The Pill: 30 Years of Safety Concerns
When the birth control pill was first introduced in 1960, the response of many Americans was like love at first sight. But soon, safety concerns took the blush off the romance, leading to reformulation and the safer lower doses now available.

Modern Diagnostics Help Detect Cancer Early
Many tests to find cancer early have improved chances that the disease can be treated in time to save lives. But to take advantage of this technology, people sometimes first need to overcome their fear of the disease.

Genetic Screening: Fetal Signposts on a Journey of Discovery
Like explorers of old, scientists are discovering the unexpected as they undertake to map all human genes. On this voyage, identification of genes for inherited disorders are leading to ways to prevent or treat these conditions in babies.

Fat Substitutes: A Taste of the Future?
"Ice cream" without fat is one promise held out by a number of fat substitutes newly approved by FDA or under development. But questions about consumer acceptance and long-term dietary advantage make the ultimate fate of some "unfats" unclear.

Getting Information from FDA
Wending your way through the bureaucracy on a quest for information can be bewildering. With a little preparation, though, you can know what information is available from FDA, how to get it—and when you'd do better asking someone else.

How to Take Your Medicine: Beta Blocker Drugs
One of the most common therapies for high blood pressure is discussed in a continuation of the series on proper drug use.

Inside Front Cover Photo: A technician views a screen providing a three-dimensional image of the brain with the help of computer technology as the patient lies in unit where brain is scanned. Computed axial tomography (CAT) is one of the diagnostic techniques improving the outlook for some cancer patients discussed in the article that begins on page 12.
Teenagers Blase About Steroid Use

American teenagers are turning a deaf ear to the dangers of anabolic steroids and are using the drugs in increasing numbers to build athletic prowess and improve their appearances, a 1990 Department of Health and Human Services report concludes.

At the same time, the report says, parents, coaches and peers are indirectly contributing to the problem by failing to discourage non-medical illegal use of steroids by adolescents.

In a survey of 72 current and former steroid users who began their use before age 19, HHS found that most were aware of health problems associated with steroid use (see Chart 1).

Yet many current users surveyed said they discounted warnings about these possibilities (see Chart 2).

Almost all of the respondents, who had been on steroids for an average of three years, reported that use among senior high school students was up. None said it had decreased. And almost half said use is increasing among junior high students, as well.

The major reason teenagers use steroids, the survey found, is their desire to do well in sports, whether traditional athletics or bodybuilding. Ninety-six percent of respondents acknowledged being in a competitive sport or weight-training program at the time they began using steroids. Nearly two-thirds cited desire to improve appearance as another major reason.

Steroid users appear to be getting little discouragement from their friends, family and coaches, the survey found. For example, 93 percent of current users agreed with the statement, “Overall, people like the effects steroids have had on me.” Over half said, “My parents probably know that I use steroids.” And of the 41 users who had coaches, 61 percent disagreed with the statement, “My coaches really believe that steroid use is a bad idea.”

HHS is sponsoring the Interagency Task Force on Anabolic Steroids, which will identify new approaches to dealing with the problem. In addition, FDA is redou-
bling its educational campaign, which targets high school principals, school superintendents, and high school and college coaches, physical education instructors, and others.

(For more information on steroid abuse, see “Athletes and Steroids: Playing a Deadly Game” in the November 1987 FDA Consumer.)

4-Year-Old Infused After Human Gene Therapy Approval

Four hours after FDA approved the first human gene therapy study last Sept. 14, scientists at the National Institutes of Health began infusing a 4-year-old girl with altered white blood cells that may save her life.

The patient suffers from ADA deficiency, a rare genetic disease in which the gene responsible for producing the enzyme adenosine deaminase (ADA) is defective. The ADA enzyme helps remove toxic byproducts in cells. Without it, waste accumulates, damaging white cells called T lymphocytes, which are critical components of the immune system. The resultant immune deficiency leaves patients with little resistance to infections and, without treatment, they often die within the first years of life.

ADA deficiency occurs in fewer than 1 in every 100,000 births worldwide. Fewer than 10 children with the disease are born in the United States each year.

Previous treatment for ADA deficiency consisted of bone marrow transplants. However, matching donors cannot be found for most children with the disease, and the chance of success with partially matched bone marrow is about 50 percent. In March 1990, FDA licensed a new drug, PEG-ADA, which contains ADA enzyme from cows, to treat the disease. Weekly injections of the drug raise blood ADA enzyme levels and decrease the severity of infections in some patients, but this therapy has not fully restored the immune systems of most patients. (See “Rare Disease Treatments: ‘Orphans’ Saving Lives” in the November 1990 FDA Consumer.)

The new human gene therapy study will continue for two to three years to evaluate the effect on immune function in patients given the gene, and to evaluate survival of the genetically corrected T cells and the length of time the inserted gene produces the missing enzyme.

FDA has approved the study for up to 10 patients. Two or three patients will be treated in the first year of the study. To be admitted to a study, patients must:

- have documented ADA deficiency with low numbers and poor functioning of T cells
- have been on PEG-ADA therapy for more than nine months with only poor to moderate results
- not be a candidate for bone marrow transplantation.

Patients given the new gene therapy will continue to receive PEG-ADA while in the study.

Approval for this first human gene therapy study was granted only after extensive review by numerous FDA and NIH committees of the safety concerns and the scientific, ethical and legal issues. Final approval came from the acting FDA commissioner and the acting NIH director.

Treatment IND for Product to Help Bone Marrow Recipients

Wider use of an experimental, genetically engineered version of a human protein may help save bone marrow recipients from life-threatening infections when transplants fail or are slow to “take.”

On Sept. 24, FDA authorized the expanded use of granulocyte macrophage-colony stimulating factor, or GM-CSF, under its treatment IND (investigational new drug) program, which allows desperately ill patients to use promising experimental therapies before the complete review needed for final approval.

Patients who are to receive a transplant of donor marrow or their own marrow, removed and stored, must first undergo intensive chemotherapy to help prevent rejection of the graft. This is sometimes combined with total body irradiation.

Once a graft “takes,” normally within 20 to 30 days, it begins producing disease-fighting neutrophils, a type of white blood cell. However, up to 20 percent of bone marrow transplant patients have engraftment delay beyond 20 to 30 days or outright graft failure. Levels of white blood cells become dangerously low, leaving these patients highly susceptible to bacterial and fungal infections. Indeed, despite treatment with antibiotics and other supportive measures, many die from overwhelming infection.

GM-CSF is the first product to promote development of specific bone marrow cells that, in turn, produce circulating neutrophils. (See “Genetic Engineering Yields Disease-Fighting Hormones” in the July-August 1990 FDA Consumer.) Administered through a vein, GM-CSF
may cause relatively mild side effects, including fever, nausea, swelling, and skin rash.

Researchers at more than 25 medical centers tested GM-CSF in about 100 patients who had graft delay or failure. Most had a rise in neutrophils within two weeks, and survival rates appear to be higher in the drug-treated groups.

Upon request, the manufacturer, Immunex Corporation of Seattle, Wash., will provide GM-CSF at no cost to physicians performing bone marrow transplants. The firm's telephone number is (206) 587-0430.

Heart Pump Implant Patients Can Live at 'Family House'

For the first time, heart transplant candidates temporarily implanted with the Novacor heart-pump device can wait in a home-like environment rather than a hospital until their donor hearts are available. The Novacor is a left ventricular heart assist system (LVAS), the first LVAS approved by FDA for use in patients in out-of-hospital placement.

The University of Pittsburgh Medical Center announced last August that selected patients at the center's Presbyterian University Hospital will live nearby at Family House, a nonprofit home for these patients and families. Patients are accepted on the basis of recovery from the implant surgery: They may not be undergoing therapy for complications and must be able to walk and take care of their daily needs.

Family House three-room suites accommodate a Novacor patient's specific needs. For instance, the patient bedroom contains a bath designed for someone who is disabled, a sitting room provides added privacy when medical staff visit, and the third room houses a bioengineer accredited in the technology used for the Novacor for round-the-clock attendance. The building also is equipped with an emergency generator.

The Novacor is implanted in the pelvic area beneath the abdominal muscles to assist the heart's main pumping chamber, the left ventricle. Time on the device has ranged from 2 to 144 days, averaging 52 days. Since the program began in July 1987, 20 people have been implanted. The first patient moved into Family House Aug. 22, 1990. The Novacor LVAS is manufactured by Novacor of Oakland, Calif., a division of Baxter Healthcare Corp.

(For more information about products used to replace malfunctioning parts of the heart and blood vessels, see "Cardiovascular Spare Parts" in the May 1990 FDA Consumer.)

FDA Urges Firmer Egg-Handling Standards

To curb outbreaks of salmonellosis caused by contaminated eggs, FDA last September mailed notices urging more stringent egg-handling standards to the food industry and state and local health and food protection agencies.

Scientists believe the Salmonella enteritidis organism can sometimes be transmitted during ovulation from the hen to the inside of the egg before the shell forms. (See "Salmonella Enteritidis: From the Chicken to the Egg," in the April 1990 FDA Consumer.) For this reason, FDA recommends redesignating intact shell eggs as a "potentially hazardous food," a technical term that does not imply a food is inherently unhealthful but, rather, identifies foods requiring proper refrigeration, cooking and handling.

Other foods so designated include most meats, poultry, fish, dairy products, and cooked vegetables. Generally, state and local regulatory agencies can establish refrigeration and cooking requirements only for products with this designation.

FDA recommends that retailers refrigerate raw shell eggs at 45 degrees Fahrenheit or less until sold or used. Recommendations aimed particularly at restaurants and other food service operations include:

- Do not use raw eggs in uncooked, ready-to-eat menu items.
- Substitute pasteurized eggs and egg products for shell eggs in recipes that traditionally call for raw eggs, such as Caesar salad or uncooked hollandaise sauce.
- Avoid mixing and pooling raw eggs in a container (for scrambled eggs, omelets, and French toast, for example) except for immediate use.

As a rule of thumb, FDA advises scrambling eggs until firm throughout and cooking whole eggs until the white is completely firm and the yolk at least begins to thicken. FDA, Cornell University, the American Egg Board, and the Egg Nutrition Center recommend the following cooking times:

- Scrambled—1 minute at medium stove-top setting (250 F for electric frying pans)
- Sunny side—7 minutes at 250 F, or cook covered 4 minutes at 250 F
- Fried, over easy—3 minutes at medium setting (250 F)
on one side, then turn and fry 2 minutes on the other side
• Poached—5 minutes in boiling water
• Boiled—7 minutes in boiling water

Drug Claims on Toothpaste, Mouthwash

Manufacturers of toothpastes and mouthwashes who claim that their products prevent dental plaque and related conditions have been asked to submit scientific data to support such statements to FDA.

If the agency—with the support of a panel of non-government, oral health-care experts—finds that scientific data fail to support the claims, FDA would require the manufacturer to drop the unsupported claims.

Dental plaque is defined as a thin film of food debris and other materials that forms on the teeth, providing a medium for bacterial growth. Studies show it is directly linked to the development of cavities and to gingivitis, a painful inflammation of the gums.

According to manufacturers, toothpastes contain abrasives that provide mechanical action to remove plaque.

Mouthwash manufacturers claim that their products remove plaque with antimicrobial or chemical agents.

Manufacturers have included such statements on their labels as “for the reduction or prevention of plaque, tartar, calculus, film, sticky deposits, bacterial build-up, and gingivitis.” Other labeling claims that the dental products are effective in the “reduction, prevention or treatment of gum disease, inflamed gums, swollen gums, bleeding gums, pyorrhea, trench mouth, periodontal disease or tooth-destroying acids.”

According to the Federal Food, Drug, and Cosmetic Act, such statements are drug claims because they deal with treating or preventing disease and because they affect the structure or function of the body.

(See “Brushing Up on Gum Disease” in the May 1990 FDA Consumer.)

Losec Changes Name

The manufacturer of the drug omeprazole has changed the trade name from Losec to Prilosec because some dispensers were confusing the former name with Lasix, a totally different drug.

Losec is prescribed for patients with certain digestive disorders, whereas Lasix is used to treat high blood pressure and swelling associated with congestive heart failure.

FDA and Merck Sharp & Dohme of West Point, Pa., the manufacturer of Losec, had received reports of dispensing errors involving Losec and Lasix. In most cases, the firm said, patients prescribed Losec were erroneously given Lasix. When the potential for confusion between the two products became clear, the firm, working closely with FDA, informed physicians and pharmacists and determined that a change in Losec’s name was needed to remedy the situation. FDA concurred on the new name and packaging materials.

Merck began marketing Prilosec on Oct. 1, but asked pharmacists and pharmaceutical suppliers to use up existing inventories of Losec.

(For more information about Losec, see “First in New Class of GI Drugs Approved” in the Updates section of the March 1990 FDA Consumer.)

Home-Use Fetal Monitor

For the first time, pregnant women at risk of premature birth can use, at home, an electronic monitor that helps detect premature labor so that they can get early treatment.

FDA approved the Genesis Home Uterine Activity Monitoring System, a prescription device, last September for use after the 24th week of pregnancy by women with a history of premature labor. It is to be used in conjunction with usual care for such patients.

The monitor is used one hour per day, morning and evening. The woman places electrodes attached to the monitor onto her abdomen, where they pick up electrical impulses indicating uterine contractions. After each session, the monitor transmits the information by telephone. If contractions exceed four per hour, trained personnel...
call the patient to come in immediately for evaluation and, possibly, therapy to prevent labor.

The Genesis System was tested on 187 pregnant women with a history of premature birth. All received standard care, but half also used the device. Among the women diagnosed as having premature labor, those using the monitor had less dilation of the cervix—an indicator of imminent labor. While the study didn’t prove monitor users had fewer premature births, it did enable these women to get earlier treatment. Because of this, FDA will allow the manufacturer to state that the device can aid in early detection of premature labor but will not allow claims that it can reduce premature births.

The device is made by Physiologic Diagnostic Service, Inc., of Atlanta, Ga., a subsidiary of Tokos Medical Corporation, Santa Ana, Calif.

FDA Tests Drugs With Narrow Therapeutic Range

Twenty-four types of drugs whose effectiveness, and possibly safety, depend on near perfect delivery of the active ingredient meet government standards, according to recent FDA tests.

The agency analyzed samples from more than 400 batches of drugs known as “narrow-therapeutic-range” drugs. The drugs included types of contraceptives, antiasthmatics, antibiotics, antidepressants, anticonvulsants, antihypertensives, antiarrhythmics, and anticoagulants. Most other drugs have much wider margins for safety and effectiveness.

The tests, conducted by FDA at 16 agency laboratories throughout the United States, found problems with only five batches of the anti-asthma drug aminophylline from two manufacturers. The problem, incorrect amounts of a stabilizing ingredient, did not pose a health hazard.

Nevertheless, the manufacturers, West-Ward Pharmaceuticals of Eatontown, N.J., and Duramed Pharmaceuticals of Cincinnati, Ohio, recalled the five batches. As an extra precaution, Duramed is also recalling all other batches of its aminophylline product. FDA is working with both firms to eliminate the problems that caused the five batches to fail.

The samples tested included both brand name and generic products.

“These results should be reassuring to consumers who use generic drugs,” said HHS Secretary Louis W. Sullivan, M.D., “since the drugs that were examined are the kind that critics of generics are most likely to claim could cause problems.”

Researchers Report Arthritis Gene

A team of researchers reports finding a gene that causes osteoarthritis, the most common form of arthritis.

The report in the Sept. 4 Proceedings of the National Academy of Sciences discusses results of a study of 19 members of a three-generation family, including nine family members affected with osteoarthritis, a condition that causes protective cartilage to fray, wear, and, in extreme cases, disappear entirely, leaving a bone-on-bone joint.

Using techniques of molecular biology, researchers at Thomas Jefferson University in Philadelphia isolated and characterized a faulty gene for collagen II, a protein that strengthens the cartilage that cushions joints. The faulty gene directed the production of the amino acid cysteine, instead of the amino acid arginine, found in normal collagen II. The single amino acid mutation (among more than 1,000 amino acids in the protein) was found in all members of the family who had osteoarthritis, but not in any of the unaffected members tested or in 57 unrelated individuals.

The family members were initially examined for osteoarthritis by University Hospitals at Case Western Reserve University. Clinicians there performed research to rule out potential causes of the disorder and collaborated with Thomas Jefferson researchers in their search for a causative gene. Research at both facilities was funded by the National Institute of Arthritis and Musculoskeletal Diseases.

Although it is known that secondary osteoarthritis can be caused by joint injuries and congenital bone defects, the cause of primary generalized osteoarthritis remained unknown. The condition can affect many parts of the body, including hands, feet, hips, and knees. Osteoarthritis is a major reason for the more than 150,000 total joint replacement procedures performed in this country every year.

