny time pill" capsules is based on an erosion system. It consists of coated and uncoated granules that erode at various rates, thus releasing the drug at varying rates and providing relief for an extended period.

Skin Patches

Some drugs that have the right properties to penetrate the skin and are potent enough to be effective at low doses can be delivered transdermally (through the skin). The first transdermal patch was approved by FDA in 1979. It contained the drug scopolamine, used to treat motion sickness.

Scopolamine can cause dry mouth, drowsiness, blurred vision and other eye

problems, and sometimes more serious side effects, including dizziness and confusion, hallucinations, difficulty urinating, and rashes. Delivered through the skin at a slow rate in small amounts over three days, however, the drug can protect against motion sickness with fewer or less severe side effects.

One patch design consists of four layers of thin, flexible membranes: an impermeable backing, a drug reservoir, a rate-controlling membrane, and an adhesive. When the patch is applied, the drug begins flowing through the skin into the bloodstream at a rate regulated by the membrane, pre-programmed to keep the drug at levels that provide effectiveness with acceptable adverse effects.

Another transdermal preparation is a nitroglycerin patch for patients with angina pectoris (chest pain). Unlike nitroglycerin tablets placed under the tongue at the onset of an attack to relieve pain, the patch is applied once a day (usually to the chest) to help prevent angina attacks. As with scopolamine, a goal of delivering a steady concentration of nitro-

glycerin was to provide the lowest effective blood level of the drug while minimizing adverse effects, such as headaches in the case of nitroglycerin.

With the nitroglycerin patch, however, it was discovered that maintaining constant blood levels is not advantageous. Studies showed that when patches are worn continuously, drug tolerance develops within 24 hours and the medication is no longer effective. Revised labeling recently approved by FDA recommends a dosing schedule alternating a daily patch-on period of 12 to 14 hours a day with a patch-off period of 10 to 12 hours.

Another extended-release preparation that did not prove as successful as originally expected is Ocusert, a reservoir system in a wafer-like disk, designed to treat glaucoma. Glaucoma is characterized by increased pressure in the eye that can cause blindness. At the time Ocusert was developed, the standard treatment for glaucoma was application four times a day of eye drops containing the pressure-lowering drug pilocarpine. The drops often caused side effects, however, and patients sometimes did not take them as prescribed. Ocusert, on the other hand, placed in the lower eyelid, where it floats in the tear film, delivers low-dose pilocarpine continuously for one week.

Although it was seen as having the potential to solve patient compliance problems, Ocusert was never widely used, in part because older patients were reluctant to place the object in their eyes. Also, Ocusert costs the patient approximately five times more than the pilocarpine drops. A new drug, timolol, has since been developed, which, although not a controlled-release preparation, requires only two applications of drops a day instead of the four needed with pilocarpine.

Implants and Intrauterine Devices

Devices implanted under the skin are also being developed to deliver drugs at a controlled rate. FDA approved one such device for contraception in December 1990. The Norplant system is implanted under the skin and protects against pregnancy for five years, unless removed sooner. It consists of six flexible silicone tubes filled with a five-year supply of the hormone levonorgestrel. It is implanted in the upper arm, and small amounts of the hormone continuously seep through the permeable tubes into the bloodstream, providing contraception. (For more on this device, see

"Norplant: Birth Control at Arm's Reach" in the May 1991 *FDA Consumer*.)

Similarly, an intrauterine device called Progestasert releases the hormone progesterone directly into the uterus for one year to prevent pregnancy. An advantage of these controlled-release contraceptives over contraceptive pills is convenience; their effectiveness does not depend on remembering to take a daily pill.

The Mechanical Pump

Although the advantages of a steady rate of drug release are evident, some drugs are more effective given in intervals. Infusion pumps can be programmed to deliver drugs at very precise dosages and delivery rates. These pumps may have a feedback device that controls drug delivery according to need.

"I think we're going to see more complex dosing patterns that are going to be more difficult to regulate orally," says Amidon. "With further development of electronics and miniaturization of pumps and sensors, we'll be able to monitor various vital signs, and that will lead to feedback systems." Such a feedback system could monitor blood glucose levels and deliver insulin when needed.

Amidon explains that the size of the pump depends on the amount of drug and the intended length of treatment. Some pumps are portable, some wearable. For miniaturized, implantable pumps, methods will have to be devised to refill the device externally, perhaps once a month or once a year, through a catheter.

"I would say that 50 years from now we're going to have implantable pumps with multiple drugs that we can externally program once a month and, rather than going to the doctor for checkups, we will plug ourselves into a telephone monitoring device," Amidon predicts. "To solve problems like drug tolerance, we're going to have to develop drug delivery programs that are not constant, but programmed with time or circadian doses. We're going to see more complicated therapy in order to be able to reduce the amount of drug exposure and increase its efficacy."

If Amidon's vision is to become reality, several technological roadblocks will have to be solved first. Donald Marlowe, director of FDA's division of mechanics and material science, points out just one, as an example. Before feedback technology can be applied in humans, problems

with the pump's sensor mechanism must be overcome, Marlowe says. "For example," he explains, "contact with body proteins causes reduced sensitivity of the sensors, compromising [feedback] reliability."

One implanted pump, approved by FDA in 1982, allows chronic infusion of the liver cancer drug FUDR directly into the artery leading to that organ, thereby delivering a high concentration of the drug to the target organ.

William Enslinger, M.D., Ph.D., professor of Internal Medicine and Pharmacy at the University of Michigan Medical School in Ann Arbor, says that people live and function with implanted pumps quite well. One of his patients had a pump for eight years, which was refilled every couple of weeks. "We've had other people who have had them in for four years and a few people who have had them taken out when the liver tumor was eradicated."

Last July, FDA approved a concentrated form of morphine specially developed for microinfusion pumps that can be implanted under the skin of the abdomen or worn outside the body. Given this way, the drug can provide more constant relief to people in severe pain, such as terminal cancer patients. Programmed with dosing information before it is filled with the concentrated morphine, the pump constantly delivers fractional doses of the drug. The dose can be changed by beaming information through skin and tissues to the implanted pump.

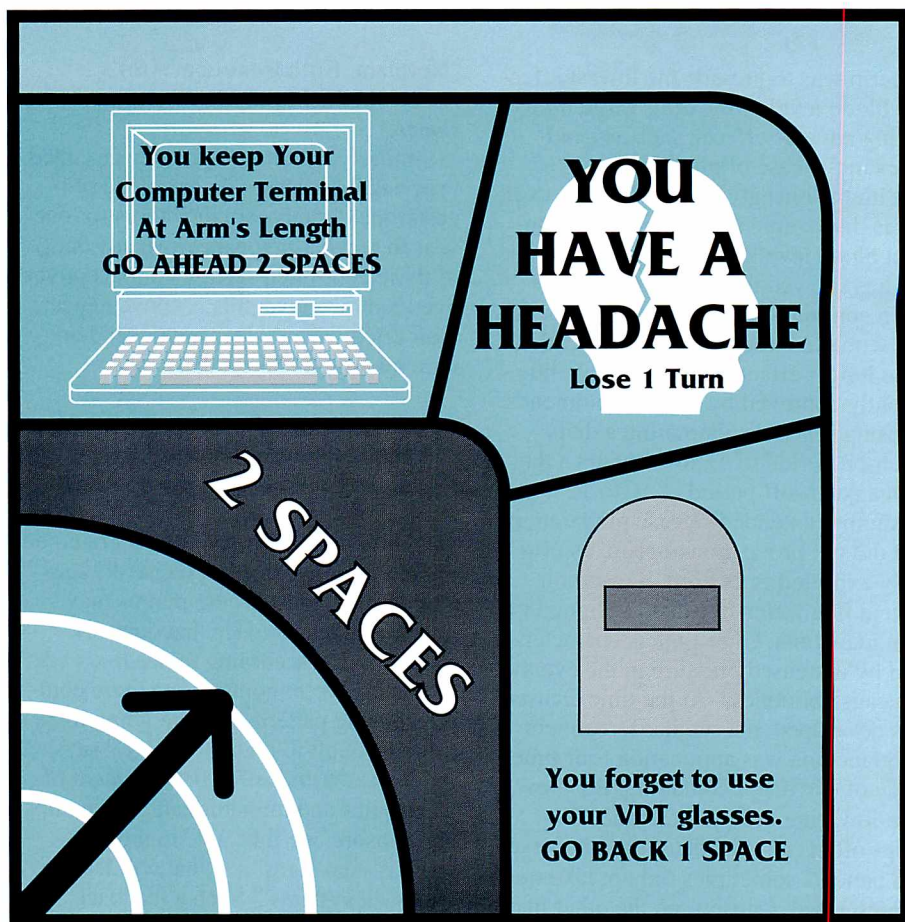
Concentrated morphine can have severe side effects, such as seizures and respiratory depression if the starting dose is misjudged. Therefore, patients must be monitored in a fully equipped and staffed facility for at least 24 hours after the initial "test" dose. Patients may then go home and return periodically—sometimes as seldom as once a month—for a physician to refill the reservoir in the pump.

It's clear that we're witnessing an evolution—or revolution—in drug delivery, with many innovations in administering drugs to improve safety and effectiveness. The process continues, using techniques as varied as advanced electronics and genetic engineering. ■

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

Playing It Safe At Work

by Jessica Auerbach



When most people think of workplace hazards, they picture mines, factories, or a construction site. Not many would consider a school gymnasium or a comfortable office an unsafe place to work. However, even the most mundane work environments can pose health hazards that might range from mild discomfort to serious injury or illness. In some cases, the Food and Drug Administration plays a role in limiting these hazards.

Mercury Vapor Lamps

Mercury vapor lamps, most often used to light streets, gymnasiums, sports arenas, banks, and stores must be maintained properly to be safe. These lamps are composed of an inner quartz tube containing the mercury vapor, enclosed by an outer envelope that filters out harmful short wavelength ultraviolet radiation. If the outer envelope is broken and the lamp continues to operate, intense ultraviolet radiation is emitted.

UV exposure at this level has produced photokeratitis (corneal burns) and reddening of the skin, as well as blurred or double vision, headaches, nausea, and

diarrhea. Most injuries have occurred in school gymnasiums after the lamps were struck and partially broken by sports equipment.

FDA issued a performance standard for high-intensity mercury vapor discharge lamps on March 7, 1980, allowing the manufacture of two types of mercury vapor lamps. One type, marked "T," is equipped with a self-extinguishing device that shuts the lamp off within 15 minutes after the outer envelope is broken. The other type of lamp, marked "R," does not contain a self-extinguishing feature. It may be used only in a fixture with a glass or plastic shield capable of absorbing hazardous ultraviolet radiation, or in areas where people will not be exposed to UV radiation if the outer globe is broken.

A 1980 FDA alert defines labeling that must appear on non-self-extinguishing mercury vapor lamps. This labeling includes the following instructions:

- Check the lamps regularly for missing, broken or punctured outer bulbs. This should be done with the lamps off.
- If a lamp is broken, turn the lamp off immediately.

- Replace lamps only when the lamps are off.
- Persons exposed to ultraviolet radiation from a damaged lamp should see a doctor if symptoms of skin burns or eye irritation occur.
- Report injuries to your state health department and to FDA.

The labeling for self-extinguishing "T" lamps must also state, "This lamp should self-extinguish within 15 minutes after the outer envelope is broken or punctured. If such damage occurs, **TURN OFF AND REMOVE LAMP** to avoid possible injury from hazardous short-wave ultraviolet radiation."

People near a broken mercury vapor lamp should leave the area immediately while taking steps to limit UV exposure to their eyes and skin by donning outerwear (coats or sweaters, for example) and sunglasses.

Radiation

At the end of World War II, the forerunner of the Nuclear Regulatory Commission was given jurisdiction over all radioactive materials capable of being used to build atomic weapons, including

those used for medical diagnosis and treatment. FDA has jurisdiction over products that emit x-rays, overseeing their safety and effectiveness, while individual states have the power to set licensing standards for both facilities using x-rays and the technicians who use such equipment.

Public Law 90-602, enacted in the 1960s, gives FDA jurisdiction over electronic products that emit nonionizing radiation, such as microwave ovens and color televisions. FDA develops performance standards for these products and provides educational materials for consumers. The National Council on Radiation Protection, with input from experts around the country, formulates guidelines on radiation safety that are nationally accepted.

If you have any questions about radiation safety from ionizing materials, contact your individual state radiation control office. FDA's Center for Devices and Radiological Health's consumer affairs division has consumer information on nonionizing radiation—such as that from microwave ovens, electric blankets, and televisions—and also has consumer information on products such as lasers (both medical and entertainment), airport x-ray machines, and medical x-rays.

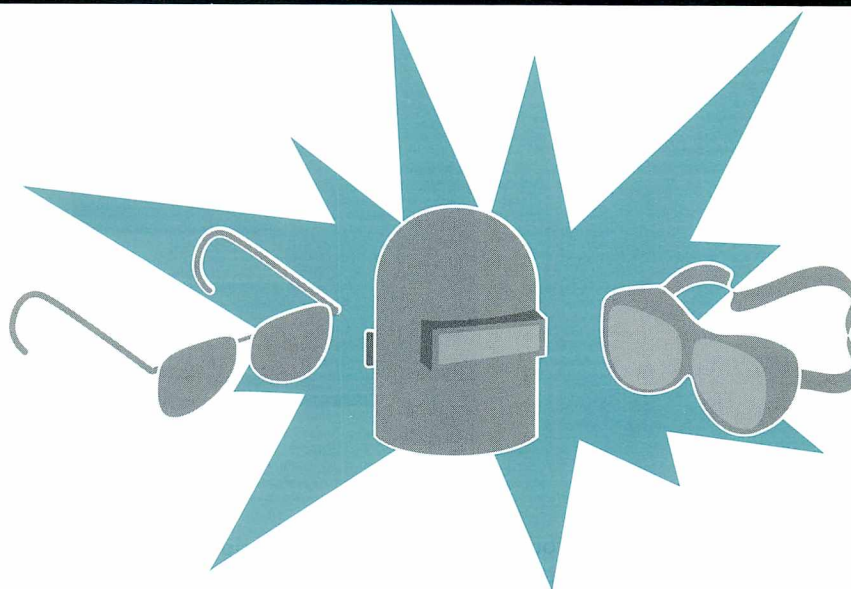
Video Display Terminals

Video display terminals (VDTs) are a staple in today's workplace. While some people use their terminals only intermittently during the day, others face their screens constantly as part of their jobs—making airline or concert reservations, for example. Despite lack of scientific data on serious health hazards, some people still fear that VDTs may cause cancer, immune system irregularities, or miscarriages.

