

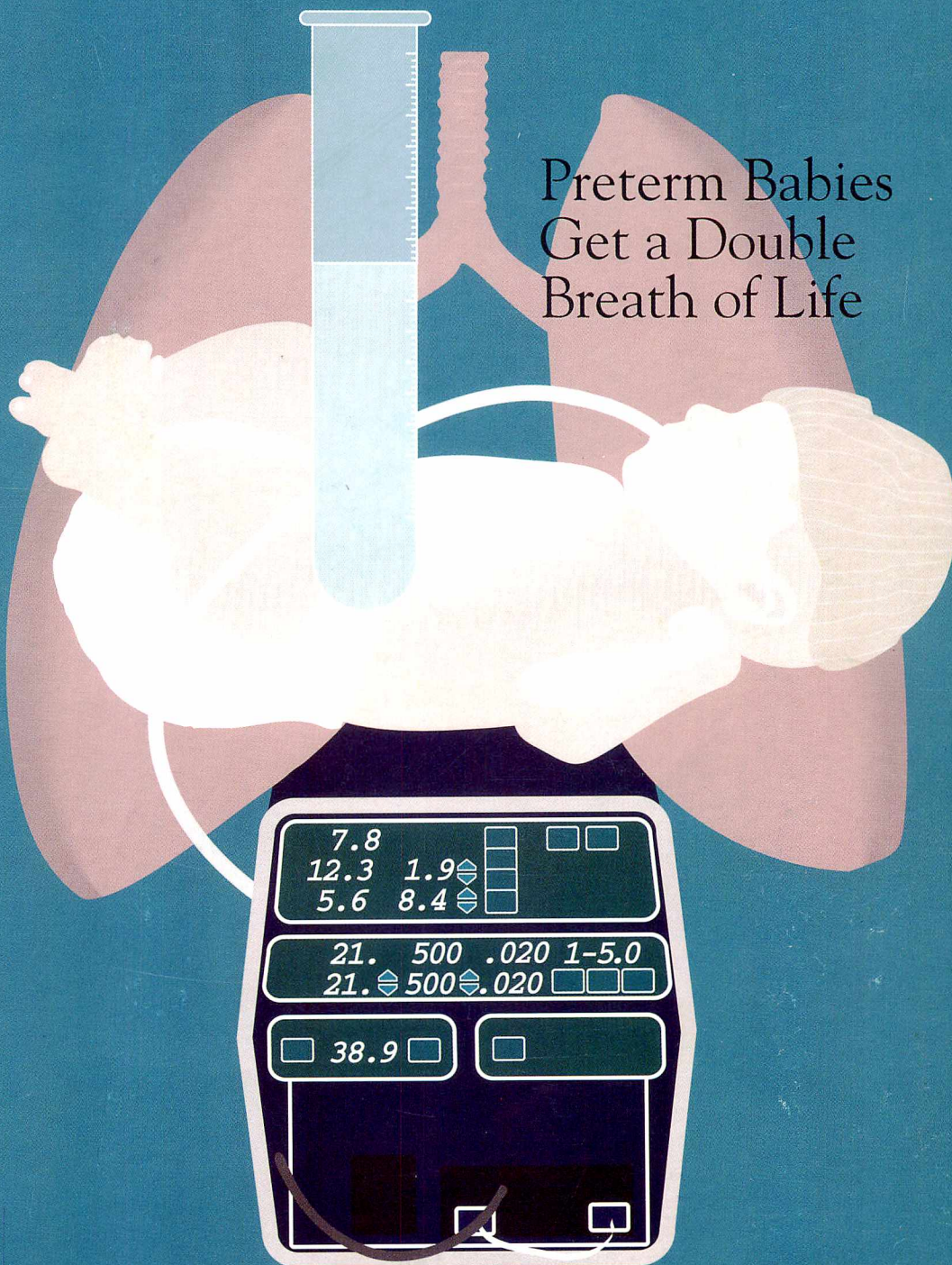
FDA CONSUMER

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

• VOL. 26 NO. 3

APRIL 1992 •

Preterm Babies
Get a Double
Breath of Life





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Preterm Babies Get a Double Breath of Life

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A lifesaving drug has cut in half deaths from respiratory distress syndrome in low-birthweight babies born prematurely. New, high-frequency ventilators are also being used to help such "preemies."

Not Only Sugar Is Sweet

16

People come by their love for sweetness naturally. Sugar—in moderation—may not be the villain it was made out to be a few years back. Its many forms, as well as its substitutes, give consumers a wide selection of ways to make life sweeter.

Panic Disorder: The Heart That Goes Thump in the Night—and Day

22

A pounding heart, uncontrollable shaking, and altered perceptions are just a few of the scary symptoms of panic disorder. Drug treatment may give relief but may not be without risks.

Prostate Problems Plague Older Men

28

More than half of American men over 50 have symptoms of an enlarged prostate gland. The problem is not hard to diagnose, but most men don't have the examination. Treatments include surgery or insertion of a special type of balloon. A new drug treatment is also being considered.

Beyond Measles and Chickenpox: Other Childhood Diseases Cause Rashes

32

Childhood diseases other than measles and chickenpox cause rashes and often befuddle parents. The rashes usually appear in specific places or have distinctive patterns and affect children only of a particular age.

On the Teen Scene: Good News About Good Nutrition

36

How can you gain weight that's muscle, not fat? What's a healthy weight for you? How can you squeeze in a good, meal after school before you have to be at your part-time job? Modern nutrition provides some very palatable answers.

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Inside Front Cover Photo: *How's a teenager to get good nutrition and still eat the food she likes? See page 36.*



Panel Recommends Restricting Silicone Breast Implants

Citing continuing safety concerns, an FDA panel of outside experts recommended on Feb. 20 that silicone gel-filled breast implants be available only to women participating in clinical studies designed to answer questions about the risks of the implants. The panel recommended that women who already have the implants have the devices checked regularly by their doctors.

For three days, FDA's General and Plastic Surgery Devices Advisory Panel heard testimony by doctors, manufacturers and consumers on the benefits and problems associated with implants. While expressing concern about the risks, the panel noted that women with conditions such as breast cancer have a special medical need for the implants. Therefore, the panel recommended that all women who require breast reconstruction after mastectomy or because of certain breast abnormalities (such as those which result from injury or birth defects) and need the silicone-gel implants be allowed to participate in clinical studies. The panel recommended only limited trials to study women who choose the implants for augmentation (breast enlargement) purposes. The number of augmentation patients to be studied should be determined by the nature of the scientific questions being asked, the panel said.

The panel advised that women with implants should:

- see their doctors regularly and, if an implant ruptures, have it removed
- follow established cancer screening recommendations
- tell their mammography facility that they have implants, so that special techniques can be used by personnel trained in examining women with breast implants.

Whenever possible, these women should seek a mammography facility accredited by the American College of Radiology and certified by Medicare. The panel did *not* recommend that women without symptoms undergo routine mammography just to look for a rupture.

The panel said it could not reach a conclusion about the possible link between the implants and certain immune-related or connective tissue disorders because the data are insufficient.

Advisory panel recommendations are not binding on

FDA, but the agency gives them careful consideration. At press time, FDA Commissioner David A. Kessler, M.D., was expected to make a decision on the implants by April 20. Until this decision is made, the moratorium on the use of implants, begun last Jan. 6, will remain in effect.

Implant Registry Established

A nonprofit registry for women with breast implants has been established to provide registrants with up-to-date information about implants. The service does not provide medical advice.

The registry, established last January by Medic Alert Foundation International in Turlock, Calif., will link women, their physicians, and hospitals with information made available from FDA and implant manufacturers.

Registrants may also record and update symptoms possibly related to their implants and will have the option of participating in future medical research studies. The registry is confidential and no information will be released without the registrant's permission.

The registry is independent of all implant manufacturers and is funded by registration fees and donations. The initial fee is \$25 with annual renewal fees of \$15. Women who wish to enroll in the registry or request information about it can call toll-free (1-800) 892-9211 from 8 a.m. to 11 p.m. Eastern Time, seven days a week.

Care Needed When Giving Children Medicine

When fighting flu and colds, parents should be careful not to overdose their children with over-the-counter liquid medicines, FDA recently warned consumers.

Parents have accidentally given too much medicine using the plastic "dose cups" often packaged with liquid medicines. They have either misread markings on the cups or haven't followed dose directions carefully, FDA said.

Even small overdoses of the painkiller acetaminophen, given over a period of several days, can be dangerous.

"If the label says to give two teaspoons every four

hours, that's the amount the child should get at the prescribed intervals," said FDA Commissioner David A. Kessler, M.D. He also urged parents to read ingredient labels carefully, so they don't provide the same ingredient in two medications.

"If the condition worsens or fails to improve, the child should be seen by a physician," Kessler said. "If parents have any questions about the proper dose of a medication, they should consult their pharmacist or physician."

FDA began investigating accidental overdosing after a child was given three times the recommended dose of a medicine.

The child's parents measured to the "two tablespoon" level marked on the dose cup instead of the recommended two teaspoons. The cup had no teaspoon markings.

FDA has begun a survey of liquid medicines to make sure the dose cups are labeled properly. Manufacturers of these medicines have said they would review the packaging as well.

Though no serious injuries have been reported involving dose cups, two manufacturers have recalled products with dose cups that are incompatible with the labeling or difficult to read.

Doc Gets Jail, Fine For Illegal Steroid Distribution

A Pennsylvania doctor received 36 months in jail for illegally distributing anabolic steroids to professional wrestlers.

Judge William W. Caldwell, U.S. district judge for the Middle District of Pennsylvania, sentenced George T. Zahorian III, M.D., of Harrisburg, on Dec. 27, 1991, to 36 months imprisonment followed by two years of supervised release on each of the 12 counts of conviction. Zahorian will serve the sentences concurrently. The judge also fined Zahorian \$12,700.

The sentencing follows Zahorian's conviction last June for violation of the Anti-Drug Abuse Act of 1988, which prohibits distributing anabolic steroids for any use other than the treatment of a disease under a physician's orders. (See "Physician Convicted in Steroid Distribution," in the November 1991 *FDA Consumer*.)

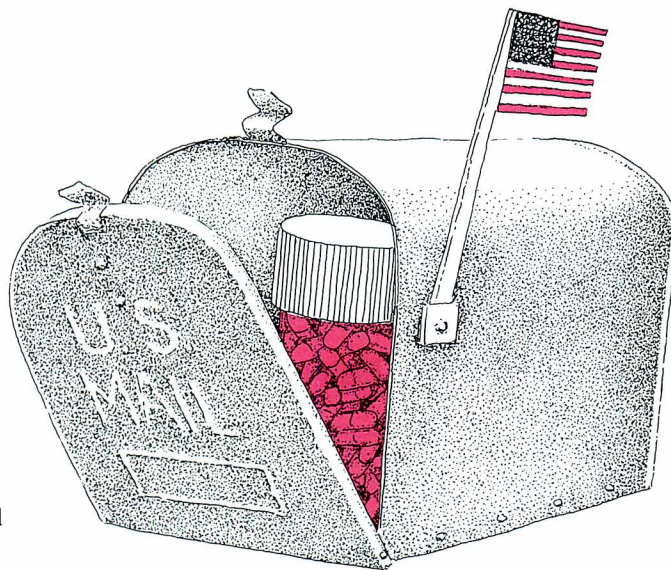
Anabolic steroids are synthetic derivatives of testoster-

one, a male sex hormone. Approved for limited use in treating some debilitating diseases, these drugs are being misused by some athletes and bodybuilders who hope to develop stronger, more muscular bodies. (See "Steroids and Sports: A Losing Proposition" in the September 1991 *FDA Consumer*.)

Import Alert for Unapproved Drugs by Mail

Unapproved mail-order drugs coming into the United States have been targeted for automatic detention by FDA.

The agency issued an import alert on Jan. 30, instruct-



ing field offices to detain all imported unapproved prescription products manufactured by six overseas firms: Interpharm, Inc., and Northam Medication Service International Pharmacy, both of Nassau, Bahamas; Inhome Services of Delemont, Switzerland; International Products of Hanover, Germany; Azteca Trio Internacional, S.A. de

C.V. of Zona Rio Tijuana, Mexico; and Interlab of London, England.

FDA permits field offices to use their discretion in allowing entry of small "personal-use" quantities (usually enough to treat for three months or less) of foreign drugs not approved in this country. The policy was designed to allow individuals with serious illnesses access to drugs they believe may be helpful. This applies in cases in which satisfactory treatment for the condition is not available in this country, the drugs pose no unreasonable safety risk, and their use is not promoted in the United States. However, such is not the case with these mail-order drugs.

The companies have been promoting a variety of products purported to treat depression, high blood pressure, fungal infections, fatigue, chronic bronchitis, and hair loss. Many have been advertised in periodicals and through direct mail as less expensive "foreign versions" of prescription drugs approved in the United States.

FDA Commissioner David A. Kessler, M.D., warned that these "foreign versions" are often of unknown quality with inadequate directions for use and, in some cases, are counterfeit.

The unapproved drugs promoted by these overseas operations lack the quality assurance standards and safeguards of drugs approved here. FDA warns that severe adverse reactions, including death, can result from use of prescription drugs that have not been properly produced.

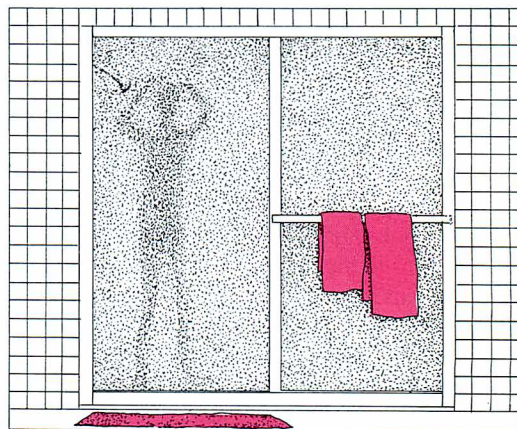
FDA OKs Five Flake Fighters

Only five flake-fighting ingredients in dandruff shampoos will safely scrub away those itchy scales.

In a final rule, published in the *Federal Register* on Dec. 4, FDA announced that five active ingredients are safe and effective for treating dandruff. These are coal-tar preparations, pyrithione zinc, salicylic acid, selenium sulfide, sulfur, or a combination of sulfur and salicylic acid.

Most popular dandruff shampoos already contain one of these ingredients. But some treatments for cradle cap, such as Diaparene Cradol, will be removed from the market because their active ingredient, methylbenzethonium chloride, doesn't work.

For the severe dandruff called seborrheic dermatitis, only four ingredients are approved: coal-tar preparations,



pyrithione zinc, salicylic acid, or selenium sulfide. For psoriasis, the list includes only two ingredients—coal-tar preparations and salicylic acid.

In November 1990, FDA banned 27 ingredients in dandruff shampoos because they weren't safe and effective.

30 New Molecular Entities Approved in 1991

Thirty new molecular entities (NMEs)—drugs distinctly different from those already on the market—were among the 327 FDA approvals for new and generic drugs and biologics in 1991.

Five of the 30 NMEs were classified 1A, meaning the drugs provide significant therapeutic gains. They are:

- Ceredase (alglucerase), for an inherited enzyme deficiency, Type I Gaucher disease, manufactured by Genzyme Corp.
- Fludara (fludarabine phosphate), for chronic lymphocytic leukemia, manufactured by Berlex Laboratories
- Videx (didanosine), to treat advanced HIV infection, manufactured by Bristol-Myers Squibb Co.
- Nipent (pentostatin), for hairy cell leukemia, manufactured by Parke-Davis
- Supprelin (histrelin acetate), for control of precocious puberty, manufactured by R.W. Johnson.

Among the biologics approved were:

- a new pertussis (whooping cough) vaccine that lessens the chance of a severe reaction because it is made from

only the coating of the virus instead of the whole virus, manufactured by Lederle Labs/Takeda

- interferon alfa-2b, for treatment of chronic non-A, non-B/C hepatitis
- three diagnostics, two to test for reactivity to HIV, and one to detect antibodies to hepatitis B.

In addition to new molecular entities, other important approvals included: a new once-a-day capsule form of Marion Merrell Dow's blood pressure drug Cardizem; Triostat, SmithKline Beecham's orphan drug injection for use in treating hypothyroidism; and two nicotine transdermal patches—Ciba Geigy's Habitrol and Marion Merrell Dow's Nicoderm—to help people stop smoking.

Vaginal Pouch Gets Advisory Panel Nod

FDA's Obstetrics and Gynecology Devices Advisory Panel recommended conditional approval of a vaginal pouch designed to protect women against sexually transmitted diseases (STDs) as well as pregnancy.

The Reality vaginal pouch, sometimes called a "female condom," is the first product of its kind to be reviewed by the agency. The same length as a male condom, but wider, the pouch consists of a silicone-lubricated polyurethane sheath with a flexible polyurethane ring on each end. One ring is used to insert the pouch into the vagina, much like a diaphragm. The other ring remains outside the vagina, covering the labia.

In 1989, the panel developed guidelines for manufacturers who wished to market a female contraceptive that also protects against STDs. The panel required specific tests to show the product is safe and effective for those purposes. For example, the panel specified that in order to show effectiveness, a study had to be conducted with a minimum of 200 women over 12 months to determine the pregnancy rate. The panel said a pregnancy study could be used as a surrogate for testing the pouch's effectiveness against STDs.

When the panel met Jan. 31, it expressed concern about data presented by the manufacturer, Wisconsin Pharmacal Company of Jackson. The firm had only studied 81 women for six months to gain information about usage, effectiveness, and the pregnancy rate.

Nevertheless, the panel advised conditional approval

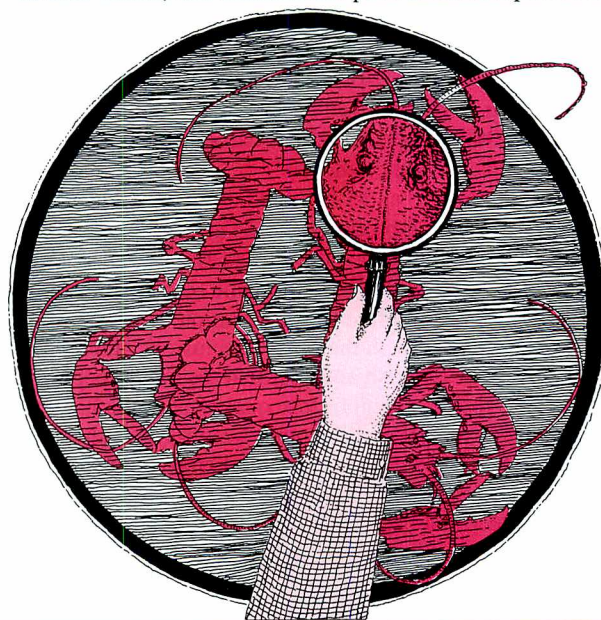
because of the great need for a device women can use to help prevent transmission of STDs, especially AIDS. The pouch may be useful for women who cannot convince their partners to use male condoms. The panel recommended that, before being granted FDA's approval, the firm meet certain conditions, including:

- completing all preclinical studies mentioned during the panel meeting, including meeting good manufacturing practices
- completing a study with 200 women to show there is no increase in the pregnancy rate, which in current studies is no greater than 15 pregnancies per 100 women per six months
- revising labeling to ensure claims do not go beyond study data.

FDA is not bound by advisory committee recommendations but gives them serious weight in deciding whether to approve products.

NAS Says Most Seafood Safe

Most seafood is safe to eat, according to a 1991 report by the National Academy of Sciences (NAS). In its February issue, *Consumer Reports* magazine, published by Consumers Union, had claimed that poor sanitation practices



at the retail level and environmental contaminants made some fish unsafe to eat.

NAS did, however, recommend strengthening government regulation and enforcement through use of a Hazard Analysis Critical Control Point (HACCP) program to enhance the safety of this highly perishable food. FDA and the National Oceanic and Atmospheric Administration's National Marine Fisheries Service began a pilot HACCP program last October, working with retail stores to identify critical points at which problems might occur to concentrate preventive efforts there. Twenty-five supermarkets operated by 13 chains in 12 states are participating.

FDA established a new Office of Seafood early in 1991 to strengthen its enforcement, research, education, and training programs. At the same time, the agency announced that in order to better identify problem areas in the industry it would inspect all seafood processing plants. By the end of the year, it had completed 3,541 inspections (in the United States there are some 3,852 seafood processing plants). Preliminary data from these inspections indicate substantial compliance with FDA requirements. The rest of the plants will be inspected this year.

The agency has increased from 600 in 1991 to 900 in 1992 the number of domestic seafood samples to be analyzed for industrial chemicals and pesticides, and it plans similar analyses of 350 samples of the fish produced through aquaculture on so-called "fish farms." The agency also has doubled—from 400 to 800—the number of import shipments to be analyzed for pesticides and industrial chemicals (about 60 percent of the seafood consumed in the United States is imported).

In fiscal years 1990 and 1991, FDA initiated 50 recalls of adulterated seafood products and 23 actions against firms for misbranding. Since the start of fiscal year 1992, FDA has issued 16 warning letters to the seafood industry, 11 for misbranding and five for adulteration.

The agency agrees with the NAS conclusions and reminds consumers that fish and shellfish are highly perishable products that can spoil or lose quality between harvesting and consumption. Like other flesh foods, fish and shellfish should be examined carefully before purchase and should be consumed shortly thereafter. Consumers should also heed state advisories on local contaminant problems.

Las Medicinas y la Vejez



Spanish, English Pubs Available

Six reprints of *FDA Consumer* articles and one FDA backgrounder are newly available.

Five of the reprints are in Spanish: "La Decadencia Del Síndrome de Reye" ("Reye Syndrome: The Decline of a Disease" FDA91-1172S), "Las Medicinas y la Vejez" ("Testing Drugs in Older People" FDA91-3185S), "Cómo Tomar Las Medicinas: Los Diuréticos" ("How to Take Your Medicine: Diuretics" FDA91-3167S), "Cómo Tomar Las Medicinas: Los Estrógenos" ("How to Take Your Medicine: Estrogens" FDA92-3186S), and "Los Peligros Del Plomo" ("An Unwanted Souvenir: Lead in Ceramic Ware" FDA92-2259S).

Available in English is the reprint "Get Hooked on Seafood Safety" (FDA91-2246) and the backgrounder "Reducing Exposure to Lead from Ceramic Ware" (No. BG 91-8.2).

To order single copies, write to the Food and Drug Administration, HFE-88, 5600 Fishers Lane, Rockville, MD 20857, or call (301) 443-3170. To order up to 100 copies of reprints, or negatives, write to FDA, HFI-40, at the same address. All orders should include title and publication number.