(For more information about genetically transmitted conditions, see “Genetic Screening, Fetal Signs on a Journey of Discovery,” in this issue of FDA Consumer.)

FDA Consumer welcomes comments from readers. Send letters to: Editor, FDA Consumer, HFI-40, 5600 Fishers Lane, Rockville, Md. 20857.
Progress Reports in the Battle Against Acquired Immune Deficiency Syndrome

Community-Based Clinics Providing Study Data

A study designed to amass the most comprehensive collection of information on HIV-infected people in the history of the AIDS epidemic is under way at more than 30 community-based clinics in the United States and Canada.

The Observational Data Base Project, the largest study of its kind ever conducted, will provide information on how infection with the AIDS virus progresses, which AIDS symptoms and related diseases are most common in different groups of people, and what types of treatment people are using, including "alternative" therapies.

It will also help doctors and researchers identify changes in the way the virus manifests itself over time and analyze factors that influence disease outcome.

Several thousand patients and several hundred primary care physicians are participating in the study, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and the American Foundation for AIDS Research (AmFAR).

In addition to increasing understanding of the nature of the AIDS epidemic, the study will help identify areas where new research is needed and possibly result in new approaches to treatment, according to Anthony S. Fauci, M.D., director of NIAID.

Participants are being drawn from the 18 Community Programs for Clinical Research on AIDS sponsored by NIAID and 15 programs in the Community-Based Clinical Trials Network sponsored by AmFAR. Both programs are designed to increase the number of HIV-infected women, minorities, and intravenous drug users in AIDS studies. These groups have previously been underrepresented in AIDS research.

Every three to six months, during regular visits to their clinics, study participants will be asked questions about their health and medicine. Information about their current symptoms, diagnoses, and results of their laboratory tests will be documented by clinic physicians. No special clinic visits, lab tests, or treatments are required.

To participate, a person must have HIV infection or an opportunistic infection or other AIDS-related illness, be under the care of a doctor in one of the NIAID or AmFAR community programs, and be at least 13 years old.

The study began in late September and will continue indefinitely.

Study to Compare Drugs For Opportunistic Infection

The National Institute of Allergy and Infectious Diseases will sponsor a three-year, community-based study to compare the effectiveness of two widely available drugs in preventing toxoplastic encephalitis in people with AIDS.

The drugs—clindamycin, an antibiotic, and pyrimethamine, an antiparasitic—will be given to 750 people infected with the AIDS virus in 14 cities.

Toxoplastic encephalitis, a life-threatening parasitic infection of the central nervous system, is the most common opportunistic infection of the brain in persons with AIDS and is a major cause of death in these people. It is usually treated with a combination of pyrimethamine and sulfadiazine. This treatment is effective in most cases, but is required over a lifetime to prevent the disease from recurring. Long-term use of the drugs frequently causes serious reactions, such as severe skin rash or bone marrow suppression, that force treatment to be stopped.

The study is the first to be conducted under the institute's Community Programs for Clinical Research on AIDS. The program is designed to increase participation of HIV-infected women, minorities, and intravenous drug users and their sexual partners in AIDS clinical trials. These groups have been underrepresented in AIDS research.

The study will enroll both women and men who are at least 13 years old. Participants must be HIV positive or diagnosed with an AIDS-related illness and have a T4 cell count below 200. (T4 cells are a type of white blood cell that is severely decreased in people with AIDS and some AIDS-related illnesses.) Participants must have toxoplastic antibodies but no history of toxoplasma gondii disease of the eyes, lungs, or central nervous system. Persons with AIDS dementia or other neurologic problems, except for peripheral neuropathy (nerve damage in the hands or feet), will be excluded.

The study will compare each of the two drugs against a placebo: 250 people will receive clindamycin and 125 will receive a placebo; 250 persons will receive pyrimethamine and 125 will receive a placebo. Bone marrow suppression in those receiving pyrimethamine is not expected to occur because of the relatively low dose; if it does occur, the patients will also be given leucovorin calcium to lessen the drug's toxicity.

For further information on this or any other AIDS clinical trial, call 800-TRIALS-A.
The Pill
30 Years of Safety Concerns
by Sharon Snider
When the birth control pill was introduced in 1960, it was a major medical achievement that rewrote the future of women and family life. For the first time in history, it became possible for a woman to safely and effectively control childbearing by taking a pill.

This year "the pill," as it is commonly referred to, is celebrating its 30th anniversary. Since its introduction, it has been used by more than 60 million women worldwide. It has proved to be, in the opinion of many, the most socially significant medical advance of the century.

American women were quick to accept the pill. Within two years, approximately 1.2 million women were using it, within five years, 5 million, and by 1973, about 10 million. In the early '80s, following reports of possible harmful side effects, use of the pill dropped to 8.4 million. Today, however, with safer, low-dose versions on the market, use is back up. Approximately 10.7 million American women now use the pill. It is the most popular method of non-surgical contraception.

Concerns about side effects have dogged the pill over the years. And rightly so. Does the pill present society with problems unique in the history of medicine? As an FDA advisory committee on the pill noted in the mid '60s, never would so many people take such a potent drug voluntarily over such a long period for a reason other than to cure disease.

"Since probably no substance, even common table salt, and certainly no effective drug, can be taken over a long period of time without some risk," the advisory committee warned, the pill's potential side effects "must be recognized and kept under continual surveillance."

Oral contraceptives have been kept under surveillance for 30 years. In fact, over the years, more studies have been done on the pill to look for serious side effects than have been done on any other medicine in history, according to FDA.

Fears about blood clots, heart attack, and stroke, which spurred exhaustive research on oral contraceptives in the '60s and '70s, have largely been laid to rest by the safer, low-dose birth control pills on the market today. Current research suggests that healthy, non-smoking women have little if any greater risk of these serious health problems than do women who do not use the pill.

Questions about the pill's association with cancer, however, remain. Some widely reported recent studies support the hypothesis that in certain groups of women the risk of breast cancer increases with oral contraceptive use. A larger number of studies, however, found no significant increased risk. Nor is it definitely known yet whether or not the pill causes cervical cancer in some groups of women. So far, a cause-and-effect relationship has not been established.

But the pill has been found to help prevent two major types of cancer—cancer of the ovaries and cancer of the endometrium (the lining of the uterus).

Last December, an FDA advisory committee, reviewing the relative risks and benefits of today's birth control pills, recommended that the upper age limit of 40 then in use for the pill be lifted for healthy, non-smoking women, thereby making this popular, effective means of contraception available until menopause.

How the Pill Was Developed

It was 1950 when Dr. Gregory Pincus, an American biologist, was invited by the Planned Parenthood Federation of America to develop an ideal contraceptive—one that Planned Parenthood stipulated would be "harmless, entirely reliable, simple, practical, universally applicable and aesthetically satisfactory to both husband and wife."

Planned Parenthood donated $2,100 to the project. Another $20,000 to $30,000 had to be raised from government and private sources before research could get under way.

Within a few years, an oral contraceptive was being clinically tested in 6,000 women in Puerto Rico and Haiti. In 1960, the first commercially produced birth control pill, Enovid-10, was marketed in the United States.

What Dr. Pincus and colleagues developed was a pill containing estrogen and progestin, synthetic hormones similar to those produced naturally in a woman's body. The pill works primarily by suppressing the release of eggs from a woman's ovaries.

The first oral contraceptives contained 100 micrograms (mcg) to 150 mcg of estrogen and as much as 10 milligrams (mg) of progestin—significantly higher levels of both hormones than in today's pill. They were 99 percent effective if taken as directed—the highest rate of contraceptive protection available except sterilization.

Concerns About Side Effects

Although the pill was widely welcomed, it wasn't long before concerns were raised about possible serious side effects.

As early as 1961, suspicions arose in the United States and England that the pill might predispose some women to heart attack and stroke. Evidence of blood clotting had been reported in a few women taking the pill. Blood clots can cause life-threatening heart attacks and strokes.

In 1965, spurred by further reports, FDA awarded a research contract to a scientist at the Johns Hopkins School of Hygiene and Public Health to investigate exactly how widespread the problem was.

At the same time, the agency established its first advisory committee—the Advisory Committee on Obstetrics and Gynecology—to review contraceptive products and to find out what effect, if any, oral contraceptives had on blood clotting. The committee was also directed to review existing data for clues to the pill's potential to cause cancer of the breast, cervix and endometrium.

In 1966, the advisory committee reported that it found "no adequate scientific data, at this time, to prove the pill unsafe for human use."

FDA Calls for Study

However, FDA expressed reservations about the pill's "very infrequent but serious" side effects and the lack of scientific data to adequately assess those side effects. It called for a large, case-control study of the relationship between oral contraceptives and blood clotting.

As for cancer, the advisory committee concluded the pill hadn't been in use long enough to draw valid conclusions about its carcinogenic effects. For example, it would be at least another 10 years before the risk of uterine cancer could be accurately assessed.

The advisory committee's findings on the possible relationship between the pill...
Estrogen Levels of Pill Drop

The amount of estrogen in oral contraceptives has declined significantly over the past 30 years, making today's pill considerably safer than the pill of the 60s.

1960s

100-150 mcg estrogen

50 mcg or less estrogen

30-35 mcg estrogen

1970s

1980s-90

and blood-clotting and cancer were supported by a World Health Organization scientific group, which independently had reached the same conclusions.

However, by 1968, amid further reports of blood clots and new evidence from British studies showing an increased incidence of blood clots among women taking the pill, FDA added information about the results of those studies to the product labeling for oral contraceptives. A year later, the agency again revised the labeling, this time to include the results of U.S. studies that supported the British findings.

By 1969, ongoing research had revealed that the risks of blood clots, heart attack, and stroke were directly related to the amount of estrogen in the various versions of the pill. Research also showed that the same rate of contraceptive effectiveness could be maintained with only 50 mcg of estrogen. By that time, 7.5 million women were using oral contraceptives—up from 408,000 women in 1961.

As the 1970s began, FDA issued a bulletin to doctors about the danger of blood clots. It advised using the lowest effective dose of estrogen possible when prescribing oral contraceptives. The agency also revised the product labeling once again to include the “lowest effective dose” recommendation. And, for the first time, FDA required that information for patients about the drug’s risks be included in every package of oral contraceptives.

‘Mini-Pill’ Introduced

In the early 1970s, the “mini-pill,” an oral contraceptive containing only progesterin, was introduced. Unlike the estrogen-progestin pill, which works primarily by suppressing ovulation, the mini-pill works by creating changes in the cervix and uterus that make it difficult for sperm to unite with an egg. Since mini-pills contain no estrogen, they pose few of the risks associated with the combination pill. However, mini-pills have two drawbacks: They cause irregular bleeding in some women, and they have proven to be less effective in preventing pregnancy. As a result, their use has been limited.

By the mid '70s, most women who used oral contraceptives were taking pills that contained 50 mcg or less of estrogen—a considerable decrease over the original 10 mg to between 2.5 mg and 0.15 mg.

Between 1973 and 1974, FDA approved several low-dose pills containing as little as 20 to 35 mcg of estrogen. Most pills prescribed today contain 30 to 35 mcg of estrogen and 0.5 mg to 1 mg progesterin.

In 1982, a new version of the pill, called the “biphasic” pill, was introduced. Two years later, three “triphasic” pills were introduced. These “multiphasic” oral contraceptives are low-dose pills in which the ratio of progesterin to estrogen changes during the 21 days the pill is taken.

By 1986, use of high-dose estrogen pills had been drastically reduced—to 3.4 percent of the oral contraceptive market.

Nevertheless, some 400,000 women were still using high-dose estrogen pills. Most were between 30 and 39 years of age, the age group most at risk of serious side effects.

High-Dose Estrogen Pills Withdrawn

In 1988, at FDA’s urging, the three drug companies still manufacturing high-dose estrogen oral contraceptives voluntarily withdrew from the market all remaining products containing over 50 mcg estrogen.

The latest development in the 30-year saga of the pill was its approval last year for use in healthy, non-smoking women over 40. The impact of this move, in terms of the number of women who will choose to continue or start using the pill after they turn 40, remains to be seen.

But an estimated 1 million to 1.5 million women between 40 and 54, including the baby boomers, could be affected.
Preventing Pregnancy

Actual effectiveness rates of the various forms of contraception (per 100 women per year of use)

<table>
<thead>
<tr>
<th>Method</th>
<th>Effectiveness Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterilization</td>
<td>99+</td>
</tr>
<tr>
<td>The pill</td>
<td>97%</td>
</tr>
<tr>
<td>IUD</td>
<td>94%–97%</td>
</tr>
<tr>
<td>Condom alone</td>
<td>88%</td>
</tr>
<tr>
<td>Diaphragm with spermicides</td>
<td>82%</td>
</tr>
<tr>
<td>Cervical cap</td>
<td>82%</td>
</tr>
<tr>
<td>Periodic abstinence</td>
<td>80%</td>
</tr>
<tr>
<td>Spermicides alone</td>
<td>79%</td>
</tr>
<tr>
<td>Vaginal sponge</td>
<td>72%–82%</td>
</tr>
</tbody>
</table>

Today's Pill Safer

Today's oral contraceptives are considerably safer than the pill of the '60s because they contain less estrogen and progestin. Over the years, the amount of estrogen has been reduced to one-third or less of that in the first birth control pills, and the progestin has been decreased to one-tenth or less.

The risks of blood clots, heart attacks, and stroke have decreased correspondingly for healthy, non-smoking women. There is a slightly increased risk of cardiovascular disease for women over 40 who use the pill, but the benefits of contraception are considered to outweigh the risk in most women, says Philip Corfman, M.D., of FDA's division of metabolism and endocrine drug products.

Most side effects of the pill are not medically serious. The most common are nausea, breakthrough bleeding (bleeding between menstrual periods), and mood changes, including depression. Some women may also experience weight gain, breast tenderness, and difficulty wearing contact lenses due to eye dryness. These side effects, especially nausea, usually subside within the first three months of use.

Health Benefits

In addition to its contraceptive effectiveness, the pill has proven to have significant health benefits. Studies show that the incidence of ovarian and endometrial cancers, benign cysts of the ovaries and breasts, and pelvic inflammatory disease decreases with pill use. The pill also prevents heavy and irregular menstrual periods, a common cause of anemia that leads to surgical procedures, including hysterectomy, in older women.

Whether these benefits will continue with the newer, low-dose pill remains to be seen. The present benefits are associated with oral contraceptives containing 50 mcg of estrogen. As yet, no scientific data are available on the effects of those containing 30 to 35 mcg or less.

Not Safe for All

As safe as today's pill is for most healthy, non-smoking women, it is still not safe for all women. The risk of serious illness and death increases significantly for certain groups:

- Women who smoke—particularly those over 35 who are heavy smokers (more than 14 cigarettes a day)—have a significantly increased risk of heart attack and stroke. This risk increases with age.

- Women who use oral contraceptives are strongly advised not to smoke.

- Women who are obese or have underlying health problems, such as diabetes, high blood pressure, or high cholesterol, also have a significantly increased risk of serious side effects from using the pill.

- Women who have a history of blood clots, heart attack, stroke, liver disease, or cancer of the breast or sex organs should not use oral contraceptives.

- Women who become pregnant while on the pill should immediately discontinue taking it because of a risk of birth defects in the child.

Uncertainties remain about whether the pill causes breast or cervical cancer in some groups of women. Despite many studies over the years, there is still insufficient evidence to definitely rule out these possibilities.

While there are conflicting results among studies on breast cancer and the pill, most investigations have found that women who have taken the pill have no increased risk of developing breast cancer. However, the product labeling on oral contraceptives recommends that women who use the pill and have a strong family history of breast cancer or who have breast lumps or abnormal mammograms be closely monitored by their doctors.

Some studies have found an increase in the incidence of cervical cancer in women who use the pill, but this may not necessarily be related to the pill, scientists say.

One of the major problems of the studies to date, says Corfman, is that all the data reflect the effects of the higher-dose pills (those containing more than 50 mcg of estrogen). No studies have been done on the low-dose pills, and none are under way. The cancer-pill issue is very complicated and therefore difficult to study, and the research is expensive, he says.

"We really need another breast cancer study on the low-dose pills," Corfman says. "We have the capability of finding out about breast cancer, but no one is doing the research."

Researchers may never find out whether the pill causes cancer of the cervix, Corfman says, because the development of cervical cancer can be affected by numerous other factors, such as the age a woman begins having sex and the number of sexual partners. Corfman says he suspects, however, that such research would show that the risk of getting cervical cancer from the pill is so small as to be outweighed by the benefits of contraception.

Though some safety questions remain unsettled, for most healthy women the pill provides a safe, effective means of birth control with some possible beneficial health effects.