The most common complaints from constant VDT users are dry or burning eyes, eye fatigue, blurred vision, and aches in the neck and back. A few simple steps can alleviate these discomforts:

- Use good room lighting. Adjust the room lighting levels and properly position the computer to get the room lighting that is most comfortable. The typical office lighting may be too bright for computer work.
- Eliminate sources of glare. Use drapes and blinds on windows. Don't sit facing a bright window. If necessary, use screen hoods or glare shields over the screen. Lower light levels in the room may reduce glare.
- Adjust the screen brightness and con-

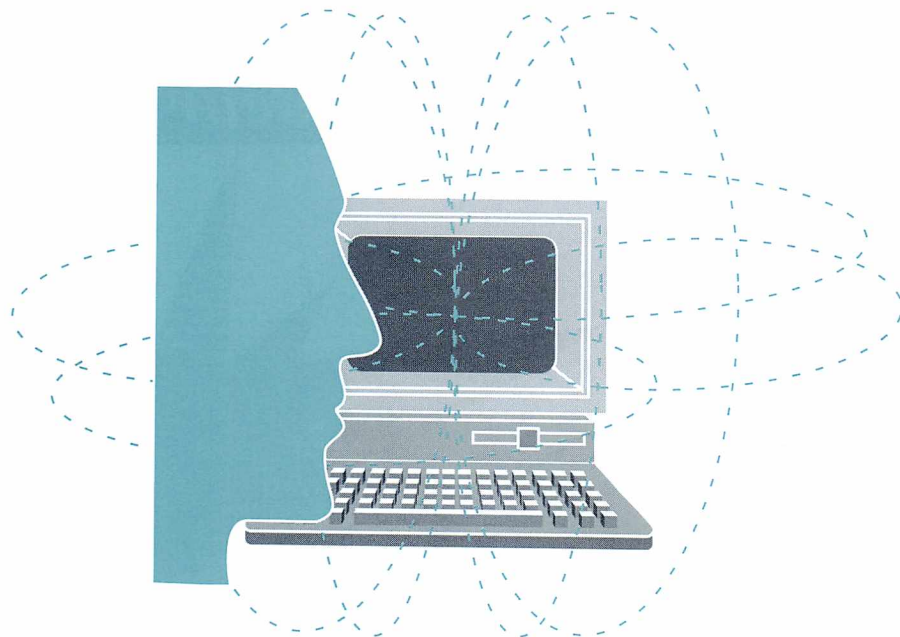
Protective Gear



Please note that face shields or welding helmets should be worn over safety glasses or goggles.

Job	Hazard	Protective Eyewear
Chemical handling	splash, acid burns	goggles (eyecup and cover types), face shields for severe exposure
Construction (chipping, grinding, machining, masonry, riveting, sanding)	flying objects, sand, dirt	safety glasses or goggles, face shields for severe exposure
Furnace operations (pouring, casting, hot dipping, gas cutting, welding)	sparks	goggles and safety glasses, face shields for severe exposure
	splash from molten metals	goggles, face shields
	heat	screen or reflective face shields
Welding	electric arc	welding helmets equipped with special filter lenses, welding shields
	gas	welding goggles or welding face shields
Woodworking	dust	goggles (eyecup and cover types)

(Source: Occupational Safety and Health Administration)



trast so that it is comfortable for you.

- Rest occasionally during periods of intense concentration. The National Institute of Occupational Safety and Health recommends taking a 15-minute rest break every hour from highly demanding computer tasks. Don't forget to blink frequently to reduce dryness and irritation. Looking at a distant object can relax your eyes. Closing your eyes can also help.

- Maintain a good viewing distance. Close viewing may cause focusing fatigue. Adjust the workstation so that keyboard, screen, and paper copy are an equal distance from the eyes with the screen slightly (about 20 degrees) below eye level. It is helpful to use a copyholder. A good viewing distance is 22 to 26 inches.

- Talk to an eye-care professional about special glasses or an altered prescription. Some people may need special glasses for focusing at the intermediate distance that is neither as long a dis-

tance as prescriptions for nearsightedness usually encompass, nor a typical reading distance. This is particularly true if you wear reading glasses or bifocals. Tell your eye-care professional if you use a computer for long periods, and discuss any eye discomfort you have.

- Keep the work environment free of dust. Dust can make the eyes tear, feel gritty, or turn red. Proper humidity and ventilation are important. There are cleaners available to remove dust from the screen.

What About ELF?

Another serious concern associated with VDTs is the extremely low frequency (ELF) electromagnetic fields they produce. Alternating only 60 times a second, the effects of these fields are at the center of a scientific controversy. Some studies of humans exposed to ELF radiation have suggested an association between this exposure and certain types of cancer. But the evidence is not clear.

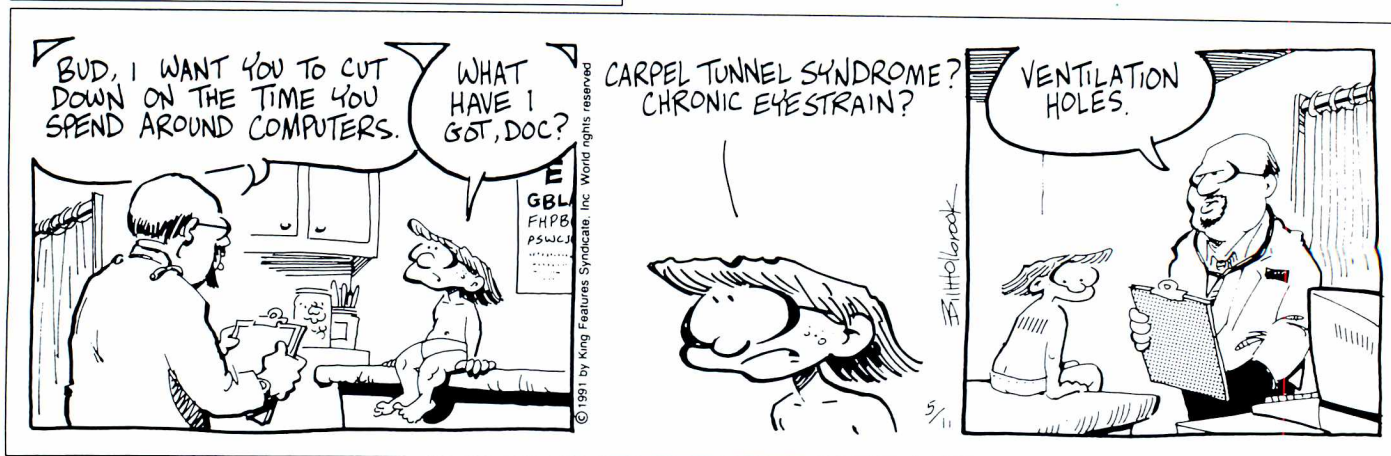
For example, other human studies do not show an increased cancer risk. Even those studies with positive results have not been able to accurately determine how much ELF radiation people in the studies received, making it difficult to determine the risk, if any. And animal experiments have thus far failed to show a cancer-causing effect.

Some studies have also raised the question of an increased risk of miscarriages and other problems during pregnancy among women exposed to ELF fields. The evidence for these effects is even more uncertain than that for cancer.

Although existing studies raise concerns about the possibility of health effects from ELF radiation, the scientific evidence is not sufficient at present to warrant regulatory action by FDA. The agency believes that the most prudent course of action is for it to continue to monitor the research in this field and, in the meantime, to work with manufacturers to reduce levels of ELF radiation.

ON THE FASTTRACK

By Bill Holbrook



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To address these concerns, some VDT manufacturers are beginning to produce terminals that emit less ELF radiation. In the meantime, some people may wish to reduce their exposure, despite the absence of scientific evidence pointing to a clear health hazard by taking three simple steps:

- Turn off the VDT when not in use.
- Position yourself approximately 22 to 28 inches (arm's length) from the screen when using the VDT. If possible, use an adjustable computer shelf so you can position the keyboard further from the screen. ELF emissions fall off drastically after a distance of 28 inches, so sitting at least that far from the screen will reduce exposure.
- Position yourself approximately four feet from the sides and rear of other terminals. ELF emissions are greater from these parts of VDTs than from the front screen.

Carpal Tunnel Syndrome

VDTs have also spawned a rise in carpal tunnel syndrome, or repetitive motion injury. This hand condition results from performing the same motions for hours at a time, as when a terminal operator types continuously. The syndrome is named for the narrow tunnel in the wrist formed by ligament and bone. Tendons that enable the hand to close pass through the carpal tunnel. Injury to this part of the body can cause numbness or weakness, tingling and burning in the fingers and hands, or difficulty opening and closing hands. If the condition is not treated, permanent injury and loss of the use of the hand are possible.

The American Physical Therapy Association recommends several steps to prevent or alleviate the symptoms of carpal tunnel syndrome:

- Keep wrists relaxed and straight, using only finger movements to strike the keys. Your typing table should be slightly higher than your elbows when your arms are held relaxed by your sides. Rest your elbows by your sides or support them with special arm rests now available on some office chairs. Relax your shoulders and keep them level.
- Press keys with the minimum pressure necessary. Make sure the keyboard is kept clean and in good working order to minimize resistance.
- Move your entire hand to press hard-to-reach keys rather than overextending your fingers. Use two hands if necessary to execute combination keystrokes, such as shifting to upper case.

Additional Advice

For more information on workplace safety, contact the following organizations:

Food and Drug Administration
Division of Consumer Affairs (HFZ-210)
Center for Devices and Radiological Health
5600 Fishers Lane
Rockville, Md. 20857

National Institute for Occupational Safety and Health
1600 Clifton Road, N.E.
Atlanta, Ga. 30333

National Council on Radiation Protection
7910 Woodmont Ave., Suite 800
Bethesda, Md. 20814

Occupational Safety and Health Administration
200 Constitution Ave., N.W.
Washington, D.C. 20210
(for the free booklet *Working Safely with VDTs*, send a self-addressed label and a request for publication #3092 to room N3101 at the above address)

The American Physical Therapy Association
1111 North Fairfax St.
Alexandria, Va. 22314
(send a self-addressed, stamped envelope for free brochures on carpal tunnel syndrome and posture and back problems related to VDTs)

- Break up typing tasks with other activities—such as proofreading, filing, or telephone work—to rest fatigued muscles.

Protective Eyewear

For students and teachers, shop and science labs pose a danger of eye injuries from foreign objects. Some sports and hobbies can also pose a risk of eye injury. Chemicals or tools can damage unprotected eyes.

Although FDA regulates regular glasses, sunglasses and goggles, the Occupational Safety and Health Administration regulates job-related protective eye equipment. All major component parts of industrial-type eye protectors that conform with the OSHA standard are marked Z87, and the manufacturer's monogram is marked on each lens. Most states require Z87 eyewear for protection for certain occupations.

Choose protective eyewear to shield you from foreign objects, heat, chemicals, dust, and radiation. Safety glasses

or goggles with side shields provide protection from frontal and side impact and are designed for such projects as wood-working. These are "primary protectors." For protection against severe hazards such as arc welding or furnace operations, face shields and welding helmets, called "secondary protectors," must be worn in addition to the safety glasses or goggles. (See chart on page 17.)

Our ability to identify deleterious health effects from advancing technology is evolving. As we attempt to keep pace with rapid workplace innovations, some basic safety rules can do much to minimize risk: Keep equipment in good working order, follow directions for use carefully, and use common sense when operating machines. ■

Jessica Auerbach is a member of FDA's division of consumer affairs in the Center for Devices and Radiological Health. Paula Silberberg of the center also contributed to this article.

Look Twice

How to Protect Yourself Against Drug Tampering

by Tom Cramer



Mom and dad taught you to look both ways before crossing the street, and now the Food and Drug Administration is urging you to look twice when you buy over-the-counter (OTC) drug products like cold medicines and pain relievers.

For nearly a decade, most of these products have been coming to us securely enclosed within sealed layers of plastic, tinfoil, and other forms of safety packaging, but FDA is growing concerned that all this "tamper-resistant" technology has made us just a little too complacent for our own good.

"People shouldn't be lulled into a false sense of security," said Daniel Michels, director of the Office of Compliance at FDA's Center for Drug Evaluation and Research. "Just because you see that a product is safety sealed, don't assume you shouldn't examine the product carefully. No product is tamper-proof."