Correction

On page 17 of the January-February 1992 *FDA Consumer*, cryptococcal meningitis was identified as a bacterial infection. This is incorrect; it is a fungal infection.



Reye Warning Voluntarily Added To Pepto-Bismol Labeling

We have read your article "Using Over-the-Counter Medications Wisely" in your November issue of *FDA Consumer*. We support the intent and recognize the importance of your article in educating consumers about self-medication. . . .

Regarding Reye Syndrome, epidemiologic studies conducted by the Institute of Medicine of the National Academy of Sciences have shown an association between ingestion of aspirin during the antecedent illness and the onset of Reye Syndrome. . . . Based on the results of the epidemiology studies, on June 6, 1988, the FDA concluded that requiring a Reye Syndrome warning on the labeling of non-aspirin, salicylate-containing drug products was not justified by existing clinical research.

In 1985, we voluntarily added a warning statement on Pepto-Bismol. The purpose of this warning was to prevent *delaying* diagnosis and prompt treatment of Reye Syndrome since our product may be taken for nausea, a symptom of Reye Syndrome. . . . This warning statement reads: "Children and teenagers who have or are recovering from the chicken pox or flu should not use this medicine to treat

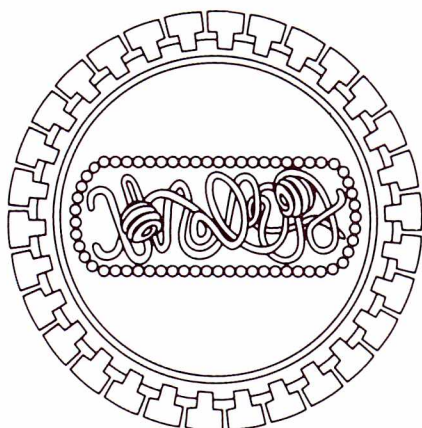
vomiting. If vomiting is present, consult a doctor because this could be an early sign of Reye Syndrome, a rare but serious illness. Also, as with any drug, if you are pregnant or nursing, seek the advice of a health professional before using this product."

You noted Pepto-Bismol is currently being reviewed by the FDA for treatment of diarrhea. On July 26, 1991, the FDA's Gastrointestinal Drugs Advisory Committee unanimously concluded that Pepto-Bismol is safe and effective for the treatment of acute diarrhea, including travelers' diarrhea.

Martha R. Feller, Ph.D.
Associate Director
Worldwide Medical Affairs
The Procter & Gamble Company

(Editor's Note: At press time, FDA was reviewing the recommendation of this advisory committee.)

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



AIDS Drugs Being Studied

More than 360 ongoing human studies have FDA's sanction to test drugs that may treat AIDS or related conditions. Many studies use two or more experimental therapies in combination. Sponsors of the following drugs and biologicals have publicly acknowledged that the products are under study as potential AIDS therapies. Information requests should be made to the sponsor or to the AIDS Clinical Trials Information Service, which can be reached at 1-800-TRIALS-A.

Anti-Virals

- **GLQ223**, GeneLabs Inc., Redwood City, Calif., (415) 369-9500
- **SC48334**, G.D. Searle & Co., Chicago, (708) 982-7000
- **DHEA**, Elan Corp., Atlanta, (404) 534-8239
- **ribavirin**, Viratek/ICN Pharmaceuticals, Costa Mesa, Calif., (1-800) 556-1937
- **DDC (dideoxycytidine)**, Hoffmann-La Roche Inc., Nutley, N.J., (201) 235-5000, and the National Cancer Institute (NCI), Bethesda, Md., (301) 496-6631
- **AL 721**, National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, Md., (301) 496-5717
- **dextran sulfate (UA001)**, Ueno Fine Chemicals Industry Ltd., New York (212) 452-8666; NIAID, Bethesda, Md., (301) 496-5717; and the National Jewish Center for Immunology and Respiratory Diseases, Denver, (303) 388-4461
- **r-beta-ser interferon**, Berlex Laboratories, Alameda, Calif., (510) 769-5200
- **d4T (didehydrodeoxythymidine)**, Bristol Myers,

Wallingford, Conn., (203) 284-6000

- **AzdU (azidouridine)**, Berlex Laboratories, Alameda, Calif., (510) 769-5200

Immuno-Modulating Agents

- **VaxSyn HIV-I**, MicroGeneSys Inc., Meriden, Conn., (203) 686-0800
- **DTC (imuthiol)**, Connaught Labs, Swiftwater, Pa., (717) 839-7187
- **thymopentin**, Immunobiology Research Institute, Annandale, N.J., (201) 730-1799
- **peptide-T**, National Institute of Mental Health, Rockville, Md., (301) 443-4515, and Reed, McFadden, Toronto, (416) 941-9739
- **isoprinosine**, Newport Pharmaceuticals, Newport Beach, Calif., (714) 642-7511
- **alpha interferon**, Hoffmann-La Roche Inc., Nutley, N.J., (201) 235-5000, and Schering-Plough Corp., Kenilworth, N.J., (908) 298-4000
- **oral alpha interferon**, Interferon Science, New Brunswick, N.J., (908) 249-3250
- **gamma interferon**, Genentech Inc., San Francisco, (1-800) 821-8590
- **CD4 protein**, Genentech Inc., San Francisco, (1-800) 821-8590, and Biogen, Inc., Cambridge, Mass., (617) 864-8900
- **AS-101**, NPDC-AS101, Inc., New Brunswick, N.J., (908) 249-3232
- **CD4-IgG**, Genentech Inc., San Francisco, (1-800) 821-8590
- **interleukin-II**, Hoffmann-La Roche Inc., Nutley, N.J., (201) 235-5000
- **r-GM-growth colony stimulating factor**, Sandoz Pharmaceuticals Corp., East Hanover, N.J., (201) 503-7500, and Schering-Plough Corp., Kenilworth, N.J., (908) 298-4000
- **r-granulocyte colony stimulating factor**, Amgen, Thousand Oaks, Calif., (805) 499-5725
- **soluble CD4-PE 40 (pseudomonas exotoxin A)**, The Upjohn Company, Kalamazoo, Mich., (616) 323-4696.

Vaccines

- **AIDS vaccine (r-gp 160)**, Immuno AG, New York (212) 951-5430, for AIDS
- **gp120**, Genentech Inc., S. San Francisco, (1-800) 821-8590, for HIV infection and prevention
- **HIV immuno-therapeutic vaccine (RG-83894)**, Immune Response Corp., Carlsbad, Calif., (619) 431-7080, for asymptomatic HIV-infection
- **HIV vaccine (gp120)**, Chiron, Emeryville, Calif., and

Ciba-Geigy, Basel, Switzerland, 011-4161-696-5961, for AIDS

- **VaxSyn HIV-1 (gp160)**, MicroGeneSys, Meriden, Conn., (203) 686-0800, for HIV-negative/early HIV infection
- **Vax Syn HIV-1 (rp24)**, MicroGeneSys, Meriden, Conn., (203) 686-0800, for AIDS
- **HIV vaccine (gp120—fully glycosylated recombinant protein made in CHO cells)**, Chiron Corp., Emeryville, Calif., for AIDS.

There also is an intense search for drugs to prevent or treat opportunistic infections and cancers that can be lethal to AIDS patients. The most prevalent conditions include *Pneumocystis carinii* pneumonia (PCP), a severe lung infection; candidiasis, a fungal infection of the mouth and esophagus; Kaposi's sarcoma (KS), a malignant tumor condition; cytomegalovirus (CMV), a viral infection that in AIDS patients can cause blindness, pneumonia and death; and diarrhea caused by the protozoa *Cryptosporidium*.

Anti-Infectives

- **trimetrexate**, NIAID, Bethesda, Md., (301) 496-5717, for PCP
- **ansamycin**, Adria Laboratories, Columbus, Ohio, (614) 764-8100, for preventing mycobacterium avium intracellular infection
- **piritrexim**, Burroughs Wellcome Co., Research Triangle Park, N.C., (919) 248-3000, for PCP
- **immune globulin IG-IV**, Sandoz Pharmaceuticals Corp., East Hanover, N.J., (201) 503-7500; Alpha Therapeutics, Los Angeles, (213) 227-7526; and Miles Inc., West Haven, Conn., (203) 937-2205, for various opportunistic infections and their prevention
- **nystatin**, Squibb Corp., Princeton, N.J., (609) 252-4650, for oral candidiasis prevention
- **clofazimine**, San Francisco General Hospital, San Francisco, (415) 476-9296, for mycobacterium avium intracellular
- **sandostatin**, Sandoz Research Institute, East Hanover, N.J., (201) 503-7500, for AIDS-related diarrhea
- **diclazuril**, Janssen Pharmaceutica, Piscataway, N.J., (908) 524-9591, for *Cryptosporidium* diarrhea
- **dapsone**, Jacobus Pharmaceutics, Princeton, N.J., (609) 921-7447, for PCP prevention
- **clindamycin**, Mark Jacobson, M.D., San Francisco, for toxoplasmic encephalitis
- **pyrimethamine (DARAPRIM)**, Burroughs Wellcome, Research Triangle Park, N.C., (919) 248-3000, for toxoplasmosis prevention
- **itraconazole (SPORANOX)**, Janssen Pharmaceutica,

Piscataway, N.J., (908) 524-9591, for histoplasmosis

- **FIAC and FIAU**, O'Classen Pharmaceutical, San Rafael, Calif., (415) 258-4500, for CMV retinitis

Immuno-Modulating agents

- **lymphoblastoid interferon**, Burroughs Wellcome Co., Research Triangle Park, N.C., (919) 248-3000, for KS
- **cryptosporidium immune colostrum**, Immucell Corp., Portland, Maine, (207) 878-2770, for *Cryptosporidium* diarrhea

Anti-Neoplastic Agents

- **piritrexim isethionate**, Burroughs Wellcome Co., Research Triangle Park, N.C., (919) 248-3000, for KS
- **doxorubicin**, NIAID, Bethesda, Md., (301) 496-5717, for KS
- **tumor necrosis factor**, Genentech Inc., San Francisco, (1-800) 821-8590, for KS
- **menogaril**, NCI, Bethesda, Md., (301) 496-6641, for KS
- **M-BACOD (with Retrovir)**, NIAID, Bethesda, Md., (301) 496-5717, for primary lymphoma

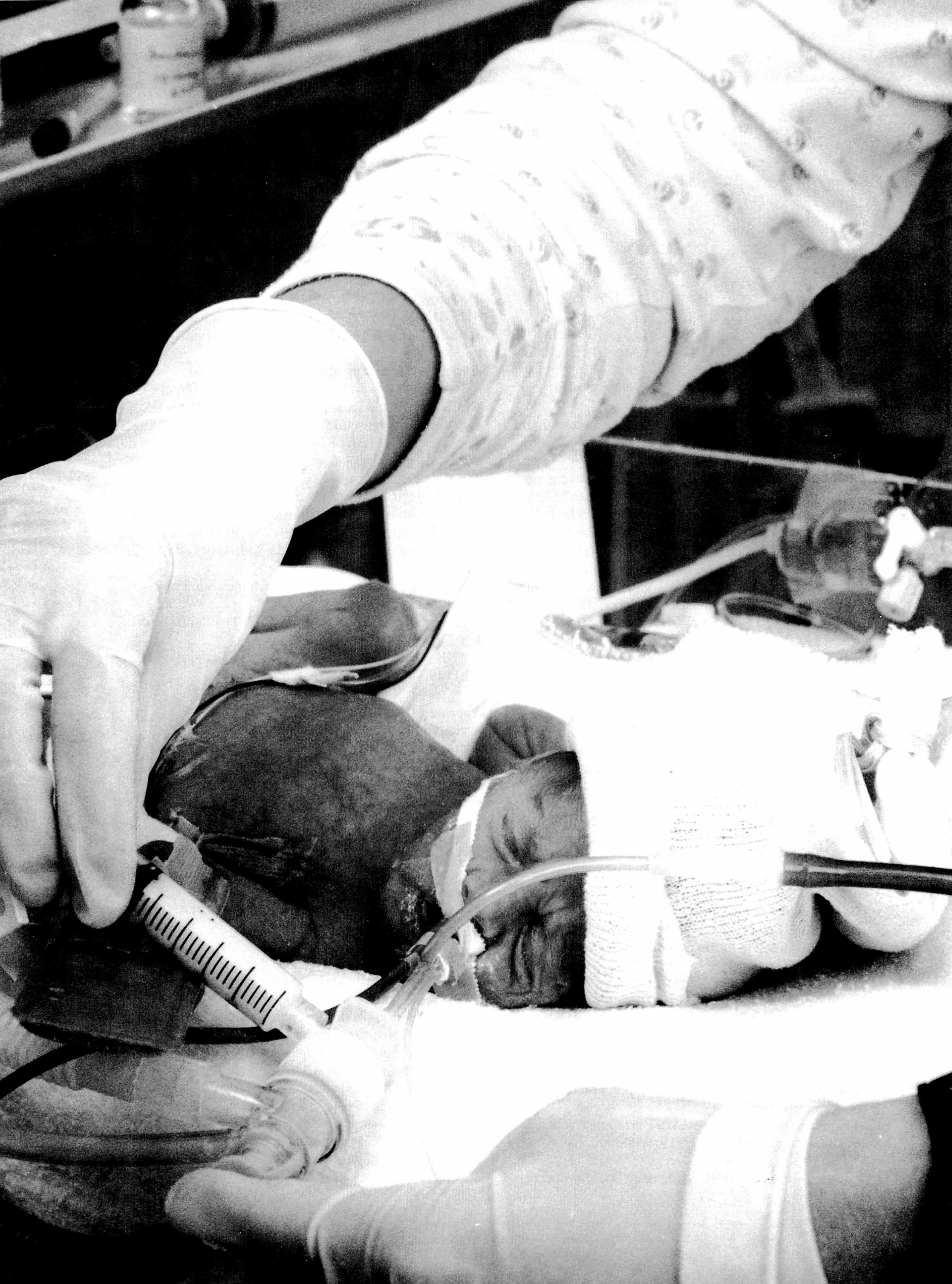
Approved Drugs

- **zidovudine** (called AZT), for AIDS
- **didanosine (DDI)**, for AIDS when patients can't tolerate AZT or have significantly deteriorated while on AZT
- **ganciclovir**, for CMV retinitis
- **pentamidine**, injectable (for PCP) and aerosolized (for preventing PCP occurrence and recurrence)
- **alpha interferons** (two versions), for KS
- **fluconazole**, for candidiasis and cryptococcal meningitis.
- **foscarnet**, for CMV retinitis
- **epoetin alfa**, genetically engineered form of the protein erythropoietin, for AZT-related anemia

Treatment INDs

FDA also has made drugs available under its treatment IND (investigational new drug) program, which allows patients with serious or life-threatening conditions for which there are no satisfactory treatments to obtain promising experimental drugs whose clinical testing shows they may be safe and effective. These AIDS drugs are:

- **DDC**, for AIDS and advanced AIDS-related complex when patients fail to benefit from or cannot tolerate the approved AIDS treatment AZT
- **566C80**, for PCP when patients cannot tolerate treatment with trimethoprim-sulfa, a standard treatment for this condition.



Preterm Babies

Get a Double Breath of Life

by Rebecca D. Williams

When Benjamin McClatchey was born almost three months premature on July 27, 1990, he weighed only 2 pounds, 13 ounces, and his underdeveloped lungs struggled for every breath.

Benjamin's parents, Steve and Trillis McClatchey of Lafayette, Ind., got only a glimpse of their son before doctors whisked him off to another hospital an hour away. They called Trillis McClatchey at 5 o'clock the next morning for her permission to give Benjamin a pulmonary surfactant, a new lifesaving drug, to help him breathe.

"[They] told us it worked best if given in the first six hours of life," McClatchey remembers. "I said, 'He was born at 11:10 last night—you have 10 minutes!'"

"The doctor laughed. He said, 'Everything's going to be fine.'"

Benjamin received the drug and is indeed fine today. But at birth he developed respiratory distress syndrome, or RDS, a life-threatening lung condition that strikes about 65,000 infants each year. RDS has become more treatable in recent years because of surfactant and new ventilators recently approved by FDA.

RDS is common among the approximately 380,000 premature infants born in the United States each year. About 3,000 infants died of RDS in 1988, making it the fourth most common cause of all infant deaths.

RDS is also called hyaline membrane disease. In 1963, a baby boy born to then-President and Mrs. John F. Kennedy died of the condition.

But neonatal medicine has improved since then, reducing deaths from RDS steadily over the last 15 years. Preliminary statistics indicate they may have fallen even further—more than 30 percent between 1987 and 1990. FDA's recent approval of several new ventilators and two kinds of surfactant to treat RDS has contributed to premature infants' chances of survival.

Lubricating Lungs

Short for "surface-active agent," a pulmonary surfactant is perhaps the most beneficial new treatment RDS patients like Benjamin can receive. FDA has approved two kinds of surfactant, the first in July 1990 and the second a year later.

A pulmonary surfactant is a foamy liquid produced naturally in human and animal lungs. It reduces the surface tension between the wet lung tissue and dry air to keep the tiny air sacs in the lungs, called alveoli, from collapsing between breaths.

Without lung surfactant, every breath requires tremendous force, like blowing up a new balloon.

Because surfactant production is one of the last processes a fetus develops in the womb, preterm infants often don't have it. Commercially prepared surfactants replace the missing natural lung surfactant until the infant can produce his or her own a few days after birth.

"Surfactant has made a dramatic difference in the survival of very-low-birthweight infants," says Dr. K.N. Siva Subramanian, the chief of the Division of

Neonatology at Georgetown University Hospital in Washington, D.C.

Georgetown has been using a surfactant in clinical trials for more than three years, and doctors say babies who get it require less intensive medical care and less time on ventilators because of it.

The first FDA-approved surfactant was Exosurf Pediatric, a synthetic compound made by Burroughs Wellcome Co. of Research Triangle Park, N.C. The second approved surfactant, Surfactant, is a compound made from cow lungs. It was developed in Japan and is distributed by Ross Laboratories of Columbus, Ohio.

Both drugs are passed down the infants' lungs through a ventilator tube. They can be given as "rescue" treatments to babies who have already developed RDS, or "prophylactic" (preventive) treatments to infants at risk of developing RDS.

In either case, studies show that surfactants reduce RDS deaths by about half. They also shorten the time infants need to be on ventilators.

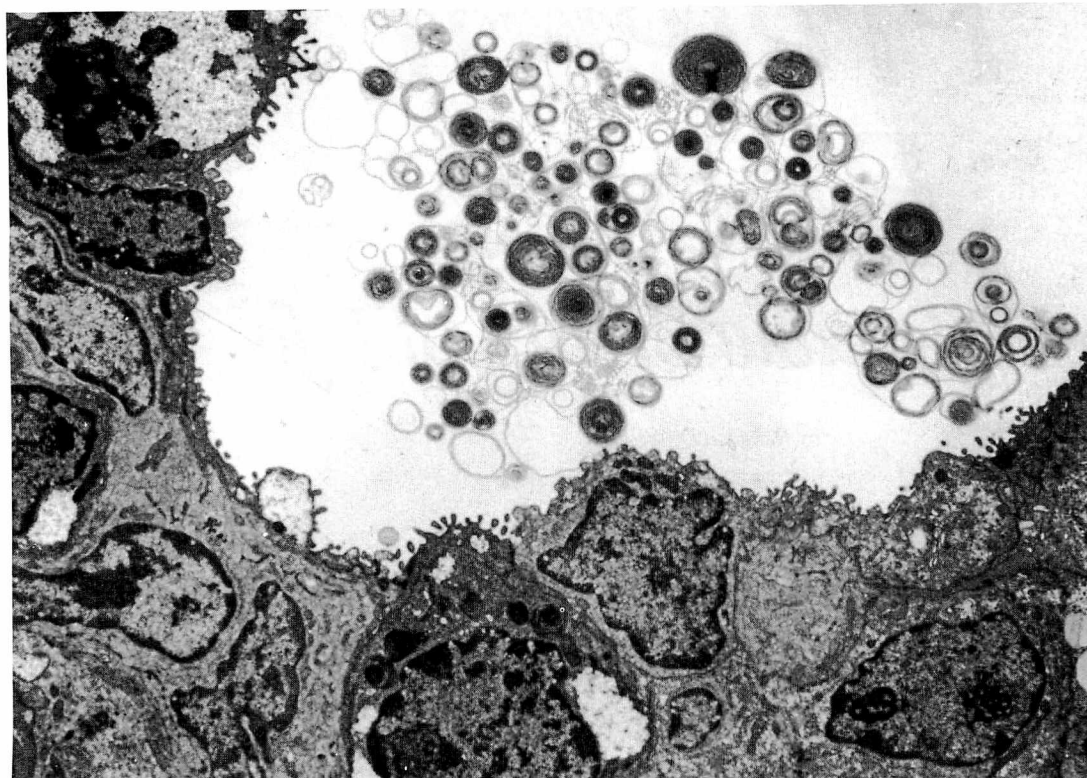
Pulmonary surfactant has been a lifesaver to children born unexpectedly early. It has also given hope to parents who know their unborn children are at high risk for prematurity.

For example, in 1990, Leslie and Matthew Carter of Carmel, Ind., chose to have their children at the Indiana University Medical Center in part because they knew the hospital had surfactant.

Leslie Carter was carrying quadruplets, and she knew she would probably deliver early, as is often the case with multiple births.

Surfactants were not approved for general use at the time, but the Indiana hospital had one through an FDA treatment pro-

A dose of pulmonary surfactant is passed down a ventilator tube at Georgetown University Medical Center to a baby born three months early.



This electron micrograph shows whorls of surfactant secreted into the air spaces of a fetal lung. Surfactant keeps lungs from collapsing between breaths. Many premature infants do not produce surfactant and develop respiratory distress syndrome. (Photo courtesy National Heart, Lung, and Blood Institute)

gram that allows lifesaving drugs to be used in certain hospitals before they receive approval.

"We were aware of the drug called surfactant," Leslie Carter remembers, "and we were really glad to be in a hospital where they could use that."

Katelin, Katherine, Abigail, and Elizabeth Carter were born nearly 10 weeks early on Jan. 30, 1990, weighing less than 3 pounds each. They all developed respiratory distress syndrome, were treated with a surfactant, and placed on ventilators. At first their progress was slow, but after about two months in the hospital, all were home and doing well.

"We've been very fortunate," their mother says. "They're really healthy."