Sharon Snider is a staff writer for FDA Consumer magazine who took the pill for nearly 15 years.

(For information about the recent conviction of individuals who counterfeited the oral contraceptive Ovulen-21, see page 35.)
Modern Diagnostics Help Detect Cancer Early

by Stephen J. Ackerman

Cancer is perhaps the disease Americans fear most. Our second leading cause of death (after heart disease) seems so formidable, so invincible a threat, that many dread it as “The Big C.” But this notion of the disease is often not realistic in this “high-tech” age, and the exaggerated dread it instills may be counterproductive.

There are many kinds of cancer, not all inevitably fatal. Our increasing ability to detect and distinguish among them saves more lives every year.

It’s more accurate to speak of various cancers rather than of cancer as a monolith, for there are some 200 such conditions, in which unrestrained growth of cells in an organ or tissue of the body causes a wide range of symptoms. Perhaps 90 percent of cancers are carcinomas, malignant tumors arising in the cells of the surface layer or lining of an organ. These cancers cause the palpable lumps so closely identified with the disease that some use “cancer” and “carcinoma” as if they were identical. Other kinds of cancer include:

- lymphoma, cancer of the immune system, usually appearing in the lymph node tissue
- myeloma, a rare cancer of the immune system appearing in the bone marrow
- leukemia, “cancer of the blood” that affects oxygen-bearing white blood cells and in which abnormally growing cells are scattered throughout the body rather than concentrated in a single tumor
- sarcoma, a relatively rare cancer in supportive tissue, such as cartilage, muscle, bone, or fat.

The relation of cancer to environmental factors has been known since the 18th-century surgeon John Pott traced the high incidence of scrotal cancer among chimney sweeps to their exposure to soot. For generations, mushroom growers in France, who apparently nibble their fibrous crops on the job, have claimed that they have almost no incidence of cancers, owing to their diet.

Hereditary factors also come into play. The recent death from pancreatic cancer of Gloria Spann, sister of former President Carter, suggested a genetic susceptibility in a well-known American family. Her father, a brother, and a sister died of the same disease, while her mother died from a primary breast cancer that spread to other organs, including the pancreas.

Treatment Helps

The earlier a cancer is detected, the likelier it is to respond to treatment. Unfortunately, this is easier with some cancers than with others. Early ovarian cancer is one with no symptoms to warn of its growth, so it’s rarely detected before an advanced stage.

Even cancers that exhibit warning signs aren’t always recognized in time for the most effective therapies. So strong is the dread of cancer that many people shy from self-examination techniques for fear that they will reveal the disease. Some men shun examining themselves for testicular cancer (most prevalent from ages 15 to 34) just as some women avoid probing for breast lumps. Even when such simple self-examinations are performed conscientiously, they can detect only tumors large enough to feel, which are therefore already somewhat developed.

About 80 percent of breast lumps are not cancerous. Timely, accurate diagnosis through physician examination and mammography screening (see accompanying article, “Protecting Yourself from Cancer”) thus can relieve anxiety as well as detecting more dangerous tumors.

Early detection increases survival rates for some cancers dramatically. The survival rate for early melanoma (a skin cancer) is 90 percent, but it decreases to under 40 percent in the later stages. If all melanomas were detected while still small and confined to one area, the cure rate could approach 100 percent. Three-fourths of colon or rectal cancer patients could be saved by early detection.

“If you can find things early enough, you can make a big difference in outcome,” generalizes Peter Shields, M.D., of George Washington University Medical Center, who is devoting a fellowship at the National Cancer Institute to refining means of finding out which individuals might be most susceptible to which cancers.

“The truth is that some cancers can be resected [excised] at an early time and cured,” says Shields as he dabs samples onto laboratory slides. Testicular cancer, he notes, is particularly receptive to chemotherapy: like some other cancers, it can be cured completely.

Shields works on devising tests to determine who is at increased risk of developing a cancer. He studies oncogenes, which in many cases started as normal genes regulating cell growth. Mutations can turn such a gene into one that permits uncontrolled growth: an oncogene. Suppressor genes, which inhibit cell growth, oppose oncogenes. By comparing these genetic variations in people not afflicted with cancer and in those who are, he tries to find which factors may predispose individuals to cancers.

“The field is called biochemical epidemiology, and we are specifically interested in things that happen to your genes that would increase your risk of cancer. Why is it,” he wonders, “that some people who smoke get lung cancer and some don’t? Why do some workers who are exposed to certain compounds get bladder cancer and others don’t?”

Hereditary, lifestyle and environment are all factors in the search. Microscope slide by slide, Shields and his colleagues around the world painstakingly sift the possibilities.

The reason early detection can be so critical isn’t simply that the growth of a tumor may be arrested. Timely response can head off metastasis, the migration of tumor cells through the blood and lymph system to other parts of the body. Undetected, the cancer can spread not just into adjacent tissue but even to distant organs.

Metastasis is partly what distinguishes a damaging malignant tumor from a “benign” tumor, which may grow more slowly and doesn’t travel through the system. But even a benign tumor can prove fatal if located in the wrong place—for instance, the brain.

(Continued on page 14)
Sophisticated tools may be necessary for diagnosing cancers that grow inside the body. At left, technician positions patient’s head before CAT scan of brain begins. Cancers that grow on the outside of the body, however, may be more obvious. Below, typical pattern of melanoma, a type of skin cancer, is enlarged to show detail.

Self-Exam

The best hope for early detection of testicular cancer is a simple three-minute monthly self-examination. The best time is after a warm bath or shower, when the scrotal skin is most relaxed.

Roll each testicle gently between the thumb and fingers of both hands. If you find any hard lumps or nodules, see your doctor promptly. They may not be malignant, but only your doctor can make the diagnosis.
Protecting Yourself from Cancer

We needn’t wait for new diagnostics to be developed and proven to protect ourselves from cancer. When experts tell us that almost a third of cancers can be traced to smoking and another third to dietary defects, there’s a lot we can do for ourselves.

Most of the information relating behavior to cancer is derived from mass data (for example, populations with high-fiber diets tend to have a lower incidence of certain cancers). But it’s hard to say with precision how this generalization applies to an individual.

Specifics of a diet beneficial for avoiding cancers are still being thrashed out. In general, more fiber and less fat in American diets might reduce cancer risks. One of the most painless suggestions for avoiding excessive intake of potential carcinogens is to vary the menu by enjoying a wide range of foods instead of subsisting on a few old favorites. By and large, it’s wise to follow the Dietary Guidelines for Americans, published by the U.S. Department of Agriculture and FDA.

Many people also incorporate into their health regimens routine screening for those cancers to which they would be most susceptible given their age, sex, and other circumstances. Although recent studies have questioned the need for an annual physical, even for older people, some cancer specialists counter that periodic checkups, with appropriate cancer screenings, can be of value even for people under 25. This they believe is particularly true for older people, more vulnerable to cancer simply because any abnormal cells have had more years to work more mutations.

Others require particular screenings. A screening test for hidden blood in feces can help prevent colorectal cancer. A recent report by the U.S. Office of Technology Assessment estimated that use of this screening test by the 2.1 million Americans age 65 or older could prevent 23,000 cases of colorectal cancer by enabling doctors to detect growths in the colon called polyps before they turn cancerous.

Younger women, for instance, might be screened for cervical cancer every one to three years. The National Cancer Institute recommends annual Pap tests from age 18, or as soon as young women become sexually active. After three or more normal readings, the tests may be taken less often. Annual mammography to screen for breast cancer is recommended for women over 50. Many health organizations also recommend less frequent screening for younger women. Though mammography, combined with physical examination, has been estimated to reduce breast-cancer mortality by 56 percent, only 5 to 15 percent of women in age groups for which the screening is recommended are availing themselves of these x-ray examinations. (See “Why Women Don’t Get Mammograms (And Why They Should),” FDA Consumer, May 1987.)

Though diagnostic tests are important, no one is recommending rushing to the doctor to demand every cancer test there is. Aside from the expense, some tests may have side effects that aren’t worth the risk if there’s no suspicion of cancer. Some tests are not always definitive.

Survival Increased

Improved detection and diagnosis have bettered the odds against the disease. Half of cancer patients now survive at least five years, while only a third survived a generation ago. If new diagnostics can spy cancers before metastasis, this rate could improve further.

Even when tests reveal that metastasis has already occurred, they can benefit the patient by eliminating the need for exploratory surgery. Moreover, they point physicians toward the most appropriate treatment approach.

Methods already in use have contributed greatly to reduce cancer deaths. The Pap test has been valuable against cervical cancer. CAT (computed axial tomography) scans, which provide three-dimensional images of the body, are significant advances over one-dimensional x-rays for detecting tumors. However, for definitive diagnosis, the CAT scan’s usefulness is limited. A scan shows the presence of a lump but doesn’t usually identify its nature. A tissue biopsy is usually needed for definitive diagnosis of the mass it has detected.

‘New Biotech’ Tests

Tests based on the “new biotechnology” supplement CAT scans, indicating the nature of any abnormalities they may reveal. “New biotechnology” tests work both in the test tube and in patients. Scientists are now able to apply monoclonal antibodies (MAB’s) or gene probes to the surfaces of cancer cells. This technology works by recognizing tumor “markers,” usually molecules present on the surfaces of cancer cells or shed by them. In the near future, the new biotech tests likely will supplement others, rather than re-
Questions About Cancer?

If you have questions about cancer, call the Cancer Information Service toll-free at 800-4-CANCER (9 a.m. to 10 p.m. Eastern Standard Time, Monday–Friday).

This national telephone inquiry system at the Johns Hopkins University Oncology Center, funded by the National Cancer Institute, will give up-to-date answers to your specific queries on cancer prevention, detection, rehabilitation, continuing care, and current research.

Information is available in Spanish as well as English. Referrals to sources in your own community are part of the service. Even physicians who are not cancer specialists consult this authoritative hot line. Because of its popularity, the line is often busy, but its service is worth a caller’s patience. ■

—S.J.A.

placing them.

The DNA found in every living cell is the key to such diagnostics. The uniqueness of small strands of DNA makes it possible to detect specific oncogenes and other markers of cancer in the test tube, using probes designed specifically to detect the genes that are marked with a radioactive (or sometimes non-radioactive) label. The MAb rushes to the abnormality it was designed to complement, if one is present.

A test-tube diagnostic called the B/T Gene Rearrangement Test for leukemia and lymphoma was approved by FDA in autumn 1989. It permits the detection of genetic abnormalities associated with certain types of leukemias and lymphomas. Comparable tests are being devised to work in the patient’s body, using safe levels of radioactivity or non-radioactive markers.

Biotech may be able to help diagnose colon cancer earlier. Colon cancer is a good example of a cancer readily treatable if detected in time. About 110,000 new cases appear in the United States yearly, 44,000 fatal. Early detection can reduce this toll.

Presently, doctors can locate suspected colon cancers by using barium, administered either through an enema or a “milkshake.” Once inside the body, barium usually highlights any tumors on an x-ray.

A more precise method is under investigation. By cloning the antibodies the immune system generates specifically to combat colon cancer, then injecting them into the body, investigators hope to follow them as they rush directly to the cancer site. Because these MAb’s are engineered to seek only colon cancer cells, they pass harmlessly from the body if none are present. If they collect at any site, however, they may signal the presence and nature of the colon cancer. Diagnostics taking this approach are in clinical trials.

Devising such tests isn’t easy, given the more than 50,000 genes in each cell of the human body. Yet, since the first FDA approval in 1982, development of molecular diagnostics has progressed. In addition to helping analyze the 75,000 new cases diagnosed in the United States annually, the DNA test mentioned above may also be useful in monitoring over 300,000 former patients against a recurrence.

A different lymphoma test is also in early clinical trials. Other diagnostic tests now in development include those for ovarian, liver, breast, and lung cancers.

Working out definitive tests can be frustratingly slow because the development of some cancers is so complex. Certain chemicals can both promote and inhibit tumors, depending on the circumstances, so their presence when detected requires painstaking analysis.

Some monoclonal antibodies go beyond improved detection. For instance, Pap tests are effective in diagnosing early cancer of the uterine cervix, but they cannot distinguish those patients likely to relapse into a more serious form of the disease after surgery. Some 15 to 20 percent of women treated for local cervical cancers fall into this category. French researchers have found that half of cervical cancer patients with high levels of a particular oncogene are disposed to a recurrence of the disease. A MAb test being developed there may help to distinguish such women early on. These women can then be offered more intense alternative treatments than usually required by other patients, hopefully heading off the need for surgery later.

Diagnostics into Therapies?

In buying critical time through early detection, the new cancer diagnostics may prolong thousands of lives. Better still, some may go beyond detecting to actually combating certain cancers.

In an experiment limited to 10 cancer patients, researchers at the National Cancer Institute (NCI) attempted for the first time to transfer foreign genes into humans. The purpose of the experiment was to determine how long tumor-invading lymphocyte (TIL) cells, which fight the cancerous cells, remain in the body.

The NCI team removed from a patient some portions of a melanoma tumor that contained TIL cells. The experimenters inserted a foreign gene derived from bacteria to make the TIL cells easier to detect. After a period of growth in the laboratory, the marked TIL cells were put into patients with various cancers. In one case, this procedure may have increased the potency of the TIL cells in attacking the cancerous cells: For one patient, the remission of a throat tumor was “dramatic.”

While one result in one patient is not scientifically significant, it encouraged the doctors to expand the 10-patient test group to as many as 50. Other experiments aimed at strengthening TIL cells to combat cancer cells are going on.

In time, genetic markers could tell us how groups of genes predispose individuals either to resist or to contract cancers and other diseases. Such understanding could show scientists ways to direct genes to resist disease.

Though cancer is still a disease that inspires high anxiety in most Americans, the many diagnostics available now and under development give hope of increased cure rates through early diagnosis.

Stephen J. Ackerman is a freelance writer in Washington, D.C., who has also written for Consumers Research and The Washington Post.
A worldwide effort to understand all our genes is well under way. Along this journey of discovery, tests are being developed to identify both healthy people who can pass a genetic disorder to a child (carriers) as well as those, including fetuses, who will actually develop symptoms.

In the past few years, scientists have identified the genes responsible for several major disorders, including cystic fibrosis, Duchenne’s muscular dystrophy, and a few inherited cancers. Applying this new and complex information to the practice of medicine will require education of health professionals, patients, and their families.

How will physicians, medical consumers, and, ultimately, the Food and Drug Administration deal with this coming avalanche of information? Fortunately, experts can turn to past experience with genetic screens to guide them in planning the programs of the future.

Urine—Clues to PKU
The age of genetic screening dawned in 1934, when a mother of two retarded children in Oslo, Norway, commented to a relative who was a chemist that her children’s diapers had an odd smell. The curious chemist analyzed the urine and found too much of one biochemical yet none of another, an enzyme (a protein that speeds a biochemical reaction). The children had an “inborn error of metabolism” called phenylketonuria (PKU), each inheriting a defective gene from each carrier parent. The combined deficit blocked production of the enzyme (phenylalanine hydroxylase) that normally breaks down phenylalanine, a protein building block. This genetic roadblock caused the mental retardation.

Knowing precisely what a faulty gene does (or doesn’t do) is half the battle in conquering an inherited disease. The story of PKU indeed has a very happy ending. In 1963, a test was approved to detect the enzyme deficiency at birth, making it possible to prevent retardation if the child follows a very low phenylalanine diet for the first 8 years. Thanks to the observant mother, today every newborn in the United States is tested for PKU, and often other inborn errors, such as sickle cell disease, hypothyroidism, galactosemia, biotinidase deficiency, and homocystinuria.

Even though PKU is rare (affecting 1 in 14,000 whites and 1 in 300,000 blacks), genetic screening makes economic sense—it costs $3.3 million a year to screen newboms, but $189 million to care for the PKU patients who would be retarded if not for the screen.

PKU screening got off to a rocky start. In the early 1960s, a few children who had transiently high levels of phenylalanine, but not PKU, were inappropriately placed on the diet. Some of them died. But PKU testing and treatment have since been perfected.

Sickle Cell Confusion
Another genetic screening program was initially disastrous. In the early 1970s, mass screening of blacks to identify carriers of sickle cell disease, a painful inherited anemia, began in earnest. (Although sickle cell disease affects other populations, notably Arabs, in the United States, it is overwhelmingly predominant among blacks.)

Semantics led to mass misunderstanding. Sickle cell disease carriers are referred to as having “sickle cell trait,” although these people in fact have no symptoms. Quite understandably, people told they had sickle cell trait feared they would develop symptoms—and also often did not understand the genetic odds their children would face. If two carriers have a child, the child has a 1 in 4 chance of having full-blown sickle cell disease, a 1 in 2 chance of being a carrier like each parent, and a 1 in 4 chance of being completely free of the sickle cell gene.