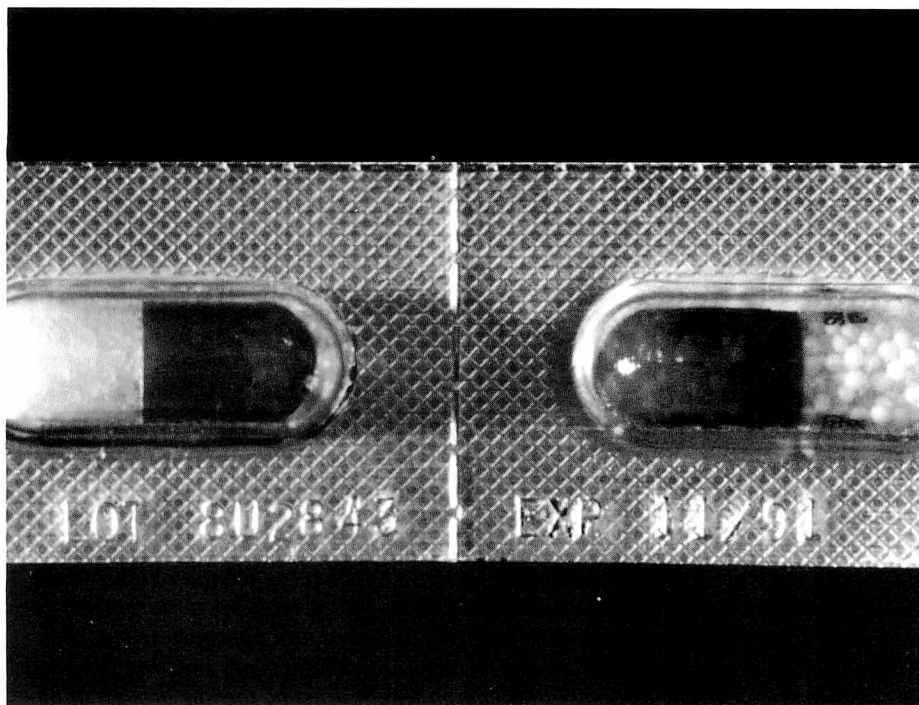
Michels, who has been involved in responding to tampering incidents, pointed out that any OTC drug product can be tampered with—no matter how many safety features it has. And it is this disturbing fact that has many FDA officials shying away from the term "tamper-resistant" when they discuss safety packaging, and embracing instead the term "tamper-evident."

Michels said the latter term is not only more accurate, but also sends a subtle message to consumers that they are ultimately responsible for their own safety.

That sobering point was driven home last February when two people in Washington state died shortly after swallowing 12-hour Sudafed capsules that had been laced with cyanide. Ironically, the tamperer did not do a particularly sophisticated job when penetrating Sudafed's various tamper-evident features, but apparently neither victim noticed anything suspicious.

"Sudafed offered state-of-the-art tamper-evident technology," said Michels. "And still the product was tampered with."

"The drug manufacturing industry, FDA, and the consumer need to work together as a team to prevent future tragedies like this. Consumer vigilance is perhaps the most important part of the whole equation."



The cyanide-filled capsules that killed two Washington state residents in February resembled genuine Sudafed capsules in some ways, but were not identical to them. This close-up photograph shows a normal Sudafed capsule (right) with its familiar white time-release beads. The capsule on the left contains cyanide, a yellowish, powdery substance that does not resemble the larger, time-release beads in the real Sudafed capsule.

Safety Issue Emerges

For years, most OTC drug products came in containers that were easy to open. Then, during the 1960s and 1970s, safety features began appearing on certain medicines to prevent children from accidentally poisoning themselves.

For the most part, however, safety was regarded as a side issue by many packagers. The emphasis remained on coming up with creative packaging that would attract the attention of consumers, not protect them from cold-blooded killers. Tampering wasn't unheard of, but it wasn't exactly a household word either.

All that changed abruptly in 1982 when seven Chicago-area residents died after swallowing cyanide-laced Tylenol capsules. Shortly after that tragedy, FDA issued regulations requiring certain OTC drugs and some other medical and cosmetic products to be marketed in tamper-resistant packaging.

Packaging Helps

FDA regulations require tamper-resistant packaging for certain OTC human drug products, cosmetic liquid oral hygiene products, vaginal products, and contact lens solutions and tablets.

Excluded from the regulations are products applied topically to the skin, dentifrices (such as toothpaste), insulin (which is usually kept behind the pharmacy counter), and lozenges (cough drops, for example). These items are not regulated because they are less vulnerable to tampering or, even if tampered with, would likely cause you considerably less injury than something that you swallow whole, inhale, insert, or use in your eyes.

A tamper-resistant package, according to FDA's regulations, "is one having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible



FDA does not have an “official list” of approved packaging technologies, but the examples shown on these pages are among those that meet FDA requirements for a tamper-resistant package if they are properly designed and appropriately used. Above is a blister or strip back, in which capsules or tablets are individually sealed in clear plastic or foil. The individual compartment must be torn or broken to obtain the product.

evidence to consumers that tampering has occurred.”

Over-the-counter drugs must have at least one—and in some cases two—of these indicators or barriers.

To prevent a tamperer from substituting the tamper-resistant feature (such as a shrink band or film wrap), the indicator or barrier to entry must be distinctive by design, or it must employ an identifying characteristic, such as a pattern, name, registered trademark, logo, or picture.

“Distinctive by design” means that the tamper-resistant feature is designed from material not readily available to the public, and therefore can’t be easily duplicated. Blister packs, aerosol containers, and individual foil pouches fall into the “distinctive by design” category.

On the other hand, materials such as plain tape and clear plastic or paper seals are considered “readily available.” Indicators or barriers using these materials must therefore have an identifying characteristic so that the substitution of the material could easily be detected by a consumer. (One brand of children’s

cold medicine, for example, uses a shrink band featuring rows of tiny blue soldiers.)

The massive conversion to tamper-resistant packaging cost the drug manufacturing industry somewhere between \$500 million and \$1 billion, according to Bill Bradley, director of technical affairs at the Nonprescription Drug Manufacturers Association in Washington, D.C.

Packaging had to be redesigned. New equipment had to be obtained, and, in some cases, new personnel and new buildings. But no one was grumbling.

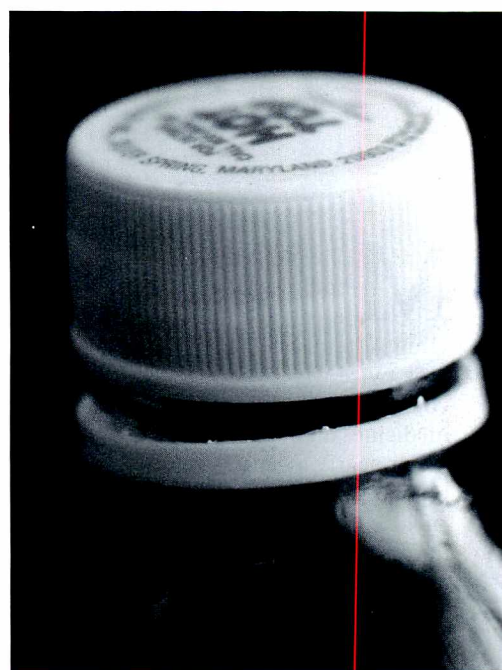
“Companies were very anxious to comply as quickly as possible,” Bradley said. “Consumer confidence was down.”

It took about three months before consumers started feeling comfortable again about OTC drugs, Bradley said.

Alert and Aware

But while FDA laid down the law concerning tamper-resistant features, its regulations stress that these features cannot prevent tampering; they simply help to alert the consumer if tampering has occurred.

“It’s very important that there be some



In a breakable cap system, the container is sealed by a plastic or metal cap that either breaks away completely when removed from the container or leaves part of the cap attached to the container.

consumer vigilance,” said FDA Commissioner David Kessler, M.D. “I don’t want people to have a false sense of confidence.

“In the instance of the 12-hour Sudafed capsule, there were three barriers,” said Kessler. “The safety tab on the carton, the blister pack with its tinfoil backing, and the capsule itself, which was safety banded. [A blue band sealed the halves of each Sudafed capsule together.] All we’re asking is that consumers look twice before they take any product.”

Said Bradley: “The Sudafed 12-hour, tamper-resistant packaging did all that it was supposed to do. Its tamper-resistant packaging was violated in a way that left evidence to the naked eye.”

Not only was Sudafed’s packaging violated, but the tainted capsules themselves looked different than the other capsules in the tampered blister packs:

- They did not have Sudafed’s characteristic blue safety band.
- They did not have the company logo or product name printed on them.
- They contained a yellowish powder instead of the familiar white time-release beads.



Bottle mouth inner seals are paper, thermal plastic, polystyrene foam, plastic film, foil, or combinations of these materials, which are sealed to the mouth of the container under the cap. The seals must have some sort of distinctive design.

• And, finally, the tinfoil that secures each capsule in its individual "blister" had been obviously cut.

"In today's environment, unfortunately, a crude product tampering can go undetected," said Bradley. "If the public does not look at OTC packaging, then no amount of tamper-resistant packaging, in and of itself, can protect the public."

The disturbing fact is that a determined tamperer simply cannot be stopped, according to Richard Swanson, director of FDA's Division of Emergency and Epidemiological Operations.

"We aren't going to be able to stop the person who wants to kill someone," Swanson said. "If that person wants to do it, he's going to find a way to do it."

Swanson, who has spent 23 years investigating tampering incidents for FDA, said tamperers can be divided into general categories. First, there are the criminals, the out-and-out murderers whose tampering is aimed at a specific victim, or whose victims are random, as was apparently the case in the 1982 Tylenol tragedy.

Then there are the "pranksters" (who find product tampering amusing), the

disgruntled (such as an angry employee seeking revenge on an employer), and the profiteers (who seek to gain financially from their tampering), according to Swanson.

"Man invented tampering a very long time ago," Swanson said. "The ancient monarchs used to have their own food tasters to make sure someone wasn't trying to poison them.

"We're never going to be able to completely stop it," he continued. "But with cooperation and a team effort, we can provide control. The consumer ultimately is the last step in the quality assurance chain. They have the responsibility to look twice at the product to make sure it's in the same condition it was in when it left the manufacturer."

Be Observant

Lana Ragazinsky, a consumer safety officer with FDA's Center for Drug Evaluation and Research, said consumers need to be more observant when they buy OTC drugs, and should check products carefully for rips, tears, or other packaging damage before purchasing them.

"If there's something on the package that looks suspicious, take it back to the store manager, or to the store's pharmacist," said Ragazinsky. "And you have to read the label. The label tells you what tamper-evident features are on the package." For example, a product may be la-

beled, "Tamper-Evident Bottle Cap. If breakable ring is separated, Do Not Use."

And the scrutiny shouldn't stop once you bring the product home, either, Ragazinsky warned. When it's time to actually take your medicine, continue to examine the product closely as you're removing it from its various layers of protective packaging, she said.

"Sometimes that's hard to do," admitted Duane Sylvia, another consumer safety officer with FDA's Center for Drug Evaluation and Research. "People will open medicine in the middle of the night, when they're still half asleep, or when they're in pain and looking for some fast relief. You tend not to be real observant at moments like these."

Sylvia emphasized the need to be cautious.

"Would you sit down to dinner in the dark, unable to see what you're eating?" he asked. "The same goes for taking medication. You have to look, and look twice."

"We can make all the rules and regulations we want, but it can't replace consumer awareness," said Ragazinsky. "You have to look at the package. You have to read the label. If the consumer doesn't look, there's nothing we can do."

Tom Cramer is a staff writer for FDA Consumer.

Be Tamper-Wise

Take a few moments to inspect the over-the-counter drug products you buy. Look for signs of tampering such as:

- broken seals
- puncture holes
- open, torn or damaged boxes
- loose, torn or missing wrappings.

Damaged packaging doesn't automatically mean a product has been tampered with; most likely it got battered during shipping or unpacking. Still, don't buy it.

At home, get into the habit of looking at your medicine before you take it. Specifically:

- Don't take medicine when you're not alert, or if you can't see clearly. (If it's the middle of the night, for example, take a few moments to wake up. Put on your glasses. Turn on a light.)
- Read the product's label; it tells you exactly what its tamper-evident features are.
- Never use any product that is discolored, has an unusual odor, or seems in any way suspicious. ■



'STREP'

Demands Immediate Care

by Margie Patlak

Few childhoods go by without the tell-tale fever and sore throat of a *Streptococcus*, or "strep," infection. Although these throat infections are common and easily treated, the recent rise of particularly deadly or troublesome strains of Group A *Streptococcus* has pushed the bacterium into the medical limelight—again.

In the past, Group A strep has played a starring role in a number of deadly medical epidemics, particularly the scourges of rheumatic fever that swept across the nation in the first half of this century, killing or debilitating thousands of children each year.

After World War II, the number of cases of rheumatic fever dramatically declined until, during the 20 years between 1965 and 1985 alone, the yearly number of cases of rheumatic fever among school-age children dropped by more than 90 percent. The medical community had assumed that less crowded living conditions and the use of antibiotics were keeping the disease at bay. Some physicians even went so far as to call rheu-

matic fever a "vanishing disease in suburbia."

That complacency was shaken in the mid-1980s when outbreaks of rheumatic fever were reported among children and young adults in various cities scattered throughout the country. Those reports were followed by others of a new and deadly form of strep infection that was afflicting adults. This disease, which is called toxic streptococcal syndrome,

seeing manifestations like rheumatic fever that we haven't seen for awhile, as well as more invasive strains of Group A strep that are making people sicker much more quickly."

The jury isn't in yet on why Americans are experiencing such a boost in the severity of strep infections. Preliminary findings by researchers at the national Centers for Disease Control in Atlanta suggest that a population increase among

previously rare strep types may be behind both the recent rheumatic fever outbreaks and cases of the new toxic streptococcal syndrome. Heightened production of disease-causing toxins by more common strep types may also be responsible for

Signs of a Group A Strep Infection

- sore throat accompanied by fever
- shortness of breath
- red rash accompanied by fever
- involuntary jerky movements
- yellow flaky crusts on the skin
- chest pain
- shock
- tender joints
- blood in urine
- puffy face and malaise

Persons developing any of these symptoms should seek immediate medical care. ■

made the headlines when public television's "Sesame Street" puppeteer Jim Henson was reported to have died from it last year. There's also evidence to suggest that blood infections caused by Group A strep are on the rise.