The Indiana University Medical Center has participated in clinical trials of both approved pulmonary surfactants for about four years, according to associate professor of pediatrics William A. Engle, M.D., who treated the Carter quadruplets and Benjamin McClatchey.

He says his colleagues have used both kinds, with promising results.

"I think the major benefit of surfactant is that it reduces the risks associated with respiratory distress syndrome," Engle says, "and we know that about 50 percent of the babies less than 1,500 grams [3.3 pounds] will have severe hyaline membrane disease."

Bellows for Baby

A surfactant is no miracle cure for respiratory distress syndrome, however. Like Benjamin McClatchey and the Carter quadruplets, infants born too early may still spend months hooked to ventilators to help them breathe.

The newest kind of respirator for newborns is called a "high-frequency ventilator," which works very differently from the older, conventional ventilators.

Conventional ventilators have been used on infants for years and are largely responsible for the drastic drop in infant deaths from RDS throughout the 1970s. The high-frequency concept, a modification of conventional ventilation, was first described in 1959 but wasn't tested on infants until the early 1980s or approved by FDA until 1987.

Conventional ventilators force air down an infant's lungs with pressures high enough to expand them, sometimes damaging the delicate airways in the process.

A high-frequency ventilator, however, supplies oxygen to the baby through tiny, rapid puffs of air that barely move the lungs. It creates a vibrating column of air in the lungs without forcing them to expand in the traditional manner.

While a conventional ventilator "breathes" only about 14 times per minute, a high-frequency ventilator puffs at least 150 times per minute.

It's still not scientifically proven, however, whether high-frequency ventilators are better in the long run than the older machines for all premature infants. Doctors use them mostly when conventional ventilation isn't successful.

Since 1987, FDA has approved for use on infants three high-frequency ventilators made by Bunnell Inc. of Salt Lake City, Utah, Infrasonics Inc. of San Diego, Calif., and SensorMedics Corp. of Yorba Linda, Calif.

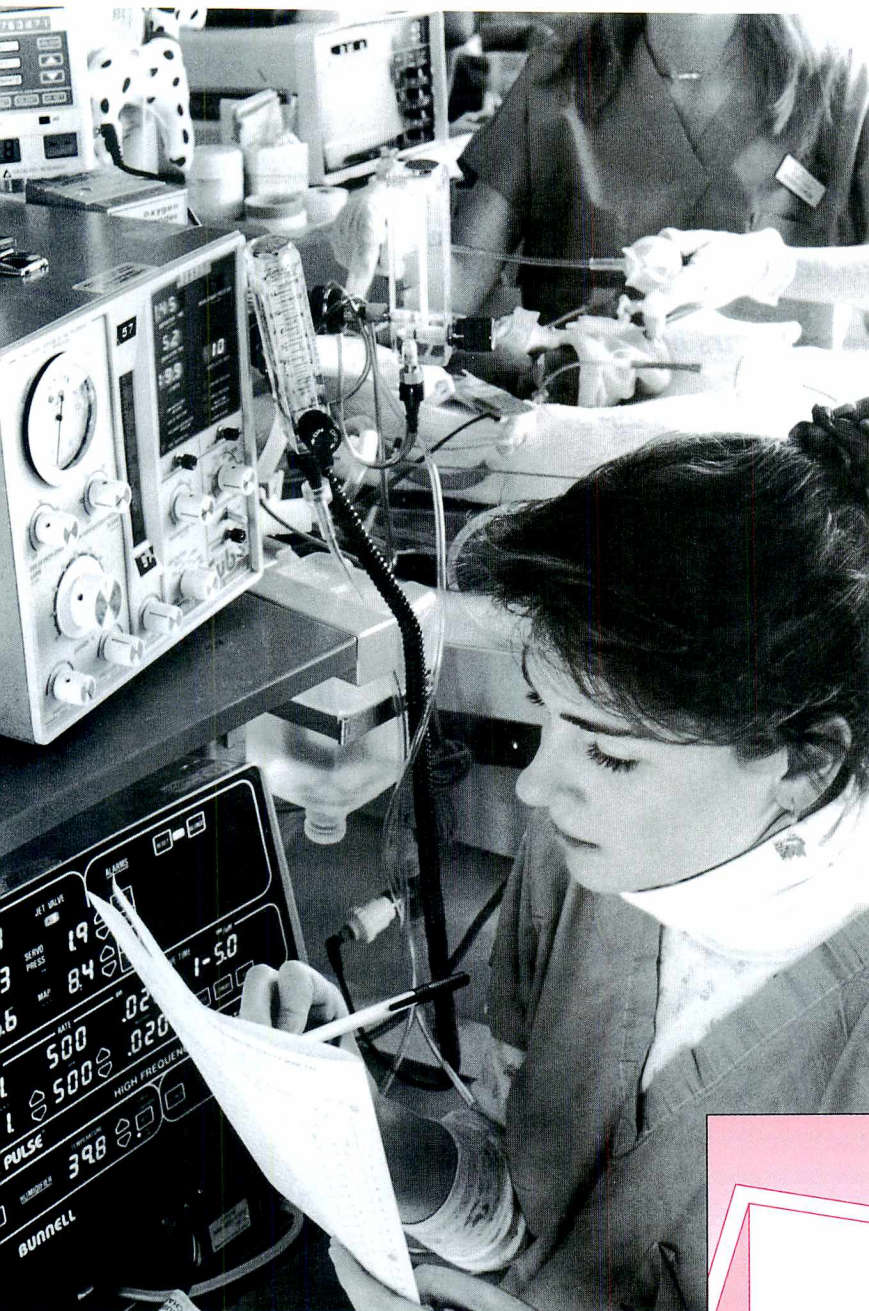
Despite the benefits of both surfactants and high-frequency ventilators, problems remain.

Neither the surfactant drugs nor the high-frequency ventilators seem to reduce the incidence of a chronic lung condition stemming from long-term ventilator use called bronchopulmonary dysplasia, or BPD.

"That's kind of disappointing," says Dorothy Gail, Ph.D., chief of the Cell and Developmental Biology Branch at the National Heart, Lung, and Blood Institute. "Surfactant's great for RDS, but as far as the more chronic lung diseases go, it's not what everyone had hoped."

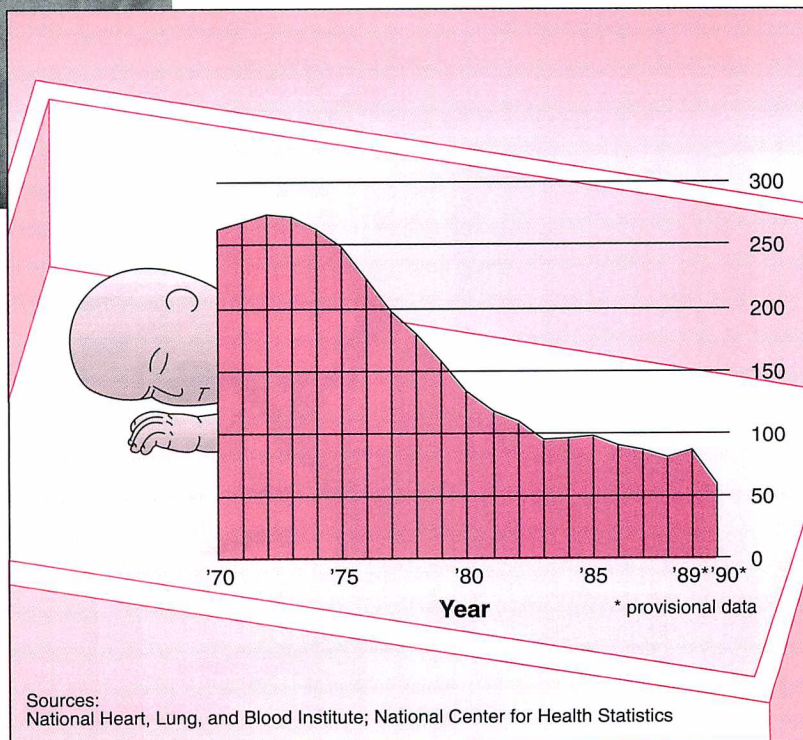
Benjamin McClatchey, for example, developed BPD. He still requires oxygen fed to his nose from a portable tank at home.

Babies on high-frequency ventilators develop other common side effects found with conventional ventilation, such as high



Jennifer Bell, R.N., demonstrates how a nurse monitors a high-frequency ventilator in the neonatal intensive-care unit at Georgetown University Medical Center, Washington, D.C. The ventilator, recently approved by FDA, supplies tiny puffs of air to the delicate lungs of premature infants.

Infant mortality from neonatal RDS per 100,000 live births in the United States, 1970-1990



***R**espiratory distress syndrome, the fourth most common cause of infant death in 1988, has become more treatable in recent years because of new drugs and devices approved by FDA.*



***P*ulmonary surfactant has
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Benjamin, shown here on a ventilator shortly after birth, weighed 2 pounds, 13 ounces. He was hospitalized 7 out of his first 10 months of life.

Steve and Trillis McClatchey of Lafayette, Ind., hold their son, Benjamin, who developed respiratory distress syndrome shortly after his premature birth in 1990. Benjamin survived with the help of ventilators and a new drug approved by FDA, but in this picture, which was taken at 18 months, he still requires oxygen to help him breathe.

blood pressure, a rise in heart rate, brain hemorrhaging, and a condition called pneumothorax, in which air blows out the side of the lungs and into the chest cavity.

"High-frequency ventilation is just not natural, so the body perceives it as something different and reacts to it," says Jim Dillard, a review scientist at FDA. "Over time, more light will be shed on the overall survival improvements with high-frequency ventilators, if any."

At Indiana University's Riley Hospital for Children, where Benjamin and the Carter quadruplets were treated, doctors use high-frequency ventilators in the severest cases.

Two of the Carters' daughters developed more serious lung problems, and one of them, Abigail, was placed on a Bunnell high-frequency ventilator. The other, Katelin, had similar problems but was placed on a conventional ventilator.

"Abigail's lungs healed a lot better and she did a lot better than Katelin did. And their problems were very, very similar," Carter says. "We felt the [high-frequency ventilator] really helped."

"I think it's been moderately successful," says Engle, of the Riley Hospital program. "Babies that would have had less than a 20 percent chance of survival [on conventional ventilation] now have a 50 to 60 percent chance."

Looking for Tomorrow's Cures

In the future, scientists hope to provide even better chances for premature infants like Benjamin and the Carter quadruplets.

Last October, a scientist from The Scripps Research Institute in La Jolla, Calif., described in the journal *Science* a new kind of surfactant he manufactured with

synthetic human proteins. He said the synthetic human surfactant, if successful in humans, could be more like human surfactant than those presently on the market. It has not been tested in humans to show effectiveness and safety, however, one requirement for FDA approval.

According to the National Heart, Lung, and Blood Institute, scientists are examining human surfactant in a number of studies, researching its basic genetic makeup and how it is produced and used by lungs.

In clinical settings, doctors are still testing for the best possible dose and time to give a surfactant to newborns, as well as ways to use the drug to treat adult lung disorders.

For many premature children, new technologies have already eased their untimely transitions from the womb to the world.

The Carter quadruplets, for example, are still not as physically mature as other 2-year-olds, but in other ways they have developed normally. "They're doing just wonderfully," their mother says.

Benjamin McClatchey also is doing well. Now nearly 2 years old, he talks as well as any child his age, even though he, too, is catching up to his peers physically.

"I don't let that get me down," says his mother. "He spent a total of seven months in the hospital out of his first 10 months of life, and a baby can't develop in a hospital bed.

"But he's made a lot of progress since we've had him home. He's doing just great." ■

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



Not Only Sugar Is Sweet

by Alexandra Greeley

Plain table sugar and its numerous taste-alikes may be one of our most popular food commodities. People come by their love for sweetness naturally. According to the experts, humans are born generally preferring sweet over bitter or sour tastes.

Sweeteners make many foods taste better. And natural sugars have a host of other valuable culinary—and practical—uses, including adding bulk to baked goods, helping foods to brown, and facilitating fermentation. But despite their immense popularity, sweeteners, particularly table sugar, have generated their share of sour publicity because of health concerns.

What Is Sugar?

Traditionally, for most consumers the generic term “sugar” means simply the white sugar crystals, or table sugar, that are stirred into or sprinkled on foods.

These familiar crystals are technically known as sucrose. Sucrose is a disaccharide—that is, it’s composed of two simple sugar units, in this case, glucose and fructose. White sugar comes from sugar cane or sugar beets that have undergone a rigorous refining process. White sugar crystals can be used as is, compressed into cubes, or further pulverized to superfine, then to confectioner’s, or powdered, sugar. Brown sugar results from mixing white sugar crystals with molasses. Other forms of sucrose are beet sugar, maple sugar, turbinado sugar, and raw sugar.

Sucrose, however, is only one of a subgroup of sugars (see accompanying chart), and all sugars are carbohydrates. Monosaccharides, or single sugar units, include glucose, fructose and galactose. Monosaccharides also are the digestive end product of polysaccharides, the complex carbohydrates (starches) in fruits, grains and vegetables. Other disaccharides besides sucrose include lactose (glucose and galactose), also called milk sugar, and maltose (two units of glucose), also called malt sugar.

For labeling use and for making comparative claims, the Food and Drug Ad-

ministration defines sugars as all mono-, di-, tri-, and tetrasaccharides and their derivatives, such as sugar alcohol, says Youngme Park, Ph.D., a nutritionist with FDA’s Center for Food Safety and Applied Nutrition. He says this includes all carbohydrate sweeteners with the same functional and physiological effect that can be used interchangeably in the food supply.

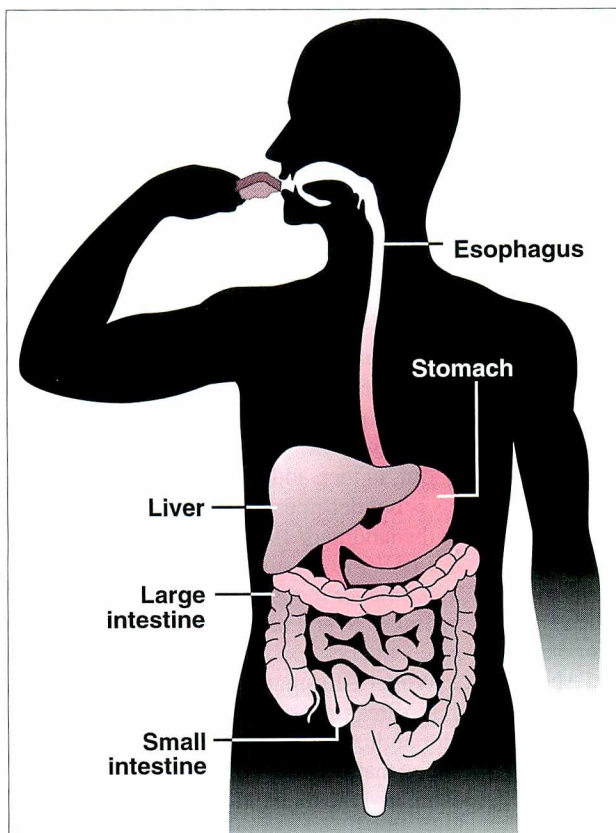
After complex carbohydrates are broken down to simple sugars (most sugars and carbohydrates are eventually broken down to glucose), the sugars are absorbed into the bloodstream and go to the liver. There they may be stored as glycogen or used immediately as glucose for energy by the body or brain.

“The body uses glucose as its simplest form of energy,” says Judith Wurtman,

Ph.D., research scientist in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology. “So for people who need calories—that is, those who are recovering from an operation or who are shipwrecked—sugar can keep them alive.”

Thomas Jukes, Ph.D., professor of biophysics at the University of California at Berkeley, tells of his experiments feeding laboratory rats protein, vitamins, minerals, and sugar as the sole source of carbohydrates. The rats thrived, he says. “Fish is not a brain food,” concludes Jukes. “Glucose is.”

Sucrose occurs naturally in most green plants, says Sarah Setton, vice president for public affairs, The Sugar Association, Washington, D.C. It is produced by photosynthesis, which is the use of the sun’s en-



As soon as carbohydrates enter the mouth, they begin to change to sugars. The process continues as the food is swallowed and travels through the esophagus to the stomach. But the greatest part of the conversion occurs in the small intestine. The simple sugars then enter the bloodstream and are carried to the liver, where they may be used immediately as glucose for energy or stored as glycogen.

“*P*eople seem to think that there is a difference between sugar in an apple and sugar in the sugar bowl. . . . But the body can’t tell where the sugar is from.”

—Sarah Setton, *The Sugar Association*

ergy in the formation of food by plants. People would have to stop eating fruits and vegetables and any products incorporating them to cut sugar out of their diet. “People seem to think that there is a difference between sugar in an apple and sugar in the sugar bowl,” she adds. “But the way the body uses sugar is all the same. The body can’t tell where the sugar is from.”

A Taste for Sweets

Americans have become conspicuous consumers of sugar and sweet-tasting foods and beverages. We have developed a relentless sweet tooth, “a severe addiction to sweetness,” says Joan Gussov, Ed.D., professor of nutrition and education at Columbia Teachers College, Columbia University in New York City.

According to U.S. Department of Agriculture data on the amount of caloric sweeteners used in food, there has been an increase of more than 16 percent on a per person basis over the past two decades, and more than half of the increase has occurred in the past five years. Caloric sweeteners include sugar, high-fructose corn syrup, pure honey, and edible syrups.

Paul Lachance, chairman of the department of food science at Rutgers University in New Jersey, states it another way. He estimates that, based on a 2,000-calorie-a-day diet, the average American consumes about 300 calories from sugars added to food. That comes to nearly 14 teaspoons of table sugar a day.

Gussov has her own theory about why sugar is so prominent in the American diet. It’s for taste, she says. “I grow my own vegetables and fruit. And when I pick, cook and eat my parsnips, for example, they are as sweet as sugar,” she says. “But food is shipped all over the place, and when food gets too old, much of the sugar turns to starch. The natural sweetness is gone, and people sugar food to give it flavor.”

As yet, no scientist has established any limits for sugar consumption. In the typical American diet today (composed of about 45 percent carbohydrates, 20 percent protein, and 30 to 35 percent fat) all added and naturally occurring sugars account for about 21 percent of the total daily caloric intake. A 1986 FDA report estimated that sugars added to food accounted for 11 percent of calories consumed.

Yet, if people eat increasingly larger quantities of caloric (nutritive) sweeteners in general, these could compete with and crowd out other nutrients, warns Jane Hurley, associate nutritionist at the Center for Science in the Public Interest, Washington, D.C. People may consume many of their calories each day from a sugary soft drink or candy bar. “Those foods have few important nutrients we need,” she says. “People are better off having an apple as a snack than a candy bar.”

The Safety Issue

Over the last several decades, sugar has taken on the villain’s role in the American diet. General sugar-bashing has led to “sugarphobia”—as Jukes calls it—and the unfounded fear that eating refined sugar causes many health problems, including heart disease, diabetes, anxiety, fatigue, depression, hyperactivity, and even criminal behavior.

But, in fact, added sugar at current levels is not detrimental to health. According to the landmark 1986 *FDA Report of Sugars Task Force*, sugar—when consumed in normal or moderate quantities—cannot be linked to any disease, nor does it create a dependency.

Walter Glinsmann, M.D., FDA’s associate director for clinical nutrition and senior author of the task force report, explains that members of the task force estimated the intake figures and trends of both added and naturally occurring sugars,

based on USDA data. They also reviewed the scientific literature dealing with possible harmful effects of sugar consumption on numerous conditions, including tooth decay, glucose tolerance, diabetes mellitus, lipidemias (high blood fat), cardiovascular diseases, obesity, gallstones, and cancer. “Based on that work,” says Glinsmann, “we decided that sugars are safe as they are now used in the food supply.” If there is a significant change in the way Americans consume sugars, he adds, then scientists must reevaluate their role.

As Glinsmann observes, FDA does not say that eating unlimited amounts of sugars is safe. “There are not good or bad foods, only good or bad diets,” he says. “If half your diet is pure sugar, that is not healthy. . . . In a normal, varied diet, there are no adverse effects of sugar itself.”

The task force did find that sugar can cause dental cavities, he says, but adds that so can other fermentable carbohydrates, such as dried fruit and honey, under the right conditions.

Despite the report, some consumers persist in linking sugar consumption with assorted ills, such as hyperactivity and aggressive behavior in children. This is often reported by parents who say that their children are uncontrollable after eating candy and other sugary sweets.

Glinsmann points out that sugar has not been shown to be a factor in hyperactivity. Studies of children and adolescents at the National Institutes of Health in Bethesda, Md., and elsewhere have looked at groups of individuals served sugar or a placebo (an inactive substance given as a control when testing another substance). Glinsmann points out that no researcher has found that sugar has had any discernible negative effect on children’s behavior. To the contrary, sugar often has a soothing effect.

It also calms adults, says Wurtman, who has studied the relationship between car-

After eating sugar, people become calm or even sleepy.

—Judith Wurtman, Ph.D., Massachusetts Institute of Technology



bohydrate consumption and mood. When people report having a sugar high or jitters, Wurtman asks them what was happening before they took a mouthful of something sweet. "When people feel the need to eat," she says, "They usually are jittery. But 20 minutes after eating, they are no longer jittery." In fact, the opposite happens: After eating sugar, people become calm or even sleepy, she says, an effect caused by sugar raising the level of a calming brain chemical called serotonin. Sugar in its pure form is the best nonprescription antidepressant, she says.

Sugar by Other Names

Numerous nutritive and nonnutritive substitutes for sucrose vie for its place as a sweetener. All nutritive substitutes—such as honey, concentrated fruit juices, dextrose (also known as glucose), maple and corn syrups, fructose (levulose or fruit sugar), sugar alcohols, and high-fructose corn syrup—contain and contribute calories.

Perhaps the most commonly used nutritive sweetener is high-fructose corn syrup, a sweet product manufactured from cornstarch and containing a high level of fructose, explains Kyd Brenner, director of public affairs for the Corn Refiners Association in Washington, D.C. High-fructose corn syrup is very close to the composition and calorie content of cane sugar, he says, and the syrup can be used as a direct—and inexpensive—substitute for cane sugar when liquid sweeteners are called for. It is used extensively in soft drinks, condiments, jams, jellies, and wine and is not available for home use.