Discrimination against carriers was widespread. In Massachusetts, black children had to be screened for sickle cell trait before they would be admitted to public school. In New York, the test was mandated when applying for a marriage license. Carriers were denied health and life insurance and entrance to the U.S. Air Force Academy. As geneticists began to recognize in the late 1970s that being a sickle cell disease carrier does not adversely affect health, these restrictions were lifted.

Newborn screening is useful when early diagnosis is coupled with treatment. Screening newborns for sickle cell disease is now mandatory, because it is known that daily penicillin can ward off life-threatening infections (see “New Hope for Children with Sickle Cell Disease” in the March 1989 FDA Consumer).

Marilyn Gaston, M.D., deputy chief of the sickle cell disease branch of the Na-
Genetic screens for phenylketonuria, sickle cell disease, and Tay Sachs disease were possible because the abnormal proteins causing the symptoms were known.

Tay Sachs Success

Ironically, at the same time that the sickle cell carrier screening program was causing unwarranted panic, another screen for a genetic disease—Tay Sachs—was quite successful.

In a child with Tay Sachs disease, a missing enzyme (hexosaminidase) leads to buildup of fat on nerve cells, destroying the nervous system. The child begins to lose developmental skills from about the age of 6 months, and by 2 years of age can no longer see or hear. Death comes by age 4. Like PKU and sickle cell disease, a Tay Sachs child usually comes as a surprise to two healthy parents who each carry the gene.

Tay Sachs disease is 100 times more prevalent among Jewish people of eastern European descent than in other populations. In this ethnic group, 1 in 3,000 newborns has the disease, and 1 person in 27 is a carrier. A pilot screening program in the early 1970s searched for carriers among the Jewish community in the Washington, D.C., area, and other programs followed. Because most couples found to be at risk of having a Tay Sachs child (that is, both parents were carriers) chose not to have children, the number of children born with Tay Sachs disease has since dropped by 90 percent.

The secret to the success of Tay Sachs screening, experts agree, was education. Community and religious leaders were first informed by the physicians in charge, and they informed the public. Testing was widely available on college campuses and in synagogues, community centers, and shops, and offered at times convenient for young people.

Clues in DNA

The sequence of a gene’s building blocks (called bases) instructs the cell to string together amino acids to build a particular protein. Screens for PKU, sickle cell disease, and Tay Sachs disease were possible because the abnormal proteins causing the symptoms were known.

But knowing which protein lurks behind a genetic disease is rare. Still, with much work and luck, researchers can pinpoint the stretch of DNA that causes a disease, even if its corresponding protein is not known. Zeroing in on the few thousand DNA bases whose activity causes a disease, among the 3 billion bases wound into every human cell, is a needle-in-a-haystack quest of daunting proportions. Even narrowing the gene search down to a specific chromosome is a tall order. (Chromosomes are rod-shaped bodies that carry the genes.) Often, this search can be expedited by very special patients.

In the 1970s, for example, a few young people with Duchenne’s muscular dystrophy (DMD) and similarly broken X chromosomes (the X chromosome and Y chromosome determine sex; females are XX, and males are XY) led researchers to the precise location of the DMD gene—the site of the chromosome break. Then, in 1985, a boy was found who not only had DMD, but two other diseases linked to his X chromosome. In addition, his X chromosome had a tiny gap in it. The gap corresponded to the region of the break in the already-known unusual chromosomes.

It wasn’t long before Louis Kunkel, Ph.D., at Harvard Medical School used a technique called “chromosome walking” to find that these patients’ X chromosomes were missing a huge gene. That gene normally encodes a protein called dystrophin, which is present, sparingly, just beneath the surfaces of muscle cells and is essential for their activity. Because boys inheriting DMD from carrier mothers lack dystrophin, they become wheelchair bound by puberty, and die by their 20s. Thanks to the discovery of dystrophin’s role, cell transplants are now being tested to treat DMD (see accompanying article, “Treating the Fetus and Child”).

Patients with unusual chromosomes have also helped to unravel the genes behind Wilms’ tumor (a childhood kidney cancer) and neurofibromatosis (also known, erroneously, as Elephant Man disease), which causes benign tumors to grow beneath the skin.

Genetic Markers

Even without unusual chromosomes as clues, some genes can be tracked by studying the DNA neighboring them—a little like judging a party by surveying the guests, even if the host is not in sight. The neighboring DNA is called a genetic marker, and it provides an indirect glimpse of a gene.

A genetic marker is an unusual sequence of DNA located near an unknown disease-causing gene. In certain families, a marker is found in every person who has the disease, but not in healthy relatives. Finding a marker is a laborious process, involving cutting DNA from many family members and meticulously searching for a piece of an unusual size found only among the ill.

A genetic marker allows detection of a disease-causing gene before symptoms arise. It can be tracked in a person of any age, as well as a fetus, because all genes (Continued on page 20)
## HOW DISEASES ARE INHERITED

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are present from conception. For “marked” genes whose associated diseases are currently untreated, such as those that cause the uncontrollable movements and personality changes of Huntington disease and the mental deterioration of inherited Alzheimer’s disease, the value of predicting future ills may be questionable. Some healthy individuals, told they have such genetic diseases in their futures, may become suicidal. Others, however, may want to know the prognosis so they can plan their lives.

The promise of a genetic marker, though, is that it tells investigators where to hunt for the disease-causing gene. Once that is known, the gene’s protein can be deduced from the gene’s sequence. The biochemical basis of the symptoms revealed. Treatment may follow.

For example, in 1988 a marker for neurofibromatosis was found, and the gene was identified in July 1990. In August 1990, a University of Utah team led by Ray White, Ph.D., deciphered the gene’s product. It is a protein that normally suppresses certain cancer-causing genes (oncogenes). White says that “future experiments . . . may suggest new means of therapy. It may become possible, for example, to develop a blocking agent to halt the stimulation of cell growth in a developing neurofibroma [tumor]. Or, it might also be possible to deliver the gene product locally, likewise inhibiting development of neurofibromas.”

Cystic Fibrosis and Beyond

Soon, mass population screening may begin for cystic fibrosis, the most common inherited disease of whites. In cystic fibrosis, glands in the lungs and pancreas secrete abnormally thick mucus that obstructs these structures. Also, sweat is very salty. The protein behind cystic fibrosis normally forms a channel in certain cells that controls passage of salts. A marker for cystic fibrosis was found in 1985, but, like all marker tests, it requires that several family members participate so that the unusual sequence of DNA that travels with the disease-causing
FROM GENE TO PROTEIN

CHROMOSOME

DNA DOUBLE HELIX

DNA SECTION (GENE)  \[ACTGTCAGTCAT...\]

AMINO ACID CHAIN (PROTEIN)

- Hemoglobin
- Hexosaminidase
- Dystrophin
- Phenylalanine hydroxylase
- Transmembrane protein

Diseases:
- Sickle Cell Disease
- Tay Sachs Disease
- Duchenne's Muscular Dystrophy
- PKU
- Cystic Fibrosis
Knowing precisely what a faulty gene does (or doesn’t do) is half the battle in conquering an inherited disease.

(Continued from page 20)

As genetic researchers work their way through human genetic material, their discoveries are expected to spawn many diagnostic tests and, ultimately, treatments. What scientists have learned from experience will enable them to make the best use of this new information. Genetic screening, then, promises to be very much a part of FDA’s—and the consumer’s—future. 11

Ricki Lewis teaches biology at SUNY (State University of New York) Albany, is a genetic counselor, and author of a book, Beginnings of Life.
Prenatal Peeks

Ultrasound
In an ultrasound exam, a device called a transducer passed over the abdomen or inserted into the vagina bounces sound waves off the fetus, much like sonar locating a submarine. A computer converts the sound waves into an image. Many studies show it is very safe to mother and fetus.

Ultrasound can establish the date of conception, the presence of twins, and monitor development. By 8 weeks, an image resembling a lima bean with a pulsating blip in the middle is an assurance that a "viable fetus"—with its blip of a heartbeat—is there.

By 15 weeks, a trained eye can discern major organs. While the parents happily count toes and fingers, a physician may measure the length of the leg bones or check facial features for signs of Down syndrome.

By 20 weeks, a penis—or lack of one—may be apparent. By 35 weeks, calcium deposits in the placenta, the organ linking mother to child, signal lung maturity. As the birth day nears, ultrasound reveals the fetal position.

Amniocentesis
Through amniocentesis, the amniotic fluid surrounding the fetus is sampled with a needle inserted into the woman's abdomen. Fetal cells floating in the fluid are grown and examined for chromosomal abnormalities, such as the extra chromosome 21 that causes Down syndrome. Biochemicals in the fluid also provide diagnostic clues to several inborn errors of metabolism. Approved since 1967, amniocentesis is offered to women over 35, the age when the risk of the procedure causing a miscarriage is equal to the risk of the woman carrying a fetus with a detectable chromosomal problem (this risk increases with age). Women younger than 35 may have the procedure if a relative has a detectable abnormality. Amniocentesis can rule out many disorders, but it cannot guarantee a healthy baby.

The major drawback of amniocentesis is that it cannot safely be performed until the 16th week of pregnancy, and it takes 10 days or longer for fetal cells to be cultured and results to be known. However, several medical centers are experimenting with performing amniocentesis as early as 12 weeks.

Another advance is the use of automated, computerized chromosome sorters that are programmed to scan for abnormalities. This replaces technicians cutting up photographs of chromosomes and arranging them into a standard chart, then searching visually for aberrations—a time-consuming process.

Yet another new approach to viewing chromosomes is "in situ hybridization," a technique that uses DNA probes (bits of DNA tagged with a chemical) to locate and highlight specific chromosomes with no need to culture them first. This approach, still for research use only, can identify the extra chromosome of Down syndrome in hours.

Chorionic Villus Sampling (CVS)
In CVS, recently approved by FDA, a catheter inserted through the vagina samples chorionic villi, finger-like structures that form the placenta by 10 weeks of prenatal development. Because villi cells descend from the fertilized egg, their chromosomes match those of the fetus.

The great advantage of CVS is that it can be performed as early as 8 weeks, and results are ready within days.

In the March 9, 1989, New England Journal of Medicine, George G. Rhoads, M.D., and co-workers at the National Institute of Child Health and Human Development reported on a seven-center study comparing CVS to amniocentesis. They conclude, "CVS is a safe and effective technique for the early prenatal diagnosis of cytogenetic abnormalities, but it probably entails a slightly higher risk of procedure failure and fetal loss than does amniocentesis." The risk of amniocentesis causing miscarriage is 0.5 percent; that of CVS is 1.3 percent. Miscarriages are more often associated when CVS is performed more than twice.

The Triple Test—AFP-Plus
In 1975, scientists found a link between high levels of alpha-fetoprotein (AFP) in pregnant women's blood and a type of fetal abnormality called a neural tube defect, which includes spina bifida (an open spine) and anencephaly (lack of higher brain structures). The open lesions of such defects allow AFP to leak faster than normal from the fetus' liver into the mother's bloodstream, causing the elevated levels.

In 1984, studies linked too little of the substance to Down syndrome. After this discovery, measuring AFP at 15 weeks for use as a prenatal warning greatly expanded. This helps in spotting Down syndrome in women under 35, who would usually not have amniocentesis. Abnormal AFP levels may also be associated with other birth defects and with late miscarriage, low birth weight, toxemia (very high blood pressure in a woman in the last trimester of pregnancy), premature delivery, and other birth defects.

How can one substance show so much? "We think the abnormal readings reflect something wrong with the placenta," says Washington Hill, M.D., director of maternal-fetal medicine at the Creighton University School of Medicine in Omaha.

AFP testing has a very high false-positive rate, because the level of AFP can be thrown off by such factors as a miscalculated due date, obesity, twins, or being black or diabetic. In 1987, accuracy was improved by considering levels of human chorionic gonadotropin, too, which is high in Down syndrome. The recent addition of a third measurement—unconjugated estriol—may make readings even more accurate.

By indicating a low risk, the use of this "triple test" could spare some women over 35 from amniocentesis recommended only because of their age. However, this is a screening test, not a diagnostic test, cautions George J. Knight, Ph.D., of the Foundation for Blood Research in Scarborough, Maine, where the test was developed. Women with abnormal results must undergo more definitive tests, such as ultrasound and amniocentesis, before the diagnosis is considered final.

—R.L.
Ice cream is the nectar of the gods. This is a fat-free nectar. According to USA Today, that’s what its reporter Pat Guy had to say about the new frozen dessert Simple Pleasures.

Mark Memmott of the same paper was less enthusiastic. “The chocolate leaves a rather unpleasant aftertaste,” he said. “I wouldn’t serve it to my dog. I’d give it to the cat. I don’t like the cat.” Editor Ray Goldbacher’s verdict was more middle-of-the-road: “I don’t think anyone will mistake this for super-premium ice cream, but it’s not bad.”

Pronouncements on the taste of this new dessert varied similarly among others present at the press conference held last February to introduce the product to the public.

What’s all the fuss about? It’s about ice cream without fat. Ice cream without guilt. (Well, maybe some guilt—even though it’s fat-free, it’s not calorie-free.)

Simple Pleasures is a frozen dessert made with Simplesse, the first fat substitute approved by the Food and Drug Administration. In fact, legally, Simple Pleasures cannot be called ice cream because FDA’s standards of identity require that ice cream contain at least 10 percent butterfat. Both Simple Pleasures and Simplesse are products of NutraSweet Co., a subsidiary of Monsanto Co. of St. Louis, Mo. (NutraSweet also makes aspartame, the sugar substitute widely used in low-calorie beverages and other products.)

Simplesse is promoted as a competitor for premium ice creams. In petitioning FDA for approval of Simplesse, NutraSweet compared the fat, cholesterol and caloric content of a super-premium vanilla ice cream containing 16 percent butterfat with a frozen dessert using Simplesse. A 4-ounce serving of the ice cream provided 19 grams of fat, 97 milligrams of cholesterol, and 274 calories, whereas the same size serving of Simple Pleasures contained less than 1 gram of fat, 14 milligrams of cholesterol, and 120 calories. Regular ice cream, with approximately 10 percent fat, contains about 7 grams of fat, 30 milligrams of cholesterol, and 135 calories per 4-ounce serving. (Simplesse is not yet available in vanilla because, the company says, it hasn’t yet been able to get the taste just right. It now offers toffee crunch, chocolate, strawberry, coffee, peach, and rum raisin.)

Generally Recognized as Safe

Simplesse is made from egg white and milk protein blended and heated in a process called microparticulation, in which the protein is shaped into microscopic round particles that roll easily over one another. The aim of the process is to create the feel of a creamy liquid with the texture of fat.

It works. Because its components have long been used as foods, FDA, on Feb. 23, 1990, affirmed Simplesse as “generally recognized as safe” (GRAS) for use as a thickener or texturizer in frozen dessert products. Safety studies were not required.

NutraSweet plans to seek FDA approval for use of Simplesse in additional products, such as mayonnaise, salad dressing, yogurt, dips, sour cream, butter, margarine, and cheese spreads. Simplesse cannot be used in cooking because baking or frying causes it to lose its creaminess. NutraSweet says, however, that “products made with Simplesse can be enjoyed with many hot foods.” For example, it can be used in an imitation butter spread on toast or in a sour cream-type sauce used to top a baked potato.

NutraSweet estimates that full use of Simplesse has the potential to decrease total dietary fat consumption by Americans by 14 percent and dietary cholesterol intake by 5 percent.

Others Being Developed

Other fat substitutes are under development or awaiting FDA approval. Kraft General Foods has petitioned the agency for GRAS approval of Trailblazer, which, like Simplesse, is made from egg and milk protein processed to mimic the “mouth feel” of fat.

Procter and Gamble’s fat substitute Olestra, however, is a different matter. Developed for use in hot foods as well as cold, it is a new substance that, according to the company, is “almost a carbon copy of regular fat, but with a molecule of sugar at its core instead of glycerine, and up to eight fatty acids attached to the core instead of the customary three.”

Because it is a new molecular structure that does not break down to its component parts during digestion, Olestra must be approved as a new food additive rather than as a GRAS substance, which means that studies must be done to ensure its safety.

(Continued on page 27)
Simple Pleasures, the frozen dessert made with the fat substitute Simplesse, is lower in fat, cholesterol and calories than regular and premium ice creams. The question remains whether products made with fat substitutes will effectively reduce overall fat intake by Americans.
Procter and Gamble says its product looks, tastes, feels, and behaves like fat. It cooks without breaking down under heat, yet it cannot be digested and absorbed, so it passes through the body "contribution no calories, no cholesterol, and no fat." The company is asking for approval of Olestra for deep-frying savory snacks such as chips and puffs made from potatoes and corn.