"Group A *Streptococcus* seems to have taken a little twist again," says Rosemary Roberts, M.D., a medical officer with the Food and Drug Administration's division of anti-infective drug products. "We're

the latest strep casualties.

There are more than 80 known types of Group A *Streptococcus*, which can cause more than a dozen different illnesses. Group A *Streptococcus*, in turn, is part of a broader category of strep organisms that cause an even larger number of diseases. (See box on next page.)

Some of the more well-known Group A strep afflictions include upper respiratory diseases such as strep throat and

scarlet fever, skin disorders such as impetigo, and inflammatory diseases such as rheumatic fever or kidney disease. In addition, blood infections due to Group A strep are a serious and frequent complication of wounds or surgery.

Group A strep infections are treatable with antibiotics, the drug of choice being penicillin. Other antibiotics, such as erythromycin and various cephalosporins, are effective alternatives for patients allergic to penicillin. FDA is responsible for ensuring the safety and effectiveness of these drugs.

Strep Throat

Strep throat (streptococcal pharyngitis) is probably the most well-known Group A strep infection. Although strep throat can occur at any age and at any time of the year, it mainly afflicts school-age children during the winter and spring. The many symptoms of strep throat include an extremely red and painful sore throat, ear pain, fever, enlarged and tender lymph nodes in the neck, white spots on the tonsils, or dark red spots on the soft palette. However, about 1 out of 5 people who has strep throat experiences no symptoms.

Because nearly all the symptoms of strep throat can also occur with viral infections, laboratory tests are used to confirm a doctor's suspicion that a patient's sore throat is caused by Group A strep. The traditional laboratory test to identify strep is a throat culture. To isolate and identify Group A strep from a throat swab takes from one to three days using the culture method. In recent years, a number of tests have become available that use antibodies to detect the presence of Group A strep directly on a throat swab, and these devices can provide test results in a matter of minutes. Many physicians feel that the rapid tests do not detect as many positive results as the culture method, so if the rapid test results are negative, a follow-up throat culture is recommended.

Strep throat is highly contagious among children because they are in close contact with one another. In addition, they have not yet developed resistance to any of the strains, as adults have.

The Streptococci Family

The streptococcal bacteria are extremely versatile and common. Able to invade almost any part of the body, streptococci cause a host of diseases. These microbes are divided into more than a dozen different groups, based on the proteins they harbor in their cell walls and their performance on various laboratory tests. Here's a list of some of the more troublesome categories or species of *Streptococcus* and the diseases for which they are well known:

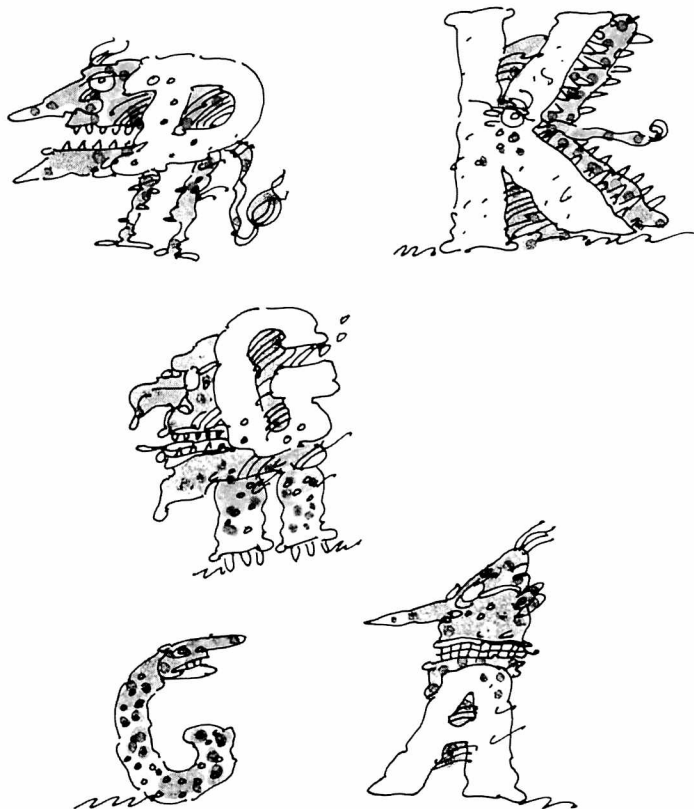
Group A: strep throat, scarlet fever, rheumatic fever, impetigo, toxic streptococcal syndrome, streptococcal kidney disease, blood infections


Group B: blood infections in newborns, meningitis, childbed fever

Groups C,D,G,H,K: urinary tract infections, heart infections, meningitis, upper and lower respiratory tract infections

Streptococcus mutans: dental caries (cavities)

Streptococcus pneumoniae: pneumonia, ear infections, meningitis, sinus infections. ■





***T*here is evidence to suggest that blood infections caused by Group A strep are on the rise.**

The incubation period for strep throat is two to five days. During epidemics, siblings of a strep throat patient have a fifty-fifty chance of also succumbing to the disease, whereas only 20 percent of the parents of such patients will develop strep throat. Children with strep throat should not return to school until their fever returns to normal and they've had at least a day's worth of antibiotics.

Strep throat is easily treated with antibiotics. Treatment is usually not necessary for those individuals who harbor the strep throat microbe but show no signs of an active infection. These people are unlikely to spread infection to others, according to the American Academy of Pediatrics, or experience the complications of a strep infection, which include rheumatic fever and kidney disease.

Scarlet Fever

One of the more colorful variants of a strep infection is scarlet fever. The hallmarks of this disease include a bright red tongue, a brilliant scarlet rash (particularly on the trunk, arms and thighs), a flushed face, sore throat, and fever.

"Scarlet fever is simply strep throat with a rash," says Roberts. The red rash that typifies this disease is prompted by a toxin generated by the *Streptococcus* bacterium. The striking symptoms of scarlet fever make it easy to diagnose, but most physicians confirm their clinical

diagnosis with laboratory tests.

Like strep throat, scarlet fever primarily afflicts school-aged children during the winter and spring months. Scarlet fever is easily treated with antibiotics, and, if left untended, the disease can foster the same complications prompted by strep throat.

Rheumatic Fever

Lurking behind several types of strep infections is the possibility of rheumatic fever. Although a relatively uncommon disease, the effects of rheumatic fever are serious enough to warrant concern. Signs of rheumatic fever include a red rash, pea-sized lumps under the skin, tender joints, fever, involuntary jerky movements, heart palpitations, chest pain, and, in severe cases, heart failure. Although most symptoms disappear within weeks to months, about half the time the disease leaves behind deformed heart valves that may limit patients' physical activities and foster premature death from heart failure.

Diagnosis of rheumatic fever is based on its symptoms in conjunction with a history of a recent strep infection, which can be confirmed by tests for strep antibodies in the blood.

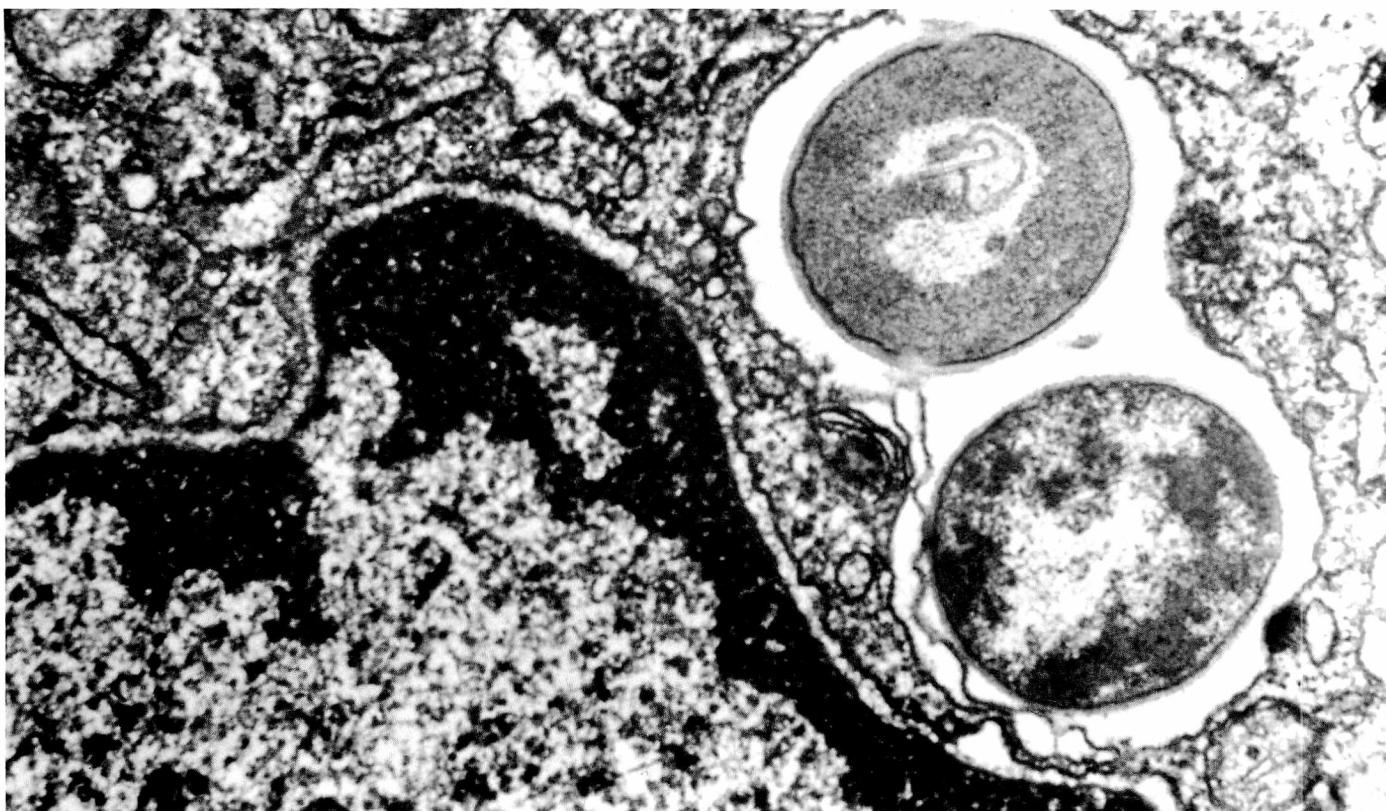
Rheumatic fever is thought to be triggered by an overly active immune system, which inadvertently destroys body tissues in its zeal to rid the body of a

strep infection. Most symptoms of rheumatic fever crop up one to four weeks after a strep infection, although involuntary jerky movements may not surface for as long as six months after infection. About half of the recent cases of rheumatic fever, however, developed with mild to no previous signs of a strep throat infection, such as a sore throat with fever.

It's these signs of a strep infection that physicians rely on to prevent rheumatic fever. As many as 3 percent of untreated cases of strep throat can develop into rheumatic fever. But antibiotic treatment, even if it's not started until several days after the onset of symptoms, can squelch the possibility of rheumatic fever.

Once rheumatic fever occurs, doctors can do little to prevent its damage in the body. Anti-inflammatory drugs (such as aspirin or steroids) can ease many of the symptoms and possibly prevent some of rheumatic fever's more serious developments. Antibiotics are also used to treat any lingering strep infections. But even with such therapies, the disease often wreaks such damage on heart valves that they have to be surgically repaired or replaced with synthetic or animal implants.

Rheumatic fever usually recurs whenever its victims experience any new strep infections. To prevent such flare-ups, the American Heart Association recommends that anyone who has experienced



A white cell ingests two round streptococci.
(Source: National Institute of Allergy and Infectious Diseases)

rheumatic fever take prophylactic (preventive) doses of antibiotics. How long rheumatic fever patients require such a preventive drug regime depends on whether they experienced heart damage and whether they're likely to develop a future strep infection. Children who've had rheumatic fever, for example, generally take antibiotics on a daily basis until they reach adulthood, when the risk of a strep infection greatly diminishes.

Skin Infection

When Group A *Streptococci* literally get under the skin, they can foster a common skin disease known as impetigo. This contagious disease frequently afflicts mainly children during the *summer*, when insect bites, cuts and scrapes are prevalent. These skin infringements serve as portals of entry for the *Streptococci*.

Impetigo starts out as a rash of pin-head-sized blisters or pimples that rapidly run together to form yellow, flaky crusts. The impetigo rash may itch or burn, but rarely causes pain. The disease is diagnosed with the aid of cultures of the fluid lodged beneath the crusts. If large numbers of strep bacteria crop up in these cultures, their guilt in causing the disease is firmly established. Impetigo can also be caused by other bacteria, including *Staphylococcus*, or by mixtures of staphylococcal and streptococcal bacteria.


Impetigo is combated with the use of topical or oral antibiotics, depending on its severity and frequency within a given population. Doctors advise impetigo patients to remove the skin crusts and wash their rash with soap on a regular basis. Occasionally, if not treated, streptococcal impetigo develops into a blood infection, and it can also foster kidney disease.

Kidney Disease

All kinds of strep infections can foster an inflammation of the kidneys (acute glomerulonephritis), although the disease most often follows impetigo. Less than 1 percent of all strep infections foster kidney disease, but because certain strains of strep are particularly prone to causing this complication, small epidemics of acute glomerulonephritis can crop up in private homes or in schools.

Symptoms of the disorder include a puffy face due to water retention, blood in the urine, pain in the loins, malaise, nausea, headache, and high blood pressure. These symptoms usually surface one to three weeks following a strep infection and subside within the same amount of time.