Of the sugar alcohols, sorbitol (60 percent as sweet as sucrose with about the same number of calories per gram) is used in such products as hard and soft candies and chewing gums. Xylitol, another sugar alcohol, has limited FDA approval for special dietary uses. A third sugar alcohol,

Sweet Talk



Type of Sweetener

Regulatory Status

Common Sugars

Monosaccharides

glucose (also called dextrose)
fructose (also called levulose)
fruit sugar
galactose

GRAS (generally recognized as safe)
GRAS

none; cannot be directly added to food

Disaccharides

sucrose (glucose + fructose)
white table sugar, beet sugar,
turbinado sugar, raw sugar
lactose (glucose + galactose)
milk sugar
maltose (glucose + glucose)
malt sugar

GRAS

GRAS petition under consideration

GRAS

Sugar Alcohols

sorbitol
xylitol
mannitol

GRAS
limited FDA approval for special uses,
removed from GRAS; regulated as
“interim food additive”

Nonnutritive and High-Intensity Sweeteners

aspartame
acesulfame K
cyclamate
saccharin

approved
approved
banned
remains on market through
congressional moratorium

mannitol, has been removed from the GRAS (generally recognized as safe) list, and is regulated as an “interim” food additive. This means that its current use is considered safe, but some questions have been raised that must be resolved to fully determine what limitations, if any, should be imposed. Mannitol is still being used in some products.

Both mannitol and sorbitol, when taken in large amounts, can cause diarrhea. Products whose reasonably foreseeable consumption may result in a daily ingestion of 50 grams of sorbitol or 20 grams mannitol must bear the labeling statement: “Excess consumption may have a laxative effect.”

The sugar polymer polydextrose, because of its bulking properties, is used to replace a number of the technical effects of sucrose in various baked goods, salad dressings, frozen desserts, and candies. Because of its structure, polydextrose is not readily digested, so it is a low-calorie sucrose substitute. But it does not provide sweetness, so it is likely to be used with a nonnutritive sweetener. FDA is presently considering petitions for its use in other products such as in fruit and peanut butter spreads, sweet sauces, toppings, and syrups, and as a formulation aid in film coatings in vitamin and mineral supplement tablets.

Nonnutritive Sweeteners

Nonnutritive, or high-intensity, sweeteners satisfy America’s sweet tooth without adding calories. Presently, manufacturers are using three such sweeteners to replace sugar in a variety of food and nonfood items such as mouthwashes and pill coatings.

One of these is saccharin, 300 times sweeter than table sugar and with zero calories. It is sold in liquid, tablets, packets, and in bulk. Saccharin has had a stormy past, with studies in the United States and Canada implicating it in the development of certain cancers. In the late 1970s, FDA contracted with the National Academy of Sciences (NAS) to study cancer-causing agents and toxic substances in foods, including saccharin. NAS reports showed that saccharin is a potential cancer-causing agent in humans. A congressional moratorium protecting saccharin’s continued use has been renewed periodically by Congress. The required label warning on saccharin states,

"Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals."

Aspartame—about 200 times sweeter than table sugar and with the same number of calories per teaspoonful—has been shown to be safe. However, some people have reported that they are sensitive to it, although such a sensitivity has not been confirmed by scientific studies. Certain individuals suffering from a rare genetic disease called phenylketonuria cannot tolerate the amino acid phenylalanine, one of the building blocks of aspartame as well as naturally occurring proteins. Therefore, products containing aspartame must bear on the label a statement that they contain phenylalanine. Aspartame is available in packets and is used in numerous foods, including cereals, beverage bases, and ready-to-drink iced tea, but because it is not generally heat stable, it is not used for cooking. Food technologists have been working on ways to overcome this instability.

Acesulfame K (K is the chemical symbol for potassium)—130 times sweeter than table sugar—was approved by FDA in July 1988 as a sugar substitute in packets or tablets and as an ingredient in such products as chewing gum, dry drink mixes, and gelatins. The body does not metabolize acesulfame K so it contributes no calories. Soluble in water, it is stable at normal temperatures and does not break down during cooking.

FDA banned the use of the sweetener cyclamate in 1970 because of concerns over its safety, but cyclamate is again under consideration for use in specific products, such as tabletop sweeteners and non-alcoholic beverages.

Under Development

Scientists continue to develop new sugar substitutes. For example, among the nutritive sweeteners, petitions for the use of the sugar alcohols isomalt (in gelatins, hard and soft candies, and baked goods), maltitol (in candy and cough drops), lactitol (in candy, chewing gum, baked goods, and frozen dairy desserts), and hydrogenated starch hydrolysis (in candy, chewing gum, and confections) are under current FDA review, says Art Lipman, Ph.D., a supervisory consumer safety officer with FDA's direct additives branch.

FDA has also received numerous in-

quiries about the regulatory status of a naturally occurring high-intensity sweetener known as stevia (or stevioside), says Lipman. Extracted from a plant grown in South America, stevia is 300 times sweeter than table sugar and is used for sweetening in Japan and other countries. Lipman says no petition has been filed for its use in the United States.

Two nonnutritive sweeteners are being studied, says George Pauli, Ph.D., chief of the novel ingredients and policy development branch. These are alitame (Pfizer), which is chemically similar to aspartame, and sucralose (McNeil Specialty Products Co.), a chlorinated sucrose that has been made indigestible. FDA is also considering petitions for additional uses of the sweetener acesulfame K in beverages and baked goods and of aspartame for bulk use and in breakfast cereals, malt beverages, candies, and cooked foods.

Eating foods sweetened with nonnutritive sweeteners rather than sugar is an individual choice, says Laura Tarantino, an FDA consumer safety officer. "Our law says only that we [FDA] need to assess the safety of a new food additive and its technical effect," she says. "Nonnutritive sweeteners are safe to use. But we don't tell people to replace sugar

with artificial sweeteners."

In the future, consumers wanting to know which sweeteners are present in their foods need only read the label. According to an FDA labeling proposal, all sweeteners will be listed together in the ingredient list, under the collective term "sweetener," when more than one sweetener is used in a product (following the collective term, each sweetener would be listed in parentheses in descending order of predominance by weight of the sweetener in the food). According to an FDA proposal published late in 1991, it would be mandatory for all complex carbohydrates and simple sugars to be listed on the nutrition label, says Lynn Larsen, Ph.D., director of the Center for Food Safety and Applied Nutrition's Executive Operations Staff.

People may have an inherent preference for sweetness, and that may have helped our ancestors survive, since bitter-tasting plants are generally not fit to eat. But beyond survival, people seem to have discovered that sweet flavors really help make eating pleasurable. ■

Alexandra Greeley is a freelance writer in Reston, Va.





PANIC DISORDER

The Heart That Goes Thump in the Night—and Day

by Marian Segal

Every night for five years, Sherry Menter would postpone sleep as long as she could. When it beckoned, she would clean the house, sew, read, bake cookies—do anything to avoid the terror she had come to expect once she drifted off. But eventually, sleep overtook her, and with it, the inevitable.

"I could hear a noise like a siren or freight train coming in my head," she says. "I could feel my jaw lock, my teeth grind, and my limbs become totally immobilized, yet shaking uncontrollably, while this freight train comes charging into my head, and by the time the train gets there I'm consumed by fear. I feel my heart pounding and there have been times when I thought I stopped breathing. I guess my conscious mind takes over and I think, 'Oh my God, your heart's not beating. You're going to die.' And I scream at the top of my lungs for anybody to wake me."

Menter is describing a panic attack. She says that while it's happening, she's aware that she's asleep and that in order to make the fear stop, she has to wake up. So she screams for someone to wake her. But those who have heard her "screams" tell her that, in reality, they are just "squeaky little noises."

More than a million Americans, like Menter, suffer from panic disorder, according to a statement issued by a panel of

experts at a National Institutes of Health (NIH) consensus development conference last September. It is not a new phenomenon; among its many past rubrics it has been known as "housewife's disease" and "soldier's heart". For most, the attacks begin in the middle teens or early adult years, but they can start at any age.

FDA recently approved panic disorder as an additional indication for a drug already approved for treating anxiety. Other marketed drugs, although not specifically approved for panic disorder, have been reported helpful in treating the condition.

The illness is characterized by episodes of intense fear that occur "out of the blue," says Thomas W. Uhde, M.D., chief, Section on Anxiety and Affective Disorders at the National Institute of Mental Health in Bethesda, Md. "They typically last from 2 to 10 minutes and are associated with a number of different psychological and physiological symptoms."

Unlike Menter, whose attacks occur only during sleep, most patients experience attacks while awake. Uhde says that 60 to 69 percent of patients will have at least one severe sleep panic attack in their lifetime, about a third of patients have recurring sleep panic attacks, and 5 percent have panic attacks more often during sleep than while awake.

Many patients experiencing a panic attack for the first time rush to an emer-

gency room complaining of chest pain, shortness of breath, flushes or sweating, and rapid, irregular heartbeat. Many fear they are dying or going crazy. They may have chills, dizziness, shaking or trembling, choking, nausea or abdominal discomfort, and numbness or tingling sensations as well.

"Some people also have a profoundly altered perception of the environment. They might perceive objects as particularly bright or dull, sounds can be experienced as dull or unusually sharp, and there may be alterations in the sense of time," Uhde says. Patients sometimes feel "depersonalized," as if they're somehow strange or different and disconnected from the immediate environment.

"Distancing" a Symptom

Patti Griffith (not her real name) felt herself becoming "distanced" from the people and things around her when she had her first attack a year ago at age 35. It happened suddenly during a business meeting that ended for Griffith in a four-hour hospital emergency room stay, where doctors tried in vain to discover what was wrong.

"I had a sensation almost like going into a tunnel and the light was receding. I could hear people talking, but they were like 'other.' I had to recede from the activity and try to focus all my thoughts on try-

ing to stay calm, because I knew that if I could talk myself into calming down, maybe I could get my heart to slow down.”

Panic attacks do not inevitably signal panic disorder. Some people have only one isolated incident of a panic episode or perhaps experience them just occasionally, with no lasting impact on their well-being.

According to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, panic disorder is diagnosed only in people who have at least four attacks within four weeks, or one or more attacks followed by at least a month of persistent fear of having another. At least some of the attacks must occur spontaneously and unexpectedly, not in response to a phobic trigger such as snakes, closed spaces, public speaking, or other objects or situations that evoke fearful avoidance in some people.

“If panic attacks continue without treatment, people begin to wonder about the causes,” says Uhde. “Are they crazy? Is it something they did or didn't do? Or is there something about the situation in which they had the attack that somehow makes them vulnerable?”

Context Not the Cause

In trying to come up with an answer, he says, people may misattribute the cause of the attacks to the context in which they occurred. For example, if someone has an attack while driving a car, that person may begin to believe there is something about driving—or about their destination—that causes the panic attack. This often leads to development of agoraphobia, a condition in which the person begins to avoid places where they fear a panic attack may occur. They may develop a fear of bridges, tunnels, shopping malls, grocery stores, or travel by public transportation, for example.

“What really underlies the fear is whether or not they'll be in a place or situation that is safe and where they can get immediate help in the case of a sudden or unexpected panic attack,” says Uhde. “These patients have an increasingly constricted lifestyle. Ultimately, they can become homebound and, in some cases, patients may become totally constricted to a room within their house.” Approximately one-third of patients with panic disorder develop agoraphobia, although there is no way to predict whether or not it will develop in a particular patient.

Griffith stopped going on business trips because, she says, “I had experienced enough of the ‘heart jumping’ thing that I thought, ‘I don't want to be that far away from home. I don't want to be in a strange hotel room somewhere and have this happen to me.’” She also stopped eating at restaurants for a time, because she initially thought the attacks might have been related to eating out. “I would go out to dinner and have a sense of my heart skipping or start to get flushed and, because I was trying to diagnose myself, it seemed to me that it happened frequently when I went out to dinner. So I thought it might be spices or something in the food.”

As many as 70 percent of panic disorder patients may suffer from other psychiatric conditions as well—most commonly depression—according to the NIH panel. Alcohol and drug abuse are also common among these individuals. In fact, it is not uncommon for alcoholism to be diagnosed, especially in men, while the underlying cause goes undetected (see accompanying article, “Gender Difference?”).

For many panic disorder patients the most frightening aspect of the illness is not knowing what is happening to them or why. This is not uncommon since the symptoms mimic so many other disorders and diagnosis is often elusive. According to the NIH panel, many patients see 10 or more doctors before being accurately diagnosed.

Bad Nights

Menter's attacks began in 1981, when she was 20 years old. They occurred about twice a month. At first, she simply attributed them to “bad nights” or bad nightmares, even though she now says she knew they weren't nightmares.

“A nightmare is a story, a bad dream,” she says. “When you wake up from a nightmare, you know the source of your fears. It's easy to examine it and reason it away. It's more abstract. A panic attack is just a sensation with no context. They're so real, and they can't be reasoned away.”

Over time, Menter's attacks came more frequently, and finally, after two years of having attacks every night, she went to the doctor. He prescribed a low dose of the benzodiazepine alprazolam (Xanax) to relieve stress, but the medication didn't seem to help. Menter didn't seek help again until three years later when, in late 1989, she heard Uhde discussing sleep panic attacks in a radio interview.

“I was just stunned that somebody was describing what I thought I had exclusively all to myself,” she says. “That was the major step—identifying it—because at that time I was almost convinced that I was just crazy. Finally, I could stick a label to it.”

She called the National Institute of Mental Health in Bethesda, Md., the next day and entered a research program on panic disorder.

Drugs May Help

Treatment is not clear-cut; it must be tailored to the individual, taking into account the patient's history, other medical and psychological conditions, and degree of impact of the disorder on the patient's life.

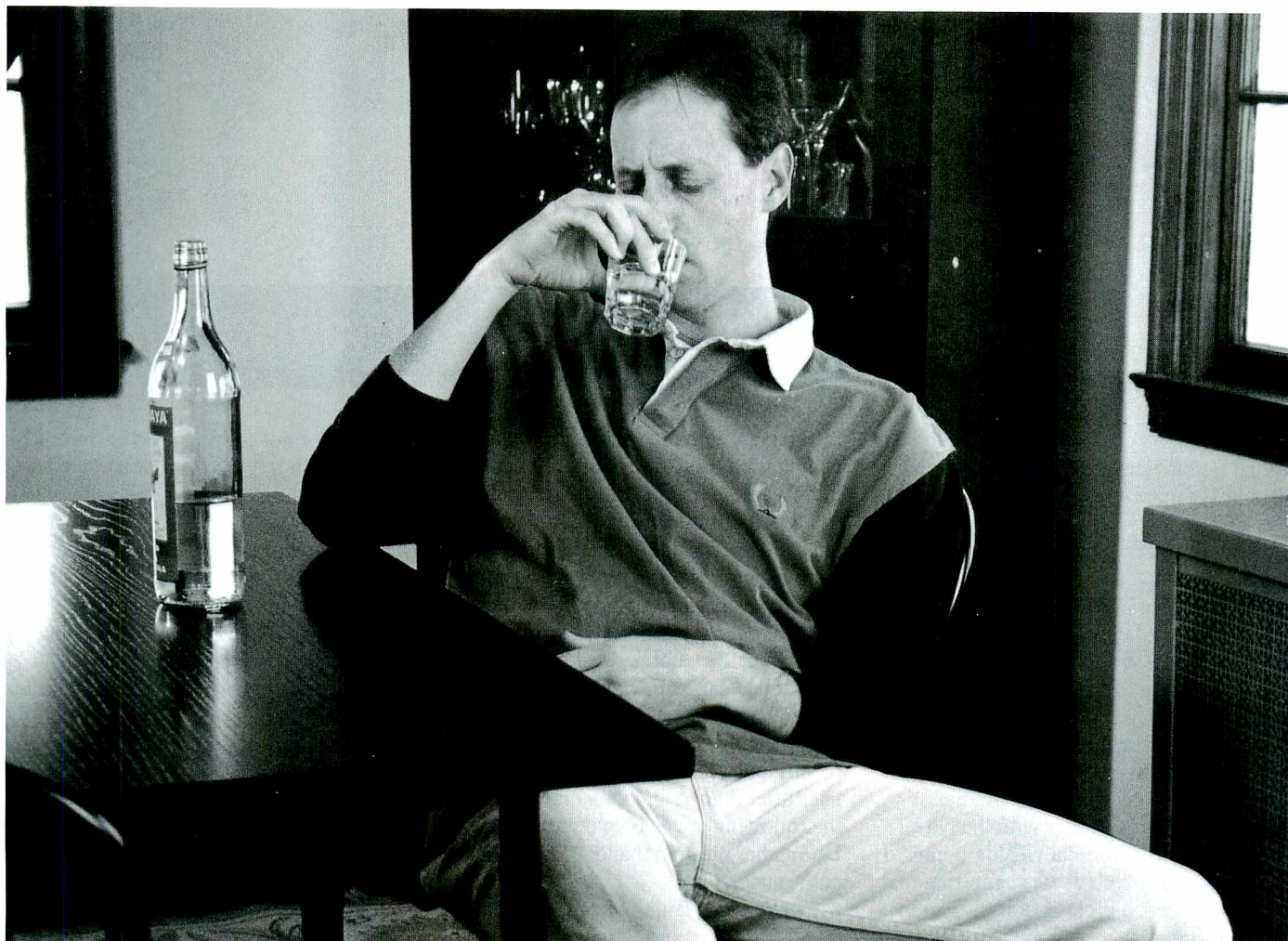
Only one drug, alprazolam, has been approved by FDA for treating panic disorder. Originally approved by the agency in 1981 to treat anxiety, alprazolam received approval for this new indication in November 1990. Side effects include drowsiness and lightheadedness, but the most serious risk is dependence.

“Withdrawal symptoms are common in patients who are trying to come off Xanax,” says Thomas Laughren, M.D., of FDA's division of neuropharmacological drug products. “The risk of dependence and its severity appear to be greater in patients treated with relatively high doses [above 4 milligrams per day] and for longer periods of time [more than 8 to 12 weeks]. A higher dose may be an especially important predictor of the development of physical dependence.”

Because dosages of more than 4 milligrams per day are often required in treating panic disorder, the risk of dependence among these patients may be greater than in those taking the drug at lower doses for less severe anxiety. The drug's labeling carries a warning about the risk of dependence and provides recommendations for initial dosing and increasing the dose in specific increments at specific intervals until therapeutic levels are achieved.

Other drugs have been reported to help reduce or eliminate panic attacks; however, FDA has not received any well-controlled studies to review them for this use. They include tricyclic antidepressants, such as imipramine (Tofranil), and monoamine oxidase (MAO) inhibitor antidepressants, such as phenelzine (Nardil).

While the tricyclics have no risk of dependence, they can cause a variety of ad-



Gender Differences?

Panic disorder affects both men and women. The condition is, however, diagnosed about twice as often in women as in men, and twice as many women as men go on to develop agoraphobia. The reasons why are not known; they may be cultural or biological, or perhaps a combination.

"Physicians are probably more likely to recognize psychological disorders in women, while attributing the same symptoms in

men to physical ailments," says Wayne Katon, M.D., professor of psychiatry at the University of Washington Medical School. "Before inquiring about a psychiatric disorder, the examination of the male patient would most likely involve multiple tests such as an echocardiogram or a stress test," he says.

Another reason panic disorder may not be detected as readily in men is their response to the attacks; men are often reluctant to seek help in dealing with emotional stress and attempt to self-treat instead.

"For example," says the National Institute of Mental Health's Thomas W. Uhde, M.D., "there is some evidence to suggest that men resort to the use of alcohol to alleviate their symptoms and eventually are diagnosed with alcoholism rather than panic disorder. In fact, if you look in clinics that specialize in alcoholism and drug addiction, you'll find a high rate of anxiety disorders in patients with alcoholism." ■

—M.S.

Why Panic?

The Search for a Cause

Unknowns cry out for answers, and so it is that researchers are trying to discover the elusive culprit responsible for panic disorder.

"There is a general difficulty in knowing how best to classify psychiatric disorders that relates in part to the difficulty in understanding their pathophysiology," says Thomas P. Laughren, M.D., of FDA's division of neuropharmacological drug products.

This may make the search a bit more complicated, but clues can appear if you know how to look for them. Thomas W. Uhde, M.D., a researcher with the National Institute of Mental Health, points to several factors he views as suggesting that there is, indeed, a biological basis for panic disorder:

- It affects two to three times as many women as men.
- Genetic factors appear to influence its transmission.
- Attacks occur spontaneously and are different in quality from other forms of anxiety (often described by patients as totally different from anything else they've experienced).
- Attacks can be induced or blocked with specific drugs.
- Sleep panic attacks occur during non-dream sleep stages, and therefore are not associated with disturbed thoughts, vivid images, or dreams.

Studies have shown that injections of lactate, a chemical normally produced by

the body, will induce panic attacks in people with panic disorder; but in normal individuals given the same dose, panic attacks will occur less frequently or not at all. Caffeine increases lactate and, in sufficient quantity (four to five cups), can induce panic attacks in panic-prone individuals, but not in normal control subjects.

Patti Griffith (not her real name) is convinced that caffeine precipitated her first panic attack. While out of town for a business meeting, she had drunk several cups of strong tea in the evening, had chocolates after dinner, and then drank more tea the following day at breakfast and lunch. During her meeting that day, she had a panic attack.

"All of a sudden, my heart was beating out of my chest, and I thought I was going to die," she says. "Finally, I had to go into the other room and lie still. My heart was beating irregularly and my head, chest and hands were hot and sweaty. This went on for quite some time, until I had to end the meeting and call for an ambulance."

Caffeine influences noradrenaline, a chemical messenger produced by the body that affects state of arousal and perhaps human emotion. One hypothesis is that panic disorder is caused by central nervous system "excitability" related to noradrenergic hyperactivity. Xanax and other benzodiazepines may work to block the effects of these chemical messengers.

"In studying noradrenergic activity in panic disorder patients," Uhde says, "scientists stumbled on the finding that these patients have lower levels of growth hormone than other adults, opening new areas of investigation into other avenues of treatment." It also raised questions of

whether or not children also have panic disorder, and, if so, whether it could lead to short stature or other growth abnormalities.

"We have seen two children with panic disorder who have fairly significant disturbances in stature or growth velocity," Uhde says, "and we are now investigating the prevalence of panic disorder in children and its effect on growth and development."

Researchers also speculate that the underlying mechanism causing panic disorder in a subgroup of patients is increased levels of carbon dioxide. "These patients tend to be chronic hyperventilators," says Uhde. "The hyperventilation causes alterations in respiratory system sensitivities. When they relax or go to sleep, they have a lowered respiratory rate and relative increase in carbon dioxide, which sets off a panic episode much as carbon dioxide inhalation will do."