Help for the Health-Conscious

Health- and weight-conscious consumers are expected to welcome fat-free products that taste like the real thing. In fact, a recent survey by the Calorie Control Council, an association of low-calorie and diet food manufacturers, found that 57 percent of adult Americans believe there is a need for fat substitutes.

According to the 1988 Surgeon General's Report on Nutrition and Health, high intake of fat is associated with increased risk for obesity, some types of cancer (breast, colon, prostate, rectum, ovaries, and endometrium), and possibly gallbladder disease. Studies also show strong evidence of a relationship between high saturated fat intake and a high blood cholesterol level, which is a risk factor for coronary heart disease.

The report also states that because obesity is a risk factor for several chronic diseases, it is important to maintain a desirable weight. Obesity increases the risk of high blood pressure and, consequently, stroke. It also increases blood cholesterol and may, by itself, be a risk factor for coronary heart disease.

Because fat contributes nine calories per gram, fat substitution would significantly reduce the calorie content of a food. Excess calories from fat are readily stored and cause weight gain.

A 1985 national survey by the U.S. Department of Agriculture found that fat contributed 34 percent of total calorie intake for children ages 1 to 5, 36 percent for men ages 19 to 50, and 37 percent for women ages 19 to 50.

The National Cholesterol Education Program of the National Heart, Lung, and Blood Institute, along with other health groups, recommends that all healthy Americans 2 and older limit their total daily fat intake to no more than 30 percent of total calories and that less than 10 percent of the total calories should be from saturated fat. Cholesterol should be kept to less than 300 milligrams per day, and the total calorie intake should be what is needed to reach or maintain a desirable weight. (People with certain illnesses or conditions may have different requirements.)

Health Outcome Unknown

It remains to be seen, however, whether consumers will, indeed, become healthier by using products with fat substitutes. According to the June 15, 1990, issue of The Medical Letter, a professional publication on drugs and therapeutics, no clinical studies have shown that use of either Simplesse or Trailblazer leads to weight reduction or decreases blood lipid (fat) concentrations.

Moreover, some nutritionists are concerned that people who eat products made with fat substitutes will feel freer to eat more of other high-fat foods, rationalizing that they are "saving" on those made with substitutes. Another possibility experts anticipate is that people will eat more fat-free double-dip ice cream cones, leaving less room for the more nutritious foods they need.

A more basic, as yet unanswered, question is whether nonfat foods will satisfy as well as the traditional foods they replace and, therefore, whether they will really help people reduce fat consumption.

Lisa Lefferts, staff scientist with the Washington-based consumer advocacy group Center for Science in the Public Interest, points to the experience with sugar substitutes: "We're eating four times the amount of sugar substitutes as we were in 1975, but sugar consumption has gone up as well, so clearly sugar substitutes are not substituting for sugar." Lefferts says that the effect of fat substitutes on the diet is unclear. "Fat substitutes such as Simplesse are a step in the right direction," she says, "but we would encourage that their use be monitored in order to assess their true impact."

FDA, too, has questions about the impact of fat substitutes in the food supply. "There are two categories of fat substitutes to consider," says Walter Glinsmann, M.D., associate director for clinical nutrition. "Products like Simplesse are processed from substances already in the diet, and they are digested and used by the body in the same way as the original substances. Others, like Olestra, are new, undigestible molecules never before in the food supply."

The possible health effects of consuming large amounts of a novel substance must be carefully researched and reviewed before such a product can be marketed. "When you consider that fat intake is about 35 to 40 percent of the daily caloric intake and that half of that fat is derived from foods in which the fat can be replaced with a substitute, you need to take a hard look at the potential health effects," Glinsmann cautions.

Some of the questions to be considered are:

• If the materials are absorbed in the body—even in very small amounts—are they toxic?
• If they are not absorbed, how do they affect gastrointestinal functions? For example, could they interfere with the absorption of nutrients or drugs?
• Are the substitutes suitable for general use or only for subpopulations of the general public?

The financial impact of fat substitutes may be easier to predict than the health and dietary effects. In February 1990, The Wall Street Journal reported that some estimates have Simplesse becoming a $500-million-a-year or bigger business by the mid-1990s. It is not surprising that still more firms, in addition to Kraft and Procter and Gamble, are entering the race for these consumer dollars.

Marian Segal is a member of FDA's public affairs staff.
A woman called the Food and Drug Administration’s office in Orlando, Fla., to thank consumer affairs officer Lynne Isaacs for the nutrition and diet information Isaacs had sent a few weeks before. “She told me that she was ready for a serious well-balanced diet,” Isaacs said. “She had tried all the fad diets and knew they didn’t work. Then she admitted there was one fad she had never tried—a product that claims to burn the fat off while you sleep. She said that because she was an insomniac she figured the product would never get a chance to work. Of course that product doesn’t work anyway, but I think her reason for not trying it may have been unique.”

Thousands of people call or write FDA each year wanting information on a gamut of FDA-regulated items, from aspirin, tongue depressors, and canned green beans to cancer drugs, heart pacemakers, and infant formula.

Exactly what information does FDA have for consumers, and how can they get it?

Consumer Affairs Officers

FDA has consumer affairs officers (also known as public affairs specialists) throughout the country who can respond to questions about the agency and what it regulates.

“Every time there’s something in the news about infant formula or baby food, mothers start calling,” says Marie Ekvall, FDA’s consumer affairs officer in Chicago. “I can hear the baby crying; sometimes the mother’s crying, too.”

Ekvall can usually give enough information over the phone to help the mother determine if there is any risk for her baby. As a follow-up, Ekvall then sends a reprint from FDA Consumer that will give the mother detailed information on infant nutrition.

In addition to reprints of articles from FDA Consumer, CAOs also have brochures, posters, teacher kits, press releases, and background papers on all kinds of FDA-related topics.

Consumers interested in audiovisuals can borrow or buy agency-produced slide shows, videotapes and films. CAOs have information on the titles available, prices, and how to order audiovisuals.

CAOs are also available to speak to consumer and other groups on specific topics such as food labeling, health fraud, or AIDS.

To get in touch with your area’s CAO, look for the Food and Drug Administration entry under the Department of Health and Human Services in the U.S. Government section of your local phone book.

Consumer Inquiries Staff

FDA’s Consumer Inquiries Staff, located at agency headquarters in metropolitan Washington, D.C., is devoted solely to answering consumers’ questions. The staff often consults various other FDA offices to find answers to detailed or complicated questions. Last year, Consumer Inquiries received an average of 2,400 requests per month for information.

Send requests for information to FDA, Consumer Inquiries Staff, HFE-88, Room 16-63, 5600 Fishers Lane, Rockville, Md. 20857; telephone (301) 443-3170.

Electronic Bulletin Board

Most people would describe a bulletin board as a piece of cork, some thumbtacks, and lots of papers with important information and announcements. But tacks and cork have been replaced by computers and modems on FDA’s electronic bulletin board, which contains:

• press releases
• the FDA Enforcement Report’s listing of recalls and litigations
• drug and device approvals
• congressional testimony
• speeches by FDA’s commissioner
• FDA Federal Register summaries
• current information on AIDS, including published information on experimental drugs
• articles from FDA Consumer
• articles from the FDA Drug Bulletin.

Consumers who have computers with modems can subscribe to FDA’s bulletin board by contacting BT Tymnet, 6120 Executive Blvd., Rockville, Md. 20852; telephone 800-872-7654.

For more details on the types of information “posted” on the bulletin board, contact Karen Malone, FDA Press Office, HFI-20, Rockville, Md. 20857; telephone (301) 443-3285.

Freedom of Information Staff

The Freedom of Information Act makes most unpublished documents con-

(Continued on page 30)
FDA doesn’t have all the answers. Several other government agencies have responsibilities closely related to FDA’s, so it isn’t unusual for consumers to be confused about who watches over what. Here’s a confusion-controlling list of subjects consumers often call FDA about, but which are under the purview of another agency. (All addresses listed below are for headquarters offices in Washington, D.C. Local offices are listed in the phone book under U.S. Government.)

Alcohol
The labeling and quality of alcoholic beverages are regulated by the Treasury Department’s Bureau of Alcohol, Tobacco, and Firearms. ATF’s address is Room 4402, Ariel Rios Federal Building, 1200 Pennsylvania Ave., N.W., Washington, D.C. 20226; telephone (202) 566-7135.

Information on drug and alcohol abuse, including counseling information, is available from the Alcohol, Drug Abuse, and Mental Health Administration’s National Clearinghouse for Alcohol and Drug Abuse, P.O. Box 2345, Washington, D.C. 20013; telephone (202) 629-1500.

Consumer Products
While FDA keeps watch over the quality of bread, the toaster used to brown it (and processed foods), it is the responsibility of the Consumer Product Safety Commission. Household appliances (except those that emit radiation), baby furniture, and toys are some of the more common products CPSC covers. Letters can be sent to CPSC, Washington, D.C. 20207, or the commission can be called toll free on 800-638-2772.

Drugs
Drugs of Abuse: Illegal drugs with no approved medical uses, such as heroin, are the sole responsibility of the Drug Enforcement Administration. Because some medically accepted drugs have a potential for abuse (for example, amphetamines, barbiturates and morphine), FDA assists DEA in deciding how stringent DEA controls on such drugs should be. DEA also limits the amount of these drugs that can be manufactured each year. Everyone who markets controlled drugs, from manufacturers and distributors to pharmacists, must register with DEA. Questions about these responsibilities should be sent to the Drug Enforcement Administration, U.S. Department of Justice, Washington, D.C. 20537; telephone (202) 307-1000.

Nonprescription Drug Advertising: The Federal Trade Commission is the primary agency for regulating ads for nonprescription drugs. The commission’s address is 6th St. and Pennsylvania Ave., N.W., Washington, D.C. 20580; telephone (202) 326-2180.

Child-Resistant Packages: The Consumer Product Safety Commission is responsible for child-resistant packages. See address above.

Food Stamps
The federal food stamp program is administered by local governments, usually as part of their social service departments.

Meat and Poultry
The U.S. Department of Agriculture’s Food Safety and Inspection Service is responsible for the safety, labeling, and all other issues concerning meat and poultry. Consumers with questions on these issues, as well as how to safely handle, prepare and store chicken, beef and pork, should write or call the Food Safety and Inspection Service’s Meat and Poultry Hotline, Room 1635S, Washington, D.C. 20250; telephone 800-535-4555.

Pesticides
FDA, USDA, and the Environmental Protection Agency share the responsibility for regulating pesticides. EPA determines the safety and effectiveness of the chemicals and establishes tolerance levels for residues on feed crops and raw and processed foods. These tolerance levels (the amount of pesticide allowed to remain on a crop after harvesting) are normally set 100 times below the level that might cause harm to people or the environment. To ensure that pesticide residues do not exceed the allowable levels, FDA tests all foods except meat and poultry, which fall under USDA’s jurisdiction. Questions for EPA can be sent to Room W311, Mail Code A-107, 401 M St., S.W., Washington, D.C. 20460; telephone (202) 382-4361.

Radiation
Environmental: EPA monitors radiation in the environment.
Nuclear Industry: Licensing and regulation of the nuclear industry is the Nuclear Regulatory Commission’s responsibility. NRC also ensures that the public is protected from hazards arising from nuclear materials in power reactors, hospitals, research laboratories, or other commercial facilities. Questions for NRC should be sent to the NRC Office of Public Affairs, Washington, D.C. 20555; telephone (202)-492-7715.

Restaurants and Grocery Stores
Inspections and licensing of restaurants and grocery stores are usually handled by local health departments.

Tobacco
Collecting taxes on cigarettes and other tobacco products is ATF’s responsibility. Information on the health effects of smoking is available from the Office of Smoking and Health, Centers for Disease Control, 5600 Fishers Lane, Rockville, Md. 20857; telephone (301) 443-5287.

Veterinary Products
EPA regulates products used directly on animals to control pests. USDA’s Animal and Plant Health Inspection Service handles animal vaccines. The inspection service’s address is APHIS, Veterinary Services, U.S. Department of Agriculture, Washington, D.C. 20250; telephone (202) 447-5193.

Water
Depending on how it gets to consumers, water is regulated by either FDA or EPA. If the water comes through the tap, it must meet EPA’s national standards for drinking water. Bottled water, however, is FDA’s responsibility.
Concerning FDA’s regulatory activities available to the public. These include:

- enforcement records, including product recall notifications
- summaries of safety and effectiveness data from approved new drug applications
- regulatory letters telling companies to correct violations found during FDA inspections.

An FOI request for agency records can be denied only under set guidelines. Documents that may be exempt from public disclosure under the Freedom of Information Act include:

- trade secrets and confidential commercial or financial information
- certain interagency or intra-agency memos or letters
- personnel, medical and similar files that, if released, would constitute an invasion of privacy
- certain records compiled for law enforcement purposes

All FOI requests should be in writing. For consumers, there is a copying fee of 10 cents per page and a search fee of $10 per hour. No fee is charged if the total is less than $10.

For more information or to make an FOI request, contact the Freedom of Information Staff, HFI-35, FDA, Room 12A-16, 5600 Fishers Lane, Rockville, Md. 20857.

What Does FDA Regulate?

FDA’s responsibilities include foods, drugs, cosmetics, biological products, medical devices, and veterinary products sold in interstate commerce. (For information about what FDA does not regulate, see accompanying article.)

Some of the agency’s specific responsibilities include:

**Drugs:**
- new drug approval
- good manufacturing practices for all prescription and nonprescription drug manufacturers
- prescription drug advertising
- tamper-resistant packaging

**Biolgies:**
- human vaccine licensing
- blood banks
- allergenic product licensing
- licensing of test kits to screen blood for the AIDS virus

**Foods:**
- labeling
- safety of all food products except meat and poultry (see accompanying article)
- good manufacturing practices
- bottled water

**Medical Devices:**
- pre-market approval of new devices
- manufacturing controls
- medical device reporting of malfunctions or serious adverse reactions
- registration and device listing

**Electronic Products:**
- radiation safety performance standards for microwave ovens, television receivers, diagnostic x-ray equipment, cabinet x-ray systems (e.g., baggage x-rays at airports), laser products, ultrasonic therapy equipment, mercury vapor lamps, and sunlamps
- guidance to health professionals and consumers about recommended practices to reduce unnecessary exposure to radiation

**Veterinary Products:**
- livestock feeds
- pet foods
- veterinary drugs and devices

**Our Lips Are Sealed**

Some of the hardest questions FDA has to deal with are ones about a specific drug, says Marie Ekvall, FDA’s consumer affairs officer in Chicago. “I encourage [callers] to talk to [their] doctor or pharmacist, and I let them know about resource books like the *Physicians’ Desk Reference*, but I have to be careful not to play doctor,” she says.

“We get a lot of calls that, by law, we simply aren’t allowed to answer,” says Janet McDonald, San Francisco’s CAO. For example, FDA employees cannot release any confidential information on unapproved drugs, including clinical trials, unless the manufacturer gives the agency permission or has already released the information to the public.

“This is information people usually have to get from their physicians or from private, nonprofit organizations such as those that deal with Alzheimer’s disease or arthritis,” says McDonald.

But there are some calls that just can’t be answered by FDA or anyone else. For example, there’s the boy who wrote Orlando’s Isaacs to find out where he could buy a “hoverboard,” one of those flying skateboards in the movie “Back to the Future II.”

“They things haven’t been invented yet—I’d know because my 8-year-old would be begging for one,” says Isaacs. “But if they were real, I guess they’d belong to the Consumer Product Safety Commission.”

Dori Stehlin is a staff writer for FDA Consumer. Monica Arcarese, a student at Towson State University, also contributed to the article while a summer intern at FDA.
How to Take Your Medicine

Beta Blocker Drugs

How you take a drug can be very important to both its effectiveness and safety. Sometimes it can be almost as important as what you take. Timing, what you eat and when you eat, proper dose, and many other factors can mean the difference between feeling better, staying the same, or even feeling worse. This drug information page is intended to help you make your treatment work as effectively as possible. It is important to note, however, that this is only a guideline. You should talk to your doctor about how and when to take any prescribed drugs.

The sixth installment of this series features a group of drugs called beta blockers.

Conditions These Drugs Treat

All beta blockers are used to treat high blood pressure. Many are also used to prevent the heart-related chest pain or pressure associated with angina pectoris (a condition often occurring during exertion where too little blood reaches the heart). Atenolol, metoprolol, timolol, and propranolol are used to improve survival after a heart attack. Propranolol is used to treat heart rhythm problems, other specific heart conditions, migraine headaches, and tremors. Beta blockers can be used for other conditions as determined by your doctor.