Diagnosis of acute post-streptococcal glomerulonephritis is based on symptoms, a history of a recent strep infection, and elevated levels of antibodies to strep in the blood. This form of kidney disease, like rheumatic fever, is thought



Only about 4 to 5 people out of 100,000 develop bloodstream infections due to Group A strep, but of those who do get infected, nearly a third die.

to stem from an overactive immune response to strep.

Little can be done to prevent this heightened immune response once it's begun, although various drugs (such as diuretics) and dietary measures (such as restricted salt or protein intake) can ease many of its symptoms. Most patients recover without any permanent problems, although occasionally kidney damage inflicted by the disease may require dialysis or a kidney transplant.

Patients rarely experience a recurrence of acute glomerulonephritis following additional strep infections because of the immunity they develop to the specific type of strep bacterium that caused their disorder. (Only a handful of strep types can cause glomerulonephritis, and most cases of the disorder can be traced to a specific Group A streptococcal strain known as Type 12.)

Blood Infection

Although the number of bloodstream infections (septicemia) of Group A strep appears to be on the rise, they are still extremely rare. Only about 4 to 5 people out of 100,000 develop these infections each year, according to the national Centers for Disease Control in Atlanta. But nearly one-third of all patients with *Streptococcus* blood infections will die from them.

Septicemia usually gets its start when

streptococcal bacteria on the skin delve into an opening as large as a surgical or battle wound or as small as a minor cut or scrape. Normally, the body's immune system checks these bloodstream invaders before they wreak havoc in the body. In those individuals whose resistance is lowered, however, *Streptococcus* travels far and wide, causing such symptoms as fever, low blood pressure, chills, confusion, diarrhea, vomiting, or a red skin rash. Septicemia usually afflicts people over 60 who have an underlying disease such as diabetes or renal failure that compromises their immune defenses.

In addition to relying on clinical signs to diagnose septicemia, physicians use laboratory findings, including positive blood cultures, positive antibody tests, and extremely high numbers of white blood cells in the blood.

Toxic Streptococcal Syndrome

The new toxic streptococcal syndrome, first described in 1987 in this country, is similar to septicemia. Patients with this disorder have many of the same symptoms as those of septicemia, but because of the disease's rapid progression, by the time they seek treatment they are often gravely ill. Toxic streptococcal syndrome patients frequently go into shock and experience multi-organ failure, as well as complications such as the pneumonia that reportedly killed Jim Henson.

Only 1 or 2 people out of 100,000 fall prey to toxic streptococcal syndrome each year. Unlike septicemics, most of these patients don't have any underlying diseases hampering their immune defenses. Of 21 cases studied extensively by researchers, most patients were in their 30s and the youngest was 25 years old.

"The individuals who are getting strep septicemia and toxic strep syndrome," points out CDC epidemiologist Walter Straus, "are not the same ones who are getting strep throat."

Patients with toxic streptococcal syndrome are treated with antibiotics as well as with medical measures aimed at curbing the severe complications of the disease. The sooner patients are treated with antibiotics, the more likely they will recover from the syndrome, which kills about one-third of its victims.

Whether Group A *Streptococcus* infects the skin, blood, internal organs, or the throat, it is usually checked by prompt and appropriate antibiotic therapy. This is why, though recent outbreaks of serious strep infections are cause for some concern, they are not likely to prompt the extensive death or debilitation once tied to them. ■

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



On the *Teen Scene*

TSS

Reducing the Risk

by Dixie Farley

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

Young women 15 to 19 years old are the most frequent victims of toxic shock syndrome, or TSS, a rare but serious—and sometimes fatal—disease that mainly strikes tampon users under 30.

The Food and Drug Administration's Center for Devices and Radiological Health, which regulates tampons, estimates that 1 to 17 of every 100,000 menstruating women develop TSS each year. The disease also affects people who don't use tampons and has occurred in children, men, and non-menstruating women.

TSS and Tampons

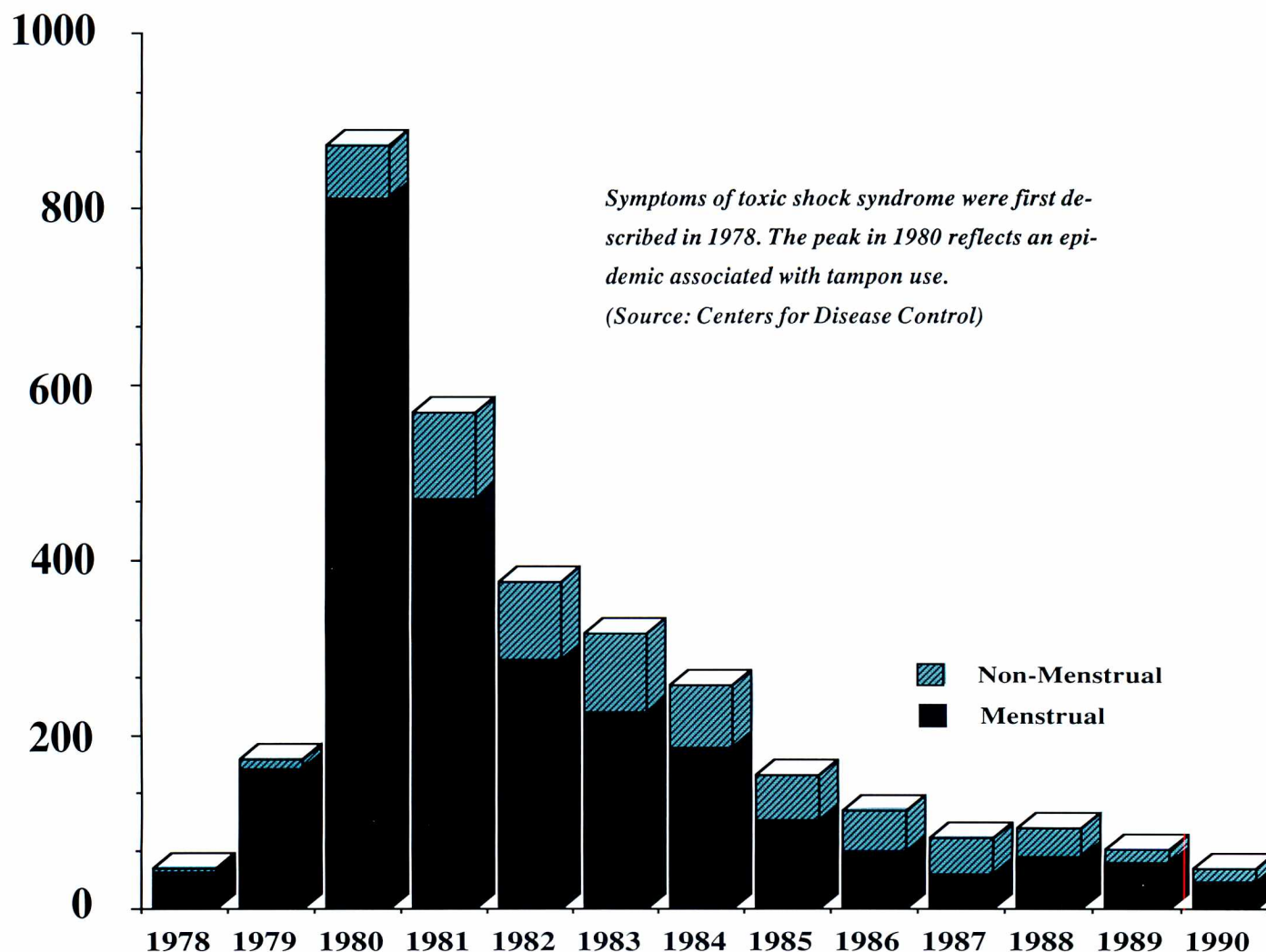
Scientists first described TSS symptoms as a distinct disease in 1978. Two years later, reports of TSS increased among young women who had become ill during or just after menstruation. Studies showed that the use of tampons, especially high-absorbency tampons, was associated with TSS, but the exact connection remains unclear.

Scientists think that in order for the disease to develop, bacteria called *Staphylococcus aureus* must be present. These bacteria release one or more toxins (poisons)

If you get flu-like symptoms during or just after your menstrual period, it's a good idea to check with your doctor. You may have TSS.



Decrease in Tampon-Associated TSS



into the bloodstream. *S. aureus* bacteria commonly live in body areas such as the nose, skin or vagina and usually cause no problem, says Gordon Johnson, M.D., director of the center's office of health affairs. "But the bacteria also can lead to serious infection after a deep wound or surgery or, for reasons not fully understood, during tampon use."

About 5 percent of TSS cases are fatal. Through FDA's Medical Device Reporting Program, the agency since 1984 (when the program began) has received 69 reports of death related to tampon use. Scientific evaluation showed that all but three of the deaths resulted from TSS.

Risk of death from TSS is higher in cases *not* related to menstruation, says Anne Schuchat, M.D., an expert on TSS at the national Centers for Disease Control. "This may be because of the different toxins involved," she says. "At least two *S. aureus* toxins have been identified in TSS cases, and we think there may be more."

Lowering Your Risk

If you've ever had TSS, get medical advice before using tampons.

You can dramatically reduce your risk of TSS if you don't use tampons. But whether the benefits of using tampons—particularly high-absorbency ones—are worth the increased risk of TSS is an individual decision.

Because the TSS risk increases with tampon absorbency, if you use tampons, you should use products with the lowest absorbency that meets your needs. There's usually less need for high absorbency at the end of a menstrual period. You can find what's best for you by experimenting with different sizes and different brands, beginning with the least absorbent.

To help women compare absorbency from brand to brand, FDA requires that manufacturers use a standard test to measure absorbency and that the absorbency be stated on the label using standard terminology. When shopping for tampons, look on the packages for the following absorbency terms and ranges and then compare brands before you make your selection.

<i>If the package says:</i>	<i>The absorbency range is:</i>
Junior Absorbency	6 grams and under
Regular Absorbency	6 to 9 grams
Super Absorbency	9 to 12 grams
Super Plus Absorbency	12 to 15 grams

- It also helps to:
- follow the manufacturer's instructions
 - store tampons in a clean, dry place
 - wash hands with soap and water before and after inserting or removing a tampon
 - try a less absorbent variety if a tampon is irritating or difficult to remove.

FDA also requires manufacturers to give information about

TSS on the tampon box or in a package insert. This information must include a warning about the association between TSS and high-absorbency tampons. You can stay up-to-date on TSS by reading the package information when you buy tampons and asking about TSS when you get a medical checkup.

TSS Symptoms

Remove your tampon if you're using one and get medical help right away if you have the following symptoms during menstruation:

- sudden high fever—102 degrees Fahrenheit or higher
- vomiting
- diarrhea
- dizziness, fainting, or near fainting when standing up
- a rash that looks like a sunburn

Symptoms may not appear until the first few days after the end of your period. Be sure to explain to your doctor what your symptoms are, when your period began, and whether you've ever had TSS before. If you use tampons, mention what absorbency you use.

TSS symptoms appear quickly and are often severe. Not all cases are exactly alike, and you may not have all the symptoms. You may have aching muscles, bloodshot eyes, or a sore throat, making it seem like the flu. The sunburn-like rash may not develop until you're very ill or may go unnoticed if it's only on a small area. Later, the skin on your palms and soles may flake or peel. A first episode may be so mild that you don't connect the symptoms with TSS, but the next time, the symptoms may be severe. Once you've had TSS, you're more likely to get it than someone who never has had it.

Deaths, though rare, tend to happen during the first week of illness. The danger lies in a sudden drop in blood pressure, which could lead to shock if not treated in time.

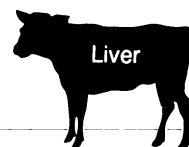
TSS is usually treated with drugs to lower temperature and large amounts of fluids and electrolytes (essential body chemicals) to raise lowered blood pressure. Blood and other specimens from the body are analyzed in a lab to identify bacteria. Antibiotics are given to help prevent recurrence. Patients often are hospitalized, and severe cases require intensive care. With proper treatment, patients generally recover within three weeks.

While TSS is rare, it's an important health concern for young women, since they're the age group most at risk. Knowing how to prevent it and recognizing its symptoms can do much to reduce its dangers. ■

Dixie Farley is a staff writer for FDA Consumer.



BIOTIN
BIOTIN
BIOTIN
BIOTIN



U.S. Recommended Daily Allowances

Infants (0–12 mo.)	Children (1–3 years)	Adults and Children 4 Years +	Pregnant or Nursing Women
50 micrograms	150 mcg	300 mcg	300 mcg

(The U.S. RDA amounts are sufficient to meet the needs of practically all healthy people. FDA set these based on the 1968 Recommended Dietary Allowances by the National Research Council of the National Academy of Sciences. However, in 1989, the council lowered its ranges of safe and adequate daily dietary intakes for biotin to 10 to 15 micrograms for infants, 20 to 30 mcg for children, and 30 to 100 mcg for adults. FDA is in the process of revising its U.S. RDAs.)

This article is the 12th in a series giving essential facts and figures on different vitamins.

Biotin is a sulfur-containing, B-complex vitamin found in foods and produced by microorganisms in the lower gastrointestinal tract.

Functions: Activates certain enzymes that aid in metabolism of carbon dioxide; involved in metabolism of protein, fats and carbohydrates.

Sources: Widely distributed in foods that are sources of B vitamins, including cereal-grain products, liver, egg yolk, soy flour, and yeast.

Deficiency: Signs include loss of appetite, nausea, vomiting, inflammation of the tongue, pallor, depression, hair loss, and dry, scaly skin. Some rare biotin-related inborn errors of metabolism may cause deficiency; otherwise, deficiency is extremely rare in the United States.

Excess: No effects have been reported. ■

Paula Kurtzweil, R.D., of FDA's Office of Public Affairs, and Theresa A. Young, of FDA's Philadelphia district office, contributed to this series.