In fact, carbon dioxide inhalation-induced panic and sleep panic may be caused by the same underlying mechanism—increased exposure to carbon dioxide, says Uhde. When patients become relaxed, they seem to be more vulnerable to having a sleep panic episode.

"The current view," according to Uhde, "is that panic disorder patients need to maintain their level of arousal within a very narrow window, because if they become too relaxed or overly aroused, they are vulnerable to a panic attack." ■

“What really underlies the fear [of agoraphobics] is whether or not they’ll be in a place or situation that is safe and where they can get immediate help in the case of a sudden or unexpected panic attack.”

—Thomas Uhde, National Institute of Mental Health

verse side effects, including low blood pressure, abnormal heart rhythms, weight gain, tremors, and seizures. Patients with certain heart problems, urinary retention, narrow-angle glaucoma, and other medical conditions should not take these drugs.

MAO inhibitors have also been used and also carry a low risk of dependence. Their side effects include low blood pressure, sexual dysfunction, and weight gain. In addition, patients on these drugs must follow a diet low in tyramine. This means avoiding high-protein foods that have been aged, fermented, pickled, or smoked, including cheeses, beer, wine, liver, salami, and yogurt.

Psychotherapy

Behavioral therapy, aimed at helping patients confront fearful situations and develop coping skills, and cognitive therapy, aimed at treating panic attacks directly by restructuring self-defeating thought processes, may also be incorporated into the treatment plan.

Uhde is not convinced that psychotherapy alone can combat panic disorder. He feels it is of value in helping patients get back on the subway or into their cars or offices and function despite their anxiety. “But that may not be treating the whole syndrome,” he says. He points specifically to sleep panic attacks, which he views as probably representing a pure physiological form of panic attack, with no psychological component (see accompanying article, “Why Panic? Search for the Cause”).

The NIH panel recommended that any treatment that fails to produce an effect within eight weeks should be reassessed.

One question that looms large is,

“When should therapy stop?” Little is known about the long-term course of panic disorder. In most cases, according to the NIH panel, it is a chronic disorder that waxes and wanes in severity. Some people, however, experience only a short-term problem that never recurs, while others may suffer a severe, chronic illness. Patients with agoraphobia tend to have a more severe and complicated illness, according to the panel.

Long-Term Outlook

Much remains to be learned also about the long-term effectiveness of maintenance doses of medication, psychotherapy, and lifestyle changes. Uhde says that, in general, he keeps patients on medication from 6 to 12 months before attempting a drug-free trial. After that, he says, there is a wide range of relapse. “My experience is that approximately 60 percent of patients will require drug treatment again within two years after the medication was stopped.”

Regarding Xanax, Laughren says there are inadequate data to guide physicians in how to use the drug beyond the acute treatment phase. “Because panic disorder is a chronic condition,” he says, “it may require continued treatment. The labeling suggests that the necessary duration of treatment for patients who respond is unknown, but it recommends that gradual dose reduction and withdrawal be attempted after ‘a period of extended freedom from attacks’.”

However, the labeling provides only rough guidance about how to withdraw patients from Xanax. “While the necessary research to establish optimal withdrawal strategies has not been done,” Laughren

says, “clinical experience has led to more conservative recommendations in labeling for withdrawing patients.”

At a September 1989 meeting of FDA’s Psychopharmacological Drugs Advisory Panel, one participant likened the dilemma of Xanax to taking off in a plane without landing instructions. “He suggested that we know how to get patients up in the air, but it isn’t clear how long to keep them there or how best to get them down,” says Laughren. “That is, we don’t know how long it is necessary to maintain responding patients on the drug, and we don’t know how best to withdraw them from treatment.”

With all its uncertainties, treatment seems to be working for both Menter and Griffith. Both are in programs at the National Institute of Mental Health. Menter started treatment with imipramine, but is now in a “blind” study, so she doesn’t know what drug or combination she’s receiving. She still has about two panic attacks a month, but she’s not as apprehensive about sleeping now.

“Even though the episodes of panic are as frightening as always,” she says, “I know I’m not crazy and I’m trying to do something about it. I can deal with it. One of my biggest fears, I think, was giving in to this thing and maybe one day becoming a crazy person who couldn’t take care of herself.”

Griffith is taking Xanax and an antidepressant, and is being tapered off Xanax. She hasn’t had an attack for several months and is back to traveling to business meetings and eating out at restaurants. ■

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

Prostate Problems Plague Older Men

by Ken Fieger

By current estimates, somewhat more than half of all American men over 50 have symptoms caused by an enlarged prostate gland. A frequent, even urgent, need to urinate, getting up in the night to urinate, a sense of fullness after urination—signs like these suggest that an enlarged prostate is interfering with the normal workings of the urinary tract.

Many men just put up with such complaints as part of the downside of getting older. They don't take advantage of, or don't have access to, routine examinations that can detect prostate problems early

and open the way to effective treatment. But the price of stoicism or neglect can be high. Prostate-related problems can cause or be caused by serious, even life-threatening, illness that requires careful diagnosis and specific treatment.

Role of the Prostate

The prostate is part of the male reproductive system. It helps produce semen, the thick, whitish fluid that transports sperm. It's roughly doughnut-shaped and about the size of a walnut. Located just below the bladder and in front of the rectum,



the prostate surrounds the first inch or so of the urethra, the tube that carries urine from the bladder (see accompanying diagram).

Prostate function and growth depend on the male hormone testosterone, which is produced in the testes. With advancing age—for reasons that are not entirely clear—the prostate in most, but not all, men will grow to a size that puts pressure on the urethra. At first there may be no symptoms. But, as the urethra becomes more and more compressed, urination fails to completely empty the bladder. It refills rapidly, giving rise to the need for frequent urination. More serious complications can follow. Urine remaining in the bladder for a long time can lead to infection, bladder stones, and kidney disease. A completely blocked urethra is a medical emergency requiring immediate measures to allow urine to escape from the bladder, followed by treatment directed at the underlying prostate problem.

Not all types of prostate disease cause excessive growth of the gland (see accompanying article). Prostatitis—inflammation of the prostate—sometimes results from bacterial infection, but more commonly has no known cause. Low back pain and difficult or painful urination (often accompanied by a burning sensation) are the usual signs of prostatitis. If acute or recurrent bacterial infection is the cause, the patient may also experience chills and a high fever.

Patients with bacterial prostatitis are helped by bed rest, fluids, and drugs to relieve pain and attack the bacteria causing the disease. The nonbacterial form of prostatitis is more difficult to treat effectively. Hot sitz baths and drugs for pain are of some help, and certain patients benefit from periodic prostate massage.

Men Neglect Exam

An enlarged prostate can be detected during a routine physical examination. The doctor feels the prostate gland by inserting a gloved finger into the rectum in a procedure that takes less than a minute. What this reveals about the size, firmness and texture of the prostate helps the physician decide what, if any, further tests or treatment are called for. The American Cancer Society and the National Cancer Institute recommend that all men age 40 and older have the examination yearly as part of a regular health checkup.

But most men don't. Many say they find the procedure embarrassing and uncom-

fortable, and studies also suggest that some physicians choose not to do rectal examinations on their over-40 male patients. Other ways to check for an enlarged prostate have been developed. One uses transrectal ultrasound to make a visual image of the gland. A probe that emits and picks up high-frequency sound waves is inserted into the rectum. The pattern of sound that bounces off the prostate is converted electronically into a video picture showing any abnormalities.

Both patients and physicians would welcome a simple and dependable laboratory test for prostate cancer, and work is under way to develop one. One possibility is a blood test that measures the amount of a protein called prostate-specific antigen (PSA), which is now used to monitor the results of prostate cancer therapy. PSA is produced by cells of the prostate gland, including prostate cancer cells that have spread to other parts of the body. Changes in PSA blood levels show whether the cancer is growing or shrinking. A clinical study reported in the April 25, 1991, issue of the *New England Journal of Medicine* showed that the PSA blood test could detect early, highly curable prostate cancer, the kind that a digital rectal exam might miss.

Urologists and cancer authorities agree, however, that the PSA blood test is not a replacement for the rectal exam. In the 1991 study, PSA testing failed to detect prostate cancer in about 20 to 30 percent of men who actually had the disease, and

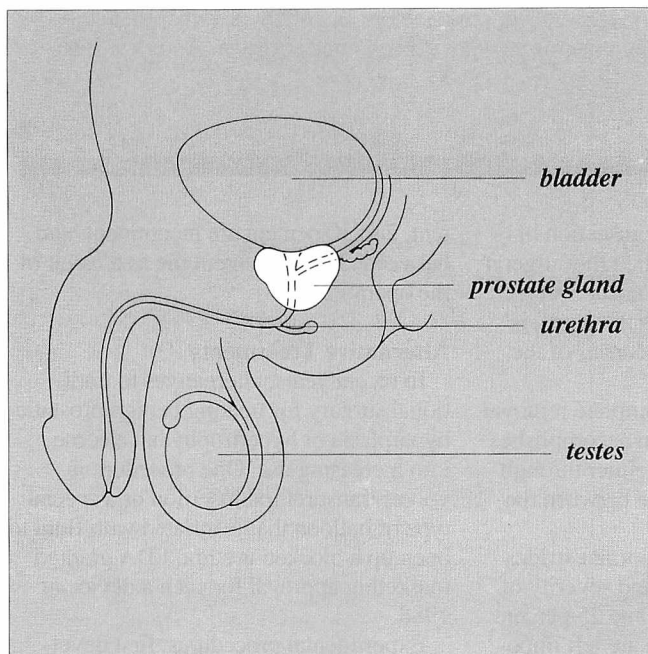
it signaled cancer in 16 percent of those who were cancer free. The problem seems to be that some early cancers do not cause PSA levels to rise, leading to a false negative finding, while noncancerous conditions sometimes raise PSA blood levels enough to give a false positive result.

Experts think the test can be made more reliable. At this point, however, the simple and relatively inexpensive digital rectal examination is still the mainstay technique for initially detecting and evaluating an enlarged prostate. More elaborate tests are required to establish whether prostate growth is malignant and, if so, whether it has spread beyond the prostate—factors that help determine the course of treatment.

The array of treatments for an enlarged prostate covers an expanding spectrum of medical technology—from surgery, radiation and drugs to microwaves and balloons. Choosing the appropriate treatment for an individual patient involves weighing the severity of urinary tract and other complications, whether the condition is benign or malignant and, if cancerous, whether it is confined to, or has advanced beyond, the prostate. Other factors that physicians have to consider are the patient's age and general health and his willingness to undergo therapy that may have major, unwelcome side effects.

Surgery

For decades, surgery has been the standard method of treating benign prostate



The first inch or so of the urethra, which carries urine from the bladder, is surrounded by the prostate gland. Prostate function and growth depend on the hormone testosterone, produced in the testes. In many older men, the prostate enlarges, putting pressure on the urethra and causing urinary problems.

A Growing Concern

Prostate disease, characterized by excessive growth of the gland and progressive blockage of urinary flow, is of essentially two kinds:

- benign prostatic hyperplasia or hypertrophy (BPH), which does not spread beyond the gland itself
- cancer of the prostate, which in advanced stages can spread to remote parts of the body, principally bone.

Both conditions are serious. About 400,000 men in the United States undergo surgery each year for BPH, while prostate cancer is the most common cancer—and the second leading cause of death from malignant disease—among American men, exceeded only by cancer of the lung. An estimated 122,000 men will be diagnosed with prostate cancer this year, and 32,000 will die of it. Despite the fact that both conditions arise in the same organ, scientists think that having BPH neither increases nor decreases an individual's chance of developing cancer of the prostate.

Prostate growth is dependent on testosterone, but no one knows what causes malignant prostate disease to develop or how to prevent it. A man's risk of developing benign prostate disease may relate to his family's history of BPH. As for prostate cancer, evidence suggests that it may be associated with occupational exposure to cadmium used in welding, or to an occupational risk involved in manufacturing alkaline batteries. But a cause-and-effect relationship between prostate cancer and these occupational hazards has not been firmly established.

Dietary fat, however, is known to play a role in prostate cancer, and in November 1991, FDA proposed that labels on certain low-fat foods be allowed to state that diets high in fat are associated with an increased risk of breast, colon and prostate cancer.

For whatever reason, prostate disease in this country is on the increase. The incidence of cancer of the prostate rose 47 percent between 1973 and 1987, and is still going up. The increase is thought to result in part from improved detection, but other explanations for the rise in prostate cancer are elusive.

The incidence of prostate cancer among African-American men has risen sharply during the last few decades, and today black Americans have the highest prostate cancer rates in the world. Evidence that black men living in Africa are considerably less likely to develop prostate cancer than American blacks leads investigators to speculate that socioeconomic factors and lifestyle, rather than genetics, account for the high rate of prostate cancer among African Americans. ■

—K.F.

enlargement. Transurethral resection of the prostate (TURP), in which the surgeon trims away excess prostate tissue using an instrument inserted through the penis, is also used to treat localized cancer of the prostate.

Some patients require complete removal of the prostate. The surgeon accomplishes this by making an incision either through the abdomen or in the space between the scrotum and anus.

Surgeons have made important strides in reducing the frequency and severity of adverse after-effects, but some 25 percent of prostate surgery patients are left impo-

tent, 2 to 10 percent are incontinent, and between .2 and 2 percent die as a result of the operation.

Alternative Treatments

In recent years, alternatives to traditional surgery for treating benign prostatic hyperplasia or hypertrophy have come into increasing use. One procedure involves transurethral insertion of a special type of balloon that is inflated with fluid to open up a blocked urethra. FDA granted marketing approval for such a device in 1988.

Experimental procedures, first devel-

oped in Israel and France and being studied in the United States, use microwaves produced by instruments inserted through the urethra or rectum to destroy excess prostate tissue. Investigators think such techniques may prove useful in about 25 percent of patients, those with minimal prostate enlargement who would otherwise be candidates for surgery.

The advisory committee to FDA on endocrine and metabolic drugs recently recommended approval of the drug Proscar, which acts by blocking testosterone's growth-stimulating effect on the prostate. Researchers reported that Proscar reduced the size of enlarged prostates in about 30 percent of the men who took it in a year-long clinical trial and gave symptomatic relief to some 70 percent of those receiving the drug. At press time, FDA was reviewing the data on Proscar, manufactured by Merck, Sharp & Dohme Inc., before reaching a decision on its approval.

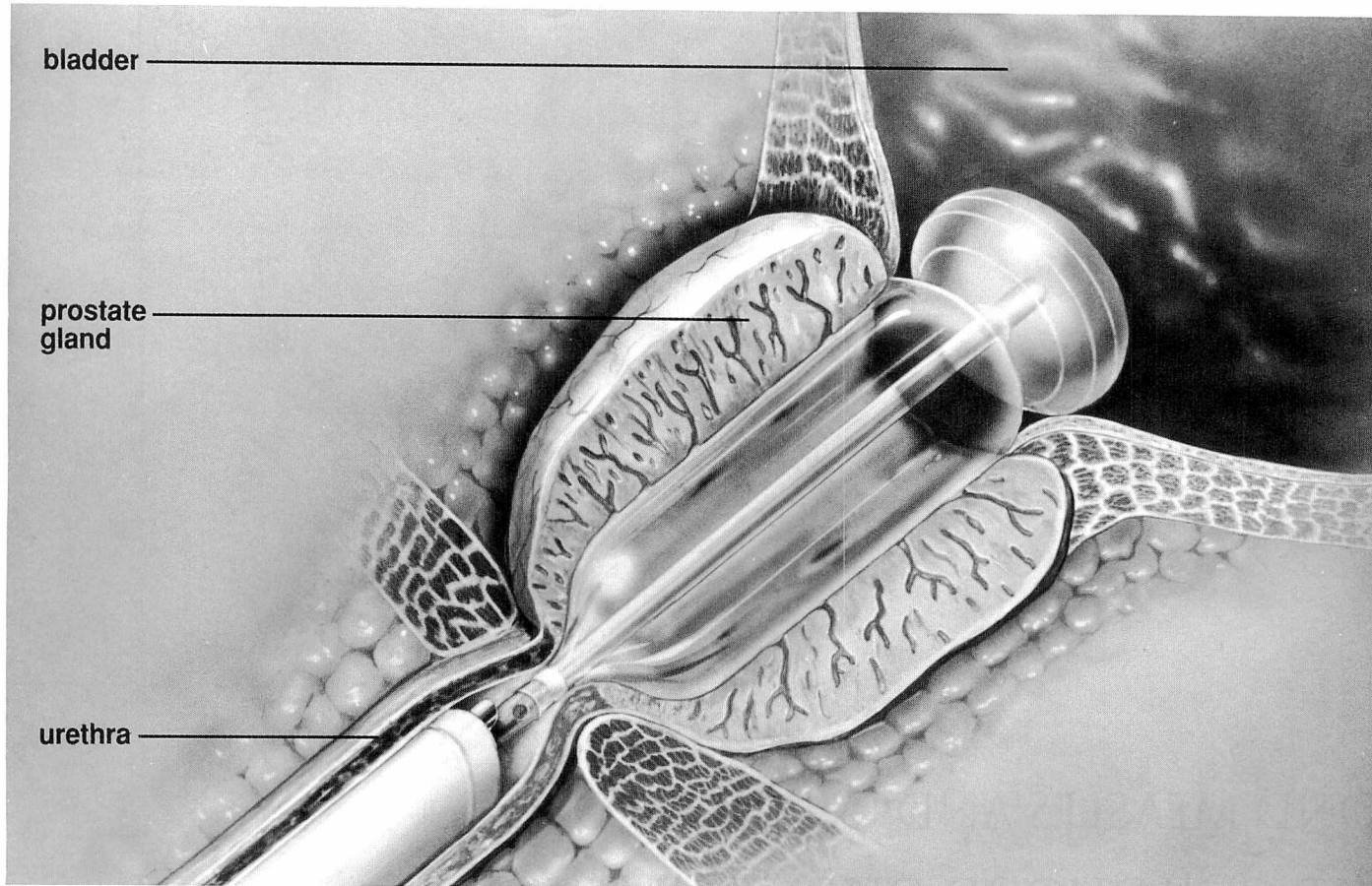
Prostate Cancer

Surgery continues to be the most widely used treatment for prostate cancer. Early prostate cancer that is confined to the gland itself is nearly 100 percent curable by surgical removal of the diseased prostate. More extensive surgery is called for if the cancer has spread to surrounding tissue or lymph nodes. The patient's overall state of health, his willingness to undergo prostate surgery, and the stage of his disease may necessitate one or more other forms of treatment.

Because malignant prostate cells are highly sensitive to radiation, disease that has spread beyond the prostate is often treated by radiation. Several kinds of drugs also are effective against prostate cancer. These include hormonal agents that block or counteract testosterone, and certain anti-cancer drugs that attack tumor cells. Although not curative, hormone or drug therapy, alone or in combination with surgery or radiation, can prolong a patient's life for many years. It's not uncommon for prostate cancer patients to die of other causes long after their prostate cancer was discovered.

Is Treatment Always Wise?

It's also true that men with untreated prostate cancer can and do survive—often with no symptoms whatever—for a very long time, eventually dying from a cause unrelated to their malignancy. This



In an alternative to surgery for benign prostatic hyperplasia or hypertrophy, a balloon device is inserted through the urethra to the area of the prostate gland and then expanded with fluid to unblock the urethra.

prompts some authorities to question whether it's a good idea to try to find and treat every case of prostate cancer. Expert opinion is divided.

Generally speaking, cancer of the prostate is a slow-growing tumor. In men under 50, the disease progresses rapidly. But in the typical older patient, prostate cancer develops slowly, often over a period of many years.

Investigators at the University of Chicago, Gerald W. Chodak, M.D., and Glenn S. Gerber, M.D., point out that autopsy studies have shown that more than 50 percent of men over 50 have microscopic evidence of prostate cancer. "Yet," they observe in a recent article in the *Journal of the National Cancer Institute*, "the vast majority of these patients will never have any clinical manifestations of disease." Chodak goes on to note that if

screening led to detection and treatment of these microscopic cancers, some lives would be saved. But, he says, most of these men, destined to die of other causes, would suffer needlessly from cancer treatment.

On the other hand, William J. Catalona, M.D., chief of urologic surgery at Washington University Medical Center in St. Louis, says that 7 out of 10 prostate cancers have spread beyond the gland by the time they are detected. Effective treatment begun at this stage can arrest the disease, often for many years, but cure is considerably less likely than it is with early, localized disease. Nonetheless, the overall five-year survival rate for prostate cancer is better than 60 percent for white men and 50 percent for blacks.

Investigators are looking for ways to determine which patients will benefit most

from aggressive treatment. A testing procedure that measured PSA blood levels and also factored in prostate size might distinguish patients at high risk of developing prostate cancer. A National Cancer Institute study will try to find genetic clues to distinguish between slow-growing tumors unlikely to cause problems and those expected to progress rapidly.

Over the longer term, a major National Cancer Institute project that won't be finished until well into the 21st century will attempt to find out whether the digital rectal examination, in combination with PSA testing and ultrasound, actually improves survival rates among the 75,000 men expected to take part. ■

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

FIFTH DISEASE

IMPETIGO

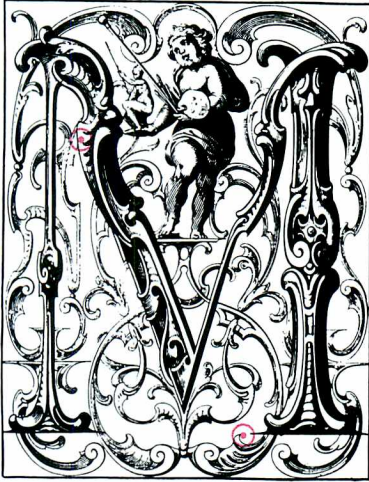
ROSEOLA

SCARLET FEVER

BEYOND MEASLES AND CHICKENPOX:
OTHER CHILDHOOD DISEASES CAUSE

RASHES

by Dori Stehlin



measles and chickenpox are pretty much household words. Other contagious rash diseases of childhood—fifth disease, roseola, scarlet fever, and impetigo—may not have the same amount of name recognition, but lack of fame doesn't mean that they don't cause problems!

To treat or relieve the symptoms of these diseases, products regulated by the Food and Drug Administration are frequently used.

Fifth Disease (Erythema Infectiosum)

"I used to ask my students, 'Who was Dr. Fifth?' " says Paul F. Wehrle, M.D., professor emeritus in pediatrics at the University of Southern California. "They used to come up with some really interesting answers."