Beta blockers cannot cure these conditions. However, by blocking certain receptors in the body, beta blockers lower and regulate the heartbeat and lessen the heart’s workload.

While taking beta blockers, it is important that you continue any diet and exercise program prescribed by your doctor, as these are often important parts of the therapy for the conditions being treated.

How to Take

Beta blockers can be taken either with food or on an empty stomach.

If you are taking an extended-release product such as Inderal LAR (propranolol), swallow it whole. Don’t chew it or crush it in any way.

If you are taking the concentrated solution of propranolol, always use the dropper provided. You can mix the solution with water or any other beverage (or, if you prefer, pudding or applesauce). After taking a dose, rinse the glass with some liquid and drink that liquid as well to be sure that the entire dose is taken.

Be sure to take the right number of tablets or capsules for each dose. Taking your medicine at the same time each day will help you remember to take it regularly.

Missed Doses

Do not suddenly stop taking a beta blocker without first talking to your doctor. Your condition could worsen if you stop taking this medicine or miss many doses.

If you miss a dose, take it as soon as you remember. If you take the beta blocker once a day, you can take it up to eight hours before the next scheduled dose. If you take the medication more often than once a day, you can take it up to four hours before the next scheduled dose. Ask your doctor or pharmacist if you have questions.

Never take two doses at the same time. Always have enough of your beta blocker medicine to last over weekends, holiday periods, and when you travel.

(Continued on next page)
Drug Tips

Don’t store drugs in the bathroom medicine cabinet. Heat and humidity may cause the medicine to lose its effectiveness. Keep all medicines, even those with child-resistant caps, out of the reach of children. Remember, the caps are child-resistant, not child-proof. Discard medicines that have reached the expiration date.

Relief of Symptoms

For conditions such as high blood pressure, angina, heart rhythm disturbances, or tremors, some effects can be seen immediately and usually peak within a week. If treating migraine headaches, it may take up to six weeks before the full effects occur. For any of these conditions, the dosage of the beta blocker may need to be adjusted by your doctor when you first begin taking it. Also, the appropriate dosage can vary greatly among people, depending on individual response.

Since many of the conditions that beta blockers treat are chronic, you may have to take this medicine for the rest of your life.

Side Effects and Risks

Common side effects include slowed heartbeat, tiredness, nausea, diarrhea, constipation, and decreased sexual ability. Other mild side effects can include difficulty sleeping or nightmares, headache, drowsiness, and numbness or tingling of the fingers, toes or scalp. Also, if you have diabetes, beta blockers can obscure some of the signs of low blood sugar, such as tremors or rapid heartbeat. Check with your doctor if any of these side effects seems troublesome or if you have any questions.

More serious reactions can sometimes occur with beta blockers. These include the following:

• the beginning or worsening of heart failure. Symptoms of this include shortness of breath (especially on exertion), coughing, weakness, weight gain, and swelling of feet, ankles, or lower legs.
• severe wheezing or difficulty breathing, especially in people who have or have had asthma, chronic bronchitis, emphysema, or other breathing conditions. Because beta blockers can trigger or worsen these conditions, make sure your doctor knows about them.
• an extremely slow heartbeat (less than 50 beats per minute)
• cold hands and feet or blue fingernails, which could mean reduced circulation to these areas
• confusion, hallucinations or depression. If any of these or other serious reactions occur, call your doctor immediately.

Precautions and Warnings

If you suddenly stop taking a beta blocker, you could worsen your condition and experience potentially dangerous side effects, such as chest pain, fast or irregular heartbeat, high blood pressure, and headaches. Always check with your doctor before discontinuing a beta blocker.

Consult with your doctor if you think you could become pregnant or plan to breast-feed while on a beta blocker.

Learn how the medicine affects you.

Don’t drive or operate machines if this medicine makes you drowsy, dizzy or lightheaded. If you are taking labetalol, dizziness or lightheadedness can occur when getting up from sitting or lying down. If this happens, sit up slowly, placing your legs over the side of the bed or couch, and stay there for a few minutes before trying to stand.

Before any surgery or dental work, tell the physician or dentist that you are taking beta blockers. Tell your physician if you are taking or considering taking any other prescription or nonprescription medication.

Drinking alcohol while on beta blockers can sometimes increase the chance of side effects such as dizziness or tiredness.

Igor Cerney is on the staff of FDA’s Drug Labeling, Education and Research Branch.
There are no U.S. RDAs for Vitamin K established yet by FDA for food labeling purposes; however, in the 10th edition of Recommended Dietary Allowances, the National Research Council of the National Academy of Sciences for the first time recommended allowances for vitamin K—for example, 80 micrograms for males 25 years and older and 65 micrograms for females of same age.

**Vitamin K** is a fat-soluble vitamin usually formed in the body by intestinal bacteria but also available from some plant and animal sources.

**Function:** Essential in the formation of prothrombin, a substance necessary for proper clotting of blood, and at least five other blood-clotting factors.

**Sources:** All green leafy vegetables (including lettuce, spinach, kale, and cabbage), eggs, meats, cereal grain products, fruits, and milk and dairy products.

**Deficiency:** Vitamin K deficiency may cause bleeding disorders in premature infants with inadequate amounts of stored vitamin K, and in people on blood-thinning medications and those with fat malabsorption syndromes.

**Excess:** Natural forms have no known toxic effects; large doses of the synthetic version, menadione, and its derivatives cause anemia and kernicterus, a condition characterized by jaundice, in infants.

Paula Kurtzweil, R.D., of FDA’s Office of Public Affairs, and Theresa A. Young, of FDA’s Philadelphia district office, contributed to this series.
The Notebook: a potpourri of items of interest gathered from FDA news releases, other news sources, and the Federal Register (designated FR, with date of publication). The Federal Register is available in many public libraries.

- **Chlorofluorocarbon propellant** may now be used in a metered-dose atropine sulfate aerosol administered by oral inhalation. Chlorofluorocarbon propellant may be used only in products considered “essential” by FDA because it may reduce the amount of ozone in the atmosphere. The agency concluded that atropine sulfate aerosol with chlorofluorocarbon is uniquely beneficial for treating nerve gas poisoning, and FDA approved its use in a response to a petition submitted by the Office of the Surgeon General, Department of the Army. For further information, contact Adele S. Seifried, Center for Drug Evaluation and Research (HFD-362), FDA, 5600 Fishers Lane, Rockville, Md. 20857, telephone (301) 295-8046. (FR Sept. 26.)

- **Some cancer death rates** have increased dramatically since 1968, according to a study published in a recent issue of The Lancet, a British medical journal. Researchers noted that the incidence of brain tumors, multiple myeloma (a tumor of white blood cells), breast cancer, and malignant melanoma has risen sharply in all six countries studied—the United States, England and Wales, France, West Germany, Italy, and Japan.

- **“Light sour cream,”** a product from Old Home Foods, Inc., that contains 9 percent fat (compared to the 18 percent fat content normally required in sour cream under FDA’s standards of identity), will be test-marketed for 15 months, beginning no later than Dec. 11. It was developed to offer consumers a product nutritionally equivalent to sour cream but with fewer calories and less fat. For further information, contact Shellee A. Davis, Center for Food Safety and Applied Nutrition (HFF-414), FDA, 200 C St., S.W., Washington, D.C. 20204, telephone (202) 426-9463. (FR Sept. 10.)

- **An Office of Research on Women’s Health** has been created at the National Institutes of Health. The office is charged with ensuring that research into women’s health issues is appropriately supported by NIH, the U.S. government’s top biomedical research center, and with seeing that women are adequately represented in clinical tests.

- **Iron-fortified formula** should be used for all formula-fed infants, according to the American Academy of Pediatrics’ Committee on Nutrition. The committee found no supporting data that iron-fortified formulas produce more gastrointestinal discomfort than low-iron formulas. Nor does iron in formulas interfere significantly with the absorption of other minerals, such as zinc and copper.

- **Carnation Follow-Up Formula’s** claim that it is nutritionally superior to other infant formulas will be halted, the Carnation Company has agreed. The claim was reviewed by the National Advertising Division of the Council of Better Business Bureaus, Inc., after a competitor questioned Carnation’s statement that its product “means extra nutritional assurance for your baby.” (NAD Case Report, Sept. 17.)

- **Gellan gum** may now be used as a stabilizer and thickener in frostings, glazes, icings, jams, and jellies. FDA approved the use in response to a petition filed by Kelco, a division of Merck & Co., Inc. For further information, contact Blondell Anderson, Center for Food Safety and Applied Nutrition (HFF-334), FDA, 200 C St., S.W., Washington, D.C. 20204, telephone (202) 426-9463. (FR Sept. 28.)

- **Weight Watchers Frozen Entrées** may continue to be advertised as “Health Watchers,” the National Advertising Division (NAD) of the Council of Better Business Bureaus determined after a competitor challenged the claim. NAD agreed with H.J. Heinz Co., maker of Weight Watchers Frozen Entrées, that the meals fit well within the National Cholesterol Education Program dietary guidelines for regulating intake of fats, cholesterol and sodium. NAD also noted that at this time there is no accepted government or industry definition of a “healthy” food. (NAD Case Report, Aug. 20.)

- **Sweet ’N Low,** the sugar substitute, will no longer be advertised as the sweetener consumers prefer. A competitor challenged Sweet Foods Corporation, the product’s manufacturer, saying that the advertiser based its taste preference claim solely on market share data. The National Advertising Division of the Council of Better Business Bureaus, Inc., agreed that accepted industry practice is to substantiate a comparative taste claim by means of a taste test, not by market share data. (NAD Case Report, Sept. 17.)
Counterfeit Pills Buy Prison Time

by Dixie Farley

A pharmacist in Racine, Wis., noticed that the brand name on some Ovulen-21 tablets was spelled wrong.

A pharmaceutical purchasing agent in Clearwater, Fla., received complaints that Ovulen-21 birth control pills had caused breakthrough bleeding in some users.

A Chicago pharmacist wondered why the price of his latest order of Ovulen-21 was so much cheaper than previous batches.

These were the first clues in a two-year FDA investigation that led to the exposure of an international drug counterfeiting ring, seizure of some 1.5 million bogus Ovulen-21 tablets, and the longest prison terms ever imposed for violation of the federal Food, Drug, and Cosmetic Act. The case culminated in convictions of seven individuals, including an 11-year prison term for a defendant who went to trial last March, after five postponements and a mistrial, and 24-year prison terms for two others.

After receiving reports of the initial problems, G.D. Searle and Company of Skokie, Ill., the registered manufacturer of Ovulen-21 oral contraceptives, notified FDA's Chicago district office on Oct. 16, 1984, that counterfeit Ovulen-21 tablets were on the market. Analyses of the two drug lots in question showed that the pills were not only counterfeit, but also subpotent, thus providing unreliable contraception.

On Oct. 17, the Tennessee and Kentucky State Boards of Pharmacy informed FDA's Nashville office that some complaints had been received from pharmacies in Kentucky and Tennessee. FDA traced sales of the tablets to Interstate Drug Exchange, Inc. (IDE), in Plainview, N.Y. Inspection of IDE by FDA's New York office revealed that the firm had bought the phony Ovulen-21 from Lantor Corp., Miami. IDE recalled the pills from its consignees on Oct. 25, and investigators from FDA's Orlando office inspected Lantor. They learned from Fermin Alfonso, the firm's president, that Lantor also had sold the counterfeit drugs to other New York distributors: Interstate Cigar Company in Westbury and Quality King Distributors, Inc., in Deer Park.

Alfonso, however, denied knowing anything about the origin of the pills, claiming a wholesaler in Panama had obtained them for him. He denied knowing about some shipments FDA already had documented.

On Nov. 1, Searle initiated a recall of the two suspect drug lots, including authentic tablets. The decision cost the company more than a million dollars but provided immediate notification of the problem to the public and removed the
lots from the market.

In an interview on Nov. 12, Alfonso mentioned that he had borrowed money for his business from a friend, Beatriz Villalon.

FDA suspected Alfonso and Villalon were involved in counterfeiting the Ovulen-21 because, among other things, Alfonso persisted in trying—unsuccessfully—to sell the tablets, even after Searle’s announced recall and after FDA had talked with him.

Visits to various drug distributors in November by investigators from FDA offices resulted in 13 seizures of the counterfeit drugs at locations in Alabama, California, Florida, Illinois, Kentucky, Mississippi, New York, Rhode Island, Tennessee, Texas, and Washington.

Investigation of some of the seized product led to Gulfcoast Drug Supply, Inc., Miami. From Gulfcoast’s president, Robert Pollock, FDA learned about another suspect, Sheldon Harwin.

But here the trail cooled. As a result of previous, unrelated charges, Harwin was in prison and refused to talk to FDA.

To try to document the origin of the counterfeit Ovulen-21 and find out other facts, FDA in 1985 and 1986 extended its investigation to foreign countries, enlisted Interpol and the U.S. Customs Service, and visited additional drug distributors and other businesses, including airlines, telephone companies, banks, and printing and packaging firms.

Agency investigators interviewed individuals repeatedly and pored over hundreds of documents.

Gradually, two conspiracies emerged: The first one began in 1981 and involved imported drugs from Spain; the second began in 1984 with drugs smuggled from Guatemala.

One of the leads in FDA’s investigation pointed to involvement by Gilbert Yurubi, Alfonso’s cousin. FDA questioned Yurubi during 1985 and early in 1986. He agreed to cooperate and provided information that confirmed the first conspiracy. Following other leads, agency investigators in June 1986 visited the manufacturer involved in the second conspiracy.

On July 7, 1986, after release from jail, Harwin provided some information, including the name of the Barcelona, Spain, manufacturer, whom FDA interviewed in August.

The First Conspiracy

In December 1981 at a bank office building in Coral Gables, Fla., Sheldon Harwin and Edward Peterson met with the owner of a Barcelona pharmaceutical company to arrange purchase of oral contraceptives. Within a few weeks, 10,000 cycles of the pills were shipped through Texas to Monterrey, Mexico, from where they could later be smuggled.

For help with the smuggling, Peterson contacted a person known as “J.J.,” who Peterson believed was a smuggler but actually was an undercover agent for the U.S. Drug Enforcement Administration (DEA). Thinking Peterson was smuggling controlled drugs, the agent agreed to help Peterson, and the pills were smuggled back into Texas in January 1982. (The DEA tape recordings of the conversations between J.J. and Peterson provided early records for FDA’s investigation.)

In July, Harwin, using the name “J. Black” and claiming to work for Searle, placed an order with a Hollywood, Fla., firm to print the Ovulen-21 trademark and logo in brown ink on 10,000 blue envelopes. These were outer envelopes; the pills were sealed in one-month cycle blister packs.

Harwin sold the drugs to Gulfcoast Drug Supply for $39,720, splitting the profits with Peterson. This was Peterson’s last known participation in the conspiracy.

In September 1982, Harwin again met the Barcelona manufacturer in Coral Gables to discuss another shipment. A month later, Harwin asked Fermín Alfonso to help bring the pills into the United States. Alfonso agreed and introduced Harwin to a contact at a commercial airline who could smuggle pills into the United States when they came through the Miami airport en route to Haiti. The plan worked. Harwin received 50,000 cycles in December.

Harwin had more “Ovulen” packaging printed and in January 1983 made a deal to sell the entire shipment to Gulfcoast. The pills were delivered to Gulfcoast on Feb. 2. But Gulfcoast’s Pollock noticed the pills weren’t exactly like Searle’s Ovulen-21 and decided they weren’t authentic. He telephoned Harwin to cancel the deal and returned the shipment to Harwin at a warehouse in Hollywood, Fla. Pollock retained more than 3,000 cycles, however, which he later sold to a drug distributor—knowing they were counterfeit.

Meanwhile, a Florida judge revoked Harwin’s previous probation and on March 30 sentenced him to five years in prison for an unrelated offense.

Shortly after Harwin was jailed, Alfonso and Beatriz Villalon delivered part of the stored pills to another buyer, a Florida agent for H.L. Moore Drug Exchange of Melville, N.Y. But Searle was now using white envelopes instead of blue, and the agent noticed the envelopes were the wrong color and decided the pills were counterfeit. Like Pollock, the agent refused delivery but, also like Pol-
lock, didn’t notify FDA.

During the summer, Villalon and Alfonso approached Gilbert Yurubi and Jacques Behar, a business partner of Yurubi, and persuaded them to invest $40,000 to buy the Barcelona pills from Harwin for a share of the profits. Yurubi paid the $40,000 to Harwin’s son, and the Barcelona pills were turned over to Alfonso, Villalon, Behar, and Yurubi.

About this same time, Alfonso made arrangements with a Miami printer to have envelopes printed in blue ink on white paper to resemble Searle’s new packaging.