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.

■ **Aspartame**, a low-calorie sweetener used in many diet soft drinks, was the subject of almost 5,500 consumer complaints as of July 1, 1991. Headaches were the most common malady reported (18.5 percent of complaints). Almost 40 percent of all food-related complaints cited diet soft drinks as the source of the problem.

■ **Gloves for medical procedures** are the subject of a report available from FDA. "Surgeons' Gloves and Patient Examination Gloves; Defects-Criteria for Direct Reference Seizure" examines the role gloves play as a barrier against transmission of human immunodeficiency virus (HIV) and other blood and body fluid-borne illnesses, as well as the FDA standards for their manufacture. For a free copy, write to: Division of Small Manufacturers Assistance, Center for Devices and Radiological Health (HFZ-220), Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857. (FR July 17)

■ **Three dairies** have urged FDA to make frozen yogurt standards more flexible. The Brown Swiss-Gillette, Gillette Dairy, and Nebraska Dairies Inc. suggested that the proposed standards should allow a minimum titratable acidity of 0.25 to 0.30. They also recommended that frozen yogurt manufacturers should have the option of developing viable bacteria cells for their products by culturing the mix or by adding the culture after the mix is pasteurized. (Food Chemical News, July 22)

■ **Taking prescription drugs** safely and most effectively is the subject of a booklet for older adults released by The Council on Family Health, a nonprofit organization that educates consumers on the proper use of medicines. *Medicines and You: A Guide for Older Americans* discusses topics such as medicines and the changing body, interactions between medicine, food and alcohol, how to work effectively with your health-care professional, and tips on getting help from a pharmacist. For a free copy, write: The Council on Family Health, 225 Park Avenue South, Suite 1700, New York, N.Y. 10003.

■ **A hazardous substance training program** for fire fighters is being planned by the national Centers for Disease Control. For more information, contact: Lisa Tamaroff, Grants Management Branch, Procurement and Grants Office, Centers for Disease Control, 255 East Paces Ferry Road, N.E., Room 300, Mail Stop E-14, Atlanta, Ga. 30305; telephone (404) 842-6630. (FR July 16)

■ **Health care for adolescents** ages 11 to 20 from 1985 to the present is the subject of a report now available from the Centers for Disease Control's National Center for Health Statistics National Ambulatory Medical Care Survey. Data are available by physician specialty, reason for the patient's visit, diagnostic services, physician's diagnosis, and medication and non-medication therapy. To obtain a free copy of "Office Visits by Adolescents," write: Scientific and Technical Information Branch, NCHS, CDC, Room 1064, 6525 Belcrest Road, Hyattsville, Md. 20782; telephone (301) 436-8500.

■ **Statistics on inpatient hospital use** in 1989 is the topic of a report released by the Centers for Disease Control's National Center for Health Statistics. The survey data, compiled from almost 233,000 medical records of 408 short-stay, non-federal hospitals, include statistics on the average length of stay by age, sex, and geographical region. To obtain a free copy of "1989 Summary: National Hospital Discharge Survey," write: Scientific and Technical Information Branch, NCHS, CDC, Room 1064, 6525 Belcrest Road, Hyattsville, Md. 20782; telephone (301) 436-8500.

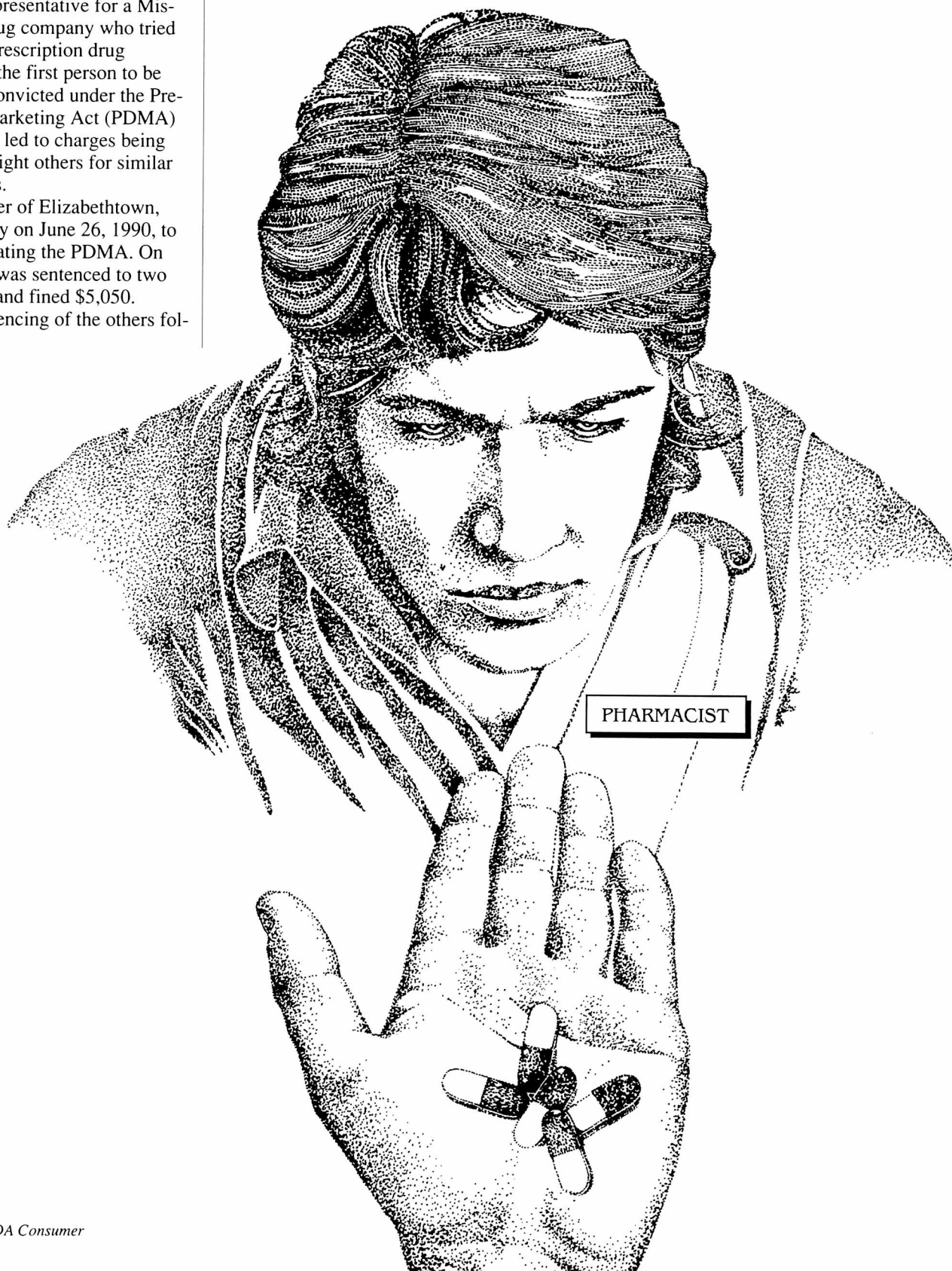


Sales Rep Convicted for Selling Prescription Drug Samples

by Dori Stehlin

A sales representative for a Missouri drug company who tried to sell prescription drug samples became the first person to be prosecuted and convicted under the Prescription Drug Marketing Act (PDMA) of 1988. His case led to charges being brought against eight others for similar PDMA violations.

David B. Snyder of Elizabethtown, Pa., pleaded guilty on June 26, 1990, to one count of violating the PDMA. On Dec. 7, 1990, he was sentenced to two years' probation and fined \$5,050. Charges and sentencing of the others followed.



The PDMA prohibits selling, buying, trading, or offering to sell, buy or trade prescription drug samples. Pharmaceutical manufacturers and distributors routinely provide samples of their prescription drugs free to physicians who, in turn, give them to their patients either in place of a prescription, or to get the patient started on medication until the prescription can be filled. Diversion of samples from their intended use creates a risk that counterfeit, adulterated, misbranded, subpotent, or expired drugs will be sold to American consumers.

One thing that concerns FDA about these cases, says Eugene Schultz, a compliance officer in FDA's Philadelphia district office, is that "some sales reps gather the [stolen drug samples], throw them in the trunk [of their cars], and keep them there for possibly six months." That may affect the quality of the drugs, he explains, since the storage conditions are not properly controlled.

He adds that the agency is also concerned about the integrity of the drugs if the samples are removed from their original packaging.

Pharmacist Helps

A pharmacist in Harrisburg brought Snyder's illegal activities to the attention of federal authorities. According to the pharmacist, Snyder had overheard him complain about how discount store prescription drug prices were hurting his business. Snyder offered to sell to the pharmacist samples of prescription drugs that were intended to be distributed free to physicians. Snyder indicated that the pharmacist would have to pay much less for the samples than he would normally pay for the same drugs purchased through a legitimate wholesaler.

The pharmacist reported Snyder's offer to the Drug Enforcement Administration's Harrisburg office in the middle of April 1989. Because the drugs Snyder was offering were not controlled substances, DEA contacted Charles Thorne, FDA's director of compliance in the agency's Philadelphia district office, on April 26, 1989, and Thorne called the pharmacist the next day.

Thorne said the pharmacist thought

Snyder would be back within the week, expecting to make a sale, and asked the agency's advice on how to proceed.

After consulting with several FDA offices, Thorne and Dave Chesney, director of investigations, decided to set up undercover surveillance at the pharmacy in anticipation of Snyder's next visit. They enlisted the help of the Federal Bureau of Investigation.

FBI agents James Barnacle and John Hartmann set up electronic surveillance equipment on the morning of May 5 and, with FDA investigators William Griffin and Marsha Major and supervisory investigator James Warn, watched the pharmacy from a van parked across the street.

Their wait was short. Snyder arrived at the pharmacy that afternoon and sold the pharmacist 18 different prescription drug products from 16 different manufacturers, including the antidepressant Prozac; ulcer treatments Tagamet, Carafate and Zantac; the anti-inflammatory Feldene; and the asthma drug Alupent.

Snyder had used acetone to remove the "sample" logo from about half of the 351 capsules of Feldene he sold to the pharmacist. Altering the capsules in that way is considered adulteration under the Federal Food, Drug, and Cosmetic Act, but the risk from any acetone residue would be minimal, according to Malcolm Williams, a toxicologist with the national Centers for Disease Control. "If he used any significant amount of acetone, it would dissolve the whole capsule," says Williams.

The pharmacist paid Snyder \$1,600, which FDA had supplied to him. However, the agency estimates that the equivalent amount of bulk drugs would have had a wholesale price of approximately \$3,200. After the drugs and the money changed hands, the FBI agents detained Snyder.

Others Violate PDMA

Following the detention, the U.S. attorney for the Middle District of Pennsylvania, with assistance from the FBI and FDA's general counsel, reached a plea agreement with Snyder and his attorney on May 24, 1989.

Under the plea agreement, Snyder was to help the FBI and the Department of Health and Human Services' inspector general identify other sales representatives and pharmacists who might be illegally buying and selling prescription drug samples. On Aug. 17, 1989, Snyder met with Saliba Shunnara, one of the pharmacists Snyder identified, in Mechanicsburg, Pa., and completed a sale of drug samples. Shunnara was summoned to court and eventually charged with PDMA violations.

Information obtained from Shunnara and Snyder led to charges against three other sales representatives and four other pharmacists for PDMA violations. FDA assisted in these cases by providing technical information on the drugs involved.

Snyder and the other eight were charged in June 1990 with the sale, purchase, or offer to sell or purchase prescription drug samples.

Shunnara was sentenced on March 5, 1991, to one year's probation and fined \$3,000. Michael Stephan, a sales representative for a Pennsylvania drug company, was sentenced on Jan. 25, 1991, to one year of probation and fined \$250.

The charges may be dismissed for four of the pharmacists, Philip Winand of New Oxford, Pa., William Welfley of Newport, Pa., Herbert Gilbert of Harrisburg, Pa., and Gerald Wynn of Camp Hill, Pa., and two of the sales representatives, Paul Carls and William Hoover, both of Harrisburg, after a period of time set by the court if they meet the requirements of a pre-trial diversion program. The program requirements include regularly working in a lawful occupation, reporting to a government supervisor as directed, and performing 50 hours of community service. The court set the diversion program time at 12 months for all but Welfley, for whom it was set at six months.

Under the provisions of the PDMA, the pharmacist who helped the government apprehend Snyder is entitled to half of Snyder's \$5,050 fine.

Dori Stehlin is a staff writer for FDA Consumer.

FDA Nabs Husband and Wife For Selling Fake Steroids

Using their Kansas City home as a base of operations, a man and his wife raked in huge profits by manufacturing and selling counterfeit steroids—illegal and potentially harmful products that may have seriously endangered the health of many athletes who used them.

David Rumley, 32, and Cathy Rumley, 31, are now in the hands of federal authorities, as are their accomplices in the counterfeiting.

Throughout the 1980s, David Rumley built up a large, mail-order steroids distribution operation and made, according to Justice Department estimates, close to half a million dollars from the enterprise.

Rumley began his operation by selling

authentic steroids, but later switched to counterfeit products because of the increased profit potential. He bought thousands of bottles of caffeine tablets, paying about 84 cents per bottle, and then resold the bottles on the black market for as much as \$25 each.

In addition to tablets, the Rumleys also sold fake steroids in injectable liquid form. One of Rumley's partners, Kansas City resident Andy Rynard, obtained small vials (similar to the kind used in doctors' offices to collect blood specimens) and filled them with corn oil purchased at local grocery stores. He chose corn oil because it has the color and consistency of a genuine liquid steroid product.

At Rumley's suggestion, Rynard sprinkled a small amount of camphor in each vial to give the oil a medicinal smell.