The real answer, however, is that there was no Dr. Fifth. The common name for erythema infectiosum came from its fifth position on a list developed in the early 1900s of childhood rash diseases. (Measles topped the list, followed by scarlet fever and rubella. Number four—Filatow-Dukes disease—turned out to be a mild form of scarlet fever.)

Those medical students weren't alone. Many people have never heard of fifth disease even though most have been infected with it.

"I thought my doctor was joking when he said [my son] Sammy had fifth disease," says Corinne Denlinger of Gaithersburg, Md. "Fifth disease? Not very 'medical' sounding. And why hadn't I ever heard of it before?"

"Fifth disease doesn't make a lasting impression," says Thomas J. Torok, M.D., a specialist on erythema infectiosum with the national Centers for Disease Control. He explains that in many children the symptoms are mild, and in approximately 20 percent of those infected, there are no symptoms at all.

"It's so mild, most mothers never remember that their children had it," he says.

Usually, the first symptoms of fifth disease—low-grade fever and general feeling of malaise—are indistinguishable from a mild case of the flu. Then, anywhere from seven to 10 days later, the rash will appear.

If anything about fifth disease can make a lasting impression, it's the distinctive "slapped cheek" appearance of the facial rash. The rash then spreads to the trunk and extremities, frequently developing a lacy pattern. The rash generally fades within two weeks, but external factors such as sun exposure, bathing, excitement, or exercise can cause it to reappear several weeks later.

Caused by the human parvovirus B19, there is no oral drug treatment for fifth disease. If the rash itches, "plain calamine lotion and cool water should provide enough relief," says John Lowe, M.D., a pediatrician in private practice in Wheaton, Md.

Most cases of fifth disease occur in children 5 to 14 years old, and outbreaks are more common during winter and spring. Once infected, a person has lifelong immunity.

For adults who passed through childhood without catching fifth disease, symptoms can be more severe, including arthritis and arthralgias (joint pains). Occasionally, these painful symptoms can last for years.

While not a serious infection among the general population, fifth disease can cause a life-threatening anemic reaction in certain people, such as those with sickle cell anemia.

According to CDC, fifth disease may increase the risk of miscarriage if a woman is infected during the first 20 weeks of pregnancy.

"The risk [of miscarriage] is small," says CDC's Torok. He explains that most adults are immune, since they were infected as children. In addition, even in those mothers who aren't immune, an infection doesn't automatically cause a miscarriage. There is no evidence that fifth disease causes any birth defects, according to CDC.

"More than 90 percent of women infected deliver healthy, term babies," says Torok.

Some physicians have recommended that if an outbreak of fifth disease occurs at a school, pregnant school employees should stay home for two to three weeks after the last case has been diagnosed.

"That's a totally illogical reaction," says Torok. "First of all, outbreaks can last for months. And second, the disease is in the community, not just the school. Staying away from the school accomplishes nothing."

Lowe agrees, explaining that by the time the rash breaks out, the child is no longer contagious.

Roseola Infantum (Exanthem Subitum)

Roseola commonly starts with a high fever, frequently as high as 40 degrees Celsius (104 degrees Fahrenheit). The fever usually lasts for three to five days, although the very high temperatures may be intermittent. Roseola's high fevers are a common cause of febrile (feverish) convulsions during the first two years of life.

Although a convulsion can be quite frightening, especially for the parents, "they're not harmful," says Lowe. "A convulsion with fever is just the response of the immature brain to the rapid changes in temperature."

Except for the convulsions, children usually don't appear as sick as might be expected with such a high fever, says Lowe.

On the fourth or fifth day the temperature drops to normal and then the rash suddenly appears.

"It's not like other rashes where first a few spots appear and slowly the rest of the body gets covered," says Lowe. "This pops up everywhere all at once, and disappears just as quickly."

Although the rash can last as long as two days, sometimes it can come and go in only a few hours. "If the baby gets it during the night, the parents may miss it completely," says Lowe.

Also known as baby measles, 82 percent of all roseola cases occur in infants 6 to 24 months old.

The cause of roseola is herpesvirus-6. There is no cure except time; treatment is directed to alleviating the symptoms. "Push fluids," says Lowe. He explains that a high fever increases the risk of dehydration.

To reduce the fever, acetaminophen, not aspirin, should be used, says Lowe. (See accompanying article, "Treating a Child's Fever.")

(Continued)

Scarlet fever ●

- most cases in children 3 years and older
- sudden high fever, sore throat, headache, severe stomach pains, and vomiting
- rash appears 12 to 24 hours after initial symptoms
- rash starts below the ears and on the chest and underarms
- treat with antibiotics



Impetigo ●

- thin-walled blisters or thick, crusted lesions
- treat with antibiotics



Roseola ▲

- most cases in infants 6 to 24 months old
- high fever
- four or five days later, temperature drops to normal
- rash appears suddenly, covers entire body
- acetaminophen for fever



Fifth disease ★

- most cases in children 5 to 14 years old
- low-grade fever, general feeling of malaise
- rash appears seven to 10 days later
- “slapped cheek” facial rash
- lacy pattern on extremities
- calamine lotion can be used to relieve symptoms

A QUICK LOOK AT RASH DISEASES

Treating a Child's Fever

Reye syndrome is a rare but sometimes fatal condition in children and teens. While its cause is unknown, studies have linked the onset of the disease to aspirin use during a bout with the flu or chickenpox.

No link between aspirin use during other childhood diseases and Reye has been established. But, when a child begins running a fever, it is difficult—if not impossible—to know whether a child is suffering from flu, chickenpox, or some other illness. Therefore, most doctors now advise against using aspirin for any childhood fever and recommend using acetaminophen (brand names include Tylenol and Tempra) instead.

—D.S.

Scarlet Fever

A case of scarlet fever used to mean quarantines by public health officials, months of convalescence, and, sometimes, serious and permanent disabilities, even death.

Then two things—one from human ingenuity, the other from natural evolution—changed the face of the disease.

The first was the discovery in 1928 of penicillin; the second, the strains of Group A streptococcus responsible for scarlet fever becoming less virulent in the 1930s and 40s.

Today, treatment with penicillin or other antibiotics such as erythromycin can stop the disease before some of the characteristic symptoms—especially the bright red “strawberry tongue”—appear.

In addition, even though some strains of Group A strep are becoming more virulent, so far the strains responsible for scarlet fever aren't, and cases of scarlet fever are “mostly still mild,” says Bascom Anthony, M.D., director of FDA's division of bacterial products. (For more information on changes in Group A streptococcus, see “‘Strep’ Demands Immediate Care” in the October 1991 *FDA Consumer*.)

“Scarlet fever is basically strep throat with a rash,” says Rosemary Roberts, M.D., a pediatrician with FDA's division of anti-infective drug products. The infection usually starts with a sudden, high fever of about 40 C (104 F), sore throat, headache, severe stomach pains, and vomiting. The pharynx and tonsils are beefy red. Sometime between 12 and 48 hours later the rash appears below the ears and on the chest and underarms. Eventually, it may spread to the abdomen, arms, legs, and face.

Without treatment, the rash may give

the skin a rough texture frequently described by doctors as “sunburn with goose pimples” or “alligator skin.” The strawberry tongue usually appears on day four or five. If allowed to run its course, the fever would last about six days and the rash for about a week. Since modern-day scarlet fever is relatively mild, serious complications rarely occur.

One symptom, peeling skin, especially on the hands and feet, usually can't be stopped even with antibiotics. The peeling starts about 10 days after infection and may continue for six weeks.

Infection results in lifelong immunity, but because there are so many strains of Group A strep, a person can get scarlet fever more than once.

Although the symptoms are usually clear-cut from the beginning, diagnosis should not be based on clinical signs alone, says Lowe. He explains that a throat culture is necessary “to differentiate [the cause] from other things such as toxic shock syndrome and Kawasaki disease.” (Toxic shock syndrome is caused by *Staphylococcus aureus* bacteria; the cause of Kawasaki disease is unknown. Both require different courses of treatment than scarlet fever.)

Impetigo

Impetigo is the most common skin infection in children.

“It spreads like wildfire in kids, because they're always touching each other,” says Lowe.

Unlike the other three rashes, which are caused by internal infections, the impetigo rash is caused by an external infection with *Staphylococcus aureus*, *Streptococcus pyogenes*, or a combination of the two bacteria. Thin-walled blisters usually result

when the culprit is staphylococci; strep usually causes thick, crusted lesions.

Until the early 1980s, the medical community considered strep the main cause of impetigo. Although several recent studies have suggested that staphylococci may be winning out as the major cause, “impetigo is still a mixed bag,” says FDA's Anthony. “Clearly, there are many cases that are still caused by strep.”

Because many strains of staphylococcus are resistant to penicillin, doctors usually prescribe alternative antibiotics.

A small, localized infection can be treated with the antibiotic ointment mupirocin. FDA's Roberts cautions, however, that the ointment must be put on every single blister or lesion. “If the rash is spreading all over the body,” she says, “a systemic [oral antibiotic] would be better.”

In addition to antibiotic treatment, a few simple steps can help stop the spread of the infection, says Andrew Gellady, M.D., a spokesman for the American Academy of Pediatrics. “Make sure no one shares a towel, and wash sheets and towels in hot water,” he says.

There is no reason to pop the blisters or scrub the lesions, says Gellady. “Leave the rash alone.”

Because there are several strains of both staph and strep, a person can get impetigo more than once.

Though they may seem severe and even scary to parents when they occur, in retrospect these diseases are often remembered as uncomfortable but controllable and fortunately fleeting childhood experiences. ■

Dori Stehlin is a staff writer for FDA Consumer.

*On the
Teen Scene*

Good News About Good Nutrition

by Judith E. Foulke





ou've heard it all before. For as long as you can remember, your parents, your teachers, perhaps even your doctor, have been telling you to eat your vegetables, limit sweets, drink your milk.

Now, in your teen years, this advice takes on new meaning for a lot of very different reasons: How can you gain weight to put on muscle instead of fat? What's a healthy weight for you? How can you squeeze in a good, quick meal after school and before you have to be at your part-time job? All good questions, and because of the enormous changes that are going on in your body, the way you decide to deal with your nutrition needs now can make a big difference not only in how you feel today, but also in your well-being in years to come.

If you are between 15 and 18, you're completing your final major growth spurt, and are in the process of putting on nature's finishing touches for adulthood. For girls, the finishing touch means adding some fat padding. For boys, it means adding muscle and increasing the volume of blood. These changes often encourage girls to diet unnecessarily to stay slim, while boys may overeat to satisfy their appetites. Both can lead to health problems down the road, and, incidentally, probably will not do the job you want right now.

So what is the right approach to healthy eating?

A good start is to eat a variety of foods, as suggested in the *Dietary Guidelines for Americans*, published by the U.S. departments of Agriculture and Health and Human Services. Get the many nutrients your body needs by choosing a variety of foods from each of these groups:

- vegetables
- fruits
- breads, cereals, rice, and pasta
- milk, yogurt and cheese
- meat, poultry, fish, dried beans and peas, eggs, and nuts.

What's So Junky About "Junk" Food?

The pace for teens is fast and getting faster. Added to pressures from school to prepare for college or a job, many teens take part in sports and work part-time. This often means eating on the run. Stack that on top of the snack foods you eat on dates or when you and your friends just get together, and the balance of your nutrients can get way out of kilter.

Many snacks, such as potato chips, fast-food cheeseburgers, and fries, have high levels of fat, sugar or salt—ingredients that are usually best limited to a small portion of your diet. Healthy eating doesn't mean that you can't have your favorite foods, but the *Dietary Guidelines* advise you to be selective and limit the total fat, saturated fat, cholesterol, and sodium you eat. Our main source of saturated fat comes from animal products and hydrogenated vegetable oils, with tropical oils—coconut and palm—providing smaller amounts. Only animal fat provides cholesterol. Sodium mostly comes from salt added to foods during processing, home preparation, or at the table.

Fats are our most concentrated source of energy and supply about 40 percent of the

total calories in typical American diets. Scientists know that eating too much fat, especially saturated fat and cholesterol, increases blood cholesterol levels, and therefore increases your risk of heart disease. Too much fat also may lead to overweight and increase your risk of some cancers.

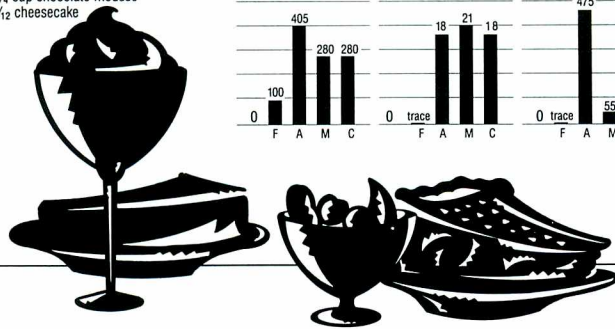
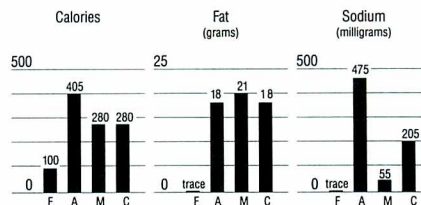
Dietitians recommend that no more than 30 percent of your calories come from fats, and not more than 10 percent of these calories should be from saturated fat. Choose lean meats, fish, poultry without skin, and low-fat dairy products whenever you can. When you eat out, particularly at fast-food restaurants, look for broiled or baked rather than fried foods. Try the salad bars more often, but pass up creamy items and limit the amount of salad dressing you use to keep down the fat and calories. Look for milk-based high-calcium foods with reduced fat.

Spare the Sugar and Salt

Most people like the taste of table sugar. But did you know that other sweeteners are sometimes "hidden" in foods? There are sugars in honey, dried fruits, concentrated fruit juices, and ingredients such as corn syrup that are added to soft drinks,

Taking a Close Look At Desserts

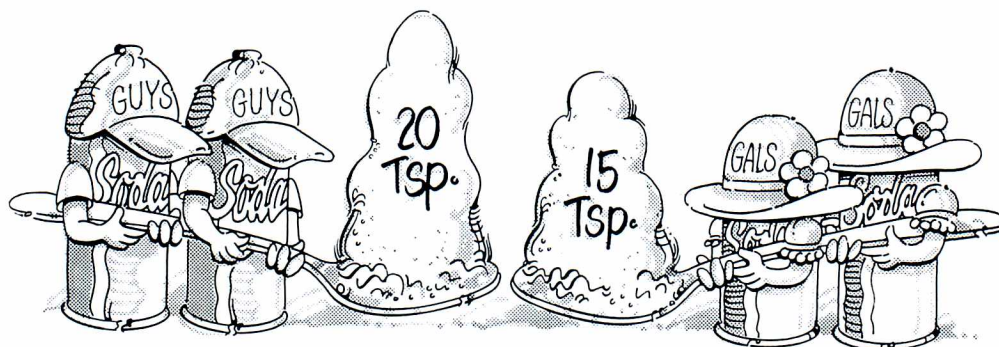
Key:
F = fresh fruit cup
A = 1/8 apple pie
M = 3/4 cup chocolate mousse
C = 1/12 cheesecake



Here's how much fat, sodium and calories you get from a few popular desserts. The estimates are based on usual portion sizes, which take into account that cheesecake is often served in portions half the size of a slice of apple pie. (Source: U.S. Department of Agriculture)

Soda Sippers

How much sugar do you get from soda each day? Here's what a recent USDA survey shows:



A higher percentage of 12 to 29 year olds drink regular soda than any other group. Males average about two cans a day, females one and a half cans.

NOTE: There are 10 teaspoons of sugar in one can (12 ounces) of regular soda !!

cookies, and many other processed foods. (See "Not Only Sugar Is Sweet" on page 16.) You can see what sugars are in packaged foods by looking at the ingredient list.

If you are a very active teen with high-energy needs, sweets can be an additional source of calories. But keep in mind that they contain only limited nutrients and that both sugars and starches can contribute to tooth decay.

A moderate amount of sodium in your diet is necessary, because sodium, along with potassium, maintains the water balance in your body. But for some people, too much sodium can be a factor in high blood pressure. Since processed foods often contain large amounts of sodium, it's wise to use salt sparingly when cooking or at the table—and to avoid overeating salty snacks like pretzels and chips.

When you exercise heavily and sweat profusely, you can deplete your sodium reserve, unbalance your body chemistry, and possibly become dehydrated. In extreme cases of profuse sweating, such as during training or competition, a dilute glucose-electrolyte drink may become necessary, but always with an abundance of water to make up for sweat losses.

What's All This About Fiber?

Whole-grain breads and cereals, dried beans and peas, vegetables, and fruits con-

tain various types of dietary fiber essential for proper bowel function. Eating plenty of these fiber-rich foods may reduce your risk of cancer and heart disease.

The benefits from a high-fiber diet may be related to the foods themselves and not to fiber alone. For this reason, it's best to get fiber from foods rather than from the fiber supplements you can purchase in a store.

Be Aware of Alcohol

Alcoholic beverages deserve special mention. Drinking them risks good health and can cause other serious problems for teens. And although it is illegal for teens to buy alcoholic beverages, a 1991 survey conducted by the Department of Health and Human Services shows that over half of 10.7 million junior and senior high school students have had at least one drink within the past year. Eight million students drink weekly, and almost half a million binge (five or more drinks at one time) weekly.

Teens who drink risk impaired judgment in their social relationships and endanger their own and others' lives if they drive after drinking. The U.S. Department of Transportation reports that in 1989, 2,800 students between 15 and 19 years of age died in alcohol-related traffic accidents. Almost half of all traffic accidents involving this age group, whether or not

someone died, were alcohol-related.

Alcoholic beverages contain calories but few if any nutrients. Drinking heavily can lead to poor nutrition if alcoholic beverages replace foods with needed nutrients, and alcoholism is not unknown among teenagers.

What About Vegetarians?

There are many types of vegetarian diets, but the two most common are the lacto-ovo, which includes eggs and milk products but not meat, and vegan, which eliminates all forms of animal products. Teens who are lacto-ovo vegetarians can usually get enough nutrients in their diets, with the possible exception of iron, says Marilyn Stephenson, a dietitian with the Food and Drug Administration's Office of Nutrition and Food Sciences.

Getting enough iron is especially important to teens. The need for iron for both boys and girls increases between the ages of 11 and 18. The National Academy of Sciences recommends teenage boys get 12 milligrams of iron a day, mostly to sustain their rapidly enlarging body mass. For girls, the recommended daily requirement is 15 milligrams to offset menstrual losses that begin during this time.

It's important to plan how to get adequate iron in your diet. Iron from meat, poultry and fish is better absorbed by your body than the iron from plant sources.

Dietary Guidelines for All Americans

What should Americans eat to stay healthy? These guidelines, published by the U.S. departments of Agriculture and Health and Human Services, reflect recommendations of nutrition authorities who agree that enough is known about the effect of diet on health to encourage certain dietary practices. The guidelines are:

- Eat a variety of foods.
- Maintain a healthy weight.
- Choose a diet low in fat, saturated fat, and cholesterol.
- Choose a diet with plenty of vegetables, fruits, and grain products.
- Use sugars only in moderation.
- Use salt and sodium only in moderation.
- Children and adolescents should not drink alcoholic beverages.

The *Dietary Guidelines* suggest at least the following number of servings from each of these food groups:

Vegetables	3-5 servings
Fruits	2-4 servings
Breads, cereals, rice, and pasta	6-11 servings
Milk, yogurt and cheese	2-3 servings*
Meats, poultry, fish, dried beans and peas, eggs, and nuts	2-3 servings

* People aged 12 through 24 years should have three or more servings daily of foods rich in calcium.

However, the absorption of iron from plants is improved by eating fruit or drinking juice that contains vitamin C with the iron-rich food.

Vegan vegetarians are vulnerable to deficiencies of several nutrients, particularly vitamins D and B₁₂, calcium, iron, zinc, and perhaps other trace elements. Like all essential nutrients, these vitamins and minerals are required to maintain proper growth.

Teens need extra calcium to store up an optimal amount of bone (called "peak" bone mass). The richest sources of calcium are milk and other dairy products. Building optimal bone mass through a balanced diet, including adequate calcium, may help delay the onset or limit your chances of developing osteoporosis later in life. Osteoporosis is a disease in which reduced bone mass causes bones to break easily. It occurs in both men and women, but is more common among older women.

If it is important to you to be a vegetarian, it is easier to achieve good nutrition with the lacto-ovo form. A dietitian (or

your school nurse) can help you plan a vegetarian diet that provides you with the nutrients you need for growth and development during the teen years.

What's a Healthy Weight?

Some teens have a difficult time projecting a healthy weight for themselves. Girls especially may think they need to be thinner than they are, or should be. Extraordinary concern or obsession for thinness leads some teens to the eating disorders of anorexia nervosa (dieting to starvation) or bulimia (overeating and then vomiting). (See *FDA Consumer*, March 1992.)

If you're concerned about your weight, it's important to talk to a health professional such as your family doctor or the school nurse. That person can help you decide whether you do need to lose weight and, if so, the best way to achieve and maintain a weight that is healthy for you.

If health professionals recommend that you need to lose weight, most experts say it's best to increase your exercise as the

first step. Often that's all teens need to do for weight control because they're rapidly growing. If eating less is also necessary, it is best to continue eating a variety of foods while cutting down on fats and sugars.

Losing weight quickly on a very-low-calorie diet is never a good idea for anyone. And if you're into sports, you should be aware that it could affect your athletic performance. Under no circumstances should you drink less fluid to lose weight. A steady loss of a pound or so a week until you reach your goal is generally safe, and you're more likely to be able to maintain your weight loss.

Skipping meals to lose weight is another poor idea. You're likely to overeat at the next meal just because you're so hungry. And surveys show that people who skip breakfast or other meals tend to have poorer nutrition than those who don't.

Help for Healthy Eating Is on the Way

Food processors and many grocery stores are preparing now to help nutrition-conscious people make wise food choices. This can be important to teens who sometimes shop not only for themselves, but also for the whole family. While many food labels already voluntarily show nutrition information, new legislation, the Nutrition Labeling and Education Act, enforced by FDA, requires food products to be labeled with the nutritive values they contain per serving size (which will be standardized and realistic). There will be no implied or misleading claims. And all this must be in easy-to-read and easy-to-understand terms.

All food labels must have this information in place by 1993. Look for more information about the new labeling from FDA and USDA.

Thanks to growing scientific knowledge about several diet and health relationships, healthy eating is more socially "in" than ever before. Eating a healthy diet is not difficult with knowledge of a few of the basics, and can help you excel on the playing field, in school, and in your social life. ■

Judith Foulke is a staff writer for FDA Consumer.



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.