In October 1983, Alfonso and Villalon delivered 20,250 blister packs to Interstate Drug Exchange for $115,425. Payment was made by wire to bank accounts in Panama City, and on Nov. 28, they delivered another 25,550 packs for $107,000, also wired to a Panama account.

The Second Conspiracy

In March 1984, Alfonso and Villalon traveled to Guatemala City and met with the owner of a small pharmaceutical laboratory there. The owner refused to make tablets with the name “SEARLE” but did agree to make products imprinted “SEABLE.”

The conspirators obtained the active ingredients and packaging materials and shipped them to the Guatemalan laboratory, usually using the name Vibe Export Corporation (Villalon’s company). They ordered 50,000 cycles in unlabeled packets from the owner, reformulated to reduce by half the tablets’ estrogen component and to substitute progesterone hormone for the tablets’ other active ingredient, ethynodiol diacetate. In turn, the laboratory supplied 43,267 cycles to a Guatemala City exporter, who sent them to a Panama firm for labeling and subsequent shipment to the United States.

In August 1984, Alfonso and Villalon sold 12,000 cycles of the pills to Interstate Cigar Company. In September and early October, under the name Fenix World Trade Corporation, they sold some 22,000 cycles to Quality King Distributors, with delivery through a shipping company in Panama.

Over the summer and fall of 1984, Alfonso and Villalon had ordered approximately 319,000 more Ovulen envelopes, visited packaging-machine manufacturers in Florida and New Jersey to look into buying automated equipment (even after they knew FDA was aware of the counterfeiting), and ordered 250,000 envelopes for Demulen, another Searle contraceptive. The two were gearing up for large-scale counterfeiting of additional prescription drugs for U.S. distribution. This never happened.

Justice

On Feb. 11, 1987, six defendants were charged in a 29-count indictment in the U.S. District Court for the Southern District of Florida. Due to Harwin’s complaints of poor health, his trial was delayed several times until March 1990.

A seventh defendant, Pollock, pleaded guilty to one count of distributing a counterfeit drug and cooperated with the government. He received six months’ probation and a $7,500 fine.

Behar and Yurubi pleaded guilty to one count each of conspiracy and cooperated with the government. Peterson pleaded guilty to one count of conspiracy and a second count of distributing a counterfeit drug. Behar and Yurubi were each given jail terms of 10 months and Peterson, five years. All three have since been released on probation.

Alfonso and Villalon pleaded not guilty and waived a jury trial. On July 13, 1987, the judge found them guilty on all 21 counts charged, and they were sentenced the following September to 24 years in prison, which they are currently serving in the Federal Bureau of Prisons.

Harwin initially signed a plea bargain and cooperated but withdrew the plea on the eve of the Alfonso-Villalon trial. He was ultimately found guilty on the five counts charged and was sentenced on May 1, 1990, to 11 years in jail. He reported June 1 to prison and must serve at least 48 months before becoming eligible for parole.

The press has reported lawsuits over pregnancies allegedly resulting from use of the bogus drugs, but FDA is unaware of any final judgments.

As a result of these and other prescription drug smuggling schemes, FDA has stepped up efforts to prevent unauthorized reimportation of prescription drugs. In September 1985, the agency issued an import alert by which prescription drugs returned to the United States are automatically detained at the border until documents are produced to show they originated here. In addition, the U.S. Congress enacted the Prescription Drug Marketing Act of 1987, which bans the reimportation of drugs produced in the United States unless the drug is imported at the time of any final judgments.

For information about legitimate oral contraceptives, see “The Pill: 30 Years of Safety Concerns” on page 7 of this issue.)

Dixie Farley is a staff writer for FDA Consumer. Edward Atkins, director of compliance for FDA’s Orlando district office, also contributed to this story.
Sale of Peroxy Products Halted

Hydrogen peroxide, a blonde's best friend, can do more than lighten the locks, according to an entrepreneur in Minneapolis. Maybe so, but it can't, FDA decided, do all that the Minnesota manufacturer claimed.

In a pamphlet he distributed, Conrad LeBeau, president of Vital Health Products, claimed that Peroxy Gel and Peroxy Spray—his two products made with hydrogen peroxide and aloe vera—could treat AIDS, cancer, multiple sclerosis, emphysema, and heart disease. LeBeau's promotional material further claimed that Peroxy Gel was an "anti-infective agent that kills germs, virus and fungi on contact." Rubbed into the skin, it leads to "better detoxification, ph balancing and quenching free radicals." LeBeau also claimed that a dab on your toothbrush "may be used orally to kill plaque causing bacteria."

FDA officials, however, became suspicious of such claims and decided to investigate.

An ad for these products in a monthly midwestern magazine brought them to FDA's attention. In November 1987, investigators from the agency's Minneapolis district office inspected LeBeau's home, which also served as his office, and collected samples of the products for analysis. Laboratory analysis showed that the gel and spray contained only aloe vera and hydrogen peroxide—neither approved as safe and effective for the diseases they claimed to cure.

On March 14, 1988, FDA sent LeBeau a letter warning that his products "made therapeutic claims for which there was no scientific or medical evidence." LeBeau responded in a letter March 22 that his company had "discontinued promotional materials for Aloe Vera Oxygel suggesting its use for AIDS, arthritis and cancer," and that it had stopped selling the product "on or around Dec. 1, 1987."

A subsequent investigation in the fall of 1988 showed that nothing had changed. LeBeau still sold Peroxy Gel and Peroxy Spray with labels and literature claiming that his products cured a host of diseases.

At FDA's request, the U.S. District Court for the Eastern District of Wisconsin issued an order on Feb. 3, 1989, to seize LeBeau's products. U.S. marshals seized approximately $1,300 worth of Peroxy Gel and Peroxy Spray from LeBeau's home. The products were subsequently destroyed.

Solid Gold Fraud

A San Diego businesswoman and her corporation were found guilty of criminal contempt for selling fraudulent pet "medicines" despite a court-ordered permanent injunction forbidding her to do so.

A three-day trial in the U.S. District Court for the Southern District of California, ending on July 12, 1990, brought to a close 12 years of FDA actions to put a halt to the fraud. In his summary statement, presiding Judge Gordon Thompson Jr. said that Sissy Harrington-McGill, president and owner of Solid Gold Health Products for Pets, doing business as Solid Gold Holistic Animal-Equine Nutrition Center, had never really intended to comply with the terms of the injunction, but instead had continued to market her products over the last two years with the same prohibited therapeutic claims and product names.

Harrington-McGill had claimed her products—sold under such names as "Solid Gold Energy Plus," "Solid Gold Concept-A-Mare," "Solid Gold Yucca/Anise Combination," and "Solid Gold Herbal Wermor"—could cure or treat animal diseases such as cancer, arthritis, cataracts, hip dysplasia, immunological and vascular disorders, parasitic infestations, conception problems, nervous tension, and muscle cramps. She claimed that one of her products, "Solid Gold Herbal Extension," could cure feline leukemia, a disease that strikes 1 million cats each year. (There is no cure for feline leukemia. An approved vaccine to prevent the disease is available.) Most of her products consisted of herbal mixtures, vitamin or mineral supplements, and unapproved food additives that have not been shown to be effective in treating animal diseases.

Harrington-McGill set up her pet supply business initially at her residence in La Mesa, Calif., a suburb of San Diego, in the late 1970s. A complaint received by FDA's Center for Veterinary Medicine led to inspection of the firm in 1978 by the Los Angeles district office, and, in January 1979, FDA sent Harrington-McGill a letter warning her to stop making health claims for two of her pet products, "Scorbate" and "Animal Skin Cream." Harrington-McGill did remove the claims from the product labels, but the claims later showed up in the firm's promotional literature.

FDA's inspection of the firm in December 1979 revealed that a product called "Petzyme," made largely from brewer's yeast, was being marketed as a flea repellent for dogs and cats. Although
In May 1980 the firm entered into a voluntary agreement with the government not to market the product as a flea repellent, it continued to do so until March 1982, when, at FDA's request, federal marshals seized approximately $30,000 worth of "Petzyme" at Harrington-McGill's residence. On May 24, Harrington-McGill signed a consent decree agreeing to stop making such claims. She also changed the name of the product to "Veterinary Brewer's Yeast." However, she continued to market the product, claiming it would get rid of fleas on dogs and cats. Subsequent advertising referred to the product as "Formerly Petzymes Against Fleas."

Following inspection of Solid Gold in 1985, FDA sent the firm and Harrington-McGill another letter in March 1986, citing unfounded animal health claims for five additional products and requesting that she stop making such claims. Again, changes to the immediate product labels only were made, with no perceptible changes to the immediate product labels. But many of the new stick-on labels failed to adhere or obscure the former names. Moreover, some of the new stick-on labels were placed over the old product labels to conceal their identities, she had merely changed the name of the product to "Veterinary Brewer's Yeast." However, she continued to market the product, claiming it would get rid of fleas on dogs and cats. Subsequent advertising referred to the product as "Formerly Petzymes Against Fleas."

On April 22, 1988, at FDA's request, Harrington-McGill signed a consent decree of permanent injunction, barring her and her firm from making unfounded health claims and from selling 13 of her products even without such claims unless the names were changed. The injunction also required her to submit all labeling and other promotional material to FDA for approval before she could resume marketing these products and barred the distribution of a product description list that made express or implied therapeutic claims. The injunction also required her to recall affected products and to notify all of her employees of the prohibitions of the decree.

Approximately one month later, in May 1988, FDA investigator Thomas R. Beilke, posing as a customer, visited the Solid Gold retail store and found that Harrington-McGill was still selling two products she had been explicitly enjoined from distributing by those names. A telephone order to Solid Gold by FDA investigator Armando Chavez and a visit to the El Cajon facility by investigators William Bowman and Robert Rast in early July revealed the firm was further violating terms of the injunction by continuing to make therapeutic claims in product description lists, product labels, and promotional materials. She also was selling products forbidden by the decree to be marketed under these names. To conceal their identities, she had merely placed new labels over the old product names. Many of the new stick-on labels failed to adhere or obscure the former names. Moreover, some of the name changes had not been authorized by FDA as required by the injunction.

When the investigators asked Harrington-McGill to provide them with sales and distribution records, she refused, in a direct violation of the decree. She further violated the decree by not conducting a satisfactory product recall, not advising her customers that such products had not been proven effective for their labeled indications, and not properly notifying her employees, distributors, and other individuals associated with the firm of the prohibitions of the decree.

On Oct. 31, 1988, FDA received a complaint from James E. Corbin, Ph.D., a former professor of animal science at the University of Illinois. Corbin had attended a pet industry trade show in Chicago two weeks earlier and had seen an exhibition booth in which Harrington-McGill displayed signs making unfounded therapeutic claims for several Solid Gold Products.

On Jan. 16, 1989, FDA investigator Evangel Strickland, posing as a potential customer, telephoned Solid Gold. He said he was ordering several products for his "sick dog with arthritis" and mentioned that his dog had trouble conceiving. Harrington-McGill took the phone order and told him that Solid Gold's "Yucca-Anise" would "clear up arthritis by rebuilding the damaged tissue with new cells." She also sold Strickland three other products—"SeaMeal," "Concept-A-Bitch," and "Positive Perls Oil of Evening Primrose"—which she claimed would relieve swelling, clear up rashes, and aid conception during breeding. The products soon arrived by mail.

FDA immediately began preparing documents for the Department of Justice. On Feb. 27, 1990, the assistant U.S. attorney...
in San Diego handling the case filed papers charging Harrington-McGill with contempt.

On Aug. 27, 1990, following a July 12 guilty verdict, Judge Thompson sentenced Harrington-McGill to 179 days in jail, and fined the company $10,000 and placed it on five years’ probation.

Spiked Wheat

A tip from a disgruntled former employee of a large Minnesota grain company led to court-ordered heavy fines and probation for the owners last February.

Schuler Grain Co. in Breckenridge, Minn., was using an additive to artificially boost the protein content of its wheat and thereby increase the price it brought on the market. Ultimately, the Schulers’ profit came out of the consumer’s pocket—for higher-priced baked goods at the grocery store.

In August 1985, the tipster told the U.S. Department of Agriculture about the firm’s illegal activities. USDA in turn notified FDA.

Investigation by FDA’s Minneapolis district office confirmed that urea, a chemical used primarily in fertilizer and feed for cattle, was being illegally added to the wheat before being sold to flour companies.


They were fined $250,000 each and placed on three years’ probation. Earlier, they had agreed to to pay more than $400,000 to the Pillsbury Co., which had purchased the adulterated wheat.

“Adding urea to wheat is a blatant effort to make a fast buck by deceiving buyers,” said assistant U.S. attorney Douglas R. Peterson, who prosecuted the case. He added that the Schulers “enjoyed artificial profits while grain buyers were bilked.”

The price of wheat is determined by the protein content. Buyers test for protein by measuring the amount of nitrogen in the grain. The addition of urea, a high-nitrogen chemical, increases the protein test results.

Wheat typically contains from 11 to 14 percent protein and sells for from $2.50 to $4.50 per bushel, depending on the market. A 1 percent difference in protein can make a 5 to 80 cent difference in price per bushel. (In terms of value, 11 percent protein is considered low and 14 percent is considered high.)

When FDA received the tip about the company, it sent its investigators to inspect the Schulers’ operation. When Thomas Nelson and Dirk Mow arrived at the company’s grain elevators, there was no sign of the tanks and pipes needed to treat wheat with urea—just a suspiciously empty steel building smelling strongly of ammonia.

“One thing for sure about inspecting grain elevators,” Nelson said, “you always get dirty. This particular building was clean as a whistle. We learned later they had dismantled all their treating equipment. Someone apparently had warned them we were coming.”

The investigators spent a day and a half on the premises. During that time, they collected wheat scrapings from one of the grain dryers that FDA lab analysis later revealed contained as much as 33 percent urea. During the next 10 days, FDA investigators took wheat samples from local farm bins where Schuler wheat was stored. One percent of urea was found in some of the wheat.

As a result of FDA’s investigation, during October and November 1985, U.S. marshals seized three bins and 26 railroad cars of wheat in the St. Paul-Minneapolis area and two barges of wheat—two in New Orleans and one in Chattanooga—bound for foreign ports.

What the Schulers did, said Walter Stauffacher, FDA compliance officer for the Minneapolis district, was to wait for a period when the nitrogen content of local wheat was about 11 percent, buy it from farmers at the low market price, then sell it to companies such as Pillsbury for a higher price per bushel. Higher nitrogen wheat is believed to produce superior baked goods.

Pillsbury passed the higher cost on to bakeries, which in turn passed the cost on to consumers. “It was the consumer who ultimately got shortchanged,” Stauffacher said.

In 1985, the Schulers made an estimated $750,000 on adulterated wheat. During FDA’s investigation, evidence was found that suggested the Schulers also sold adulterated wheat in 1975 and 1981, Stauffacher said.

The urea did not pose a health hazard, he said, because there is no known toxic effect of 1 percent levels of urea in food. Urea is currently approved by FDA as an additive in yeast used for baked goods and alcoholic beverages.

During sentencing, the brothers had difficulty admitting they had done anything wrong, Nelson said.

“They maintained they were just trying to enhance the protein content of wheat to increase their profit margin. To them, increasing the profit margin with an illegal additive and cheating were not the same thing.”

—This small sample of reports from the field was prepared by Judy Folkenberg, Richard Nelson, and Sharon Snider.
Summaries of Court Actions

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

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

SEIZURE ACTIONS

Food/Poisonous and Deleterious Substances

CHARGED 10-1-89: While held for sale, the article contained the pesticide chemical ethylene dibromide, and no tolerance or exemption had been granted for such pesticide in honey—402(a)(2)(B).
DISPOSITION: Default—destruction. (F.D.C. No. 65645; S. No. 89-447-941; S.J. No. 1)

Food/Contamination, Decomposition, Insanitary Handling

PRODUCT: Beans, black, and sesame seeds, at Los Angeles, C. Dist. Calif.; Civil No. 89-322-Civ-Orl-18.
CHARGED 4-11-89: When returned to Brady Honey Farm, St. Cloud, Fla., the article contained the pesticide chemical ethylene dibromide, and no tolerance or exemption had been granted for such pesticide in honey—402(a)(2)(B).
DISPOSITION: Default—destruction. (F.D.C. No. 65645; S. No. 89-447-941; S.J. No. 1)

CHARGED 12-1-88: While held for sale, the articles contained insect, rodent and other filth—402(a)(3); and the articles had been held under insanitary conditions—402(a)(4).
DISPOSITION: The articles were claimed by Companhia de Navegacao Lloyd Brasileiro, New York, N.Y., who stated that “the claimant avers upon information and belief that it was at the time of the filing of the Complaint herein, and still is, the true and bonafide owner.” Subsequently, pursuant to the complaint and warrant, the articles were seized by the U.S. marshal. The claimant and the government discussed a proposed consent decree of condemnation that authorized release of the articles to the claimant for salvaging.