Rynard manufactured thousands of these oil-filled vials in his home under unsterile conditions. Rumley then sold the vials for up to \$40 apiece.

The labels on Rumley's bogus steroids were professionally printed and bore the trademarks and trade names of legitimate drug manufacturers.

Rumley did not sell directly to users. He sold his products to 160 distributors in 28 states. The distributors sold them to sub-distributors, who in turn sold them directly to users.

FDA investigators learned of Rumley's activities from informants in early 1988 while investigating other ille-



gal steroid operations throughout the country. A number of people apprehended for steroid distribution had revealed to FDA investigators their dealings with Rumley.

In June 1988, FDA investigators and Postal Service agents armed with search warrants went through Rumley's home, his storage facility, and his automobiles and seized more than \$200,000 worth of steroids and counterfeit steroids, and \$12,000 in cash.

On Dec. 6, 1989, a grand jury indicted Rumley, and on Jan. 12, 1990, he pleaded guilty to four counts of an original 21-count indictment, specifically: conspiracy, mail fraud, mail fraud using a fictitious name, and drug counterfeiting. He is serving five years in a federal penitentiary.

On Feb. 23, 1990, Cathy Rumley pleaded guilty to drug counterfeiting. She was sentenced to 10 months' incarceration. Because of her comparatively minor role in the steroid distribution operation, however, and because she and Rumley have two small children who remain in her care, she is being allowed to serve her time via electronically monitored home confinement.

During sentencing on Feb. 13, 1991, Judge Joseph E. Stevens Jr. told the couple they were lucky they weren't facing murder charges.

Andy Rynard pleaded guilty to a felony conspiracy count and a felony of manufacturing counterfeit steroids.

Besides Rynard, Rumley also bought large amounts of counterfeit steroids from Clark Daniels and Justin Routt of Florida. Daniels and Routt pleaded guilty to three and five felony counts, respectively, of conspiring to violate the Food, Drug, and Cosmetic Act and of manufacturing and distributing counterfeit steroids. Routt was sentenced to 22 months in jail, and Daniels received 18 months imprisonment.

FDA has no information on how many people may have suffered adverse health effects from using Rumley's corn oil concoctions, or the nature or extent of those effects. Because the vials were not filled under sterile conditions, they likely

contained bacteria that could be harmful.

Infested Food Seized Swiftly

Within three days of a plant inspection last April by FDA, U.S. marshals seized some 100,000 pounds of food from a Syrian bakery in Chicago. In its seizure request, FDA cited extensive evidence that the goods were contaminated with filth.

This swiftness was possible because of FDA's new "direct reference authority," a one-year pilot program that took effect Nov. 2, 1990. Under this authority, when requests for mass seizures are based on the suspicion that stored food or feed will likely become contaminated by filth from infestation, field offices can bypass review by the agency's Center for Food Safety and Applied Nutrition or Center for Veterinary Medicine.

On March 13, 1991, Harry Richmond and Roger Finner, investigators from FDA's Chicago district office, began what they thought was a routine inspection of the Ziyad Brothers Division of Syrian Bakery and Grocery Company, Inc., which makes, repacks and distributes products such as pita bread, spices, olives, nuts, beans, and oils. But by April 1, nine visits later, they had found in or around the food and equipment and throughout the building more than 80 instances of filth, including live and dead rodents and insects and other signs of infestation, such as nesting materials and excrement.

They also noticed poor employee practices and housekeeping conditions. For instance, one worker picked up dough that had fallen onto the floor and put it into the dough-making machine. Another took dough from the machine, held it against his dirty shirt and the skin on his chest and neck, and then put it back into the machine for more processing. Richmond and Finner saw water leaking from the ceiling onto pita bread, food waste and floor trash in the dough troughs, pools of stagnant liquid on the floor, and grease and food residues on the dough conveyor belt. Outside, the inspectors noted debris, including food trash that at-

tracted birds to feed, and numerous rodent burrows.

According to Richmond, when he spoke to Nemer Ziyad, the general manager, about these conditions, Ziyad contended that all bakeries and warehouses have rodents and insects. Richmond asserted that this was untrue, adding that it was Ziyad's responsibility to ensure that the building was free of infestation. Ziyad argued further that, while he used to have rats there, he'd gotten rid of them with traps. He said his firm employed the Marks Pest Control Company for services twice a week.

Checking with the Marks general manager, Richmond learned that the pest control company hadn't been in the Ziyad bakery in two years and that they had been "kicked out" by Ziyad officials.

Richmond returned to the plant and told Ziyad he had a serious infestation problem. To document the filthy conditions, Richmond and Finner collected more than a dozen obviously contaminated samples and took photographs.

Meanwhile, on the basis of FDA's findings, Chicago health officials from the City of Chicago Board of Health Inspectors inspected Ziyad Brothers on March 20 and then revoked the firm's license, closed the bakery, and embargoed the food in the warehouse pending seizure of the goods.

On March 21, the firm entered into a new contract with Marks Pest Control for service twice a month.

On April 1, Richmond and Finner reported their observations to Nemer Ziyad and sales manager Nasseem Ziyad, another relative. (Ahmed Ziyad, the bakery's president and Nemer's father, chose not to receive the list, claiming that his heart condition, coupled with FDA's report, would cause him stress.)

The inspectors said that Nemer agreed to take whatever steps were needed to rectify the problems. He said they would destroy contaminated products, clean up the inside and outside of the building and make needed repairs, establish a sanitary maintenance schedule for the bakery, take the bakery equipment apart each week for cleaning, and train workers to



clean their work areas.

On April 2, Robert Sittig from FDA's Chicago office flew to FDA headquarters in Rockville, Md., to obtain the necessary signatures on a seizure recommendation. Agency officials approved and signed the recommendation, and a seizure request was drawn up. Sittig returned to Chicago, and the U.S. attorney filed the seizure request the afternoon of April 3 in the U.S. District Court for the Northern District of Illinois, Eastern Division. A U.S. marshal, accompanied by Richmond and Finner, seized the food that day, placing it under quarantine.

Ziyad signed a consent decree on May 14, agreeing to meet FDA's terms for reconditioning or destroying the food and improving the facilities and practices. FDA will monitor these activities to completion.

On June 4, at FDA's request, U.S. marshals seized two lots of Ziyad products that had already been distributed: Greek olives at the firm's location and pita bread at Quality Food Products, Inc., a dealer in Chicago. According to Sittig, these lots are not reconditionable, and

FDA plans to witness their destruction.

As far as the agency knows, there are no other unused distributed lots.

Methadone Center Warned

FDA recently warned a methadone treatment program in New York City that its program approval would be revoked if it did not comply with safety standards.

Methadone, a synthetic opiate, can help wean heroin addicts from that illegal and potentially fatal drug.

Used in hospital drug treatment centers, methadone blocks the euphoric effects and withdrawal symptoms of heroin. But it also sets up a new addiction as well—to methadone—and withdrawal from the treatment can be just as painful as from heroin itself. Therefore, FDA requires all narcotics treatment centers to meet certain program standards for safety.

Montefiore Methadone Maintenance Treatment Program Unit III, of the Bronx, repeatedly violated standards concerning medical orders, attendance

schedules for patients, record keeping, confidentiality of medical charts, urinalyses, and admissions to the program.

FDA found the violations during a routine inspection in February 1985 and then during follow-up inspections in March 1987 and July 1989. FDA sent the treatment center a notice of adverse findings in June 1985 and regulatory letters in June 1987 and January 1990. The program managers responded in June 1985, August 1987, and January 1990 with written plans for correcting the problems.

FDA officials from the New York district also met with Montefiore managers in July 1987 and December 1989 to discuss the violations and plans for correcting them.

When FDA inspected again in September 1990 and found the same violations, the agency said it would revoke approval of the Montefiore program unless its president, Spencer Foreman, M.D., came to FDA headquarters in Rockville, Md., to explain why the program should remain in business and to outline plans for correcting violations.

On March 22, 1991, Foreman met with FDA officials in Rockville. He assured FDA that the program, plus two others owned by the Montefiore Medical Center, would implement a number of new procedures in line with federal regulations.

Foreman said the New York State Division of Substance Abuse Services would help review and redesign procedures at the center.

Foreman also said the Montefiore program director had established methods of auditing patients' files regularly to ensure they have adequate treatment plans, proper drug orders, attendance requirements, and admission evaluations. He promised to hold in-service training programs for the staff to teach them about federal standards, and he said he instructed them to change record-keeping procedures so that patients' identities would remain confidential. A new computer system would help keep track of random urinalysis tests, he said.

After the hearing, FDA decided not to revoke Montefiore's program approval at the time, but the agency will verify the program's progress through regular reinspections.

—This small sample of reports from the field was prepared by Tom Cramer, Dixie Farley, and Rebecca Williams.

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 the Food and Drug Division, Office of the General Counsel, HHS.

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

SEIZURE ACTIONS

Food/Poisonous and Deleterious Substances

PRODUCT: **Mushrooms, canned**, at Los Angeles, C. Dist. Calif.; Civil No. 90-0258-RSWL.

CHARGED 11-17-90: While held for sale after being imported from China, the article contained the poisonous or deleterious substance staphylococcal enterotoxin—402(a)(1).

DISPOSITION: A default decree ordered the article destroyed. Subsequently, the dealer, Princeton International Inc., Los Angeles, Calif., moved to set aside the default decree on the grounds of excusable neglect. The excusable neglect alleged was that the dealer's president was out of the country on a trip to Taiwan to visit his gravely ill mother. The dealer wished to export the mushrooms to the country of origin in order to obtain a refund for the defective mushrooms. The government opposed the dealer's motion on the grounds that the dealer had no meritorious defense to the underlying action and that it was FDA's unalterable position that export of the article infected with the highly deleterious staphylococcal enterotoxin would never be allowed, as there would be a significant danger that the article would enter the food chain in some foreign country under circumstances in which the presence of the enterotoxin would not be apparent to a consumer.

The court denied the dealer's motion. Although the court acknowledged that the illness and death of a family member

qualified as excusable neglect, the dealer had admitted that it had no meritorious defense (i.e., one that might cause a different result to be reached at trial from the one reached by default). Lacking a meritorious defense, the dealer failed to meet its burden of proof, and the court had to deny its motion. Accordingly, the article was destroyed. (F.D.C. No. 65799; S. No. 89-444-448; S.J. No. 1)

Food/Contamination, Spoilage, Insanitary Handling

PRODUCT: **Apricots, pitted, dried, and Basmati rice**, at Linden, Dist. N.J.; Civil No. 89-5428.

CHARGED 12-29-89: While held by Commodity Warehouse Services, Inc., Linden, N.J., the articles contained insect and rodent filth, and the rice had been held under insanitary conditions—402(a)(3), 402(a)(4).

DISPOSITION: The rice was claimed by Dharma Corp. (Jan S. Yadav), Edison, N.J., and a consent decree of condemnation authorized release of the rice to the claimant for salvaging. A default decree ordered the apricots destroyed. (F.D.C. No. 65794; S. Nos. 90-524-094/5; S.J. No. 2)

PRODUCT: **Cornmeal and soy protein**, at Madison, S. Dist. Ill.; Civil No. 90-5091.

CHARGED 5-1-90: While held by Tarlas Meat & Food Co., Madison, Ill., the articles had been held under insanitary conditions—402(a)(4).

DISPOSITION: Consent—destruction. (F.D.C. No. 65861; S. Nos. 90-434-2199/220; S.J. No. 3)

PRODUCT: **Shrimp pieces, frozen**, at Nashville, M. Dist. Tenn.; Civil No. 3:90-0919.

CHARGED 10-19-90: While held for sale, the article contained rodent filth—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65946; S. No. 90-608-325; S.J. No. 4)

PRODUCT: **Spaghetti and lasagna**, at Melrose Park, N. Dist. Ill.; Civil No. 90-C-6064.

CHARGED 10-18-90: When shipped from Norfolk, Va., the articles labeled "Lasagna Festonate [or "Enriched Spaghetti"] . . . Pantanella Sud S.P.A. . . . Pomezia (Roma) Italy" contained insect filth—402(a)(3).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65951; S. No. 90-576-696 et al.; S.J. No. 5)

Food/Economic and Labeling Violations

PRODUCT: **"Orange roughy" fish fillets, frozen**, at Pittsburgh, W. Dist. Pa.; Civil No. 89-0663.

CHARGED 3-30-89: When shipped by Silver Seas Sales Co., Columbus, Ohio, the article labeled "Blueseas . . . Orange Roughy Hoplostethus Atlanticus . . . Packed by Skeggs Foods Ltd. Port Nelson, New Zealand" had had oreo dory substituted for orange roughy—402(b)(2); the article's labeling was false and misleading in claiming the article as orange roughy—403(a)(1); the article (oreo dory) was offered for sale under the name of another food—403(b); and the article's labeling lacked the common or usual name of the food—403(j).

DISPOSITION: Default—ordered delivered to charitable institution. (F.D.C. No. 65631; S. No. 89-436-867; S.J. No. 6)

Drugs/Human Use

PRODUCT: **Diosgenin in a bulk drum**, at Cudahy, E. Dist. W. Wis.; Civil No. 90-C-0848.

CHARGED 8-24-90: When shipped from Orizaba, Mexico, the labeling of the article labeled "CBS Chemicals . . . Milwaukee WI. . . Sonoran Exporters . . . Nogales, Arizona . . . Diosgenin . . . Producto de Mexico" lacked adequate directions for use and was not exempt—502(f)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65890; I.S. No. 708790; S.J. No. 7)

PRODUCT: **Various Oriental drugs and foods**, at Boston, Dist. Mass; Civil No. 65523.