■ **Annual reports of FDA advisory committees** that held closed meetings between Oct. 1, 1990, and Sept. 30, 1991, have been filed with the Library of Congress, as required by the Federal Advisory Committee Act. Copies are available from the Dockets Management Branch (HFA-305), FDA, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857; telephone (301) 443-1751. Further information is available from Donna Combs, Committee Management Office (HFA-306), FDA, 5600 Fishers Lane, Rockville, MD 20857; telephone (301) 443-2765. (FR Jan. 7)

■ **A total of 206,392 AIDS cases**, including 133,232 deaths, had been reported in the United States as of Dec. 31, 1991. The 100,000th AIDS case was reported in August 1989. It took just 26 months for the next 100,000 cases to be reported. Of the second 100,000 cases, 7 percent were attributed to heterosexual transmission, a 44 percent increase from the first 100,000. Women accounted for 9 percent of the first 100,000 cases, and for 12 percent of the second 100,000. (*Morbidity and Mortality Weekly Report*, Jan. 17)

■ **Cosmetic companies** may voluntarily file their cosmetic product formulations and raw material compositions with FDA, and the agency has now modified the filing process to encourage participation in the voluntary program. Further information on program changes are available from Mary W. Lipien, Center for Food Safety and Applied Nutrition, 200 C St., S.W., Washington, DC 20204; telephone (202) 245-1707. (FR Jan. 28)

■ **Two commonly prescribed anti-ulcer drugs** may increase the ease with which a person becomes intoxicated after consuming a relatively small amount of alcohol. In a study involving 20 men aged 24 to 46, Tagamet (cimetidine) caused blood alcohol concentrations to be 92 percent higher than if the drug had not been taken. Zantac (ranitidine) caused peak blood alcohol concentrations to be 34 percent higher. (*JAMA* Jan. 1)

■ **The number of tuberculosis cases** reported to the national Centers for Disease Control has been increasing since 1988, after a long decline. In 1990, 25,701 cases were reported, 9.4 percent more than in 1989 and the largest annual increase since 1953. The largest increase in reported cases occurred in the 25- to 44-year age group; this increase may be largely attributable to rising numbers of tuberculosis cases among persons with HIV infection and AIDS. Notable increases also occurred among children. (*MMWR* 1991)

■ **The Advisory Commission on Childhood Vaccines** has filed its annual report with the Library of Congress, where it is available for public inspection in Room 1026, Thomas Jefferson Building, Second St. and Independence Ave., S.E., Washington, DC. Copies of the report may be obtained by contacting Matthew Barry, Vaccine Injury Compensation Program, Bureau of Health Professions, Room 702, 6001 Montrose Road, Rockville, MD 20852; telephone (301) 443-6593. (FR Jan. 31)



■ **PHS technology transfer program** information is available from the National Institutes of Health. The information includes lists of PHS scientists interested in forming collaborations with industry and of government-owned inventions for licensing to interested companies. Inquiries should be directed to Steven Ferguson, Technology Management Specialist, Office of Technology Transfer, National Institutes of Health, Box OTT, Bethesda, MD 20892; telephone (301) 496-0750; facsimile (301) 402-0220. (FR Jan. 3)

■ **Eliminating hepatitis B transmission** in the United States is the objective of recommendations released by the Immunization Practices Advisory Committee, the advisory arm of CDC. The strategy includes making hepatitis B vaccine routine for all infants. (*MMWR* Nov. 22)

■ **Child day-care health** will be the subject of an international conference from June 15 to 17 in Atlanta, sponsored by CDC. Topics for the scientific sessions will include infectious diseases, injuries and hazards, children with special needs and disabilities, and environmental health. More information is available from Lillian Glickman, telephone (404) 633-8610, facsimile (404) 633-8745. (*MMWR* Jan. 3)



Drug Firm Agrees to Correct Naprosyn False Advertising

by Rebecca D. Williams

All good advertisements pitch their products in the best possible light. But when it comes to advertising drugs, FDA won't allow those ads to be colored with deception.

FDA made that point clear recently in an investigation of Syntex Laboratories of Palo Alto, Calif., which had been advertising unapproved uses for an arthritis drug. Last October, FDA and Syntex signed a consent decree requiring the firm to stop the misleading advertising and set up a \$2 million account to pay for a campaign to correct the misinformation.

The action came as part of a larger FDA initiative pushing for accurate labeling in thousands of foods, drugs, and medical devices and was hailed by FDA Commissioner David Kessler, M.D., as a landmark case and "an important and innovative approach to remedying promotional abuses by drug companies."

Syntex Laboratories had advertised that its top-selling product, a prescription arthritis drug called Naprosyn, was "arthroprotective"—that is, it could prevent joint deterioration from arthritis. In fact, no clinical studies have proven that claim. Naprosyn has been approved by FDA only for treating pain, inflammation and fever in people with arthritis and other inflammatory conditions.

Syntex promoted Naprosyn's alleged arthroprotective qualities in brochures, print advertisements, video programs and advertisements, and a seminar set up to look like an impartial medical forum.

FDA first learned of these violations in 1988 through routine checks of the company's advertisements. Whenever drug companies run new ads for print, video or radio, they must also submit copies to FDA before the ads run.

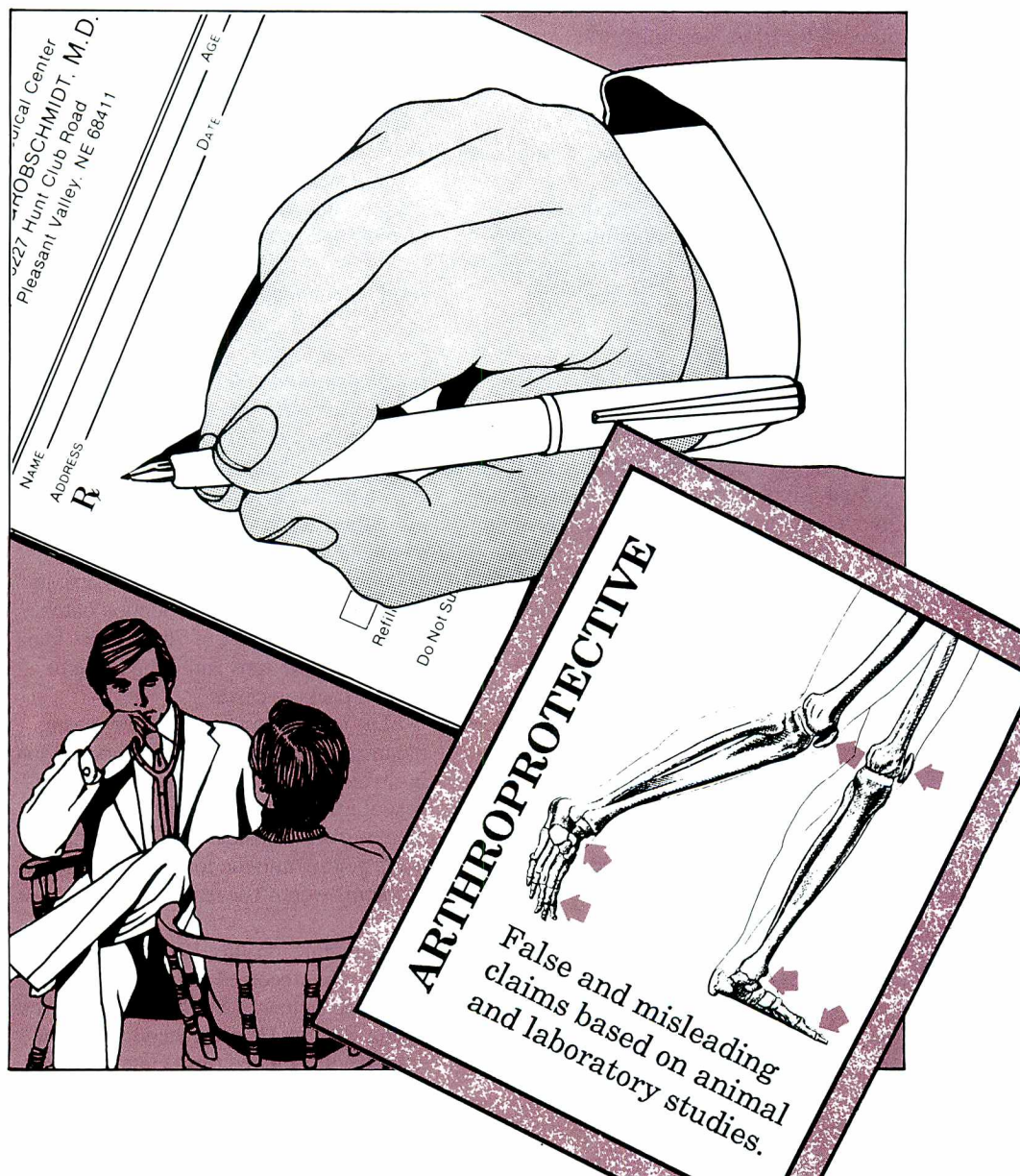
FDA warned Syntex that its advertisements were in violation of the Food, Drug, and Cosmetic Act. Syntex said it would stop using the term "arthroprotective"—yet it continued to suggest in promotional activities and materials that the drug could prevent joint deterioration.

In May 1991, Syntex advertised those claims again in a promotional booklet used by its sales representatives. David Banks, a consumer safety officer with FDA's division of drug advertising and labeling in Rockville, Md., quickly saw that the booklet violated FDA rules.

"They had been told specifically and repeatedly not to make claims of this type," says Banks, "and they went ahead and did it."

Since Syntex had repeatedly ignored FDA's warnings, Banks requested an on-site inspection of the company in Palo Alto, Calif. FDA investigators also took inventory of Naprosyn stock in two Syntex warehouses to prepare for a seizure if necessary.

FDA investigators Paul Peterson and Brian Hasselbalch from the San Francisco district office began their investigation in May 1991. They spent nearly 1,000 hours



over three months interviewing Syntex employees and poring through about 60 boxes of files. The investigators gathered advertisements, material on marketing strategies and training, internal memos, and other information on how Syntex handled its Naprosyn advertising campaigns. At headquarters, the division of drug labeling compliance also reviewed the materials to determine the appropriate charges the agency would cite in its action.

The investigation marked a new approach for FDA, according to Peterson, since advertising cases have rarely involved on-site inspections.

During the investigation, Hasselbalch and Peterson found a number of violations by Syntex Laboratories:

- Syntex based its "arthroprotective" claims on animal and laboratory studies. But those studies did not prove the drug is useful in humans.

- The company had been promoting Naprosyn through a number of activities disguised as impartial scientific presentations, including a 30-minute program on Lifetime Medical Television, a medical symposium in Hawaii, dinner meetings with doctors, articles prepared by medical writers, and lecture slide kits.
- Syntex paid researchers and scientific advisors to speak at these meetings and on television about arthritis treatments without revealing that the speakers were hired by the company or that many were consultants to the firm.

In the consent decree, Syntex admitted no wrongdoing, but agreed to launch an advertising campaign that may go on for as long as a year to correct the previous misinformation about Naprosyn and to reimburse the government \$131,000 for the cost of the investigation.

As part of the arrangement, Syntex must send letters to approximately 250,000 or-

thopedic surgeons, rheumatologists, and general practitioners acknowledging the false and misleading nature of its Naprosyn ads.

The company must also run advertisements on Lifetime Medical Television and in 18 major medical journals correcting the previous advertisements.

If Syntex sponsors any promotional activities in the form of physician education meetings or scientific articles, it must inform the audience if the featured speaker or writer is paid by Syntex.

The company must also clear all Naprosyn advertisements and promotional activities with FDA for the next two years.

FDA did not take Naprosyn off the market because it is still considered safe and effective for treating the symptoms of arthritis.

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

'Recycled' Tuna Seized

A woman in Deer Park, Wis., was cleaning an empty 6.5-ounce can of IGA Chunk Light Tuna, getting it ready for the recycling bin. But when she removed the label, she saw some "recycling" had already occurred. Another label identified the product as 7th Heaven Tuna Cat Treat.

On July 17, 1991, the woman complained about the double labeling to FDA's Minneapolis district office, which has jurisdiction in Wisconsin.

It turned out that many cans of IGA tuna had previous lives. But FDA made sure this one was their last. At the agency's request, U.S. district courts ordered the destruction of 1,100 cases of the product, valued at about \$25,000.

On July 18 and 19, FDA investigators Bill Keer and Greg Abel inspected Gateway Foods, Inc., the IGA distributor in LaCrosse. Gateway also had a warehouse in Superior, Wis., as well as a warehouse in Minneapolis. Examination of the firm's

records showed that two shipments of the suspect tuna had been purchased from Ocean King Foods of New York City.

Upon inspecting some 2,000 cans of the IGA tuna, the investigators noticed that more than 200 had abnormalities, such as swelling, and that there were more than 800 labeling codes amongst the cans, indicating many different production batches. They detected pieces of 7th Heaven Tuna labels on some cans and lying loose in several packing cases.

FDA tested samples collected during the inspection and found decomposed tuna in several cans. Tuna in many other cans was of inferior quality. Some cans were breaking down inside, with the components getting into the food. However, the problems weren't severe enough to cause illness.

Meanwhile, on July 19, FDA's Minneapolis office received a similar complaint from a consumer in St. Paul, Minn. Investigator Sharon Thoma traced this can of tuna to a lot shipped from Gateway in

LaCrosse to the Minneapolis warehouse.

Gateway voluntarily recalled hundreds of its 6.5-ounce IGA tuna from markets in Minnesota and Wisconsin, and the product was embargoed by the two states' Agriculture departments.

Then, a truck driver who became aware of the problem through local press coverage informed the agency about another fishy incident. He reported that on May 3 he picked up a tuna shipment at a firm for delivery to Gateway in LaCrosse. But he had to wait several hours, he said, during which time he saw two people remove 7th Heaven labels from cans and relabel them with IGA labels.

From Ocean King documents, FDA learned the tuna had been imported from Star Kist of New Brunswick, Canada. FDA had monitored the importation. The agency's inspection revealed the Canadian firm had canned the tuna for human consumption in 1985, as shown by the codes on the cans. The Canadian Government had closed the plant for poor manufactur-

ing practices, seizing the 1985 production. Star Kist was allowed to relabel some cans as pet food for sale in the United States.

Foods marketed for pets normally are as wholesome as foods marketed for people, but they often contain animal byproducts not ordinarily eaten by people. In this case, an inferior quality of tuna was used, and analysis found it to be decomposed.

On Nov. 7, 1991, FDA asked the U.S. Attorney's Office in the Western District of Wisconsin in Madison, to file a complaint for seizure and condemnation of 923 cases at Gateway Foods in LaCrosse and 74 cases at Gateway in Superior. The request was based on charges of adulteration from decomposition and concealing inferiority and of misbranding because the product was marketed under the name of another food—IGA Chunk Light Tuna rather than 7th Heaven Tuna Cat Treat. The agency also requested seizure and condemnation of 103 cases of the mis-

branded tuna at Gateway's warehouse in Minneapolis.

U.S. marshals, accompanied by Keer and Abel, seized the cans at LaCrosse on Nov. 12, at Minneapolis on Nov. 26, and at Superior on Dec. 5. No one claimed the product, and FDA had it destroyed.

The agency's investigation hasn't yet determined who is responsible for the relabeling.

—Dixie Farley

Animal Drug Smuggling Cut Off at Source

A four-year investigation by FDA's National Animal Drug Investigation Team led to the conviction of a Canadian man charged with smuggling more than 7 tons of unapproved and misbranded animal drugs into the United States.

Patrick Murphy, 48, of Ontario, was convicted in October, following a two-week jury trial in the U.S. District Court for the District of Nebraska, in Omaha. The jury found him guilty of three counts of introducing misbranded and adulterated drugs into interstate commerce, three counts of smuggling, one count of conspiracy, and one count of introducing mislabeled drugs with intent to defraud and mislead.

On Jan. 8, Judge Lyle Strom sentenced Murphy to six and a half years in prison.

Murphy had been indicted by a federal grand jury in Omaha in 1988—three years before his arrest. The indictment was kept sealed until his capture in May 1991.

Murphy first came under FDA scrutiny in 1986. In January of that year, members of the agency's Animal Drug Investigation Team inspected Custom Feed Blenders—a medicated premix manufacturing plant in Fort Dodge, Iowa—and seized a number of illegal animal drug products that were being stored or processed at the facility.

The plant's former manager, Jeffrey Engel, later pleaded guilty to three felonies involving the distribution of illegal animal drugs. He was fined \$10,000 and

sentenced to six months in prison. (See "Snaring Smugglers of Animal Drugs" in the June 1989 *FDA Consumer*.)

(Animal drugs that have not received FDA approval may lack the proper strength, quality and purity, and may not effectively treat the disease for which they are given. They may also leave toxic residues in the animal's meat, milk or eggs, which might then be consumed by humans.)

Further investigation revealed that the drugs seized at Custom Feed Blenders had been smuggled into the United States from a Canadian business known as Agri-feed Additives. Murphy was Agri-feed's sales manager.

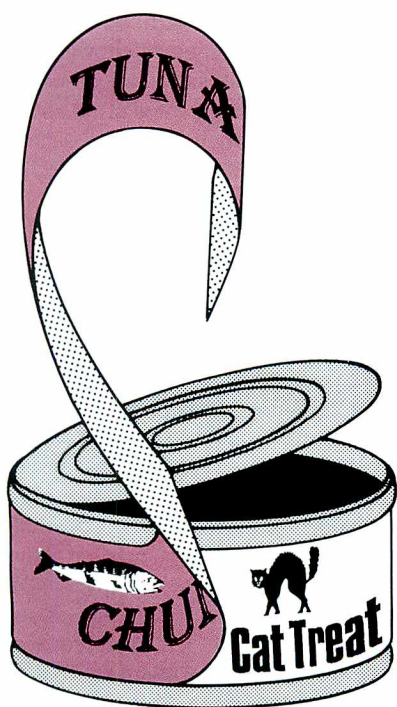
Agri-feed Additives brokered and distributed feed ingredients and other legitimate products to buyers in Canada and the United States. Murphy, however, was chiefly occupied with procuring unapproved animal drugs from overseas and smuggling them into the United States.

In the spring of 1986, Murphy made contact with International Manufacturing and Sales (IMS) in Omaha, Neb., and from May through June smuggled almost 6 tons of unapproved drugs to that company. The drugs were trucked across the U.S.-Canadian border in three separate shipments, hidden behind bales of wood shavings.

In July 1986, acting on a tip from an informant, members of FDA's Animal Drug Investigation Team went to IMS and discovered furazolidone and streptomycin sulfate—unapproved antibiotics—in a storage shed near the plant. Continued investigation showed that Murphy had smuggled the drugs into the United States.

(The owner and two employees of IMS pleaded guilty in 1989 to misdemeanor charges of bringing mislabeled animal drugs into the United States and were fined along with the company. They later testified against Murphy.)

The Animal Drug Investigation Team then focused on cutting off the smuggling



operation at its source. The source was Murphy, but U.S. officials could not arrest him in Canada.

The FDA team first attempted to get Murphy into the United States in 1988 through a sting operation. In July of that year, FDA investigator Jan Longnecker—posing as a businessman—met Murphy at the airport in Omaha. Longnecker offered Murphy \$70,000 for unapproved animal drugs that he was to smuggle into the United States.

Murphy later became suspicious and never delivered the unapproved drugs. However, during the airport meeting, Murphy talked about some of his past smuggling activities. His statements were recorded by a hidden microphone Longnecker was wearing.

The recording became an important piece of evidence when it was played in open court during Murphy's trial.

In the spring of 1991, FDA investigators again decided to try enticing Murphy into the country. This time the bait was not money, but a lucrative job offer.

To accomplish this, the agency enlisted the help of a legitimate animal drug distribution company in the United States. Officials at the firm contacted Murphy and arranged a "job interview" with him for a high-paying position with the company.

Murphy flew to the United States for his interview. Instead of a job offer, however, he was met with an arrest warrant. When he stepped off the plane on May 29, 1991, U.S. marshals arrested him.

—Tom Cramer

Generic Drugs Seized in 6 States

Generic prescription drugs manufactured by a Denver pharmaceutical firm were seized by U.S. marshals in six states after the company refused FDA's request for a voluntary recall of the products.

The seizures, carried out in August, September and October of 1991, involved 62 generic drugs manufactured by Pharmaceutical Basics, Inc. FDA wanted the



products pulled from the market because the firm's applications for drug approval contained false and incomplete information.

FDA has received no reports of adverse reactions from use of the products, which included antibiotics and tranquilizers, as well as drugs for pain, depression, anxiety, hypertension, diabetes, and Parkinson's disease.

Before FDA approves a generic drug for marketing, the manufacturer must submit an abbreviated new drug application to the agency. The application must be supported by data showing that the generic drug has the same therapeutic effects as the original brand-name product.

In December 1990, PBI discovered that some of the supporting data it had submitted to FDA contained false statements,

discrepancies, and omissions. In January 1991, the firm stopped manufacturing and distributing the products involved and informed FDA of the situation.

FDA investigators reviewed PBI's records and, in the summer of 1991, asked the company to recall 62 of its generic prescription drugs from distributors, pharmacies and hospitals. The products involved were being sold under PBI's own name as well as the names of over a dozen private and "store brand" labels.

FDA determined that a class II recall was necessary, since the bioequivalence of the 62 products was in question; that is, it was not certain that the products produced the same therapeutic effects as their brand-name counterparts.

In a class II recall, the product in question is regarded as having the capacity to cause temporary or reversible adverse health effects.

PBI officials argued, however, that a class II recall was not necessary and that a class III recall, in which the product is believed not likely to cause adverse health consequences, would be more appropriate.

Because of its disagreement with FDA, PBI took no immediate action to recall the 62 products. After repeated efforts by FDA failed to convince PBI that a class II recall was warranted, the agency decided to request seizure of the products.

In the fall of 1991, selected PBI generic drug products, valued at roughly \$20,000, were seized at distributors and wholesalers in New Jersey, Pennsylvania, Utah, New York, Louisiana, and Florida. The seizures were based on a charge that the product labeling was false or misleading since it failed to reveal that data contained in abbreviated new drug applications for the products was false or fraudulent.

In November 1991, PBI began voluntarily recalling the products, sending about 60,000 recall letters to pharmacies and direct distributors.

FDA has notified PBI that approval of the products is being withdrawn.

—Tom Cramer

Summaries of Court Actions



SEIZURE ACTIONS

Food/Poisonous and Deleterious Substances

PRODUCT: **Fish, whole, frozen**, at Wilmington, C. Dist. Calif.; Civil No. 90-3381-DT(Gx).