However, the claimant filed a “Withdrawal of Claim of Interest.” The government treated such “Withdrawal of Claim of Interest” as a request that the court allow the claimant to withdraw and stated that the Federal Food, Drug, and Cosmetic Act [304(e)] clearly provided that costs incurred in seizure and condemnation proceedings were to be “awarded against the person, if any, intervening as claimant of the article.” Noting that the government did not oppose the withdrawal of the claim of the claimant (Lloyd Brasileiro), but did seek costs pursuant to 304(e), the court ruled for the government. In the face of Lloyd Brasileiro’s assertion that the statute should not apply because it was not the owner of the article, the court noted that the statute did not facially contemplate an exception for any but successful claimants and that Lloyd Brasileiro provided no evidence to counter the claim of ownership that it initially advanced upon intervention. Accordingly, the court ordered that Lloyd Brasileiro be allowed to withdraw as intervenor, but to remain subject to costs upon entry of the decree of condemnation. The government opposed Lloyd Brasileiro’s motion for reconsideration and moved for a default decree of condemnation. In response to the government’s motion for a
default decree, Lloyd Brasileiro requested that the court strike the paragraph of the decree which imposed costs. Ultimately, pursuant to stipulation, Lloyd Brasileiro agreed to pay costs of $2,500. The motion for reconsideration was withdrawn, the articles were destroyed pursuant to a default decree, and the $2,500 was paid. (F.D.C. No. 65559; S. No. 88-569-244; S.J. No. 4)

PRODUCT: Chocolates containing various liquor-flavored fillings, Winters, at Charlotte, W. Dist. N.C.; Civil No. C-C-87-581-M.
CHARGED 12-29-87 and amended 12-30-87: When shipped by Winters Original Chocolate Liquor Bottles, Inc., Garfield, N.J., the articles’ labels lacked the name and place of business of the manufacturer, packer or distributor—402(a)(3), 402(a)(4); the articles were also in violation of the Fair Packaging and Labeling Act, since the net weight statement was in a type size less than 1/8-inch high and appeared on the back of the package rather than as a distinct statement in the bottom 30 percent of the principal display panel, which had an area of more than 5 square inches—15 U.S.C. 1453(a)(2) & 1453(a)(3)(C)(i).
DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65288; S. No. 87-537-140; S.J. No. 8)

PRODUCT: Mineral water, macaroni, instant potatoes, and cereal, at Fall River, Dist. Mass.; Civil No. 89-0698 N.
CHARGED 3-29-89: When imported from Portugal, required information was not prominently placed on the articles’ labels in such terms as to be likely to be understood, since such information was not in English—403(f); and the labeling of the cereal was misleading because it declared the presence of mineral salts and vitamins but lacked required nutrition labeling information—403(a)(1); the label of the cereal lacked the common or usual name of the food—403(i)(1); and the label of the cereal lacked the common or usual name of each ingredient—403(i)(2).
DISPOSITION: Consent—authorized release to Cosmos Import & Export, Inc., Fall River, Mass., for salvaging of the mineral water and cereal, and also authorized constructive destruction of the macaroni and instant potatoes by donation to charity or government. (F.D.C. No. 65585; S. No. 89-561-551 et al.; S.J. No. 9)

PRODUCT: Gloves, latex, for medical examination, at Los Alamitos, C. Dist. Calif.; Civil No. 89-00625.
CHARGED 8-10-89: When shipped by Galletti Bros. Foods, Los Angeles, Calif., the labeling of the gloves (i.e., “Pacific Red Snapper”) was false and misleading when applied to fish that was not Lutjanus peru; and the gloves’ label lacked the common or usual name of the fish since “Pacific Red Snapper” was not a correct designation of the fish—403(a)(1), 403(i)(1); the label of the “Imitation Crab Meat Flakes” fish product lacked the term “Imitation” in a type of uniform size and prominence to that of the term “Crab Meat Flakes”; “Imitation Crab Meat Flakes” was not an appropriately descriptive term for artificially crab-flavored fish product—403(e), 403(i)(1); and both articles were in violation of the Fair Packaging and Labeling Act since the net quantity of contents was not stated on the label of the tray packs—15 U.S.C. 1453(a)(2).
DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65733; S. Nos. 89-540-339/9; S.J. No. 10)

Drugs/Human Use

PRODUCT: Butalbital-aspirin-caffeine-codeine capsules, at West Hempstead, E. Dist. N.Y.; Civil No. 90-0495.
CHARGED 2-7-90: While held for sale, the article (labeled “Rugby Isollyl...capsules...Manufactured for Rugby Laboratories, Inc., Rockville Center L.I., N.Y....Manufactured by Halsey Drug Co., Inc., Brooklyn, N.Y.”) was a new drug without an effective approved New Drug Application—505(a); and the article’s labeling lacked adequate directions for use due to the article’s new drug status—502(f)(1).
DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65796; S. No. 90-521-579; S.J. No. 11)

Medical Devices

PRODUCT: Gloves, latex, for medical examination, at Los Alamitos, C. Dist. Calif.; Civil No. 89-0163 JGD(Sx).

CHARGED 1-11-89: That the quality of the articles, which were labeled (987-case lot) “Latex exam gloves non sterile ... Made In Taiwan” and (768-case lot) “Latex Exam Gloves Non Sterile ... Distributed by ACP, Santa Ana, CA ... Unilab, Los Alamitos, CA ... Made In Taiwan,” fell below their purported quality since they contained holes—501(c); and the packages of the 987-case lot lacked a label containing the name and place of business of the manufacturer, packer or distributor—502(b). DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65578; S. No. 89-444-149 et al.; S.J. No. 12)

PRODUCT: Gloves, latex, for medical examination, at Memphis, W. Dist. Tenn.; Civil No. 89-2807GA. CHARGED 9-11-89: The quality of the article, which was labeled “C & K Manufacturing ... Bay Village, OH ... Latex Examination Gloves Made in China,” fell below the article’s purported quality, since the article contained excessive holes—501(c). DISPOSITION: Default—ordered destroyed. (F.D.C. No. 65748; S. No. 89-574-205 et al.; S.J. No. 13)

PRODUCT: Gloves, vinyl, for medical examination, at Earth City, E. Dist. Mo.; Civil No. 89-0386-C-3. CHARGED 3-2-89: The quality of the article, which was labeled “Vinyl Non-Sterile Floor/Exam Gloves ... Made In Taiwan,” fell below its purported quality since the gloves contained holes—501(c); and the label of the articles lacked the name and place of business of the manufacturer, packer or distributor—502(b)(1). DISPOSITION: Consent—ordered destroyed. (F.D.C. No. 65625; S. No. 89-526-146; S.J. No. 14)

PRODUCT: Hyperbaric oxygen chamber of fiberglass, at Dallas, N. Dist. Texas; Civil No. 3-89-0458-G. CHARGED 2-15-89: The article was misbranded since the manufacturer had not provided FDA with the required pre-market notice to determine the classification of the device—502(o). DISPOSITION: Frencos Laboratories, Inc., Dallas, Texas, filed an answer to the complaint for forfeiture asserting that the machine was unlabeled, that it was being used for experimental purposes only and was not destined for use in commerce or for the treatment of humans, and that the machine was not unlawful per se. The government moved to strike the answer because no claim to the device had been filed. Subsequently, Frencos Laboratories, Inc., filed a claim to the article, and the government’s motion to strike the answer was denied. The government served requests for admissions, written interrogatories, and requests for the production of documents. Ultimately, a consent decree condemned the article and ordered destruction. (F.D.C. No. 65579; S. No. 88-582-326; S.J. No. 15)

CRIMINAL ACTIONS

DEFENDANTS: Don L. Tirado, Carol L. Stasi, and Eric D. Swanbott, Saratoga, N. Dist. Calif.; Criminal No. 89-20094RFP. CHARGED 6-29-89 by grand jury: That the three named defendants conspired (count 1) to commit offenses (21 U.S.C. 331 & 333) against the United States; that the objects of the conspiracy included the following: the manufacture, packaging, labeling, and the interstate distribution of counterfeit and misbranded drugs; using the U.S. Postal Service in a scheme to defraud; conducting financial transactions with the proceeds of such scheme to promote, to conceal and disguise the source, ownership and control of the proceeds of the scheme, and to avoid a federal transaction reporting requirement; that the means and manner of the conspiracy included the following: to manufacture, package and label counterfeit articles of drug (i.e., counterfeit Andriol-50, Deca-Durabolin, Dianabol, Equipoise, Finajet 30, Nolvadex, Pregnyl, Testosterone (cyonionate, enanthate & propionate), and Winstrol-V); to package and label (thereby misbranding) the above articles and the methandrostenolone and parabolin, representing such counterfeit articles and other articles as containing active ingredients although those articles did not have active ingredients—502(a); to receive letters delivered by the U.S. Postal Service for the purpose of executing their scheme; to instruct customers to pay in cash; and to purchase cashier’s checks to conceal and disguise the nature, location, source, and ownership of the proceeds of the unlawful activity; that the defendants and co-conspirators committed a number of overt acts, including the following: the purchase of quantities of clear glass vials and grey butyl rubber stoppers; the cash payment to a graphic artist for typesetting and layout for labels, boxes and inserts for Pregnyl and Deca-Durabolin; the ordering of the cutting and assembly of printed cartons bearing the label Winstrol V; the ordering, using an alias, of 300,000 vitamin tablets with magnesium and the payment using a third-party cashier’s check and blank money orders; the similar ordering, using an alias, of 270,000 vitamin tablets with magnesium and 3 million vitamin tablets with zinc; the shipment to Buffalo, N.Y., using the name European Health Products, of specified quantities of counterfeit and misbranded drugs (e.g., 50,000 tablets “Andriol-50,” 6,250 vials “Dea Durabolin,” 1 million tablets methandrostenolone, and 459,500 tablets “Nelavor”) while representing the shipment contents as tanning oils and vitamins; and the storage at one conspirator’s residence of at least 100 bottles of each of seven specified counterfeit drugs; and that on the specified occasions, money orders (i.e., 55 money orders totaling $53,300, 23 money orders totaling $17,789.99, and 58 money orders totaling $10,241.42) were endorsed for payment or deposit—18 U.S.C. 371.

Counts 2 through 10 charged the violative holding for sale of nine specified counterfeit drugs in that the drugs’ containers and labeling bore without authorization the trademark, trade names, or other identifying mark of drug manufacturers or distributors other than the person who in fact manufactured and distributed the drugs—201(g)(2). Counts 11 through 22 charged the violative shipment to Buffalo, N.Y., of 12 drugs whose labels were false and misleading because they claimed a specific active ingredient when in fact none of the drugs contained any active ingredient at all—502(a). Count 23 charged the violative shipment of a drug labeled as “Pregnyl,” which was dangerous to health when used as directed for intramuscular injection in that the drug contained bacteria and pyrogens—502(j). Count 24 charged a financial
transaction involving the proceeds of a mail fraud scheme to sell counterfeit drugs, which transaction was designed to avoid the federal IRS reporting requirement concerning cash transactions in excess of $10,000, in that, using cash, a $9,000 cashier’s check, and a $9,500 cashier’s check were purchased—18 U.S.C. 1956(a)(1)(B)(ii). The last count of the indictment charged a financial transaction involving the proceeds of a mail fraud scheme to sell counterfeit drugs, in that a $426 money order was endorsed using an alias as partial payment for serum vials, bottles, stoppers, crimper, and a bottle filler—18 U.S.C. 1956(a)(1)(A)(i).

DISPOSITION: The defendants pleaded guilty; Swahnolt pleaded guilty to the first, the 23rd, and the last counts, and was placed on probation for one year plus other special conditions, including 300 hours of community service. Stasi pleaded guilty to the conspiracy charge (count 1) and was sentenced to three years imprisonment (suspended) and 120 hours of community service; and Tirado pleaded guilty to the conspiracy charge (count 1) and to counts 2 and 24, and was sentenced to four years imprisonment. (F.D.C. No. 64307TD; S.J. No. 16)

**MISCELLANEOUS ACTIONS**

SUBJECT: FDA new drug approval letter for Marinol brand of dronabinol capsules, and expiration of time to file for the drug’s patent term extension, Washington, Dist. Columbia; Civil No. 88-2480.

CHARGED 9-1-88 by Unimed, Inc., Somerville, N.J., and Theodor Petrzilka, Erlinback, Switzerland, against Donald J. Quigg, Commissioner of Patents and Trademarks, in a complaint for injunctive and declaratory judgment: That Unimed, Inc., the exclusive licensee of the patent for dronabinol (a synthetic equivalent of an isomer of delta-9-tetrahydrocannabinol, a psychoactive substance), and Petrzilka, the patentor of dronabinol, had been denied a patent term extension by Commissioner Quigg, on the sole basis that the extension application had not been filed in timely fashion within 60 days from the date the drug “received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use”—35 U.S.C. 156(d)(1).

Petrzilka had submitted his application for such extension two weeks after May 13, 1986, when the Drug Enforcement Agency (DEA) had removed dronabinol from Schedule I to Schedule II, clearing the way for commercial marketing of the drug; Commissioner Quigg’s position was that the relevant date to begin the 60-day filing period was the date of FDA’s New Drug Application approval letter (i.e., FDA’s letter was dated May 31, 1985; it approved Marinol capsules for use as an antiemetic and antinauseant; and it reminded Unimed, Inc., that Marinol might not be legally marketed until DEA had completed rescheduling activities as required by the Controlled Substances Act).

Unless a certificate of patent term extension was issued or an interim extension of patent term was granted, the dronabinol patent would irrevocably expire on June 6, 1989, and the plaintiffs would be deprived of market exclusivity for their drug. Accordingly, the plaintiffs prayed as follows: (a) that a declaratory judgment should issue declaring that failure to extend the patent was unlawful; (b) that an order should be issued enjoining the defendant to extend the patent; and (c) that an order should issue enjoining the defendant to grant an interim extension of the patent.

**DISPOSITION: District Court**—After the defendant denied the charges, the plaintiffs moved for partial summary judgment. The defendant filed a cross-motion for summary judgment. The district court noted that the outcome of the case depended on whether the plaintiff had applied for an extension within the prescribed 60-day period, and that the gist of the plaintiffs’ argument was that it was unfair to require a patent-extension application within 60 days of FDA’s NDA approval on May 31, 1985, when the drug couldn’t be marketed for another year due to DEA’s pending rescheduling action (May 13, 1986).

The district court noted that FDA’s NDA approval letter informed Unimed that it could not market Marinol until DEA had rescheduled the drug; that, clearly, “DEA rescheduling was a precondition to marketing; and that to ignore such a roadblock to marketing would fail to give meaning to the clause “for commercial marketing or use.” Since permission for commercial marketing or use awaited a further regulatory barrier in the shape of a DEA review, the district court concluded that it would be contrary to the purpose of the Patent Term Restoration Act to start the clock ticking on the patent holder’s right to apply for an extension during a period when the product could not be marketed. Accordingly, the court ordered that the denial of the extension application be set aside, ordered the application remanded to the Patent and Trademark Office for consideration on its merits, and ordered the grant of an interim extension. The district court’s action was appealed to the U.S. Court of Appeals for the Federal Circuit.

**Court of Appeals**—Upon appeal, the judgment of the district court was reversed and Commissioner Quigg’s denial of a patent extension was reinstated. The Court of Appeals noted that the timelessness issue boiled down to whether the specified 60-day period began when FDA sent its approval letter or when DEA rescheduled Marinol nearly a year later. The court found that the Patent Term Restoration Act took into account only the FDA regulatory review and no other government obstacle to marketing. After FDA’s letter of final approval, nothing more from FDA was needed. Although DEA rescheduling was a legal prerequisite to Unimed’s “commercial marketing or use” of Marinol, the applicable regulatory review period did not comprehend it.

Since the provisions of the Patent Term Restoration Act were clear and unambiguous, resort to legislative history of the statute was unnecessary. Nevertheless, the court’s construction of the applicable provisions was, happily, consistent with the legislative history since a broader coverage had been rejected by Congress and what became law was circumscribed, limiting the extension only to the period of FDA review. The Court of Appeals noted that it might appear to be incongruent that the operative review period would not include activities by government entities other than FDA, but the court concluded that it should not distort the statute to “fix” what Congress either intentionally or inadvertently failed to anticipate. Accordingly, the judgment of the district court was reversed. (Misc. No. 913; S.J. No. 17)
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