CHARGED 10-4-88: When the drugs (i.e., articles labeled "African Sea-Coconut . . . Cough Mixture . . . Luen Fook Medicine Co. . . Singapore," "Boying Pills . . . Prepared by Eu Yang Sang . . . Hong Kong," "Chang Chun Yaochiew . . . Packed By China National Tea & Native Produce Import & Export Corp. . . Swatow Office," "Gejie DaBu Wan . . . Yulin Drug Manufactory Kwangsi, China," "Musk Chilli Plaster . . . Hangzhou, China," and "Shang Shi Bao Zhen Gao . . . Shanghai Medicine Works Shanghai, China") were imported, they were new drugs without effective approved New Drug Applications—505(a); the labeling of the drugs was false and misleading in representing and suggesting that there was substantial scientific evidence to establish that the drugs were safe and effective for use in the conditions listed in their labeling—502(a); and the labeling lacked adequate directions for use in the treatment of conditions listed in the labeling—502(f)(1). As to the imported foods (i.e., bamboo tips, canned mushrooms, cooking wine, dried salted fish, egg noodles, ginseng drink, and Miso soup mix), the dried salted fish contained decomposed fish, and the label lacked an accurate quantity of contents statement—402(a)(3), 403(e)(2); the Miso soup mix and canned mushrooms were low-acid foods prepared, packed and held under conditions contrary to regulations since the foreign manufacturers had failed to register as low-acid canned food manufacturers and had failed to file with FDA the prescribed scheduled processes—402(a)(4); the egg noodles contained the nonconforming color

additive FD&C Yellow No. 5, because its presence was not declared on the label; and the egg noodles' label included the words "highly nutritious" but lacked required nutrition labeling information—402(c), 403(a)(1); and various required information was not prominently placed on the labels of various foods as required by law: e.g., the cooking wine lacked the common or usual name of the food (as well as other required information) in English, the Miso soup mix had all of its principal display panel information in Chinese rather than in English, the quantity of contents statement of the bamboo tips was in Chinese rather than in English, and the quantity of contents statement of the ginseng drink was expressed as "120 ml" rather than as required—403(f).

In addition, the egg noodles failed to conform to the definition and standard of identity for egg noodles since they contained an artificial color—403(g)(1); and the labels of the bamboo tips, dried salted fish, and ginseng drink lacked the common or usual name of each of its ingredients—403(i)(2).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65523; S. No. 88-568-302 et al.; S.J. No. 8)

Medical Devices

PRODUCT: **Balloon dilation system**, at Billerica, Dist. Mass.; Civil No. 90-10417-WF.

CHARGED 2-21-90: The article (which had been manufactured by USCI Division, C.R. Bard, Inc., Billerica, Mass., and labeled "USCI . . . Probe Dilation System Balloon-On-A-Wire Device . . . Bard, Inc. . . Mass") had been manufactured, packed or stored under circumstances that failed to conform with good manufacturing practice regulations for medical devices—501(h). DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65815; S. No. 90-564-585; S.J. No. 9)

PRODUCT: **Gloves, latex** (five lots for medical examination and one lot for surgical use), at Ponce, Dist. Puerto Rico; Civil No. 90-1349(JP).

CHARGED 3-9-90: The quality of the articles (which had been manufactured by various firms in China and Taiwan) fell below their purported quality because the gloves contained excessive holes and leaked—501(c); the circumstances used for the packaging of the lot of gloves for surgical use (which were labeled "Surgimed . . . Surgical Gloves . . . Examination Gloves . . . Packed & Sterilized By Surgimed De Puerto Rico Inc., . . . Ponce, Puerto Rico") failed to conform with good manufacturing practice regulations, and the labeling of that lot of gloves for surgical use was false and misleading in claiming that the gloves were sterile examination and surgical gloves, when those gloves were not surgical gloves—501(h), 502(a); the labels of the other five lots of gloves failed to bear the name and place of business of the manufacturer, packer or distributor—502(b)(1); and the labels of the "surgical" gloves and one lot of the other gloves failed to contain an accurate quantity of contents statement in terms of numerical amount—502(b)(2).

DISPOSITION: The articles were claimed by FGI Corp. (James L. Carlo), Hato Rey, P.R., which admitted that the articles were

unfit for either hospital, surgical or laboratory work and sought to enter into a consent decree to repackage the gloves for household and industrial use. However, the claimant subsequently found that the required bond could not be posted and accordingly consented to the condemnation and destruction of the articles. Accordingly, upon motion of the government, the articles were ordered destroyed. (F.D.C. No. 65819; S. No. 90-510-783 et al.; S.J. No. 10)

PRODUCT: Shoulder ligament prosthetic implant device for surgical repairs, at Kalamazoo, W. Dist. Mich.; Civil No. K84-502.

CHARGED 11-20-84: The article, which was labeled "Stryker Dacron Ligament Prosthesis . . . Stryker . . . Kalamazoo, MI . . . Shoulder 130-10 Manufactured by Meadox Medicals, Inc. . . . Oakland, New Jersey," was a class III device lacking the required effective approved pre-market approval application—501(f)(1)(B); and a required pre-market notification had not been submitted for the article, and the article had not been listed as required by 502(o).

DISPOSITION: The article was claimed by Stryker Corp., Kalamazoo, Mich. The claimant moved for summary judgment, asserting that the device was exempt from pre-market notice and approval because it was in commercial distribution before May 28, 1976, for the specific intended use of surgical repair of Grade III shoulder separations. The claimant also moved to expedite a hearing on its summary judgment motion, or, in the alternative, for an injunction order canceling the warrant of seizure for the seized devices. Upon joint motions of the parties, the government's time to respond to the claimant's motion for summary judgment was extended in order to negotiate a schedule for discovery, the filing of the government's response, and a date for a hearing. The government served on the claimant written interrogatories and a request for the production of documents. Subsequently, the government filed a cross-motion for summary judgment in its favor.

After a hearing on the motion for summary judgment, the court denied the claimant's motion for summary judgment and granted the government's summary judgment motion.

The court noted the government's argument that the article (which was manufactured by Meadox Medicals, Inc., and distributed by Stryker Corp.) lacked both pre-market notification and a 510(j) listing, as well as Stryker's argument that the article was exempt under 21 *CFR* 807.81(a)(3) because changes in the article since 1976 did not rise to the article being significantly changed or modified. However, the court found that Stryker misinterpreted such exempting regulations because it applied only to those persons (e.g., Meadox) who had a device in commercial distribution at the time the modification was about to be made and because Stryker, by its own admission, did not begin distributing the device itself until June 1982.

Although a Meadox Dacron vascular graft product had been used with Meadox's knowledge by an orthopedic surgeon for shoulder repair of acromioclavicular separations before October 1975 and Meadox had continued to sell such product to that surgeon knowing of such use, the court agreed with the government that the seized device was not the same device manufactured

by Meadox prior to enactment of the Medical Device Amendments of 1976. The claimant's affidavits, deposition testimony, and brief did not create any material issue of fact; and, instead, they supported the government's assertions that the seized device was undergoing research and development until 1978 or 1979 (i.e., the orthopedic surgeon using the early Dacron graft product had requested Meadox to make the graft smaller and less elastic; a Meadox manager, effecting such requested changes, had increased the tension in the yarn and had added what was known as "H-Beam" longitudinal sewing configuration; and the double velour vascular graft product had evolved from no beam, to one beam, to three beams, to the "H-beam" configuration). The court held that the seized device did not exist before 1978 and necessarily did not meet the exemption of the Compliance Policy Guide interpretation of "commercial distribution before May 28, 1976."

As to listing required by 510(j) of the Food, Drug, and Cosmetic Act, Stryker asserted that Meadox's listing for vascular graft products was a sufficient listing for the seized device until FDA had finalized regulations concerning the classification name of the device. However, it was apparent to the court that *all* medical devices must be listed even though no final classification name yet existed and that Stryker understood FDA's instructions to place the word "none" in the classification space when no classification name had been finally promulgated.

As to the device's class III status and requirement of pre-market approval, the court had found that the device in question did not exist before May 28, 1976, and accordingly was necessarily "new" upon its introduction to the market in 1978 or 1979. It therefore was automatically placed in the class III device category and required an approved application for pre-market approval before being marketed. Stryker had argued that the modifications of the device were not so substantial that they rendered it a new device and that it might be reclassified as "substantially equivalent" to an "old device"; however, the court found that such a determination was, in the first instance, FDA's to make, that no petition for reclassification had been filed with FDA for the Stryker device, and that no provision in the act allowed a court to bypass FDA's reclassification procedures.

In addition to the government's request for condemnation of the seized devices, which the court granted, the government had also requested at oral argument an injunction against Stryker to prevent the commercial distribution of any dacron orthopedic device in an "H-Beam" configuration. The court noted that such an injunction would sweep within its prohibition Stryker's "H-Beam" devices for knees and ankles; and the court agreed with Stryker that the government had no authority to reach out to other Stryker products because it had seized one product. Accordingly, the request for injunctive relief concerning other devices was denied, although the seized devices were condemned.

In accordance with the court's judgment and decree, Stryker had a year to bring the condemned devices into compliance and to obtain their release, after which any remaining devices were to be destroyed. Subsequently, after more than a year, all of the articles were destroyed pursuant to the court's judgment and decree. (F.D.C. No. 64410; S. No. 84-309-360; S.J. No. 11)

CRIMINAL ACTIONS

DEFENDANTS: **Hoechst Aktiengesellschaft** (owner of Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.) and **Rainer Zapf**, M.D., Clinical Research Division Director, Frankfurt am Main, Germany; Dist. N.J. Criminal Nos. 90-598 and 90-597.

CHARGED on or about 11-15-90: That the defendants failed to ensure the prompt reporting to FDA of certain findings associated with the use of nomifensine (a drug for which clinical studies were authorized by FDA pursuant to an Investigational Exemption for a New Drug)—i.e., the death of a patient reported to the firm by the firm's subsidiary in Italy in which a patient died while being treated with nomifensine and data suggested that the patient's death had probably been due to hemolytic anemia and that her hemolytic anemia might have been caused by the drug, and the death of patient reported to the defendant firm by the firm's subsidiary in France in which a patient died of hemolytic anemia after ingesting nomifensine as a means of committing suicide—505(i); and that the defendant firm subsequently failed to ensure the prompt reporting to FDA of the above findings associated with the use of nomifensine (a drug for which an approved New Drug Application had become effective on Dec. 1, 1984, but which, because of increased incidence of hemolytic anemia, was withdrawn from the market in 1986)—505(i).

DISPOSITION: Guilty pleas; individual fined \$2,000 and firm fined \$202,000. (F.D.C. No. 65703; S.J. No. 12)

MISCELLANEOUS ACTIONS

SUBJECT: **Dioxin in fish and FDA denial of petition to establish a tolerance for such dioxin**, Court of Appeals for the Sixth Circuit, Cincinnati, Ohio; Civil No. 85-3943.

PETITIONED 11-12-85 for judicial review by National Wildlife Federation (NWF), Ann Arbor, Mich., against HHS Secretary Margaret M. Heckler and FDA Commissioner Frank E. Young: That FDA had denied NWF's petition requesting the establishment of a "tolerance" for the contamination of fish and other food products with dioxin; that the members of NWF (a 4.5-million-member, nongovernmental conservation organization) regularly used U.S. waters, including the Great Lakes, for sport fishing; that they frequently consume the fish they catch, which are contaminated with dioxin, and thus they are at increased risk of various maladies associated with exposure to dioxin; that NWF had filed a petition (in which the toxicity of dioxin and the dioxin contami-

nation of fish were summarized) requesting that FDA set a "tolerance" limiting the acceptable amounts of dioxin in fish; and that FDA had denied NWF's petition. Accordingly, NWF petitioned the court for a review of such denial.

DISPOSITION: FDA's decision was affirmed by the court. NWF argued that their submitted evidence demonstrated that FDA's 1981 informal guideline for dioxin contamination of sport fish was not adequate to protect public health and that the states and provinces bordering the Great Lakes had been unable to establish consistent fish consumption advisories for dioxin-contaminated sport fish. NWF cited the 1985 D.C. Circuit Court of Appeals' opinion in *Community Nutrition Institute v. Young* and asserted that FDA unlawfully found that it lacked jurisdiction to issue such a tolerance and unlawfully refused to commence a tolerance setting proceeding. The states of Michigan, Illinois, New York, Wisconsin, Indiana, and Pennsylvania, as *amici curiae*, submitted a brief in support of NWF's petition.

Meanwhile, in light of the inherent ambiguity of 21 U.S.C. 346 and the reasonableness of FDA's interpretation thereof, the Supreme Court had reversed the decision of the D.C. Circuit Court of Appeal in *Community Nutrition Institute v. Young* and had held that the Federal Food, Drug, and Cosmetic Act allowed, but did not require, the use of formal rule-making proceedings to set allowable contamination levels for foods unavoidably contaminated with poisonous or deleterious substances.

Subsequently, NWF, in a supplemental brief, argued that the Supreme Court's ruling did not affect the gravamen of NWF's petition because FDA's denial of NWF's petition was premised on FDA's incorrect assumption that it had no jurisdiction over dioxin-contaminated sport fish. The court of appeals in the instant case found that NWF was in error.

In affirming FDA's decision, the court said that FDA's letter denying NWF's petition revealed that FDA had considered relevant animal and human exposure data, including the risks posed by the consumption of dioxin-contaminated Great Lakes sport fish. The court noted that FDA, using National Marine Fisheries Service data, had determined the risks of such exposure, had found that the advisory adequately protected those consumers, and had concluded that the consumption of Great Lakes sport fish would not result in significant dioxin exposure to the general population. The court found that FDA clearly had the discretion not to issue a tolerance even if a deleterious or poisonous substance had been added to food and the contamination was unavoidable. (Misc. No. 790; S.J. No. 13)



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