CHARGED 6-28-90: When shipped from Ruskin, Fla., the article labeled "J.O. Guthrie Fish Co. Inc. . . . Ruskin, Florida . . . LG Mullet" contained a poisonous or deleterious substance—402(a)(1).
DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65881; S. No. 90-615-855; S.J. No. 1)

Food/Decomposition, Spoilage, Insanitary Handling

PRODUCT: **Angelica, ginseng, and other food stocks**, at Oakland, N. Dist. Calif.; Civil No. C90-3369 SAW.

CHARGED 11-28-90: While held by May Hing Import & Export, Oakland, Calif., the articles had been held under insanitary conditions—402(a)(4).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65976; S. No. 90-540-617; S.J. No. 2)

PRODUCT: **Rice, beans, lentils, and other food stocks**, at Kent, W. Dist. Wash.; Civil No. 90-1361 WD.

CHARGED 9-28-90: While held by Mills Bros. International, Inc., Kent, Wash., the articles had been held under insanitary conditions—402(a)(4).

DISPOSITION: Consent decree authorized release of the articles to the dealer for salvaging provided the dealer would stop preparing, packing, holding, or shipping foods if within 18 months FDA advised that the dealer's facility again rendered foods adulterated. (F.D.C. No. 65948; S. No. 90-534-825 et al.; S.J. No. 3)

PRODUCT: **Tomato paste, canned**, at Wood-Ridge, Dist. N.J.; Civil No. 90-4620 (AJL)

CHARGED 11-21-90: While held for sale, the article was contained in swollen and leaking cans, and one lot of the article contained decomposed tomato material—402(a)(3).

DISPOSITION: Consent—authorized release to Bedemco Import & Export Inc., White Plains, N.Y., for export to the original foreign supplier. (F.D.C. No. 65954; S. No. 90-509-815; S.J. No. 4)

PRODUCT: **Wheat, flour, and other food stocks**, at Chicago, N. Dist. Ill.; Civil No. 91-C-1976.

CHARGED 4-3-91: While held by Ziyad Brothers (Div. of Syrian Bakery & Grocery Co., Inc.), Chicago, Ill., the articles had been prepared, packed and held under insanitary conditions—402(a)(4).
DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 66080; S. No. 91-610-417 et al.; S.J. No. 5)

Drugs/Human Use

PRODUCT: **Beta-2 isoetharine HCl inhalant, MicroNefrin Mist dl-epinephrine HCl inhalant, Adreno Mist epinephrine HCl inhalant, and components**, at Mukilteo, W. Dist. Wash.; Civil No. 91-721.

CHARGED 5-24-91: While held by B&C Laboratories, Mukilteo, Wash., who was manufacturing the finished articles using interstate components, the circumstances used for the articles' manufacturing, processing, packing, and holding failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 66054; S. No. 91-536-046 et al.; S.J. No. 6)

PRODUCT: **Oxygen, in cylinders and in bulk**, at Nashville, M. Dist. Tenn.; Civil No. 3-90-0755.

CHARGED 8-24-90: While held by Volunteer Welding Supply, Inc., Nashville, Tenn., the circumstances used for the article's manufacture, processing, packing, and holding failed to conform with current good manufacturing practice—501(a)(2)(B).

DISPOSITION: All of the articles were claimed by the dealer except for the D-Size cylinders marked "Metro-owned," which were claimed by the local government. Subsequently, a consent decree of condemnation authorized release of the cylinders claimed by the local government after such cylinders had been drained of their contents. The consent decree also authorized the release to the dealer of the remainder of the seized property for bringing into compliance. (F.D.C. No. 65903; S. No. 90-574-699 et al.; S.J. No. 7)

PRODUCT: **Oxygen, U.S.P., in cylinders**, at Cincinnati, S. Dist. Ohio; Civil No. C-1-91-401.

CHARGED 6-18-91: While held by Bernens Medical (Bernens Convalescent Pharmacy Inc.), Cincinnati, Ohio, the circumstances used for the article's packaging and holding failed to conform with current good manufacturing practice—501(a)(2)(B); and the label of the article lacked a quantity of contents statement—502(b)(2).

DISPOSITION: Consent—authorized release to the dealer for salvaging. In addition, the claimant agreed not to fill or pack gas for medical use unless and until prescribed good manufacturing practices were established, as well as agreeing to a number of other conditions. (F.D.C. No. 66091; S. No. 91-620-035; S.J. No. 8)

PRODUCT: **Oxygen, U.S.P., in various size cylinders**, at Tullahoma, E. Dist. Tenn.; Civil No. 4-90-174.

CHARGED 8-30-90: While held by Volunteer Welding Supply, Inc., Tullahoma, Tenn., the circumstances used for the manufacture, processing, packing, and holding of the articles failed to conform with current good manufacturing practice—501(a)(2)(B); the articles' labeling was false and misleading due to failure to bear the correct name and place of business of the manufacturer—502(a); the articles' labels lacked an accurate quantity of contents statement—502(b)(2); the articles' labeling lacked adequate directions for use—502(f)(1); and their labeling failed to indicate, as required by the U.S.P., whether or not the articles had been produced by the air-liquefaction process—502(g).

DISPOSITION: Consent—authorized release to the dealer for salvaging. (F.D.C. No. 65906; S. No. 90-574-699 et al.; S.J. No. 9)

Medical Devices

PRODUCT: **Forceps and scissors**, at Addison, N. Dist. Ill.; Civil No. 91 C 4129.

CHARGED 7-3-91: The quality of the articles, which were labeled (bag) "Magnum Instruments, Inc. Kelly Forcep" and (forcep) "Stainless Pakistan" or "SS Pakistan" and (carton) "Iris Scissors 4 1/2" STR/CUR" and (scissor) "S.S. Pakistan", fell below their purported quality, since the articles, represented as stainless steel surgical instruments, lacked enough chromium to ensure adequate performance—501(c); and the articles' labeling contained false and misleading claims suggesting that the devices contained a certain amount of chromium, when in fact the articles did not contain such amount of chromium—502(a).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 66211; S. Nos. 91-610-413/4; S.J. No. 10)

PRODUCT: **Gloves, latex and PVC vinyl, for examination**, at Baltimore, Dist. Md.; Civil No. HM-91-883.

CHARGED 3-28-91: The quality of the articles labeled (case) "Non-Sterile Latex Examination Gloves . . . Made In Malaysia" and (case) "Gloves Vinyl Le Havre" and (carton) "PVC Vinyl Gloves . . . Made In China" fell below the articles' purported quality due to excessive holes—501(c); and the articles lacked labels containing the name and place of business of the manufacturer, packer or distributor—502(b)(1).

DISPOSITION: Default—ordered destroyed. (F.D.C. No. 66057; S. No. 91-549-796 et al.; S.J. No. 11)

PRODUCT: **Intraocular lenses**, two seizure actions, at St. Petersburg and Tarpon Springs, M. Dist. Fla.; Civil Nos. 87-1556-CIV-T-17A & 87-1555-CIV-T-15C.

CHARGED 10-20-87 and (Tarpon Springs seizure amended) 10-21-87: the quality of the articles (which were manufactured by Rophae Lens Co., Inc., St. Petersburg, Fla., using plastic from Blackpool, England, and which were labeled [some boxes] "Rophae Lens Co. Inc. . . . St. Petersburg, FL. . . Federal Law (USA) Restricts . . . To Sale By Or On The Order Of A Physician . . . Investigational Device", and [one lot] "Manufactured For Trans Global Enterprises") fell below their purported quality since the lenses did not conform to their represented strength—501(c); the 1,311-lens lot at Tarpon Springs and a 10,884-lens lot at St. Petersburg were devices for which a 360j(g)(2) exemption had been granted but for which the manufacturer had failed to comply with regulations—501(i); a 2,535-lens lot and a 105-lens lot at St. Petersburg were class III devices lacking the required effective approved Premarket Device Application, and had been manufactured, packed and stored under circumstances not in conformity with regulations—501(f)(1)(C) and 501(h).

DISPOSITION: The articles were claimed by the dealer, who denied the charges and moved to dismiss. The government served answers to standard interrogatories. The actions were consolidated, and ultimately, a consent decree ordered the devices destroyed. (F.D.C. Nos. 65278/9; S. No. 87-447-533 et al.; S.J. No. 12)

INJUNCTION ACTIONS

DEFENDANTS: **The Homestyle Bakery, Inc.**, and **Angeline M. Kaitschuck**, president, and **Daniel M. Kaitschuck**, general manager, Redmond, W. Dist. Wash.; Civil No. C89-389Z.

CHARGED 3-17-89 in a complaint for injunction: That the defendants prepared, packed and held interstate flour and other bakery-product ingredients and shipped in interstate commerce finished bakery products; that the flour and bread at the defendants' bakery had been held, prepared or packed under insanitary conditions—402(a)(4); that FDA inspections showed a number of specified insanitary conditions; and that the defendants were well-aware that their manner of operation of the bakery violated the law.

DISPOSITION: A consent decree of permanent injunction enjoined the complained-of violations. The decree also enjoined the defendants from receiving, preparing, packing, and holding interstate foods or shipping in interstate commerce their bakery products unless and until a number of specified conditions had been met, including the following: the elimination of insects from the bakery, the thorough cleaning of the bakery and the bakery equipment; the establishment of a sanitation control program; the submission of a report to FDA by an expert selected by the defendant concerning the defendants' compliance; and all foods on hand were examined, necessary analyses were made, and all contaminated food was destroyed or otherwise brought into compliance.

Subsequently, FDA inspection showed that the defendants' bakery was in compliance; and the defendants were authorized to resume operations. (Inj. No. 1209; S. No. 89-502-701 et al.; S.J. No. 13)

DEFENDANT: **ICN Pharmaceuticals, Inc.**, Costa Mesa, C. Dist. Calif.; Civil No. 91-28535 RMT (JR).

CHARGED 5-24-91 in a complaint for injunction: That the defendant marketed, promoted and sold Virazole (ribavirin) as a treatment for AIDS and related diseases, although FDA had approved the promotion of Virazole (ribavirin) only for the treatment of respiratory syncytial virus; and that the defendant violated the law by shipping in interstate commerce such drug, an unapproved new drug when intended for use in the treatment of AIDS—505(a).

DISPOSITION: The parties entered into a consent decree of injunction against the defendant, with the defendant not admitting or denying the charges and the government agreeing that nothing was to be construed as an admission against the defendant. The defendant, Viratek, SPI, and each of the affiliates, branches, divisions, groups, operations, units, plants, and joint ventures were restrained and enjoined from a number of specified acts, including the following: (A) trafficking in any new drug for any disease unless and until (i) an approved NDA was in effect authorizing such action for that particular disease, (ii) an Investigational NDA was in effect for that particular disease, or (iii) a designated FDA official received and granted a written request for permission for action concerning that particular disease and (B) promoting, selling, soliciting, advertising, or marketing any new drug as being safe or effective for any disease unless and until the above restrictions and the restrictions of the regulation on drug advertising were satisfied. Other provisions of the decree of injunction authorized the disclosure of required information and required notice by the defendants of such disclosure, required asking the intended use for any new drug by a physician prior to sale of the drug, required the appointment of a regulatory officer to implement regulatory procedures and provide advice to ICN, SPI and Viratek, and required the dissolution of the decree within 36 months, unless the government instituted an action

alleging violations of the decree.

The decree also ordered ICN to pay \$400,000 for damages caused to FDA for conduct alleged in the complaint and to pay FDA \$200,000 as reimbursement for costs incurred in the investigation of the matter. (F.D.C. No. 65010; S. No. 87-374-800; S.J. No. 14)

DEFENDANTS: Stewart Sandwiches, Inc., and Theodore J. Broecker, president, and **Donald R. Beard**, senior vice president, at Norfolk, E. Dist. Va.; Civil No. 90-1344-N.

CHARGED 5-31-90 in a complaint for injunction: That the defendants prepared, held for sale, and shipped in interstate commerce sandwiches that contained a poisonous and deleterious substance (*Listeria monocytogenes*), which might render such food injurious to health—402(a)(1). FDA had been notified that 10 sandwiches manufactured at the defendants' facility at Norfolk, Va., had been determined to be contaminated with *Listeria monocytogenes*, and FDA learned that private laboratory tests, known to the defendants, had revealed the presence of *Listeria monocytogenes* in a swab on a meat slicer in the defendants' cooked food section. The government believed that unless restrained by the court, the defendants would continue to violate the law.

DISPOSITION: Upon agreement by the defendants to undertake additional sanitizing and testing measures, the hearing date for the government's motion for a preliminary injunction was postponed. Subsequently, a consent decree of permanent injunction enjoined the complained-of violations. In addition, the decree acknowledged the following: that the defendant firm had hired outside expert consultants to revise its food operations; that a qualified expert had certified to FDA that a revised sanitation control program had been established to prevent contamination; and that, based on such representations, FDA had notified the defendants that the food on hand had been or would be tested for bacterial contamination, necessary examination and additional analyses were to be made, and all contaminated food would be destroyed. (Inj. No. 1233; S. No. 89-550161/162 et al.; S.J. No. 15)

DEFENDANTS: Sudreca Surgical Dressings, Inc. (t/a PharmaMedic, Inc.), and Francisco J. Martinez, president, Charlotte, W. Dist. N.C.; Civil No. C-C-88-0068-M.

CHARGED 2-10-88 in a complaint for injunction: that the defendants manufactured, packed, labeled, and distributed in interstate commerce various medical devices, including sterile gauze (used in surgical and other medical procedures) and sterile surgical scrub brushes; that the purity or quality of some of the devices fell below their purported purity or quality because the sealed packages used to maintain sterility of the devices contained defects such as openings in the seams—501(c); that the circumstances used for the manufacture, packing, storage, or installation of medical devices labeled as sterile failed to conform to current good manufacturing practice regulations—502(h); and that the defendants were well-aware that their activities were in violation of the law.

DISPOSITION: A consent decree of permanent injunction enjoined the complained-of violations. The decree also enjoined specified acts concerning any medical device labeled as sterile, including the interstate shipment or the manufacturing, packing or labeling of any such device at the defendants' facility unless and until a number of

specified conditions were met, including the following: inspecting the packaging machines to ensure package integrity for sterile devices, calibration testing of the instruments measuring package sealing operations, establishing procedures for in-process and finished product seal-integrity testing, implementing controls to prevent labeling mix-ups, reporting by a qualified expert to FDA concerning actions taken by the defendants to ensure conformity with good manufacturing practice and the above conditions, and examining all devices on hand and destroying or otherwise bringing into compliance all of such devices. (Inj. No. 1182; S. No. 87-505-225 et al.; S.J. No. 16)

DEFENDANTS: Swanson Health Products, Inc., Jay L. Swanson, president, and **Leland A. Swanson**, vice president, Fargo, Dist. N.D.; Civil No. A3-91-78.

CHARGED 5-7-91 in a complaint for injunction: That the defendants, at their Fargo, N.D., facility repacked, labeled, distributed, and promoted a number of interstate products made by various manufacturers and shipped such products in interstate commerce; that the defendants' promotional materials, repeatedly, made claims that such products were useful in the prevention and treatment of numerous diseases and conditions, including immune system deficiencies, heart conditions, stress, cholesterol, circulatory function, arterial function, arthritis, aging, severe burns, damaged nerves, cataracts, digestive disorders, weight loss, yeast infections, travelers disease, acne, and gum disease; that such products (i.e., Acidophilus, Co-Enzyme Q-10, Cardio Life, Gymerea Sylvestre, Heart Food, Willard Water Concentrate, and Cata Rx) were drugs intended for use in the cure, mitigation, treatment, and prevention of disease in man and were "new drugs" without effective approved New Drug Applications, since they were not generally recognized as being safe and effective for their labeled indications—505(a); and that such products' labeling lacked adequate directions for the articles' intended uses—502(f)(1). The complaint also alleged that the defendants had been notified and were aware that their activities violated the law; and, despite warnings from FDA, the defendants continued to promote and market such violative drugs. The government prayed that the court enjoin such violations.

DISPOSITION: The defendants moved to dismiss the complaint on the ground that the products were foods and not drugs. After a hearing on the defendants' motion to dismiss and on the government's motion for a preliminary injunction, the court took the defendants' motion under advisement and withheld a decision on the government's motion until a later date. Ultimately, the parties entered into a consent decree of permanent injunction, and the court denied the defendants' motion to dismiss, agreeing that the overriding issue in the case was whether, because of promotional claims, the seven cited health food products had become subject to regulation as drugs and concluding that the government might be able to prove its claims. The consent decree of permanent injunction enjoined the defendants from the following acts: packing, repacking, labeling, holding for sale, or shipping in interstate commerce Cardio-Life, Heart Food, Cata Rx, and Gymerea; packaging, repacking, labeling, holding for sale, or shipping in interstate commerce Acidophilus, Co-Enzyme Q-10, or Willard Water unless the product was neither adulterated nor misbranded; promoting, labeling, representing, or suggesting

either orally or in writing that any of the named products, or any equivalent product, were safe and effective in the cure, mitigation, treatment, or prevention of any disease, unless and until an approved New Drug Application was in effect or FDA advised the defendants that such representations did not misbrand the product. (Inj. No. 1245; S. No. 90-622-130 et al.; S.J. No. 17)

DEFENDANTS: Tally-Ann Baking Co., Inc., and Domenic Mastrangelo, president, Philadelphia, E. Dist. Pa.; Civil No. 90-6346.

CHARGED 10-2-90 in a complaint for injunction: That the defendants manufactured, processed, packed, held for sale, and shipped in interstate commerce foods such as bread, rolls, and bread crumbs that had been prepared, packed and held under insanitary conditions—402(a)(4). In addition, bread manufactured at the defendants' bakery contained insect fragments—402(a)(3). FDA inspections established a history of sanitation control problems, and the defendants were well aware that their operations violated the law.

DISPOSITION OF INJUNCTION: A consent decree of permanent injunction enjoined the complained-of violations.

CHARGED on or about 10-19-90 in a civil contempt petition: That, based upon assurances made on Oct. 16, 1990, by the individual defendant, his sanitation expert, and his attorney that the defendants were in compliance with the terms of the consent decree, and, at the defendants' request, an FDA inspection of the bakery was performed on the same day; that that inspection revealed that extensive insanitary conditions still existed at the bakery; and that the defendants continued to operate their bakery under insanitary conditions in violation of the consent decree of permanent injunction.

DISPOSITION OF CIVIL CONTEMPT: Upon consideration of the government's petition, the court found the defendants in civil contempt. Accordingly, the court ordered the following: all operations in the defendants' bakery, both manufacturing and shipping (with the exception of resale bread products manufactured by other bakeries), should promptly cease unless and until (a) the defendants provided a letter of compliance from their outside sanitation expert and (b) FDA inspected and notified the defendants that they were in compliance with the consent decree of injunction. The court also ordered the following: a \$10,000 per day fine for each day the bakery remained in operation in violation of the civil contempt order; an FDA follow-up inspection within the next six months; and the payment by the defendants of \$798 for the costs of the FDA inspections already conducted. A subsequent FDA inspection revealed that the defendants were in compliance with the law. (Inj. No. 1229; S. No. 89-569-093; S.J. No. 18)

MISCELLANEOUS ACTIONS

SUBJECT: Intraocular lenses, relocation of lens manufacturing facility, and FDA requirement of a Pre-Market Approval (PMA) supplement, Dist. Md.; Civil No. WN 90-2794.

CHARGED 10-26-90 by Ioptex Research, Inc., Irwindale, Calif., against the United States of America, HHS Secretary Louis W. Sullivan, M.D., and the Food and Drug Administration, Rockville, Md., in a complaint for declaratory judgment and injunction: That Ioptex had obtained (from FDA) a Pre-Market Approval (PMA) for

its Model 304-01 intraocular lens; that such PMA included a standard list of conditions of approval, including one condition requiring the submission of a PMA supplement before making any change affecting the safety or effectiveness of the lens; that Ioptex had moved its manufacturing facility a distance of four blocks—from Azusa, Calif., to its new Irwindale, Calif., facility; that Ioptex, before moving had sought guidance from FDA and had notified FDA that it would be moving; that, based on Ioptex's injuries, Ioptex understood that no separate PMA supplement was necessary because the same equipment, manufacturing processes, and quality control procedures would be used at the new Azusa facility; that the lenses manufactured at the new facility caused approximately the same number of adverse reactions as those made at Ioptex's Irwindale facility; that on Aug. 17, 1990, FDA sent a letter to the Health Industry Manufacturer's Association asking for comments on a draft "PMA Supplements Concepts" document that identified changes and modifications that in all cases required a PMA supplement and included a change in facility as a "clarification" of FDA supplement requirements; that, thereafter, FDA attempted to enforce this unadopted amendment against Ioptex and advised Ioptex, in a letter, that lenses manufactured at Irwindale were considered "adulterated" simply because of the failure to file a PMA supplement; that FDA inspectors had made five inspectional observations at FDA's inspection of the Irwindale plant all of which were attributable to human error or vendor error, none of which were related to the change in facility, and each of which had been completely and adequately responded to by Ioptex; that on Oct. 2, 1990, Ioptex had submitted a PMA supplement detailing its change in facilities; and that Ioptex had exhausted its administrative remedies, and had no adequate remedy at law, and therefore prayed for a declaratory judgment and injunction.

DISPOSITION: The court denied Ioptex's request for a temporary restraining order upon the government's offer not to take any action against Ioptex, which would have the effect of putting them out of business before the time set for the hearing on Ioptex's motion for a preliminary injunction.

Subsequently, upon the consent of the parties, Ioptex dismissed its complaint, and a consent decree of permanent injunction against Ioptex, Garry Weaver, operations vice president, Terrace H. Gregg, regulation affairs vice president, and Ioptex directors, officers and agents was entered. It was decreed as follows: (I) that a new PMA approval or PMA supplement would be submitted and approved before making a change affecting the safety or effectiveness of medical devices, including the use of a different facility; (II) Ioptex did not have approval of a PMA supplement for its intraocular lenses, which were subject to PMA 860059 and which were manufactured at Irwindale, Calif.; (III) when such devices were shipped, they were in violation of 501(f). Accordingly, Ioptex and its officers were perpetually enjoined from shipping such devices from the Irwindale facility unless or until FDA had approved a PMA supplement for such devices at that facility. Ioptex was to recall all such devices shipped in interstate commerce, and all of the devices on hand were not to be shipped in interstate commerce unless or until FDA had approved such a PMA supplement. (Misc. No. 934; S.J. No. 19)

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